

**TREATMENT OF NONSPECIFIC DNA-PROTEIN CONTACTS AND APPLICATION
TO THE EXCISION MECHANISM OF A UNIQUE HUMAN DNA GLYCOSYLASE**

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To Dad.

You and Mom have always been my first and best teachers, who taught me that I
“gotta put my good foot forward and stop being influenced by fools.”

“May your heart always be joyful. May your song always be sung.”

For me, your memory will stay forever young.

Abstract

This thesis concentrates on understanding how individual nonspecific DNA–protein contacts are used in the excision mechanism of the human DNA repair enzyme, alkyladenine DNA glycosylase (AAG). Initially, studies focus on understanding the structure and magnitude of these fundamentally different DNA–protein stacking and T-shaped interactions to be applied to the active site of AAG. High-level *ab initio* techniques revealed fundamental knowledge about the structure and magnitude of these distinctly different π – π and π^+ – π contacts between (one or two) conjugated amino acid(s) and one nucleobase. Additionally, the mechanism used by AAG to excise (neutral and cationic) damaged nucleotides was investigated using a hybrid ONIOM approach. Reaction potential energy surfaces reveal that AAG prefers to excise both neutral and cationic substrates through a concerted mechanism, yet the nonspecific contacts present in the active site are only catalytic for the cleavage of the neutral substrates.

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List of Abbreviations

1MeA	1-methyladenine
1MeG	1-methylguanine
2AP	2-aminopurine
3EtU	3-ethyluracil
3MeA	3-methyladenine
3MeC	3-methylcytosine
3MeT	3-methylthymine
3MeU	3-methyluracil
7MeG	7-methylguanine
A	adenine
AAG	alkyladenine DNA glycosylase (human)
AlkA	3-methyladenine DNA glycosylase II (<i>E. Coli</i>)
A _N D _N	concerted, synchronous mechanism
AP	apurinic/apyrimidinic
APE1	AP endonuclease 1 in humans
au	atomic units
BCP	bond critical point
BER	base excision repair
BL	bond length
BPL	bond path length
BSSE	basis set superpoistion error
C	cytosine
CBS	complete basis set
CCP	cage critical point
D	debyes
dA	2'-deoxyadenosine
dC	2'-deoxycytidine
DCPs	dispersion correcting potentials
DFT	density functional theory
dG	2'-deoxyguanosine
D _N *A _N	stepwise mechanism, where the first step involves dissociation of the leaving group to form an intermediate, followed by an associative transition state to form the product
DNA	deoxyribonucleic acid
dRP lyase	5'-deoxyribosephosphate lyase
dsDNA	double-stranded deoxyribonucleic acid
dT	thymidine
EA	1,N ⁶ -ethanoadenine
EC#	enzyme commission number
ESP	electrostatic potential
G	guanine
GGA	generalized-gradient approximation

H(r)	total electron density
HhH	helix-hairpin-helix
Hx	hypoxanthine
I	intermediate
lp	lone pair
MM	molecular mechanics
MMS	methyl methanesulfonate
MNU	N-methyl-N-nitrosourea
MSE	mean signed error
MUE	mean unsigned error
MutY	MutY DNA glycosylase
NCP	nuclear critical point
NDB	nucleic acids database
O ² MeT	O ² -methylthymine
O ⁴ MeC	O ⁴ -methylcytosine
O ⁴ MeT	O ⁴ -methylthymine
O ⁶ MeG	O ⁶ -methylguanine
ONIOM	our own N-layered integrated molecular orbital and molecular mechanics
P	product
PDB	protein data bank
PES	potential energy surface
pyr	pyrrolidine abasic site
QM	quantum mechanics
QTAIM	quantum theory of atoms in molecules
R	reactant
RCP	ring critical point
RESP	restrained electrostatic potential
RNA	ribonucleic acid
S22	small (22) noncovalent benchmark database of Hobza and coworkers
SAM	S-adenosylmethionine
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
ssDNA	single-stranded deoxyribonucleic acid
T	thymine
TS	transition state
U	uracil
UDG	uracil DNA glycosylase
Xan	xanthine
∇ ² ρ(r)	Laplacian of the electron density
°	degrees
Å	angstrom, 10 ⁻¹⁰ m
Δ80AAG	alkyladenine DNA glycosylase (human) where the first 80 N-terminus amino acids have been removed

ϵA	1,N ⁶ -ethenoadenine
ϵC	3,N ⁴ -ethenocytosine
ϵG	1,N ² -ethenoguanine
$\rho(r)$	electron density

Chapter 1. Introduction

1.1. General Overview

Proteins are arguably the most fascinating and complex biomacromolecules. Structurally and functionally, these molecules are incredibly diverse and dynamic, which allows them to play major roles in almost all cellular processes.¹ The structure of all proteins starts with at least one polymer chain of amino acids linked together through peptide bonds (Figure 1.1), which generally fold into very unique three-dimensional structures that are exquisitely suited to its intended function.² Together, proteins perform many tasks, such as repelling invaders in cells, acting as delivery systems, as well as catalyzing biochemical reactions with extraordinary specificity and rates that synthetic chemical catalysts can only strive to achieve.¹⁻²

The structural integrity of deoxyribonucleic acid (DNA, Figure 1.2) relies on the intricate function of proteins.³ Indeed, an elaborate machinery comprised of proteins is responsible for producing two identical copies of the DNA helix in the replication process. For instance, at the outset, a DNA helicase unwinds the double helix to form a replication fork to allow DNA polymerase and clamp proteins to work together to read the parent-template and synthesize the complementary strand.¹⁻² In addition, when alterations in the chemical structure of DNA occur, enzymes recognize sites of DNA damage and catalyze the repair of this molecule. Therefore, the exceptional chemical stability of DNA is ultimately governed by unique interfacial DNA-protein interactions, which help the enzyme recognize the specific DNA target, provide structural stability to the entire complex throughout the dynamic biochemical process, and then allow the DNA-protein complex to dissociate when the purpose is complete.³ Unfortunately, the individual contacts found in DNA-protein complexes are generally not well understood, and therefore the role that these noncovalent

interactions play in the overall biological function is also not fully appreciated.

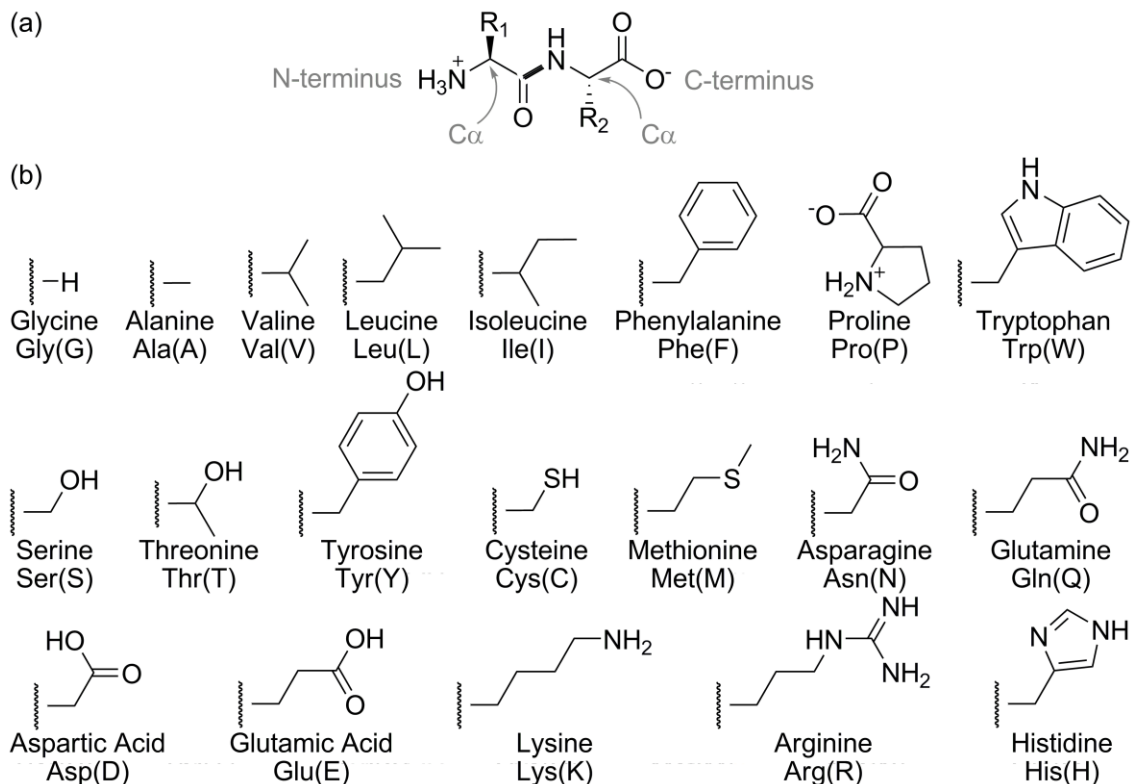


Figure 1.1. Structures of (a) a dipeptide composed of two amino acids (side chains indicated by R_1 and R_2) linked through a peptide bond (bold), and (b) the side chains of the twenty amino acids. In the case of proline, the backbone is also included.

This thesis concentrates on understanding how individual DNA–protein interactions are used to catalyze the repair of DNA alkylation, a very common type of DNA damage, in humans. The following sections will introduce alkylation damage, the general pathway used to repair this damage, and how computational chemistry techniques have been used throughout this thesis to describe interfacial DNA–protein interactions, as well as the excision mechanism of this DNA repair process.

1.2. DNA Damage

Despite the stability of DNA, many spontaneous reactions can alter its chemical

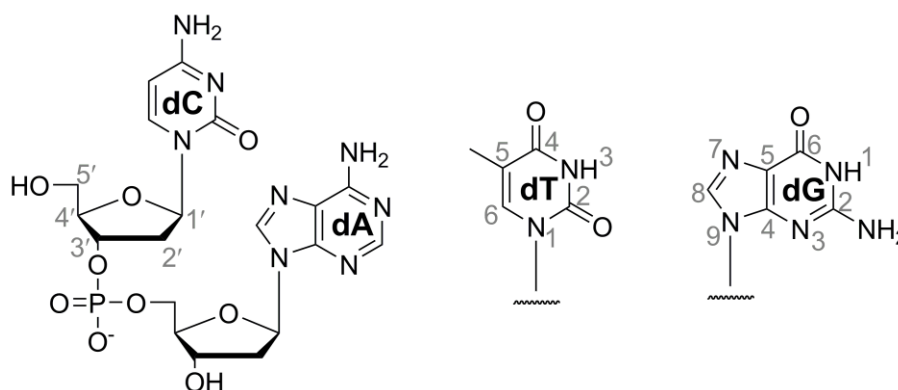


Figure 1.2. Structures of the four natural DNA nucleic acids (2'-deoxycytidine (**dC**, nucleoside form), 2'-deoxyadenosine (**dA**, nucleotide form), thymidine (**dT**), and 2'-deoxyguanosine (**dG**)), as well as the atomic numbering for the deoxyribose, pyrimidine (dT, dC), and purine (dG, dA) rings.

structure.⁴ Indeed, even slow reactions can cause a significant number of DNA damage lesions on biologically-relevant time scales due to the large size of the genome.⁵ Also, remarkably minor alterations in the structure of DNA can change the stability of the helix or the hydrogen-bonding potential of the nucleobases, which can eventually cause errors during DNA replication or transcription processes and thereby lead to mutations in the genome or cell function.

There are copious mechanisms that alter the structure of DNA, where nucleobase modification is the most common type of DNA damage.⁴ Of these, the hydrolytic deamination of the exocyclic amino groups of cytosine, adenine and guanine is the most prevalent, which results in uracil, hypoxanthine, and xanthine, respectively (Figure 1.3).⁵ Since the 4-amino group of cytosine is the most unstable of the nucleobases,^{4,6} formation of uracil is widespread and can induce a C:G to T:A point mutation if not repaired.⁴ In addition to deamination, a large number of other chemical reactions can alter the DNA nucleobases. One such reaction is DNA alkylation, which is the focus of this thesis and is described in the following section.

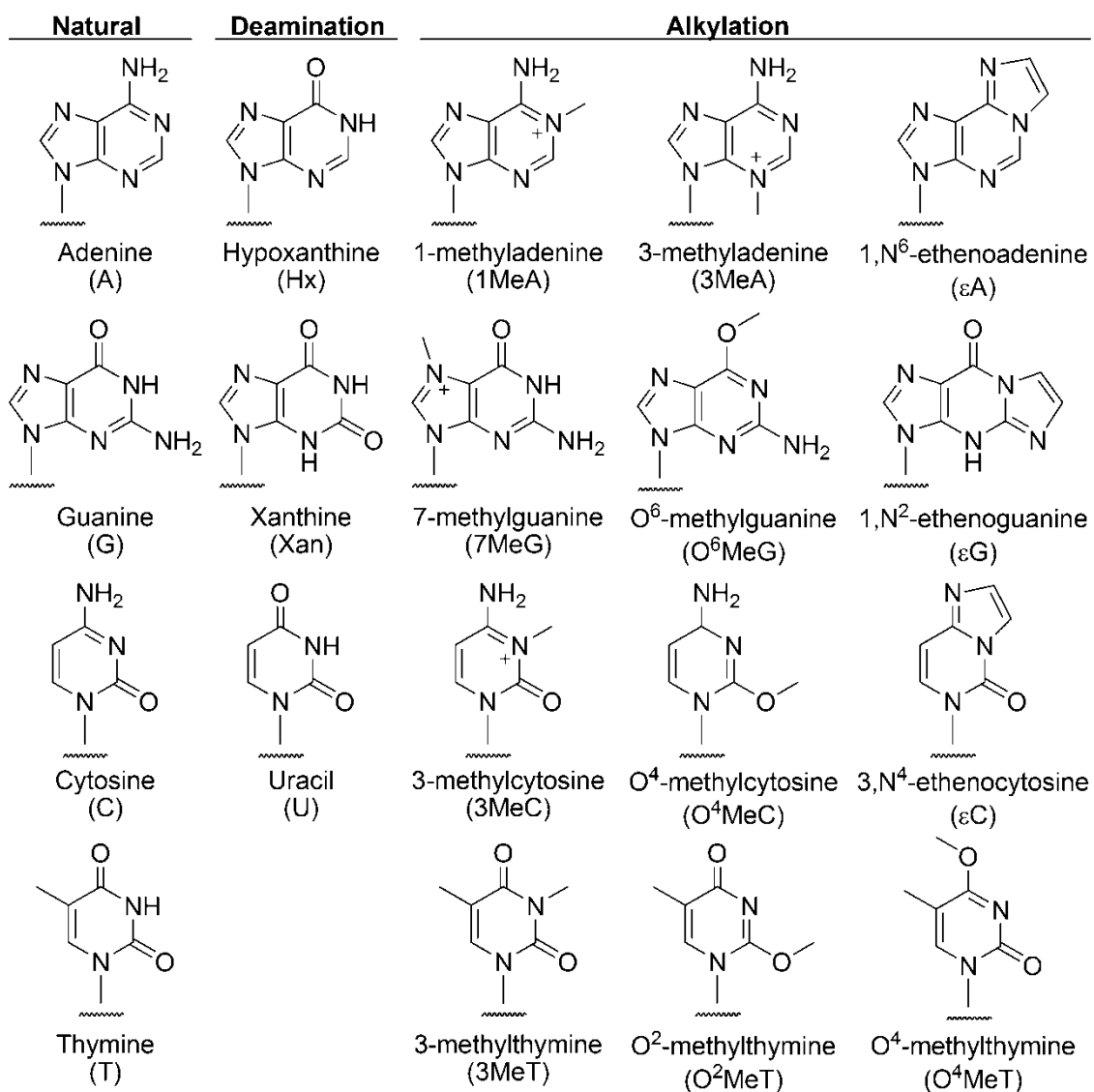


Figure 1.3. Natural and common damaged nucleobases found in DNA (abbreviations provided in parentheses).

1.2.1. DNA Alkylation

Alkylation damage can be caused by organic or inorganic chemical agents or by enzymes that promote natural methylation, such as members of the S-adenosylmethionine (SAM)-dependent methyltransferase family.⁷⁻¹⁰ In addition, alkylating agents have been exploited as cytotoxic drugs in cancer therapies, where the doses of these agents far exceed those that humans are exposed to from other sources.¹¹ These extracellularly generated and endogenously produced electrophiles give rise to a number of alkylation products due to

the abundance of nucleophilic sites on the DNA nucleobases.^{7,10} For example, alkyl groups of varying size may attach to numerous sites, where the methylated versions are shown in Figure 1.3. The type of damaged lesion that results ultimately depends on the alkylating agent, as well as the form of the DNA strand being modified. For instance, 1-methyladenine (1MeA) is a common alkylation product when single-stranded DNA (ssDNA) is exposed to a methylating agent, yet it occurs much less frequently within double stranded DNA (dsDNA) since the N1 site of adenine is shielded through hydrogen-bonding interactions with thymine.^{7,10,12}

The most chemically vulnerable site for alkylation damage in dsDNA is the N7 site of guanine since it has the highest negative electrostatic potential among all the nucleobases.¹⁰ When dsDNA is exposed to a common S_N2 methylating agent, methyl methanesulfonate (MMS, Figure 1.4a), 83% of the methylation occurs at N7 of G.¹² Similarly, when dsDNA is exposed to S_N1 methylating agents (such as N-methyl-N-nitrosourea, MNU, Figure 1.4b), 67% of the methylation occurs at N7.¹² 7MeG has been detected in human DNA at the level of a few lesions per 10^7 nucleobases,¹³ yet this lesion is not cytotoxic.¹⁰ Instead, methylation at the N7 site of guanine destabilizes the glycosidic bond connecting N9 of this base to C1' of the sugar moiety,¹⁴ and therefore rapid spontaneous depurination occurs. The resulting abasic site can lead to mutations if not repaired before replication.¹⁰

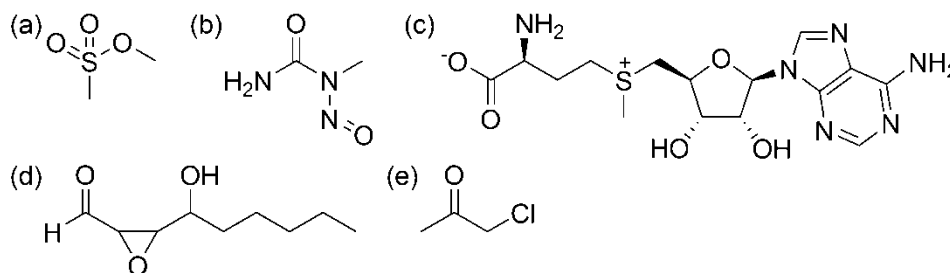


Figure 1.4. Structures of common alkylating agents (a) methyl methanesulfonate (MMS), (b) N-methyl-N-nitrosourea (MNU), (c) S-adenosylmethionine (SAM), (d) 2,3-epoxy-4-hydroxynonalal, and (e) chloroacetaldehyde.

Following the N7 site of guanine, N3 of adenine is the next most susceptible site to

alkylation damage.¹² 3-methyladenine (3MeA) can be formed in dsDNA by exposure to methylating agents like MMS and MNU, or non-enzymatically by intracellular SAM (Figure 1.4c).¹⁰ 3MeA is estimated to be generated more than 600 times per cell per day;¹⁵ however, it has been found to exhibit only cytotoxic properties.¹⁰ Indeed, the methyl group sterically interferes with the polymerase replication enzyme and thereby stops DNA replication.¹⁶ Therefore it is essential for 3MeA to be repaired, and DNA repair enzymes have evolved to remove this damaged lesion through the base excision repair (BER) pathway.

The above examples, as well as those shown in Figure 1.3, illustrate the vast array of alkylation damage that results from alkyl groups attaching to one nucleobase site. However, DNA alkylation lesions that attach to two nucleobase sites,¹⁰ like 1,N⁶-ethenoadenine (ϵ A) and 1,N²-ethenoguanine (ϵ G), also occur (Figure 1.3). These damaged bases are unique in structure, and can arise from either endogenous or exogenous sources. For instance, ϵ A is produced under normal conditions in humans when adenine reacts with products of unsaturated lipid peroxidation, such as 2,3-epoxy-4-hydroxynonalal (Figure 1.4d).¹⁷⁻²⁰ Recently, toxicological concerns have also been raised about ϵ A since it is also formed when adenine reacts with the common industrial agent vinyl chloride and its metabolites, such as chloroacetaldehyde (Figure 1.4e).^{10,21} This lesion is believed to be mutagenic since it has been observed to pair with both G and C, resulting in an A $\rightarrow$ C or A $\rightarrow$ G mutation if not repaired.¹⁰ Despite their different effects, both ϵ A and 3MeA are repaired in humans through the BER pathway, as discussed in the following section.

1.3. Base Excision Repair (BER)

Nonbulky damage to the nucleobases within DNA is commonly repaired through the BER pathway (Figure 1.5).⁵ Indeed, BER is generally considered as the main “housekeeping” pathway for the repair of lesions that occur as part of normal metabolism.²² In regards to DNA alkylation lesions, the primary repair pathway is BER;²³ however, some alkylated

nucleobases, like O⁴MeT and O⁶MeG (Figure 1.3), are repaired through the direct reversal pathway used by the O⁶-methyltransferase enzymes.²⁴ These direct pathways are often called suicide reactions because the stoichiometric transfer of the alkyl group to the active-site cysteine cannot be reversed to regenerate the active protein, thereby killing the enzyme.^{5,25-27} However, the BER pathway is preferred over direct repair for most alkylation lesions.⁵

The first step of the BER pathway involves the DNA glycosylases, which are the largest class of DNA repair enzymes that scan the genome in search of damaged bases.⁵ Once a damaged base is identified, these enzymes initiate the BER pathway by flipping the damaged nucleotide into the active site and cleaving the N-glycosidic bond to release the damaged base.²⁸⁻³¹ In humans, twelve DNA glycosylases have been identified, where each enzyme is responsible for excising different lesions.^{22,28-32} In some cases, however, there is more than one glycosylase responsible for identifying the same damaged base. DNA glycosylases are commonly classified as monofunctional or bifunctional according to the reactions they catalyze. The monofunctional glycosylases use water as the nucleophile to attack C1' of the sugar moiety and result in an AP (apurinic/apyrimidinic) site. The bifunctional glycosylase/AP lyase enzymes commonly use an active site amine (such as lysine or proline) to form a Schiff base intermediate covalently bound to the enzyme, and then cleave the phosphodiester bond of the damaged nucleotide at the 3' position (β -elimination) and in some cases also the 5' position (β,δ -elimination, Figure 1.5). Both the AP site and the nicked DNA intermediates are potentially mutagenic lesions at this stage of the repair pathway since DNA replication could result in misincorporation. Therefore, it is essential that these DNA intermediates be further processed by the rest of the BER

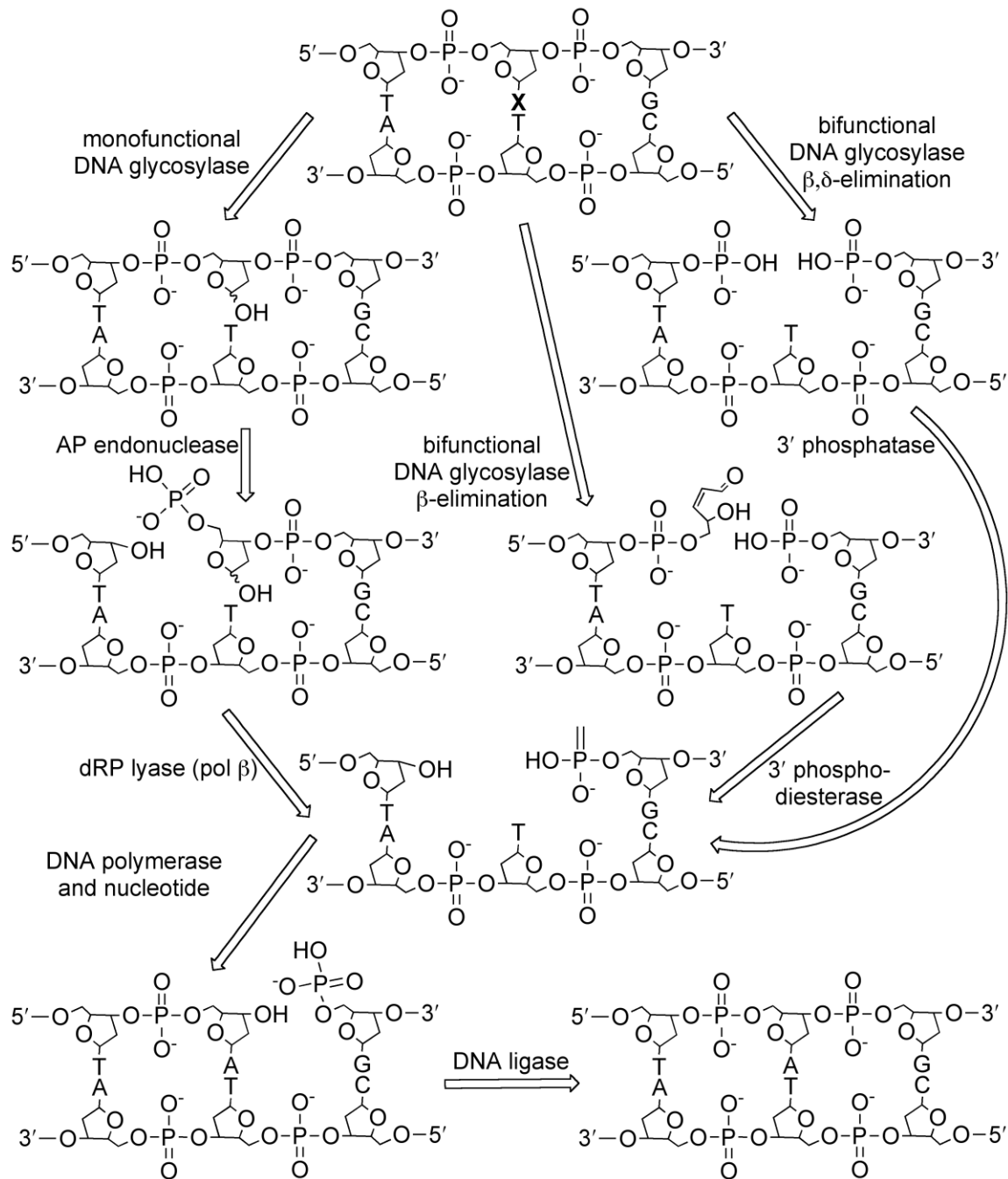


Figure 1.5. Biochemical pathways used in the base excision repair (BER) process. If a base lesion (X) is recognized by a monofunctional DNA glycosylase (left), then subsequent actions of an AP endonuclease, 5'-deoxyribosephosphate lyase (dRP lyase), DNA polymerase and DNA ligase are required. If a bifunctional DNA glycosylase with β-elimination (center) initiates repair (or a β,δ-elimination, right), then a 3'-phosphodiesterase (3'-phosphatase) is needed before the DNA polymerase and DNA ligase.

enzymes. Indeed, how this pathway proceeds depends on the type of glycosylase used for the repair; however, the mechanism must consist of a DNA polymerase (such as polβ)

adding the replacement nucleotide into the DNA strand, and a DNA ligase completing the process by closing the nick in the backbone. In the case of the monofunctional glycosylases, an AP endonuclease and an AP lyase are needed before polymerase recognition (Figure 1.5). In the case of the bifunctional (β - or β,δ -elimination) glycosylases, a 3'-phosphodiesterase or 3'-phosphatase is needed before polymerase recognition, respectively (Figure 1.5).

Eleven of the twelve human DNA glycosylases can be divided into one of three families that are conserved through evolution.²² Indeed, the largest family share a helix-hairpin-helix (HhH) motif as a defining feature, while the other families share common substrates (uracil/thymine-specific glycosylases) or similar mechanistic features (bifunctional glycosylase/AP lyase). However, the human DNA glycosylase that is responsible for removing DNA alkylation damage, (monofunctional) alkyladenine DNA glycosylase (AAG), is an outlier and does not belong to any of these families. AAG is a very unique glycosylase in that it processes structurally diverse lesions, yet its mechanism-of-action is still poorly understood. The following subsections will illustrate what is known about this perplexing repair enzyme, and the questions that still remain to be answered about this unusual glycosylase.

1.4. Human Alkyladenine DNA Glycosylase (AAG)

Alkyladenine DNA glycosylase (also sometimes referred to as N-methylpurine DNA glycosylase, EC# 3.2.2.21) is a 33 kDa monomeric protein with 298 amino acid residues.⁴ This enzyme was first recognized to remove 3-methyladenine (3MeA), resulting in the name 3-methyladenine DNA glycosylase.³³ However, AAG has since been found to have broad substrate specificity and has been reported to remove many different damaged bases.³⁴⁻⁴⁴ Specifically, AAG is the only known human glycosylase to excise 1,N⁶-ethenoadenine (ϵ A) and hypoxanthine (Hx). It is also widely accepted that this glycosylase removes 3MeA and 7MeG from dsDNA. Biochemists have proposed that AAG might have evolved as a

hypoxanthine DNA glycosylase due to its large excision preference for Hx.⁴⁰ However, it should be noted that AAG is the most inefficient of the DNA glycosylases,²⁸ where this enzyme has been shown to enhance the glycosidic bond cleavage rate of the non-enzymatic reaction by 10^3 – 10^7 ,⁴⁰ as compared to the 10^{10} – 10^{26} rate enhancements reported for other DNA glycosylases.⁴⁵ This low catalytic power has been proposed to reflect the fine balance between efficiently excising a variety of damaged bases and keeping the cleavage of natural bases at an acceptably low level.⁴⁰

Studies focusing on understanding how this glycosylase functions in nature determined that AAG initially binds to the DNA helix and diffuses along the strand through a processive search for DNA damage (Figure 1.6).⁴⁶⁻⁴⁸ Once a damaged lesion is found, two distinct steps must occur: (1) the nucleotide-flipping step that alters the conformation of the DNA strand to flip the damaged nucleotide into the active site; and (2) the chemical step that cleaves the glycosidic bond with a water nucleophile, which may occur in a stepwise or concerted manner. Additionally, once AAG releases the damaged base, the DNA helix is allowed to return to its natural configuration. Next, AAG dissociates from the AP site, which has been shown to be enhanced when an AP endonuclease (AP endonuclease 1 (APE1) in humans) is present to induce this dissociation,⁴⁹ leaving AAG to continue a processive search along the strand for more damaged nucleobases.

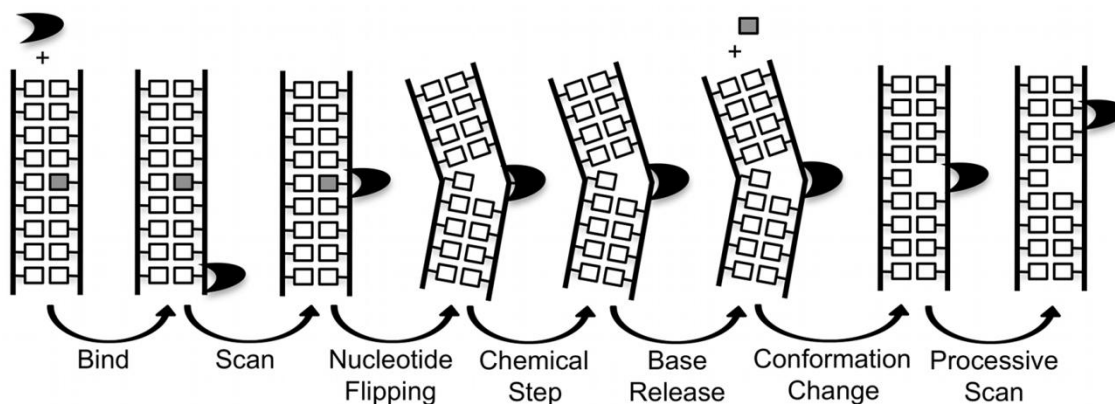


Figure 1.6. Alkyladenine DNA glycosylases (AAG) complete mechanism-of-action.

Due to the broad substrate specificity unique to AAG, many studies have attempted to determine if the lesions recognized and excised by this enzyme share common structural features.³⁴⁻⁴⁴ It should be noted that these studies have investigated both the full length protein and a truncated version of AAG, which is missing the 80 N-terminal amino acids (commonly referred to as $\Delta 80$ AAG) and is easier to purify. These studies have shown that the glycosidic-bond cleavage activity of this truncated version is nearly identical to the full length protein, with the exception of U, which is only excised by the full length protein.⁴⁴ Therefore, it is generally accepted that the first 80 amino acids do not contribute to the chemical step of this enzyme,⁴⁹ yet are important for the processive search along the DNA strand.⁴⁶ Thus, experimental studies almost exclusively focus on the truncated protein.

AAG has been found to bind to a wide variety of DNA substrates with different affinities (Figure 1.7).⁴⁴ Interestingly, AAG preferentially binds with similar affinity to 3,N⁴-ethenocytosine (ϵ C) and ϵ A. However, in the case of ϵ C, the lesion is not excised by AAG, but instead inhibits glycosylase activity by creating a stable AAG–DNA complex that stalls replication.⁵⁰ Indeed, only the substrates shown in bold in Figure 1.7 are found to be excised, and it is generally accepted that AAG excises the most common lesions with the following efficiencies: Hx > ϵ A > 3MeA > 7MeG. The insignificant rate enhancement that AAG exhibits for the natural bases A and G, as well as 2-aminopurine (2AP), generally leads to these bases being ignored from the excision list.⁴⁰ Although a similar function is expected for the *Escherichia coli* form of this enzyme, 3-methyladenine DNA glycosylase II (AlkA), AAG is actually quite different since AlkA is known to excise both of the natural purines.²⁸ In addition, AlkA can remove some damaged pyrimidines like 3-methylcytosine (3MeC),⁵¹ while AAG has little to no activity for most pyrimidines. Also, the structural forms of these two enzymes are very different, and they are therefore expected to employ very different reaction mechanisms.⁵²

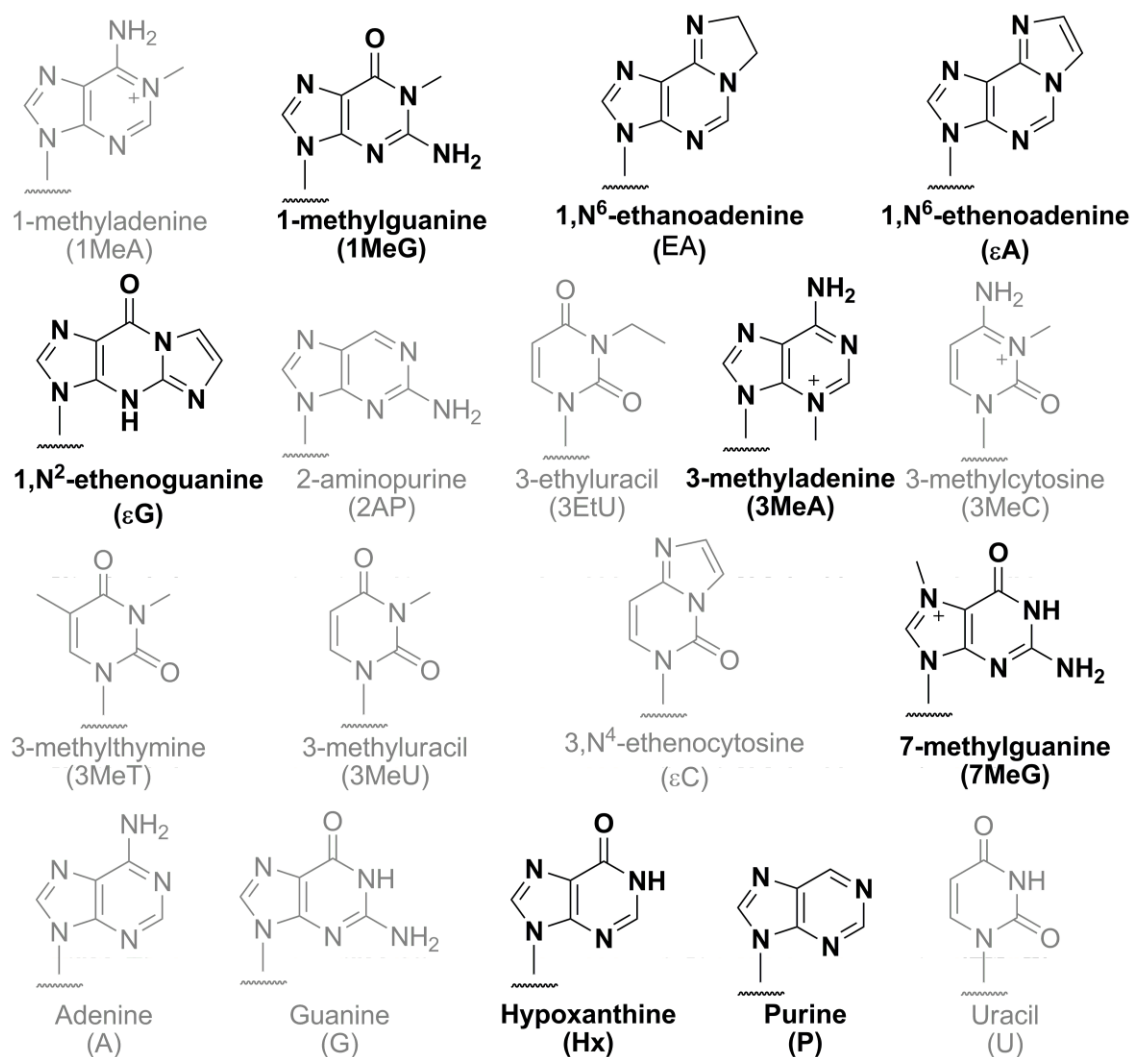


Figure 1.7. Alphabetical listing of the structures and abbreviations for DNA substrates identified in binding studies to be recognized by AAG, where damaged bases in bold indicate glycosidic-bond cleavage activity.

It is believed that the different efficiencies for excision of a variety of damaged lesions are influenced by the nucleotide-flipping step more for AAG than any other DNA glycosylase.^{39,41,47,53-54} This nucleotide-flipping step has been shown to be highly-dependent on the local environment of the damaged lesion, where the identity of the opposing base, as well as the flanking bases in the dsDNA sequence, can have large effects on the excision rate.^{39,41,47,53-54} Therefore, interplay between the nucleotide-flipping step and the hydrolysis of the glycosidic bond is reflected in the measured excision rates of the various nucleobases.

To complicate matters further, recent work has shown that the rate at which AAG flips ϵ A into its active site is very fast, and therefore the chemical step is the rate-determining step for this substrate.⁴⁷ However, it has been proposed that the nucleotide-flipping step is highly unfavourable for Hx,^{47,54} meaning that the previously measured excision rates for this substrate are highly dependent on this step, and perhaps only provide a lower bound for the chemical step for this substrate. The involvement of the nucleotide-flipping step for other substrates is currently unknown. Therefore, future studies need to explicitly investigate these two glycosylase steps for all substrates excised by AAG. The next section will discuss the significant information obtained from the crystal structure of AAG, and how mutational analysis has provided important clues about the central residues involved in the excision mechanism of this DNA repair enzyme.

1.4.1. AAG Crystal Structure and Mutational Analysis

The first crystal structure of AAG, published in 1998, provided a large amount of information about the mechanism-of-action of this DNA glycosylase.⁵⁵ This crystal structure (Protein Data Bank (PDB) entry 1BNK, 2.7 Å resolution) is the Δ 80AAG enzyme complexed to DNA containing a transition state mimic (pyrrolidine abasic nucleotide (pyr, Figure 1.8), which is electrostatically similar to the rate-limiting oxacarbenium ion transition state of most DNA glycosylases).⁵⁶ In 2000, three crystal structures (PDB entry 1F60, 2.4 Å resolution; PDB entry 1EWN, 2.1 Å resolution; PDB entry 1F4R, 2.4 Å resolution) were reported for Δ 80AAG.⁵⁷ 1F60 is similar to the original crystal structure, with the wild-type protein bound to pyr. 1EWN reveals the Δ 80AAG protein containing the E125Q mutation bound to ϵ A-containing DNA with an intact N-glycosidic bond. Interestingly, the 1F4R structure of the wild-type Δ 80AAG complexed with ϵ A-containing DNA also has an intact glycosidic bond. This perplexing structure exhibits only a 0.4 Å rmsd from the pyr bound crystal structure (1F60). Later experiments showed that the catalytic activity of AAG is

significantly inhibited in the presence of divalent metal ions, including Zn^{2+} , Ca^{2+} , Cd^{2+} , Ni^{2+} , and most importantly, Mn^{2+} that was present in the crystallization buffer.⁵⁸⁻⁵⁹ However, since no Mn^{2+} ions were present in this crystal structure,⁵⁷ the mechanism for metal inhibition remained puzzling. Most recently, a crystal structure was reported (PDB entry 3QI5, 2.2 Å resolution, EC# 3.2.2.21) that shows $\Delta 80\text{AAG}$ bound to ϵC -containing DNA,⁶⁰ which is a known inhibitor. From all of these structures, a proposal for how AAG catalyzes the glycosidic-bond cleavage mechanism of a range of alkylation lesions has been developed.

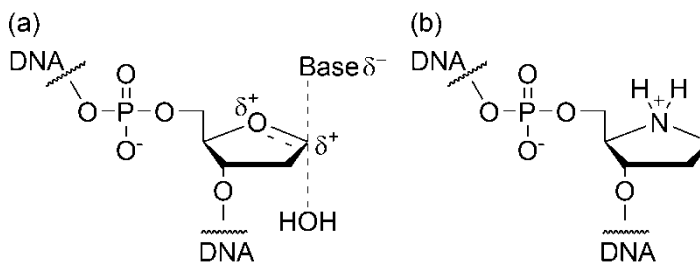


Figure 1.8. Electrostatic similarity between (a) the proposed transition structure of AAG, and (b) the pyrrolidine abasic site analog (pyr).

By examining the active site of the wild-type and E125Q $\Delta 80\text{AAG}$ structures bound to ϵA -containing DNA, it can be seen that there are minimal changes in the active site amino acids, with the exception of changes in the hydrogen-bonding interactions with residue 125 due to electrostatic changes in the mutant.⁵⁷ Therefore, the remaining discussion will concentrate on the structure of the wild-type ϵA bound structure, unless otherwise indicated. However, it should be noted that these observations are derived from static crystal structures, and there is no structure of AAG bound to a cationic nucleobase since the half-life of these lesions is much shorter than the duration of crystal structure experiments.²⁸ Therefore, it is possible that structures containing bound cationic substrates are quite different from structures that are currently available. Indeed, even shifts in the orientations of the amino acid side chains observed in the crystal structures of AAG/ ϵA - or

ϵ C-containing DNA complexes illustrate these potential structural changes upon binding of cationic substrates.^{57,60}

The first major observation from the crystal structures is that AAG bends the DNA strand away from the protein by about 20° (Figure 1.9), and the width of the minor groove increases by more than 2 Å. This is consistent with distortions caused by other DNA glycosylases, which are believed to be necessary for the nucleotide-flipping step.^{57,61-63} The side chain of Tyr162 inserts into the minor groove of DNA when the flipped nucleotide is found in the active site of the protein. Indeed, Y162A mutations show very little glycosylase activity due to this important stabilizing interaction during this step of enzyme catalysis.⁵⁷ Interestingly, there is no observed interaction between AAG and the opposing base in DNA, which indicates that the dependence on the opposing base-sequence observed for this enzyme happens prior to formation of the flipped-out nucleotide complex.⁵⁷

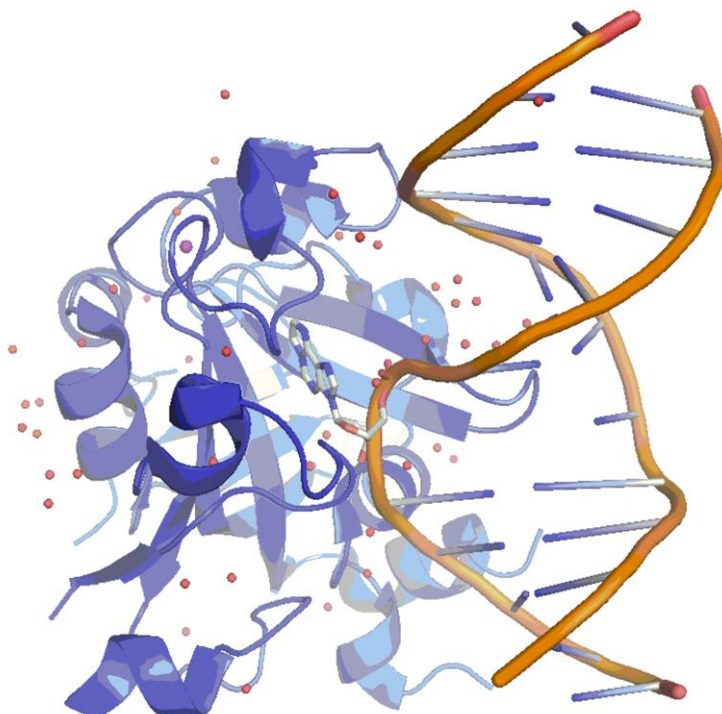


Figure 1.9. Crystal structure of the $\Delta 80$ AAG/ ϵ A-DNA complex (PDB entry: 1F4R) showing the conformational change of DNA upon flipping ϵ A (shown as tubes) into the active site of AAG.

In the active site, there is one water molecule that is very close to C1' of the flipped-out

ϵ A nucleotide.⁵⁷ It has been proposed that the position of this water molecule suggests a more associative mechanism for the AAG catalyzed cleavage of ϵ A.²⁸ This water has been found to donate a hydrogen bond to Glu125 and to the carbonyl oxygen of Val262, while accepting a hydrogen bond from Arg182 (Figure 1.10). Tyr127 donates a hydrogen bond to Glu125, which is suspected to be important for stabilizing the substrate binding pocket.⁵⁷ Glu125 was proposed to act as the general base in the chemical step of enzyme catalysis,⁵⁵ where E125Q and E125A mutations completely eliminate detectable glycosylase activity.⁶⁴ The E125C mutation was also shown to decrease AAG activity for the ϵ A and 7MeG substrates by up to 4000 fold.⁶⁴ This experimental evidence has led to the wide acceptance that Glu125 is the general base responsible for activating the water nucleophile.

The 5'-phosphate of the ϵ A nucleotide accepts a hydrogen bond from both His136 and Tyr159.⁵⁷ Mutational analysis of H136A noted a decrease in glycosylase activity by 16 and 160 fold for the ϵ A and 7MeG substrates, which suggests that His136 is important in the mechanism, but not essential.⁶⁴ In addition, the backbone nitrogen of His136 is found to donate a hydrogen bond to the N6 site of ϵ A, which has been proposed to be an important interaction for discriminating against the natural base adenine through unfavourable electrostatic interactions with the N6 amino group.⁵⁷ Additionally, Asn169 is located near N2 of ϵ A and is believed to provide another important interaction for discriminating against the natural base guanine through steric hindrance with the N2 amino group.⁵⁷ Indeed, removing this steric clash in the N169A mutant⁶⁵⁻⁶⁶ was found to increase the rate of excision for G mispairs over the wild-type protein.⁶⁵

Interestingly, Tyr127 forms a π - π (face-to-face) stacking interaction on one side of the ϵ A base, while two (edge-to-face) T-shaped interactions occur on the other side of ϵ A with

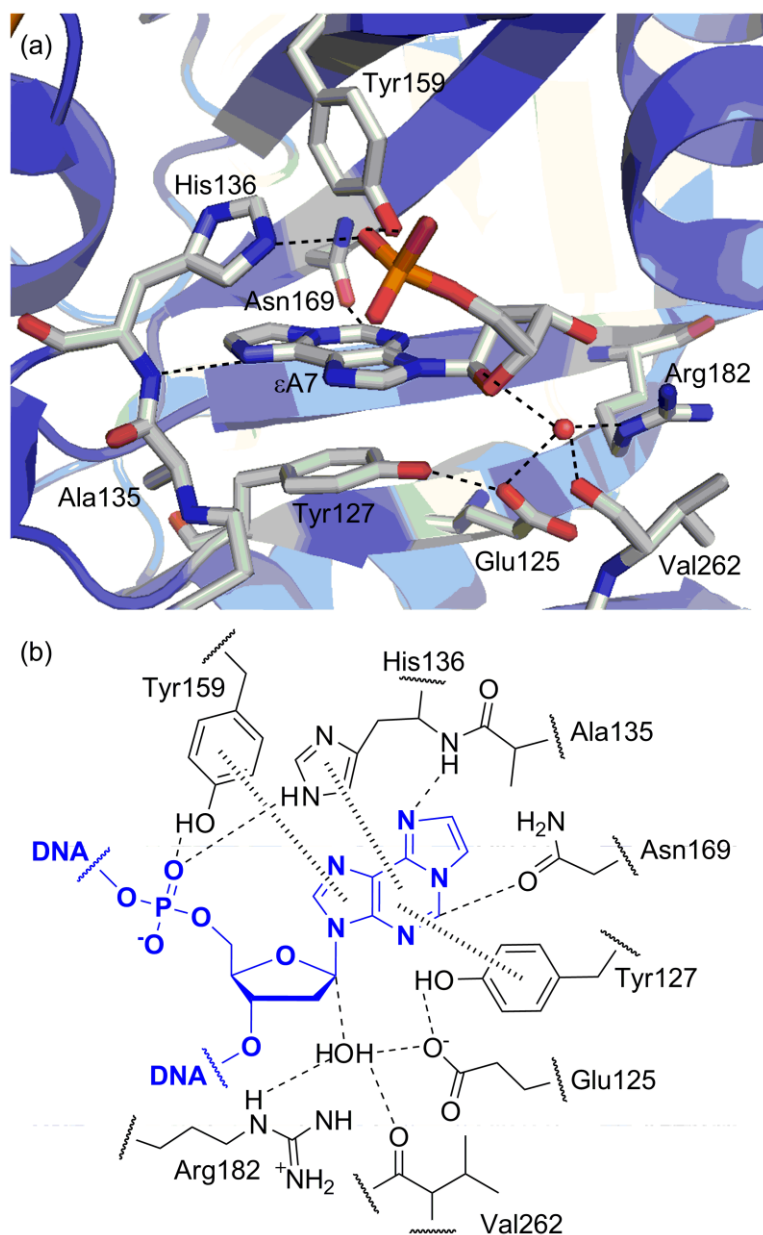


Figure 1.10. Important active site residues identified for AAG through crystal structure analysis, where (a) displays the important hydrogen-bonding interactions in the $\Delta 80$ AAG/ ϵ A-DNA complex (PDB entry 1F4R), and (b) also indicates the important π - π interactions between the ϵ A7 nucleotide (bold) and the protein residues (plain).

His136 and Tyr159 (Figure 1.10).⁵⁷ Recent work has mutated each tyrosine residue to tryptophan,⁶⁴ and found that the barrier heights for cleaving the glycosidic bond of ϵ A increase from 90.7 kJ mol⁻¹ for the wild-type protein to 94.0 and 92.8 kJ mol⁻¹ for Y127W and Y159W, respectively.⁶⁷ It is quite unique that AAG relies so heavily on these nonspecific

π - π contacts, and indeed it is only found for this human DNA glycosylase. However, the role of these amino acids in this chemical mechanism is not well understood. It has been suggested that residues with the potential for π - π interactions line the active site of AAG to accommodate broad substrate specificity.^{55,57} However, it has also been proposed that these interactions do not provide enough stability for this catalytic process and cannot account for the discrimination in binding of the various excised substrates.²⁸ Furthermore, it has been suggested that these residues could be anticatalytic by preferentially binding to the more electron deficient nucleobase lesions, which would help draw the substrate into the active site, but would not drive the reaction forward.²⁸ Therefore, it is clear that more mechanistic studies need to be done to confirm or dismiss these hypotheses and to help identify the role of the π -systems of these amino acids in the active site.

1.4.2. Further Studies of the Proposed Mechanism for the Chemical Step

In 2003, it was proposed that AAG uses acid-base catalysis for the excision of damaged purines.⁶⁴ Specifically, the pH dependencies of the overall rates of the excision of Hx, ϵ A, and 7MeG were determined to address whether the same catalytic groups are required for the reaction with positively charged and neutral substrates. While the neutral substrates indicate the involvement of two essential groups, 7MeG was found to only require one.⁶⁴ This study suggests that AAG uses a general base for the excision of all substrates, yet it activates neutral lesions by protonating the nucleobase leaving group. Since it is more difficult to protonate the pyrimidines, these results provide a rationale for why AAG removes damaged purines but excludes pyrimidines.⁶⁸⁻⁶⁹ Furthermore, the non-enzymatic (dissociative) excision of the natural purines,⁷⁰ as well as the MutY DNA glycosylase, which excises natural adenine mispaired with the damaged lesion 8-oxoguanine,^{28-29,71} involves protonation at N7 to achieve glycosidic-bond cleavage.

This same study also used mutations in an attempt to identify the amino acid acting as

the general acid in the neutral lesion excision mechanism.⁶⁴ However, after mutating all potential active site residues identified in the crystal structures, the general acid involved in the hydrolysis of neutral substrates could not be identified. Although it is possible that large structural rearrangements could occur in this protein that reorient another amino acid residue to fill this role,⁶⁴ crystal structures of various substrates determined that AAG generally has a consistent structure that does not drastically change upon binding.⁵⁷ Furthermore, the most recent crystal structure of active $\Delta 80$ AAG bound to ϵ C-containing DNA shows no new amino acid residues that could be acting as the general acid.⁶⁰ Additionally, molecular dynamics simulations examining the binding preferences of ϵ A and EA substrates,⁷² as well as recent Monte Carlo simulations of AAG/Hx-containing and AAG/A-containing DNA complexes,⁷³ indicate that the conformation of AAG is not largely influenced by adduct binding. Therefore, it was suggested that this enzyme has access to multiple pathways for proton transfer that therefore cannot be determined through single point mutations.⁶⁴ However, examination of the $\Delta 80$ AAG-E125Q/ ϵ A-containing DNA crystal structure⁵⁷ reveals a water chain between C1' of the sugar and N7 of ϵ A that could act as the general acid in the mechanism of the neutral substrates (Figure 1.11). Indeed, the location of the water molecule near N7 of ϵ A in the $\Delta 80$ AAG-E125Q crystal structure was recently proposed in the literature⁶⁰ to potentially act as the general acid for the excision of neutral substrates by AAG.

Computational work has investigated the proton affinity and acidity of ϵ A⁷⁴ and Hx⁷⁵ to determine if these lesions are cleaved with or without the general acid. These calculations reveal that glycosidic bonds of Hx and ϵ A are more acidic than the natural purines, which suggests that they are naturally better leaving groups than A or G in their neutral form. It

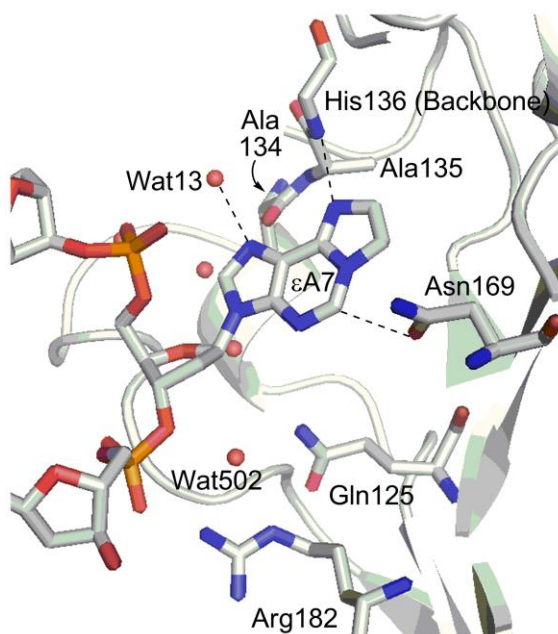


Figure 1.11. The $\Delta 80$ AAG-E125Q crystal structure complexed to ϵ A-containing DNA indicating the water molecules (spheres) present near the substrate in the active site.

was also shown that protonation of Hx and ϵ A at N7 is energetically less favourable due to their lower proton affinity compared with the natural bases. This suggests that AAG may cleave these neutral alkylation lesions without this protonation step to provide further discrimination against the natural purines (A and G). Therefore, Lee and coworkers⁷⁴⁻⁷⁵ proposed that AAG does not require a general acid to cleave the glycosidic bond of neutral substrates excised by this enzyme.

The above discussion indicates that the excision mechanism of AAG is still perplexing and controversial. Indeed, there are many unanswered questions related to AAG which include: How does AAG discriminate against the neutral bases yet excise a wide variety of structurally diverse damaged lesions? Are neutral lesions protonated prior to glycosidic-bond cleavage? Is the chemical step of AAG stepwise or concerted? Does the mechanism for the chemical step depend on the charge of the damaged lesion? What is the role of the amino acids with conjugated π -rings in the active site? Do these amino acids retain the same π - π conformation as the reaction proceeds? Do these π - π interactions affect the catalytic

power of the enzyme? Undeniably, there is still a lot of research needed to gain a full appreciation of this DNA repair enzyme.

To date, no computational studies have directly examined the hydrolysis mechanism of AAG, despite the fact that computational techniques can yield an atomistic understanding of how this reaction proceeds. Indeed, computational methodologies have taken an increasingly important role in studying enzymatic mechanisms due to their capacity to characterize both the structure and energy of short-lived intermediates and transition states, which can be very challenging to study experimentally.⁷⁶ Additionally, computational chemistry has the capability of examining the roles of the amino acids with conjugated π -rings throughout the DNA repair reaction, which is of great interest since an understanding of how π - π interactions contribute to this biological process is generally lacking.⁷⁷ Nevertheless, there are difficulties associated with accurately and efficiently modeling enzymatic environments and active site π - π contacts. Computational approaches to overcome these issues will be the topic of the following section.

1.5. Computational Challenges and Approaches for Modeling Noncovalent Interactions in Enzymatic Systems

Despite the power of current computational facilities, molecular modeling of big (thousands of atoms) enzymatic systems remains a challenge to computational chemists.⁷⁸ The use of classical mechanics within molecular mechanics (MM) force fields are popular in structural studies of large and complex organic and biomolecular systems.⁷⁹⁻⁸⁰ However, these methods are unable to describe the changes in the electronic structure of a system undergoing a chemical reaction. Indeed, processes involving bond-breaking and bond formation require the use of quantum mechanics (QM) for proper treatment. These methods can be very computationally demanding, and therefore smaller system sizes of tens to several hundreds of atoms must be employed.

A promising computational approach for the study of enzymes involves hybrid techniques,^{78,81-83} which combine two or more methods and/or levels of theory. These methodologies allow for an accurate quantum mechanical description of the chemistry in a localized (high-level) region (such as an active site), while describing the rest of the protein with a less accurate (faster) computational method (low-level region).⁷⁸ These schemes can be applied in a variety of ways. The QM/MM methodology, which combines a quantum mechanical technique with a molecular mechanics method, is the most common class of hybrid approaches.^{78,83} ONIOM (our Own N-layer Integrated molecular Orbital molecular Mechanics) is another promising hybrid technique that is also used to study enzymatic systems.⁸¹⁻⁸² This is perhaps a more general scheme due to its ability to combine any number of molecular orbital, as well as molecular mechanics, methods.⁸¹⁻⁸²

Most recent QM/MM and ONIOM studies of enzymatic systems use density functional theory (DFT) to describe the quantum mechanical region due to its greater efficiency compared with popular wavefunction-based approaches.⁸⁰ Although the great success of DFT cannot be ignored, some of its drawbacks have attracted much attention in recent years.⁸⁴ Specifically, most of the common density functionals are incapable of accurately describing dispersion interactions.⁸⁴ Indeed, the attractive dispersion interaction, which is commonly described as the interaction between instantaneous dipole moments within electron distributions of two atoms or molecules, plays a very important role in many areas of chemistry.⁸⁵ It was historically believed that dispersion energy is a small contributor to the overall stabilization of complexes;⁸⁵ however, it has been shown more recently that this energetic contribution between two systems with delocalized electrons is substantial.⁸⁶ This finding has cast new light on the nature of the stabilization of biomacromolecules such as DNA and proteins,^{77,85} and it has become evident that dispersion plays a much wider role in biology. Indeed, the difficulties associated with modeling dispersion interactions represents

one of the key problems of computational science today.⁸⁷

Therefore, in order to computationally examine enzymatic reactions that highly depend on dispersion interactions, as well as the role of various interfacial noncovalent interactions in the active site, computational chemists are faced with a very unique problem. One way to address the problem is to simplify the model by truncating the biomacromolecular system into smaller representative components which can be examined using high-level computational techniques to accurately describe these interactions.⁸⁷ Despite the fact that this ignores the enzymatic environment, a proper description of the dispersion interactions can be obtained, ultimately leading to a better understanding of these systems of interest. Indeed, much progress has been made in the study of interaction energies between π -ring systems using highly-accurate *ab initio* methods that recover a very large portion of the electron correlation and use large basis sets.⁸⁵ Since such highly demanding techniques need to be used for the most accurate descriptions, the size of the system must be as small as possible.

It is therefore not surprising that the first complex to be investigated was the simplest system of two interacting π -rings, the benzene dimer.⁸⁵ Indeed, this dimer has become the prototypical π - π interaction complex, especially due to the ease of examining substituent effects. However, initial investigations determined that this relatively simple system has a vastly elaborate potential energy surface (PES), which is extremely flat with very small energy barriers between the local minima (which is characteristic of all noncovalent complexes).⁸⁵ This further complicates the methods used to determine the geometry of this twenty-four atom system. Indeed, various global minima of the benzene dimer (Figure 1.12) have been proposed (see, for example, references 88–102). The maximum dispersion interaction occurs in the sandwich structure (S, Figure 1.12), which was originally proposed through experiments to be the global minimum.⁸⁸⁻⁸⁹ However, more recent experimental

work suggested the global minimum is a T-shaped structure (T and TT, Figure 1.12).⁹⁰ Advances in computational resources have allowed for the most accurate computations on this dimer (coupled cluster (CC) calculations (specifically, CCSD(T)) at large basis sets (aug-cc-pVQZ), which were further extrapolated to an infinite basis set (complete basis set (CBS) limit)).¹⁰¹ These calculations have determined that the T-shaped structure with C_{2v} symmetry (T, Figure 1.12) corresponds to a transition state connecting the T-shaped (TT, Figure 1.12) and the parallel displaced (PD, Figure 1.12) minima, which are isoenergetic. Very recent efforts are still being devoted to understanding the differences between these stacked and T-shaped complexes since crystal structures of π -systems generally prefer parallel-displaced over T-shaped orientations.^{85,102-103} Therefore, it has been suggested that perhaps a dynamic average structure must replace the current description of the benzene dimer.¹⁰²

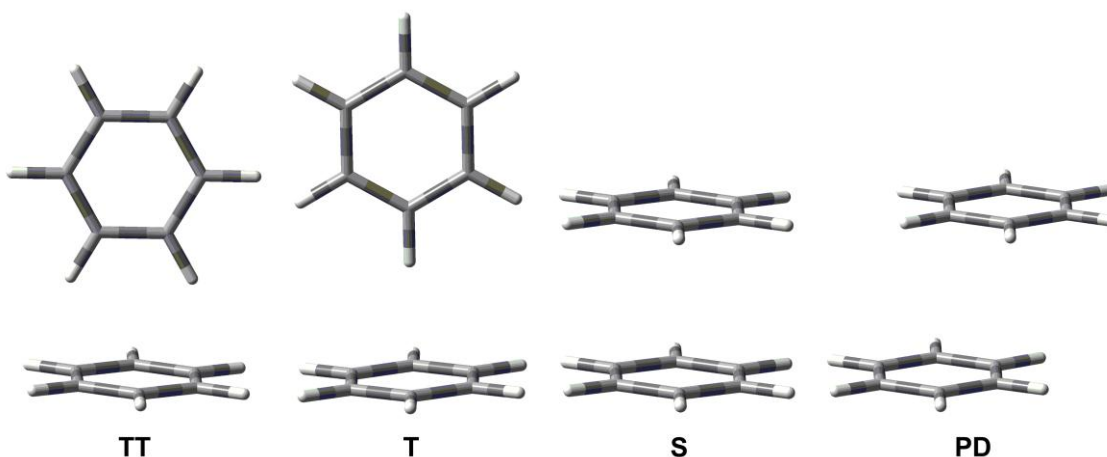


Figure 1.12. Structures of the benzene dimer in T-shaped (**TT** (C_s symmetry), and **T** (C_{2v})) and stacked (sandwich (**S** (D_{6h})) and parallel-displaced (**PD** (C_{2h}))) orientations.

In the area of noncovalent interactions between biomacromolecules, Hobza and coworkers have made a substantial contribution primarily by studying the interactions between the DNA nucleobases. Their work over the last two decades has examined the two qualitatively different interactions of the DNA helix: hydrogen-bonding and π - π stacking

interactions (see, for example, references 87, and 104–121). Despite the fact that there is an abundance of nucleic-acid structures available in the PDB and Nucleic Acids Database (NDB), this group chose to examine the nature of binding between nucleobase dimers, and therefore studies of the preferred structures of these systems were performed in the gas phase.⁸⁵ They believe that examination of the potential energy surface for these dimers is of key importance for understanding the fundamentals of these interaction energies. Therefore, their work initially concentrated on scanning the potential energy surface between fixed nucleobase monomers through high-level *ab initio* single-point calculations,^{104-105,112,114} which were subsequently used as starting points in full optimizations of these stacked dimers.^{108-109,114} Their approach allows for the relative structure and magnitude of these different noncovalent complexes to be examined.

Recent work from the Hobza group has concentrated on developing databases of highly-accurate structures and interaction energies for a variety of noncovalent dimer complexes at the CCSD(T)/CBS level of theory.^{87,112,116} In 2006, Hobza and coworkers published their most commonly-used test set (called the smaller training set (S22)), which has seven hydrogen-bonded, eight dispersion-dominated, and seven other dimer complexes that range in size from the water dimer to the adenine–thymine stacked dimer.⁸⁷ Their original intention for this work was to expand the benchmark data available to help theoretical developers estimate the accuracy of new computational approaches for determining the interaction energies in noncovalent systems. Indeed, within the last few years, theoretical techniques have been undergoing constant development to improve the description of noncovalent interactions. In fact, through testing against the S22 training set, a few new computational methods have shown promising performance for biologically-oriented applications (see, for example, references 122–130).

It has been recently mentioned that the S22 test set is quite small, and the density

functional performance for these specific interactions does not necessarily correlate with good functional performance for other applications.¹³¹⁻¹³³ Indeed, very recent efforts have been devoted to expanding this test set.¹³³⁻¹³⁴ However, these test sets still have a very small percentage of π - π interactions, and perhaps more importantly, they have left out a very important group of biologically-relevant interactions, specifically the π - π interactions between DNA and proteins. In fact, the π - π interactions between DNA and proteins have not been thoroughly studied in the literature. Undeniably, before the undertaking of this thesis, very little *ab initio* computations had been completed on the π - π interactions between DNA and protein components.¹³⁵⁻¹³⁶ The Hu group searched the PDB for structures that contained adenine to understand how binding proteins recognize this nucleobase.¹³⁵ In total, 66 amino acids with conjugated π -rings (Phe, Tyr, and Trp) were located within 5.6 Å of the adenine base in 44 structures. They further investigated the π - π stacking interactions of nine complexes of adenine with amino acids containing conjugated π -ring found in crystal structures (six with Phe, two with Tyr, and one with Trp) using MP2/6-311+G(d). These calculations reveal that the interactions depend on the intermolecular distance, orientation, and extent of π - π overlap, where the strongest crystal structure interaction was found to be -26.6 kJ mol⁻¹ (adenine-phenylalanine complex modeled as the adenine-toluene heterodimer). In 2005, the Rooman group examined adenine-histidine contacts within the PDB, where six of the 14 complexes were found to correspond to T-shaped orientations.¹³⁶ The (gas-phase) average MP2/6-31G(2d(0.8,0.2)) interaction energies between A and His observed in these crystal structures is -15 kJ mol⁻¹. Furthermore, the strongest stacking interaction is -21 kJ mol⁻¹, which was determined to be stabilized by significant dispersion interactions.

While this thesis was in progress, the unique scaffolding that the DNA nucleobases and amino acids with conjugated π -rings provide for studying hydrogen-bonding, stacking, and

T-shaped interactions has attracted more attention.¹³⁷⁻¹⁴⁰ In fact, significant contributions include the work of Cysewski, who studied the stacking interactions between the amino acids with conjugated π -rings and cytosine or uracil using MP2/aug-cc-pVDZ potential energy surface scans and full optimizations.¹³⁸ Additionally, 26 crystal structures from the PDB were identified by the Tschumper group that involve stacking interactions between adenine and phenylalanine.¹³⁷ The interaction energies of these 26 complexes (modeled as 9-methyladenine–toluene dimers) were investigated at the MP2 level and extrapolated to the CCSD(T)/CBS level of theory, and determined to range between -13.3 and -28.3 kJ mol⁻¹. This study also optimized these complexes (MP2/DZP++), which resulted in only six unique structures with CCSD(T)/CBS binding strengths ranging from -24.8 to -29.5 kJ mol⁻¹.

Despite these contributions, many questions remain about the π - π interactions between DNA and protein components, such as: How strong are these contacts? How does the relative nucleobase–amino acid side-chain orientation affect the strength of these interactions? What is the interplay of the attractive forces which stabilize these complexes? Do the amino acids with conjugated π -rings play a role in DNA–protein complex stability and/or nucleobase recognition? Is there a simple way to predict the strength of these interactions in nucleobase–amino acid complexes observed in experimental crystal structures? Therefore, it is apparent that these interactions need to be studied at a fundamental level with very accurate computational techniques before large biomacromolecular complexes between DNA and repair proteins are examined.

1.6. Thesis Overview

As outlined in the present chapter, the repair of DNA alkylation damage is of great interest, and provides a unique, challenging framework for a computational investigation. Indeed, many questions remain about the role played by the amino acids with conjugated

π -rings in the DNA–AAG complex, as well as the excision mechanism used to cleave the glycosidic bond of many different alkylation substrates.

In order to understand how damaged DNA interacts with amino acids containing conjugated π -rings, an understanding of the natural DNA–protein interactions must first be obtained. Therefore, Chapter 2 begins by investigating the structure and magnitude of the stacked and T-shaped interactions between the amino acids with conjugated π -rings and the natural DNA nucleobases. The methodology developed in this chapter uses potential energy surface (PES) scans and *ab initio* (MP2/6-31G*(0.25)) techniques. Further extrapolations to the CCSD(T)/CBS level show that this approach accurately describes both stacked and T-shaped interactions while providing more than just optimal structures and magnitude estimates for these interactions. Indeed, this chapter illustrates how this work can be used to predict the magnitude of π – π interactions in the active sites of a variety of DNA–protein complexes.

Using the methodology developed in Chapter 2, the next chapter examines the stacking and T-shaped interactions between the amino acids with conjugated π -rings and damaged nucleobases. Neutral ϵ A, as well as cationic 3MeA, are compared to the (neutral) natural base adenine to understand how damage, as well as charge, affects the structure and stabilization of π – π noncovalent interactions. This chapter also investigates the nature of the attractive forces present in π – π and π^+ – π interactions by dissecting interaction energies into their fundamental components (dispersion, electrostatics, etc). Chapter 4 examines how additional amino acids affect the π – π and π^+ – π dimer interactions, where systems with more than one amino acid are commonly observed in nature.

Using the 148 nucleobase–amino acid CCSD(T)/CBS interaction energies determined in the preceding chapters as reference data, Chapter 5 tests the ability of various density functionals with double-zeta quality basis sets, as well as some semi-empirical and

molecular mechanics methods, to accurately describe noncovalent DNA-protein π - π and π^+ - π interactions. Once an appropriate method is determined, large-scale modeling of the AAG glycosidic-bond cleavage mechanism is examined for the ϵ A, 3MeA, and A substrates (Chapter 6). This work provides evidence for how the chemical step used by AAG proceeds for neutral and cationic substrates, and helps determine the role of the amino acids with conjugated π -rings in the active site of this human DNA glycosylase.

Finally, Chapter 7 summarizes how this thesis has contributed to the general understanding of DNA-protein noncovalent interactions, as well as the mechanism-of-action of AAG. This chapter also describes future research avenues that will build upon the current work to help further describe noncovalent interactions and this unique DNA repair enzyme.

Chapter 2. Modeling π - π Stacking and T-shaped Interactions Between DNA/RNA Nucleobases and the Amino Acids with Conjugated π -Rings^{a,b}

2.1. Introduction

As discussed in Chapter 1, before an understanding of how the amino acids with conjugated π -rings interact with damaged DNA nucleobases can occur, the preferred structures of the natural DNA/RNA-amino acid complexes must be examined. Indeed, these interactions also play an important role in many biological processes. In fact, a recent study searched 141 DNA-protein and 61 RNA-protein complexes found in the Protein Data Bank (PDB) and revealed that the four amino acids with conjugated π -rings appear in nucleic acid binding sites more frequently than expected.¹⁴¹ Indeed, 532 and 242 π - π nucleobase-amino acid contacts were identified in DNA and RNA containing structures, respectively.¹⁴¹ Since these complexes involve all amino acids with conjugated π -rings, it has been proposed that any side chain involving π -rings may play a role in binding nucleic acid bases.¹⁴¹

Identifying a large number of nucleic acid-protein π - π interactions is indeed the first step for demonstrating the importance of these contacts in biological processes. As discussed in Section 1.5, computational modeling of π - π interactions can provide valuable insights into the structures and magnitudes of these interactions to further expand the understanding of these complexes. Unfortunately, few accurate *ab initio* calculations have been conducted on stacked or T-shaped orientations between nucleobases and amino acids with conjugated π -rings.¹³⁵⁻¹³⁸ Indeed, to the best of my knowledge, a full study of the

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^b Reprinted with permission from Rutledge, L. R.; Durst, H. F.; Wetmore, S. D. *J. Chem. Theory Comput.* **2009**, 5, 1400–1410. Copyright 2009 American Chemical Society.

heterodimers of the amino acids with conjugated π -rings and nucleobases in both stacked and T-shaped geometries has not yet been performed.

This work presents the first systematic investigation of both stacked and T-shaped interactions between all amino acids with conjugated π -rings (histidine (His), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp)) and natural nucleobases (adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U)) at the highest levels of accuracy possible for these systems. Specifically, MP2/6-31G*(0.25) is used to scan the potential energy surface (PES) of the nucleobase–amino acid dimers. Subsequently, the dimer orientations that yield the strongest interactions were further examined at the CCSD(T)/CBS level. The unique methodology developed in this chapter for scanning the PES reveals more information than simply identifying the important minima on these dimer surfaces. For example, this study uncovers how geometrical changes in the relative orientations of stacked and T-shaped dimers dictate the strength of π – π contacts in a variety of orientations. These calculations also characterize the interactions that may not correspond to the global minimum, but may be important in biological systems due to natural dynamics or structural constraints of proteins or DNA. This methodology also reveals significant information about the magnitude of these biologically-relevant contacts by providing the most accurate comparison in the literature to date of the stacking and T-shaped interactions between all amino acids with conjugated π -rings and DNA and RNA nucleobases.

2.2. Computational Details

As discussed in Section 1.5, the literature has indicated that π – π stacking and T-shaped interactions are sensitive to the level of theory and basis set implemented, where appropriate levels of theory for studying these interactions in biological systems have been identified.^{85,109} This thesis uses an approach similar to that of Hobza and Šponer to study the stacking interactions between DNA nucleobases.^{109,111,113,142} Specifically, monomers were

optimized in fixed planar (C_s) symmetry using MP2/6-31G(d). The nucleobase monomers were modeled by replacing the sugar-phosphate backbone with a hydrogen atom, while the protein backbone and β -carbon of the amino acids was replaced by a hydrogen atom (Figure 2.1). Therefore, His was modeled as imidazole, Phe as benzene, Tyr as indole and Tyr as phenol.

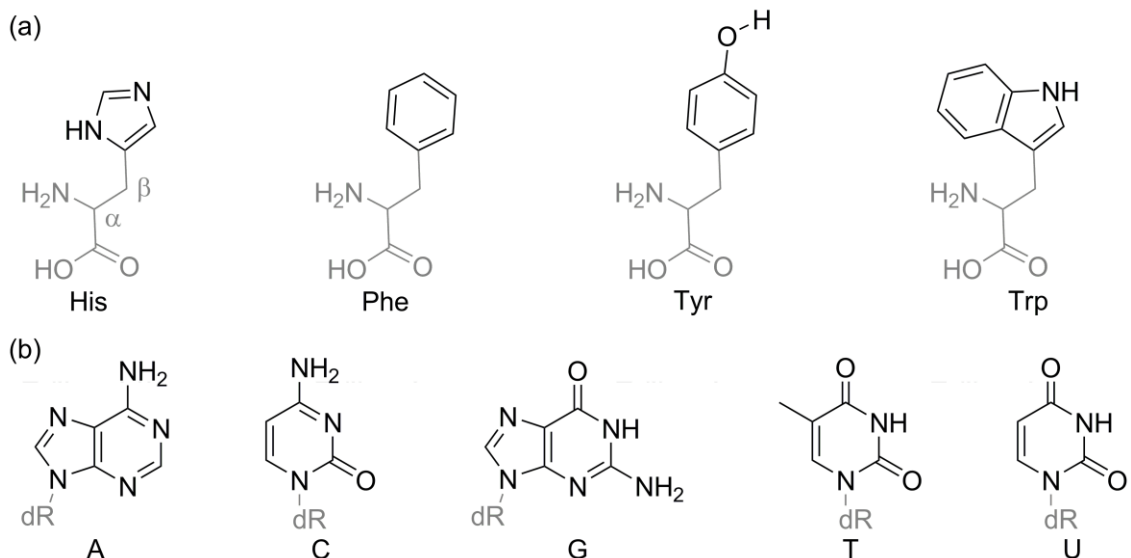


Figure 2.1. Structures of (a) the amino acids with conjugated π -rings (histidine (His), phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp)) and (b) the natural DNA and RNA nucleobases (adenine (A), cytosine (C), guanine (G), thymine (T) and uracil (U)) considered, where fragments highlighted in lighter text were replaced by a hydrogen atom in the present work.

Since the potential energy surfaces of these heterodimers are very flat, gas-phase PES scans between monomers were performed using basis set superposition error (BSSE)-corrected¹⁴³ MP2 single-point calculations with the 6-31G*(0.25) basis set, which replaces the standard d-exponent for second-row atoms (0.8) with 0.25.^{108,110,112,135} Previous studies on aromatic stacked systems have concluded that MP2 calculations with significantly larger basis sets are not recommended due to an overestimation of the correlation energy.¹⁰⁹ MP2/6-31G*(0.25) has been previously justified for use in studying stacking interactions, and has been shown to produce the same trends as, and recover approximately 80% of, the CCSD(T) stacking energies for natural nucleobase dimers calculated at the complete basis

set (CBS) limit.^{105,107,114,116,144-145} This chapter will show an even better agreement between MP2 and CCSD(T) for nucleobase–amino acid stacking and T-shaped binding energies. During the potential energy surface scans, the relative orientations of the monomers were varied as a function of different variables as outlined in the following sections.

2.2.1. Stacking Interactions

Nucleobase–amino acid dimers were initially stacked (face-to-face) with respect to their centers of mass. Initial relative orientations of the monomers were chosen such that the model glycosidic bond (N1–H for the pyrimidines and N9–H for the purines) and the model amino acid backbone (see Figure 2.1 for the location of the corresponding C–H bond) are parallel. Two relative orientations of the monomer molecular planes were considered. The first is obtained by stacking the amino acid and nucleobase in the orientation shown in Figure 2.1. The second orientation, which is denoted with a prime (') throughout this thesis, is obtained by flipping the molecular plane of the amino acid in Figure 2.1 prior to stacking with the nucleobase. From these initial structures, three geometric variables were altered (Figure 2.2a). First, the preferred vertical separation (R_1) was determined by scanning between 3.0 and 3.8 Å by 0.1 Å increments. The preferred R_1 was held fixed for the remaining calculations. The angle of rotation (α) was then altered by rotating the amino acid every 30° in the right-hand sense about the axis that passes through the centers of mass and is perpendicular to the two molecular planes. Using the optimal R_1 and α values, the horizontal displacement (R_2) was considered. The amino acid was shifted in its molecular plane (relative to the nucleobase) across a grid. Specifically, the center of mass of the amino acid was shifted from the grid origin (0,0) (the nucleobase center of mass) by three displacement distances (0.5, 1.0 and 1.5 Å) along the X-axis (perpendicular to the glycosidic bond) and the Y-axis (parallel to the glycosidic bond), where a positive shift along the X axis corresponds to a shift towards the Watson–Crick bonding face, and a negative

shift along the Y axis corresponds to a shift towards the glycosidic bond. Initial calculations determined that tilting the amino acid generally weakens the interaction energy, and therefore this variable was not further examined. The structures which correspond to the strongest (most negative) MP2/6-31G*(0.25) stacking energies were used for higher-level calculations (discussed below in Section 2.2.3).

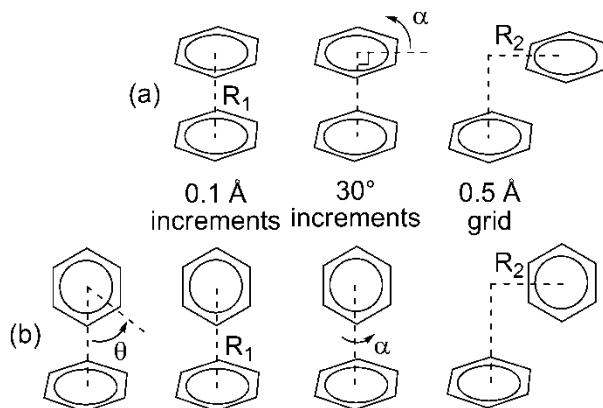


Figure 2.2. The definition of the geometric variables considered and increments used in potential energy surface scans of (a) stacked and (b) T-shaped dimers (angle of 'edge' rotation (θ), vertical separation (R_1), angle of rotation (α), and horizontal displacement (R_2)).

2.2.2. T-shaped Interactions

To characterize a different part of the same potential energy surface examined in the nucleobase–amino acid stacking interactions, four geometric variables were considered in MP2/6-31G*(0.25) PES scans of T-shaped dimers (Figure 2.2b). First, the angles of 'edge' rotation (θ) were chosen, which define the ring edge (monomer edge) directed towards the center of mass of the π -system (monomer face). Figure 2.3 shows the amino acid and nucleobase edges considered. This nomenclature uses numbers to indicate the atom directed towards the center of mass of the π -system and letters to indicate a bridged structure involving more than one atom directed towards the π -system. For example, in dimers involving a PHE edge, $\theta=1$ indicates a hydrogen from the PHE ring is directed at the center of mass of the nucleobase, while $\theta=A$ indicates a C–C bond of the benzene ring is

parallel to the nucleobase molecular plane.^c In total, two different edges were considered for PHE,^c 10 for HIS and TRP, 12 for TYR, 16 for A and G, 14 for C, and 12 for T and U. Therefore, 450 different monomer orientations were considered (i.e., 170 amino acid edge and 280 nucleobase edge interactions). It should be emphasized that in addition to identifying the strongest T-shaped interactions between each amino acid and natural nucleobase, this methodology also characterizes interactions that may not correspond to the global minimum, but may be important in biological systems due to natural dynamics or structural constraints of proteins or DNA.

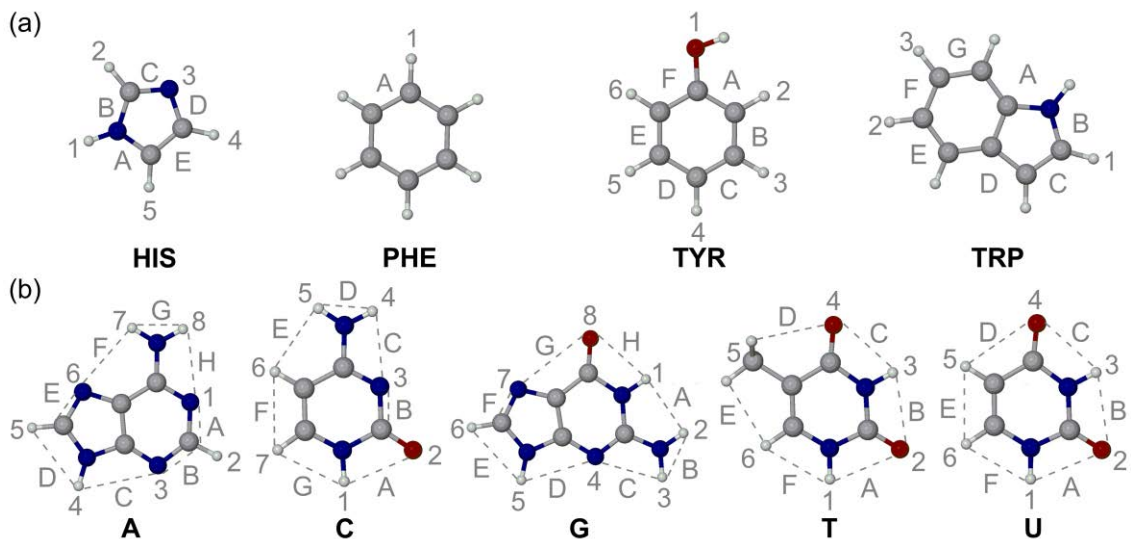


Figure 2.3. The definition of θ for (a) amino acid edges and (b) nucleobase edges considered in potential energy surface scans of T-shaped nucleobase–amino acid dimers.

The initial structures for dimers involving an amino acid edge were obtained by aligning the centers of mass of the amino acid and nucleobase and setting the molecular planes perpendicular. For dimers involving a nucleobase edge, when initial structures with aligned centers of mass are considered, the edge of interest is sometimes located off the amino acid π -system due to the smaller size of the amino acids. Therefore, when a

^c Initial calculations were completed where the PHE edge was rotated about its center of mass every 5° to give five dimers between $\theta=1$ and $\theta=A$. Since maximum and minimum structures were found at $\theta=1$ and $\theta=A$, respectively, only these two extremes were modeled for the remaining dimers.

nucleobase atom edge was directed towards the amino acid face (θ = number, Figure 2.3b), the atom was placed directly on top of the center of mass of the amino acid in the initial structure. Alternatively, when a nucleobase bond was set parallel to the amino acid face (θ = letter, Figure 2.3b), a dummy atom was placed at the midpoint between the atoms linked by the dotted lines in Figure 2.3b, and the dummy atom was aligned with the amino acid center of mass. In all T-shaped calculations, $\alpha=0^\circ$ was defined as the structure with the monomer face in the XY plane, where the model glycosidic (nucleobase face) or peptide backbone (amino acid face) bond is parallel to the Y-axis, and the monomer edge in the YZ plane, where the molecular plane is parallel to the glycosidic (nucleobase face) or peptide backbone (amino acid face) bond.

Once the edges (θ) were chosen and $\alpha=0^\circ$ was defined, the vertical separation distance (R_1) was altered by 0.1 Å increments along the Z-axis. For dimers involving the amino acid edge, R_1 is the distance between the center of mass of the two monomers. For the nucleobase edge dimers, R_1 is the distance between the amino acid center of mass and the nucleobase atom (θ = number) or the dummy atom at the midpoint of the line connecting the two atoms that define the monomer edge (θ = letter). Once the preferred vertical separation was determined, R_1 was held fixed in the remaining calculations.

Next, the angle of rotation (α) was altered by rotating the monomer edge in 30° increments in the right-hand sense. For dimers involving the amino acid edge, the rotation axis passes through the centers of mass of both monomers. For the nucleobase edge dimers, the rotational axis passes through the center of mass of the amino acid and the nucleobase atom (θ = number) or the dummy atom defining the midpoint of the line connecting the two relevant base atoms (θ = letter).

Finally, the horizontal 'edge' displacement (R_2) was considered. Due to the large number of calculations required to completely scan the monomer faces (81 calculations for

HIS face and up to 187 calculations for G face), only the strongest 124 edges (out of 450) that lead to the strongest interactions (most negative) after varying R_1 and α for each monomer pair were considered in R_2 scans. To perform the R_2 shift, the center of mass of the monomer face (in the XY plane) was defined as the origin (0,0). For all dimers, the Y-axis was defined to be parallel to the glycosidic (nucleobase face) or peptide backbone (amino acid face) bond, where a positive shift along the X axis corresponds to a shift towards the Watson–Crick bonding face, and a negative shift along the Y axis corresponds to a shift towards the glycosidic bond. The monomer edge was shifted by 0.5 Å along the X and Y axis, where single-point calculations were completed at each increment over the entire monomer face. Thus, despite the reduction in the number of edges considered for R_2 scans, dimers involving an amino acid edge still required approximately 225 (PHE edge) to 900 (TRP edge) calculations per nucleobase–amino acid pair, while dimers involving a nucleobase edge required approximately 425 (PHE face) to 700 (TRP face) calculations per pair.

2.2.3. Higher-level *ab initio* Methods and Extrapolation Techniques

To verify this computational approach, higher-level calculations were performed on all dimers yielding the strongest (most negative) interaction energies as identified from the MP2/6-31G*(0.25) potential energy surface scans. Specifically, all 35 stacked dimers, the 20 strongest amino acid edge dimers, the 20 strongest nucleobase edge dimers that involved the model N–H glycosidic bond (relevant for nucleobases), and the 20 strongest nucleobase edge dimers that do not involve the model glycosidic bond (relevant for nucleotides and nucleosides) were considered. Since extrapolation techniques have been shown to accurately estimate the stacking interactions between the natural DNA nucleobases at the limit of large basis sets and high levels of correlation,^{112,115,146} a similar approach was used in the present study to approximate CCSD(T)/CBS results. Specifically, the Helgaker basis set extrapolation technique was used,¹⁴⁷⁻¹⁴⁸ which uses MP2/aug-cc-pVDZ and

MP2/aug-cc-pVTZ calculations to extrapolate to the MP2/CBS level (see Appendix A for further details). This extrapolation technique has been used previously for many different systems and has been specifically shown to work well for T-shaped interactions in general,¹⁴⁹⁻¹⁵² as well as stacking interactions between the DNA nucleobases.^{87,112,114,116,146,153} Previous results for the hydrogen bonded and stacked DNA and RNA nucleobases showed that this extrapolation scheme was only improved by 2 kJ mol⁻¹ when increased to the aug-cc-pVTZ and aug-cc-pVQZ extrapolation,⁸⁷ and MP2/aug-cc-pVQZ calculations were not feasible for the size and number of complexes examined in the present study. In addition, a $\Delta(\text{CCSD(T)}-\text{MP2})$ correlation correction factor was evaluated using the 6-31G*(0.25) basis set, which was subsequently added to the MP2/CBS binding strengths to yield estimated CCSD(T)/CBS results. Previous work supports this extrapolation approach for the correlation effects, where the 6-31G*(0.25) basis set was determined to yield a satisfactory $\Delta(\text{CCSD(T)}-\text{MP2})$ correction for the natural DNA nucleobases due to the basis set insensitivity of this correction.^{86,111,113,115,139,146}

All reported interaction energies include basis set superposition error (BSSE) corrections,¹⁴³ and is evaluated as the difference between the (BSSE-corrected) energy of the complex and the sum of the monomer energies (supramolecular approach). All MP2 calculations were performed using Gaussian 03,¹⁵⁴ while CCSD(T) calculations were completed using MOLPRO.¹⁵⁵

2.3. Results and Discussion

2.3.1. Dependence of π - π Interactions on Structural Characteristics

In contrast to optimization calculations, scanning the MP2/6-31G*(0.25) potential energy surface provides more information than simply the optimal stacked and T-shaped orientations. Specifically, these calculations also provide information on how adjusting the relative orientation of monomers in different ways affects the strength of each interaction.

Along with the minimum energy structures, this knowledge can be used to understand the relative strength of interactions between nucleobases and amino acid side chains in a variety of orientations. For example, the data from these calculations can be used to understand contacts observed in nature as demonstrated in Section 2.3.4, using π - π DNA-protein interactions found in the PDB.

As a consequence of the large number of data points and dimers considered in this study, select examples will be discussed in this section to illustrate the major findings of the dependence of π - π interactions on structural characteristics. However, all MP2/6-31G*(0.25) binding strengths for all dimers considered are provided in Appendix B, which allows the reader to gain a more complete understanding of any given dimer. Additionally, the overall strongest MP2/6-31G*(0.25) interaction energies after considering all variables are presented in Appendix C.

A direct comparison of the R_1 distances for all dimers is not meaningful since the definition of R_1 changes depending on the type of dimer examined. Instead, the most important conclusion for R_1 in both stacked and T-shaped geometries is that the interaction energies are not highly dependent upon changes in the vertical separation between the monomers (R_1). Specifically, for all dimers examined in this study, the interaction energy changes by less than 1.3 kJ mol⁻¹ when R_1 deviates from the optimal vertical separation distance by 0.1 Å. Stacked dimers typically have a larger dependence on the vertical separation between monomers than T-shaped dimers, where this trend is generally independent of the monomers involved.

The interaction energy generally has a much larger dependence on the relative angle of rotation (α) than on the vertical separation (R_1). Furthermore, the magnitude of this dependence is related to the type of interaction, as well as the monomers involved. In stacked dimers, α rotations affect the dipole-dipole interactions between monomers, where

the dipole moment vectors of the nucleobase and amino acid are aligned in opposing directions in preferred structures. This conclusion is illustrated in Figure 2.4, where the structures of the HIS stacked dimers are illustrated. In particular, there is a strong correlation between the relative orientation of monomers in dimers with the preferred angle of rotation as identified from the PES scans (Figure 2.4b) and the dimers built by aligning the dipole moment vectors in opposite directions (Figure 2.4a). The slight variations in the structures shown in Figure 2.4 may arise due to unfavourable steric interactions when the dipole moments are aligned in opposite directions. However, it is likely that the differences in the structures could arise due to the limitations in the scanning procedure, where smaller than 30° increments would yield even better agreement.

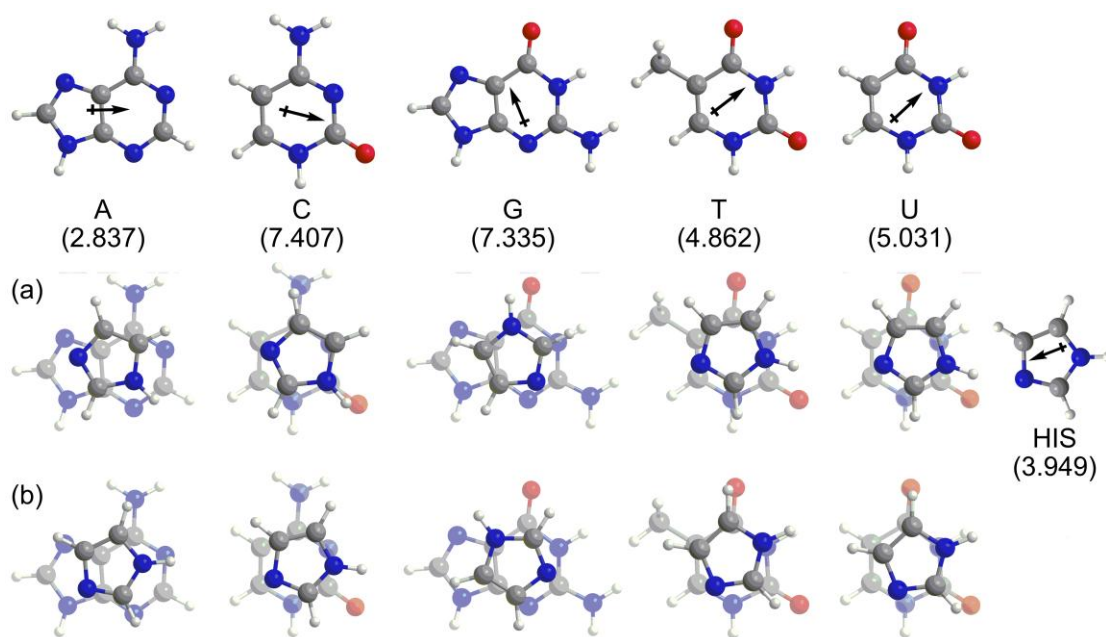


Figure 2.4. MP2/6-31G(d) dipole moment vectors (magnitude (Debyes) included in parentheses) for HIS and the nucleobase monomers. Dimer structures were obtained from (a) aligning the dipole moment vectors of the monomers in opposing directions, and (b) potential energy surfaces scan calculations which determined the optimal angle of rotation (α).

In addition, the magnitude of the dipole moments of the monomers largely governs the degree that the stacking interaction energy is dependent on α . For instance, since PHE (modeled as benzene) has no dipole moment, the stacking interaction energy has little to no

dependence on α . However, HIS has the largest dependence on the dipole–dipole alignment since it is the amino acid with the largest dipole moment (HIS (3.949 D) > TRP (1.926 D) > TYR (1.480 D)). Indeed, as shown in Figure 2.5a, the α dependency of HIS dimers ranges from 10.3 kJ mol⁻¹ for A (which has the smallest nucleobase dipole moment) to 21.8 kJ mol⁻¹ for C (which has the largest nucleobase dipole moment).

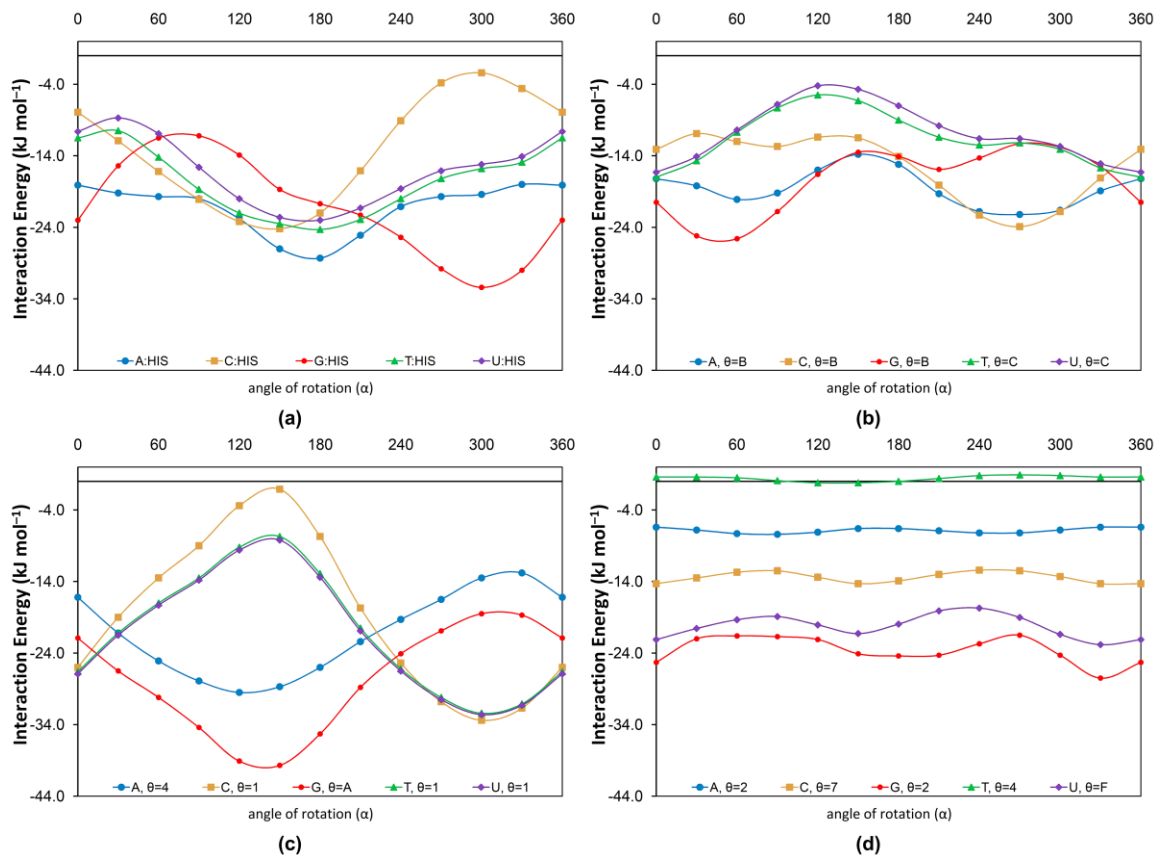


Figure 2.5. Interaction energy as a function of α rotation for (a) HIS stacked dimers, (b) HIS edge T-shaped dimers with the optimal θ , (c) HIS face T-shaped dimers with optimal θ , and (d) HIS face T-shaped dimers for θ with the weakest α dependence. In all graphs, dimers with adenine are large blue circles, cytosine are orange squares, guanine are small red circles, thymine are green triangles, and uracil are purple diamonds.

In T-shaped dimers, the geometric variable α affects how the monomer edge aligns with the monomer face, where the preferred orientation arises when acid–base interactions or secondary intermolecular contacts are maximized. For example, in HIS edge interactions, acidic HIS protons align with basic nucleobase sites (see Figure 2.6a, where the preferred

alignment of secondary intermolecular contacts are indicated with dotted lines). Therefore, the relative strengths of the intermolecular contacts govern the α dependence. Furthermore, since these secondary intermolecular interactions in amino acid edge dimers are weaker than the dipole–dipole interactions in stacking interactions, the α dependency is smaller in amino acid edge dimers. For example, the α dependence for optimal HIS edge dimers (Figure 2.5b) ranges from 5.1 (G) to 13.0 (C) kJ mol⁻¹.

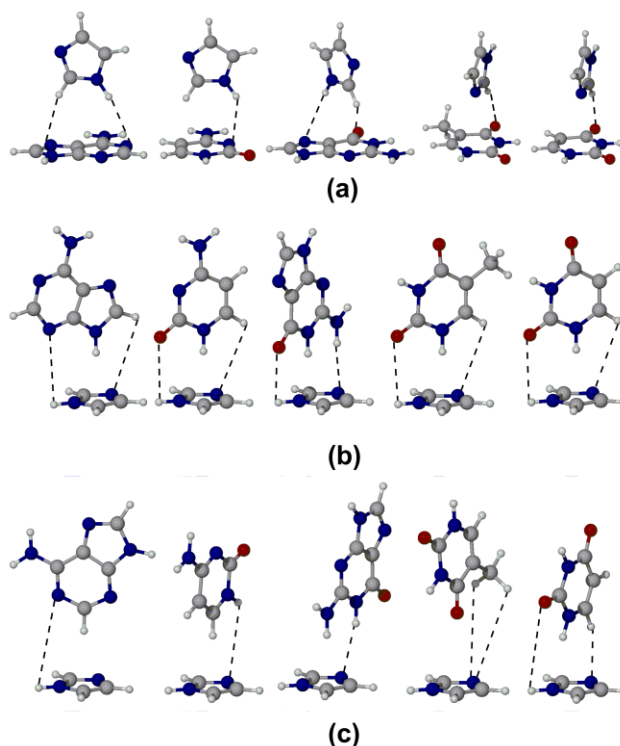


Figure 2.6. T-shaped ($R_2=(0 \text{ \AA}, 0 \text{ \AA})$) dimers for (left to right) adenine, cytosine, guanine, thymine, and uracil with (a) HIS edge with optimal θ , (b) HIS face with optimal θ , and (c) HIS face for θ with the weakest α dependence.

Similar to amino acid edge dimers, α rotations in nucleobase edge dimers are affected by the strength of secondary intermolecular hydrogen bonds. For example, Figures 2.6b and c illustrate how nucleobase edges prefer to align basic or acidic edge atoms with the acidic N–H or basic N atom of the HIS face, respectively. When the intermolecular bonds are strong, as found for nucleobase edges with the strongest interactions (see, for example, HIS face dimers in Figure 2.6b), the α dependence is very large (up to 32.3 kJ mol⁻¹ for HIS

dimers in Figure 2.5c). In fact, the α dependence for these nucleobase edge dimers is greater than that observed for stacked dimers. However, other dimers have much weaker intermolecular hydrogen bonds, and therefore a very small dependence on α . For example, the HIS face dimers in Figure 2.6c lead to a small (1.0 to 6.0 kJ mol⁻¹) dependence on α (Figure 2.5d).

In both stacked and T-shaped dimers, only small changes (less than 2.0 kJ mol⁻¹ for 98 of the 159 dimers considered) in the interaction energies are observed when one monomer is shifted in the molecular plane relative to the other (R_2 scans) from (0 Å, 0 Å) to the preferred R_2 . Additionally, 104 of the 159 R_2 scans reveal that the monomers prefer to be shifted by 1.0 Å or less. These relatively small energetic and geometrical effects indicate that optimal interaction energies are generally observed when the centers of mass of the nucleobase and amino acid are aligned (stacked and amino acid edge interactions) or when the nucleobase edge interacts with the amino acid center of mass. When R_2 shifts strengthen stacked dimers, the preferred shift allows for more π - π overlap and/or decreases repulsion between ring atoms. However, in T-shaped dimers, the preferred R_2 moves the acidic and/or basic regions in the monomer edge closer to the corresponding basic and/or acidic sites in the monomer face to maximize electrostatic interactions. However, performing R_2 scans does not change the preferred θ edge for any T-shaped dimer, justifying the decision to only consider R_2 effects for select θ for each complex.

As previously mentioned, a large number of both amino acid and nucleobase edges (θ) were considered for T-shaped dimers. All T-shaped interactions examined in this study have a very large dependence on the nature of the monomer edge (θ) interacting with the π -system. This can be seen in Figure 2.7 for the adenine and histidine T-shaped dimers since the separation between lines (dependence on θ) is larger than variations within a line (dependence on α). This large dependence is due to variations in the acidic and basic

properties of different monomer edges, where monomers with large dipole moments (and therefore a large variance in the acidic and basic properties of its edges) led to a larger dependence on θ . The strongest interactions occur when the monomer edges with the largest (Lewis) acidity are directed towards the π -system. For example, in nucleobase edge dimers, the strongest interactions generally involve the most acidic model (N-H) glycosidic bond of the nucleobases (Figure 2.6b). However, in the case of guanine, the strongest interaction occurs when two strongly acidic N1-H and N2-H bonds¹⁵⁶ interact with the amino acid face ($\theta=A$, Figure 2.3) rather than one strongly acidic bond¹⁵⁶ ($\theta=5$, Figure 2.3) or one strongly and one weakly acidic bond¹⁵⁶ ($\theta=E$, Figure 2.3). Similarly, in amino acid edge dimers, the acidic N-H bond of TRP is included in the preferred edge ($\theta=A$), while in HIS edge dimers with A, G or C (Figure 4b), the optimal T-shaped interaction involves the acidic N-H bond ($\theta=B$, Figure 4b). The only exception is the HIS edge dimer with T or U, where the basic N atom of HIS ($\theta=C$) interacts with the nucleobase π -system in the optimal T-shaped dimer (Figure 2.6a). This exception occurs since T and U have more positive π -systems, and therefore have a greater (Lewis) acidity, due to the two electron-withdrawing carbonyl groups. Recent electron affinity data supports this statement since T and U have the largest electron affinities among all DNA and RNA nucleobases.¹⁵⁷ However, it should also be mentioned that the acidic HIS edge preferred by A, C and G ($\theta=B$) binds by only 0.4 and 1.1 kJ mol⁻¹ weaker to T and U, respectively, than the basic ($\theta=C$) edge.

Another important conclusion about the geometries of T-shaped complexes is that, regardless of the nucleobase, a stronger interaction is generally observed for dimers with the monomer edge bridging the π -system (θ = letter) compared to edges involving a single atom (θ = number) due to greater overlap. Although early studies on the benzene dimer have also identified bridged structures to be the most stable T-shaped orientations,⁹¹ the

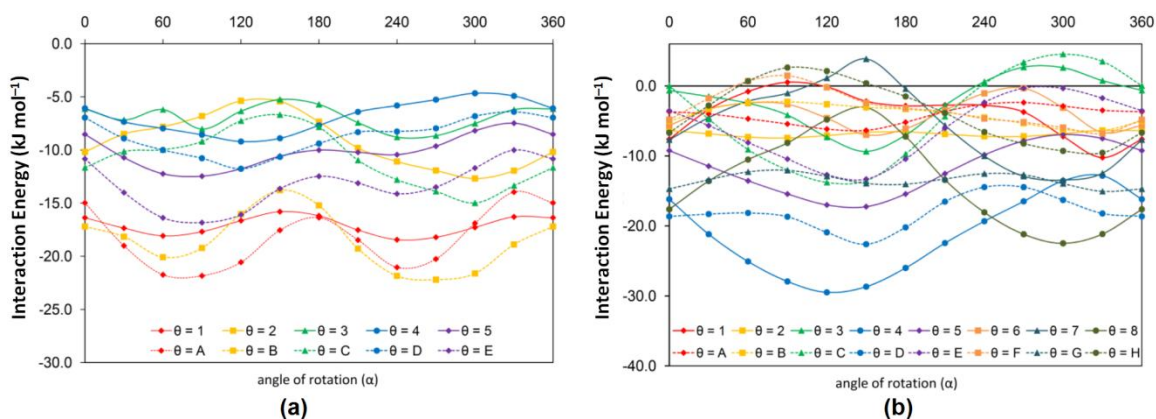


Figure 2.7. Interaction energy as a function of α for dimers between adenine and (a) HIS edge, and (b) HIS face for all edges (θ) considered in this study.

majority of recent studies on T-shaped complexes have only considered interactions that involve a particular atom directed at the π -system.^{136,150,158} In cases where bridged structures involving small molecules directed towards a π -ring are considered,¹⁵⁹ only select combinations of molecules are examined and no systematic investigation has been done. Furthermore, studies of T-shaped interactions involving amino acids have not considered bridged structures.¹³⁶ The results presented in this chapter clearly indicate that to identify global minima, and fully understand these interactions, the bridged structures must be examined.

Since PES scans reveal how nucleobase–amino acid π – π contacts depend on several geometric variables, some general conclusions can be drawn about the nature of these attractive interactions. First, although stacking interactions are known to be highly dependent on dispersion,^{97,101} the stacking interactions examined in this study are also highly dependent on the electrostatic contribution. Specifically, results indicate that the strongest interactions occur when the nucleobase and amino acid dipole moment vectors are aligned in opposing directions, and the interaction energies vary by up to 24 kJ mol⁻¹ when one monomer is rotated (by α , Figure 2.5a) relative to the other. Additionally, this work finds that electrostatics play an even bigger role in T-shaped interactions compared

with stacking. For example, the binding strengths of T-shaped dimers vary by up to 56 kJ mol⁻¹ by changing the edge (θ , Figure 2.2) interacting with the π -system. Thus, these potential energy surface scans show that, although dispersion interactions are very important for the attractive nature of these interactions, electrostatics also play an essential role in determining the relative orientations of monomers.

2.3.2. Magnitude of the Strongest Interactions

As previously mentioned, monomer orientations with the strongest interactions were further examined by extrapolating the corresponding interaction energies to the CCSD(T) level at the complete basis set (CBS) limit. All stacked dimers, the strongest amino acid edge dimers, the strongest nucleobase edge dimers that involve the model N–H glycosidic bond (relevant for nucleobases) and the strongest nucleobase edge dimers that do not involve the model glycosidic bond (relevant for nucleotides and nucleosides) were examined, where the MP2/6-31G*(0.25) and CCSD(T)/CBS interaction energies are reported in Table 2.1 and Table 2.2, and all of the interaction energies required to estimate the CCSD(T)/CBS binding strengths are included in Appendix D.

Examination of Tables 2.1 and 2.2 reveals that MP2/6-31G*(0.25) interaction energies account for 80–110% of the CCSD(T)/CBS binding strengths in all nucleobase–amino acid dimers. Interestingly, the $\Delta(\text{CCSD(T)}-\text{MP2})$ correction is repulsive for all interaction energies examined, while the $\Delta(\text{MP2/CBS}-\text{MP2/6-31G}^*(0.25))$ correction is attractive (Appendix D). Therefore, the present MP2/6-31G*(0.25) interaction energies are very close to the CCSD(T)/CBS results due to the cancelation of errors between basis set incompleteness and the missing electron correlation effects. Nevertheless, the remarkable agreement between these methods verifies that MP2/6-31G*(0.25) very accurately describes the potential energy surfaces of nucleobase–amino acid dimers in both stacked

Table 2.1. MP2/6-31G*(0.25) and CCSD(T)/CBS stacked and T-shaped interaction energies (kJ mol⁻¹) between the amino acids with conjugated π -rings and the natural purine nucleobases (adenine and guanine).^[a]

	θ	Adenine		θ	Guanine	
		MP2 ^[b]	CCSD(T) ^[c]		MP2 ^[b]	CCSD(T) ^[c]
HIS stacked		-29.7	-29.8		-35.3	-37.8
HIS' stacked		-27.2	-27.8		-31.4	-32.7
PHE stacked		-24.3	-23.3		-25.3	-25.3
TYR stacked		-28.9	-28.4		-32.8	-35.2
TYR' stacked		-30.7	-30.0		-33.4	-34.1
TRP stacked		-32.0	-30.6		-42.4	-42.1
TRP' stacked		-35.0	-33.5		-42.5	-43.1
HIS edge	B	-22.5	-22.4	B	-27.7	-27.2
PHE edge	A	-14.1	-15.2	A	-14.5	-16.0
TYR edge	A	-21.9	-22.4	A	-21.8	-21.8
TRP edge	A	-23.2	-22.9	A	-28.7	-28.9
HIS face ^[d]	4	-33.6	-33.3	5	-26.7	-26.7
	(8)	(-22.6)	(-23.6)	(A)	(-46.4)	(-48.4)
PHE face ^[d]	4	-25.6	-26.4	5	-23.7	-24.3
	(8)	(-16.0)	(-17.4)	(A)	(-31.6)	(-33.2)
TYR face ^[d]	4	-27.8	-28.3	E	-24.6	-24.9
	(8)	(-18.4)	(-20.0)	(A)	(-36.2)	(-37.8)
TRP face ^[d]	4	-34.8	-34.8	E	-32.5	-32.4
	(8)	(-23.1)	(-24.0)	(A)	(-47.3)	(-49.5)

^[a] See Figures 2.2 and 2.3 for definitions of θ and the edges considered in this study. ^[b] MP2/6-31G*(0.25) interaction energies. ^[c] CCSD(T)/CBS interaction energies. ^[d] Nucleobase edge interactions involving the model glycosidic bond and not involving the glycosidic bond (in parentheses).

and T-shaped orientations, and suggests that this method is correctly identifying the preferred orientations for these π - π contacts. This also suggests that the MP2/6-31G*(0.25) interaction energies reported in this work for all relative monomer orientations are reliable and can be used to characterize interactions observed in nature (to be discussed in a subsequent section).

One of the most important findings in this study is the magnitude of these π - π interactions. At the most accurate level of theory used to date for nucleobase-amino acid with conjugated π -ring stacked and T-shaped dimers (CCSD(T)/CBS), stacking interaction energies range between -20 and -43 kJ mol⁻¹, while the corresponding T-shaped interactions range between -12 and -50 kJ mol⁻¹ at optimal monomer orientations. Thus,

Table 2.2. MP2/6-31G*(0.25) and CCSD(T)/CBS stacked and T-shaped interaction energies (kJ mol⁻¹) between the amino acids with conjugated π -rings and the natural pyrimidine nucleobases (cytosine, thymine, and uracil).^[a]

	θ	Cytosine		θ	Thymine		θ	Uracil	
		MP2 ^[b]	CCSD(T) ^[c]		MP2 ^[b]	CCSD(T) ^[c]		MP2 ^[b]	CCSD(T) ^[c]
HIS stacked		-26.9	-29.5		-25.0	-27.1		-23.6	-26.0
HIS' stacked		-26.0	-29.1		-26.8	-29.3		-26.4	-29.1
PHE stacked		-18.4	-20.6		-22.4	-24.5		-20.1	-21.7
TYR stacked		-24.2	-27.1		-26.1	-28.3		-25.2	-27.6
TYR' stacked		-22.7	-25.0		-25.5	-27.5		-25.7	-27.7
TRP stacked		-33.4	-35.4		-36.0	-37.8		-34.5	-36.8
TRP' stacked		-32.9	-35.4		-36.4	-38.5		-34.0	-36.1
HIS edge	B	-26.4	-27.5	C	-19.1	-23.3	C	-18.4	-22.8
PHE edge	A	-12.1	-14.0	A	-10.8	-12.3	A	-9.7	-11.7
TYR edge	A	-22.5	-23.7	A	-15.7	-16.6	1	-14.9	-18.0
TRP edge	A	-27.4	-28.8	A	-20.9	-22.1	A	-18.3	-19.2
HIS face ^[d]	1	-33.6	-36.1	1	-34.2	-34.2	1	-34.7	-36.9
	(4)	(-31.2)	(-33.7)	(3)	(-22.5)	(-24.4)	(3)	(-23.0)	(-24.9)
PHE face ^[d]	1	-22.5	-25.4	1	-24.7	-22.2	1	-25.3	-27.6
	(5)	(-19.5)	(-21.8)	(3)	(-18.9)	(-21.6)	(3)	(-19.1)	(-21.7)
TYR face ^[d]	1	-26.7	-29.1	1	-27.6	-29.4	1	-27.8	-29.7
	(4)	(-25.3)	(-28.2)	(3)	(-20.6)	(-22.9)	(3)	(-20.8)	(-23.1)
TRP face ^[d]	1	-34.5	-36.6	F	-37.0	-37.9	F	-36.7	-37.7
	(4)	(-32.2)	(-33.9)	(3)	(-25.4)	(-27.2)	(3)	(-25.7)	(-27.4)

^[a] See Figures 2.2 and 2.3 for definitions of θ and the edges considered in this study. ^[b] MP2/6-31G*(0.25) interaction energies. ^[c] CCSD(T)/CBS interaction energies. ^[d] Nucleobase edge interactions involving the model glycosidic bond and not involving the glycosidic bond (in parentheses).

both the stacking and T-shaped interactions approach the adenine–thymine Watson-Crick hydrogen-bond strength (–70 kJ mol⁻¹) calculated at the same level of theory,⁸⁷ which involves at least two strong hydrogen bonds. Additionally, the binding strengths for stacking and T-shaped interactions are very similar in magnitude for all nucleobases, where the amino acid edge interactions are slightly weaker than the nucleobase edge interactions. Indeed, the most favourable nucleobase edge interactions are as strong, if not stronger, than the corresponding stacking interactions in the same dimer. Therefore, stacking arrangements are not the only orientations that are significantly attractive, but rather T-shaped interactions can also play stabilizing roles in nucleobase–amino acid complexes found in nature.

Comparison of the largest interaction energy for each dimer reveals interesting

information about the trends in the binding energy with respect to the amino acid or nucleobase. Specifically, the strongest stacking interactions are found to increase as PHE << TYR $\approx$ HIS < TRP, where similar stabilization energies are observed for HIS, TYR, and TRP. This trend is dictated by the relative dipole moments and sizes of the π -systems of the amino acids. The same trend is also found for amino acid edge and nucleobase edge T-shaped interactions, which depend on the strength of secondary intermolecular contacts between the acidic and basic sites in the amino acid and the nucleobase. However, when the trend with respect to the nucleobase is considered, no clear affinity is observed. Due to the similar interaction strengths, it is difficult to determine if these contacts are selective enough to be used for recognition of specific nucleobases. However, these calculations do suggest that these interactions are most certainly important for providing stability of DNA/RNA-protein complexes.

2.3.3. Additional T-shaped Contacts that May Stabilize DNA/RNA-Protein Complexes

As previously mentioned, the method used in this chapter to examine nucleobase-amino acid T-shaped interactions reveals more information than simply the identity of edges that lead to the strongest interactions. Specifically, this study characterized the potential energy surfaces of all atom-directed and bridge-directed edges for these systems, where full results (Appendix B) show that many monomer edges lead to attractive interactions. For instance, a large number of C-H $\cdots\pi$ interactions have been characterized, which have been extensively studied computationally,^{150,158-163} where the present nucleobase-amino acid interactions are found to be up to -26 kJ mol^{-1} . For example, in TRP edge dimers, the bridged edge involving two C-H $\cdots\pi$ interactions ($\theta=\text{C}$) is only 0.8 (U) to 7.8 (A) kJ mol^{-1} weaker than the strongest interactions observed with a bridged edge involving a N-H and C-H bond ($\theta=\text{A}$). Additionally, in TRP face dimers, interactions involving only one

C-H $\cdots\pi$ contact are up to -18.5 (A, $\theta=5$) or -18.9 (G, $\theta=6$) kJ mol^{-1} .

This work also examined lone pair (lp)- π interactions for a variety of dimers, which have been studied computationally,^{152,161} and recently reviewed by Egli et al.¹⁶⁴ In nucleobase edge dimers, lp- π interactions involving carbonyl oxygens were found to be unstable (i.e., no minimum was identified for U ($\theta=2$ and $\theta=4$) and C ($\theta=2$)) or very weak (i.e., less than -1 kJ mol^{-1} for G ($\theta=8$) and T ($\theta=2$ and $\theta=4$)). However, some nitrogen lp- π interactions are as strong as -23 kJ mol^{-1} . For example, all HIS edge dimers involving the lone pair N ($\theta=3$) were found to be quite stable, where the interaction energies range from -8.2 to -15.2 kJ mol^{-1} . Furthermore, the interactions with N7 of G ($\theta=7$) can be up to -13.8 kJ mol^{-1} , while contacts with N3 of C ($\theta=3$) were found to be up to -23.0 kJ mol^{-1} . Therefore, these calculations suggest that even non-optimal contacts that might arise in nature can help stabilize DNA/RNA-protein complexes.

2.3.4. Quantifying Experimentally Observed Nucleobase-Amino Acid π - π Interactions

It should be noted that the most favourable structures and interaction energies of nucleobase-amino acid dimers identified in the present study may not appear in nature, where additional effects, such as protein folding or other (steric) constraints, come into play. However, by carefully searching the potential energy surface of stacked and T-shaped dimers, these calculations have revealed how the interaction energies in these noncovalent complexes generally depend on different geometric variables. For example, due to the small dependence on the vertical separation between monomers (R_1), deviations from the reported optimal R_1 distances will have a small effect on the interaction energies. Conversely, large deviations from the reported preferred angle of rotation (α) between stacked monomers will have significant effects on the interaction energy between monomers with large dipole moments. Alternatively, deviations from the optimal α for T-

shaped dimers will affect the interaction energy in different ways and therefore the properties of the edge involved must be carefully considered. The present calculations also suggest that changes in the optimal horizontal displacement (R_2) between monomers can weaken the (strongest) reported interaction energies, where the effect is dependent on the monomers involved, as well as the size and direction of the shift.

In addition to the general conclusions mentioned above, the current results from these detailed potential energy surface scans can be used in a quantitative, predictive way. Specifically, in addition to the optimal interaction energies presented in Tables 2.1 and 2.2, the interaction energies calculated for a range of geometric variables are reported in Appendix B for all natural nucleobase–amino acid dimers. These results can be compared to any stacked or T-shaped contact found in nature, not just those corresponding to minima on the calculated surfaces. This complete data set will allow biochemists to accurately determine the relative magnitude of different DNA/RNA–protein contacts.

To illustrate how this data can be used in conjunction with experimental structures to gain a better understanding of DNA–protein interactions that appear in nature, the following subsections will discuss three crystal structures containing representative examples of nucleobase–amino acid stacking (Figure 2.8a), amino acid edge T-shaped (Figure 2.8b), and nucleobase edge T-shaped (Figure 2.8c) interactions. Appendix B will be used to estimate the interaction energy of each dimer, which will be compared to the interaction energy calculated using the exact crystal structure orientation (see Appendix E for details of how the interaction energies were calculated in crystal structure orientations).

2.3.4.1. Stacking Interaction between Guanine and Phenylalanine

The crystal structure of HMG1 domain A bound to a cisplatin-modified DNA duplex

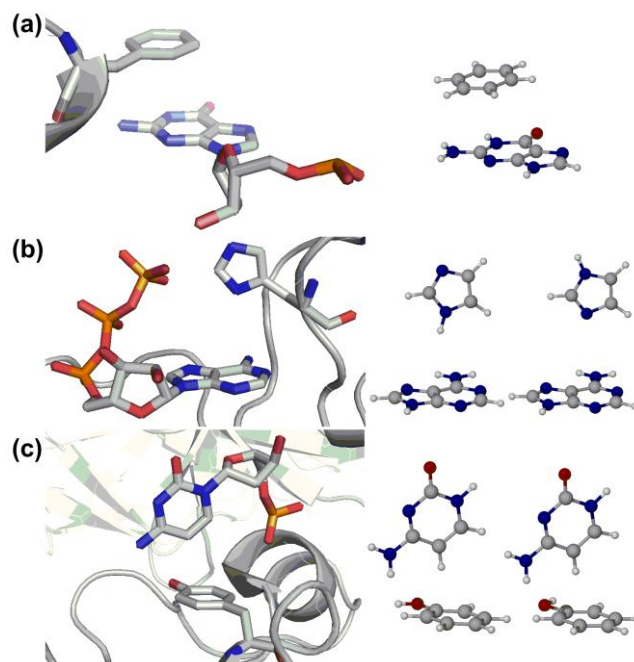


Figure 2.8. Examples of nucleobase–amino acid interactions observed in nature (a) G:PHE stacked (PDB entry: 1CKT with DG109 and F37 highlighted),¹⁶⁵ (b) A:HIS edge T-shaped (PDB entry: 1B8A with ATP1500 and H1223 highlighted),¹⁶⁶ and (c) C:TYR face T-shaped (PDB entry: 1P7H with DC11 (chain B) and Y424 (chain M) highlighted).¹⁶⁷

contains a stacked orientation between guanine (DG109) and phenylalanine (F37).¹⁶⁵ Table 2.3 reports relevant geometric parameters measured from the crystal structure that define this stacking orientation (column "crystal"). These parameters can subsequently be compared to the closest corresponding point on the scanned potential energy surface (column "scan"). For example, in this crystal structure, the orientation between G and PHE is most closely described by the point on the calculated potential energy surface with a vertical separation (R_1) of 3.5 Å, an angle of rotation (α) of 30° and a horizontal displacement (R_2) of (1.5 Å, 1.5 Å). PES calculations (Appendix B) reveal that an R_2 shift of (1.5 Å, 1.5 Å) has a corresponding interaction energy of $-22.9 \text{ kJ mol}^{-1}$. However, this interaction was calculated for a (R_1) vertical separation distance of 3.4 Å and $\alpha=0^\circ$. Nevertheless, corrections based on the PES scans can be added to this interaction energy. Specifically, the R_1 scan for this dimer reveals that increasing the vertical separation from

3.4 to 3.5 Å weakens the interaction energy by 0.6 kJ mol⁻¹. Additionally, an α rotation from 0 to 30° weakens the interaction energy by 0.1 kJ mol⁻¹. Therefore, the interaction between G and PHE in the crystal structure geometry of HMG1 domain A is estimated from the potential energy surface scans to be -22.2 kJ mol⁻¹ (i.e., (-22.9 + 0.6 + 0.1) kJ mol⁻¹). Interestingly, when optimized monomers are overlaid onto this crystal structure, the calculated interaction energy is also found to be -22.2 kJ mol⁻¹. This is in astounding agreement with the estimate from the calculated potential energy surfaces, especially since additivity of the effects of different geometric variables has been assumed in this comparison.

Table 2.3. Structural characteristics measured for three representative nucleobase–amino acid interactions observed in nature (crystal) and the closest corresponding point from potential energy surface scans (scan).

	<u>G:PHE stacked</u> ¹⁶⁵		<u>A:HIS edge</u> ¹⁶⁶		<u>C:TYR face</u> ¹⁶⁷	
	crystal	scan	crystal	scan	crystal	scan
Angle (°)	4.44 ^[a]	0	88.90 ^[a]	90	82.72 ^[a]	90
Vertical separation distance (R ₁ , Å)	3.51 ^[b]	3.5	4.48 ^[b]	4.5	4.02 ^[c]	3.0 ^[d]
Angle of rotation (α , °)	18.8 ^[e]	30	67.8 ^[e]	60 ($\theta=3$), 300 ($\theta=1$)	66.3 ^[e]	60, 300
Horizontal Shift distance (R ₂ , Å and (Å,Å))	~2.2 ^[f]	(1.5, 1.5)	~3.1 ^[f]	(0.5, 2.5)	~2.7 ^[f]	(2.5, 0)

[a] Angle measured between molecular planes formed by ring atoms of nucleobase and amino acid. [b] Vertical separation measured between the molecular planes (stacked orientation), or the center of the ring (monomer edge) and monomer face molecular plane (T-shaped orientations). [c] Vertical separation measured between C5 of C and molecular plane of TYR. [d] The R₁ distance from potential energy surface scans measured between the midpoint of the H4–C5 edge of C ($\theta=E$) and the center of mass of TYR, which has the closest corresponding vertical separation measured between C5 of C and the center of the TYR ring. [e] The dihedral angle measured between the glycosidic bond and the peptide backbone bond of the amino acid (stacked orientation), the glycosidic bond and C1' plane and the molecular plane of the amino acid (amino acid edge), or the peptide backbone bond plane of the amino acid and the molecular plane of the nucleobase (nucleobase edge). [f] The distance estimated between the centers of monomer rings in two dimensions.

2.3.4.2. Amino Acid Edge Interaction between Histidine and Adenine

In the crystal structure of aspartyl-tRNA synthetase, the edge of HIS (H1223) interacts with the face of adenine (ATP1500).¹⁶⁶ Since protein crystal structures do not show the positions of hydrogen atoms, it is not clear whether the histidine N atom or N–H bond is

directed towards A. Therefore, both HIS edge interactions ($\theta=3$ and $\theta=1$, Figure 2) are considered, where Table 2.3 outlines the geometric information obtained from the crystal structure and identifies the closest corresponding point on the potential energy surface scan for each histidine orientation ($R_1=4.5$ Å, $R_2=(0.5$ Å, 2.5 Å), and $\alpha=60^\circ$ ($\theta=3$) or 300° ($\theta=1$), see Appendix B).

When the nitrogen lone pair of HIS is directed towards A ($\theta=3$), the interaction energy is calculated to be -6.2 kJ mol $^{-1}$ for the α value (60°) closest to that in the crystal structure, $R_1=4.4$ Å and $R_2=(0$ Å, 0 Å). To determine the binding in the crystal structure orientation, the potential energy surface scans reveal that the binding strength is weakened by 8.1 kJ mol $^{-1}$ when HIS is shifted across the face of A from $(0$ Å, 0 Å) to $(0.5$ Å, 2.5 Å), and weakened by 0.1 kJ mol $^{-1}$ when the vertical separation is increased to 4.5 Å. These additive effects result in a weakly ($+2$ kJ mol $^{-1}$) repulsive interaction for the $\theta=3$ HIS (edge): A (face) interaction, while crystal structure overlay calculations determine this interaction to be only slightly more favourable (-2.1 kJ mol $^{-1}$).

When the N-H bond of histidine is directed towards A ($\theta=1$, Figure 1), the potential energy surface scan determines the interaction energy to be -17.3 kJ mol $^{-1}$ for the angle of rotation ($\alpha=300^\circ$) and vertical separation distance ($R_1=4.5$ Å) observed in the crystal structure. Although this interaction energy was calculated for $R_2=(0$ Å, 0 Å), accounting for the correct horizontal displacement yields an interaction energy of -9.2 kJ mol $^{-1}$. In comparison, the crystal structure overlay calculations determine this interaction to be -10.0 kJ mol $^{-1}$. This example again provides strong evidence that the calculated potential energy surfaces accurately describe the interaction energies in a range of nucleobase–amino acid dimers.

2.3.4.3. Nucleobase Edge Interaction between Cytosine and Tyrosine

The crystal structure of NFAT1 bound to the HIV-1 LTR kB element reveals the edge of

C (DC11 (chain B)) interacting with the face of TYR (Y424 (chain M)).¹⁶⁷ Due to an uncertainty in the orientation of the hydroxyl hydrogen of TYR, both possible (in-plane) orientations were considered, namely OH directed towards and away from C (Figure 2.8c). The nucleobase edge interaction in the crystal structure with the hydroxyl group directed away from C ($\theta=E$) best corresponds to $\alpha=60^\circ$, which has a calculated interaction energy of $-18.8 \text{ kJ mol}^{-1}$ for $R_1=2.6 \text{ \AA}$ and $R_2=(0 \text{ \AA}, 0 \text{ \AA})$ (Appendix B). When a ($\sim 10 \text{ kJ mol}^{-1}$) correction for the horizontal shift and a (3.2 kJ mol^{-1}) correction for the vertical separation are taken into account, the interaction energy is predicted to be -5.6 kJ mol^{-1} , which is very consistent with the interaction energy calculated from a crystal structure overlay (-4.7 kJ mol^{-1}). Alternatively, when the hydroxyl group of TYR is directed towards C ($\theta=E$, $\alpha=300^\circ$), the interaction energy is estimated to be -3.5 kJ mol^{-1} (i.e., $-16.7 (\alpha=300^\circ, R_1=2.6 \text{ \AA}, R_2=(0 \text{ \AA}, 0 \text{ \AA})) + 3.2 (R_1 \text{ correction}) + 10.0 \text{ kJ mol}^{-1} (R_2 \text{ correction})$), while the overlay calculation determines an interaction energy of -5.5 kJ mol^{-1} . Therefore, predictions using the data set generated from the present potential energy surface scans are very similar to those determined from crystal structure overlay calculations.

In summary, this section illustrates how the data reported in Appendix B can help predict the stabilizing and functional role of nucleobase–amino acid π – π interactions in a variety of biological structures. The results presented in this chapter can therefore be used in the future by biochemists in a similar fashion to accurately estimate the magnitude of these interactions in DNA/RNA–protein active sites identified in experimental structures. Thus, this data complements experimental structural data and helps reveal the potential importance of π – π contacts in a variety of DNA/RNA–protein systems.

2.4. Conclusions

This is the first extensive study of both stacking and T-shaped interactions between all amino acids with conjugated π -rings and natural nucleobases. The present work used a

unique methodology for identifying important contacts on the potential energy surface, which provides an understanding of how a variety of geometric criteria determine the strength of these contacts. The interaction energies were generally found to have a small dependence on the vertical separation between the monomers, while the dependence on the angle of rotation, as well as horizontal displacement, was found to be much greater. Additionally, stacked complexes prefer to have monomer dipole moment vectors aligned in opposing directions, while preferred T-shaped orientations direct the most (Lewis) acidic edge of one monomer towards the π -system of the second monomer.

The present *ab initio* calculations reveal that the strongest possible π - π interaction for each nucleobase–amino acid combination is very large. Indeed, at the highest level of theory possible for these systems, both stacking and T-shaped interactions are found to be very close in magnitude to biologically-relevant hydrogen bonds. Additionally, T-shaped interactions are as strong, if not stronger, than the corresponding stacking interactions. Most importantly, not only has the current work fully characterized structures with the strongest interactions, but a wide variety of other nucleobase–amino acid interactions have been examined, including C–H $\cdots\pi$, N–H $\cdots\pi$, and lp– π interactions, where this work reveals that these contacts are also very favourable.

Based on these calculations, most π - π nucleobase–amino acid interactions are very stabilizing and can play important roles in biological processes and therefore cannot be ignored. However, a large difference between the binding strengths with the natural bases for any given amino acid is not found. Therefore, it is difficult to determine whether these interactions play a role in selective nucleobase recognition. Nevertheless, due to the large magnitude of their π -interactions, the amino acids with conjugated π -rings can take advantage of their π -clouds to add to the stability of DNA/RNA–protein complexes already provided by hydrogen-bonding interactions with these or other protein side chains.

High accuracy results (CCSD(T)/CBS) indicate that the MP2/6-31G*(0.25) binding strengths provided in Appendix B are very accurate for all 485 dimers investigated in this chapter. Therefore, MP2 can provide reliable estimates of the magnitude of interactions present in a variety of experimental DNA/RNA–protein crystal structures of low polarity.⁷⁷ Indeed, this chapter has demonstrated how this additional, detailed data set can be used to estimate dimer interaction energies for contacts found in the PDB, where the estimates shown in Section 2.3.4 are very close to interaction energies calculated using exact crystal structure orientations. Thus, the present work can be used by biochemists to accurately approximate the magnitude and potential importance of π -interactions in DNA/RNA–protein active sites identified in experiments.

Chapter 3. The Effects of Nucleobase Alkylation on DNA-Protein Stacking and T-shaped Interactions^{a,b}

3.1. Introduction

As mentioned in Chapter 1, many questions remain about the roles played by the amino acids with conjugated π -rings in the active site of AAG. Indeed, the π - π interactions between damaged DNA and protein components have not been well characterized in the literature, and the influence of a cationic charge on the structure and magnitude of these interactions is even less understood. Therefore, the present chapter examines the structure and magnitude of the stacking and T-shaped interactions between 1,N⁶-ethenoadenine (ϵ A, Figure 3.1) or 3-methyladenine (3MeA, Figure 3.1) and the amino acids with conjugated π -rings. The neutral and cationic π - π interactions involving ϵ A and 3MeA, respectively, will be determined using the methodology developed and discussed in Chapter 2, which will allow for comparison between these results and those found previously for the (neutral) natural base adenine. Additionally, this chapter expands upon the fundamental knowledge of (neutral and cationic) noncovalent interactions, where most investigations of cationic π -systems have not distinguished these contacts from π - π or cation(metallic)- π contacts,^{136,152} with the exception of one study that classified these systems as a different type of noncovalent interaction altogether.¹⁶⁸ This work will contribute to the understanding of how alkylation damage, as well as charge, alters the preferred structure and stabilization of these π - π complexes. Additionally, the calculations presented in this

^a Reprinted with permission from Rutledge, L. R.; Wetmore, S. D. *J. Chem. Theory Comput.* **2008**, *4*, 1768–1780. Copyright 2008 American Chemical Society.

^b Reprinted with permission from Rutledge, L. R.; Czyżnikowska, Ż.; Wetmore, S. D. *In preparation*.

chapter can be used to provide insights into how these interactions are involved in the recognition and repair mechanisms used by AAG.

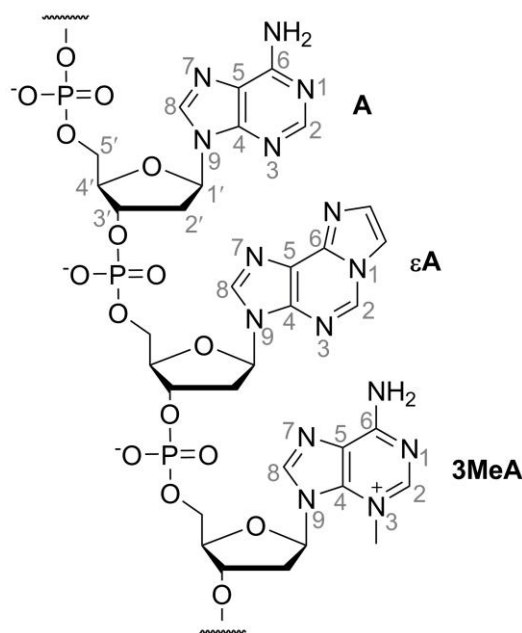


Figure 3.1. Structure of an oligonucleotide containing the natural nucleotide adenine (A) and the corresponding DNA alkylation lesions 1,N⁶-ethenoadenine (εA) and 3-methyladenine (3MeA). Atomic numbering for the nucleobases and the sugar moiety are provided in gray.

3.2. Computational Details

In order to accurately compare the DNA-protein interactions of the natural and alkylated nucleobases, the methodology presented in Chapter 2 will be used to examine the stacking and T-shaped interactions between each amino acid and εA or 3MeA. Specifically, C_s symmetric εA and 3MeA nucleobase monomers (Figure 3.2) were optimized with MP2/6-31G(d), while the amino acid monomers were obtained from the previous chapter. Initial relative orientations of the monomers were generated in a similar manner to those described for the natural nucleobase-amino acid dimers (stacked and T-shaped discussed in Sections 2.2.1 and 2.2.2, respectively). In particular, monomers were stacked (face-to-face) with respect to their centers of mass, where two molecular faces were considered for HIS, TYR, and TRP dimers. The first molecular plane is defined by stacking the amino acid

and nucleobase in the orientation shown in Figure 3.2 and the second (denoted as ') is obtained by flipping the amino acid relative to Figure 3.2 prior to stacking with the nucleobase. Amino acid edge and nucleobase edge dimers were constructed by directing the monomer edges towards the π -system of the monomer face as defined in Figure 3.2. Once these initial stacked and T-shaped dimer structures were defined, gas-phase BSSE-corrected MP2/6-31G*(0.25) potential energy surface scans were then completed by altering three geometric variables (Figure 2.2); vertical separation (R_1), angle of rotation (α), and horizontal displacement (R_2) as described in Sections 2.2.1 and 2.2.2. The R_2 variable was considered for all stacked dimers, yet was only considered for the edges (up to 8) that lead to the strongest T-shaped interactions after varying R_1 and α for each monomer pair.

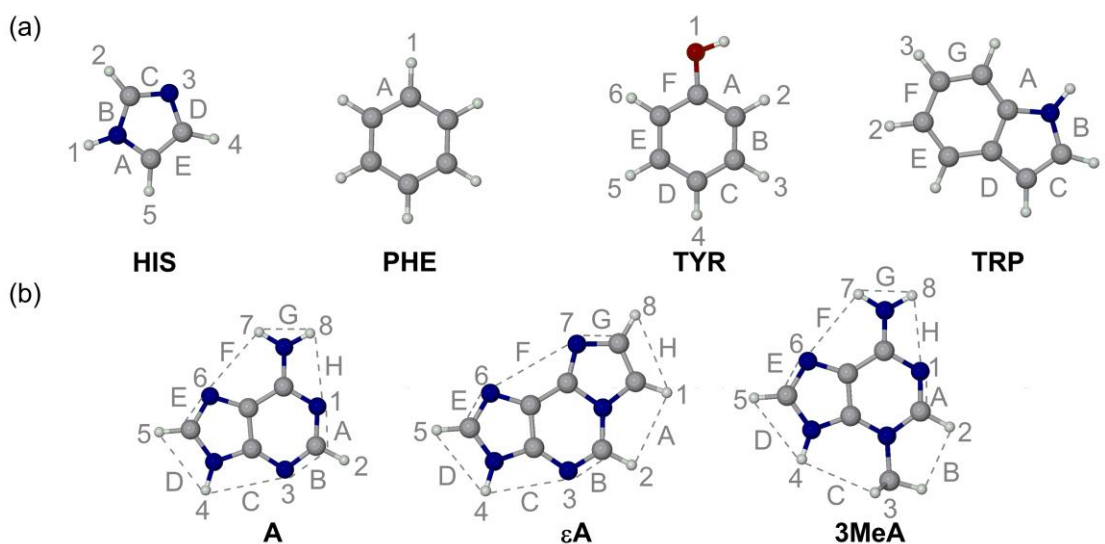


Figure 3.2. The definition of θ for (a) amino acid edges and (b) nucleobase edges considered in potential energy surface scans.

The MP2 binding strengths for the orientations with the strongest (most negative) interactions as identified in potential energy surface scans were extrapolated to the CCSD(T) level at the complete basis set (CBS) limit as described in Section 2.2.3 and Appendix A. In particular, all stacked dimers, the strongest amino acid edge dimers, the

strongest nucleobase edge dimers that involve the model N–H glycosidic bond (relevant for nucleobases) and the strongest nucleobase edge dimers that do not involve the model glycosidic bond (relevant for nucleotides and nucleosides) were considered through these high-level calculations.

All reported interaction energies include basis set superposition error corrections.¹⁴³ MP2 and CCSD(T) calculations were performed with Gaussian03¹⁵⁴ and MolPro,¹⁵⁵ respectively.

3.3. Results and Discussion

One of the driving forces of the present study is to address unanswered questions regarding the structure and magnitude of the π – π interactions between the amino acids with conjugated π -rings and natural versus (neutral and cationic) damaged nucleobases. The approach for scanning the potential energy surface as a function of geometric variables allows for an understanding of how the interaction energy depends on the relative monomer orientation. Therefore the following section begins by discussing how the structural dependencies of the damaged nucleobase–amino acid dimers compare to those discussed for the natural nucleobase complexes (Section 2.3.1). Additionally, the geometry of the preferred T-shaped dimers with adenine, 1,N⁶-ethenoadenine and 3-methyladenine will be discussed and compared, and important structural characteristics that maximize T-shaped interaction energies will be summarized. Next, the dependence of the stacking and T-shaped interaction energies on nucleobase alkylation and charge will be highlighted, where results from the MP2/6-31G*(0.25) scans will be further validated using CCSD(T)/CBS calculations.

3.3.1. Dependence of Optimal Structures on Nucleobase Alkylation

The following discussion concentrates on select examples to illustrate the major

findings from the potential energy surface scans for each monomer pair. Data tables in Appendix C summarize the optimal MP2/6-31G*(0.25) interaction energies after consideration of each variable, where the overall strongest interaction energies for each dimer after considering all variables are provided in Table 3.1.

Table 3.1. MP2/6-31G*(0.25) and CCSD(T)/CBS stacked and T-shaped interaction energies (kJ mol⁻¹) between the amino acids with conjugated π -rings and adenine, 1,N⁶-ethenoadenine or 3-methyladenine.^[a]

	θ	Adenine		θ	1,N ⁶ -ethenoadenine		θ	3-methyladenine	
		MP2 ^[b]	CCSD(T) ^[c]		MP2 ^[b]	CCSD(T) ^[c]		MP2 ^[b]	CCSD(T) ^[c]
HIS stacked		-29.7	-29.8		-37.4	-37.3		-51.7	-48.4
HIS' stacked		-27.2	-27.8		-36.5	-35.9		-52.7	-49.3
PHE stacked		-24.3	-23.3		-31.3	-28.8		-48.6	-44.2
TYR stacked		-28.9	-28.4		-38.0	-36.2		-53.9	-49.6
TYR' stacked		-30.7	-30.0		-36.4	-34.7		-55.0	-50.9
TRP stacked		-32.0	-30.6		-47.5	-43.7		-71.5	-65.5
TRP' stacked		-35.0	-33.5		-49.2	-45.1		-69.7	-64.2
HIS edge	B	-22.5	-22.4	B	-29.0	-28.4	3	-61.6	-61.6
PHE edge	A	-14.1	-15.2	A	-16.2	-17.0	A	-16.8	-17.8
TYR edge	A	-21.9	-22.4	A	-25.9	-26.6	F	-33.9	-35.2
TRP edge	A	-23.2	-22.9	A	-31.7	-31.2	E	-28.0	-28.2
HIS face ^[d]	4	-33.6	-33.3	4	-31.7	-31.2	4	-64.5	-65.1
	(8)	(-22.6)	(-23.6)	(2)	(-21.6)	(-23.5)	(B)	(-43.1)	(-43.5)
PHE face ^[d]	4	-25.6	-26.4	4	-26.3	-26.6	D	-46.4	-45.6
	(8)	(-16.0)	(-17.4)	(2)	(-17.5)	(-18.6)	(G)	(-37.2)	(-35.4)
TYR face ^[d]	4	-27.8	-28.3	4	-27.4	-27.4	D	-54.1	-52.9
	(8)	(-18.4)	(-20.0)	(2)	(-20.3)	(-22.1)	(B)	(-39.2)	(-40.8)
TRP face ^[d]	4	-34.8	-34.8	D	-34.8	-34.1	D	-72.0	-70.1
	(8)	(-23.1)	(-24.0)	(A)	(-26.9)	(-28.4)	(B)	(-52.6)	(-53.9)

^[a] See Figures 2.2 and 3.2 for definitions of θ and the edges considered in this study. ^[b] MP2/6-31G*(0.25) interaction energies. ^[c] CCSD(T)/CBS interaction energies. ^[d] Nucleobase edge interactions involving the model glycosidic bond and not involving the glycosidic bond (in parentheses).

Similar to the results in Section 2.3.1, the stacking interactions between the damaged nucleobases and the amino acids with conjugated π -rings are largely dependent on the relative orientation of the monomers, where the angle of rotation was found to most significantly alter the stacking energy compared with the vertical and horizontal displacements. Specifically, the magnitude of the dipole moments of the monomers largely affects the degree that the stacking interaction is dependent on α , where HIS has the largest dependence since it has the largest dipole moment among the amino acids. Indeed, the α

dependencies for HIS dimers are $10.3 \text{ kJ mol}^{-1} (\text{A}) < 21.3 \text{ kJ mol}^{-1} (\epsilon\text{A}) < 24.5 \text{ kJ mol}^{-1} (3\text{MeA})$, which is also the respective trend for nucleobase dipole moments ($2.837 \text{ D} (\text{A}) < 3.701 \text{ D} (\epsilon\text{A}) < 4.847 \text{ D} (3\text{MeA})$). Additionally, the preferred relative orientation of monomers aligns the dipole moment vectors of the nucleobase and amino acid in opposing directions, where the steric interactions between the monomers are minimized. Thus, stacking interactions are largely dependent on electrostatic interactions, which are strongly dictated by the dipole–dipole interactions between the π -systems.

Similarly to stacked dimers, the interaction energies of T-shaped complexes are more strongly affected by the α variable when compared to the vertical and horizontal displacements. For example, complexes involving a HIS edge display an α dependence of up to 8.4 kJ mol^{-1} ($\theta=\text{B}$) for A, 24.7 kJ mol^{-1} ($\theta=\text{C}$) for ϵA , and 20.0 kJ mol^{-1} ($\theta=\text{C}$) for 3MeA. Similarly, when a neutral edge interacts with the HIS face, the largest effect of α is 20 and 22 kJ mol^{-1} ($\theta=8$ and $\theta=\text{E}$ for A and ϵA , respectively), while the largest effect for a cationic 3MeA edge is 29 kJ mol^{-1} ($\theta=4$, Figure 3.3). Although the potential energy surface for rotation about α can be shallow for some monomer edges, the magnitude of this α dependence is due to the strength of secondary intramolecular interactions. Figure 3.3 shows the orientations with the strongest interactions (after considering R_1 and α) for HIS complexes, where the secondary intramolecular interactions that govern the optimal α alignment are highlighted with dotted lines.

Although the T-shaped interaction energies are strongly affected by the angle of rotation (α), both neutral and cationic interaction energies have a larger dependence on θ , as previously discussed for the dimers involving the natural nucleobase (Section 2.3.1).

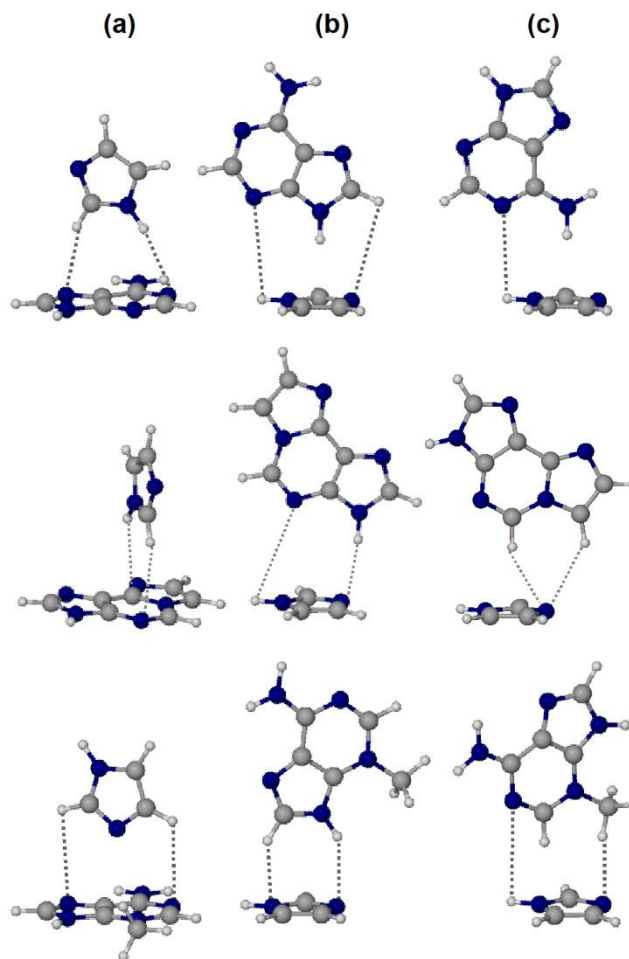


Figure 3.3. T-shaped dimers involving adenine (top), 1,N⁶-ethenoadenine (middle), 3-methyladenine (bottom) and (a) HIS edge, (b) HIS face (nucleobase edge involving the model glycosidic bond) and (c) HIS face (nucleobase edge not involving model glycosidic bond).

In fact, the range in the interaction energy as a function of θ falls between 3.3 and 55.5 kJ mol⁻¹ for each monomer. This large effect is partially due to variations in the acidic/basic properties of the monomer edges. For example, the acidic $\theta=1$ edge of HIS is very different from the basic $\theta=3$ edge, leading to a very large θ dependence for both neutral and cationic HIS edge dimers.

Intriguingly, the preferred T-shaped orientation depends on the charge of the interacting π -system. For neutral dimers with an amino acid edge interacting with the face of A or ϵ A, the most (Lewis) acidic edge of the amino acid prefers to be directed towards the

electron-rich π -system. For example, in the HIS edge complexes shown in Figure 3.3, the optimal structure directs the acidic N–H and the C–H bonds towards A or ϵ A ($\theta=B$). On the contrary, for cationic dimers with an amino acid edge interacting with the face of 3MeA, the most (Lewis) basic edge of the amino acid prefers to be directed towards the cationic nucleobase. The best example is the HIS complex, where directing the HIS lone pair towards the cationic face ($\theta=3$) results in the strongest interaction energy ($-61.6 \text{ kJ mol}^{-1}$, Table 3.1). Alternatively, when an acidic edge of HIS ($\theta=1$) is directed towards 3MeA, the interaction is extremely repulsive ($+13.8 \text{ kJ mol}^{-1}$). This is opposite to the trend discussed for A or ϵ A, where the $\theta=1$ acidic edge leads to a stronger interaction ($-18.4 \text{ kJ mol}^{-1}$ (A) or $-18.2 \text{ kJ mol}^{-1}$ (ϵ A)) than the $\theta=3$ basic edge (-8.8 kJ mol^{-1} (A) or 15.5 kJ mol^{-1} (ϵ A)). Indeed, the optimal orientation for HIS edge interacting with these neutral π -systems ($\theta=B$) leads to a very weak interaction with 3-methyladenine (-0.3 kJ mol^{-1}). Similarly, for the TYR edge, the most stable complexes involve the hydroxyl lone pair directed towards 3MeA ($\theta=F$), but the acidic hydroxyl hydrogen directed towards A or ϵ A ($\theta=A$). These results show that the cationic charge of the damaged nucleobase dictates the relative orientation of the amino acid and base, and therefore plays a large role in the nature of T-shaped interactions. Indeed, these results suggest that T-shaped interactions are highly dependent on electrostatic interactions, which is perhaps more pronounced in the cationic system.

Due to the differences in charge, it is not surprising that the interaction energies for these nucleobases have a different dependence on the amino acid edge. Indeed, the strongest interactions for adenine and 1,N⁶-ethenoadenine face dimers increase as PHE < TYR < HIS < TRP, which is due to the relative dipole moments and size of the π -system of the various amino acids with conjugated π -rings, while the strengths of dimers involving 3-methyladenine face increase as PHE < TRP < TYR < HIS, which is due to the increasing basicity of the amino acid. Since the favoured monomer orientation in nucleobase face

dimers depends on the relative acidity and basicity of the amino acid edge, a larger amino acid dipole moment causes a larger variation in the interaction energies as a function of θ .

For complexes involving amino acid faces, the optimal interaction occurs with the most acidic nucleobase edge, the model glycosidic bond ($\theta=4$ (A, ϵ A, or 3MeA) and $\theta=D$ (ϵ A or 3MeA)), directed towards the electron-rich amino acid π -system. The present observations for 3-methyladenine edge dimers are consistent with previous research on the benzene (face)–pyridinium cation (edge) interactions,¹⁵² where the strongest T-shaped complex directs the N–H bond of pyridinium towards the π -system of benzene. For the interactions that do not involve the glycosidic bond, the strongest binding occurs when one N–H bond of the amino group of A ($\theta=8$) or two C–H bonds of ϵ A ($\theta=2$ or A) interact with the amino acid π -system (Figure 3.3c). Although the amino group of 3MeA ($\theta=G$) interacts with PHE in the most stable complex, two C–H $\cdots\pi$ interactions ($\theta=B$) yield the strongest binding with the remaining amino acid faces. Due to the similarity in the structures of A, ϵ A, and 3MeA edges, the optimal interactions for amino acid face dimers generally increase with the dipole moments, as well as the size of the π -system, of the amino acids with conjugated π -rings (PHE < TYR < HIS < TRP) in the strongest complexes. Collectively, these results suggest that electrostatics play a very important role in the structure of T-shaped complexes.

3.3.2. Effects of Nucleobase Alkylation on the Magnitude of T-shaped and Stacking Interactions

To fully examine the magnitude of the nucleobase–amino acid interactions and further validate the use of MP2/6-31G*(0.25), the stacking and T-shaped interactions for structures with the strongest (most negative) interactions as found in the MP2/6-31G*(0.25) potential energy surface scans were estimated at the CCSD(T)/CBS limit. Table 3.1 displays the MP2/6-31G*(0.25) interaction energies and the CCSD(T)/CBS estimates. These high-level calculations show that CCSD(T)/CBS and MP2/6-31G*(0.25) results deviate by 0.5–6 kJ

mol⁻¹ (up to 10%) for all stacked dimers and 0–2 kJ mol⁻¹ (up to 9%) for all T-shaped dimers. Therefore, the MP2/6-31G*(0.25) calculations account for 92–110% of the CCSD(T)/CBS interaction energies. This is an even better agreement between MP2/6-31G*(0.25) and CCSD(T)/CBS energies than previously reported in Section 2.3.2 (80–110%), as well as those reported for the stacking interactions between the natural nucleobases (only 80% of the CCSD(T)/CBS stacking interaction is recovered at the MP2/6-31G*(0.25) level).^{87,105,107,114,144} This expands upon the original justification for the use of MP2/6-31G*(0.25) potential energy surface scans as a balance between cost and accuracy. Nevertheless, CCSD(T)/CBS is found to strengthen T-shaped interactions (by up to 9%) and weaken stacking interactions (by up to 10%). These differences indicate that the strength of the stacking and T-shaped complexes are even more similar at the CCSD(T)/CBS level of theory compared with MP2/6-31G*(0.25). Therefore, in order to provide an accurate comparison for these systems, it is important to examine the T-shaped and stacking interactions of nucleobase–amino acid dimers at the CCSD(T)/CBS level, therefore only these CCSD(T) results will be discussed below.

The calculated binding strengths for adenine dimers are found to range from –15 to –35 kJ mol⁻¹. These interactions increase slightly upon alkylation to form εA, which has interaction energies ranging between –17 to –46 kJ mol⁻¹. In contrast, the interactions with (cationic) 3MeA are even larger (ranging from –18 to –71 kJ mol⁻¹). This suggests that alkylation to generate a charged nucleobase has a more substantial effect on the preferred stacking and T-shaped interaction energies than neutral alkylation damage.

Closer examination of these interaction energies indicate that any given stacked complex increases in strength by 15–43% upon alkylation of adenine to εA, or 62–114% for 3MeA. Additionally, amino acid edge complexes increase in interaction energy by 12–36% or 17–176% upon alkylation to εA or 3MeA, respectively. Interestingly, these increases in

strength for ϵ A complexes correspond to the same θ edges as A, yet large structural changes occur when the π -system of 3MeA is involved. Indeed, the largest geometric effect is observed for the HIS edge ($\theta=3$) interacting with the π -system of 3MeA ($-61.6 \text{ kJ mol}^{-1}$, Table 3.1), where this geometry and interaction energy is consistent with a previously published pyridinium (edge)–benzene (face) interaction ($-61.7 \text{ kJ mol}^{-1}$ at the same level of theory).¹⁵² The magnitude of this HIS edge interaction is also consistent with the magnitude of similar lp– π interactions involving various cationic nucleobases calculated by Egli et al.¹⁶⁴

Intriguingly, T-shaped interactions involving the edge of ϵ A were found to decrease slightly (0.8–7%) from the corresponding natural (A) nucleobase edge interactions with HIS, TYR, and TRP, which is partially due to the fact that ϵ A only has one acidic N–H bond. Although there is not a large change in the preferred nucleobase orientation upon alkylation to 3MeA, the cationic charge increases the acidity of the nucleobase bonds interacting with the amino acid face, which results in stronger nucleobase interaction energies. Indeed, the effect of alkylation in these 3MeA complexes corresponds to a 72–125% increase in interaction strength. In summary, alkylation to ϵ A corresponds to a slight increase (up to 43%) or decrease (up to 7%) in the preferred π – π interactions found for the natural base, yet 3MeA has a much larger effect (up to 175%) on the adenine interactions.

This study has been instrumental in understanding the energetic and geometric significance of adding a cationic charge to DNA–protein complexes. Indeed, Kim and coworkers investigated stacked and T-shaped π^+ – π interactions involving one cationic π -system and benzene, and suggested that stacked π^+ – π complexes are a special type of noncovalent interaction that cannot be described as either a (neutral) π – π or cation(metal)– π interaction.¹⁶⁸ However, it is uncertain whether this π^+ – π interaction classification is only relevant for stacked orientations, or whether it also becomes important in other noncovalent (T-shaped or hydrogen-bonded) systems that involve monomers other

than benzene. Therefore, the next section will examine the interplay of the attractive (electrostatic, dispersion, and induction) and repulsive (exchange repulsion) forces responsible for stabilizing these potentially different noncovalent complexes.

3.3.3. Fundamental Differences Between Noncovalent Interactions

To gain further insights into whether $\pi^+ - \pi$ contacts are indeed a unique type of noncovalent interaction, a detailed interaction energy analysis using DFT-symmetry-adapted perturbation theory (DFT-SAPT) was completed on the strongest stacked and T-shaped complexes between histidine and neutral adenine or cationic 3-methyladenine. These systems were chosen due to their strong geometric variable dependence, where A and 3MeA are structurally similar, but still provide insights into how a cationic charge on the π -system changes the interaction energy components in these different structural arrangements. Additionally, the corresponding hydrogen-bonded structures with histidine (Figure 3.4) are included for comparison to the stacked and T-shaped interactions (Figure 3.3 top and bottom), which will indicate whether these two (nonspecific) types of interactions are distinct noncovalent contacts from each other, as well as from (specific) hydrogen-bonding interactions.

DFT-SAPT calculations examine the competing forces present in DNA-protein systems by dissecting the total interaction energy (E_{int}) into physically meaningful components (electrostatic (E_{elec}), induction (E_{ind}), dispersion (E_{disp}) and exchange repulsion (E_{exch}), Table 3.2). This method has been shown to provide accurate information about the fundamental interactions present in a variety of biomolecular systems.^{117,119,169-175} Full computational details for these calculations, as well as the approach taken to study the hydrogen-bonded dimers, are reported in Appendix F.

To examine the fundamental differences between a variety of noncovalent interactions,

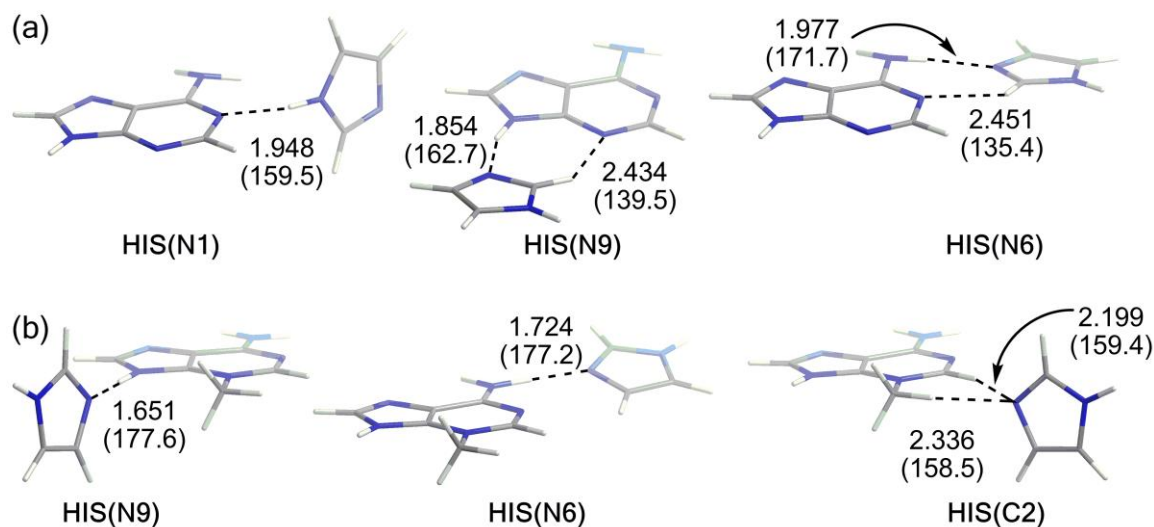


Figure 3.4. MP2/6-31+G(d,p) structures (distances (Å) and angles (°, in parentheses)) and nomenclature for hydrogen-bonded systems involving histidine and (a) adenine or (b) 3-methyladenine.

Table 3.2. Intermolecular interaction energies (kJ mol⁻¹) and percentages of energy components in histidine noncovalent complexes.

	Complex	E _{int}	E _{elec}	E _{ind}	E _{disp}	E _{exch}	E _{attract} ^[a]	%E _{elec} ^[b]	%E _{ind} ^[c]	%E _{disp} ^[d]
Adenine	HIS stacked	-23.5	-22.3	-4.6	-33.2	73.5	-60.1	37.1	7.7	55.2
	HIS' stacked	-20.6	-20.6	-4.5	-34.7	89.7	-59.8	34.4	7.5	58.0
	HIS edge	-19.2	-13.4	-4.3	-18.0	68.0	-35.7	37.5	12.0	50.4
	HIS face ^[e]	-30.2	-26.5	-9.6	-15.3	36.6	-51.4	51.6	18.7	29.8
		-20.7	-18.4	-5.5	-15.4	39.2	-39.3	46.8	14.0	39.2
	HIS(N1) ^[f]	-34.0	-62.9	-22.4	-22.2	16.5	-107.5	58.5	20.8	20.7
	HIS(N9) ^[f]	-52.4	-83.6	-33.7	-24.8	21.2	-142.1	58.8	23.7	17.5
	HIS(N6) ^[f]	-35.7	-60.9	-21.3	-21.5	18.6	-103.7	58.7	20.5	20.7
3-methyladenine	HIS stacked	-39.9	-33.7	-10.5	-35.9	40.2	-80.1	42.1	13.1	44.8
	HIS' stacked	-41.1	-35.3	-10.1	-35.4	39.7	-80.8	43.7	12.5	43.8
	HIS edge	-56.1	-51.4	-12.6	-19.9	27.8	-83.9	61.3	15.0	23.7
	HIS face ^[e]	-58.7	-44.2	-18.7	-13.6	17.8	-76.5	57.8	24.4	17.8
		-40.2	-30.2	-12.3	-14.9	17.2	-57.4	52.6	21.4	26.0
	HIS(N9) ^[f]	-105.4	-136.5	-75.5	-28.5	135.1	-240.5	56.8	31.4	11.9
	HIS(N6) ^[f]	-74.1	-106.1	-52.3	-24.1	108.4	-182.5	58.1	28.7	13.2
	HIS(C2) ^[f]	-62.5	-73.2	-23.2	-18.3	52.2	-114.7	63.8	20.2	16.0

[a] E_{attract} = E_{elec} + E_{ind} + E_{disp}. [b] %E_{elec} is E_{elec}/E_{attract} and represented as a percentage. [c] %E_{ind} is E_{ind}/E_{attract} and represented as a percentage. [d] %E_{disp} is E_{disp}/E_{attract} and represented as a percentage. [e] Nucleobase edge interactions involving the model glycosidic bond are reported first, followed by the nucleobase edge interaction that does not involve the glycosidic bond. [f] See Figure 3.4 for the structures and nomenclature of hydrogen-bonded complexes.

the (percent) contribution of electrostatic, induction, and dispersion energies to the total (attractive) interaction energy were analyzed using an approach similar to that originally implemented by Kim and coworkers.¹⁶⁸ Therefore, Table 3.2 reports the total attractive

interaction energy (E_{attract}) and the corresponding percentage contributions from each attractive force. It should be noted that the total interaction energy calculated with DFT-SAPT underestimates the MP2/6-31G*(0.25) stabilization energy (Table 3.1) by 26–32% for stacked systems, but much closer agreement is observed for T-shaped complexes (7–17%). Nevertheless, general trends in the stabilization energies are still present at this level of theory, and therefore this analysis is not expected to be greatly affected by the interaction energy discrepancy.

The examined stacking interactions exhibit very large dispersion energies corresponding to over 50% of the stabilization for neutral, and ~44% for cationic systems. This observation is consistent with investigations of the classically studied benzene dimer, as well as the general acceptance that (neutral) stacked complexes are largely dominated by dispersion interactions.^{98,101} However, in the $\pi^+-\pi$ stacked system, an almost equal percentage of stabilization is obtained from the electrostatic component, and there is a slightly larger induction dependence (13%) than observed for the neutral dimers (7%). Therefore, the present results are consistent with the trends observed by Kim and coworkers for benzene containing systems,¹⁶⁸ suggesting that $\pi-\pi$ stacked conformations for a variety of π -systems are dominated by dispersion, yet $\pi^+-\pi$ dimers rely on both dispersion and electrostatics.

In T-shaped complexes, the neutral systems exhibit a stronger dependence on electrostatics (ranging from 38–52% of attractive forces), which leads to a slightly lower percentage of dispersion than observed for the stacked dimers. However, the dispersion component ranges from 30–50%, and therefore also plays a significant role in neutral T-shaped complexes. When a cationic charge is present in the T-shaped system, the electrostatic contribution is dominant, being on average 57% of the attractive forces. Indeed, this leaves induction and dispersion to play an almost equal role, averaging 20%

and 22% of the overall attractive interaction energy, respectively. Therefore, it appears that both π - π and π^+ - π interactions, as well as stacked and T-shaped orientations, are governed by different attractive forces, and therefore are indeed very distinct classes of interactions.

As proposed in Sections 3.3.1 and 3.3.2, this data indicates that cationic T-shaped complexes exhibit a much larger electrostatic dependence than the neutral dimers. Although speculations have been made that such T-shaped complexes are simply hydrogen-bonding interactions,¹⁵² Table 3.2 shows that (cationic) hydrogen-bonding interactions form yet another distinct class of noncovalent interactions. In particular, these contacts exhibit much stronger induction dependencies than either the stacked or T-shaped dimers. Additionally, as a consequence of the large induction and electrostatic components, the dispersion contribution for hydrogen-bonded complexes is much smaller than observed for T-shaped interactions. Therefore, it is proposed that neutral and cationic noncovalent interactions between two π -systems are a separate class of interactions in T-shaped, stacked, or hydrogen-bonded orientations since they are fundamentally governed by different attractive forces.

3.4. Conclusions

Stacking and T-shaped interactions between all amino acids with conjugated π -rings and 1,N⁶-ethenoadenine or 3-methyladenine were investigated to gain information about how neutral and cationic nucleobase alkylation affects the geometry and magnitude of preferred noncovalent complexes. Additionally, the present work expanded upon the understanding of these interactions by extrapolating the strongest interaction energies to the CCSD(T)/CBS level, where these results emphasize the importance of comparing these interactions at the highest level of theory possible. These calculations determined that the structure of stacked dimers are not largely affected by neutral or cationic alkylation damage, yet the structure of the preferred T-shaped interactions are highly dependent on

the charge of the system. Indeed, the strongest T-shaped interactions depend on the properties of the monomer face and monomer edge, where the most acidic edge is directed towards the (neutral) π -systems of A or ϵ A and the amino acids, while the most basic edge is directed towards (cationic) 3MeA. In fact, the interaction energy decomposition calculations presented in this chapter suggest that the π - π stacking and T-shaped interactions that occur in neutral or cationic systems are fundamentally different, where all three noncovalent interactions (stacking, T-shaped, and hydrogen-bonding) are governed by a distinct interplay of attractive forces. Indeed, this work proposes that chemists examining noncovalent interactions in many molecular environments (biological molecules, self-assembly in materials chemistry, etc.) must view these interactions as distinct noncovalent contacts to obtain a full representation of these systems.

It was found that the magnitude of these π - π interactions involving neutral nucleobases are up to -35 (A) or -46 kJ mol^{-1} (ϵ A), which is comparable to biologically-relevant hydrogen bonds evaluated at the same high level of theory. However, the effect of alkylating to ϵ A was found to only slightly decrease (up to 7%) or increase (up to 43%) the π - π interaction energies of natural A, indicating that these interactions alone cannot provide a discriminatory recognition or binding step for neutral substrates of AAG. Remarkably, interactions involving cationic 3-methyladenine are found to be very strong (up to -70 kJ mol^{-1}), which is much larger than the corresponding adenine interactions (up to 176% increase upon alkylation). Thus, the present work indicates that the charge of the π -system is the most important factor governing the preferred relative orientation of the amino acid and nucleobase. This provides clues about potential binding preferences of the cationic substrates within the active site of AAG.

Despite the fact that this chapter provides significant insights into the fundamental forces governing noncovalent dimers, as well as their application to the DNA repair

mechanism used by AAG, the systems studied only involve one nucleobase interacting with one conjugated amino acid. Indeed, stacking and T-shaped interactions with multiple amino acids commonly occur in nature and it is currently unclear what implications additional amino acids might have on these noncovalent contacts. For instance, the differences between the π - π and π^+ - π stabilities observed in this chapter may diminish as the charge delocalizes over a larger system. Therefore, further studies must examine larger (trimer) complexes with both neutral and cationic π -systems, which is the subject of the next chapter.

Chapter 4. Additivity of π - π and π^+ - π Stacking and T-shaped Interactions^a

4.1. Introduction

Chapters 2 and 3 have illustrated the importance of studying nucleobase–amino acid stacking and T-shaped dimers between the four amino acids with conjugated π -rings and natural or damaged nucleobases. However, more than one noncovalent interaction can simultaneously occur in nature. For example, in the human alkyladenine DNA glycosylase (AAG), multiple stacking and T-shaped interactions are exploited to bind substrates in the active site (Figure 1.10).⁵⁷ Therefore, it is important to investigate how additional amino acids affect the π - π interactions in nucleobase–amino acid dimers. In fact, both the geometry and binding energy of a dimer may be affected by additional contacts. Alternatively, it is possible that the monomers in the trimer retain their preferred relative orientations in the dimer (geometric additivity) and the resulting interactions between monomers are of equal strength in the dimer and trimer (energetic additivity).

Previous computational studies have examined the geometric and energetic additivity of a variety of noncovalent interactions (such as hydrogen-bonding, π - π stacking, T-shaped, small molecule $X-H\cdots\pi$ ($X=N, C, O, S$), cation- π (involving a cationic point charge), and π^+ - π (involving a cationic π -system)) in biological and non-biological systems (for select studies see references 100, 106, 139, 168, and 176–195). For example, extensive studies have been conducted on the π - π stacking and T-shaped interactions between benzene rings in trimers and tetramers.^{100,176,188} DNA nucleobase trimers have also been investigated to understand

^a Reprinted with permission from Rutledge, L. R.; Churchill, C. D. M.; Wetmore, S. D. *J. Phys. Chem. B* **2010**, *114*, 3355–3367. Copyright 2010 American Chemical Society.

the additivity of stacking and hydrogen-bonding interactions.^{106,181-182,187} A recent study investigated the additivity of π - π stacking and Na^+ - π interactions in trimers composed of uracil, phenylalanine and sodium ions.¹³⁹ Furthermore, a large number of calculations have been conducted by Frontera et al. that study the interplay between a wide range of noncovalent interactions involving various molecular systems.^{178,180,183-185,189-192}

Despite the significant number of complexes studied in the literature, very few groups have considered the geometry and binding strength of (edge-to-face) T-shaped interactions between π -ring systems in trimers.^{100,168,176,184-185,189,193} Additionally, complexes previously investigated involve symmetric molecules, which result in highly-symmetric trimers.^{98, 174,182-183,187,191} To the best of my knowledge, only one study considered T-shaped interactions between two π -systems in asymmetric (C_1) trimers other than benzene.¹⁶⁸ Although the effects of hydrogen bonding a small molecule (H_2O , Cl^- or Br^-) to a T-shaped interaction were considered in trimers,¹⁶⁸ the additivity of T-shaped contacts with other π - π contacts was not studied. Therefore, in order to truly understand the interplay between stacking and T-shaped interactions between two π -systems in biological complexes (such as those in the active site of AAG), trimers involving many relative arrangements of the nucleobases and the amino acids with conjugated π -rings must be investigated.

To complement geometric and energetic information for trimers, some researchers have used Bader's Quantum Theory of Atoms in Molecules (QTAIM)¹⁹⁶⁻¹⁹⁹ analysis. QTAIM has been widely used to characterize a large assortment of noncovalent interactions (for examples, see references 110, 139, 177-179, 183-185, 189, 191-193, and 200-220), and may be quite powerful for analyzing the cooperative effects of the interactions within trimers. However, QTAIM analyses for π - π and π^+ - π stacked and T-shaped systems are scarce in the literature, and few studies have examined systems with C_1 symmetry and/or biologically-relevant molecules.^{139,188,204-206,209-211,220}

This chapter investigates the geometries and binding strengths of amino acid–nucleobase–amino acid trimers, which will be compared to the corresponding dimers previously studied.²²¹ As a test case, this work concentrates on systems containing the natural nucleobase adenine (A) or the (cationic) damaged counterpart, 3-methyladenine (3MeA), and the amino acid histidine, in both the neutral (His) and protonated (His⁺) forms (Figure 4.1). These systems were chosen since Chapter 3 has shown the importance and distinct differences between π – π and π^+ – π interactions, which need to be further examined in larger trimer systems. Previous work in the Wetmore group has considered the stacking and T-shaped interactions between protonated histidine and the natural nucleobases²²¹ since histidine can be present in a neutral or protonated form under physiological conditions.¹³⁶ Therefore, the systems studied will provide an additional avenue for investigating π^+ – π interactions within trimers by introducing the cationic charge in the central nucleobase (3MeA) or the terminal amino acid (His⁺).

This chapter will provide information about the geometric and energetic additivity of π – π stacking and π – π T-shaped interactions in asymmetric systems. It has been proposed that cation– π interactions strengthen in trimers and result in a greater than additive interaction energy.^{139,178,180,183,186,190,192} However, since π^+ – π interactions are quite different from the typically examined cation– π interactions involving a cationic point charge, it is unclear how these different interactions will behave in trimers. Finally, this chapter will use QTAIM to analyze the interaction energies in nucleobase–amino acid dimers and trimers to help bridge the gap in the current QTAIM (trimers) literature.

4.2. Computational Details

4.2.1. Geometries of Dimers

The optimal stacked and T-shaped orientations of nucleobase–amino acid dimers

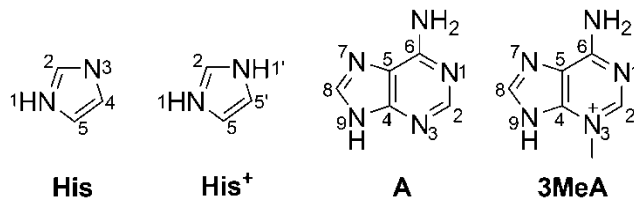


Figure 4.1. Structure and atomic numbering of neutral and protonated histidine (His and His⁺, respectively) and the natural (adenine (A)) and damaged (3-methyladenine (3MeA)) nucleobases considered in this chapter.

identified through MP2/6-31G*(0.25) potential energy surface scans in Chapters 2 and 3 for adenine and 3-methyladenine, respectively, as well as previous work for protonated histidine,²²¹ were examined in the present study. Specifically, the strongest HIS and HIS' stacked dimers, as well as the HIS edge T-shaped interactions (referred to as HIS(edge)) were considered. Due to the symmetry of protonated histidine, only one stacked dimer is possible (HIS⁺), and the HIS⁺ edge T-shaped dimers (HIS⁺(edge)) directs the acidic N-H bond towards the π -system of neutral adenine. This results in a total of eight stacked and T-shaped dimer geometries for the present work.

4.2.2. Geometry of Trimers

Trimers composed of one amino acid located directly above, and a second amino acid directly below the molecular plane of the nucleobase were investigated due to their greater relevance to the AAG active site. All combinations of stacked and T-shaped orientations were considered to yield three possible trimer arrangements: (1) stacked_stacked, (2) stacked_T-shaped, and (3) T-shaped_T-shaped. To distinguish between the geometries and molecules examined, each trimer is named according to its corresponding dimers. For example, in the HIS_A_HIS(edge) trimer, one histidine is stacked (HIS) with adenine, which is the central monomer, and another histidine is T-shaped (HIS(edge)) relative to adenine. Due to the choice in molecules and differences in their total charges, three types of trimers were considered: A and two neutral His (His:A:His), cationic 3MeA and two neutral His (His:3MeA:His), and A with one neutral His and one charged His⁺ (His:A:His⁺). In the case of

T-shaped trimers, only the optimal amino acid-edge previously identified for the dimers was considered.²²¹ This combination of stacked (HIS, HIS' or HIS⁺) or T-shaped (HIS(edge) or HIS⁺(edge)) orientations yields 18 trimers (six His:A:His, six His:3MeA:His, and six His:A:His⁺). It should be noted that because the nucleobases are fixed in planar C_s symmetry, the same trimer is obtained whether the interactions occur 'above' or 'below' the plane of the nucleobase.

MP2/6-31G*(0.25) potential energy surface scans were performed for six representative trimers to determine how the preferred trimer geometry differs from the preferred dimer geometries. This choice in trimers will provide an understanding of the interplay between two π - π or two π^+ - π interactions, which are specific to the intended application (AAG repair). These trimers are expected to exhibit the largest geometrical changes (if any) from the relative dimers. Specifically, for the HIS_A_HIS, HIS_A_HIS(edge), HIS(edge)_A_HIS(edge), HIS'_3MeA_HIS', HIS'_3MeA_HIS(edge), and HIS(edge)_3MeA_HIS(edge) trimers, the monomers were first aligned according to their centers of mass. Next, an R₁ scan (vertical separation, Figure 2.2) was performed for one amino acid in 0.1 Å increments. At each of these R₁ values, a full R₁ scan was completed for the second amino acid. Once the lowest energy structure was identified, the preferred R₁ distances were held constant and the preferred α values (angle of rotation, Figure 2.2) were determined. Specifically, for every 30° rotation of one amino acid, a full α scan was completed for the other amino acid, and vice versa. Once the best α values were determined for both amino acids, R₂ scans (horizontal displacement, Figure 2.2) were performed simultaneously on the area surrounding the dimer global minima. This procedure resulted in over 950 points scanned for each trimer.

4.2.3. Interaction Energy of Trimers

For each amino acid–nucleobase dimer and amino acid–nucleobase–amino acid trimer,

the MP2/6-31G*(0.25) interaction energies (ΔE_{dimer} and ΔE_{trimer}) were evaluated using the supramolecular approach.^b To further evaluate the interplay of stacking and T-shaped interactions in trimers, two quantities denoted as E_{syn} (synergy energy) and E_{add} (additivity energy) were calculated. The MP2/6-31G*(0.25) synergy energy (E_{syn}) is the difference between the trimer interaction energy ($\Delta E_{\text{trimer}(123)}$) and the two nucleobase–amino acid dimer interaction energies ($\Delta E_{\text{dimer}(12)}$ and $\Delta E_{\text{dimer}(23)}$). The MP2/6-31G*(0.25) additivity energy (E_{add}) is the difference between the trimer interaction energy ($\Delta E_{\text{trimer}(123)}$) and the sum of all pairwise interaction energies ($\Delta E_{\text{dimer}(12)}$, $\Delta E_{\text{dimer}(23)}$ and $\Delta E_{\text{dimer}(13)}$).

All trimer potential energy surface scans and interaction energy calculations were completed with Gaussian 03.¹⁵⁴ To further investigate the synergy and additivity of these noncovalent interactions, MP2/6-31G*(0.25) electron densities for dimers and trimers were generated with Gaussian 09,²²² and analyzed according to the quantum theory of atoms in molecules (QTAIM).¹⁹⁶⁻¹⁹⁸ Explicitly, AIMAll²²³ was used for electron density critical point analysis and the AIM2000²²⁴ program was used to generate molecular graphs. All reported interaction energies correspond to (BSSE-free) counterpoise-corrected¹⁴³ MP2/6-31G*(0.25).

4.3. Results and Discussion

4.3.1. Geometric Additivity in Trimers

As mentioned in Section 4.2.2, it is important to determine whether the geometries of the nucleobase–amino acid dimers change upon inclusion of an additional amino acid in the trimer. To determine the preferred trimer geometries, six test cases were considered and potential energy surface scans of both amino acids in these trimers were completed

^b For example, the interaction energy for a nucleobase–amino acid dimer ($\Delta E_{\text{dimer}(12)}$), or amino acid–nucleobase–amino acid trimer ($\Delta E_{\text{trimer}(123)}$), is evaluated as: $\Delta E_{\text{dimer}(12)} = E_{12} - E_1 - E_2$ or $\Delta E_{\text{trimer}(123)} = E_{123} - E_1 - E_2 - E_3$. E_{12} (E_{123}) is the MP2/6-31G*(0.25) energy of the dimer (trimer) which includes a BSSE correction, where E_1 and E_3 are the amino acid monomer energies, and E_2 is the nucleobase monomer energy.

simultaneously. For five of the six trimers (HIS_A_HIS, HIS_A_HIS(edge), HIS(edge)_A_HIS(edge), HIS'_3MeA_HIS(edge), HIS(edge)_3MeA_HIS(edge)), all preferred R_1 and α values for the trimer match the optimal geometric parameters for the respective dimers previously determined (see Appendix G for the HIS_A_HIS(edge) example). Additionally, R_2 scans were performed on points surrounding the dimer global minima and revealed that the trimer R_2 minima occur at the same point on the potential energy surface as the corresponding dimer minima (Appendix G).

In the case of HIS'_3MeA_HIS', the optimal R_1 and R_2 values for the trimer matched those for the dimer (see Appendix G). However, the preferred α minimum for the histidine and 3-methyladenine dimer ($\alpha=180^\circ$) was obtained for one stacked histidine in the trimer, but the other stacked histidine prefers $\alpha=150^\circ$. Nevertheless, the 3MeA_HIS' dimer with $\alpha=180^\circ$ ($-52.3 \text{ kJ mol}^{-1}$) is only 0.1 kJ mol^{-1} more stable than the structure with $\alpha=150^\circ$. Since the preferred α for the trimer and dimer differ by only one (30°) increment, an additional α scan was performed on the HIS'_3MeA_HIS' trimer and 3MeA_HIS' dimer using smaller (3°) increments. In both the dimer and trimer, the more refined search determined the minimum to occur at $\alpha=165^\circ$ (Appendix G), where the dimer (trimer) with $\alpha=165^\circ$ is only 0.7 (1.2) kJ mol^{-1} more stable than the original minimum. Therefore, although the HIS'_3MeA_HIS' trimer is sensitive to the increments originally used in potential energy surface scans, the geometries are in fact additive.

The present finding that the preferred trimer geometries match those for the corresponding dimers is consistent with previous work on the benzene (sandwich) trimer.¹⁷⁶ Specifically, the intermolecular separation distance in the benzene trimer is increased by only $0.05 \text{ \AA}$ relative to the dimer, which results in a total energy change of only 0.1 kJ mol^{-1} . The present study reveals that this geometric additivity holds for both stacked and T-shaped interactions between two π -systems, as well as both π - π and π^+ - π

interactions. Thus, all trimers discussed in the remainder of this study were constructed using the geometric variables previously determined to yield the strongest (most negative) dimer interaction energies (Chapter 2 and 3, as well as reference 221).

4.3.2. Interaction Energy of Trimers

The interaction energies computed for the 18 amino acid–nucleobase–amino acid trimers, as well as the corresponding dimers, are summarized in Table 4.1. An energetic dissection of each trimer energy into the dimer components, as well as the synergy (E_{syn}) and additivity (E_{add}) energy are also included. To clarify these energetic components, the HIS_A_HIS(edge) trimer is illustrated in Figure 4.2. In this trimer, one histidine is stacked with A (HIS) and one histidine is T-shaped with A (HIS(edge)). The total counterpoise-corrected binding energy for this three component system is $-52.5 \text{ kJ mol}^{-1}$ (Figure 4.2a). The nearest-neighbor nucleobase–amino acid dimers have interaction energies of -22.5 (HIS(edge), Figure 4.2b) and -29.7 (HIS, Figure 4.2c) kJ mol^{-1} , and therefore their sum is $-52.2 \text{ kJ mol}^{-1}$. By subtracting the sum of these nucleobase–amino acid dimer energies ($\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)}$, Table 4.1) from the total trimer interaction energy, the synergy energy is obtained ($E_{\text{syn}} = -0.3 \text{ kJ mol}^{-1}$). E_{syn} provides valuable information regarding the interplay between two nucleobase–amino acid interactions, where the slightly negative value for the HIS_A_HIS(edge) trimer indicates that the total binding energy of the trimer is only marginally stronger than the sum of the two nearest-neighbour dimer interactions. Table 4.1 also reports the interaction energy between the two amino acids when the nucleobase is not present ($\Delta E_{\text{dimer}(13)}$). In the HIS_A_HIS(edge) trimer, the histidine–histidine interaction (Figure 4.2d) is slightly attractive (-0.4 kJ mol^{-1}). The mutual influence of both nucleobase–amino acid interactions is evaluated by including this interaction energy ($E_{\text{add}} = E_{\text{syn}} - \Delta E_{\text{dimer}(13)}$). $E_{\text{add}} = 0.1 \text{ kJ mol}^{-1}$ indicates that the HIS_A_HIS(edge) trimer interaction can be predicted as a sum of the three pairwise binding energies, or that these

interactions are additive.

Table 4.1. MP2/6-31G*(0.25) total dimer and trimer interaction energies, as well as synergy (E_{syn}) and additivity (E_{add}) energies for the trimers (kJ mol⁻¹).

Complex	$\Delta E^{[a]}$	$\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)}^{[b]}$	$E_{\text{syn}}^{[c]}$	$\Delta E_{\text{dimer}(13)}^{[d]}$	$\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)} + \Delta E_{\text{dimer}(13)}^{[e]}$	$E_{\text{add}}^{[f]}$
A_HIS	-29.7	—	—	—	—	—
A_HIS'	-27.2	—	—	—	—	—
A_HIS(edge)	-22.5	—	—	—	—	—
3MeA_HIS	-51.7	—	—	—	—	—
3MeA_HIS'	-52.7	—	—	—	—	—
3MeA_HIS(edge)	-61.6	—	—	—	—	—
A_HIS ⁺	-58.4	—	—	—	—	—
A_HIS ⁺ (edge)	-66.0	—	—	—	—	—
HIS_A_HIS	-58.7	-59.4	0.7	2.2	-57.2	-1.5
HIS'_A_HIS'	-53.6	-54.4	0.8	2.2	-52.2	-1.4
HIS_A_HIS'	-56.5	-56.9	0.4	1.7	-55.2	-1.3
HIS_A_HIS(edge)	-52.5	-52.2	-0.3	-0.4	-52.6	0.1
HIS'_A_HIS(edge)	-50.8	-49.7	-1.1	0.5	-49.2	-1.6
HIS(edge)_A_HIS(edge)	-41.5	-45.0	3.5	2.6	-42.4	0.9
HIS_A_HIS ⁺	-92.8	-88.1	-4.7	-2.6	-90.7	-2.1
HIS'_A_HIS ⁺	-91.0	-85.6	-5.4	-3.2	-88.8	-2.2
HIS(edge)_A_HIS ⁺	-64.9	-80.9	16.0	11.4	-69.5	4.6
HIS_A_HIS ⁺ (edge)	-94.0	-95.7	1.7	3.2	-92.5	-1.5
HIS'_A_HIS ⁺ (edge)	-94.5	-93.2	-1.3	1.2	-92.0	-2.5
HIS(edge)_A_HIS ⁺ (edge)	-71.4	-88.5	17.1	13.6	-74.9	3.5
HIS_3MeA_HIS	-101.0	-103.5	2.5	2.2	-101.3	0.3
HIS'_3MeA_HIS'	-102.6	-105.3	2.7	2.2	-103.1	0.5
HIS_3MeA_HIS'	-102.2	-104.4	2.2	1.7	-102.7	0.5
HIS_3MeA_HIS(edge)	-109.6	-113.3	3.7	1.9	-111.4	1.8
HIS'_3MeA_HIS(edge)	-110.1	-114.3	4.2	2.2	-112.1	2.0
HIS(edge)_3MeA_HIS(edge)	-115.4	-123.2	7.8	3.9	-119.3	3.9

^[a] ΔE is the interaction energy of the dimer or trimer. ^[b] $\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)}$ is the sum of the (nearest neighbor) nucleobase–amino acid dimer interaction energies. ^[c] The synergy energy ($E_{\text{syn}} = \Delta E_{\text{trimer}(123)} - \Delta E_{\text{dimer}(12)} - \Delta E_{\text{dimer}(23)}$). ^[d] $\Delta E_{\text{dimer}(13)}$ is the interaction energy of the amino acid–amino acid dimer in the trimer geometry. ^[e] $\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)} + \Delta E_{\text{dimer}(13)}$ is the sum of all dimer interaction energies. ^[f] The additivity energy ($E_{\text{add}} = \Delta E_{\text{trimer}(123)} - \Delta E_{\text{dimer}(12)} - \Delta E_{\text{dimer}(23)} - \Delta E_{\text{dimer}(13)}$).

Examination of E_{syn} (Table 4.1) indicates that trimers involving adenine as the central nucleobase (His:A:His and His:A:His⁺ complexes) are either strengthened ($E_{\text{syn}} < 0$) or weakened ($E_{\text{syn}} > 0$) when compared to the two corresponding nucleobase–amino acid dimers. However, the magnitude of E_{syn} is smallest for the neutral His:A:His trimers,

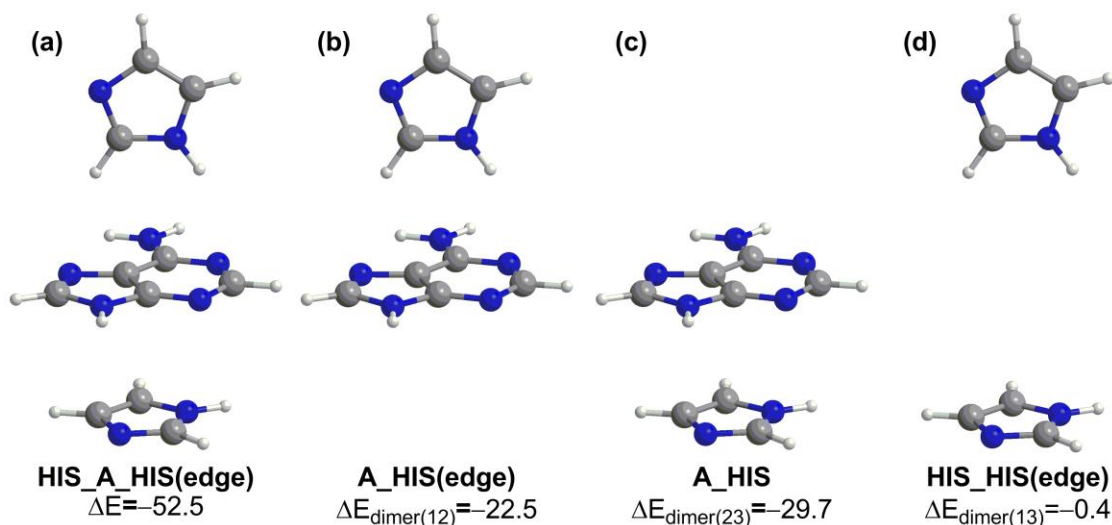


Figure 4.2. A representative example of the MP2/6-31G*(0.25) interaction energies (kJ mol⁻¹, Table 4.1) for the (a) HIS_A_HIS(edge) trimer, which contains two nearest-neighbour nucleobase–amino acid dimer interactions ((b) T-shaped adenine and histidine (HIS(edge))) and (c) stacked adenine and histidine (HIS)), as well as (d) one histidine–histidine interaction.

suggesting that π – π interactions have different properties from π^+ – π interactions. For trimers containing 3MeA, E_{syn} is positive, which indicates that the trimer interaction energy is weaker than predicted from the sum of two nucleobase–amino acid dimers. In 3MeA trimers, any given dimer interaction weakens since the cationic charge located on the central monomer becomes delocalized over the entire complex upon trimer formation. These results are consistent with the work by Kim and coworkers,¹⁶⁸ where weakening of π^+ – π interactions (methyl imidazolium–benzene) in H₂O– π^+ – π trimers (water molecule hydrogen bonded to methyl imidazolium) was observed. Contrary to 3MeA trimers, the cationic charge in His:A:His⁺ trimers is localized at one end of the complex, which is similar to previously studied cation– π trimers involving cationic point charges (such as Li⁺ or Na⁺).^{139,178,180,183,186,190,192} These works report a significant strengthening of the cation– π interaction in the trimer compared to the dimers, which is contrary to the results for π^+ – π trimers involving His⁺ ($E_{\text{syn}} > 0$, Table 4.1). Therefore, these results again support the conclusions that π^+ – π interactions are a special type of π –interaction with features unique

from cation- π and π - π complexes, and should not be overlooked in studies of noncovalent interactions.

In most trimers examined in this work, the magnitude of E_{syn} is small, which indicates that the sum of the two nearest-neighbor dimer interactions ($\Delta E_{\text{dimer}(12)} + \Delta E_{\text{dimer}(23)}$) gives an accurate estimate of the total trimer interaction energy. Specifically, the error is less than 6%. However, there are four trimers (HIS(edge)_A_HIS(edge), HIS(edge)_3MeA_HIS(edge), HIS(edge)_A_HIS⁺(edge), and HIS(edge)_A_HIS⁺) that have large E_{syn} values (8, 6, 19, and 20% errors, respectively). In these four systems, there is significant repulsion between the two amino acids (positive $\Delta E_{\text{dimer}(13)}$, Table 4.1). This repulsion arises since two acidic or two basic regions of the amino acids are directed towards one another in the trimers. This suggests that it is sometimes important to consider the $\Delta E_{\text{dimer}(13)}$ term.

The magnitude of E_{add} is small for all trimers (error is less than 7%), which reveals whether the trimer interactions can be estimated by the sum of the three pairwise interaction energies. Despite smaller additivity than synergy terms, E_{add} values of up to 4.6 kJ mol⁻¹ are obtained. It is unknown whether these energies suggest that the trimers are nonadditive or whether they arise from errors in the computational method. For example, deviations could arise due to the large BSSE corrections for these π - π and π^+ - π complexes at the level of theory implemented. Furthermore, the method for calculating the $\Delta E_{\text{dimer}(13)}$ term in the absence of the nucleobase may overestimate the amino acid-amino acid dimer interaction. However, E_{add} is less than 2 kJ mol⁻¹ for most trimers. This fact, coupled with the geometric additivity discussed in the previous section, suggests that these interactions are additive. Regardless of the nature of the additivity, the current analysis does not provide information about the individual interactions in the trimers. Specifically, it is unclear whether the nucleobase-amino acid interactions are equivalent in dimer and trimer complexes, or whether the nucleobase-amino acid interactions are different in different

sized complexes, but sum to yield an overall additive interaction. Therefore, in hopes to gain a better understanding of the interplay between nucleobase–amino acid dimers, QTAIM will be used in the following section.

4.3.3. Quantum Theory of Atoms in Molecules (QTAIM) Analysis

QTAIM can be very useful for analyzing closed-shell bonding interactions.¹⁹⁶⁻¹⁹⁸ Topological analysis of the electron density was initially used to identify the presence of hydrogen-bonding interactions through a bond path connecting a hydrogen atom to a hydrogen acceptor (or electron donor).²⁰¹ Furthermore, the maximum electron density on the interatomic surface between these two atoms (i.e. the bond critical point (BCP)) can be correlated to the hydrogen-bond strength,²⁰³ as well as the hydrogen-bond length,²⁰⁰ while the sum of the electron density at the hydrogen-bond critical points can be correlated with the stability of the complex (see for example, references 212, and 217). Therefore, it is not surprising that the vast majority of QTAIM literature on noncovalent interactions has studied hydrogen bonding. However, very few studies have applied QTAIM to stacking and T-shaped interactions.^{139,178,180,184-185,188-190,193,204-206,209-211,220}

In 2005, Zhikol et al. were the first to analyze stacking interactions with QTAIM.²⁰⁵ In this study, ten unique π – π stacked geometries of the benzene dimer with various degrees of symmetry were characterized. In all these systems, one to twelve intermolecular bond paths between the monomers were found. Intriguingly, all dimers were characterized by one, and only one, cage critical point (CCP) between the benzene rings, and it was suggested that the existence of a CCP correlates with the phenomenon of stacking. This work was also the first to suggest that the values of the electron density ($\rho(r)$) and the Laplacian ($\nabla^2\rho(r)$) at the CCP yield a quantitative relationship with the relative dimer binding energies.

Since 2005, a limited number of studies have investigated stacked or T-shaped systems with QTAIM, and each study has had a unique set of objectives. For example, the Mosquera

group compared the changes in the electron population of monomers and dimers to quantify charge transfer in the quinhydrone stacked dimer.²¹¹ In addition, the Frontera group examined CCP properties to study the interplay of stacking^{178,185} or T-shaped^{184,189} interactions between two π -systems and other noncovalent (hydrogen-bonding, cation- π , anion- π or small molecule X-H $\cdots\pi$) interactions. The systems investigated by the Frontera group had symmetry constraints, which result in only one CCP. In contrast, multiple CCPs are typically observed for systems with no symmetry.^{139,204,206,210-211,216,220} The detailed study by Matta et al.²⁰⁶ fully characterized the interactions in experimental DNA helices with a focus on identifying BCP properties between stacked base pairs, and did not examine the properties of the multiple CCPs in their complexes. Additionally, I am unaware of any studies that have investigated T-shaped interactions between two π -systems in C_1 symmetry, even though topological analysis of the electron density may provide an interesting way to confirm the presence of T-shaped interactions through the identification of distinguishing bond paths.

In this work, the BCP and CCP properties of nucleobase-amino acid dimers will be characterized in both π - π stacked and π - π T-shaped orientations to relate these findings to previous work in the literature. Subsequently, all trimer complexes will be investigated, where the topology of the electron density will be discussed in the trimers to understand how they differ from the corresponding dimers. The end goal is to gain insight into whether individual nucleobase-amino acid interactions are equivalent or distinct in dimers and trimers.

4.3.3.1. Dimer Interactions

The molecular graphs for all nucleobase-amino acid dimers considered in this study are shown in Figure 4.3, while the corresponding BCP properties used to characterize the

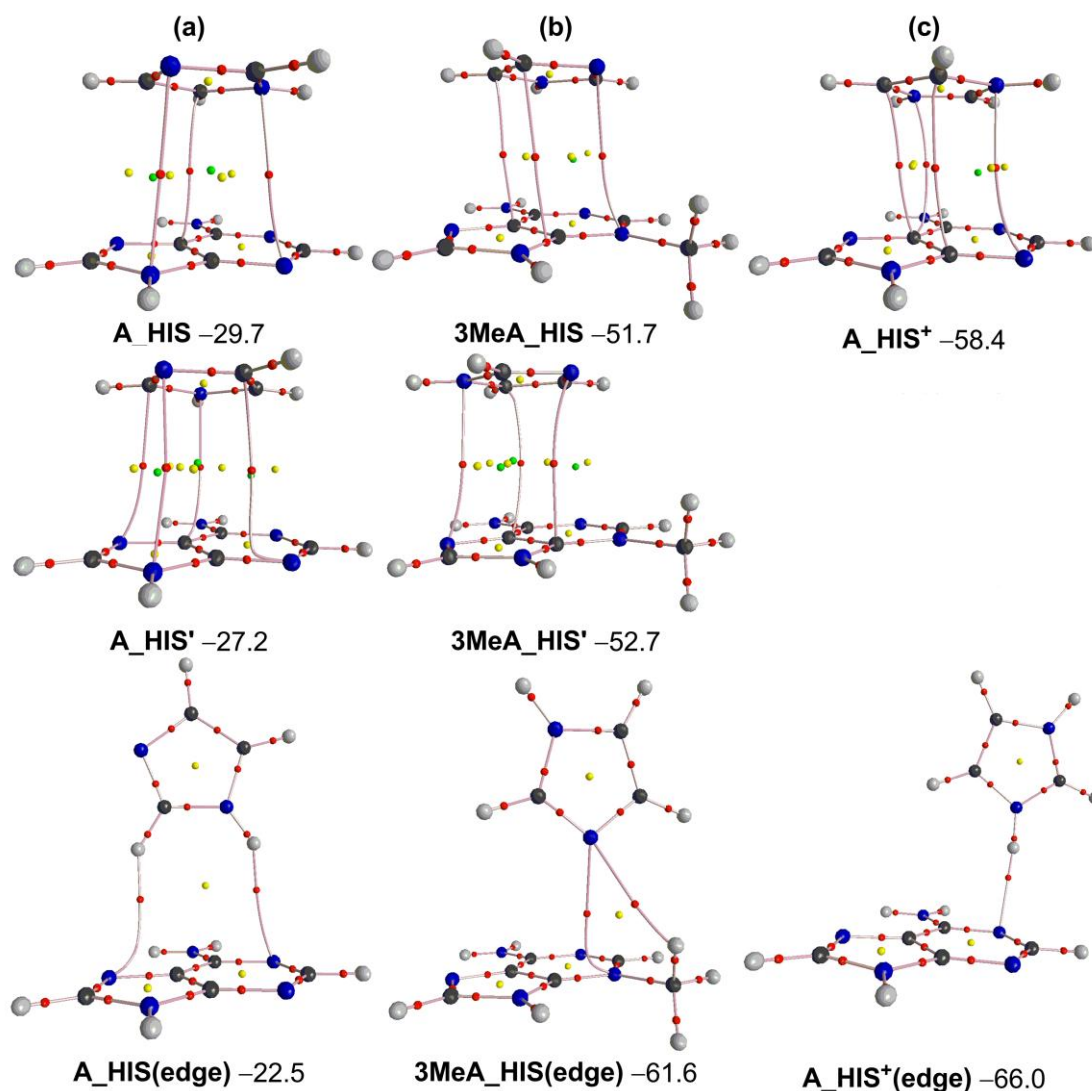


Figure 4.3. Molecular graphs and MP2/6-31G*(0.25) interaction energies (kJ mol⁻¹) for (a) adenine and histidine stacked (HIS and HIS') and T-shaped (HIS(edge)) dimers, (b) 3-methyladenine and histidine stacked (HIS and HIS') and T-shaped (HIS(edge)) dimers, and (c) adenine and protonated histidine stacked (HIS⁺) and T-shaped (HIS⁺(edge)) dimers.

intermolecular interactions are summarized in Table 4.2. This table also provides the distances between the two atoms involved in the bonding interaction (bond length, BL), as well as the corresponding bond path lengths (BPL), where their difference (BPL-BL) can be used to determine the curvature of a bond path. Large BPL-BL differences (up to 0.514 Å) suggest strain in the bonding interactions for some complexes. Although some of this strain

Table 4.2. Closed-shell bonding between nucleobase–amino acid stacked and T-shaped dimers.^[a]

Bond ^[c]	BL	BPL	BPL–BL	$\rho(r)$ ($\times 10^3$)	$\nabla^2\rho(r)$ ($\times 10^2$)	λ_1	λ_2	λ_3	ϵ	H(r)
A_HIS^[b]										
N3–N1	3.385	3.408	0.023	6.177	1.865	–0.003	–0.002	0.023	0.677	0.000
C5–C5	3.321	3.381	0.060	7.258	2.042	–0.003	–0.003	0.026	0.217	0.001
N9–N3	3.318	3.340	0.022	6.453	1.958	–0.003	–0.002	0.025	0.523	0.000
A_HIS'^[b]										
N3–C4	3.424	3.938	0.514	6.540	1.916	–0.003	–0.001	0.023	1.576	0.001
C5–N1	3.367	3.458	0.091	6.282	1.980	–0.003	–0.001	0.024	1.267	0.001
N9–N3	3.359	3.383	0.024	5.903	1.895	–0.003	–0.001	0.023	2.013	0.000
N7–C2	3.362	3.403	0.041	6.071	1.938	–0.003	–0.001	0.023	1.392	0.001
A_HIS(edge)^[b]										
N1–H1	2.739	2.780	0.041	6.207	2.269	–0.005	–0.003	0.031	0.492	0.001
N7–H2	2.714	2.919	0.205	7.263	2.573	–0.006	–0.002	0.034	1.759	0.001
3MeA_HIS^[b]										
N3–N3	3.396	3.504	0.108	6.222	1.885	–0.003	–0.001	0.023	1.937	0.000
C5–C5	3.329	3.368	0.039	6.736	2.184	–0.002	–0.001	0.025	1.146	0.001
C4–C4	3.393	3.821	0.428	6.252	2.045	–0.002	–0.001	0.023	2.538	0.001
3MeA_HIS'^[b]										
N7–N1	3.343	3.368	0.025	6.341	1.920	–0.003	–0.002	0.024	0.767	0.000
C4–N3	3.322	3.362	0.040	6.146	2.200	–0.003	–0.002	0.025	7.789	0.001
C5–C5	3.384	3.678	0.294	6.848	1.909	–0.002	–0.002	0.023	0.218	0.001
3MeA_HIS(edge)^[b]										
N3–N3	3.179	3.446	0.267	8.806	2.602	–0.006	–0.002	0.034	2.284	0.000
H3–N3	2.652	2.704	0.052	8.366	2.858	–0.007	–0.005	0.041	0.468	0.001
A_HIS⁺^[b]										
N3–N1	3.323	3.396	0.073	6.714	2.083	–0.004	–0.001	0.025	18.171	0.000
C4–C5	3.216	3.284	0.068	7.808	2.560	–0.002	–0.002	0.030	0.144	0.001
C5–C5'	3.297	3.313	0.016	7.359	2.574	–0.001	–0.001	0.028	0.813	0.001
C5–N1'	3.294	3.467	0.173	7.195	2.249	–0.004	–0.001	0.027	7.860	0.001
A_HIS⁺(edge)^[b]										
N1–H1	2.126	2.157	0.031	20.709	5.843	–0.022	–0.022	0.103	0.013	0.000

^[a] All values (electron density $\rho(r)$, Laplacian of the electron density ($\nabla^2\rho(r)$), the curvatures of the electron density (λ_1 , λ_2 , and λ_3), the bond ellipticity (ϵ), and the total electronic energy density (H(r)) are reported in atomic units (au), except for bond lengths (BL), bond path lengths (BPL), and their differences (BPL–BL), which are in angstroms (Å). ^[b] Stacked (HIS, HIS', or HIS⁺) and amino acid-edge T-shaped (HIS(edge) or HIS⁺(edge)) dimers. ^[c] Bond critical points are labelled with both atoms involved in bonding, where the first atom belongs to the nucleobase (A or 3MeA) and the second atom belongs to the amino acid (His or His⁺). See Figure 4.1 for numbering used in the present study.

may be reduced through free optimizations, these results are consistent with previous work, where (for example) highly curved bond paths (BPL–BL ranges from 0.115 to 0.565 Å) were reported for the quinhydrone stacked dimer.²¹¹ The positive values of both the Laplacian ($\nabla^2\rho(r)$) and the total energy density (H(r), Table 4.2) confirm that all intermolecular bonding considered are of the closed-shell type.

4.3.3.1.1. Stacked Dimers

QTAIM analysis of the electron density of stacked nucleobase–amino acid dimers reveals three different types of intermolecular bond paths: N–N, C–C, and N–C. The N–N bond paths in nucleobase–amino acid dimers are very similar to those in DNA nucleobase complexes,²⁰⁶ where the average N–N bond properties are comparable to the present work (in parentheses): BPL=3.486 (3.400) Å, $\rho(r)$ =0.005 (0.006) au, and $\nabla^2\rho(r)$ =0.015 (0.019) au. Similarly, the uracil–phenylalanine stacked dimer¹³⁹ has C–C and C–N bond paths with very similar properties to those observed in the present study (C–C average properties (present work in parentheses): $\rho(r)$ = 6.949×10^{-3} (7.044×10^{-3}) au, and $\nabla^2\rho(r)$ = 2.048×10^{-2} (2.219×10^{-2}) au; C–N average properties (present work in parentheses): $\rho(r)$ = 7.492×10^{-3} (6.447×10^{-3}) au, and $\nabla^2\rho(r)$ = 2.281×10^{-2} (2.057×10^{-2}) au). It should be noted that this work did not find any distinguishing differences in the bonding properties for π – π (A_HIS and A_HIS') and π^+ – π interactions (3MeA_HIS, 3MeA_HIS', and A_HIS⁺).

It has been suggested by Matta et al.²⁰⁶ that a bond critical point with $\rho(r)$ of ≈ 0.006 au can be associated with a bond energy of ~ 1 kcal mol⁻¹ (or ~ 4 kJ mol⁻¹). The authors also suggest that the cumulative effect of several weak bonding interactions leads to non-negligible stabilization energies, where very weak bonding is classified as $\rho(r) < 0.01$ au.²⁰⁶ In the present work, all BCP electron densities are very similar (≈ 0.006 – 0.008 au.) and therefore would be classified as weak bonding interactions. However, when the sum of the electron densities of all intermolecular BCPs is considered, the total BCP electron density is ≈ 0.019 – 0.029 au. Using the electron density/bond energy relationship suggested by Matta et al.,²⁰⁶ a much weaker stabilization than identified through the interaction energy analysis (Table 4.1) is obtained. This suggests that it may not be possible to describe these systems by simply considering only pairwise contacts between atoms in different monomers.²²⁵

Although the sum of the electron density at the hydrogen-bond critical points is

representative of the stability of a hydrogen-bonded complex,^{212,217} and has been previously observed for select stacked systems,²¹⁰ a similar trend is not observed for the present stacked systems. This discrepancy may arise since these dimers have different numbers of intermolecular bond paths. It is intriguing that the average BCP electron density predicts that A_HIS' (average $\rho(r)=6.199\times 10^{-3}$ au) < A_HIS (average $\rho(r)=6.629\times 10^{-3}$ au), and 3MeA_HIS (average $\rho(r)=6.403\times 10^{-3}$ au) < 3MeA_HIS' (average $\rho(r)=6.445\times 10^{-3}$ au), which corresponds to the binding energy trends. Nevertheless, this correlation could be a coincidence since the trend in binding energies for all stacked dimers cannot be predicted from the average BCP electron densities.²¹⁰

As previously mentioned, it has been proposed that cage critical points can be used to identify stacking interactions.²⁰⁵ Indeed, one to three CCPs are identified in the present C_1 symmetric stacked dimers, where the corresponding $\rho(r)$ and $\nabla^2\rho(r)$ are reported in Table 4.3. Although discussion of multiple CCPs is limited in the literature,^{188,204,211,220} close examination of published molecular graphs reveals more than one cage critical point in stacked systems of low symmetry.^{139,188,204,206,210-211,220} Since more than one CCP is present, it is difficult to relate complex stability to the cage critical point properties as previously proposed in the literature.²⁰⁵ However, the average CCP properties predict that A_HIS' (average $\rho(r)=4.616\times 10^{-3}$ au) < A_HIS (average $\rho(r)=6.646\times 10^{-3}$ au), and 3MeA_HIS (average $\rho(r)=3.937\times 10^{-3}$ au) < 3MeA_HIS' (average $\rho(r)=4.508\times 10^{-3}$ au), which again matches the trend in Table 4.1. Nevertheless, the trend in the binding energies across all stacked dimers cannot be predicted. Therefore, this work indicates that CCP properties have a weak correlation with binding strengths for C_1 symmetric systems, which is consistent with results for the uracil–phenylalanine dimer.¹³⁹

Table 4.3. Charge density ($\rho(r)$, au) and Laplacian ($\nabla^2\rho(r)$, au) at the cage critical points for nucleobase–amino acid dimers.

Dimer ^[a]	CCP Position ^[b]	$\rho(r)$ ($\times 10^3$)	$\nabla^2\rho(r)$ ($\times 10^2$)
A_HIS	C4–C5	4.257	2.067
	N7	5.034	2.025
A_HIS'	C2	4.411	1.773
	C4–C5	4.748	1.951
	N7	4.688	1.980
3MeA_HIS	C2	3.937	1.722
3MeA_HIS'	C2	4.355	1.680
	C4–C5	4.588	2.024
	N7	4.581	2.006
A_HIS⁺	C2	4.704	2.071

^[a] Stacked (HIS, HIS', or HIS⁺) and amino acid-edge T-shaped (HIS(edge) or HIS⁺(edge)) dimer orientations. ^[b] Cage critical points lie in a plane between the nucleobase and amino acid and are labelled relative to the nucleobase atoms. See Figure 4.1 for atomic numbering and Figure 4.3 for molecular graphs.

4.3.3.1.2. T-shaped Dimers

QTAIM analysis of π – π and π^+ – π T-shaped interactions reveals two types of intermolecular nucleobase–amino acid bond paths: N–N and N–H. The N–N bond path is only observed in the 3MeA_HIS(edge) dimer (Table 4.2 and Figure 4.3, bottom), where the basic N atom of histidine prefers to be in close contact with the (formally) positively charged N atom in 3-methyladenine. This dimer also has an N–H bond path connecting the basic N3 atom in histidine with the acidic H on the C3 methyl group in 3-methyladenine. In the other dimers, N–H bond paths are observed between acidic hydrogens in the monomer edge and the basic N atoms in adenine. The greater similarity is found for these bond paths and those for hydrogen-bonding compared to those for stacking interactions, confirming the larger electrostatic nature of these π – π T-shaped interactions.

Closer examination of the electron density at the N–H bond critical points (Table 4.2) indicates that these bond paths are weak (≈ 0.006 – 0.008 au for A_HIS(edge) and 3MeA_HIS(edge)). In fact, these BCP electron densities are very similar to those observed for nucleobase–amino acid stacking interactions. Indeed, even the very strong A_HIS⁺(edge) interaction (-66.0 kJ mol⁻¹), which has one N–H bond path with a BCP electron density of

0.021 au, has a weaker bond path compared to the cytosine and guanine Watson-Crick hydrogen-bonded dimer (average N-H BCP $\rho(r)$ of 0.038 au).²⁰⁶ As discussed in Chapter 3, these results also confirm that π - π T-shaped interactions have properties distinct from hydrogen-bonding interactions.

Even though the present T-shaped systems have different numbers of intermolecular bond paths, their trend in stability can be predicted by considering the sum of the electron density at the intermolecular bond critical points. Interestingly, the binding energy trends are also predicted from the average BCP electron densities. However, it is difficult to know if these trends will hold when a greater number of T-shaped interactions are examined. Additionally, in attempts to compare T-shaped and stacked dimers, a clear trend in the relative stabilities can no longer be predicted.

No cage critical points are found in the present T-shaped dimers. This is not consistent with previous work by the Frontera group that reported one CCP for (C_{2v} or C_s) symmetric T-shaped systems.^{182,187} Due to the symmetry constraints imposed in the complexes studied by Frontera et al., it is not surprising that these systems have one cage critical point (CCP), which the authors then use to characterize the noncovalent interactions present in the system. However, this work indicates that low symmetry T-shaped dimers do not necessarily have cage critical points. Therefore, further investigations must be done to understand the topology of the electron density in the same T-shaped dimers between two π -systems with and without symmetry constraints.

Although previous literature used the electron density distribution to examine the relative stability of stacked and T-shaped complexes,^{139,188,193,204-206,209-211} no clear trends are observed for these nucleobase-amino acid dimers. For example, neither the total electron density at intermolecular BCPs nor CCPs can accurately predict relative stacking strengths. Although some promise is seen when the average electron density at BCP or CCP is

considered, trends across stacked dimers containing different monomers are not correct. Since various π - π and π^+ - π interactions may involve too many relative differences in the electron density to definitively provide stability trends, this chapter proposes that more work must be done to conclusively determine how systematic changes in the geometry and size of the complex alter QTAIM predictions of complex stability. Even though these results show there is potential for predicting the relative strength of T-shaped interactions, low symmetry T-shaped dimers have no CCPs, which contrasts previous literature.^{182,187} Therefore, more work needs to be done to bridge the current gap in QTAIM analysis of T-shaped interactions, where future studies should concentrate on how symmetry alters conclusions based on the electron density.

4.3.3.2. Trimer Interactions

Since QTAIM properties have been used by many authors to examine the interplay between two noncovalent interactions in trimer complexes,^{139,178-179,183-185,188-189,191-192,194} 18 trimers were investigated in the present study, where Tables 4.4–4.6 summarize the values of the electron density ($\rho(r)$) and the Laplacian of the electron density ($\nabla^2\rho(r)$) computed at the bond critical points (stacked and T-shaped) and cage critical points (stacked only) between the nucleobase and amino acid monomers in amino acid–nucleobase–amino acid trimers. These tables also show the differences between the BCP and CCP properties for the trimer and the corresponding dimer ($\Delta\rho(r)$ and $\Delta(\nabla^2\rho(r))$).

In agreement with the geometric additivity discussed in Section 3.1, the molecular graphs for most trimers (Appendix G) are superpositions of those for the corresponding dimers (compare, for example, Figures 4.3 and 4.4). However, for six trimers, extensive searching within AIM2000,²²⁴ as well as AIMAll,²²³ was unable to identify critical points that were present in the dimers. For the HIS'_A_HIS', HIS_A_HIS', HIS'_A_HIS⁺, HIS'_A_HIS(edge)

Table 4.4. Charge density ($\rho(r)$, au) and Laplacian ($\nabla^2\rho(r)$, au) at the bond and cage critical points for His:A:His trimers, and their variation ($\Delta\rho(r)$ and $\Delta(\nabla^2\rho(r))$) with respect to the dimers.

Trimer	Dimer ^[a]	BCP or CCP ^[b]		$\rho(r)(\times 10^3)$	$\nabla^2\rho(r)(\times 10^2)$	$\Delta\rho(r)(\times 10^3)$	$\Delta(\nabla^2\rho(r))(\times 10^2)$	
HIS_A_HIS								
HIS		BCP	N3-N1	6.165	1.826	-0.012	-0.039	
		BCP	C5-C5	7.274	2.057	0.016	0.015	
		BCP	N9-N3	6.391	1.918	-0.062	-0.040	
		CCP	C4-C5	4.358	2.075	0.101	0.008	
		CCP	N7	5.054	2.003	0.020	-0.022	
HIS' _A_HIS'								
HIS'		BCP	N3-C4	6.803	1.857	0.263	-0.059	
		BCP	C5-N1	6.450	2.041	0.168	0.061	
		BCP	N9-N3	6.247	1.896	0.344	0.001	
		CCP	C2	4.382	1.768	-0.029	-0.005	
		CCP	C4-C5	4.602	1.912	-0.146	-0.039	
		CCP	N7	4.702	1.917	0.014	-0.063	
HIS_A_HIS'								
HIS		BCP	N3-N1	6.186	1.828	0.009	-0.037	
		BCP	C5-C5	7.276	2.056	0.018	0.014	
		BCP	N9-N3	6.390	1.918	-0.063	-0.040	
		CCP	C4-C5	4.357	2.077	0.100	0.010	
		CCP	N7	5.054	2.000	0.020	-0.025	
	HIS'	BCP	N3-C4	6.788	1.856	0.248	-0.060	
		BCP	C5-N1	6.496	2.043	0.214	0.063	
		BCP	N9-N3	6.246	1.897	0.343	0.002	
		CCP	C2	4.372	1.765	-0.039	-0.008	
		CCP	C4-C5	4.604	1.912	-0.144	-0.039	
		CCP	N7	4.704	1.919	0.016	-0.061	
		HIS_A_HIS(edge)						
HIS		BCP	N3-N1	6.132	1.828	-0.045	-0.037	
		BCP	C5-C5	7.268	2.054	0.010	0.012	
		BCP	N9-N3	6.317	1.918	-0.136	-0.040	
		CCP	C4-C5	4.317	2.079	0.060	0.012	
		CCP	N7	5.043	2.000	0.009	-0.025	
	HIS(edge)	BCP	N1-H1	5.889	2.201	-0.318	-0.068	
		BCP	N7-H2	7.767	2.690	0.504	0.117	
HIS' _A_HIS(edge)								
HIS'		BCP	N3-C4	6.758	1.858	0.218	-0.058	
		BCP	C5-N1	6.462	2.043	0.180	0.063	
		BCP	N9-N3	6.172	1.898	0.269	0.003	
		CCP	C2	4.355	1.767	-0.056	-0.006	
		CCP	C4-C5	4.590	1.912	-0.158	-0.039	
		CCP	N7	4.691	1.907	0.003	-0.073	
	HIS(edge)	BCP	N1-H1	5.927	2.203	-0.280	-0.066	
			BCP	N7-H2	7.736	2.691	0.473	0.118
			HIS(edge)_A_HIS(edge)					
HIS(edge)		BCP	N1-H1	5.844	2.192	-0.363	-0.077	
		BCP	N7-H2	7.691	2.688	0.428	0.115	

^[a] Stacked (HIS, HIS') and amino acid-edge T-shaped (HIS(edge)) dimers within the trimers. ^[b] Bond critical points are labelled with both atoms involved in bonding, where the first atom belongs to the nucleobase (A) and the second atom belongs to the amino acid (His). Cage critical points lie in a plane between the nucleobase and amino acid and are labelled relative to the nucleobase atoms. See Figure 4.1 for atomic numbering.

Table 4.5. Charge density ($\rho(r)$, au) and Laplacian ($\nabla^2\rho(r)$, au) at the bond and cage critical points for His:3MeA:His trimers, and their variation ($\Delta\rho(r)$ and $\Delta(\nabla^2\rho(r))$) with respect to the dimers.

Trimer	Dimer ^[a]	BCP or CCP ^[b]		$\rho(r)(\times 10^3)$	$\nabla^2\rho(r)(\times 10^2)$	$\Delta\rho(r)(\times 10^3)$	$\Delta(\nabla^2\rho(r))(\times 10^2)$
HIS_3MeA_HIS							
HIS		BCP	N3-N3	6.344	1.912	0.122	0.027
		BCP	C5-C5	6.854	2.189	0.118	0.005
		BCP	C4-C4	6.459	2.139	0.207	0.094
		CCP	C2	3.811	1.717	-0.126	-0.005
HIS'_3MeA_HIS'							
HIS'		BCP	N7-N1	6.378	1.918	0.037	-0.002
		BCP	C4-N3	6.196	2.186	0.050	-0.014
		BCP	C5-C5	6.869	1.904	0.021	-0.005
		CCP	C2	6.834	1.666	2.479	-0.014
		CCP	C4-C5	4.611	2.025	0.023	0.001
		CCP	N7	4.618	2.004	0.037	-0.002
HIS_3MeA_HIS'							
HIS		BCP	N3-N3	6.349	1.909	0.127	0.024
		BCP	C5-C5	6.844	2.195	0.108	0.011
		BCP	C4-C4	6.454	2.140	0.202	0.095
		CCP	C2	3.827	1.716	-0.110	-0.006
HIS'		BCP	N7-N1	6.406	1.916	0.065	-0.004
		BCP	C4-N3	6.206	2.184	0.060	-0.016
		BCP	C5-C5	6.871	1.902	0.023	-0.007
		CCP	C2	4.392	1.670	0.037	-0.010
		CCP	C4-C5	4.619	2.029	0.031	0.005
		CCP	N7	4.655	2.006	0.074	0.000
HIS_3MeA_HIS(edge)							
HIS		BCP	N3-N3	6.340	1.907	0.118	0.022
		BCP	C5-C5	6.821	2.208	0.085	0.024
		BCP	C4-C4	6.462	2.144	0.210	0.099
		CCP	C2	3.817	1.720	-0.120	-0.002
HIS(edge)		BCP	N3-N3	9.756	2.836	0.950	0.234
		BCP	H3-N3	8.219	2.794	-0.147	-0.064
HIS'_3MeA_HIS(edge)							
HIS'		BCP	N7-N1	6.340	1.923	-0.001	0.003
		BCP	C4-N3	6.203	2.194	0.057	-0.006
		BCP	C5-C5	6.866	1.911	0.018	0.002
		CCP	C2	4.391	1.675	0.036	-0.005
		CCP	C4-C5	4.608	2.025	0.020	0.001
		CCP	N7	4.600	2.005	0.019	-0.001
HIS(edge)		BCP	N3-N3	9.827	2.861	1.021	0.259
		BCP	H3-N3	8.297	2.821	-0.069	-0.037
HIS(edge)_3MeA_HIS(edge)							
HIS(edge)		BCP	N3-N3	9.857	2.853	1.051	0.251
		BCP	H3-N3	8.296	2.823	-0.070	-0.035

^[a] Stacked (HIS, HIS') and amino acid-edge T-shaped (HIS(edge)) dimers within the trimers. ^[b] Bond critical points are labelled with both atoms involved in bonding, where the first atom belongs to the nucleobase (A) and the second atom belongs to the amino acid (His). Cage critical points lie in a plane between the nucleobase and amino acid and are labelled relative to the nucleobase atoms. See Figure 4.1 for atomic numbering.

Table 4.6. Charge density ($\rho(r)$, au) and Laplacian ($\nabla^2\rho(r)$, au) at the bond and cage critical points for His:A:His⁺ trimers, and their variation ($\Delta\rho(r)$ and $\Delta(\nabla^2\rho(r))$) with respect to the dimers.

Trimer	Dimer ^[a]	BCP or CCP ^[b]		$\rho(r)(\times 10^3)$	$\nabla^2\rho(r)(\times 10^2)$	$\Delta\rho(r)(\times 10^3)$	$\Delta(\nabla^2\rho(r))(\times 10^2)$
HIS_A_HIS ⁺							
	HIS	BCP	N3-N1	6.117	1.830	-0.060	-0.035
		BCP	C5-C5	7.308	2.040	0.050	-0.002
		BCP	N9-N3	6.263	1.902	-0.190	-0.056
		CCP	C4-C5	4.300	2.077	0.043	0.010
		CCP	N7	5.085	1.948	0.051	-0.077
	HIS ⁺	BCP	C4-C5	7.854	2.560	0.046	0.000
		BCP	C5-C5'	7.412	2.544	0.053	-0.030
		BCP	C5-N1'	7.216	2.241	0.021	-0.008
		CCP	C2	4.751	2.059	0.047	-0.012
	HIS'_A_HIS ⁺						
	HIS'	BCP	N3-C4	6.778	1.851	0.238	-0.065
		BCP	C5-N1	6.441	2.040	0.159	0.060
		BCP	N9-N3	6.164	1.883	0.261	-0.012
		CCP	C2	4.365	1.749	-0.046	-0.024
		CCP	C4-C5	4.541	1.907	-0.207	-0.044
	HIS ⁺	BCP	C4-C5	7.850	2.561	0.042	0.001
		BCP	C5-C5'	7.389	2.553	0.030	-0.021
		BCP	C5-N1'	7.220	2.240	0.025	-0.009
		CCP	C2	4.767	2.061	0.063	-0.010
	HIS(edge)_A_HIS ⁺						
	HIS(edge)	BCP	N1-H1	5.779	2.184	-0.428	-0.085
		BCP	N7-H2	7.642	2.680	0.379	0.107
	HIS ⁺	BCP	N3-N1	6.696	2.082	-0.018	-0.001
		BCP	C4-C5	7.802	2.558	-0.006	-0.002
		BCP	C5-C5'	7.365	2.552	0.006	-0.022
		BCP	C5-N1'	7.161	2.246	-0.034	-0.003
		CCP	C2	4.717	2.061	0.013	-0.010
		HIS_A_HIS ⁺ (edge)					
	HIS	BCP	N3-N1	6.175	1.840	-0.002	-0.025
		BCP	C5-C5	7.332	2.029	0.074	-0.013
		BCP	N9-N3	6.226	1.896	-0.227	-0.062
		CCP	C4-C5	4.279	2.085	0.022	0.018
		CCP	N7	4.986	1.907	-0.048	-0.118
	HIS ⁺ (edge)	BCP	N1-H1	19.707	5.585	-1.002	-0.258
HIS'_A_HIS ⁺ (edge)							
	HIS'	BCP	N3-C4	6.777	1.852	0.237	-0.064
		BCP	C5-N1	6.491	2.036	0.209	0.056
		BCP	N9-N3	6.176	1.892	0.273	-0.003
		CCP	C2	4.343	1.759	-0.068	-0.014
		CCP	C4-C5	4.560	1.923	-0.188	-0.028
		CCP	N7	4.667	1.891	-0.021	-0.089
	HIS ⁺ (edge)	BCP	N1-H1	20.507	5.760	-0.202	-0.083
	HIS(edge)_A_HIS ⁺ (edge)						
	HIS(edge)	BCP	N1-H1	5.538	2.118	-0.669	-0.151
		BCP	N7-H2	7.822	2.784	0.559	0.211
	HIS ⁺ (edge)	BCP	N1-H1	20.665	5.915	-0.044	0.072

^[a] Stacked (HIS, HIS') and amino acid-edge T-shaped (HIS(edge)) dimers within the trimers. ^[b] Bond critical points are labelled with both atoms involved in bonding, where the first atom belongs to the nucleobase (A) and the second atom belongs to the amino acid (His). Cage critical points lie in a plane

between the nucleobase and amino acid and are labelled relative to the nucleobase atoms. See Figure 4.1 for atomic numbering.

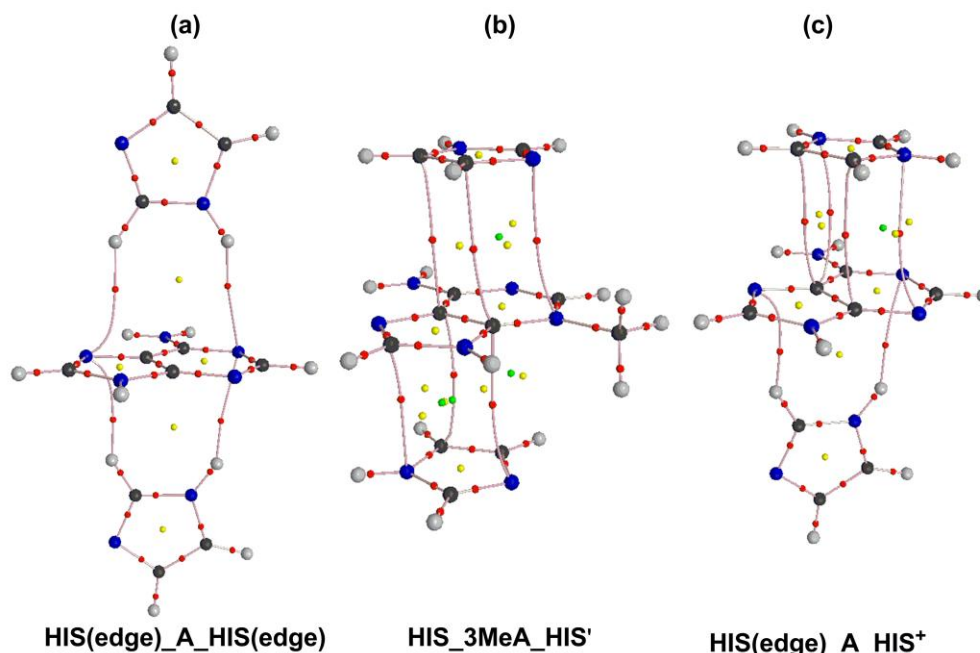


Figure 4.4. Molecular graphs for the (a) HIS(edge)_A_HIS(edge) trimer where one histidine is T-shaped (HIS(edge)) and the other histidine is T-shaped (HIS(edge)) relative to adenine, (b) HIS_3MeA_HIS' trimer where one histidine is stacked (HIS) and the other histidine is flipped prior to stacking with 3-methyladenine (HIS'), and (c) HIS(edge)_A_HIS⁺ trimer where histidine is T-shaped (HIS(edge)) and protonated histidine is stacked (HIS⁺) relative to adenine.

and HIS'_A_HIS⁺(edge) trimers, the bond path connecting N7 of adenine and C2 of histidine in the HIS'_A interaction were not able to be characterized. Also, in the HIS_A_HIS⁺ and HIS'_A_HIS⁺ trimer, the bond path connecting N3 of adenine and N1 of protonated histidine in the A_HIS⁺ interaction was not possible to characterize. In HIS'_A_HIS⁺, the CCP near N7 for the HIS'_A interaction was also not characterized. Although the Poincaré-Hopf relationship^{196-198,c} is satisfied for all trimers, this condition does not verify that critical points were not missed.¹⁹⁶⁻¹⁹⁸ Therefore, it is not clear whether missing critical points indicate changes in the electron densities between monomers in dimers and trimers, or whether this work was simply unsuccessful in finding critical points on very disperse

^c The Poincaré-Hopf relationship states that the number of nuclear critical points – number of bond critical points + number of ring critical points – number of cage critical points must equal 1 for an isolated system.

electron density surfaces.

Examination of Tables 4.4–4.6 reveals inconsistencies in the present QTAIM analysis and the interaction energy decomposition (Table 4.1). For example, in the HIS(edge)_A_HIS(edge) trimer (Figure 4.4a), E_{syn} and E_{add} suggest that the T-shaped interactions in the trimer are weaker than in the corresponding dimer. However, the BCP properties indicate that the electron density in the N1–H1 bond path is weaker and the N7–H2 bond path is stronger in the trimer, and the overall changes in the electron density (0.00013 au) suggest this trimer should exhibit stronger binding than predicted from the sum of the dimer interactions. Additionally, the calculated binding strengths suggest that the HIS_3MeA_HIS' trimer (Figure 4.4b) is weaker than predicted by the dimer interaction energies (Table 4.1), while the overall magnitudes of the electron densities and Laplacian differences (Table 4.5) suggest a stronger trimer. However, both the BCP and CCP properties indicate that the 3MeA_HIS' interaction is stronger in this trimer. BCP properties for 3MeA_HIS indicate a stronger stacking interaction in the trimer, while the CCP properties indicate a weaker stacking interaction. Similarly, the HIS(edge)_A_HIS⁺ trimer (Figure 4.4c) has a less than additive interaction energy (Table 4.1), but the overall magnitudes of the electron densities and Laplacian differences suggest a stronger trimer. Furthermore, QTAIM suggests that the HIS(edge)_A T-shaped interaction is weaker in the trimer, but the BCP properties suggest a weaker A_HIS⁺ stacking interaction in the trimer, while the CCP properties suggest a stronger interaction. Therefore, depending on the trimer considered, QTAIM results may or may not be in agreement with previous interaction energy decomposition and it is still unclear whether BCP or CCP properties of the dimers and trimers should be compared.

For all trimers investigated, the magnitude of the difference between the dimer and trimer BCP and CCP properties is extremely small. It is still not clear if these differences are

too small to be conclusive within the errors of the computational methods implemented,^{193,220} or if real changes in stacked and T-shaped systems are simply too subtle to detect with certainty. Indeed, there is not a clear consensus in the literature if QTAIM results like those presented in this chapter are indicative of additive interactions.^{185,188,191,193} This is partially a result of few investigations on π - π and π^+ - π stacking and T-shaped interactions.^{139,178,180,184-185,188-190,193,204-206,209-211,220} Therefore, this work proposes that more studies are required to clarify how QTAIM can improve the understanding of whether these interactions change in dimer and trimer systems.

It is apparent from the literature that QTAIM can provide powerful information about hydrogen-bonding interactions, which is likely due to the large electron density shared between two monomers with very specific atomic contacts. However, since the small electron densities are delocalized over the entire π -system in stacked and T-shaped complexes, several pairwise contacts are described by a QTAIM analysis. In reality, these π - π systems are difficult to describe with specific atomic contacts between the two monomers, and care should be taken when applying QTAIM analysis for these types of interactions.^{220,225} Therefore, additional studies should develop new methods that are sensitive to disperse electron densities, and able to identify and quantify π - π and π^+ - π stacking and T-shaped interaction changes in dimers and trimers.

4.4. Conclusions

Due to the potential importance of the interplay between noncovalent interactions in nature, this work investigated the geometric and energetic additivity in amino acid-nucleobase-amino acid trimers containing adenine or its (cationic) damaged counterpart, 3-methyladenine, and histidine, in both the neutral and protonated forms. For six test trimers, extensive scans of the PES reveal that both stacked and T-shaped interactions, as well as both π - π and π^+ - π interactions, exhibit geometric additivity. Subsequently, to

determine the energetic additivity, the synergy (E_{syn}) and the additivity (E_{add}) energy were examined. E_{syn} reveals that the sum of the two nucleobase–amino acid interactions is a fairly good estimate of the total trimer interaction energy. However, an even better estimate of the trimer interaction energy is obtained when the interaction between the two amino acids ($\Delta E_{\text{dimer}(13)}$) is also taken into account (E_{add}). Additionally, E_{syn} and E_{add} indicate that $\pi^+-\pi$ interactions are quite different from $\pi-\pi$ interactions, as well as the cation– π interactions (involving a cationic point charge) typically examined in trimers. Therefore, the present results reemphasize the previous work of Kim and coworkers,¹⁶⁸ which proposed that $\pi^+-\pi$ interactions are a unique type of noncovalent interaction.

The generally small magnitude of E_{add} ($< 2 \text{ kJ mol}^{-1}$) suggests that these interactions are additive. Nevertheless, this interaction energy analysis does not reveal whether the nucleobase–amino acid interactions are equivalent in dimers and trimers, or whether the nucleobase–amino acid interactions differ in different sized complexes but sum to yield an overall additive interaction. Although QTAIM has shown promise for investigating the interplay of various interactions in trimers,^{139,178-179,183-185,188-189,191-194} conclusions from the current QTAIM analysis and interaction energy evaluation are inconsistent. Furthermore, the magnitude of the differences between the dimer and trimer BCP and CCP properties are extremely small and cannot be expected to give concrete descriptions of the changes (if any) between the dimers and trimers.^{191,218} Due to the limited number of stacking and T-shaped QTAIM investigations in the literature, this chapter proposes that more studies are required to clarify how QTAIM can improve the understanding of the differences between $\pi-\pi$ and $\pi^+-\pi$ interactions in dimers and trimers. Furthermore, close examination of the literature indicates that there is no consensus on which QTAIM properties best describe these disperse interactions and should be analyzed to identify and predict the stability of $\pi-\pi$ stacked and T-shaped interactions.^{139,188,193,204-206,209-211} Therefore, this chapter proposes

that more work needs to be done to determine how the geometry, symmetry, and system size alter the QTAIM properties. Finally, the small intermolecular electron densities in stacked and T-shaped systems are delocalized over the entire π -system, which makes it difficult to describe these interactions through specific atomic contacts between two monomers.²²⁵ Therefore, additional studies must strive to develop new methods that are sensitive enough to identify and quantify differences in π - π and π^+ - π stacking and T-shaped interactions in dimer and trimer systems.

This chapter illustrates that the dimer interactions examined in Chapters 2 and 3 are pertinent for understanding the noncovalent interactions observed in larger DNA-protein complexes. Indeed, CCSD(T)/CBS calculations on nucleobase-amino acid dimers illustrated the importance of the fundamentally different π - π and π^+ - π interactions used by AAG. However, it must now be determined how these interactions contribute to the excision mechanism used by this unique DNA glycosylase, which is the focus of the remaining work presented in this thesis.

Chapter 5. The Assessment of Density Functionals for DNA-Protein Stacking and T-shaped Interactions^a

5.1. Introduction

The previous chapters in this thesis illustrate the importance of studying π - π interactions, where calculations have provided insights into how these interactions can be significant in both the recognition and binding steps of AAG. However, this thesis is ultimately focused on studying the glycosidic-bond cleavage mechanism facilitated by AAG, and the roles played by the amino acids with conjugated π -rings in this catalytic process. As discussed in Section 1.5, promising computational approaches for studying enzymes involve hybrid techniques (such as QM/MM or ONIOM). Most of the current QM/MM and ONIOM studies on enzymatic systems use density functional theory (DFT) to describe the quantum mechanical region due to its greater efficiency compared with popular wavefunction-based approaches (see, for example, references 226–240). The most common density functional used in hybrid methods is arguably B3LYP, which has been used for a wide variety of systems.^{227-228,231,233-235,237-241} Despite the good performance of B3LYP for a range of systems and properties, it generally underestimates barrier heights,²⁴² and does not provide an accurate description of dispersion interactions. Consequently, this functional should not be used to describe high-level regions of enzymes that rely heavily on dispersion dominated interactions (such as π - π stacking, $X-H\cdots\pi$ ($X=C, N, S, O$), $lp-\pi$, and/or (edge-to-face) T-shaped contacts). Therefore, until recently, studies on systems that include these types of noncovalent interactions were limited to *ab initio* electron correlation methods (such as

^a Reprinted with permission from Rutledge, L. R.; Wetmore, S. D. *Can. J. Chem.* **2010**, *88*, 815–830. Copyright 2010 Canadian Science Publishing or its licensors.

MP2), which are relatively computationally inefficient and therefore ultimately lead to the implementation of small model systems.

Fortunately, recent work in the development of density functional techniques has concentrated on methods capable of describing dispersion interactions (see, for example, references 84, 123, 125, and 242–253). Indeed, a recent review discusses the description of dispersion interactions by density functional theory.⁸⁴ Many approaches for including dispersion have emerged, and it is very important to test each functional for the specific systems of interest. As a result, an abundance of benchmarking studies have emerged in the literature (such as references 117, 119, 122, 124, 126–129, 132, and 254–267) where many use the high-level (CCSD(T)/CBS) data sets of Hobza and co-workers⁸⁷ to determine the accuracy of new density functionals for noncovalent interactions (see references 122, 127–129, 132, 258–259, and 263 for examples). Nevertheless, these test sets,⁸⁷ as well as others (such as those examined in references 117, 119, 255–257, 260–261, and 264–265), do not include the DNA–protein interactions that are important for AAG. However, the π – π and π^+ – π stacking and T-shaped interactions examined in this thesis, as well as the protonated histidine–natural nucleobase calculations examined by the Wetmore group,²²¹ present an excellent test set of high-level data to examine the performance of a variety of efficient methods for use in ONIOM or QM/MM calculations that are also capable of describing dispersion interactions.

Therefore, the present chapter uses this large test set of DNA–protein interactions to investigate the performance of a number of density functional methods. The hope is to identify an efficient method and basis set combination that is currently readily available for describing the binding strengths and potential energy surfaces of π – π stacking and T-shaped DNA–protein interactions. This study first reports an interaction energy analysis of a variety of density functionals in the current literature for the 129 nucleobase–amino acid

dimer interactions identified in this thesis and previously in the Wetmore group.²²¹ This chapter also investigates how select density functional methods describe the potential energy surfaces of three representative stacked and three representative amino acid-edge T-shaped dimers. This work is imperative for understanding how current density functionals describe DNA–protein π – π interactions in both minimum and nonminimum regions of the potential energy surfaces, which is rarely examined in the literature.¹¹⁹ It is also critical to understand how these methods describe both the energies and structures of π – π systems in order to accurately model the enzymatic reaction pathway of AAG.

5.2. Computational Details

As discussed in Chapters 2 and 3, the strongest stacked and T-shaped interactions as identified from MP2/6-31G*(0.25) potential energy surface scans were examined in this study. Specifically, nucleobase–amino acid dimers involving: (1) the four amino acids with conjugated π -rings and the five natural nucleobases, (2) the (cationic) alkylated damaged nucleobase, 3-methyladenine (3MeA) and the amino acids with conjugated π -rings; and (3) the five natural nucleobases and protonated histidine (HIS⁺)²²¹ were previously investigated at the CCSD(T)/CBS level of theory, and were used as a benchmark in this chapter. Particularly, the protonated histidine dimers examined by the Wetmore group²²¹ were included in the present test set in order to balance the total number of π – π and π^+ – π interactions, which were previously discussed to be important due to their fundamentally different attractive forces. Indeed, for the same reasons, the interactions involving ϵ A (discussed in Chapter 3) were excluded in this work due to their similarity to the other π – π data. This leads to 47 stacked and 82 T-shaped orientations (29 amino acid-edge and 53 nucleobase-edge dimers).

In the present work, a variety of density functionals that were previously shown to be promising for noncovalent interactions were tested against the 129 nucleobase–amino acid

CCSD(T)/CBS dimer interaction energies. Specifically, MPWB1K,²⁶⁸ M05-2X,²⁶⁹ M06-L,²⁷⁰ M06-2X,²⁵⁰ PBE-D,¹²³ BLYP-D,¹²³ TPSS-D,¹²³ and B97-D¹²³ were considered. For comparison, PBE, BLYP and TPSS were also considered without Grimme's dispersion correction. Additionally, B3LYP was also included due to the popularity of this approach in QM/MM and ONIOM hybrid calculations on enzymatic systems.^{225-226,229,231-233,235-239} All functionals were tested with a variety of double-zeta Pople's and Dunning's basis sets (6-31G(d), 6-31G(d,p), 6-31+G(d,p), cc-pVDZ, aug-cc-pVDZ).^b Most benchmarking studies test the performance of these functionals using basis sets for which they were originally designed. However, since these basis sets are typically large (see, for example, references 117, 119, 126, 132, 255, 260, 262, 264, and 266), this work focuses on those that are practical for enzymatic systems, where the intended application is full optimizations of enzyme-catalyzed reactions using hybrid methods.

To provide a greater understanding of the relative performance of the chosen DFT functionals, MP2 was also included for the 129 nucleobase–amino acid dimers. Due to the vast literature that has studied noncovalent complexes with MP2, the shortfalls of this method are well known, and therefore MP2 provides a good quality comparison for other methods. Additionally, the double-hybrid density functionals B2PLYP²⁴⁴ and mPW2PLYP^{127,246} were considered. Although Grimme's dispersion correction was originally designed for other functionals,¹²³ this empirical dispersion term has also been applied to these double-hybrid functionals^{125,244} to yield B2PLYP-D and mPW2PLYP-D. Although these methods are likely not practical for studying large enzymatic systems, these functionals will provide a worthy comparison to the other methods tested in this chapter due to their promise for reliably describing noncovalent π – π interactions.^{125,244}

^b PBE, BLYP, and TPSS calculations (with and without dispersion corrections) with the aug-cc-pVDZ basis set did not converge after 120 microiterations in the SCF cycle using GAMESS. Owing to the computational efficiencies of these methods, which are currently out of reach for use in hybrid optimizations, no further attempts to obtain SCF convergence were made.

In addition to active-site contacts, noncovalent π - π interactions should be accurately described throughout the entire enzymatic model. Therefore, the performance of the AMBER molecular mechanics method was also examined.²⁷¹ AMBER was selected since it was originally designed to describe both DNA and protein systems,²⁷¹ and is commonly used in hybrid techniques (see examples in references 226, 228–233, 236–237, and 272). To be consistent with the original AMBER design, HF/6-31G(d) ESP charges were calculated and used to describe each monomer, which are truncated versions of those originally used to develop the force field.²⁷¹ AMBER atom types were assigned according to the original AMBER manuscript.²⁷¹ In the nucleobase models, a hydrogen atom replaces the sugar-phosphate backbone, and was defined with the H atom type. In the case of the amino acids, this hydrogen atom was defined as H4 for histidine (neutral and protonated) and tryptophan, and HA for phenylalanine and tyrosine. ANTECHAMBER (Version 1.0)²⁷³ was used to define the atom types and parameters (Appendix H) for the damaged base, 3-methyladenine. Furthermore, since PM3 and AM1 are frequently used to describe the lower-level regions of ONIOM calculations (for example, see references 227, 234, 238, and 274–277), these semi-empirical methods, as well as the recently proposed PM6 method,²⁷⁸ were also included in this work.

All calculations were performed with Gaussian 09²²² with the exception of PBE, BLYP and TPSS (with and without dispersion corrections), which were performed with GAMESS.²⁷⁹ Despite reports that default grid sizes for various DFT methods can lead to false artifacts in the description of noncovalent interactions,²⁸⁰ the default grids in Gaussian 09 and GAMESS were used. Additionally, all interaction energies were calculated without BSSE corrections¹⁴³ (with the exception of MP2) since the goal of this work is to understand how these functionals describe noncovalent interactions in hybrid approaches, where large integration grid sizes and BSSE-free optimizations are not currently feasible.

5.3. Results and Discussion

The present study focuses on identifying suitable methodologies for hybrid QM/MM or ONIOM calculations on enzyme-catalyzed reactions, such as the AAG mechanism, that involve noncovalent π - π substrate-active site interactions. In this light, the ability of a variety of DFT functional and basis set combinations, as well as some semi-empirical and molecular mechanics methods, to reproduce CCSD(T)/CBS interaction energies for the test set of 129 π - π stacked and T-shaped nucleobase-amino acid dimers was investigated. Due to the large number of dimers and methodologies considered, the results are reported in terms of the mean unsigned error (MUE) and mean signed error (MSE) with respect to the CCSD(T)/CBS results. The largest absolute difference (MAX) and the largest percent difference (MAX %) from CCSD(T)/CBS observed among the dimers considered is also presented. Initially, the performance of the methods for each of the two main types of π - π interactions (stacking and T-shaped) considered will be discussed and subsequently summarize the overall performance of these methods for both noncovalent interactions, as well as the relative performance for dimers involving neutral and cationic monomers. Furthermore, in order to assess the ability of various functionals to accurately describe an extended portion of the potential energy surface, PES scans of select dimers will be considered for the methods that best describe the 129 dimer interaction energies with the AAG large-model goal in mind.

5.3.1. Calculation of Accurate Interaction Energies

5.3.1.1. Stacking Interactions

This section will begin by discussing the performance of MP2 with the small basis sets considered in the present work, which will illustrate how this widely used method for stacking depends on the basis set used for the systems of interest. This data will also

provide a useful reference point for discussing the basis set dependence of other methods. As previously mentioned, this chapter considers two different basis set designs of double-zeta quality since the end goal of this work is to use these methods to study enzyme-catalyzed reactions through full (hybrid) optimizations. As previously noted in the literature,¹⁰⁹ MP2 does not adequately recover CCSD(T)/CBS stacking energies in the absence of diffuse functions (6-31G(d), 6-31G(d,p), cc-pVDZ), while inclusion of diffuse functions improves the quality of the results (Table 5.1). Nevertheless, when a modified basis set (6-31G*(0.25)) that was designed to study stacking interactions between the DNA nucleobases is considered,^{109,111,113} both the MUE and MSE significantly decrease, and the MAX and MAX % drastically decrease. These results reemphasize that the 6-31G*(0.25) modified basis set provides an excellent description of DNA-protein π - π stacking interactions, and outperforms even the commonly used aug-cc-pVDZ basis set.

As previously shown in the literature, DFT functionals traditionally used in a variety of applications (structure, kinetics, hydrogen-bond strengths) do not accurately describe π - π stacking interactions (Table 5.1).⁸⁴ For stacking between nucleobase and amino acid monomers, this includes the widely used B3LYP functional. This result emphasizes that this functional should be cautiously used in hybrid approaches for studying enzyme-catalyzed reactions since many high-level regions contain π - π contacts. Furthermore, B3LYP should clearly not be used when stacking interactions have been proposed to have direct implications in substrate recognition or catalysis.

Although PBE, BLYP and TPSS also fail to recover the correct CCSD(T)/CBS stacking energies, the performance of these functionals drastically improves when Grimme's dispersion correction is included (Table 5.1). B97-D also performs very well, which further testifies to the usefulness of empirical dispersion corrections in functional design. Other

Table 5.1. Mean unsigned error(MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 47 nucleobase–amino acid stacked dimers.

Method	Basis Set	MUE	MSE	MAX	MAX %
MP2 ^[a]	6-31G*(0.25)	2.2	0.3	6.0	11.4
	6-31G(d)	12.7	12.7	19.4	-58.0
	6-31G(d,p)	12.2	12.2	18.2	-54.8
	cc-pVDZ	8.8	8.8	12.8	-39.2
	6-31+G(d,p)	4.5	4.5	7.5	-22.8
	aug-cc-pVDZ	5.0	-5.0	10.0	35.2
B3LYP	6-31G(d)	26.8	26.8	39.9	-133.2
	6-31G(d,p)	26.8	26.8	39.9	-132.5
	cc-pVDZ	27.5	27.5	42.9	-135.3
	6-31+G(d,p)	31.1	31.1	47.2	-156.2
	aug-cc-pVDZ	30.3	30.3	45.3	-149.1
PBE	6-31G(d)	20.9	20.9	30.4	-100.7
	6-31G(d,p)	20.8	20.8	30.1	-99.8
	cc-pVDZ	20.5	20.5	31.4	-97.3
	6-31+G(d,p)	23.3	23.3	34.8	-114.6
PBE-D	6-31G(d)	3.0	-3.0	8.4	21.5
	6-31G(d,p)	3.1	-3.1	8.6	21.3
	cc-pVDZ	3.1	-3.1	8.6	21.3
	6-31+G(d,p)	0.9	-0.6	4.2	14.0
BLYP	6-31G(d)	32.3	32.3	46.7	-152.2
	6-31G(d,p)	32.2	32.2	46.6	-151.4
	cc-pVDZ	33.1	33.1	50.0	-156.0
	6-31+G(d,p)	38.1	38.1	55.9	-181.4
BLYP-D	6-31G(d)	6.0	-6.0	12.3	25.1
	6-31G(d,p)	6.1	-6.1	12.4	24.8
	cc-pVDZ	5.2	-5.2	11.0	25.3
	6-31+G(d,p)	1.0	-0.2	3.7	9.3
TPSS	6-31G(d)	26.8	26.8	38.9	-127.4
	6-31G(d,p)	26.7	26.7	38.8	-126.7
	cc-pVDZ	26.1	26.1	39.9	-122.2
	6-31+G(d,p)	29.2	29.2	43.4	-141.1
TPSS-D	6-31G(d)	5.1	-5.1	11.2	23.7
	6-31G(d,p)	5.2	-5.2	11.4	23.5
	cc-pVDZ	5.8	-5.8	11.9	25.5
	6-31+G(d,p)	2.7	-2.7	7.1	16.5
B97-D	6-31G(d)	4.7	-4.7	10.1	23.8
	6-31G(d,p)	4.8	-4.8	10.2	23.6
	cc-pVDZ	4.8	-4.8	9.2	24.6
	6-31+G(d,p)	1.1	-1.0	4.1	13.8
	aug-cc-pVDZ	2.2	-2.2	5.8	18.4
MPWB1K	6-31G(d)	10.4	10.4	15.9	-52.8
	6-31G(d,p)	10.3	10.3	15.8	-52.5
	cc-pVDZ	9.5	9.5	14.9	-46.4
	6-31+G(d,p)	11.3	11.3	17.2	-61.2
	aug-cc-pVDZ	10.1	10.1	15.0	-49.9
M05-2X	6-31G(d)	4.5	4.4	8.8	-30.4
	6-31G(d,p)	4.4	4.3	8.7	-29.9
	cc-pVDZ	3.6	3.5	6.7	-25.4
	6-31+G(d,p)	4.0	3.9	8.0	-31.3

M06-2X	aug-cc-pVDZ	2.5	2.3	5.5	-19.1
	6-31G(d)	1.9	-1.5	5.2	13.1
	6-31G(d,p)	1.9	-1.5	5.1	13.5
	cc-pVDZ	2.5	-2.5	6.2	15.1
	6-31+G(d,p)	2.2	-2.1	4.4	14.3
M06-L	aug-cc-pVDZ	3.3	-3.3	7.0	17.8
	6-31G(d)	2.8	2.7	5.1	-17.0
	6-31G(d,p)	2.6	2.6	4.9	-15.8
	cc-pVDZ	2.3	2.2	4.4	-12.2
	6-31+G(d,p)	2.0	1.9	4.1	-13.6
B2PLYP	aug-cc-pVDZ	1.3	1.1	3.5	-12.6
	6-31G(d)	26.4	26.4	40.0	-135.8
	6-31G(d,p)	26.4	26.4	39.9	-135.2
	cc-pVDZ	27.2	27.2	43.0	-139.4
	6-31+G(d,p)	30.8	30.8	47.4	-160.5
B2PLYP-D	aug-cc-pVDZ	29.7	29.7	45.0	-151.7
	6-31G(d)	9.3	9.3	14.7	-55.6
	6-31G(d,p)	9.3	9.3	14.5	-55.1
	cc-pVDZ	10.2	10.2	16.3	-59.3
	6-31+G(d,p)	13.7	13.7	20.6	-80.3
mPW2PLYP	aug-cc-pVDZ	12.6	12.6	18.6	-71.5
	6-31G(d)	21.0	21.0	32.6	-111.5
	6-31G(d,p)	21.0	21.0	32.5	-111.0
	cc-pVDZ	22.0	22.0	35.8	-116.2
	6-31+G(d,p)	25.7	25.7	40.6	-138.2
mPW2PLYP-D	aug-cc-pVDZ	24.7	24.7	38.2	-129.7
	6-31G(d)	8.6	8.6	14.2	-53.3
	6-31G(d,p)	8.5	8.5	14.0	-52.7
	cc-pVDZ	9.6	9.6	16.5	-57.9
	6-31+G(d,p)	13.2	13.2	21.1	-80.0
	aug-cc-pVDZ	12.3	12.3	18.8	-71.4
AM1		42.3	42.3	66.1	-184.4
PM3		41.8	41.8	69.3	-177.1
PM6		21.2	21.2	37.5	-86.7
AMBER		3.2	2.5	12.4	-29.5

^[a] MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

tactics have also been proposed to develop DFT functionals for noncovalent π - π interactions, such as dispersion correcting potentials (DCPs).¹²⁹ Alternatively, more commonly used functionals (such as meta generalized gradient approximation (meta-GGA) or hybrid-meta GGA methods MPWB1K,²⁶⁸ M05-2X,²⁶⁹ M06-L,²⁷⁰ M06-2X,²⁵⁰) designed for these interactions were also parameterized to describe other properties (for instance, barrier heights or transition metals). Among these functional, MPWB1K does not perform as well as PBE-D for DNA-protein π - π interactions. However, newer functionals (M05-2X, M06-L, M06-2X) designed by the Truhlar group show improved performance. Indeed, the

M06-L and M06-2X functionals lead to the smallest MUE and MSE among these methods.

The relative performance of the Pople's (6-31G) and Dunning's (cc-pVDZ) basis sets depends on the functional form considered. However, in most instances, the difference is minimal when the performance of basis sets containing the same types of (polarization, diffuse) functions are compared. Methods that do not perform well for stacking (B3LYP, PBE, BLYP, TPSS), perform even worse as the basis set size increases. Although there is not a large difference in performance as polarization functions are added to the hydrogen atoms, the description of stacking becomes much poorer when diffuse functions are included for these methods. On the contrary, drastic performance improvements are found when diffuse functions are added to the basis set used with PBE-D, BLYP-D and TPSS-D. Interestingly, there is little change in the performance of M05-2X and M06-2X with an increase in the basis-set size, where inclusion of diffuse functions leads to a slightly poorer description of stacking. However, increasing the basis set for the M06-L functional leads to improved stacking interaction energies, where the aug-cc-pVDZ basis sets leads to the smallest MUE and MSE for these functionals.

A potential way to further improve upon the performance of DFT methods for the calculation of π - π interactions is to consider double-hybrid density functionals such as B2PLYP and mPW2PLYP. B2PLYP, in particular, provides an extremely small absolute mean deviation for the S22 test set when Grimme's dispersion correction is included and a large triple-zeta basis set is used.¹²⁷ Although the inclusion of the dispersion correction improves the performance of both B2PLYP and mPW2PLYP, these functionals are not as accurate as the other dispersion corrected methods considered above (Table 5.1). This could be in part due to the fact that BSSE corrections are not included in these reported binding energies since these calculations would not be realistic during each optimization step when enzyme-catalyzed reactions are considered.

Although the above discussion is for methods suitable for the highest-level region of hybrid calculations, the performance of the method used to describe the remainder of the protein environment (low-level region) must also be carefully considered. Semi-empirical methods are sometimes employed as a highly-efficient molecular orbital method for describing proteins (for examples, see references 227, 234, 238, 274–277, and 281). For instance, these techniques can be used as the high-level method, as the mid-layer region in multi-layer approaches, or as the low-level method when truncated enzyme models are used. However, the present work indicates that neither of the typically chosen semi-empirical techniques (AM1, PM3) accurately describe stacking interactions between the DNA/RNA bases and amino acids with conjugated π -rings (Table 5.1). Although the PM6 method outperforms these other semi-empirical methods, AMBER describes the stacking interactions between DNA and protein components exceptionally well and better than any semi-empirical method considered here (Table 5.1).

5.3.1.2. T-shaped Interactions

T-shaped interactions between two π -systems have been less studied compared to the large number of stacked complexes examined in the literature. In this thesis, these interactions were shown to be less dependent on dispersion than stacking and therefore more commonly-used computational techniques may be able to accurately describe these contacts. This statement is confirmed in the present work where the performance of MP2 with any of the chosen basis sets is better for T-shaped (Table 5.2) than stacking (Table 5.1) interactions. Indeed, although aug-cc-pVDZ is not the optimal choice for studying stacked systems with MP2, this combination outperforms other basis sets for T-shaped interactions. However, MP2/6-31G*(0.25), which was the best combination for the stacked orientations, also performs very well for nucleobase–amino acid T-shaped contacts.

Table 5.2. Mean unsigned error (MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 82 nucleobase–amino acid T-shaped dimers.

Method	Basis Set	MUE	MSE	MAX	MAX %
MP2 ^[a]	6-31G*(0.25)	1.5	1.2	5.7	-19.3
	6-31G(d)	6.2	6.2	12.1	-46.1
	6-31G(d,p)	6.1	6.1	11.6	-42.1
	cc-pVDZ	5.9	5.9	11.8	-40.3
	6-31+G(d,p)	4.4	4.4	8.4	-31.1
B3LYP	aug-cc-pVDZ	1.0	-0.4	4.2	12.5
	6-31G(d)	9.5	9.4	19.1	-99.2
	6-31G(d,p)	9.7	9.6	19.2	-98.0
	cc-pVDZ	10.5	10.4	24.0	-98.4
	6-31+G(d,p)	14.3	14.3	25.1	-112.3
PBE	aug-cc-pVDZ	13.8	13.8	24.1	-101.6
	6-31G(d)	5.9	5.5	13.7	-73.6
	6-31G(d,p)	5.9	5.6	13.3	-71.8
	cc-pVDZ	6.4	6.0	16.1	-71.1
	6-31+G(d,p)	9.5	9.5	16.5	-75.4
PBE-D	6-31G(d)	7.2	-7.2	12.8	47.2
	6-31G(d,p)	7.1	-7.1	12.9	46.9
	cc-pVDZ	6.6	-6.6	13.7	42.8
	6-31+G(d,p)	3.2	-3.2	6.7	23.9
BLYP	6-31G(d)	12.1	12.0	24.3	-114.6
	6-31G(d,p)	12.2	12.2	24.5	-113.6
	cc-pVDZ	13.1	13.1	29.5	-115.4
	6-31+G(d,p)	18.2	18.2	31.8	-135.2
BLYP-D	6-31G(d)	8.3	-8.3	13.7	50.1
	6-31G(d,p)	8.1	-8.1	13.6	49.2
	cc-pVDZ	7.3	-7.3	15.7	46.0
	6-31+G(d,p)	2.2	-2.1	5.1	21.5
TPSS	6-31G(d)	9.4	9.3	18.2	-96.7
	6-31G(d,p)	9.4	9.3	17.8	-94.7
	cc-pVDZ	9.8	9.8	21.4	-93.5
	6-31+G(d,p)	13.0	13.0	21.6	-105.0
TPSS-D	6-31G(d)	7.6	-7.6	13.0	49.7
	6-31G(d,p)	7.6	-7.6	13.2	49.6
	cc-pVDZ	7.1	-7.1	13.5	42.3
	6-31+G(d,p)	3.9	-3.9	8.9	27.5
B97-D	6-31G(d)	6.9	-6.8	11.9	44.4
	6-31G(d,p)	6.9	-6.8	11.6	44.1
	cc-pVDZ	6.0	-6.0	11.7	45.1
	6-31+G(d,p)	2.7	-2.5	5.8	20.3
	aug-cc-pVDZ	3.1	-2.9	6.6	31.5
MPWB1K	6-31G(d)	3.8	3.5	11.4	-57.9
	6-31G(d,p)	3.7	3.5	10.9	-55.6
	cc-pVDZ	4.0	3.8	9.8	-53.3
	6-31+G(d,p)	6.2	6.2	11.6	-54.6
	aug-cc-pVDZ	5.4	5.4	10.2	-45.3
M05-2X	6-31G(d)	1.6	-0.6	7.5	-31.8
	6-31G(d,p)	1.7	-0.8	8.0	-29.6
	cc-pVDZ	1.7	-0.5	9.3	-27.1

M06-2X	6-31+G(d,p)	1.4	1.1	5.0	-21.8
	aug-cc-pVDZ	1.1	-0.2	3.7	16.4
	6-31G(d)	1.9	-1.5	10.1	22.2
	6-31G(d,p)	2.0	-1.6	10.4	22.1
	cc-pVDZ	1.7	-1.4	11.3	15.5
M06-L	6-31+G(d,p)	1.2	0.4	4.9	-17.0
	aug-cc-pVDZ	1.3	-0.7	4.2	18.8
	6-31G(d)	2.1	2.0	4.9	-23.0
	6-31G(d,p)	1.9	1.8	4.5	-20.0
	cc-pVDZ	2.8	2.6	8.6	-27.5
B2PLYP	6-31+G(d,p)	3.1	3.1	6.0	-24.3
	aug-cc-pVDZ	2.9	2.9	6.1	-19.8
	6-31G(d)	9.5	9.5	20.3	-101.8
	6-31G(d,p)	9.7	9.6	20.0	-100.8
	cc-pVDZ	10.4	10.4	23.3	-100.3
B2PLYP-D	6-31+G(d,p)	13.8	13.8	24.4	-111.9
	aug-cc-pVDZ	13.2	13.2	22.7	-101.0
	6-31G(d)	1.7	0.2	7.1	-37.1
	6-31G(d,p)	1.7	0.3	7.1	-36.1
	cc-pVDZ	2.4	1.1	7.6	-35.5
mPW2PLYP	6-31+G(d,p)	4.5	4.5	8.4	-43.4
	aug-cc-pVDZ	3.9	3.9	6.4	-32.5
	6-31G(d)	6.3	6.0	16.4	-81.8
	6-31G(d,p)	6.5	6.2	16.1	-80.7
	cc-pVDZ	7.3	7.0	18.5	-80.4
mPW2PLYP-D	6-31+G(d,p)	10.4	10.4	19.7	-86.4
	aug-cc-pVDZ	9.8	9.8	17.9	-76.1
	6-31G(d)	1.8	-0.7	8.3	-34.7
	6-31G(d,p)	1.8	-0.6	8.3	-33.6
	cc-pVDZ	2.4	0.2	8.8	-33.4
AM1	6-31+G(d,p)	3.7	3.6	8.1	-37.6
	aug-cc-pVDZ	3.2	3.1	6.3	-28.0
		22.5	22.5	45.4	-128.0
PM3		22.5	22.5	46.4	-125.6
PM6		14.1	14.1	34.2	-79.1
AMBER		4.7	2.2	18.7	-82.3

^[a] MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

For all functionals, the basis set effects on T-shaped binding strengths (Table 5.2) are the same as those discussed for stacking interactions (Table 5.1). B3LYP more accurately describes T-shaped than stacking contacts with all basis sets considered. However, B3LYP is still much less accurate than the other functionals under analysis. Therefore, these calculations reemphasize that B3LYP should be cautiously used in hybrid approaches for studying enzyme-catalyzed reactions when the high-level region contains π - π interactions. Once again, the inclusion of an empirical dispersion correction greatly improves the accuracy of the density functionals. This supports the suggestions in this thesis that

dispersion plays a larger role in dictating the magnitude of T-shaped interactions than initially believed. Although the MUE and MSE are smaller for PBE than PBE-D, the MAX and MAX % are much larger for PBE, which makes PBE a less reliable method. Nevertheless, M05-2X and M06-2X yield interaction energies closer to the CCSD(T)/CBS results, while M06-L does not perform as well as these other Truhlar functionals. Indeed, M06-2X performs significantly better than PBE-D for nucleobase–amino acid T-shaped interactions.

AM1, PM3, and PM6 more accurately predict nucleobase–amino acid T-shaped interactions (Table 5.2) compared with the stacking binding energies (Table 5.1). However, the deviations from the CCSD(T)/CBS results are still very large and therefore these methods should be used with caution for systems that include many aromatic residues. The MUE is slightly larger for AMBER T-shaped interactions (Table 5.2) than AMBER stacking energies (Table 5.1), while the MAX and MAX % are significantly larger for T-shaped contacts. However, AMBER reasonably describes both types of interactions, especially when the computational efficiency of this method is taken into account.

5.3.1.3. Overall

The performance of DFT functionals presented thus far has provided general conclusions based on the results of all dimers. However, errors for the neutral versus cationic dimers were also determined (Appendix H) and fully analyzed. This work found that all methods describe the binding strengths of cationic dimers with slightly less accuracy than neutral dimers. Nevertheless, there are no drastic differences which warrant a detailed discussion of the performance of each method for cationic versus neutral systems.

Table 5.3 summarizes the performance of all methods for all types of (stacking and T-shaped, neutral π – π and cationic π^+ – π) interactions. Over the entire data set, AMBER is a more appropriate choice for the lower-level method in hybrid approaches than popular

semi-empirical techniques. Indeed, AMBER also outperforms many of the other methods considered in the present work, especially when the low computational cost of this technique is taken into account. This suggests that MD, QM/MM, or ONIOM calculations that implement AMBER provide a good description of the π - π interactions throughout DNA-protein systems.

Table 5.3. Mean unsigned error (MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 129 nucleobase-amino acid noncovalent dimers.

Method	Basis Set	MUE	MSE	MAX	MAX %
MP2 ^[a]	6-31G*(0.25)	1.8	0.9	6.0	-19.3
	6-31G(d)	8.6	8.6	19.4	-58.0
	6-31G(d,p)	8.3	8.3	18.2	-54.8
	cc-pVDZ	6.9	6.9	12.8	-40.3
	6-31+G(d,p)	4.5	4.5	8.4	-31.1
	aug-cc-pVDZ	2.5	-2.1	10.0	35.2
B3LYP	6-31G(d)	15.8	15.8	39.9	-133.2
	6-31G(d,p)	15.9	15.8	39.9	-132.5
	cc-pVDZ	16.7	16.7	42.9	-135.3
	6-31+G(d,p)	20.4	20.4	47.2	-156.2
	aug-cc-pVDZ	19.8	19.8	45.3	-149.1
PBE	6-31G(d)	11.2	10.9	30.4	-100.7
	6-31G(d,p)	11.1	10.9	30.1	-99.8
	cc-pVDZ	11.3	11.1	31.4	-97.3
	6-31+G(d,p)	14.3	14.3	34.8	-114.6
PBE-D	6-31G(d)	5.6	-5.6	12.8	47.2
	6-31G(d,p)	5.6	-5.6	12.9	46.9
	cc-pVDZ	5.5	-5.5	13.7	42.8
	6-31+G(d,p)	2.4	-2.3	6.7	23.9
BLYP	6-31G(d)	19.1	19.1	46.7	-152.2
	6-31G(d,p)	19.2	19.2	46.6	-151.4
	cc-pVDZ	20.0	20.0	50.0	-156.0
	6-31+G(d,p)	25.1	25.1	55.9	-181.4
BLYP-D	6-31G(d)	7.4	-7.4	13.7	50.1
	6-31G(d,p)	7.3	-7.3	13.6	49.2
	cc-pVDZ	6.5	-6.5	15.7	46.0
	6-31+G(d,p)	1.7	-1.4	5.1	21.5
TPSS	6-31G(d)	15.4	15.4	38.9	-127.4
	6-31G(d,p)	15.4	15.4	38.8	-126.7
	cc-pVDZ	15.5	15.5	39.9	-122.2
	6-31+G(d,p)	18.7	18.7	43.4	-141.1
TPSS-D	6-31G(d)	6.6	-6.6	13.0	49.7
	6-31G(d,p)	6.7	-6.7	13.2	49.6
	cc-pVDZ	6.6	-6.6	13.5	42.3
	6-31+G(d,p)	3.4	-3.4	8.9	27.5
B97-D	6-31G(d)	6.1	-6.1	11.9	44.4
	6-31G(d,p)	6.1	-6.1	11.6	44.1

	cc-pVDZ	5.6	-5.6	11.7	45.1
	6-31+G(d,p)	2.1	-1.9	5.8	20.3
	aug-cc-pVDZ	2.8	-2.7	6.6	31.5
MPWB1K	6-31G(d)	6.2	6.0	15.9	-57.9
	6-31G(d,p)	6.1	6.0	15.8	-55.6
	cc-pVDZ	6.0	5.9	14.9	-53.3
	6-31+G(d,p)	8.1	8.1	17.2	-61.2
	aug-cc-pVDZ	7.1	7.1	15.0	-49.9
M05-2X	6-31G(d)	2.7	1.2	8.8	-31.8
	6-31G(d,p)	2.7	1.1	8.7	-29.9
	cc-pVDZ	2.4	1.0	9.3	-27.1
	6-31+G(d,p)	2.3	2.1	8.0	-31.3
	aug-cc-pVDZ	1.6	0.7	5.5	-19.1
M06-2X	6-31G(d)	1.9	-1.5	10.1	22.2
	6-31G(d,p)	1.9	-1.6	10.4	22.1
	cc-pVDZ	2.0	-1.8	11.3	15.5
	6-31+G(d,p)	1.6	-0.5	4.9	-17.0
	aug-cc-pVDZ	2.0	-1.7	7.0	18.8
M06-L	6-31G(d)	2.3	2.2	5.1	-23.0
	6-31G(d,p)	2.2	2.1	4.9	-20.0
	cc-pVDZ	2.6	2.4	8.6	-27.5
	6-31+G(d,p)	2.7	2.7	6.0	-24.3
	aug-cc-pVDZ	2.3	2.2	6.1	-19.8
B2PLYP	6-31G(d)	15.7	15.6	40.0	-135.8
	6-31G(d,p)	15.7	15.7	39.9	-135.2
	cc-pVDZ	16.6	16.5	43.0	-139.4
	6-31+G(d,p)	20.0	20.0	47.4	-160.5
	aug-cc-pVDZ	19.2	19.2	45.0	-151.7
B2PLYP-D	6-31G(d)	4.5	3.5	14.7	-55.6
	6-31G(d,p)	4.5	3.6	14.5	-55.1
	cc-pVDZ	5.3	4.4	16.3	-59.3
	6-31+G(d,p)	7.8	7.8	20.6	-80.3
	aug-cc-pVDZ	7.1	7.1	18.6	-71.5
mPW2PLYP	6-31G(d)	11.7	11.5	32.6	-111.5
	6-31G(d,p)	11.7	11.6	32.5	-111.0
	cc-pVDZ	12.6	12.5	35.8	-116.2
	6-31+G(d,p)	16.0	16.0	40.6	-138.2
	aug-cc-pVDZ	15.3	15.3	38.2	-129.7
mPW2PLYP-D	6-31G(d)	4.3	2.7	14.2	-53.3
	6-31G(d,p)	4.2	2.7	14.0	-52.7
	cc-pVDZ	5.0	3.6	16.5	-57.9
	6-31+G(d,p)	7.2	7.1	21.1	-80.0
	aug-cc-pVDZ	6.5	6.4	18.8	-71.4
AM1		29.7	29.7	66.1	-184.4
PM3		29.6	29.6	69.3	-177.1
PM6		16.7	16.7	37.5	-86.7
AMBER		4.1	2.3	18.7	-82.3

^[a] MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Among the MP2 basis set combinations considered, MP2/6-31G*(0.25) provides the best description for a range of noncovalent π - π dimer interactions (Table 5.3). These results further justify the use of this method for scanning the potential energy surfaces of

stacked and T-shaped nucleobase–amino acid dimers. Furthermore, these findings suggest that MP2/6-31G*(0.25) is an efficient method for use in future work of stacked or T-shaped systems when larger systems (trimers or tetramers) are considered.

As discussed previously in the literature, double-hybrid functionals yield very good performance when an empirical dispersion correction is included in the functional form.^{127,246} Additionally, the performance reported in the present work would likely be further improved with the inclusion of BSSE corrections. However, as previously discussed, this is not a feasible approach for the intended application due to the computational scaling of these methods. Therefore, the use of these functionals for accurately determining interaction energies is currently restricted to single-point calculations with large basis sets and/or BSSE corrections.

The results in Table 5.3 suggest that within the functionals considered in the present work, the methods that best describe π – π stacking and T-shaped interaction energies are M06-2X and PBE-D. Although BLYP-D outperforms PBE-D with the 6-31+G(d,p) basis set, PBE-D performs better with the smaller 6-31G(d) basis set. However, Table 5.3 suggests that M06-2X outperforms PBE-D with both the smaller 6-31G(d) and the larger 6-31+G(d,p) basis sets. The 6-31G(d) basis set is a more computationally efficient choice for hybrid approaches since the inclusion of diffuse functions on heavy atoms and/or polarization functions on hydrogen atoms during the optimization routine drastically increases the computational resources required. Thus, M06-2X/6-31G(d) may be the best choice among those considered in the present work for describing the high-level region in hybrid approaches for large-scale modeling of enzyme-catalyzed reactions that involve DNA–protein π – π interactions.

5.3.2. Description of Potential Energy Surfaces

Although Tables 5.1 – 5.3 provide useful information about the ability of various

methods to accurately predict the strength of π - π interactions at minimum regions on the potential energy surfaces of nucleobase-amino acid dimers, this data does not necessarily reflect whether the methods provide an accurate description of the entire PES. Understanding how density functionals describe both minimum and nonminimum regions of potential energy surfaces is particularly important when applying these methods to optimize a complete reaction mechanism for DNA-protein complexes that include stacked and/or T-shaped contacts, such as AAG. Therefore, as a critical first step, the functional (M06-2X, PBE-D) and basis set (6-31G(d), 6-31+G(d,p)) combinations found to best describe nucleobase-amino acid interactions will be further scrutinized below by evaluating their ability to describe changes in both stacked and T-shaped binding strengths as a function of select geometric variables (Figure 2.2). Since MP2 is widely used to study π - π dimers in the literature, this section will compare the current results to the MP2 method that best describes stacked (MP2/6-31G*(0.25), Table 5.1) or T-shaped (MP2/aug-cc-pVDZ, Table 5.2) orientations. Nevertheless, both MP2 values are reported for both types of interactions to further illustrate the differences between these approaches. The following investigation focuses on three dimers (adenine-histidine, 3-methyladenine-histidine and adenine-protonated histidine) in both their optimal stacked and (amino acid-edge) T-shaped orientations (Figure 5.1). This choice in molecules considers similar systems that span both π - π and π^+ - π interactions, which Chapter 3 showed to have a varying dependence on the electrostatic and dispersion contributions to the interactions.

5.3.2.1. Stacked Dimers

Deviations in the MP2 calculated curves describing dimer interaction energies as a function of the vertical separation (R_1 , Figure 2.2) between the monomers are not surprising (Figure 5.2a – 5.2c) since aug-cc-pVDZ is known to overestimate stacking

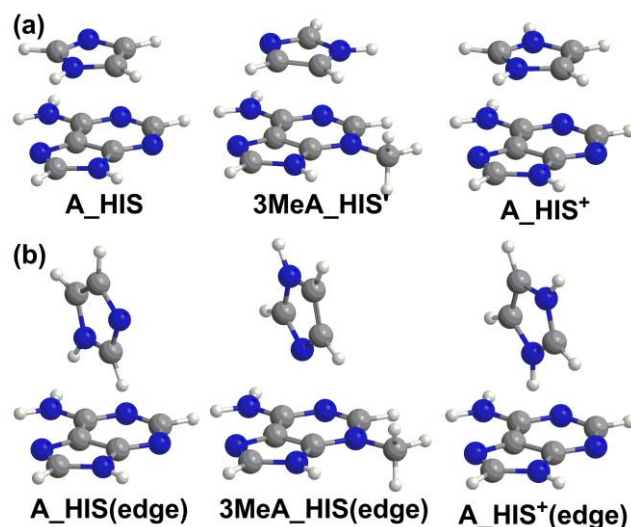


Figure 5.1. Dimers considered in vertical separation (R_1) and angle of rotation (α) potential energy surface scans for (a) stacked and (b) amino acid-edge T-shaped orientations.

interactions. However, both basis sets predict the same preferred MP2 vertical separation in the nucleobase–amino acid dimers considered in the present work (Appendix H). Furthermore, over the R_1 values investigated, the entire potential energy surfaces calculated with both basis sets are reasonably close in both magnitude and shape for the cationic systems (Figure 5.2b and 5.2c). Nevertheless, there are larger deviations in the calculated MP2 binding strengths for the neutral dimer (Figure 5.2a), where the magnitude of the deviation depends on the vertical separation and a better agreement is observed at larger vertical separations.

M06-2X leads to steeper potential energy surfaces with respect to R_1 than MP2 for stacked dimers. Specifically, this functional underestimates the binding strength at large vertical separations and overestimates the interaction energy at small R_1 distances. The M06-2X results obtained with both basis sets are in good agreement with each other, which reemphasizes that inclusion of diffuse functions does not lead to improved performance for this functional. In the absence of diffuse functions, the PES with respect to R_1 is slightly

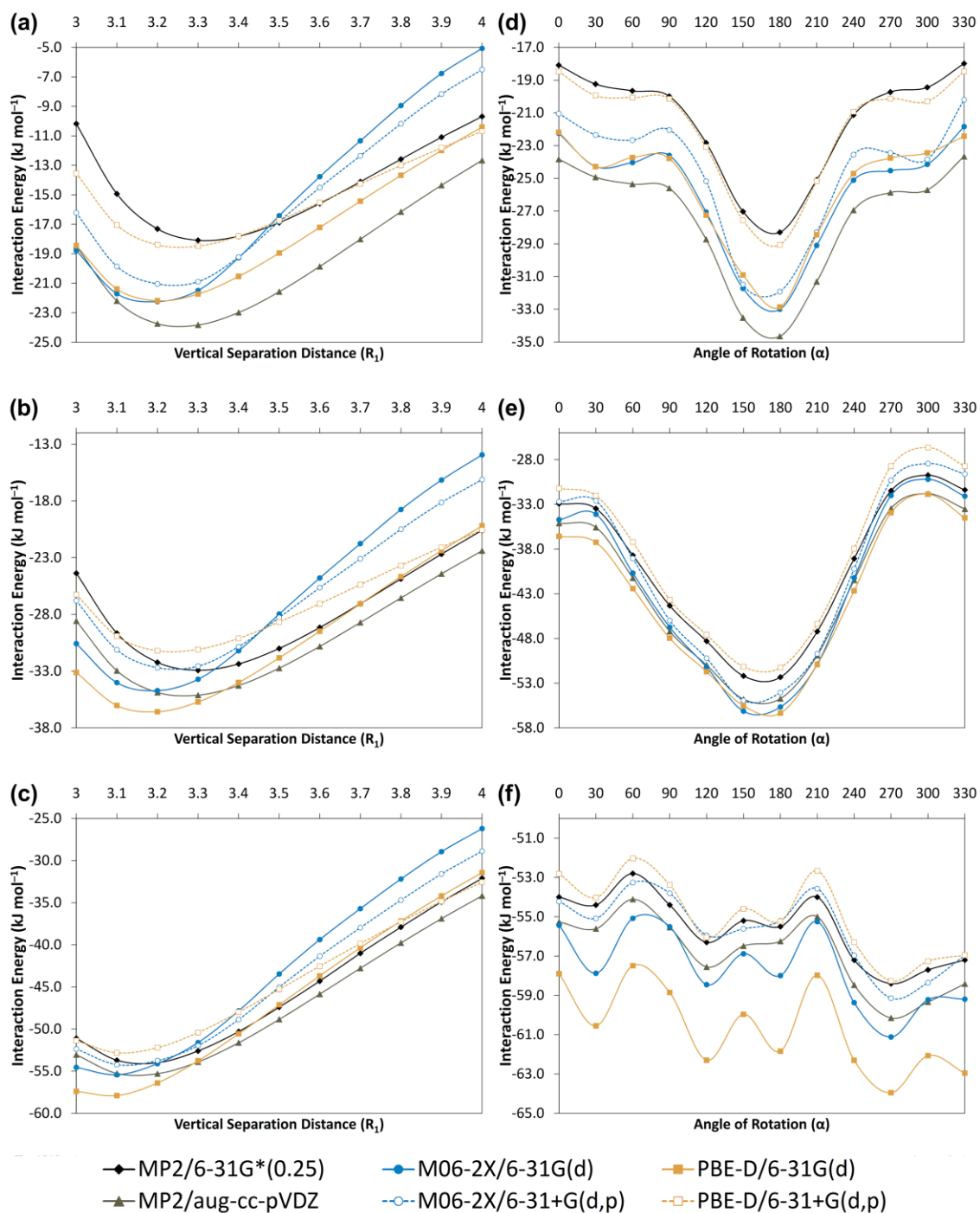


Figure 5.2. Interaction energy (kJ mol⁻¹) as a function of vertical separation distance (R_1 , Å) for the stacked dimers ((a) A_{HIS}, (b) 3MeA_{HIS'}, (c) A_{HIS}⁺) or as a function of angle of rotation (α , °) for stacked dimers ((d) A_{HIS}, (e) 3MeA_{HIS'}, and (f) A_{HIS}⁺).

steeper, which implies that deviations from MP2/6-31G*(0.25) will be larger in non-equilibrium geometries for the M06-2X/6-31G(d) combination. For all dimers, M06-2X

predicts the preferred vertical separation to be 0.1 Å smaller than MP2, which has been previously reported in the literature for the methane dimer¹³² and the sandwiched-benzene dimer¹³² and reflects stronger binding. Furthermore, when regions close to the preferred R_1 are considered, small changes in the vertical separation lead to small changes in the interaction energy. Finally, it is interesting to note that the deviations from MP2/6-31G*(0.25) are smaller for the M06-2X $\pi^+-\pi$ stacking interactions than the corresponding $\pi-\pi$ contacts. The present M06-2X surfaces are smooth despite previous reports that meta-GGA potential energy curves for the stacked benzene dimer oscillate unless very large integration grids are used.²⁸²

PBE-D/6-31+G(d,p) provides an excellent representation of the preferred MP2 geometries, as well as the interaction energies for the entire R_1 potential energy surface of stacked dimers. Indeed, PBE-D/6-31+G(d,p) likely provides a better description of both $\pi-\pi$ and $\pi^+-\pi$ contacts than M06-2X with either basis set. However, there is a much larger basis set effect for the PBE-D functional. Specifically, removal of diffuse functions from the basis set leads to a significant overestimation when compared to the MP2/6-31G*(0.25) stabilization energy, which is much more pronounced at smaller R_1 distances. Figure 5.2 also illustrates that PBE-D/6-31G(d) and MP2/6-31G*(0.25) are in better agreement in the $\pi^+-\pi$ complexes (Figure 5.2b and 5.2c) than the $\pi-\pi$ A_HIS dimer (Figure 5.2a). Furthermore, as discussed for M06-2X, PBE-D/6-31G(d) predicts R_1 to be 0.1 Å smaller than MP2, but this effect is diminished when the larger basis set is used (Appendix H).

Using the preferred R_1 distance identified for each method, the binding strength as a function of the angle of rotation of the amino acid with respect to the nucleobase (α , Figure 2.2) was considered (Figure 5.2d – 5.2f). Unlike the results for the R_1 potential energy surfaces, all methods yield the same general shape of the potential energy surface with respect to α , which is dictated by the relative orientation of the dipole moment vectors in

the monomers. Once again, the overestimation of the interaction strength at the MP2 level with the aug-cc-pVDZ compared with the 6-31G*(0.25) basis set is clearly observed.

Although M06-2X with both basis sets yields binding energies in very close agreement with one another for all α values in the A_HIS and 3MeA_HIS' stacked dimers, a larger basis set effect is seen for A_HIS⁺ (Figure 5.2f). To provide a better comparison by only examining the effects of α , an additional α scan was performed at the MP2/6-31G*(0.25) preferred vertical separation distance for cases where the DFT R_1 distance was different (Appendix H). When the same R_1 value is considered, a better agreement is observed between the M06-2X results and the MP2/6-31G*(0.25) results for this dimer (Appendix H). In comparison, PBE-D/6-31+G(d,p) produces nearly identical potential energy surfaces with respect to α in both shape and magnitude as MP2/6-31G*(0.25). However, PBE-D/6-31G(d) greatly overestimates the MP2 binding strength for all α , especially for the A_HIS⁺ dimer (see Figure 5.2f).

In summary, PBE-D in combination with basis sets that include diffuse functions yields stacking interactions in excellent agreement with MP2 for large regions of the PES and therefore this is the method of choice for describing DNA-protein stacking interactions in large-scale modeling. However, in instances when diffuse functions are prohibited due to the associated computational expense, PBE-D can yield acceptable π - π interactions, but can lead to very large overestimations, especially in π^+ - π interactions. In comparison, M06-2X has a very small basis set dependence and yields a reasonable description of both the dispersion and electrostatic components of the stacking interactions for both neutral and cationic systems. As a result, M06-2X is an efficient choice for modeling stacking interactions in large systems that require the use of small basis sets (without diffuse functions).

5.3.2.2. T-shaped Dimers

In contrast to the discussion of stacked systems, the MP2 potential energy surfaces with respect to R_1 calculated with aug-cc-pVDZ and 6-31G*(0.25) for T-shaped dimers are very similar in shape and the binding strengths are nearly identical in magnitude (within 3.3 kJ mol⁻¹, Figure 5.3a – 5.3c). M06-2X almost always underestimates the MP2 T-shaped binding strengths regardless of the basis set used, especially when interactions with a cationic monomer are considered. On the contrary, PBE-D generally overestimates the MP2 binding strength for T-shaped dimers, where this overestimation is exaggerated when diffuse functions are omitted from the basis set (see for example, Figure 5.3a and 5.3c). As discussed for the stacked dimers, all DFT methods predict a 0.1 Å shorter vertical separation than MP2 for A_HIS(edge) and 3MeA_HIS(edge) T-shaped dimers. However, the R_1 values for A_HIS⁺(edge) match the MP2 results for all combinations except M06-2X/6-31+G(d,p), which predicts a 0.1 Å larger vertical separation.

Once again, all methods yield the same general shape for the curves representing the T-shaped interaction energy as a function of the angle of rotation (α , Figure 5.3d – 5.3f). Furthermore, all other general conclusions discussed for the stacking interactions in regards to the method dependence for these potential energy surfaces hold for the T-shaped interactions. However, the effects are more pronounced in the case of T-shaped contacts. Most significantly, when diffuse functions are not included in the basis set, PBE-D drastically overestimates the T-shaped interactions. These results reemphasize the previous conclusion that PBE-D/6-31G(d) should not be used to study T-shaped contacts between two π -systems. M06-2X, on the other hand, more consistently provides a better description for a range of π - π and π^+ - π T-shaped DNA-protein interactions.

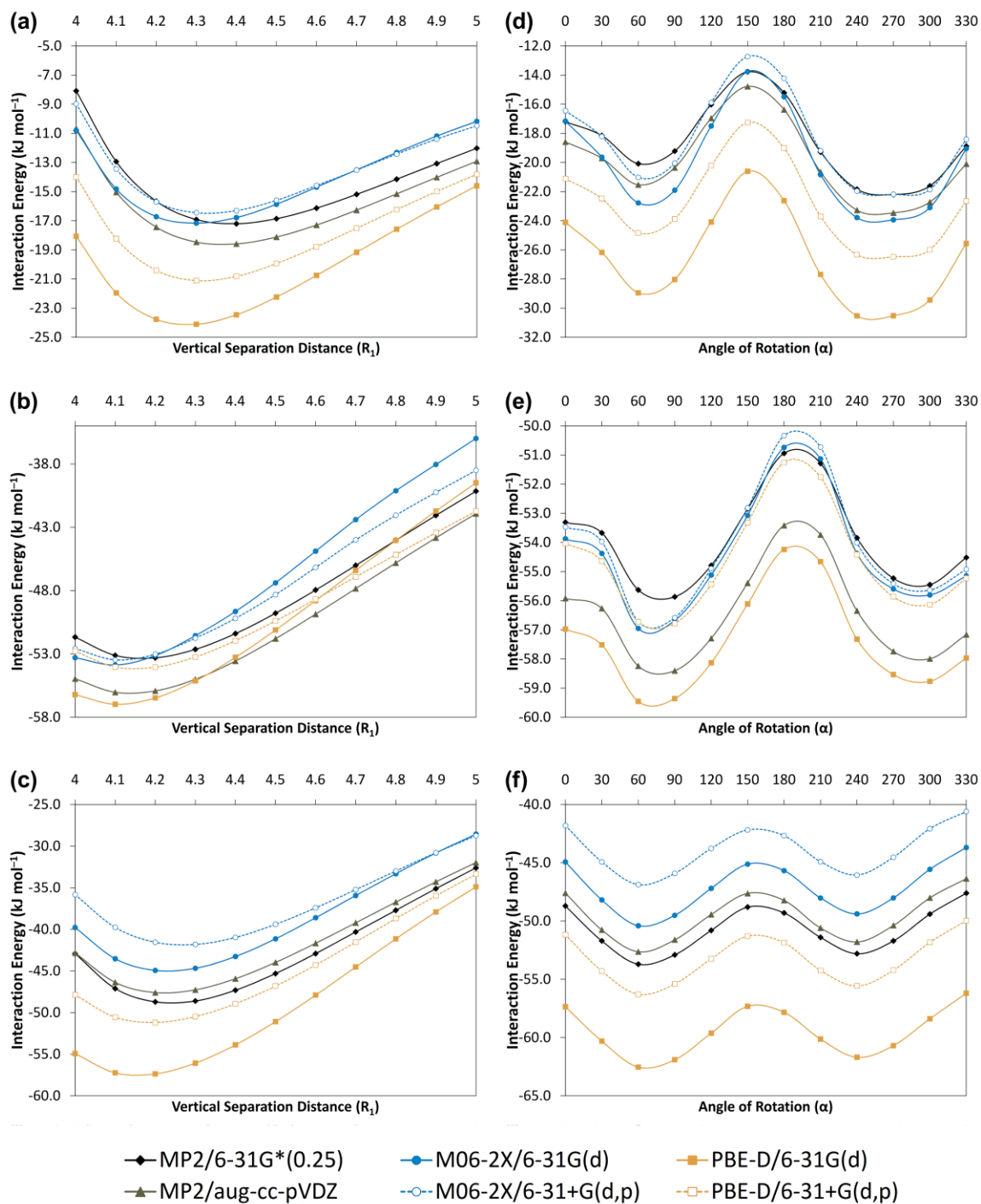


Figure 5.3. Interaction energy (kJ mol⁻¹) as a function of vertical separation distance (R_1 , Å) for the T-shaped dimers ((a) A_HIS(edge), (b) 3MeA_HIS(edge), (c) A_HIS⁺(edge)) or as a function of angle of rotation (α , °) for T-shaped dimers ((d) A_HIS(edge), (e) 3MeA_HIS(edge), and (f) A_HIS⁺(edge)).

5.3.2.3. Overall

Detailed consideration of the potential energy surfaces of π - π and π^+ - π stacked and T-

shaped dimers as a function of the vertical separation (R_1) and angle of rotation (α) between nucleobase and amino acid monomers supports the previous interaction energy analysis. Specifically, PBE-D with diffuse functions (6-31+G(d,p)) provides a very accurate description of the potential energy surface of the stacked dimers. However, the accuracy of this combination breaks down for T-shaped complexes, where these interaction energies can be drastically overestimated. PBE-D also has a very large basis set dependence, and therefore small basis sets that do not contain diffuse functions should be used in conjunction with this functional with extreme caution, especially when T-shaped contacts are considered. These results indicate that if the system of interest contains both stacked and T-shaped arrangements, then M06-2X will provide a more reliable description of all π - π interactions in the DNA-protein complex. Nevertheless, users should be aware that M06-2X generally finds the equilibrium distances to be 0.1 Å closer than other methods, and underestimates the binding at vertical separation distances larger than the equilibrium value. Nevertheless, the description of both stacked and T-shaped interactions with M06-2X looks promising for geometry optimizations in the intended application of studying DNA-protein systems with hybrid techniques. M06-2X has minimal basis set dependence for both stacked and T-shaped orientations and therefore can be used in conjunction with a small basis set to optimize large enzymatic systems. In fact, this work indicates that there is no advantage to including diffuse functions in attempts to improve the description of M06-2X stacking and T-shaped interactions, while the computational cost associated with implementing such basis sets for enzymatic systems is very high.

5.4. Conclusions

This chapter investigated the performance of a number of density functional methods, as well as other techniques currently used in hybrid approaches, to identify currently available method and basis set combinations that accurately and efficiently describe the

binding strengths and potential energy surfaces of π - π stacking and π - π T-shaped DNA-protein interactions. By benchmarking against the previously reported 129 nucleobase-amino acid dimer CCSD(T)/CBS interaction energies, this work concludes that AMBER is a more appropriate choice for the lower-level method in hybrid approaches than popular semi-empirical techniques, and suggests that hybrid techniques that implement AMBER accurately describe π - π interactions throughout DNA-protein systems. Additionally, the M06-2X and PBE-D density functional methods were found to provide very promising descriptions of the entire 129 nucleobase-amino acid dimer test set, and therefore may be the best choice for high-level regions in hybrid approaches for studying enzyme systems that involve nucleobase-amino acid π - π interactions, such as AAG.

M06-2X and PBE-D, in combination with smaller (6-31G(d)) and larger (6-31+G(d,p)) double-zeta basis sets, were further examined to determine which combinations best describe an extended portion of the potential energy surfaces of three representative stacked and three representative (amino acid-edge) T-shaped dimers. PBE-D with the larger basis set was found to provide an excellent description of stacking interactions, yet generally overestimates T-shaped interactions. However, PBE-D has a very strong basis set dependence, where the small basis set erroneously overestimates interaction energies in both neutral and cationic systems, especially for T-shaped contacts. On the other hand, M06-2X has a small basis set dependence. Indeed, M06-2X/6-31G(d) was found to provide an excellent description of both stacked and T-shaped, as well as π - π and π^+ - π , DNA-protein interactions. Therefore, this work proposes the use of PBE-D/6-31+G(d,p) to study nucleobase-amino acid systems that rely only on stacking interactions. However, if T-shaped contacts are to be considered and/or smaller basis sets must be used, M06-2X/6-31G(d) will provide an overall excellent description of the (stacking and T-shaped) interactions in the entire DNA-protein complex.

The present work is important for understanding how current density functionals describe DNA–protein π – π interactions in both minimum and nonminimum regions of the potential energy surface. Indeed, this chapter illustrates that the 129 nucleobase–amino acid benchmark data set can provide important information about the performance of a variety of functionals, suggesting that this high-level data should not be overlooked when parameterizing new force fields and new density functionals that even more reliably account for long-range dispersion interactions. This chapter has also provided critical information about methodologies that are currently available for modeling enzymatic reaction mechanisms, where the methods identified in this chapter will be used to study the excision mechanism of AAG, which is the focus of the next chapter.

Chapter 6. Modeling the Chemical Step Utilized by Human Alkyladenine DNA Glycosylase (AAG)^a

6.1. Introduction

This thesis has examined the π - π and π^+ - π interactions between the amino acids with conjugated π -rings and the natural or damaged nucleobases, where high-level quantum mechanical techniques have provided vital information about their preferred structures and stabilization energies, as well as how the interaction energies change with respect to several geometric variables. Indeed, these high-level results have become an excellent data set for benchmarking methods to be used to examine enzymatic mechanisms that rely on these nonspecific interactions. However, it is still not understood how the structures of these interactions will differ, or how they can affect the reaction barriers, in the catalytic mechanism of neutral and cationic lesions within AAG, which is the focus of the present chapter.

As mentioned in Chapter 1, very little is known about the chemical glycosidic-bond cleavage step of AAG, where most knowledge has been revealed from crystal structures of Δ 80AAG. A water molecule in the active site is ideally positioned to act as the nucleophile to attack C1' of the sugar^{55,57,60} (3.502 Å away from C1' in the wild-type structure bound to ϵ A-containing DNA, Figure 6.1a).⁵⁷ The proximity and orientation of this water relative to the side chain of Glu125 led to proposals that AAG uses a general base in the catalytic mechanism to activate this water for nucleophilic attack.⁵⁵ Indeed, mutational studies that substituted Glu125 with alanine or glutamine eliminated detectable glycosylase activity,

^a Reprinted with permission from Rutledge, L. R.; Wetmore, S. D. *J. Am. Chem. Soc.* **2011**, *Accepted*. DOI: ja07181c. Copyright 2011 American Chemical Society.

and therefore led to the E125Q-AAG bound to a (glycosidic bond intact) ϵ A-containing DNA crystal structure.⁵⁷ Additionally, pH-rate profiles clarified that AAG requires a general base for glycosidic-bond cleavage of both neutral (ϵ A, Hx) and cationic (7MeG) substrates,⁶⁴ which is also a common feature of most monofunctional glycosylases.²⁸⁻²⁹

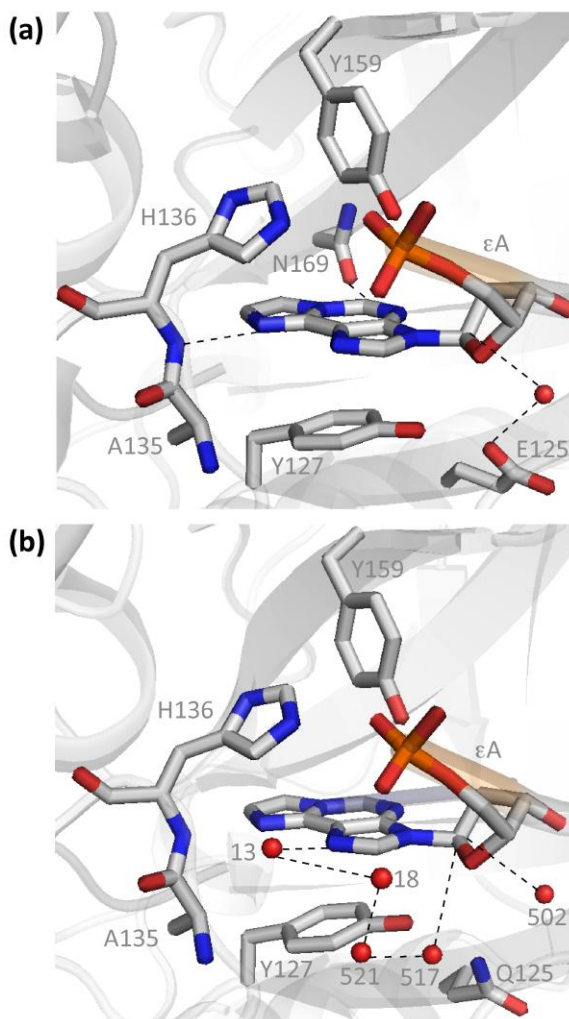


Figure 6.1. Crystal structure of (a) wild-type $\Delta 80$ AAG bound to the ϵ A-containing DNA (PDB entry 1F4R) and (b) E125Q- $\Delta 80$ AAG bound to ϵ A-containing DNA (PDB entry 1EWN).⁵⁷ Protein-bound water molecules are indicated by red spheres and are labelled according to their crystal structure.

O'Brien and Ellenberger found that the pH-rate profiles of the neutral substrates (ϵ A and Hx) are different from the cationic bases (7MeG), suggesting that the neutral lesions require the action of both a general base and a general acid, which protonates the nucleobase.⁶⁴ To pinpoint the site of protonation, the activity of AAG on Hx was compared to

that on 7-deaza-Hx, which lacks the N7 group.⁶⁴ No glycosylase activity was observed towards 7-deaza-Hx, strongly implying that N7 is directly involved in catalysis of neutral purine lesions.⁶⁴ In addition, these authors attempted to identify the general acid by mutating the protein side chains in the vicinity of the bound nucleotide in the ϵ A-containing crystal structure.⁶⁴ Unfortunately, this study was unsuccessful in identifying the general acid,⁶⁴ and it has yet to be definitively identified.

The above perplexing result led Samson and coworkers⁶⁰ to propose that a water molecule in contact with N7 of ϵ A in the crystal structure of E125Q-AAG bound to ϵ A-containing DNA ($O_{\text{Wat13}}\text{--N7}$ distance of 2.792 Å, Figure 6.1b),⁵⁷ could be responsible for protonation. In fact, closer examination of the E125Q-AAG structure bound to ϵ A-containing DNA also reveals a chain of protein-bound water molecules connecting the proposed general acid located near N7 of ϵ A (Wat13) to Wat517, which is 3.479 Å from C1' of the sugar moiety (Figure 6.1b).⁵⁷ Upon overlaying the ϵ A-⁵⁷ and ϵ C-containing⁶⁰ crystal structures, the location of Wat13 with respect to the ϵ C inhibitor led Samson and coworkers to propose that the failure of AAG to cleave ϵ C, as well as other pyrimidines, could be due to the inability of AAG to activate the leaving group by protonation.⁶⁰ Despite these proposals, computational studies by Lee and coworkers spark interesting questions about the commonly accepted general acid mechanism for excision of neutral lesions.⁷⁴⁻⁷⁵ Indeed, comparisons of the (N7) proton affinities and (N9) acidities of the Hx⁷⁵ and ϵ A⁷⁴ substrates to the natural purines A and G reveals that protonation by a general acid is not necessary for cleavage. In fact, this data suggests that AAG would have a more discriminatory chemical step in the absence of a general acid mechanism.

To date, no study has united all of the current computational and experimental results to fully describe the excision mechanism of AAG. With this goal in mind, this chapter uses ONIOM(QM:MM) calculations to examine the chemical step utilized by AAG to cleave the

glycosidic bond in ϵ A, 3MeA, and A nucleotides. Potential energy surfaces (PES) are generated to consider the complete reaction paths and determine whether the reaction is stepwise or concerted for different (neutral or cationic) lesions. These substrate choices assess the dependency of the chemical step on the charge of the substrate, and perhaps more importantly, whether the glycosidic-bond cleavage mechanism provides an extra step for AAG to discriminate against the natural purines. Furthermore, this methodology will elucidate the role of a general acid in the excision of neutral lesions by considering crystal structure orientations of protein-bound water molecules near N7 of the purines, as well as different water nucleophiles, which takes into account possible water chain proton transfer reactions. For comparisons with experiment, as well as to help clarify the role of the amino acids with conjugated π -systems (His136, Tyr127, Tyr159), mutational analysis is used to determine how the residues affect the reaction barriers of the hydrolysis reaction for both neutral and cationic substrates. Through this work, a chemical mechanism for AAG that is consistent with all previous computational and experimental results is proposed, which provides insights into the role played by various amino acids in the bond cleavage step for neutral and cationic substrates, and suggests how AAG discriminates against the natural purines at this late stage in the mechanism-of-action.

6.2. Computational Details

6.2.1. Initial Model Generation

The X-ray structure of the E125Q AAG/ ϵ A-DNA complex (1EWN PDB entry⁵⁷) was used as the starting point for this study. The R-group of amino acid residues that were not resolved in the crystal structure (His82, Glu131, Thr199, Val208, Lys210, Gln238, Glu240, and Glu269) were first added with the Leap program.²⁷³ Hydrogen atoms were then added to the DNA-protein system, which was neutralized with sodium ions and fully solvated in a

TIP3P water box with a 8 Å water buffer around the system. The ϵ A substrate present in this crystal structure was assigned AMBER²⁷¹ atom types and GAFF²⁸³ parameters using ANTECHAMBER²⁸⁴ (Appendix I). The original charges for ϵ A were obtained using the RESP (restrained electrostatic potential)²⁸⁵⁻²⁸⁶ program, which fits the partial atomic charges to the ESP grid generated in a (gas-phase) HF/6-31G(d) calculation on the (M06-2X/6-31G(d) hydrogen-atom optimized) crystal structure orientation of the nucleotide. All other residues were initially assigned AMBER charges.²⁷¹

In the present work, a two-layer (mechanical embedding) ONIOM method^{81-82,287} in Gaussian 09²²² was used for all QM/MM calculations, which has recently become an important technique for computational studies of enzymatic catalysis (see, for examples, references 236, and 288–301). Active site residues (ϵ A7 nucleotide substrate, Gln125, Tyr127, Ala135, His136, Tyr159, Wat13, Wat18, Wat19, Wat502, Wat517, Wat521) were included in the QM region (78 heavy atoms), and were described with M06-2X/6-31G(d) (Figure 6.2). Previous work from Chapter 5 of this thesis determined that M06-2X provides an overall excellent description of both types of π - π and π^+ - π interactions. The rest of the system was described with molecular mechanics (MM) using the parm96 parameters of the AMBER force field.²⁷¹

The (solvated) system was initially optimized with MM in two stages; first all non-crystallographic atoms were relaxed, and then the MM region was relaxed with the QM region fixed. Afterward, the entire QM region was relaxed to a fixed MM region within the ONIOM methodology. To reduce the computational cost for the remaining ONIOM calculations, the non-crystallographic water and counterions were removed at this stage, and residues more than 15 Å from the glycosidic bond were held fixed in this geometry. The relaxed system was mutated to generate the active form of AAG (Glu125 replaced Gln125,

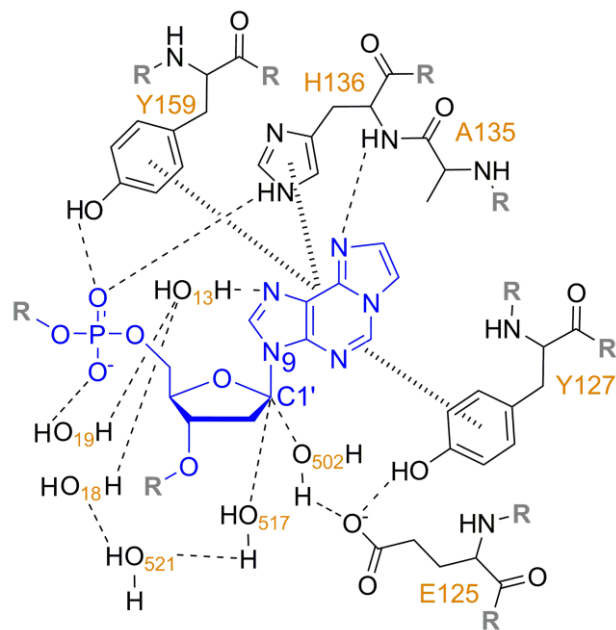


Figure 6.2. Schematic representation of the QM region used in ONIOM(M06-2X/6-31G(d):AMBER) calculations for the ϵ A substrate (blue). Link atoms (represented by hydrogen atoms in M06-2X/6-31G(d) calculations) are indicated by R (in bold).

where the AMBER charges for glutamic acid were used²⁷¹), and then optimized using the ONIOM scheme outlined above. The ϵ A nucleobase in this reactant was subsequently mutated to be adenine (A) or 3-methyladenine (3MeA) (RESP charges for the new nucleotides were obtained through HF/6-31G(d) calculations on the (M06-2X/6-31G(d)) hydrogen-atom optimized nucleotides, where 3MeA atom types and parameters are reported in Appendix I), and the new enzyme–substrate complexes were optimized within the ONIOM scheme.

Finally, to obtain the fully relaxed reactants, the partial charges of the QM region were converged with the procedure developed by Schlegel and coworkers.^{291,302} Specifically, after the initial ONIOM optimization, an improved set of (gas-phase HF/6-31G(d)) RESP charges were calculated for the entire (hydrogen-atom capped) QM region using the newly optimized structure and an additional ONIOM optimization was performed. This procedure was repeated until convergence was achieved, which required that both the difference

between the total ONIOM energies from the two last rounds of optimization calculations, as well as the difference between the total ONIOM energies in the first and last optimization steps in the final optimization calculation, be less than 4 kJ mol⁻¹. While this typically required six to ten rounds of optimization, in a few cases where both convergence criteria could not be achieved after more trials, one criterion was required to be less than 2 kJ mol⁻¹. Convergence in this manner ensures that the QM charges are conserved along the entire reaction path.^{291,302}

6.2.2. Reaction Potential Energy Surface Generation

Reaction potential energy surfaces (PES) were obtained by constraining the glycosidic (C1'-N9) and nucleophilic (C1'-O_{wat}) distances in the above reactants, where both Wat502 and Wat517 were considered as the nucleophile for all three substrates (Figure 6.2). All points on each PES were obtained by constraining the two grid coordinates and minimizing the energy with respect to the remaining parameters. For each point, the geometry was optimized with the quadratically coupled QM/MM optimizer as implemented in Gaussian 09.²²² Once a converged structure was obtained for a given point on the PES, new RESP charges for the optimized QM region were calculated (as outlined by Schlegel and coworkers^{291,302}) and used in an ONIOM single-point calculation to obtain the final reported energy. Additionally, the charges and coordinates from this single-point calculation were altered to create the starting guess for the optimization of the next point on the PES, where only one reaction coordinate was changed at a time in 0.200 Å increments. This process was repeated until all stationary points on the preferred reaction surfaces were identified.

6.2.3. Further Refinement of Stationary Points

The geometries of all stationary points identified from the preferred reaction surfaces were further refined in two manners. First, to obtain the constrained stationary points, the

C1'–N9 and C1'–O_{wat} distances were kept fixed, while the RESP charges of the QM region were fully converged as described above for the reactant structures. Second, to obtain the relaxed stationary points, the charges for the QM region were fully converged while releasing the C1'–N9 and C1'–O_{wat} distance constraints. All stationary points (constrained and relaxed) were confirmed to be minima and transition states through frequency calculations, where the one imaginary frequency found for each transition state was visually inspected to verify that it corresponds to the proper reaction coordinate. To obtain the Gibbs free energy, the corresponding (unscaled) thermal correction was added to the ONIOM energy of the complex.

6.2.4. Point Mutations

Mutations of Tyr127, His136, and Tyr159 (specifically, Y127A, H136A, and Y159A) were performed to determine the role of the active site amino acid residues in the cleavage of the glycosidic-bond of ϵ A and 3MeA. Additionally, Y127W and Y159W mutations were considered for the ϵ A substrate to allow for comparison to experimentally-measured⁶⁷ changes in the wild-type barrier height. To ensure that the stationary points did not collapse upon optimization, only constrained wild-type stationary points (C1'–N9 and C1'–O_{wat}⁵⁰² distances held fixed) were considered. Mutations of wild-type residues to alanine were generated by replacing Cy with a hydrogen atom and removing any additional atoms of the original R-group, while mutations to tryptophan were generated by positioning the new R-group to best resemble the orientation recently proposed by O'Brien and coworkers.⁶⁷ The coordinates of only the new residue was first optimized, and then the QM region was allowed to relax while keeping the entire MM region fixed. The charges of the QM region were then fully converged to allow comparison to the (wild-type) constrained stationary points, and frequency calculations were completed to confirm the nature of stationary points and obtain Gibbs free energy corrections. It should be noted that this

choice in mutational structures allows the energetic effects of the mutation to be determined rather than the structural and energetic effects considered in experimental mutational studies. Due to the lack of structural information available for these mutations, this comparison is arguably the best approach to isolate the contribution of each residue to the barrier corresponding to the wild-type mechanism.

6.3. Results

Through careful consideration of the crystal structure of E125Q-AAG bound to ϵ A-containing DNA (PDB entry 1EWN⁵⁷), reaction coordinates corresponding to the glycosidic-bond cleavage (C1'–N9) and the nucleophilic water addition (C1'–O_{wat}) were chosen to construct a series of reaction PES. Specifically, for each substrate considered (ϵ A, 3MeA, A), two water molecules (Wat502 and Wat517) were investigated as the nucleophile in the reaction since both waters are in close proximity to C1'. In particular, Wat502 is closer to Glu125 (general base), while Wat517 is connected to neutral substrates through a water chain to Wat13 (Figure 6.1b). For both nucleophile choices, Wat13 is able to protonate the neutral substrates, even though leaving-group activation is not explicitly forced through the choice of reaction coordinates. Details of the ONIOM(QM:MM) PES and refined stationary points will be presented for each substrate individually, and subsequently point mutation results for both neutral and cationic substrates will be discussed.

6.3.1. 1,N⁶-ethenoadenine (ϵ A) Substrate

The PES for excision of the ϵ A substrate using Wat502 or Wat517 as the nucleophile are shown in Figures 6.3a and 6.3b (relative energies in Appendix I), respectively. In both plots, the bottom left region contains the reactant (R), which has a glycosidic-bond distance of 1.500 Å, and C1'–O_{wat} nucleophile distance of 3.200 Å or 3.000 Å for the Wat502 or

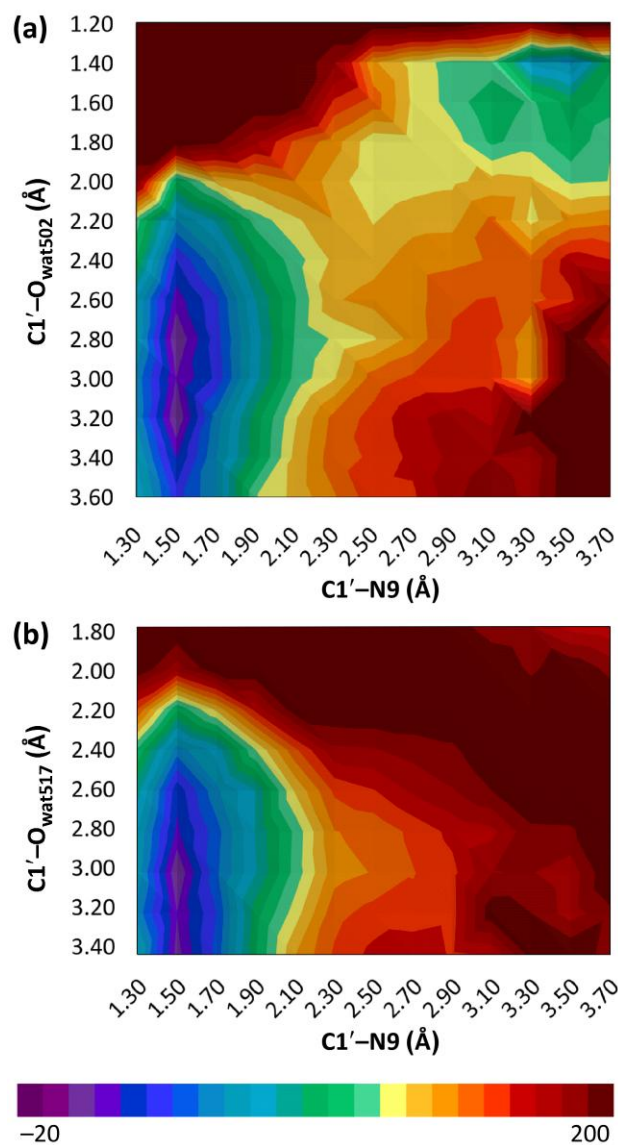


Figure 6.3. Reaction surfaces for the glycosidic-bond (C1'-N9) cleavage in the ϵ A nucleotide by AAG using (a) Wat502, or (b) Wat517 as the nucleophile. The ONIOM(M06-2X/6-31G(d):AMBER) energies (ΔE , kJ mol⁻¹) are reported relative to the respective reactant, where each colour band reflects a 10 kJ mol⁻¹ energy contour.

Wat517 nucleophile, respectively. When Wat502 acts as the nucleophile, a concerted transition state (TS) occurs at a C1'-N9 distance of 2.300 Å and C1'-O_{wat502} distance of 2.200 Å, while a dissociative TS is found for Wat517 (located at a C1'-N9 distance of 3.300 Å and C1'-O_{wat517} distance of 3.000 Å). The concerted transition state on the Wat502 surface is much lower in energy (by 51.1 kJ mol⁻¹ or 38%) than the dissociative TS found for Wat517,

implying that Wat502 is a more likely nucleophile for the glycosidic-bond cleavage mechanism. Therefore, completion of the entire PES for the reaction involving Wat517 was deemed unnecessary and this potential nucleophile was not further considered. For the Wat502 nucleophile, the endothermic product (P) is located at a C1'-N9 distance of 3.500 Å and C1'-O_{Wat502} distance of 1.400 Å.

To ensure QM charges are conserved along the entire reaction path, the RESP charges for the stationary points identified on the Wat502 PES were fully converged while maintaining fixed reaction coordinates (constrained (Table 6.1 and Appendix I)), or relaxing these reaction coordinates (relaxed (Table 6.1 and Figure 6.4)). The relaxed reactant is very similar to the constrained reaction coordinate distances, with the exception that the water nucleophile (Wat502) moves further from C1' (by 3.356 Å) to be more consistent with the crystal structure distance (3.613 Å).⁵⁷ The flipped-out nucleotide adopts the C3'-*exo* sugar puckering observed in the crystal structure, which is maintained throughout the reaction. The nucleobase-protein π - π interactions slightly change from the original crystal structure orientation, but are consistent across all (constrained and relaxed) stationary points. Specifically, Tyr127 and His136 are more tightly bound in the relaxed reactant than the crystal structure⁵⁷ (by 0.335 Å and 0.399 Å, respectively) and are more planar with respect to the nucleobase (12.1° and 40.3° becomes 4.1° and 7.7°, respectively).^b It is expected that this difference is at least in part due to the M06-2X functional slightly overbinding π - π interactions;¹³² however, deviations could also arise since comparisons are being made to a crystal structure, which represents an average geometry. By considering the TS complexes, the reaction barrier decreases by 5.2 kJ mol⁻¹ when the distance constraints are removed, due to a slight increase in the glycosidic bond distance (0.110 Å) and a small decrease in the

^b Stacking and T-shaped interaction distances (in Å) are measured between heavy atom ring centroids (Tyr127, His136, or Tyr159) and the nucleobase heavy atom ring plane, and angles (in °) are measured between heavy atom ring planes (nucleobase and Tyr127, His136, or Tyr159).

nucleophile distance (0.087 Å). Nevertheless, the relaxed TS is consistent with a concerted mechanism as determined from the original PES. The endothermic product binds more tightly to the sugar moiety when the reaction coordinates are relaxed (by 0.619 Å), leading to a decrease in the reaction energy by 19.4 kJ mol⁻¹.

Table 6.1. Relative energies (ΔE) and Gibbs free energies (ΔG) for the concerted mechanism used by AAG to excise the ϵA and 3MeA substrates.^[a]

	ϵA				3MeA			
	constrained ^[b]		relaxed ^[c]		constrained ^[b]		relaxed ^[c]	
	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG
TS	101.3	88.9	96.1	87.3	75.0	62.1	70.6	57.9
P	58.4	75.4	39.0	43.5	-98.0	-26.2	-19.1	-21.9

^[a] ONIOM(M06-2X/6-31G(d):AMBER) energies are reported in kJ mol⁻¹ and are relative to the corresponding reactant. ^[b] The C1'-N9 and C1'-O_{wat502} distances were held fixed, but the RESP charges for the QM region were fully converged. See Computational Details. ^[c] No distance constraints were enforced and the RESP charges for the QM region were fully converged. See Computational Details.

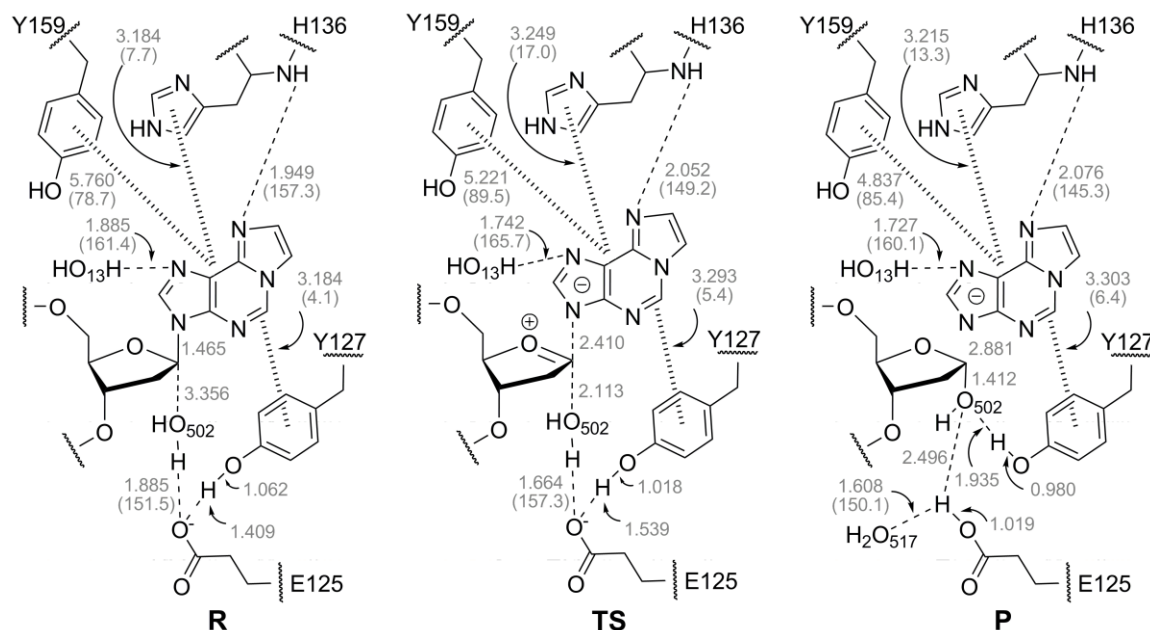


Figure 6.4. Important ONIOM(M06-2X/6-31G(d):AMBER) structural information (hydrogen-bond distances in Å (angles in ° and in parentheses)) for the fully relaxed stationary points for the excision of ϵA by AAG.^b

The geometric changes as the reaction progresses can be observed in Figure 6.5. Proceeding from the ONIOM(M06-2X/6-31G(d):AMBER) relaxed R to TS, the ϵA base tilts away from the sugar in a relatively unchanged active site (Figure 6.5a) to maintain a similar

water chain around the nucleotide (Figure 6.5b). Interestingly, the angles between the molecular planes of the nucleobase and active site amino acid rings (Tyr127, His136, and Tyr159) increase as a result of the more tilted nucleobase in the TS geometry (Figures 6.4 and 6.5c). The hydrogen-bonding distance between Wat13 and the N7 site of ϵ A decreases from the R to the TS by 0.143 Å, but proton transfer does not occur at in any stage of the reaction. Transfer of the nucleophilic water (Wat502) proton to the general base (Glu125) does not happen until after the transition state. Following proton transfer from the nucleophile, the hydrogen-bond stabilization originally provided to Glu125 by Tyr127 is replaced by Wat517 (Figure 6.4), which results in a tightly bound water chain in the product (Figure 6.5b). Interestingly, this water chain orientation is optimally positioned to regenerate the active form of this enzyme.

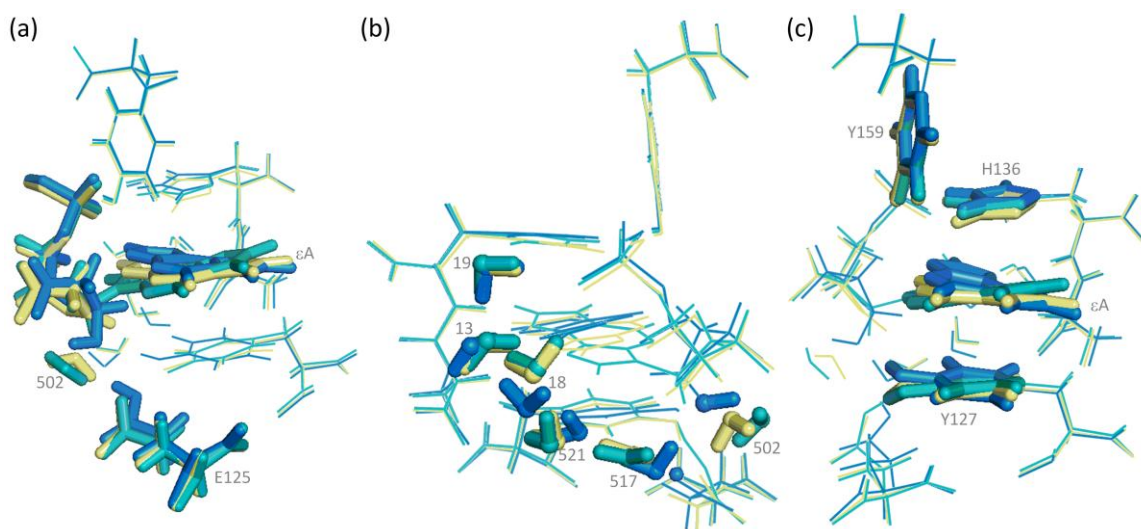


Figure 6.5. Overlay of the QM regions from relaxed ONIOM(M06-2X/6-31G(d):AMBER) calculations for excision of ϵ A by AAG, where the structure shown in green correspond to the reactant, yellow to the transition state, and blue to the product. Tube representations highlight the (a) ϵ A substrate, nucleophilic water molecule (Wat502) and the general base (Glu125), (b) active site water molecules, and (c) π - π interactions between the ϵ A nucleobase and Tyr127, His136, and Tyr159.

6.3.2. 3-methyladenine (3MeA) Substrate

When 3MeA is placed in the active site of AAG and Wat517 is considered as a

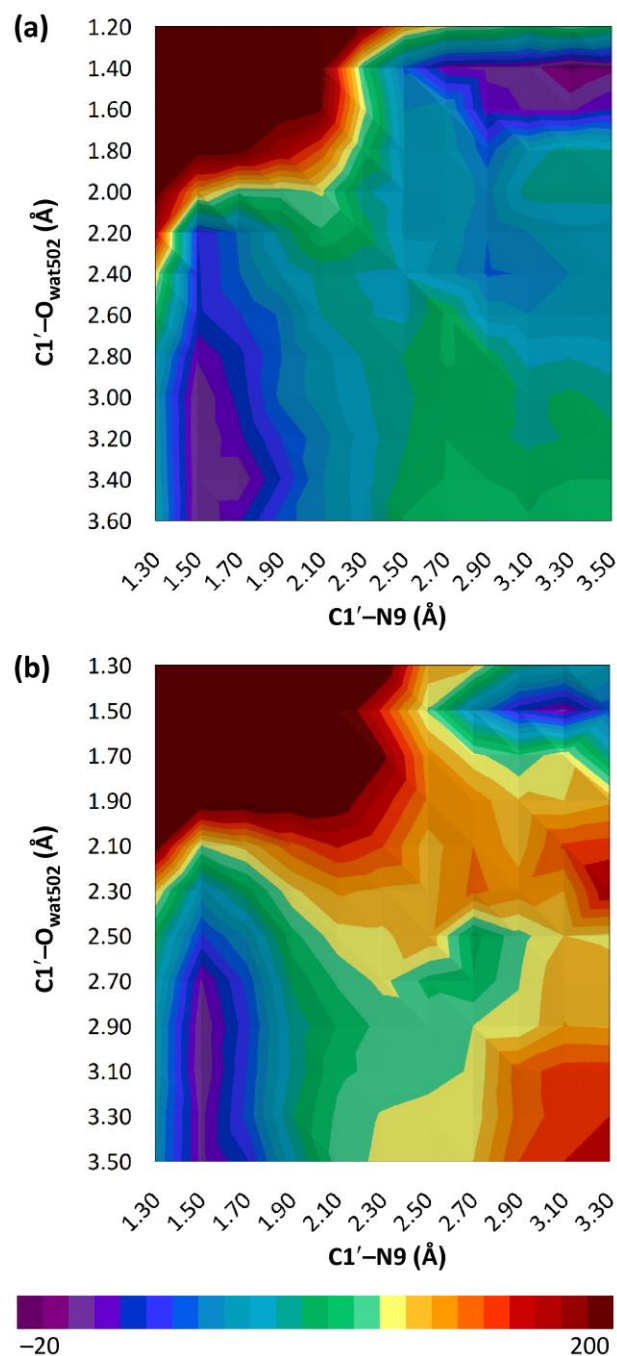


Figure 6.6. Reaction surfaces for the glycosidic-bond (C1'-N9) cleavage mechanism in the (a) 3MeA and (b) A nucleotides by AAG using Wat502 as the nucleophile. The ONIOM(M06-2X/6-31G(d):AMBER) energies (ΔE , kJ mol⁻¹) are reported relative to the respective reactant, where each colour band reflects a 10 kJ mol⁻¹ energy contour.

nucleophile, the resulting PES is too high in energy to be viable and a much more realistic PES is determined when C1'-O_{wat502} is one of the reaction coordinates (Figure 6.6a and

Appendix I). The corresponding reactant is located at a C1'–N9 distance of 1.500 Å and a C1'–O_{wat502} distance of 3.200 Å. The lowest energy transition state corresponds to a concerted pathway (C1'–N9 distance of 2.300 Å and C1'–O_{wat502} distance of 2.600 Å), where a (15.5 kJ mol⁻¹) slightly higher in energy, more dissociative TS occurs at a C1'–N9 distance of 2.700 Å and C1'–O_{wat502} distance of 3.000 Å. The overall reaction is exothermic with the product located at a C1'–N9 distance of 3.300 Å and C1'–O_{wat502} distance of 1.400 Å.

Similarly to εA, the stationary points identified from the 3MeA excision PES were refined by converging the charges in the QM region while constraining the two reaction coordinates (constrained (Table 6.1 and Appendix I)) or relaxing the two constraints (relaxed (Table 6.1 and Figure 6.7)). The energies and structures of these stationary points are in good agreement, where the (concerted) reaction barrier decreases by only 4.4 kJ mol⁻¹ when the stationary points are fully relaxed (glycosidic-bond distance increases by 0.254 Å and nucleophile distance decreases by 0.248 Å). The barrier height for the excision of

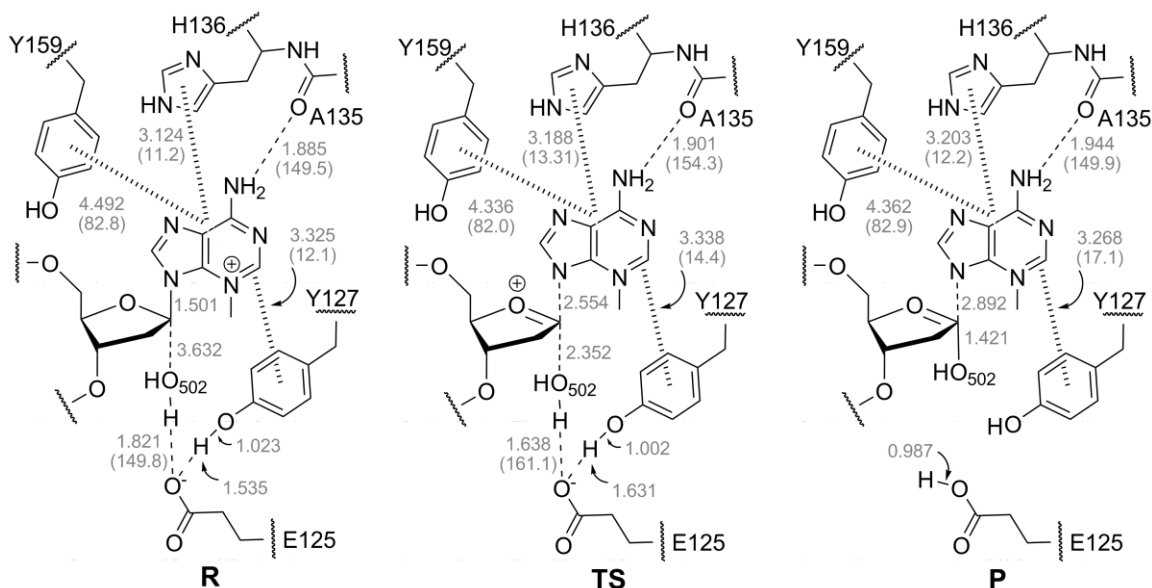


Figure 6.7. Important ONIOM(M06-2X/6-31G(d):AMBER) structural information (hydrogen-bond distances in Å (angles in ° and in parentheses)) for the fully relaxed stationary points for the excision of 3MeA by AAG.^b

3MeA is 25.5 kJ mol⁻¹ (ΔG is 29.4 kJ mol⁻¹) lower in energy than that for the ϵ A reaction, which results from the inherently-destabilized glycosidic bond in the cationic lesion.^{4,35} The relaxed product binds more tightly to the sugar moiety, but is less exothermic than the corresponding constrained stationary point.

Large structural changes occur in the active site of AAG upon binding of a cationic alkylation lesion. For example, Wat13 reorients and interacts with the backbone nitrogen of Ala135 instead of the N7 site of neutral ϵ A (Figure 6.8). Additionally, the backbone N-H of His136 that is directed towards the N6 site of ϵ A rearranges to form a hydrogen bond between the N6 amino group of 3MeA and the carbonyl oxygen in the backbone of Ala135 (Figure 6.8). Indeed, the 3MeA reactant is more tilted in the active site relative to the DNA backbone (the χ ($\angle$ (O4'-C1'-N9-C4)) dihedral angle is 173.1° compared with 180.5° for ϵ A) to maximize the interactions between the Ala135 backbone and the hydroxyl group of Tyr159 (O_{Tyr159}-H_{3MeA} distance with a N3-methyl group hydrogen atom of 3MeA is 2.270 Å). Furthermore, the DNA-protein π - π interactions between 3MeA and Tyr127 or His136 are less planar and more spatially separated than observed for ϵ A, while the opposite is true for Tyr159 (Figure 6.4 and Figure 6.7). Despite these ONIOM(QM:MM) structural differences, the PES for both the ϵ A and 3MeA substrates contain a hydrogen bond between the general base (Glu125) and Tyr127 before nucleophile (Wat502) proton transfer occurs, which is after the TS in both reactions.

6.3.3. Adenine (A) Substrate

The only energetically-feasible adenine excision pathway occurs when Wat502 is the nucleophile (Figure 6.6b and Appendix I). Therefore, as is true for all of the substrates examined in this study, a protein-bound water chain that connects C1' to the Wat13 molecule located near N7 of neutral substrates is not used to cleave the glycosidic bond. The

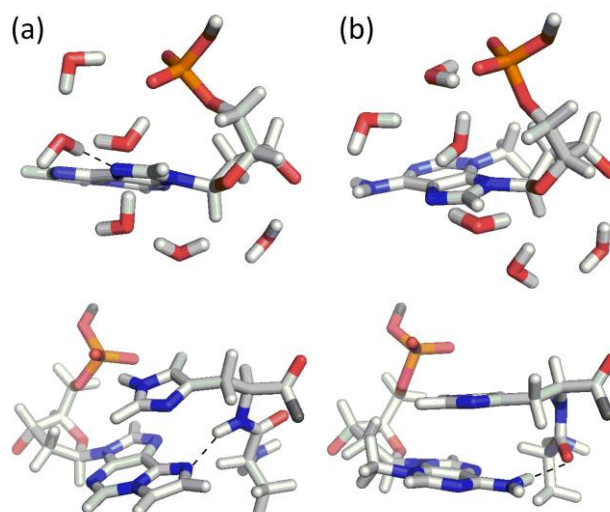


Figure 6.8. Relaxed ONIOM(M06-2X/6-31G(d):AMBER) reactants for the (a) ϵ A and (b) 3MeA substrates, highlighting the interactions between the substrate and active site water molecules (top), and the substrate, Ala135 and His136 (bottom).

adenine reactant occurs at a glycosidic-bond distance of 1.500 Å and nucleophile distance of 3.100 Å. However, unlike the surfaces calculated with ϵ A and 3MeA, the lowest energy TS is dissociative, and occurs at a C1'–N9 distance of 2.500 Å and C1'–O_{wat502} distance of 2.900 Å. This leads to an intermediate at glycosidic and nucleophilic distances of 2.700 and 2.500 Å, respectively. As the nucleophilic water molecule associates towards C1', another transition state (glycosidic distance of 2.900 and nucleophilic distance of 2.300 Å) occurs before the slightly endothermic product is formed (C1'–N9 distance of 3.100 Å and C1'–O_{wat502} distance of 1.500 Å). The PES also reveals a higher-energy (22.9 kJ mol⁻¹) concerted TS at glycosidic and nucleophilic distances of 2.300 Å and 2.300 Å, respectively.

When the charges for the QM region are fully converged for the constrained stationary points (Table 6.2 and Figure 6.9), a stepwise ($D_N^*A_N$) mechanism is confirmed since the concerted barrier is 23.5 kJ mol⁻¹ (ΔG of 20.6 kJ mol⁻¹) higher in energy than the dissociative barrier. However, this preferred mechanism for A bond cleavage is still 17.4 kJ mol⁻¹ (ΔG of 18.6 kJ mol⁻¹) higher in energy than the (concerted) barrier height for ϵ A. Full relaxation of

Table 6.2. Relative energies (ΔE) and Gibbs free energies (ΔG) for the excision of A by AAG.^[a]

	A constrained ^[b]	
	ΔE	ΔG
TS ^[c]	137.0	126.5
TS _{dissociative} ^[d]	113.5	105.9
I ^[d]	110.3	98.5
TS _{associative} ^[d]	126.3	111.9
P	34.9	34.5

^[a] ONIOM(M06-2X/6-31G(d):AMBER) energies are reported in kJ mol⁻¹ and are relative to the corresponding reactant. ^[b] The C1'-N9 and C1'-O_{wat502} distances were held fixed, but the RESP charges for the QM region were fully converged. See Computational Details. ^[c] The transition state along a concerted pathway. ^[d] Corresponds to a stepwise mechanism where the base first dissociates from the sugar (TS_{dissociative}) to form an intermediate (I) and then association of the nucleophilic water molecule (TS_{associative}) occurs.

the A stationary points was unsuccessful due to large fluctuations in the water chain within the active site. However, the constrained stationary points reveal that the N6 amino group of adenine puckers away from the backbone N-H of His136 throughout the reaction (C5-C6-N6-H6 dihedral angle ranges from 41.6° (dissociative TS) to 66.6° (R)) to reduce steric clashes. As the nucleobase dissociates from the sugar, the N7 site maximizes a hydrogen bond with Wat13 and the backbone N-H bond of His136 (Figure 6.9). The π -containing active site amino acids bind closer to A compared to ϵA , where slightly tilted interactions with Tyr127 and His136 in the reactant become much more planar as the reaction proceeds (Figure 6.9). Even more intriguing is the disappearance of the stabilizing hydrogen bond between Tyr127 and the general base (Glu125) in the A reactant (Figures 6.9 and 6.10). Instead, Wat517 simultaneously donates a hydrogen bond to Glu125 and accepts a hydrogen bond from Tyr127 in the stationary points prior to nucleophilic proton transfer (Figures 6.9 and 6.10).

6.3.4. Point Mutations

Using constrained stationary points, a mutational analysis was conducted to better understand the involvement of various amino acids in the excision of neutral and cationic

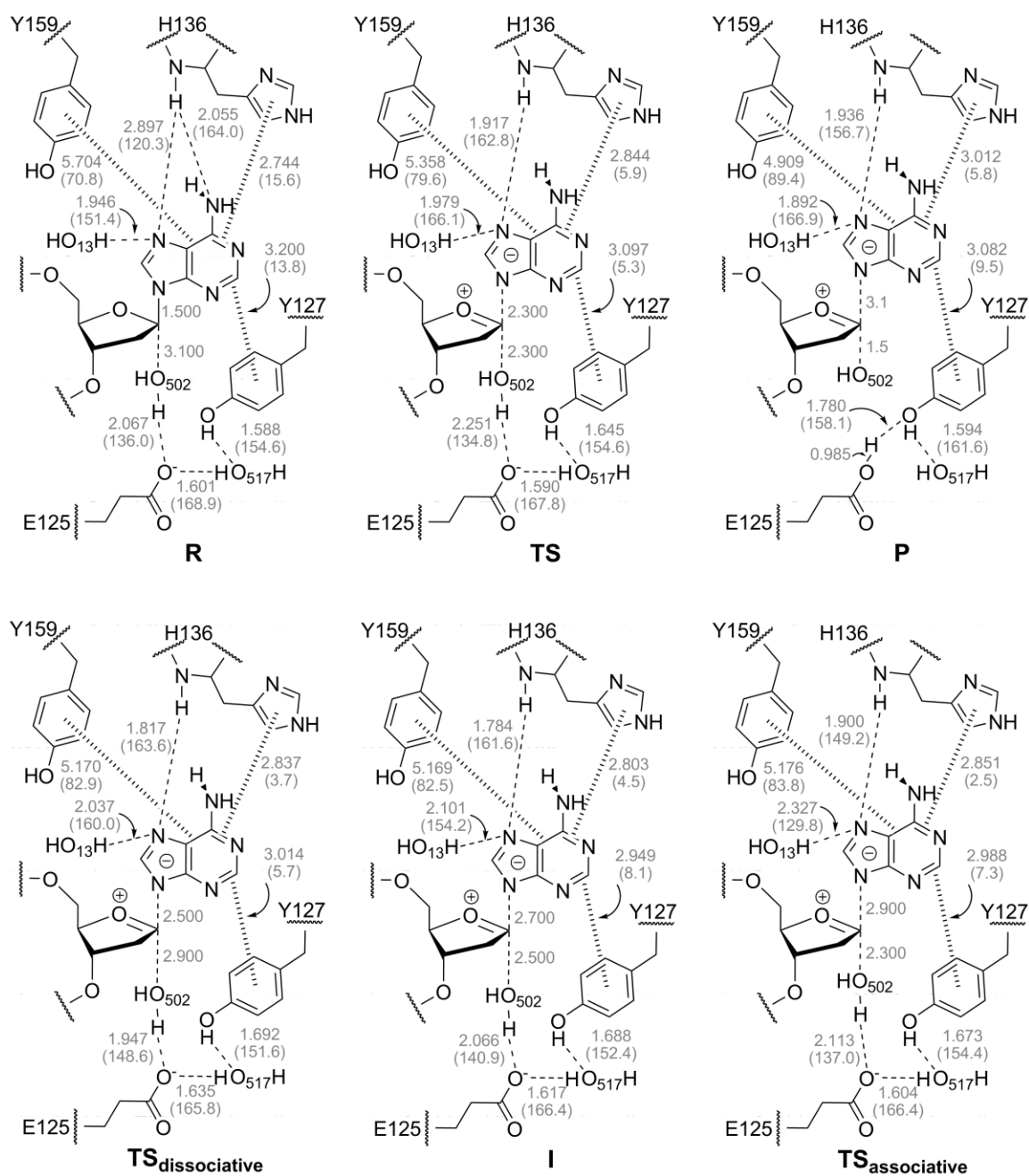


Figure 6.9. Important ONIOM(M06-2X/6-31G(d):AMBER) structural information (hydrogen-bond distances in Å (angles in ° and in parentheses)) for the constrained stationary points for the excision of A by AAG.^b

alkylation lesions (ϵ A and 3MeA, Table 6.3). Specifically, Y127A, H136A and Y159A mutations were examined to provide insights into the energetic effects of removing active site π -systems on the bond cleavage barrier for neutral and cationic lesion excision. These

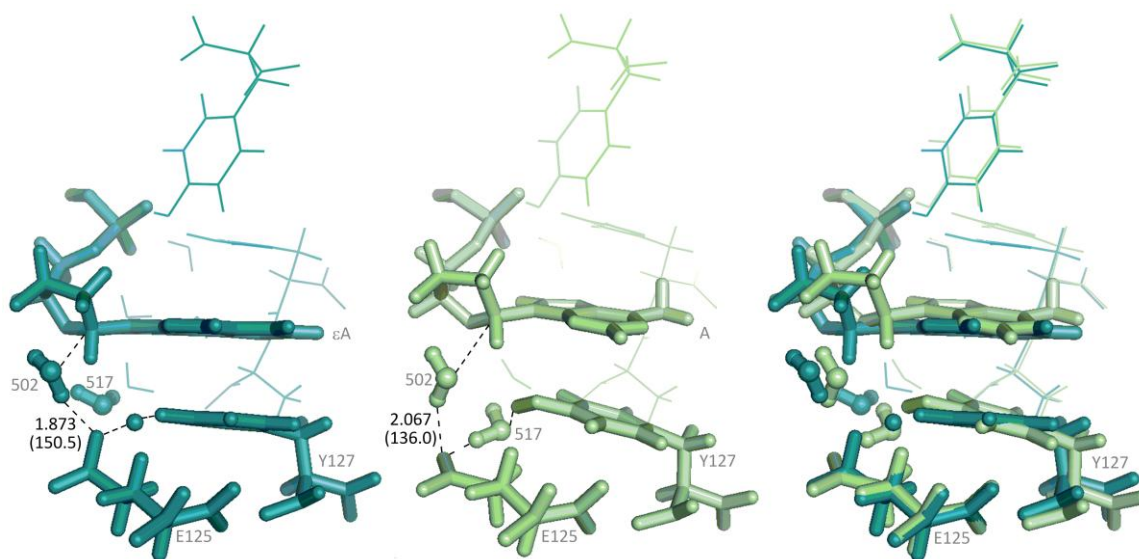


Figure 6.10. QM regions from constrained ONIOM(M06-2X/6-31G(d):AMBER) reactants for excision of εA (dark green) and A (light green) by AAG. Tube representations highlight the substrate, nucleophilic water molecule (Wat502), the general base (Glu125), Wat517, and Tyr127, where the nucleophilic activation hydrogen-bond distances (Å) and angles (°, in parentheses) are also reported.

point mutations increase the wild-type εA barrier height by 11.7 (H136A), 15.9 (Y159A), or 27.5 kJ mol⁻¹ (Y127A). Contrary to the εA results, these mutations for the 3MeA substrate result in a very small effect (0.7 kJ mol⁻¹ increase in barrier for Y159A), or a significant decrease in the reaction barrier (by up to 38.1 kJ mol⁻¹). In addition, Y127W and Y159W were examined with εA to allow for comparison of the calculated (energetic) mutational results (Table 6.3) to recently reported (chemical step) reaction barriers.⁶⁷ The Y127W mutation was found to have a larger effect on the wild-type barrier height (30.9 kJ mol⁻¹) than the Y159W mutation (27.2 kJ mol⁻¹).

6.4. Discussion

6.4.1. The Excision of εA by Wild-Type, Y127W, and Y159W Agrees with Experiment

This chapter presents the first atomic level description of the chemical step used by AAG. Detailed ONIOM(QM:MM) calculations reveal that a concerted mechanism is used to

Table 6.3. Calculated barrier heights and changes in barrier heights from single point mutations of AAG with the ϵ A and 3MeA substrates.^[a]

	<u>ϵA</u>		<u>3MeA</u>	
	ΔE	ΔG	ΔE	ΔG
Wild-type	101.3	88.9	75.0	62.1
H136A	113.0 (11.7)	111.4 (22.5)	36.9 (-38.1)	28.2 (-33.9)
Y127A	128.8 (27.5)	118.5 (29.6)	53.9 (-21.1)	45.1 (-17.0)
Y159A	117.2 (15.9)	107.6 (18.7)	75.7 (0.7)	61.9 (-0.2)
Y127W	132.2 (30.9)	124.5 (35.6)		
Y159W	128.5 (27.2)	124.6 (35.7)		

^[a] ONIOM(M06-2X/6-31G(d):AMBER) barrier heights are reported relative to the reactant (in kJ mol⁻¹). Changes in the barrier heights (in parentheses) are reported relative to the wild-type barrier, where a positive value represents an increase in barrier height upon mutation.

excise ϵ A with a 96.1 kJ mol⁻¹ reaction barrier ($\Delta G^\ddagger = 87.3$ kJ mol⁻¹). Very recent studies which measured single turnover rate constants are the only work, to the best of my knowledge, to report a barrier corresponding to the glycosidic-bond cleavage step of ϵ A excision.^{47,67} Excellent agreement between experimental (90.7 kJ mol⁻¹)^{47,67} and computational barriers provides strong support for this computational approach. Indeed, this comparison suggests that the calculations used in the present study can contribute detailed chemical insights into other aspects of the chemical mechanism with confidence.

The recent kinetic study mentioned above also examined the effects of substituting the two active site tyrosine residues with tryptophan on the nucleotide flipping and base excision steps.⁶⁷ It was determined that the Y127W and Y159W mutant proteins have robust excision activity towards ϵ A-containing DNA ($\Delta G^\ddagger$ of 94.0 and 92.8 kJ mol⁻¹, respectively).⁶⁷ Although the calculated $\Delta G^\ddagger$ barriers for these two mutations are indistinguishable, the energetic result of these mutations increases the calculated wild type barrier to 132.2 and 128.5 kJ mol⁻¹ for Y127W and Y159W, respectively (Table 6.3). Indeed, this mutational analysis predicts the experimentally observed trend that Tyr127 plays a more important role in chemical catalysis for ϵ A excision, which will be further discussed below. It is acknowledged that the calculated energetic contribution of these mutations is larger than the (energetic and structural) contributions observed through experiment.

Although better agreement is expected upon full relaxation of the system, this would require full PES scans to identify appropriate stationary points, which were deemed unnecessary since the effects of tyrosine mutations are not the focus of the current study. Nevertheless, the reasonable match further verifies the ability of the current approach to describe this enzymatic mechanism.

6.4.2. AAG Prefers an S_N2 Mechanism to Excise Both Neutral and Cationic Lesions

Since the catalytic mechanism of AAG is currently unknown, the chemical mechanism must be conjectured by considering the corresponding nonenzymatic depurination reactions^{70,303-313} and other enzymatic hydrolysis reactions.^{28-29,71,306,314} Experimental studies of spontaneous depurination^{70,303-305,307-308,310} and the reactions catalyzed by other monofunctional DNA glycosylases (uracil DNA glycosylase (UDG)³¹⁴ and MutY DNA glycosylase (MutY)⁷¹) support a dissociative ($D_N^*A_N$) N-glycosidic-bond cleavage mechanism, which results in a transition state with a positive charge accumulated on C1' and O4' of the sugar moiety and little association of the water nucleophile.²⁸⁻²⁹ Further support for a dissociative hydrolysis mechanism is gained from the ability of positively charged abasic DNA analogues (4-azaribose and 1-azaribose), which mimic an oxacarbenium ion-like transition state, to function as tight-binding inhibitors of AAG.^{56,64} However, crystal structures indicate that a more associative mechanism (such as a concerted (A_ND_N) mechanism) may be favoured by AAG since the nonspecific active site may be unable to stabilize a wide variety of leaving groups, and the nucleophilic water is wedged between the general base and the anomeric carbon.²⁸ Furthermore, there is no reason to believe that this enzyme would exploit the same mechanism as the corresponding nonenzymatic reaction.⁷¹ Indeed, many enzymes, such as some O-glycosidases,³¹⁵ stabilize transition states that are different from the uncatalyzed glycosidic-bond cleavage reaction.

Examination of the complete reaction surfaces for the ϵ A and 3MeA substrates suggests that AAG prefers to excise both (neutral and cationic) lesions through a concerted ($A_N D_N$) mechanism. In fact, one benefit of performing detailed reaction PES scans is that a concerted mechanism is revealed to be preferred over the dissociative ($D_N^* A_N$) mechanism by over 20 or 15 kJ mol⁻¹ for the ϵ A and 3MeA substrates, respectively. Therefore, these results elucidate that AAG uses a concerted ($A_N D_N$) chemical step as a nonspecific strategy to excise both neutral (ϵ A) and cationic (3MeA) lesions. Indeed, a mechanistic strategy that is not specific to the chemical composition or charge of the lesion excised may be vital in the mechanism-of-action of this promiscuous DNA glycosylase.

6.4.3. π - π Interactions Contribute Differently to Neutral and Cationic Lesion Catalysis

To better understand the role of the individual DNA-protein π - π interactions found in the active site of AAG, the catalytic contribution of each amino acid π -system to the excision of neutral (ϵ A) and cationic (3MeA) lesions was investigated. Specifically, Y127A, H136A, and Y159A mutations were considered as discussed in Section 6.2.4. Despite previous proposals that π - π interactions could be anticatalytic for neutral base excision,²⁸ the present work indicates that the π -systems of Tyr127, His136, and Tyr159 favourably contribute to catalysis by lowering $\Delta G^\ddagger$ by 29.6, 22.5, and 18.7 kJ mol⁻¹, respectively (Table 6.3). On the contrary, Tyr127, His136, and Tyr159 were found to negligibly affect or be anticatalytic towards the excision of 3MeA by increasing the $\Delta G^\ddagger$ by 17.0, 33.9, and 0.2 kJ mol⁻¹, respectively. These results are consistent with the previous high-level *ab initio* findings in this thesis that the π^+ - π stacking and T-shaped interactions between 3MeA and histidine or tyrosine can be up to 135% more stabilizing than the corresponding π - π interactions involving A. Taken together, this suggests that the anticatalytic contribution of these conjugated π -rings is due to overbinding of the cationic reaction complex.

In addition to clarifying the role of the active site π -containing amino acid residues, which is different for the neutral and cationic substrates, this work reveals for the first time how AAG balances between mechanistic specificity and catalytic power.⁴⁰ Specifically, it appears that AAG has evolved to take advantage of the amino acid π -systems to nonspecifically position a wide variety of alkylation damage products in the active site, while at the same time maximize catalytic power towards (neutral) lesions that are inherently more difficult to excise. Although the ability to also remove neutral DNA damage comes at the expense of the excision barrier for the repair of cationic lesions, stronger attraction and binding of cationic lesions is achieved through enhanced π - π contacts as AAG processively searches the DNA strand for damage.^{46,48}

6.4.4. A General Acid Contributes to Neutral Base Excision Through Hydrogen-Bond Donation

To investigate the recently proposed possibility that a protein-bound water molecule is responsible for protonation of neutral substrates,⁶⁰ the current QM/MM model unbiasedly incorporated Wat13 such that hydrogen bonding to, or protonation of, the N7 site of neutral substrates (ϵ A or A) was not explicitly forced. Although Wat13 was found to donate a hydrogen bond to N7 of ϵ A throughout the excision reaction (Figure 6.4), no proton transfer to N7 occurs. Interestingly, deletion of Wat13 from the ϵ A mechanism results in an increase in $\Delta G^\ddagger$ of 28.9 kJ mol⁻¹,^c which suggests that hydrogen-bond donation or only partial protonation is enough to catalyze this reaction. This finding challenges the generally-accepted protonation mechanism, which is a common, but not universal, feature of enzymatic purine hydrolysis reactions.³¹⁶ However, closer examination of the original study that proposed the role of this general acid reveals that hydrogen-bond donation to the

^c Calculated as the difference between the constrained ONIOM(M06-2X/6-31G(d):AMBER) barrier heights where Wat13 was present and when Wat13 was deleted. The QM charges used in the Wat13-deleted single-point calculations were derived from the constrained stationary points with Wat13 removed without further optimization calculations being considered.

neutral base can also explain the observed pH-rate profile.⁶⁴ Furthermore, this observation is consistent with the computational work by Lee and coworkers, who suggested AAG will excise ϵ A and Hx without nucleobase protonation since greater (weaker) N9 acidities (N7 proton affinities) make these lesions easier to excise (harder to protonate) than the natural purines.⁷⁴⁻⁷⁵ Interestingly, despite the large proton affinity of the N7 site of A,⁷⁴⁻⁷⁵ only hydrogen-bond stabilization with Wat13 was observed throughout the A excision mechanism (Figure 6.9). Therefore, although these results support suggestions that a general acid mechanism is important for the excision of neutral substrates, the current work proposes that hydrogen-bond donation from the general acid provides enough stabilization to lower the excision barrier. This is consistent with mechanistic proposals for UDG, where a neutral histidine residue unambiguously stabilizes the uracil leaving group only through hydrogen-bond donation.²⁸

6.4.5. AAG Also Uses the Chemical Step to Discriminate Against the Natural Purines

AAG is just one example of a broadly specific enzyme that employs a weaker catalytic mechanism to process many different lesions, and yet avoids intolerable excision of substrates that are essential to cell function.⁴⁰ The nucleotide-flipping step used by AAG provides discrimination against the natural bases since they are less readily exposed to the enzyme active site.^{40,54} Crystal structures also reveal that His136 and Asn169 in the AAG active site provide unfavourable interactions with the exocyclic amino groups of A and G, respectively.⁵⁷ However, it is currently unknown whether these interactions are enough to prevent excision of the natural purines. Therefore, it was essential for the current study to also examine the excision of A by this promiscuous enzyme.

The present calculations indicate that excision of A is higher in energy, and proceeds in a different manner, than the excision of the neutral lesion ϵ A. By comparing the stationary

points of the A substrate to those of ϵ A, insights into why these energetic and mechanistic differences are observed can be obtained. Specifically, a stabilizing hydrogen bond between the hydroxyl group of Tyr127 and the carbonyl of the general base (Glu125) is present in both the ϵ A and 3MeA surfaces, but not for A. Instead, Wat517 donates a hydrogen bond to Glu125 (accepts from Tyr127) in the stationary points that occur before nucleophilic proton transfer on the A surface (Figure 6.9). An overlay of the ϵ A and A reactants reveals that A is inserted further into the active site of AAG (Figure 6.10), which allows the active site water chain to move closer to Tyr127 and form the new hydrogen bond. As a result of this hydrogen-bond rearrangement, Glu125 in the A reactant reorients to be further from C1', which moves the water nucleophile (Wat502) further from the general base and, perhaps more importantly, Wat502 is poorly aligned for nucleophile activation. Indeed, Wat502 is misaligned throughout the entire reaction mechanism of A (Figure 6.9), which results in a large barrier for water association (Figure 6.6b). Therefore, this work indicates for the first time that Y127 not only provides stabilization to E125,⁵⁷ but also plays a larger role in orienting E125 for effective nucleophile activation. Additionally, one of the most important findings is that AAG can use the chemical step to discriminate against the natural bases by potentially misaligning and poorly activating the nucleophilic water molecule.

Support for this new proposal that Glu125 plays a key role in aligning the nucleophilic water molecule is gained from the experimentally-measured decrease in activity of the E125Q and E125A mutants towards ϵ A.⁶⁴ This suggests that the catalytic contribution from the general base is larger than expected for chemical activation of a nucleophile participating in a dissociative glycosidic-bond cleavage reaction.⁶⁴ The calculated concerted transition state found in this chapter could explain this larger catalytic contribution of Glu125 than that expected for a more dissociative mechanism. Additionally, these mutational experiments also suggest that Glu125 may play an important role in positioning

the nucleophilic water for attack at the anomeric carbon of the substrate.⁶⁴ In fact, the current work shows that the general base (Glu125) plays a very important role in activating the water nucleophile by orienting the water molecule for the concerted excision mechanism of its preferred substrates and accepting the proton from the water nucleophile in the late stages of this reaction. In addition to this newly identified role for Glu125, these calculations are consistent with the generally accepted function of this general base to stabilize the cationic charge formed on the sugar moiety in the transition state of most glycosylase excision reactions.²⁸⁻²⁹

Investigations of a recent crystal structure with the ϵ C inhibitor bound to Δ 80AAG led to a proposal that ϵ C is not excised by AAG since the leaving group cannot be activated through protonation.⁶⁰ However, the present work indicates that protonation is not necessary for glycosidic-bond cleavage to occur. Despite the fact that poor nucleophilic water activation was dismissed as the reason for low glycosylase activity towards ϵ C,⁶⁰ this crystal structure only provides an atomistic perspective of one point on the potential energy surface. In light of the current results, this structure provides further evidence for the proposed importance of nucleophile alignment since, like A, ϵ C is further inserted into the catalytically-active binding site of AAG.⁶⁰ Therefore, the computational results across the entire reaction surface indicate that AAG uses the chemical step as yet another discriminatory strategy to prevent excision of the natural purines.

6.5. Conclusions

In the present study, an atomic perspective of the repair pathway used by AAG to excise neutral 1,N⁶-ethenoadenine (ϵ A) and cationic 3-methyladenine (3MeA) was obtained for the first time. Detailed ONIOM(M06-2X/6-31G(d):AMBER) reaction potential energy surface scans provide chemical insights into the energy landscape of this enzymatic reaction, which were also used to understand whether AAG can use the cleavage step to discriminate

against the natural adenine (A) nucleotide. The excision mechanisms for ϵ A by the wild type, as well as the Y127W and Y159W mutant enzymes, are consistent with very recent experimental data,⁶⁷ which supports the use of this model and provides confidence in the description of all aspects of the chemical step of this DNA glycosylase. Indeed, this work reveals that a concerted mechanism is also preferred for excision of cationic 3MeA, which supports previous speculations that AAG uses a nonspecific strategy to excise both neutral (ϵ A) and cationic (3MeA) lesions. This thesis concludes that neutral π - π interactions cannot provide discrimination over the natural bases, while this chapter determines that these nonspecific DNA-protein contacts add to the catalytic power of this enzyme. In contrast, the conjugated π -systems are used to attract and bind the cationic nucleobases into the active site, but are either insignificant (Tyr159) or anticatalytic (Tyr127, His136) for the glycosidic-bond cleavage mechanism. Additionally, although proton transfer from the recently proposed general acid water molecule to the neutral substrates does not occur, hydrogen-bond donation was found to lower the catalytic barrier, which clarifies the role of a general acid in the excision of neutral lesions. This proposal challenges the commonly accepted protonation mechanism discussed in the literature; however, hydrogen-bond donation can also explain the original experimental pH-profiles that resulted in this general acid proposal.⁶⁴

Finally, the current work shows that the natural base A is further inserted into the active site of AAG than damaged lesions, which misaligns the general base (Glu125) and water nucleophile and leads to poor nucleophile activation. Therefore, this chapter proposes that Glu125 plays a very important role in activating and orienting the water nucleophile, which is supported by other experimental observations in the literature. In fact, this work suggests that this new role for Glu125 allows AAG to discriminate against the natural purines in the chemical step, which can also help explain the low glycosylase activity

exhibited towards some damaged pyrimidines. Therefore, future investigations are necessary to provide further insights into how AAG can bind to a large number of damaged lesions, yet is unable to excise them from DNA, which will be discussed in the next chapter.

Chapter 7. Global Conclusions and Future Work

7.1. Summary

Investigating the repair of DNA alkylation damage in humans through computational techniques provided a unique and challenging framework for this thesis. The work presented can be divided into two main themes: 1) understanding the structure and magnitude of the fundamentally different DNA–protein noncovalent interactions found in the active site of AAG, and 2) the mechanism used by this enzyme to excise both neutral and cationic damaged lesions. This chapter separately summarizes the contributions from this thesis within these two topics, where avenues for future work will also be discussed.

7.2. Noncovalent Interactions

7.2.1. Contributions from this Thesis

This thesis developed a unique methodology for identifying important contacts between the natural nucleobases and the amino acids with conjugated π -rings, which provides an understanding of how a variety of geometric criteria determine the strength of these contacts. High-level *ab initio* calculations reveal that the strongest possible π – π interaction for each nucleobase–amino acid combination is very large, where both stacking and T-shaped interactions are found to be close in magnitude to biologically-relevant hydrogen bonds. Additionally, not only has the current work fully characterized structures with the strongest interactions, but a wide variety of other nucleobase–amino acid interactions have been examined, including C–H $\cdots\pi$, N–H $\cdots\pi$, and lp– π interactions, where these contacts were revealed to also be very favourable. Indeed, the MP2 potential energy surface scans can provide reliable estimates of the magnitude of interactions present in a

variety of experimental DNA/RNA–protein crystal structures of low polarity.⁷⁷

When this methodology was expanded to investigate (neutral and cationic) damaged nucleobases in Chapter 3, the structure of stacked dimers was found to not be greatly affected by neutral or cationic alkylation damage, but the structures of the preferred T-shaped interactions are highly dependent on the charge of the system. Indeed, the strongest T-shaped interactions occur when the most acidic edge is directed towards the (neutral) π -systems of A or ϵ A and the amino acids, or when the most basic edge is directed towards (cationic) 3MeA. It was found that alkylating A to ϵ A only slightly decreases (up to 7%) or increases (up to 43%) the π – π interaction energies, indicating that these interactions alone cannot facilitate a discriminatory recognition or binding of neutral substrates by AAG. Remarkably, formation of cationic 3-methyladenine can increase the corresponding adenine interactions by up to 176%, indicating that these π – π interactions can be used to preferentially bind cationic substrates in the binding step of AAG. The interaction energy decomposition calculations presented in this chapter suggest that the stacking and T-shaped interactions in neutral or cationic systems are fundamentally different, where all three noncovalent interactions (stacking, T-shaped, and hydrogen-bonding) are governed by a distinct interplay of attractive forces.

Chapter 4 expanded upon the dimer interactions of the previous chapters to examine the potential importance of the interplay between multiple noncovalent interactions found in nature. However, extensive scans of the PES reveal that both stacked and T-shaped interactions, as well as both π – π and π^+ – π interactions, exhibit geometric additivity. When the energetic additivity was examined, the synergy energy (E_{syn}) revealed that the sum of the two nucleobase–amino acid interactions is a fairly good estimate of the total trimer interaction energy. Indeed, the generally small magnitude of the additivity energy ($E_{\text{add}} < 2$ kJ mol⁻¹) suggests that these interactions are additive, which further justifies the choice in

this thesis to extensively examine dimer interactions. QTAIM was used to help determine whether the nucleobase–amino acid interactions are equivalent in dimers and trimers, or whether the nucleobase–amino acid interactions differ in different sized complexes, but sum to yield an overall additive interaction. However, conclusions from the QTAIM analysis and interaction energy evaluation are inconsistent and therefore inconclusive.

Using the high-level dimer interaction data presented in Chapters 2 and 3, as well as a recent Wetmore group publication,²²¹ Chapter 5 investigated the performance of a number of density functional methods, as well as other techniques currently used in hybrid approaches, to accurately and efficiently describe the binding strengths and potential energy surfaces of π – π stacking and π – π T-shaped DNA–protein interactions. PBE-D/6-31+G(d,p) was found to provide an excellent description of stacking interactions, but generally overestimates T-shaped interactions. However, PBE-D has a very strong basis set dependence, where the 6-31G(d) basis set erroneously overestimates interaction energies in both neutral and cationic systems, especially for T-shaped contacts. On the other hand, M06-2X has a small basis set dependence. In fact, M06-2X/6-31G(d) was found to provide an excellent description of both stacked and T-shaped, as well as π – π and π^+ – π , DNA–protein interactions, and was therefore selected to study the mechanism of action of AAG, which heavily relies on these stacked and T-shaped contacts.

7.2.2. Future Directions

The work outlined above focused on understanding the fundamentals of stacked and T-shaped contacts, as well as how these interactions are useful in DNA repair. Therefore, future work can be extended in many different directions to further aid in understanding these contacts for this and a variety of other applications. Firstly, all of the noncovalent dimer and trimer complexes considered in this thesis were examined through gas-phase calculations and the role of solvent was neglected. Despite the fact that most interactions

inside biomacromolecular complexes correspond to this gas-phase model,⁷⁷ solvent is undeniably extremely important for gaining a complete picture of these fundamentally important interactions. Therefore, model extensions are necessary to understand how polar and nonpolar solvents affect the preferred structures and stabilities of these noncovalent complexes. Despite the fact that implicit solvation studies can be completed on these noncovalent systems, discrete contacts between solvent molecules can be essential for understanding the true structural characteristics of these complexes. Therefore, these studies could simply involve a systematic addition of individual solvent molecules, such as water, to the preferred gas-phase dimer complex to comprehend how each molecule affects the original interaction strengths.³¹⁷ However, perhaps a more global approach would be to examine how solvent affects the preferred π - π or π^+ - π geometries. Undeniably, examining these dimer complexes through explicit water (QM/MM) MD simulations would also provide valuable insights into how solvent affects these noncovalent interactions in a variety of arrangements. Additionally, research into how the nature of attraction in these solvent-phase complexes changes from the present gas-phase results would be of great interest to the noncovalent community.

The work in this thesis only examined the interactions between the conjugated ring systems of the nucleobase and amino acid. Studies have determined that the addition of the biological backbone does not affect the magnitude of the π - π stacking³¹⁸⁻³¹⁹ or T-shaped³²⁰ interactions, which justifies the model size used in this thesis. However, the addition of the biological backbone to the π - π complex was sometimes found to alter the preferred structure of these complexes due to the additional attractive backbone- π contacts.³¹⁸⁻³²⁰ Since these works only examined one select backbone orientation that was fixed relative to the π -ring system,³¹⁸⁻³²⁰ future studies need to investigate a variety of backbone orientations that are found in nature.

As previously discussed, noncovalent interactions have potential energy surfaces that are very flat and contain a large number of energy minima. Indeed, the work in this thesis is the first step in identifying important noncovalent structures on the PES of DNA–protein π – π and π^+ – π dimers. However, this work does not investigate the fully-relaxed minima, nor does it examine the structures and energetics of the transition structures, which can play important roles in determining relevant geometries of these complexes in nature. Indeed, the continuous improvement of computational techniques and facilities allows for the full relaxation of these dimer systems, and recent work has determined that the (DFT-D) energy barriers between hydrogen-bonded and stacked nucleobase dimers are comparable to their energy of thermal motion at room temperature.³²¹ In fact, the π -systems of DNA and protein components provide an interesting scaffold for further investigations, where the inclusion of biological backbones or local environments could also provide valuable insights into the π – π and π^+ – π contacts commonly observed in nature.

Due to the interplay between multiple noncovalent interactions in macromolecular systems, investigating the geometric and energetic additivity of trimer systems is very important. The work in this thesis needs to be extended to understand whether geometric additivity is truly independent of the relative arrangements of the π -systems and the level of theory used in these computational works. For example, full optimizations of trimer systems could provide insights into the true geometric additivity of these noncovalent interactions. In addition, future trimer studies could examine a cyclic structure involving three π -systems tilted with respect to one another, which has been previously proposed to be nonadditive for systems with small electrostatic components.¹⁰⁰ Even though these geometries may not be relevant to DNA–protein complexes found in nature, these π -systems do provide an interesting framework for studies that wish to examine systems with a range of dipole moments, or acidic and basic properties. Indeed, these investigations

would also need to explore different method and basis set combinations, which perhaps have been designed to have little to no basis set superposition error, to understand how various computational methodologies differ in their additivity descriptions.

Preliminary QTAIM investigations in this thesis showed that it is currently unclear how QTAIM can be used to understand π - π and π^+ - π interactions in dimers and trimers. Indeed, further studies need to consistently evaluate the electron density properties in carefully designed simple and symmetric complexes, like those between water or a cation (such as Na^+) and the π -system of pyrrole or tryptophan. Within these molecular frameworks, a number of different monomer orientations can be considered where the symmetry can systematically be reduced to determine how this affects the QTAIM analysis of π - π and π^+ - π complexes. Additionally, the development of alternative methods that are sensitive enough to accurately describe noncovalent interactions within dimer and trimer complexes would be invaluable in understanding whether noncovalent interactions truly are additive in larger complexes. In fact, preliminary works in the literature are experimenting with new ways to describe these contacts,²²⁵ which could be very promising for noncovalent interaction research in the future.

Additionally, even though it was evident before the undertaking of this thesis, the design of new DFT functionals that can accurately describe dispersion interactions is still essential since current studies still require benchmarking against high-level *ab initio* results to confidently model new noncovalent systems. Future theoretical developments in methods with small basis set dependencies, as well as the ability to properly describe barrier heights, would be beneficial to the field of computational chemistry.

7.3. Mechanism of Alkyladenine DNA Glycosylase (AAG)

7.3.1. Contributions from this Thesis

The ONIOM(M06-2X/6-31G(d):AMBER) reaction potential energy surface scans for the excision of ϵ A, 3MeA, and A nucleotides revealed vital information about the chemical mechanism of AAG. The excision mechanism of ϵ A by the wild type, as well as the Y127W and Y159W mutant enzymes, are in remarkable agreement with recently available experimental data,⁶⁷ which supports the use of this model and provides confidence in the description of all aspects of the chemical step of this DNA glycosylase. In addition, this thesis suggests that both a general base and a general acid are important for the excision of neutral lesions, where calculations revealed that the general acid only requires hydrogen-bond donation to provide enough stabilization to lower the barrier for catalysis of the neutral substrates.

For the first time, AAG was found to excise both neutral (ϵ A) and cationic (3MeA) substrates through a concerted (S_N2) mechanism, which is consistent with previous proposals for this enzyme.²⁸ Intriguingly, the conjugated ring systems of Tyr127, His136, and Tyr159 were found to play different roles in the bond cleavage mechanism of neutral and cationic substrates within AAG. Specifically, it appears that AAG has evolved to take advantage of the π -systems within the active site to nonspecifically position a wide variety of alkylation damage products in the active site, while at the same time maximizing its catalytic power towards (neutral) lesions that are inherently more difficult to excise. The ability to remove neutral DNA damage comes at the expense of the excision mechanism used to repair cationic lesions, where this thesis indicates that the conjugated π -systems are used to attract and bind the cationic nucleobases into the active site, yet are insignificant (Tyr159) or anticatalytic (Tyr127, His136) for the glycosidic-bond cleavage mechanism.

Most importantly, this thesis suggests that the chemical step used by AAG provides

another discriminatory step to avoid excising the natural purines. Calculations for the A nucleotide in this thesis indicate that Glu125 and the water nucleophile (Wat502) are poorly aligned for nucleophile activation. This reason for low glycosylase activity was recently discarded in recent crystal structure study of an ϵ C(inhibitor)–AAG complex,⁶⁰ however, their (static) structural proposal was not obtained from an atomistic perspective across the entire reaction mechanism for this enzyme. Therefore, the insights obtained from this thesis can be vital for understanding how AAG can bind to a large number of damaged lesions, yet is unable to excise all of them from DNA.

7.3.2. Future Directions

The ONIOM(M06-2X/6-31G(d):AMBER) calculations presented in Chapter 6 have contributed to understanding the excision mechanism used by AAG. However, many questions still remain about this glycosylase and further research is necessary to obtain a complete picture of this DNA repair enzyme. Although this thesis is the first study to characterize the excision mechanism utilized by AAG, this conclusion is nevertheless based on the results of only two commonly excised substrates, ϵ A and 3MeA. Therefore, future work needs to investigate additional substrates excised by AAG (such as Hx, 7MeG, EA, ϵ G) using the current computational approach developed in this thesis to determine whether the present conclusions are truly independent of the substrate. Additionally, these studies should examine whether the natural base guanine prefers an S_N1 excision mechanism to further support the conclusions found for adenine.

As discussed in Section 6.1, a very recent crystal structure of wild-type AAG bound ϵ C-containing DNA led to the proposal that ϵ C inhibits AAG activity since leaving-group protonation is not likely to take place within this tightly-bound active site.⁶⁰ Additionally, it was suggested that the water nucleophile is ideally located for activation within this (static) structure. These experimental propositions are contradicted by the present computational

observation that AAG is inactive towards some substrates (A) on account of Glu125 failing to easily activate the nucleophilic water molecule. Therefore, it is essential that further computational work unite these experimental and computational proposals by investigating the chemical mechanism of adenine and ϵ C starting from this new crystal structure orientation.⁶⁰ Not only will this work further validate or disprove the chemical mechanism utilized by AAG, considering A in this new crystal structure will provide information about how various starting structures affect reaction mechanism calculations, which is currently unclear in the computational literature.

Chapter 6 presented preliminary point-mutation calculations that investigated how Tyr127, His136, and Tyr159 affect the glycosidic-bond cleavage barrier heights. Despite the assumptions made in these calculations, they revealed vital clues about how the amino acids with conjugated π -rings play a role in neutral substrate excision, but are not catalytic for cationic substrates. Further calculations must examine the effects of these mutations on the structure of the AAG–DNA complex, where MD simulations of the entire (solvated) complex will provide important structural information for these mutational enzymes. Once structural effects are examined for various mutations, stationary points need to be characterized through hybrid (ONIOM or QM/MM) techniques before the effects of the mutations on the reaction barriers can be further examined.

As alluded to in this thesis, very little is understood about how different computational approaches affect predicted enzyme reaction mechanisms. Therefore, from a computational standpoint, it would be interesting to examine how model choice affects the AAG catalytic pathway. Indeed, further studies should examine how the mechanism used by AAG is affected by: the use of ONIOM or QM/MM hybrid approaches, the QM method, the size of the QM regions (i.e. including residues like Asn169 and Ala134), full water solvation of the AAG–DNA system, relaxing larger or smaller portions of the MM region throughout the

reaction, using unrelaxed crystal structure geometries or MD simulations as the initial reactant structures, and ONIOM versus QM/MM MD potential energy surface scans. Indeed, these different computational approaches should be integrated with the above mechanistic ideas to help provide valuable insights into computational modeling choices to be used in the future, as well as a complete picture of the mechanism used by AAG.

As discussed in Chapter 1, the nucleotide-flipping step plays an essential part in the overall mechanism-of-action of AAG.^{39,41,47,51-52} Without a doubt, both experimental and computational researchers need to expand their efforts to truly understand how AAG uses nucleotide-flipping to repair a wide variety of damage in DNA. Also, knowledge of how the nucleotide-flipping step is involved in the overall kinetic mechanism of this repair enzyme is essential to further probe the details of this unique DNA repair process.

In summary, this thesis has presented the first computational work that unites all previous results for AAG to fully describe the chemical mechanism of this unique DNA glycosylase. Indeed, this work also provides insights into the fundamentals behind important nonspecific DNA-protein contacts, and suggests different roles that π - π and π^+ - π interactions play in substrate excision by this enzyme. The work proposed in this chapter will further probe the complete mechanism of this unique glycosylase, which will aid in understanding how this enzyme repairs a wide variety of damaged nucleobases. Once these processes are well understood, researchers must also examine the full physiological function of AAG since preliminary work has shown that this enzyme can interact with nucleotide excision repair proteins, suggesting that this enzyme may also be involved in other repair pathways.³²² Indeed, although further studies are necessary, it is intriguing that the role of this unique DNA glycosylase in DNA repair is far more complex than once thought.

References

- (1) Zubay, G. *Biochemistry*. Wm. C. Brown Publishers, Dubuque, 1993.
- (2) Voet, D.; Voet, J. G. *Biochemistry*. John Wiley & Sons, 2004.
- (3) Blackburn, G. M.; Gait, M. J., Eds. *Nucleic Acids in Chemistry and Biology*; Oxford University Press: New York, 1996.
- (4) Lindahl, T. *Nature (London, U. K.)* **1993**, *362*, 709-715.
- (5) O'Brien, P. J. *Chem. Rev. (Washington, DC, U. S.)* **2006**, *106*, 720-752.
- (6) Griffiths, A. D.; Tawfik, D. S. *Curr. Opin. Biotechnol.* **2000**, *11*, 338-353.
- (7) Drablos, F.; Feyzi, E.; Aas, P. A.; Vaagbo, C. B.; Kavli, B.; Bratlie, M. S.; Pena-Diaz, J.; Otterlei, M.; Slupphaug, G.; Krokan, H. E. *DNA Repair* **2004**, *3*, 1389-1407.
- (8) Conticello, S. G. *Genome Biol.* **2008**, *9*, ARTN 229.
- (9) Loeb, L. A.; Harris, C. C. *Cancer Res.* **2008**, *68*, 6863-6872.
- (10) Shrivastav, N.; Li, D. Y.; Essigmann, J. M. *Carcinogenesis* **2010**, *31*, 59-70.
- (11) Hurley, L. H. *Nat. Rev. Cancer* **2002**, *2*, 188-200.
- (12) Shooter, K. V.; Howse, R.; Shah, S. A.; Lawley, P. D. *Biochem. J.* **1974**, *137*, 303-312.
- (13) Szyfter, K.; Hemminki, K.; Szyfter, W.; Szmeja, Z.; Banaszewski, J.; Pabiszczak, M. *Carcinogenesis* **1996**, *17*, 501-506.
- (14) Saffhill, R.; Margison, G. P.; O'Connor, P. J. *Biochim. Biophys. Acta.* **1985**, *823*, 111-145.
- (15) Rydberg, B.; Lindahl, T. *EMBO J.* **1982**, *1*, 211-216.
- (16) Fronza, G.; Gold, B. J. *Cell. Biochem.* **2004**, *91*, 250-257.
- (17) Elghissassi, F.; Barbin, A.; Nair, J.; Bartsch, H. *Chem. Res. Toxicol.* **1995**, *8*, 278-283.
- (18) Chung, F. L.; Chen, H. J. C.; Nath, R. G. *Carcinogenesis* **1996**, *17*, 2105-2111.
- (19) Marnett, L. J. *Carcinogenesis* **2000**, *21*, 361-370.
- (20) Marnett, L. J. *Toxicology* **2001**, *164*, 18-18.
- (21) Barbin, A. *Mutat. Res.-Rev. Mutat. Res.* **2000**, *462*, 55-69.
- (22) Geacintov, N. E.; Broyde, S., Eds. *The Chemical Biology of DNA Damage*; Wiley-VCH: Weinheim, 2010.
- (23) Sedgwick, B.; Bates, P. A.; Paik, J.; Jacobs, S. C.; Lindahl, T. *DNA Repair* **2007**, *6*, 429-442.
- (24) Mishina, Y.; Duguid, E. M.; He, C. *Chem. Rev. (Washington, DC, U. S.)* **2006**, *106*, 215-232.

- (25) Daniels, D. S.; Mol, C. D.; Arvai, A. S.; Kanugula, S.; Pegg, A. E.; Tainer, J. A. *EMBO J.* **2000**, *19*, 1719-1730.
- (26) Guengerich, F. P.; Fang, Q. M.; Liu, L. P.; Hachey, D. L.; Pegg, A. E. *Biochemistry* **2003**, *42*, 10965-10970.
- (27) Daniels, D. S.; Woo, T. T.; Luu, K. X.; Noll, D. M.; Clarke, N. D.; Pegg, A. E.; Tainer, J. A. *Nat. Struct. Mol. Biol.* **2004**, *11*, 714-720.
- (28) Stivers, J. T.; Jiang, Y. L. *Chem. Rev. (Washington, DC, U. S.)* **2003**, *103*, 2729-2759.
- (29) Berti, P. J.; McCann, J. A. B. *Chem. Rev. (Washington, DC, U. S.)* **2006**, *106*, 506-555.
- (30) Stivers, J. T. *Chem.-Eur. J.* **2008**, *14*, 786-793.
- (31) Friedman, J. I.; Stivers, J. T. *Biochemistry* **2010**, *49*, 4957-4967.
- (32) David, S. S.; Williams, S. D. *Chem. Rev. (Washington, DC, U. S.)* **1998**, *98*, 1221-1261.
- (33) Lindahl, T. *Nature (London, U. K.)* **1976**, *259*, 64-66.
- (34) Gallagher, P. E.; Brent, T. P. *Biochemistry* **1982**, *21*, 6404-6409.
- (35) Singer, B.; Antoccia, A.; Basu, A. K.; Dosanjh, M. K.; Fraenkelconrat, H.; Gallagher, P. E.; Kusmierek, J. T.; Qiu, Z. H.; Rydberg, B. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 9386-9390.
- (36) O'Connor, T. R. *Nucleic Acids Res.* **1993**, *21*, 5561-5569.
- (37) Engelward, B. P.; Weeda, G.; Wyatt, M. D.; Broekhof, J. L. M.; deWit, J.; Donker, I.; Allan, J. M.; Gold, B.; Hoeijmakers, J. H. J.; Samson, L. D. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 13087-13092.
- (38) Hang, B.; Singer, B.; Margison, G. P.; Elder, R. H. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 12869-12874.
- (39) Abner, C. W.; Lau, A. Y.; Ellenberger, T.; Bloom, L. B. *J. Biol. Chem.* **2001**, *276*, 13379-13387.
- (40) O'Brien, P. J.; Ellenberger, T. *J. Biol. Chem.* **2004**, *279*, 9750-9757.
- (41) Vallur, A. C.; Maher, R. L.; Bloom, L. B. *DNA Repair* **2005**, *4*, 1088-1098.
- (42) Wang, P.; Guliaev, A. B.; Elder, R. H.; Hang, B. *DNA Repair* **2006**, *5*, 23-31.
- (43) Maher, R. L.; Vallur, A. C.; Feller, J. A.; Bloom, L. B. *DNA Repair* **2007**, *6*, 71-81.
- (44) Lee, C. Y. I.; Delaney, J. C.; Kartalou, M.; Lingaraju, G. M.; Maor-Shoshani, A.; Essigmann, J. M.; Samson, L. D. *Biochemistry* **2009**, *48*, 1850-1861.
- (45) Radzicka, A.; Wolfenden, R. *Science (Washington, DC, U. S.)* **1995**, *267*, 90-93.
- (46) Hedglin, M.; O'Brien, P. J. *Biochemistry* **2008**, *47*, 11434-11445.
- (47) Wolfe, A. E.; O'Brien, P. J. *Biochemistry* **2009**, *48*, 11357-11369.

- (48) Hedglin, M.; O'Brien, P. J. *ACS Chem. Biol.* **2010**, *5*, 427-436.
- (49) Baldwin, M. R.; O'Brien, P. J. *Biochemistry* **2009**, *48*, 6022-6033.
- (50) Gros, L.; Ishchenko, A. A.; Saparbaev, M. *Mutat. Res. -Fundam. Mol. Mech. Mutag.* **2003**, *531*, 219-229.
- (51) Berdal, K. G.; Johansen, R. F.; Seeberg, E. *EMBO J.* **1998**, *17*, 363-367.
- (52) Teale, M.; Symersky, J.; DeLucas, L. *Bioconjugate Chem.* **2002**, *13*, 403-407.
- (53) Vallur, A. C.; Feller, J. A.; Abner, C. W.; Tran, R. K.; Bloom, L. B. *J. Biol. Chem.* **2002**, *277*, 31673-31678.
- (54) Lyons, D. M.; O'Brien, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 17742-17743.
- (55) Lau, A. Y.; Scharer, O. D.; Samson, L.; Verdine, G. L.; Ellenberger, E. *Cell (Cambridge, MA, U. S.)* **1998**, *95*, 249-258.
- (56) Scharer, O. D.; Nash, H. M.; Jiricny, J.; Laval, J.; Verdine, G. L. *J. Biol. Chem.* **1998**, *273*, 8592-8597.
- (57) Lau, A. Y.; Wyatt, M. D.; Glassner, B. J.; Samson, L. D.; Ellenberger, T. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 13573-13578.
- (58) Adhikari, S.; Toretsky, J. A.; Yuan, L. S.; Roy, R. *J. Biol. Chem.* **2006**, *281*, 29525-29532.
- (59) Wang, P.; Guliaev, A. B.; Hang, B. *Toxicol. Lett.* **2006**, *166*, 237-247.
- (60) Lingaraju, G. M.; Davis, C. A.; Setser, J. W.; Samson, L. D.; Drennan, C. L. *J. Biol. Chem.* **2011**, *286*, 13205-13213.
- (61) Slupphaug, G.; Mol, C. D.; Kavli, B.; Arvai, A. S.; Krokan, H. E.; Tainer, J. A. *Nature (London, U. K.)* **1996**, *384*, 87-92.
- (62) Barrett, T. E.; Savva, R.; Panayotou, G.; Barlow, T.; Brown, T.; Jiricny, J.; Pearl, L. H. *Cell (Cambridge, MA, U. S.)* **1998**, *92*, 117-129.
- (63) Parikh, S. S.; Mol, C. D.; Slupphaug, G.; Bharati, S.; Krokan, H. E.; Tainer, J. A. *EMBO J.* **1998**, *17*, 5214-5226.
- (64) O'Brien, P. J.; Ellenberger, T. *Biochemistry* **2003**, *42*, 12418-12429.
- (65) Connor, E. E.; Wyatt, M. D. *Chem. Biol.* **2002**, *9*, 1033-1041.
- (66) Connor, E. E.; Wilson, J. J.; Wyatt, M. D. *Chem. Res. Toxicol.* **2005**, *18*, 87-94.
- (67) Hendershot, J. M.; Wolfe, A. E.; O'Brien, P. J. *Biochemistry* **2011**, *50*, 1864-1874.
- (68) Drohat, A. C.; Xiao, G.; Tordova, M.; Jagadeesh, J.; Pankiewicz, K. W.; Watanabe, K. A.; Gilliland, G. L.; Stivers, J. T. *Biochemistry* **1999**, *38*, 11876-11886.
- (69) Stivers, J. T.; Pankiewicz, K. W.; Watanabe, K. A. *Biochemistry* **1999**, *38*, 952-963.

- (70) Zoltewicz, J. A.; Clark, D. F.; Sharpless, T. W.; Grahe, G. *J. Am. Chem. Soc.* **1970**, *92*, 1741-1750.
- (71) McCann, J. A. B.; Berti, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 5789-5797.
- (72) Guliaev, A. B.; Hang, B.; Singer, B. *Nucleic Acids Res.* **2002**, *30*, 3778-3787.
- (73) Alexandrova, A. N. *Biophys. Chem.* **2010**, *152*, 118-127.
- (74) Liu, M.; Xu, M.; Lee, J. K. *J. Org. Chem.* **2008**, *73*, 5907-5914.
- (75) Sun, X.; Lee, J. K. *J. Org. Chem.* **2007**, *72*, 6548-6555.
- (76) Ramos, M. J.; Fernandes, P. A. *Acc. Chem. Res.* **2008**, *41*, 689-698.
- (77) Cerny, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2007**, *9*, 5291-5303.
- (78) Lin, H.; Truhlar, D. G. *Theor. Chem. Acc.* **2007**, *117*, 185-199.
- (79) Jensen, F. *Introduction to Computational Chemistry*. Wiley, Chichester, West Sussex, England, 1999.
- (80) Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models*. Wiley, Chichester, West Sussex, England, 2004.
- (81) Vreven, T.; Byun, K. S.; Komaromi, I.; Dapprich, S.; Montgomery, J. A.; Morokuma, K.; Frisch, M. J. *J. Chem. Theory Comput.* **2006**, *2*, 815-826.
- (82) Vreven, T.; Morokuma, K. *Annu. Rep. Comput. Chem.* **2006**, *2*, 35-51.
- (83) Hu, H.; Yang, W. T. *J. Mol. Struct.: THEOCHEM* **2009**, *898*, 17-30.
- (84) Johnson, E. R.; Mackie, I. D.; DiLabio, G. A. *J. Phys. Org. Chem.* **2009**, *22*, 1127-1135.
- (85) Hobza, P.; Muller-Dethlefs, K. *Non-covalent Interactions: Theory and Experiment* Royal Society of Chemistry Publishing, Cambridge, 2010.
- (86) Muller-Dethlefs, K.; Hobza, P. *Chem. Rev. (Washington, DC, U. S.)* **2000**, *100*, 143-167.
- (87) Jurecka, P.; Sponer, J.; Cerny, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1985-1993.
- (88) Krause, H.; Ernstberger, B.; Neusser, H. J. *Chem. Phys. Lett.* **1991**, *184*, 411-417.
- (89) Krause, H.; Ernstberger, B.; Neusser, H. J. *Ber. Bunsen-Ges. Phys. Chem.* **1992**, *96*, 1183-1187.
- (90) Arunan, E.; Gutowsky, H. S. *J. Chem. Phys.* **1993**, *98*, 4294-4296.
- (91) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Am. Chem. Soc.* **1994**, *116*, 3500-3506.
- (92) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Phys. Chem.* **1996**, *100*, 18790-18794.
- (93) Williams, V. E.; Lemieux, R. P.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 1927-1933.
- (94) Sinnokrot, M. O.; Valeev, E. F.; Sherrill, C. D. *J. Am. Chem. Soc.* **2002**, *124*, 10887-10893.

- (95) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104-112.
- (96) Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2003**, *107*, 8377-8379.
- (97) Sinnokrot, M. O.; Sherrill, C. D. *J. Am. Chem. Soc.* **2004**, *126*, 7690-7697.
- (98) Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2004**, *108*, 10200-10207.
- (99) Riley, K. E.; Merz, K. M., Jr. *J. Phys. Chem. B* **2005**, *109*, 17752-17756.
- (100) Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2006**, *110*, 10656-10668.
- (101) Lee, E. C.; Kim, D.; Jurecka, P.; Tarakeshwar, P.; Hobza, P.; Kim, K. S. *J. Phys. Chem. A* **2007**, *111*, 3446-3457.
- (102) Pitonak, M.; Neogrady, P.; Rezac, J.; Jurecka, P.; Urban, M.; Hobza, P. *J. Chem. Theory Comput.* **2008**, *4*, 1829-1834.
- (103) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210-1250.
- (104) Hobza, P.; Sponer, J.; Polasek, M. *J. Am. Chem. Soc.* **1995**, *117*, 792-798.
- (105) Sponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem.* **1996**, *100*, 5590-5596.
- (106) Sponer, J.; Gabb, H. A.; Leszczynski, J.; Hobza, P. *Biophys. J.* **1997**, *73*, 76-87.
- (107) Sponer, J.; Hobza, P. *Chem. Phys. Lett.* **1997**, *267*, 263-270.
- (108) Kratochvil, M.; Engkvist, O.; Sponer, J.; Jungwirth, P.; Hobza, P. *J. Phys. Chem. A* **1998**, *102*, 6921-6926.
- (109) Hobza, P.; Sponer, J. *Chem. Rev. (Washington, DC, U. S.)* **1999**, *99*, 3247-3276.
- (110) Hobza, P.; Sponer, J.; Cubero, E.; Orozco, M.; Luque, F. J. *J. Phys. Chem. B* **2000**, *104*, 6286-6292.
- (111) Sponer, J.; Leszczynski, J.; Hobza, P. *J. Mol. Struct.: THEOCHEM* **2001**, *573*, 43-53.
- (112) Hobza, P.; Sponer, J. *J. Am. Chem. Soc.* **2002**, *124*, 11802-11808.
- (113) Sponer, J.; Leszczynski, J.; Hobza, P. *Biopolymers* **2002**, *61*, 3-31.
- (114) Jurecka, P.; Sponer, J.; Hobza, P. *J. Phys. Chem. B* **2004**, *108*, 5466-5471.
- (115) Sponer, J.; Jurecka, P.; Hobza, P. *J. Am. Chem. Soc.* **2004**, *126*, 10142-10151.
- (116) Sponer, J.; Jurecka, P.; Marchan, I.; Luque, F. J.; Orozco, M.; Hobza, P. *Chem.-Eur. J.* **2006**, *12*, 2854-2865.
- (117) Pitonak, M.; Riley, K. E.; Neogrady, P.; Hobza, P. *ChemPhysChem* **2008**, *9*, 1636-1644.
- (118) Sponer, J.; Riley, K. E.; Hobza, P. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2595-2610.

- (119) Morgado, C. A.; Jurecka, P.; Svozil, D.; Hobza, P.; Sponer, J. *J. Chem. Theory Comput.* **2009**, *5*, 1524-1544.
- (120) Morgado, C. A.; Jurecka, P.; Svozil, D.; Hobza, P.; Sponer, J. *Phys. Chem. Chem. Phys.* **2010**, *12*, 3522-3534.
- (121) Svozil, D.; Hobza, P.; Sponer, J. *J. Phys. Chem. B* **2010**, *114*, 1191-1203.
- (122) Antony, J.; Grimme, S. *Phys. Chem. Chem. Phys.* **2006**, *8*, 5287-5293.
- (123) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787-1799.
- (124) Lin, I. C.; von Lilienfeld, A.; Coutinho-Neto, M. D.; Tavernelli, I.; Rothlisberger, U. *J. Phys. Chem. B* **2007**, *111*, 14346-14354.
- (125) McNamara, J. P.; Hillier, I. H. *Phys. Chem. Chem. Phys.* **2007**, *9*, 2362-2370.
- (126) Morgado, C.; Vincent, M. A.; Hillier, I. H.; Shan, X. *Phys. Chem. Chem. Phys.* **2007**, *9*, 448-451.
- (127) Schwabe, T.; Grimme, S. *Phys. Chem. Chem. Phys.* **2007**, *9*, 3397-3406.
- (128) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2007**, *3*, 289-300.
- (129) Mackie, I. D.; DiLabio, G. A. *J. Phys. Chem. A* **2008**, *112*, 10968-10976.
- (130) Mackie, I. D.; DiLabio, G. A. *Phys. Chem. Chem. Phys.* **2010**, *12*, 6092-6098.
- (131) Sherrill, C. D. *Rev. Comput. Chem.* **2009**, *26*, 1-38.
- (132) Sherrill, C. D.; Takatani, T.; Hohenstein, E. G. *J. Phys. Chem. A* **2009**, *113*, 10146-10159.
- (133) Takatani, T.; Hohenstein, E. G.; Malagoli, M.; Marshall, M. S.; Sherrill, C. D. *J. Chem. Phys.* **2010**, *132*, 144104-144105.
- (134) Grafova, L.; Pitonak, M.; Rezac, J.; Hobza, P. *J. Chem. Theory Comput.* **2010**, *6*, 2365-2376.
- (135) Mao, L.; Wang, Y.; Liu, Y.; Hu, X. *J. Mol. Biol.* **2004**, *336*, 787-807.
- (136) Cauet, E.; Rooman, M.; Wintjens, R.; Lievin, J.; Biot, C. *J. Chem. Theory Comput.* **2005**, *1*, 472-483.
- (137) Copeland, K. L.; Anderson, J. A.; Farley, A. R.; Cox, J. R.; Tschumper, G. S. *J. Phys. Chem. B* **2008**, *112*, 14291-14295.
- (138) Cysewski, P. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2636-2645.
- (139) Ebrahimi, A.; Habibi-Khorassani, M.; Gholipour, A. R.; Masoodi, H. R. *Theor. Chem. Acc.* **2009**, *124*, 115-122.
- (140) Kee, E. A.; Livengood, M. C.; Carter, E. E.; McKenna, M.; Cafiero, M. J. *J. Phys. Chem. B* **2009**, *113*, 14810-14815.
- (141) Baker, C. M.; Grant, G. H. *Biopolymers* **2007**, *85*, 456-470.

- (142) Hobza, P. *Annu. Rep. Prog. Chem. Sect. C: Phys. Chem.* **2004**, *100*, 3-27.
- (143) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553-566.
- (144) Jurecka, P.; Nachtigall, P.; Hobza, P. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4578-4582.
- (145) Leininger, M. L.; Nielsen, I. M. B.; Colvin, M. E.; Janssen, C. L. *J. Phys. Chem. A* **2002**, *106*, 3850-3854.
- (146) Jurecka, P.; Hobza, P. *J. Am. Chem. Soc.* **2003**, *125*, 15608-15613.
- (147) Halkier, A.; Helgaker, T.; Jorgensen, P.; Klopper, W.; Koch, H.; Olsen, J.; Wilson, A. K. *Chem. Phys. Lett.* **1998**, *286*, 243-252.
- (148) Halkier, A.; Helgaker, T.; Jorgensen, P.; Klopper, W.; Olsen, J. *Chem. Phys. Lett.* **1999**, *302*, 437-446.
- (149) Ringer, A. L.; Sinnokrot, M. O.; Lively, R. P.; Sherrill, C. D. *Chem.-Eur. J.* **2006**, *12*, 3821-3828.
- (150) Shibasaki, K.; Fujii, A.; Mikami, N.; Tsuzuki, S. *J. Phys. Chem. A* **2006**, *110*, 4397-4404.
- (151) Bendova, L.; Jurecka, P.; Hobza, P.; Vondrasek, J. *J. Phys. Chem. B* **2007**, *111*, 9975-9979.
- (152) Tsuzuki, S.; Mikami, M.; Yamada, S. *J. Am. Chem. Soc.* **2007**, *129*, 8656-8662.
- (153) Dabkowska, I.; Gonzalez, H. V.; Jurecka, P.; Hobza, P. *J. Phys. Chem. A* **2005**, *109*, 1131-1136.
- (154) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03 (Revision D.02)*, Revision D.02; Gaussian, Inc.: Wallingford CT, 2004.
- (155) Werner, H.-J.; Knowles, P. J.; Lindh, R.; Manby, F. R.; Schütz, M.; Celani, P.; Korona, T.; Rauhut, G.; Amos, R. D.; Bernhardsson, A.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert, F.; Hampel, C.; Hetzer, G.; Lloyd, A. W.; McNicholas, S. J.; Meyer, W.; Mura, M. E.; Nicklass, A.; Palmieri, P.; Pitzer, R.; Schumann, U.; Stoll, H.; Stone, A. J.; Tarroni, R.; Thorsteinsson, T. *MolPro*, Version 2006.1; University College Cardiff Consultants Ltd.: Cardiff, UK, 2006.
- (156) McConnell, T. L.; Wheaton, C. A.; Hunter, K. C.; Wetmore, S. D. *J. Phys. Chem. A* **2005**, *109*, 6351-6362.
- (157) Roca-Sanjuan, D.; Merchan, M.; Serrano-Andres, L.; Rubio, M. *J. Chem. Phys.* **2008**, *129*, 095104(095111).

- (158) Gil, A.; Branchadell, V.; Bertran, J.; Oliva, A. *J. Phys. Chem. B* **2007**, *111*, 9372-9379.
- (159) Ringer, A. L.; Figgs, M. S.; Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2006**, *110*, 10822-10828.
- (160) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746-3753.
- (161) Mishra, B. K.; Sathyamurthy, N. *J. Phys. Chem. A* **2007**, *111*, 2139-2147.
- (162) Tsuzuki, S.; Fujii, A. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2584-2594.
- (163) Tsuzuki, S.; Honda, K.; Fujii, A.; Uchimaru, T.; Mikami, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2860-2865.
- (164) Egli, M.; Sarkhel, S. *Acc. Chem. Res.* **2007**, *40*, 197-205.
- (165) Ohndorf, U. M.; Rould, M. A.; He, Q.; Pabo, C. O.; Lippard, S. J. *Nature (London, U. K.)* **1999**, *399*, 708-712.
- (166) Schmitt, E.; Moulinier, L.; Fujiwara, S.; Imanaka, T.; Thierry, J. C.; Moras, D. *EMBO J.* **1998**, *17*, 5227-5237.
- (167) Giffin, M. J.; Stroud, J. C.; Bates, D. L.; von Koenig, K. D.; Hardin, J.; Chen, L. *Nature Struct. Biol.* **2003**, *10*, 800-806.
- (168) Singh, N. J.; Min, S. K.; Kim, D. Y.; Kim, K. S. *J. Chem. Theory Comput.* **2009**, *5*, 515-529.
- (169) Cybulski, H.; Sadlej, J. *J. Chem. Theory Comput.* **2008**, *4*, 892-897.
- (170) Fiethen, A.; Jansen, G.; Hesselmann, A.; SchOtz, M. *J. Am. Chem. Soc.* **2008**, *130*, 1802-1803.
- (171) Hohenstein, E. G.; Sherrill, C. D. *J. Phys. Chem. A* **2009**, *113*, 878-886.
- (172) Ran, J.; Hobza, P. *J. Chem. Theory Comput.* **2009**, *5*, 1180-1185.
- (173) Ran, J.; Hobza, P. *J. Phys. Chem. B* **2009**, *113*, 2933-2936.
- (174) Seo, J. I.; Kim, I.; Lee, Y. S. *Chem. Phys. Lett.* **2009**, *474*, 101-106.
- (175) Riley, K. E.; Pitonak, M.; Cerny, J.; Hobza, P. *J. Chem. Theory Comput.* **2010**, *6*, 66-80.
- (176) Tauer, T. P.; Sherrill, C. D. *J. Phys. Chem. A* **2005**, *109*, 10475-10478.
- (177) Pakiari, A. H.; Fakhraee, S. *J. Theor. Comput. Chem.* **2006**, *5*, 621-631.
- (178) Quinonero, D.; Frontera, A.; Garau, C.; Ballester, P.; Costa, A.; Deya, P. M. *ChemPhysChem* **2006**, *7*, 2487-2491.
- (179) Ziolkowski, M.; Grabowski, S. J.; Leszczynski, J. *J. Phys. Chem. A* **2006**, *110*, 6514-6521.
- (180) Frontera, A.; Quinonero, D.; Costa, A.; Ballester, P.; Deya, P. M. *New J. Chem.* **2007**, *31*, 556-560.

- (181) Kabelac, M.; Sherer, E. C.; Cramer, C. J.; Hobza, P. *Chem.-Eur. J.* **2007**, *13*, 2067-2077.
- (182) Kabelac, M.; Valdes, H.; Sherer, E. C.; Cramer, C. J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2007**, *9*, 5000-5008.
- (183) Escudero, D.; Frontera, A.; Quinonero, D.; Deya, P. M. *Chem. Phys. Lett.* **2008**, *456*, 257-261.
- (184) Escudero, D.; Frontera, A.; Quinonero, D.; Deya, P. M. *J. Phys. Chem. A* **2008**, *112*, 6017-6022.
- (185) Quinonero, D.; Frontera, A.; Escudero, D.; Ballester, P.; Costa, A.; Deya, P. M. *Theor. Chem. Acc.* **2008**, *120*, 385-393.
- (186) Vijay, D.; Zipse, H.; Sastry, G. N. *J. Phys. Chem. B* **2008**, *112*, 8863-8867.
- (187) Antony, J.; Bruske, B.; Grimme, S. *Phys. Chem. Chem. Phys.* **2009**, *11*, 8440-8447.
- (188) Ebrahimi, A.; Habibi, M.; Neyband, R. S.; Gholipour, A. R. *Phys. Chem. Chem. Phys.* **2009**, *11*, 11424-11431.
- (189) Escudero, D.; Estarellas, C.; Frontera, A.; Quinonero, D.; Deya, P. M. *Chem. Phys. Lett.* **2009**, *468*, 280-285.
- (190) Estarellas, C.; Escudero, D.; Frontera, A.; Quinonero, D.; Deya, P. M. *Theor. Chem. Acc.* **2009**, *122*, 325-332.
- (191) Estarellas, C.; Frontera, A.; Quinonero, D.; Alkorta, I.; Deya, P. M.; Elguero, J. *J. Phys. Chem. A* **2009**, *113*, 3266-3273.
- (192) Estarellas, C.; Frontera, A.; Quinonero, D.; Deya, P. M. *Chem. Phys. Lett.* **2009**, *479*, 316-320.
- (193) Estevez, L.; Otero, N.; Mosquera, R. A. *J. Phys. Chem. A* **2009**, *113*, 11051-11058.
- (194) Grabowski, S. J.; Leszczynski, J. *Chem. Phys.* **2009**, *355*, 169-176.
- (195) Vijay, D.; Sastry, G. N. *Chem. Phys. Lett.* **2010**, *485*, 235-242.
- (196) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory; International Series of Monographs on Chemistry*. Clarendon Press: Oxford, New York, 1990. 22.
- (197) Popelier, P. L. A. *Atoms in Molecules: An Introduction*. Prentice Hall, London, 2000.
- (198) Matta, C. F.; Boyd, R. J., Eds. *The Quantum Theory of Atoms in Molecules: From Solid State to DNA and Drug Design*; Wiley-VCH: Weinheim, 2007.
- (199) Bader, R. F. W. *J. Phys. Chem. A* **2009**, *113*, 10391-10396.
- (200) Boyd, R. J.; Choi, S. C. *Chem. Phys. Lett.* **1985**, *120*, 80-85.
- (201) Koch, U.; Popelier, P. L. A. *J. Phys. Chem.* **1995**, *99*, 9747-9754.
- (202) Parthasarathi, R.; Amutha, R.; Subramanian, V.; Nair, B. U.; Ramasami, T. *J. Phys. Chem. A* **2004**, *108*, 3817-3828.

- (203) Grabowski, S. J.; Sokalski, W. A.; Leszczynski, J. *J. Phys. Chem. A* **2005**, *109*, 4331-4341.
- (204) Parthasarathi, R.; Subramanian, V. *Struct. Chem.* **2005**, *16*, 243-255.
- (205) Zhikol, O. A.; Shishkin, O. V.; Lyssenko, K. A.; Leszczynski, J. *J. Chem. Phys.* **2005**, *122*, 144104(144108).
- (206) Matta, C. F.; Castillo, N.; Boyd, R. J. *J. Phys. Chem. B* **2006**, *110*, 563-578.
- (207) Mohajeri, A.; Karimi, E. *J. Mol. Struct.: THEOCHEM* **2006**, *774*, 71-76.
- (208) Parthasarathi, R.; Subramanian, V.; Sathyamurthy, N. *J. Phys. Chem. A* **2006**, *110*, 3349-3351.
- (209) Robertazzi, A.; Platts, J. A. *J. Phys. Chem. A* **2006**, *110*, 3992-4000.
- (210) Waller, M. P.; Robertazzi, A.; Platts, J. A.; Hibbs, D. E.; Williams, P. A. *J. Comput. Chem.* **2006**, *27*, 491-504.
- (211) Moa, M. J. G.; Mandado, M.; Mosquera, R. A. *J. Phys. Chem. A* **2007**, *111*, 1998-2001.
- (212) Parthasarathi, R.; Raman, S. S.; Subramanian, V.; Ramasami, T. *J. Phys. Chem. A* **2007**, *111*, 7141-7148.
- (213) Vener, M. V.; Egorova, A. N.; Fomin, D. P.; Tsirelson, V. G. *Chem. Phys. Lett.* **2007**, *440*, 279-285.
- (214) Keefe, C. D.; Isenor, M. *J. Phys. Chem. A* **2008**, *112*, 3127-3132.
- (215) Nakanishi, W.; Hayashi, S.; Narahara, K. *J. Phys. Chem. A* **2008**, *112*, 13593-13599.
- (216) Ebrahimi, A.; Khorassani, S. M. H.; Delarami, H. *Chem. Phys.* **2009**, *365*, 18-23.
- (217) LaPointe, S. M.; Farrag, S.; Bohorquez, H. J.; Boyd, R. J. *J. Phys. Chem. B* **2009**, *113*, 10957-10964.
- (218) Nakanishi, W.; Hayashi, S.; Narahara, K. *J. Phys. Chem. A* **2009**, *113*, 10050-10057.
- (219) Suresh, C. H.; Mohan, N.; Vijayalakshmi, K. P.; George, R.; Mathew, J. M. *J. Comput. Chem.* **2009**, *30*, 1392-1404.
- (220) Yau, A. D.; Byrd, E. F. C.; Rice, B. M. *J. Phys. Chem. A* **2009**, *113*, 6166-6171.
- (221) Churchill, C. D. M.; Wetmore, S. D. *J. Phys. Chem. B* **2009**, *113*, 16046-16058.
- (222) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Jr., J. A. M.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz,

- J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford CT, 2009.
- (223) Keith, T. A. *AIMAll*, Version 08.09.20; aim.tkgristmill.com: 2009.
- (224) Biegler-Konig, F. W.; Schonbohm, J. *AIM2000*, Version 2.0; AIM2000.de: 2002.
- (225) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506.
- (226) Robertazzi, A.; Platts, J. A. *Chem.-Eur. J.* **2006**, *12*, 5747-5756.
- (227) Yao, L. S.; Cukier, R. I.; Yan, H. G. *J. Phys. Chem. B* **2007**, *111*, 4200-4210.
- (228) Altun, A.; Yokoyama, S.; Morokuma, K. *J. Phys. Chem. B* **2008**, *112*, 6814-6827.
- (229) Banas, P.; Rulisek, L.; Hanosova, V.; Svozil, D.; Walter, N. G.; Sponer, J.; Otyepka, M. *J. Phys. Chem. B* **2008**, *112*, 11177-11187.
- (230) Fanfrlik, J.; Brynda, J.; Rezac, J.; Hobza, P.; Lepsik, M. *J. Phys. Chem. B* **2008**, *112*, 15094-15102.
- (231) Inoue, T.; Shiota, Y.; Yoshizawa, K. *J. Am. Chem. Soc.* **2008**, *130*, 16890–16897.
- (232) Morgado, C. A.; Hillier, I. H.; Burton, N. A.; McDouall, J. J. W. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2706-2714.
- (233) Rickard, G. A.; Berges, J.; Houee-Levin, C.; Rauk, A. *J. Phys. Chem. B* **2008**, *112*, 5774-5787.
- (234) Alzate-Morales, J. H.; Caballero, J.; Jague, A. V.; Nilo, F. D. G. *J. Chem. Inf. Model.* **2009**, *49*, 886-899.
- (235) Kamachi, T.; Nakayama, T.; Shitamichi, O.; Jitsumori, K.; Kurihara, T.; Esaki, N.; Yoshizawa, K. *Chem.-Eur. J.* **2009**, *15*, 7394-7403.
- (236) Li, X.; Chung, L. W.; Paneth, P.; Morokuma, K. *J. Am. Chem. Soc.* **2009**, *131*, 5115-5125.
- (237) Lundberg, M.; Kawatsu, T.; Vreven, T.; Frisch, M. J.; Morokuma, K. *J. Chem. Theory Comput.* **2009**, *5*, 222–234.
- (238) Pouilly, J. C.; Gregoire, G.; Schermann, J. P. *J. Phys. Chem. A* **2009**, *113*, 8020-8026.
- (239) Rosta, E.; Woodcock, H. L.; Brooks, B. R.; Hummer, G. *J. Comput. Chem.* **2009**, *30*, 1634-1641.
- (240) Yang, Y.; Cui, Q. *J. Phys. Chem. A* **2009**, *113*, 12439-12446.
- (241) Calvaresi, M.; Bottoni, A.; Garavelli, M. *J. Phys. Chem. B* **2007**, *111*, 6557–6570.
- (242) Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811-4815.
- (243) Grimme, S.; Antony, J.; Schwabe, T.; Muck-Lichtenfeld, C. *Org. Biomol. Chem.* **2007**, *5*, 741-758.
- (244) Neese, F.; Schwabe, T.; Grimme, S. *J. Chem. Phys.* **2007**, *126*.

- (245) Sousa, S. F.; Fernandes, P. A.; Ramos, M. J. *J. Phys. Chem. A* **2007**, *111*, 10439-10452.
- (246) Schwabe, T.; Grimme, S. *Acc. Chem. Res.* **2008**, *41*, 569-579.
- (247) Tarnopolsky, A.; Karton, A.; Sertchook, R.; Vuzman, D.; Martin, J. M. L. *J. Phys. Chem. A* **2008**, *112*, 3-8.
- (248) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157-167.
- (249) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2008**, *4*, 1849-1868.
- (250) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215-241.
- (251) Aeberhard, P. C.; Arey, J. S.; Lin, I. C.; Rothlisberger, U. *J. Chem. Theory Comput.* **2009**, *5*, 23-28.
- (252) Foster, M. E.; Sohlberg, K. *Phys. Chem. Chem. Phys.* **2009**, *12*, 307-322.
- (253) Tavernelli, I.; Lin, I. C.; Rothlisberger, U. *Phys. Rev. B* **2009**, *79*.
- (254) Cerny, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2005**, *7*, 1624-1626.
- (255) Kubar, T.; Jurecka, P.; Cerny, J.; Rezac, J.; Otyepka, M.; Valdes, H.; Hobza, P. *J. Phys. Chem. A* **2007**, *111*, 5642-5647.
- (256) Morgado, C. A.; McNamara, J. P.; Hillier, I. H.; Burton, N. A. *J. Chem. Theory Comput.* **2007**, *3*, 1656-1664.
- (257) Gu, J.; Wang, J.; Leszczynski, J.; Xie, Y.; Schafer III, H. F. *Chem. Phys. Lett.* **2008**, *459*, 164-166.
- (258) Hohenstein, E. G.; Chill, S. T.; Sherrill, C. D. *J. Chem. Theory Comput.* **2008**, *4*, 1996-2000.
- (259) Lin, I. C.; Rothlisberger, U. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2730-2734.
- (260) Sharma, R.; McNamara, J. P.; Raju, R. K.; Vincent, M. A.; Hillier, I. H.; Morgado, C. A. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2767-2774.
- (261) Bryantsev, V. S.; Diallo, M. S.; van Duin, A. C. T.; Goddard, W. A. *J. Chem. Theory Comput.* **2009**, *5*, 1016-1026.
- (262) Dey, R. C.; Seal, P.; Chakrabarti, S. *J. Phys. Chem. A* **2009**, *113*, 10113-10118.
- (263) Lill, S. O. N. *J. Phys. Chem. A* **2009**, *113*, 10321-10326.
- (264) Raju, R. K.; Ramraj, A.; Hillier, I. H.; Vincent, M. A.; Burton, N. A. *Phys. Chem. Chem. Phys.* **2009**, *11*, 3411-3416.
- (265) Valdes, H.; Pluhackova, K.; Hobza, P. *J. Chem. Theory Comput.* **2009**, *5*, 2248-2256.
- (266) Zhao, Y.; Ng, H. T.; Hanson, E. *J. Chem. Theory Comput.* **2009**, *5*, 2726-2733.
- (267) Fonseca Guerra, C.; Wijst, T.; Poater, J.; Swart, M.; Bickelhaupt, F. M. *Theor. Chem. Acc.* **2010**, *125*, 245-252.
- (268) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908-6918.

- (269) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364-382.
- (270) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 18.
- (271) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179-5197.
- (272) Matsubara, T.; Dupuis, M.; Aida, M. *J. Comput. Chem.* **2008**, *29*, 458-465.
- (273) Case, D. A.; Darden, T. A.; Cheatham, T. E., III; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Crowley, M.; Walker, R. C.; Zhang, W.; Merz, K. M.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Kolossvary, I.; Wong, K. F.; Paesani, F.; Vanicek, J.; Wu, X.; Brozell, S. R.; Steinbrecher, T.; Gohlke, H.; Yang, L.; Tan, C.; Mongan, J.; Hornak, V.; Cui, G.; Mathews, D. H.; Seetin, M. G.; Sagui, C.; Babin, V.; Kollman, P. A. *AMBER Tools*, Version 1.0; University of California: San Francisco, 2008.
- (274) O'Brien, K. A.; Salter, E. A.; Wierzbick, A. *Int. J. Quantum Chem.* **2007**, *107*, 2197-2203.
- (275) Seabra, G. M.; Walker, R. C.; Elstner, M.; Case, D. A.; Roitberg, A. E. *J. Phys. Chem. A* **2007**, *111*, 5655-5664.
- (276) Srivab, P.; Hannongbua, S. *ChemMedChem* **2008**, *3*, 803-811.
- (277) Alzate-Morales, J. H.; Caballero, J.; Gonzalez-Nilo, F. D.; Contreras, R. *Chem. Phys. Lett.* **2009**, *479*, 149-155.
- (278) Stewart, J. J. P. *J. Mol. Model.* **2007**, *13*, 1173-1213.
- (279) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347-1363.
- (280) Johnson, E. R.; Wolkow, R. A.; DiLabio, G. A. *Chem. Phys. Lett.* **2004**, *394*, 334-338.
- (281) Dinner, A. R.; Blackburn, G. M.; Karplus, M. *Nature (London, U. K.)* **2001**, *413*, 752-755.
- (282) Johnson, E. R.; Becke, A. D.; Sherrill, C. D.; DiLabio, G. A. *J. Chem. Phys.* **2009**, *131*.
- (283) Wang, J. M.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 1157-1174.
- (284) Wang, J.; Wang, W.; Kollman, P. A.; Case, D. A. *J. Mol. Graphics Modell.* **2006**, *25*, 247-260.
- (285) Bayly, C. I.; Cieplak, P.; Cornell, W. D.; Kollman, P. A. *J. Phys. Chem.* **1993**, *97*, 10269-10280.
- (286) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Kollman, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9620-9631.
- (287) Vreven, T.; Frisch, M. J.; Kudin, K. N.; Schlegel, H. B.; Morokuma, K. *Mol. Phys.* **2006**, *104*, 701-714.
- (288) Hirao, H.; Morokuma, K. *J. Am. Chem. Soc.* **2009**, *131*, 17206-17214.
- (289) Lill, S. O. N.; Siegbahn, P. E. M. *Biochemistry* **2009**, *48*, 1056-1066.

- (290) Maupin, C. M.; McKenna, R.; Silverman, D. N.; Voth, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 7598-7608.
- (291) Tao, P.; Fisher, J. F.; Shi, Q.; Vreven, T.; Mobashery, S.; Schlegel, H. B. *Biochemistry* **2009**, *48*, 9839–9847.
- (292) Tao, P.; Gatti, D. L.; Schlegel, H. B. *Biochemistry* **2009**, *48*, 11706–11714.
- (293) Tomasello, G.; Olaso-Gonzalez, G.; Altoe, P.; Stenta, M.; Serrano-Andres, L.; Merchan, M.; Orlandi, G.; Bottoni, A.; Garavelli, M. *J. Am. Chem. Soc.* **2009**, *131*, 5172-5186.
- (294) Bras, N. F.; Fernandes, P. A.; Ramos, M. J. *J. Chem. Theory Comput.* **2010**, *6*, 421-433.
- (295) Chung, L. W.; Li, X.; Sugimoto, H.; Shiro, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2010**, *132*, 11993-12005.
- (296) Hirao, H.; Morokuma, K. *J. Am. Chem. Soc.* **2010**, *132*, 17901-17909.
- (297) Illingworth, C. J. R.; Loenarz, C.; Schofield, C. J.; Domene, C. *Biochemistry* **2010**, *49*, 6936-6944.
- (298) Kurland, M. D.; Newcomer, M. B.; Peterlin, Z.; Ryan, K.; Firestein, S.; Batista, V. S. *Biochemistry* **2010**, *49*, 6302-6304.
- (299) Sekharan, S.; Altun, A.; Morokuma, K. *J. Am. Chem. Soc.* **2010**, *132*, 15856-15859.
- (300) Sekharan, S.; Morokuma, K. *J. Am. Chem. Soc.* **2011**, *133*, 4734-4737.
- (301) Shi, Q.; Meroueh, S. O.; Fisher, J. F.; Mobashery, S. *J. Am. Chem. Soc.* **2011**, *133*, 5274-5283.
- (302) Tao, P.; Schlegel, H. B. *J. Comput. Chem.* **2010**, *31*, 2363–2369.
- (303) Lindahl, T.; Nyberg, B. *Biochemistry* **1972**, *11*, 3610–3618.
- (304) Parkin, D. W.; Leung, H. B.; Schramm, V. L. *J. Biol. Chem.* **1984**, *259*, 9411-9417.
- (305) Parkin, D. W.; Schramm, V. L. *Biochemistry* **1987**, *26*, 913-920.
- (306) Barnes, J. A.; Williams, I. H. *Chem. Commun. (Cambridge, U. K.)* **1996**, 193-194.
- (307) Berti, P. J.; Schramm, V. L. *J. Am. Chem. Soc.* **1997**, *119*, 12069-12078.
- (308) McCann, J. A. B.; Berti, P. J. *J. Am. Chem. Soc.* **2007**, *129*, 7055-7064.
- (309) Rios-Font, R.; Rodriguez-Santiago, L.; Bertran, J.; Sodupe, M. *J. Phys. Chem. B* **2007**, *111*, 6071-6077.
- (310) Schroeder, G. K.; Wolfenden, R. *Biochemistry* **2007**, *46*, 13638-13647.
- (311) Przybylski, J. L.; Wetmore, S. D. *J. Phys. Chem. B* **2010**, *114*, 1104–1113.
- (312) Shishkin, O. V.; Dopieralski, P.; Palamarchuk, G. V.; Latajka, Z. *Chem. Phys. Lett.* **2010**, *490*, 221-225.

- (313) Rios-Font, R.; Bertran, J.; Sodupe, M.; Rodriguez-Santiago, L. *Theor. Chem. Acc.* **2011**, *128*, 619-626.
- (314) Werner, R. M.; Stivers, J. T. *Biochemistry* **2000**, *39*, 14054-14064.
- (315) Yip, V. L. Y.; Varrot, A.; Davies, G. J.; Rajan, S. S.; Yang, X. J.; Thompson, J.; Anderson, W. F.; Withers, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 8354-8355.
- (316) Singh, V.; Schramm, V. L. *J. Am. Chem. Soc.* **2006**, *128*, 14691-14696.
- (317) Leavens, F. M. V.; Churchill, C. D. M.; Wang, S.; Wetmore, S. D. *Accepted.* **2011**, DOI: jp205424z.
- (318) Churchill, C. D. M.; Navarro-Whyte, L.; Rutledge, L. R.; Wetmore, S. D. *Phys. Chem. Chem. Phys.* **2009**, *11*, 10657-10670.
- (319) Churchill, C. D. M.; Rutledge, L. R.; Wetmore, S. D. *Phys. Chem. Chem. Phys.* **2010**, *12*, 14515-14526.
- (320) Rutledge, L. R.; Navarro-Whyte, L.; Peterson, T. L.; Wetmore, S. D. *J. Phys. Chem. A* **2011**, DOI: 10.1021/jp203248j.
- (321) Cerny, J.; Hobza, P. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 383-385.
- (322) Miao, F.; Bouziane, M.; Dammann, R.; Masutani, C.; Hanaoka, F.; Pfeifer, G.; O'Connor, T. R. *J. Biol. Chem.* **2000**, *275*, 28433-28438.

Appendix A

Basis Set Extrapolation Details

The Helgaker^{1,2} basis set extrapolation uses MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ energies to estimate the MP2/CBS level of theory. Specifically, the total energy of the system at the MP2/aug-cc-pVDZ (E_{DZ}^{MP2}) and the MP2/aug-cc-pVTZ (E_{TZ}^{MP2}) level are first separated into their Hartree Fock (HF) and electron correlation (corr) components:

$$E_{DZ}^{MP2} = E_{DZ}^{HF} + E_{DZ}^{corr}$$

$$E_{TZ}^{MP2} = E_{TZ}^{HF} + E_{TZ}^{corr}$$

Therefore, the energy at the MP2/CBS level of theory, or the MP2 energy at an infinite basis set (E_{∞}^{MP2}), would be represented by the following:

$$E_{\infty}^{MP2} = E_{\infty}^{HF} + E_{\infty}^{corr}$$

Helgaker provided the following extrapolation relations to estimate the E_{∞}^{HF} and E_{∞}^{corr} components, which requires only one parameter, α , which was found to provide the best results when set equal to 1.43.

$$E_{DZ}^{HF} = E_{\infty}^{HF} + Ae^{-2\alpha}$$

$$E_{TZ}^{HF} = E_{\infty}^{HF} + Ae^{-3\alpha}$$

$$E_{DZ}^{corr} = E_{\infty}^{corr} + \frac{B}{8}$$

$$E_{TZ}^{corr} = E_{\infty}^{corr} + \frac{B}{27}$$

Rearrangements of the above relations result in the following equations that were used in this thesis to estimate the MP2/CBS energies:

$$E_{\infty}^{HF} = E_{TZ}^{HF} \frac{e^{3\alpha}}{e^{3\alpha} - e^{2\alpha}} - E_{DZ}^{HF} \frac{e^{2\alpha}}{e^{3\alpha} - e^{2\alpha}}$$

$$E_{\infty}^{corr} = \frac{27}{19} E_{TZ}^{corr} - \frac{8}{19} E_{DZ}^{corr}$$

¹ Halkier, A.; Helgaker, T.; Jorgensen, P.; Klopper, W.; Koch, H.; Olsen, J.; Wilson, A. K. *Chem. Phys. Lett.* **1998**, 286, 243–252.

² Halkier, A.; Helgaker, T.; Jorgensen, P.; Klopper, W.; Olsen, J. *Chem. Phys. Lett.* **1999**, 302, 437–446.

Appendix B

MP2/6-31G*(0.25) Potential Energy Surface Scan Calculations for Natural Nucleobase–Amino Acid
Dimers that Vary R_1 (Å), α (°), and R_2 (X-axis Shift (Å), Y-axis Shift (Å))

Dimers	Page
Adenine	B-2
Cytosine	B-10
Guanine	B-20
Thymine	B-29
Uracil	B-37

Adenine–Histidine Dimers

Stacked			Amino Acid Edge T-shaped												Nucleobase Edge T-shaped															
R_1	HIS'	HIS	R_1	1	2	3	4	5	A	B	C	D	E	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
3.2	-23.8	-17.3	4.0	0.7	26.2	-0.6	42.0	41.5	-2.5	-8.1	-5.9	3.5	4.5	2.0		6.2		-10.4	1.5			-8.6				21.2				41.8
3.3	-24.3	-18.1	4.1	-7.0	13.2	-3.5	26.1	24.8	-8.6	-12.9	-9.2	-1.5	-2.4	2.1		0.8		-13.9	-3.5		74.0	-13.3				5.3				20.7
3.4	-23.7	-17.8	4.2	-11.8	4.2	-5.1	14.7	12.9	-12.3	-15.7	-11.0	-4.5	-6.7	2.2		-2.7		-15.6	-6.5		50.1	-16.0				-5.3				6.5
			4.3	-14.6	-1.9	-5.9	6.8	4.6	-14.2	-16.9	-11.6	-6.1	-9.2	2.3		-4.7		-16.2	-8.3		32.4	-17.3				-12.0				-2.9
			4.4	-15.9	-5.9	-6.1	1.5	-0.9	-15.0	-17.2	-11.6	-6.8	-10.4	2.4		-5.8		-16.0	-9.0		19.5	-17.6				-15.9				-8.8
			4.5	-16.4	-8.3	-6.0	-2.0	-4.5	-15.0	-16.9	-11.2	-6.9	-10.8	2.5		-6.3		-15.2	-9.2		10.3	-17.3				-17.9				-12.2
			4.6	-16.2	-9.6	-5.6	-4.2	-6.7	-14.5	-16.1	-10.5	-6.7	-10.7	2.6		-6.4		-14.3	-9.0		3.8	-16.7				-18.6				-14.0
			4.7	-15.6	-10.2	-5.0	-5.4	-7.9	-13.8	-15.2	-9.7	-6.2	-10.2	2.7		-6.2		-13.2	-8.6		-0.7	-15.8				-18.5				-14.7
			4.8	-14.7	-10.2	-4.5	-5.9	-8.4	-12.9	-14.1	-8.8	-5.6	-9.5	2.8		-5.8		-12.0	-8.0		-3.7	-14.8				-17.9				-14.6
			4.9	-13.8	-10.0	-3.9	-6.1	-8.5	-11.9	-13.1	-7.9	-5.0	-8.8	2.9		-5.4		-10.9	-7.4		-5.7	-13.7				-16.9				-14.1
			5.0	-12.8	-9.5	-3.3	-5.9	-8.3	-10.9	-12.0	-7.0	-4.3	-8.0	3.0	-5.6	-4.9	1.4	-9.8	-6.7	-3.5	-6.8	-12.7	26.3	20.2	2.7	-15.8	18.7	-2.2	-13.3	-4.0
														3.1	-6.9		0.3			-4.9	-7.5	-11.7	15.7	10.6	1.4		10.3	-3.6	-12.4	-5.5
														3.2	-7.5		-0.4			-5.5	-7.7	-10.7	8.5	4.2	0.6		4.7	-4.4	-11.4	-6.3
														3.3	-7.6		-0.6			-5.6	-7.7	-9.8	3.6	0.1	0.2		1.1	-4.8	-10.4	-6.6
														3.4	-7.4		-0.6			-5.5	-7.4	-9.0	0.4	-2.5	0.0		-1.2	-4.8	-9.5	-6.7
														3.5	-7.0		-0.5			-5.1	-7.1	-8.3	-1.6	-4.0	0.0		-2.6	-4.7	-8.6	-6.5
														3.6	-6.5		-0.4			-4.7		-7.6	-2.8	-4.7	0.1		-3.3	-4.5		-6.2
														3.7	-6.0		-0.2			-4.3		-6.9	-3.4	-5.0	0.2		-3.5	-4.2		-5.9
														3.8	-5.5		0.0			-3.9		-6.4	-3.7	-5.0	0.4		-3.5	-3.9		-5.5
														3.9	-5.0		0.2			-3.4		-5.9	-3.7	-4.7	0.5		-3.3	-3.6		-5.1
														4.0	-4.6		0.4			-3.0		-5.4	-3.5	-4.4	0.6		-3.1	-3.3		-4.8

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped															
	HIS'	HIS	1	2	3	4	5	A	B	C	D	E	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
0	-24.3	-18.1	-16.4	-10.2	-6.1	-6.1	-8.5	-15.0	-17.2	-11.6	-6.9	-10.8	-7.6	-6.4	-0.6	-16.2	-9.2	-5.6	-7.7	-17.6	-3.7	-5.0	0.0	-18.6	-3.5	-4.8	-14.7	-6.7
30	-23.0	-19.2	-17.3	-8.5	-7.2	-7.3	-10.7	-19.0	-18.2	-10.1	-8.9	-14.0	-3.4	-6.8	-1.5	-21.2	-11.5	-3.3	-4.5	-13.6	-4.0	-3.3	-4.7	-18.3	-5.7	-1.8	-13.4	-2.8
60	-23.4	-19.7	-18.1	-7.8	-6.2	-8.0	-12.2	-21.7	-20.1	-10.0	-10.0	-16.4	-0.8	-7.3	-2.4	-25.1	-13.6	-2.4	-2.2	-10.5	-4.7	-2.4	-9.1	-18.1	-8.1	0.7	-12.3	0.7
90	-26.0	-20.0	-17.7	-6.8	-8.0	-8.6	-12.5	-21.8	-19.2	-9.2	-10.8	-16.8	0.5	-7.4	-4.2	-27.9	-15.4	-2.6	-1.0	-8.1	-5.4	-2.3	-12.0	-18.7	-10.4	1.5	-12.1	2.6
120	-27.0	-22.8	-16.6	-5.4	-6.3	-9.2	-11.8	-20.5	-16.0	-7.2	-11.8	-16.1	-0.1	-7.1	-7.3	-29.5	-17.0	-4.6	1.1	-4.8	-6.1	-2.6	-13.8	-20.9	-12.7	-0.2	-12.9	2.1
150	-23.7	-27.0	-15.8	-5.4	-5.2	-8.9	-10.6	-17.5	-13.8	-6.7	-10.6	-13.6	-2.2	-6.6	-9.4	-28.7	-17.2	-7.0	3.9	-3.1	-6.3	-3.0	-13.5	-22.6	-13.3	-2.4	-13.9	0.4
180	-19.4	-28.3	-16.2	-7.3	-5.7	-7.7	-10.0	-16.3	-15.2	-7.8	-9.4	-12.5	-2.8	-6.6	-7.0	-26.0	-15.4	-6.1	-0.4	-7.2	-5.2	-3.3	-9.7	-20.2	-10.4	-3.2	-14.0	-1.5
210	-17.4	-25.1	-17.5	-9.8	-7.4	-6.4	-10.2	-18.5	-19.3	-11.0	-8.3	-13.1	-2.7	-6.9	-2.8	-22.4	-12.5	-3.4	-5.6	-13.4	-3.6	-3.8	-4.3	-16.5	-6.0	-3.7	-13.3	-3.9
240	-16.6	-21.1	-18.4	-11.1	-8.8	-5.8	-10.4	-21.0	-21.8	-12.8	-8.3	-14.1	-2.8	-7.2	0.6	-19.3	-9.8	-1.1	-10.0	-18.1	-2.6	-4.5	0.3	-14.4	-2.3	-4.7	-12.5	-6.6
270	-15.8	-19.7	-18.2	-11.9	-8.6	-5.3	-9.6	-20.3	-22.2	-13.9	-8.0	-13.5	-3.7	-7.2	2.7	-16.5	-7.8	-0.3	-12.9	-21.2	-2.4	-5.3	3.4	-14.5	-0.3	-5.2	-12.7	-8.2
300	-18.7	-19.4	-17.3	-12.7	-7.5	-4.7	-8.2	-16.9	-21.6	-15.0	-6.8	-11.7	-7.2	-6.8	2.6	-13.5	-6.9	-3.1	-13.4	-22.5	-2.9	-6.2	4.5	-16.3	-0.3	-5.9	-14.0	-9.3
330	-23.0	-18.0	-16.3	-11.9	-6.2	-4.9	-7.5	-13.9	-18.9	-13.4	-6.4	-10.0	-10.2	-6.4	0.8	-12.8	-7.5	-6.6	-12.4	-21.2	-3.5	-6.4	3.5	-18.2	-1.7	-6.8	-15.0	-9.5

$\gamma \downarrow$ $X \rightarrow$	Stacked (HIS $R_1=3.3 \text{ \AA}$, $\alpha=180^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-14.6	-15.8	-17.0	-16.9	-15.3	-13.7	-12.7
1.0	-19.3	-20.9	-22.1	-21.7	-19.7	-17.8	-16.1
0.5	-22.6	-24.8	-26.8	-26.1	-22.5	-19.2	-16.9
0	-22.8	-25.5	-28.8	-28.3	-23.6	-19.0	-16.4
-0.5	-21.5	-24.3	-28.7	-29.2	-25.0	-20.5	-17.8
-1.0	-22.1	-24.9	-28.9	-29.7	-26.7	-23.1	-20.0
-1.5	-24.9	-27.3	-29.4	-29.0	-26.4	-23.4	-20.0

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=B$, $R_1=4.4 \text{ \AA}$, $\alpha=270^\circ$)												
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
3.5	-3.1	-4.7	-6.3	-7.4	-7.3	-6.6	-5.9	-5.6	-5.8	-6.1	-6.1	-5.6	-4.8
3.0	-5.6	-7.5	-9.7	-11.1	-11.3	-10.7	-10.0	-9.6	-9.5	-9.6	-9.4	-8.4	-7.1
2.5	-8.4	-10.3	-12.5	-14.2	-14.7	-14.6	-14.4	-14.1	-13.8	-13.4	-12.6	-11.1	-9.4
2.0	-11.4	-12.9	-14.7	-16.1	-17.0	-17.7	-18.4	-18.4	-17.7	-16.5	-14.8	-12.8	-10.9
1.5	-14.3	-15.2	-16.4	-17.5	-18.5	-19.8	-21.1	-21.3	-20.2	-18.3	-15.9	-13.5	-11.4
1.0	-16.4	-17.0	-17.8	-18.5	-19.5	-21.1	-22.4	-22.2	-20.8	-18.9	-16.4	-13.6	-11.2
0.5	-17.0	-17.7	-18.4	-18.8	-19.8	-21.4	-22.5	-21.6	-19.9	-18.4	-16.3	-13.4	-10.6
0	-15.8	-16.9	-17.7	-18.0	-19.1	-21.2	-22.2	-20.9	-18.7	-17.4	-15.8	-12.9	-9.8
-0.5	-13.3	-14.8	-15.9	-16.5	-17.9	-20.6	-22.1	-20.7	-18.3	-16.6	-14.9	-12.2	-9.4
-1.0	-10.6	-12.4	-13.8	-14.8	-16.9	-19.9	-21.8	-20.8	-18.4	-16.2	-14.1	-11.7	-9.5
-1.5	-8.3	-10.2	-11.8	-13.4	-15.9	-18.9	-20.7	-20.4	-18.5	-16.0	-13.7	-11.6	-9.9
-2.0	-6.1	-7.8	-9.6	-11.6	-14.3	-17.0	-18.7	-19.0	-17.7	-15.5	-13.3	-11.4	-10.1
-2.5	-3.4	-5.0	-6.7	-9.0	-11.6	-14.0	-15.7	-16.3	-15.6	-14.0	-12.2	-10.7	-9.6
-3.0	-0.7	-2.0	-3.6	-5.8	-8.3	-10.5	-12.1	-12.8	-12.5	-11.5	-10.3	-9.2	-8.3

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=4$, $R_1=2.3 \text{ \AA}$, $\alpha=120^\circ$)								
	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.0	-9.0	-12.9	-17.5	-22.5	-27.2	-30.3	-30.5	-27.3	-21.4
1.5	-10.5	-15.0	-20.0	-25.3	-30.1	-33.3	-33.4	-30.1	-23.8
1.0	-11.5	-16.6	-21.9	-27.0	-31.2	-33.6	-33.3	-29.9	-23.8
0.5	-11.8	-17.3	-22.7	-27.3	-30.7	-32.2	-31.3	-27.7	-22.0
0	-10.9	-16.7	-22.2	-26.5	-29.5	-30.5	-29.1	-25.3	-19.9
-0.5	-9.1	-14.9	-20.4	-24.8	-27.7	-28.7	-27.1	-23.3	-18.2
-1.0	-7.1	-12.5	-17.7	-21.9	-24.9	-25.8	-24.5	-21.1	-16.5
-1.5	-5.4	-9.9	-14.3	-17.9	-20.4	-21.4	-20.5	-17.8	-14.3
-2.0	-3.8	-7.3	-10.7	-13.4	-15.2	-16.0	-15.5	-13.9	-11.4

Adenine–Phenylalanine Dimers

R_1	Stacked	R_1	Amino Acid Edge T-shaped				Nucleobase Edge T-shaped														
	PHE		1	A	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
3.3	-24.1	4.5	6.1	-4.9	2.0		2.9		-22.0	-5.7			-5.0								
3.4	-24.3	4.6	-0.1	-8.3	2.1		-1.7		-24.5	-9.8			-10.0								
3.5	-23.5	4.7	-4.2	-10.2	2.2		-4.7		-25.6	-12.3			-13.0								
		4.8	-6.7	-11.1	2.3		-6.5		-25.5	-13.6			-14.6								
		4.9	-8.1	-11.3	2.4		-7.5		-24.8	-14.1			-15.3								
		5.0	-8.8	-11.0	2.5	46.8	-7.9	31.7	-23.6	-14.1	43.1	23.4	-15.3				-18.8			-11.7	
		5.1	-8.9	-10.4	2.6	30.0	-7.8	19.9	-22.2	-13.6	27.2	14.0	-14.9				-20.2			-14.0	
		5.2	-8.7	-9.8	2.7	18.2	-7.5	11.8	-20.7	-13.0	16.0	7.2	-14.1				-20.6			-15.1	
		5.3	-8.3	-9.0	2.8	10.0	-7.1	6.3	-19.1	-12.2	8.3	2.5	-13.3				-20.2			-15.3	
		5.4	-7.8	-8.2	2.9	4.5	-6.6	2.6	-17.5	-11.3	3.2	-0.7	-12.3				-19.4			-15.0	
		5.5	-7.2	-7.5	3.0	0.9	-6.0	0.3	-16.1	-10.5	-0.1	-2.8	-11.4	30.0	29.2	-3.2	-18.3	18.4	0.9	-14.4	0.7
				3.1	-1.4	-5.5	-1.2	-14.7	-9.7	-2.2	-4.2	-10.4	18.2	17.6	-4.6	-17.1	9.0	-1.2	-13.5	-1.5	
				3.2	-2.7	-4.9	-1.9	-13.4	-8.9	-3.4	-5.0	-9.5	10.0	9.6	-5.4	-15.8	2.6	-2.4	-12.5	-2.8	
				3.3	-3.4	-4.4	-2.3	-12.2	-8.1	-4.0	-5.3	-8.6	4.3	4.1	-5.7	-14.6	-1.6	-3.1	-11.5	-3.6	
				3.4	-3.7	-3.9	-2.4	-11.1	-7.4	-4.2	-5.5	-7.8	0.6	0.5	-5.7	-13.3	-4.2	-3.4	-10.5	-3.9	
				3.5	-3.8	-3.5	-2.4	-10.1	-6.8	-4.1	-5.4	-7.1	-1.8	-1.8	-5.5	-12.2	-5.8	-3.5	-9.6	-4.0	
		3.6	-3.6											-3.2	-3.2	-5.2	-6.5	-3.4	-8.7	-3.9	
		3.7	-3.4											-4.0	-3.9	-4.8	-6.8	-3.3	-7.9	-3.7	
		3.8	-3.1											-4.4	-4.2	-4.5	-6.8	-3.0	-7.2	-3.4	
		3.9	-2.8											-4.4	-4.3	-4.1	-6.5	-2.8	-6.5	-3.1	
		4.0	-2.5											-4.3	-4.1	-3.7	-6.1	-2.5	-5.9	-2.8	

α	Stacked	Amino Acid Edge T-shaped								Nucleobase Edge T-shaped									
	PHE	1	A	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
0	-24.3	-8.9	-11.3	-3.8	-7.9	-2.4	-25.6	-14.1	-4.2	-5.5	-15.3	-4.4	-4.3	-5.7	-20.6	-6.8	-3.5	-15.3	-4.0
30	-24.3	-9.7	-11.5	-3.8	-7.9	-2.4	-25.6	-14.1	-4.2	-5.8	-15.3	-4.4	-4.3	-5.7	-20.7	-6.9	-3.6	-15.3	-4.1
60		-10.3	-13.1																
90		-10.1	-14.1																
120		-9.4	-14.0																
150		-8.8	-12.8																

		Stacked ($R_1=3.4 \text{ \AA}$, $\alpha=0^\circ$)						
$Y \downarrow$ $X \rightarrow$		-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5		-14.5	-15.5	-16.4	-16.9	-16.7	-16.0	-15.4
1.0		-17.2	-18.3	-19.4	-19.8	-19.0	-18.0	-17.4
0.5		-19.1	-20.8	-22.7	-22.9	-20.5	-18.0	-17.0
0		-18.8	-20.8	-23.8	-24.3	-20.9	-17.0	-15.6
-0.5		-17.5	-19.3	-23.0	-24.3	-21.3	-17.5	-15.6
-1.0		-18.1	-19.4	-22.4	-23.7	-21.8	-18.9	-16.8
-1.5		-20.5	-21.3	-22.4	-22.4	-20.8	-18.7	-16.7

		Amino Acid Edge T-shaped ($\theta=A$, $R_0=4.9 \text{ \AA}$, $\alpha=90^\circ$)												
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0	
3.5	-2.5	-3.1	-3.5	-3.8	-3.8	-3.9	-4.1	-4.3	-4.3	-4.2	-4.0	-3.6	-3.1	
3.0	-3.6	-4.3	-4.9	-5.3	-5.5	-5.8	-6.1	-6.2	-6.1	-6.0	-5.8	-5.2	-4.5	
2.5	-4.9	-5.8	-6.6	-7.1	-7.5	-8.0	-8.5	-8.5	-8.2	-7.9	-7.5	-6.8	-5.9	
2.0	-6.2	-7.2	-8.2	-8.9	-9.5	-10.2	-10.7	-10.7	-10.1	-9.4	-8.7	-7.9	-6.9	
1.5	-7.4	-8.5	-9.5	-10.3	-11.0	-11.9	-12.4	-12.1	-11.3	-10.4	-9.5	-8.5	-7.5	
1.0	-8.2	-9.3	-10.4	-11.2	-12.1	-13.0	-13.3	-12.7	-11.7	-10.9	-10.0	-8.8	-7.7	
0.5	-8.5	-9.8	-10.7	-11.4	-12.5	-13.7	-13.9	-12.7	-11.4	-10.9	-10.3	-9.0	-7.5	
0	-8.4	-9.9	-10.8	-11.2	-12.2	-13.8	-14.1	-12.5	-11.0	-10.5	-10.2	-8.9	-7.2	
-0.5	-7.9	-9.5	-10.4	-10.5	-11.5	-13.2	-13.7	-12.3	-10.6	-10.0	-9.6	-8.4	-6.9	
-1.0	-7.0	-8.6	-9.4	-9.7	-10.6	-12.1	-12.7	-11.7	-10.3	-9.5	-8.9	-7.9	-6.7	
-1.5	-6.0	-7.2	-8.2	-8.8	-9.8	-10.9	-11.3	-10.7	-9.8	-9.1	-8.3	-7.5	-6.7	
-2.0	-4.9	-5.8	-6.8	-7.8	-8.8	-9.6	-9.7	-9.5	-9.0	-8.4	-7.7	-6.9	-6.4	
-2.5	-3.9	-4.6	-5.5	-6.5	-7.5	-8.0	-8.1	-8.0	-7.7	-7.2	-6.6	-6.1	-5.6	
-3.0	-2.9	-3.4	-4.2	-5.1	-5.8	-6.2	-6.2	-6.2	-6.0	-5.6	-5.2	-4.8	-4.5	

		Nucleobase Edge T-shaped ($\theta=4$, $R_1=2.2 \text{ \AA}$, $\alpha=0^\circ$)							
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-9.0	-11.5	-13.2	-14.0	-14.1	-14.0	-13.2	-11.5	-9.0
2.0	-11.0	-13.9	-16.0	-16.8	-16.9	-16.8	-16.0	-13.9	-11.0
1.5	-12.5	-15.7	-18.1	-19.2	-19.5	-19.2	-18.1	-15.7	-12.5
1.0	-13.8	-17.1	-19.9	-21.7	-22.3	-21.7	-19.9	-17.1	-13.8
0.5	-15.0	-18.3	-21.6	-24.0	-24.9	-24.0	-21.6	-18.3	-15.0
0	-15.2	-18.4	-21.8	-24.5	-25.6	-24.5	-21.8	-18.4	-15.2
-0.5	-14.0	-16.9	-20.0	-22.4	-23.3	-22.4	-20.0	-16.9	-14.0
-1.0	-11.8	-14.4	-16.8	-18.7	-19.3	-18.7	-16.8	-14.4	-11.8
-1.5	-9.6	-11.7	-13.7	-15.0	-15.4	-15.0	-13.7	-11.7	-9.6
-2.0	-7.1	-8.9	-10.5	-11.5	-11.8	-11.5	-10.5	-8.9	-7.1
-2.5	-4.6	-5.7	-6.9	-7.8	-8.1	-7.8	-6.9	-5.7	-4.6

Adenine–Tyrosine Dimers

Stacked			Amino Acid Edge T-shaped																Nucleobase Edge T-shaped													
R_1	TYR'	TYR	R_1	1	2	3	4	5	6	A	B	C	D	E	F	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
3.3	-23.7	-25.8	4.5	70.2	-12.0	40.4	99.8	41.6	-6.0	1.1	0.6	50.0	48.7	0.1	4.1	2.0	8.5		-17.2	-3.0			2.7				11.5					
3.4	-24.4	-26.3	4.6	44.1	-14.0	23.4	67.0	24.3	-8.4	-6.0	-5.1	28.6	27.8	-5.1	-1.1	2.1	2.4		-20.8	-8.1			-3.9				-3.0					
3.5	-23.9	-25.6	4.7	25.8	-14.9	11.5	42.9	12.2	-9.7	-10.4	-8.6	13.7	13.3	-8.3	-4.3	2.2	-1.7		-22.6	-11.2			-8.2				-12.6					
			4.8	13.3	-15.1	3.2	25.5	3.8	-10.2	-13.0	-10.6	3.6	3.4	-10.1	-6.1	2.3	-4.2		-23.2	-13.0			-10.8				-18.5					
			4.9	4.8	-14.7	-2.3	13.2	-1.9	-10.2	-14.3	-11.5	-3.0	-3.1	-10.9	-7.0	2.4	-5.7		-22.9	-13.8			-12.2				-21.9					
			5.0	-0.6	-14.0	-5.8	4.7	-5.4	-9.8	-14.7	-11.7	-7.2	-7.1	-11.1	-7.2	2.5	-6.5		-22.0	-13.9			-12.8				-23.5					-12.0
			5.1	-4.0	-13.1	-7.9	-1.1	-7.6	-9.3	-14.5	-11.5	-9.6	-9.5	-10.8	-7.1	2.6	-6.8		-20.8	-13.6			-12.7				-23.8				-14.1	
			5.2	-5.9	-12.1	-9.0	-4.8	-8.7	-8.6	-13.9	-10.9	-10.8	-10.7	-10.3	-6.7	2.7	-6.7		-19.5	-13.1			-12.4				-23.3				-15.0	
			5.3	-6.8	-11.2	-9.4	-7.1	-9.2	-7.9	-13.1	-10.3	-11.2	-11.1	-9.6	-6.2	2.8	-6.4		-18.1	-12.3			-11.8				-22.3				-15.1	
			5.4	-7.1	-10.2	-9.4	-8.3	-9.2	-7.2	-12.3	-9.5	-11.1	-10.9	-8.9	-5.6	2.9	-6.0		-16.6	-11.5			-11.0				-21.0				-14.8	
			5.5	-7.0	-9.3	-9.1	-8.8	-8.9	-6.5	-11.3	-8.8	-10.6	-10.5	-8.2	-5.0	3.0	-3.8	-5.6	-5.2	-15.3	-10.7	-6.1	6.7	-10.2	12.9	22.8	-12.7	-19.6	3.0	0.2	-14.1	0.9
			5.6				-8.9									3.1	-6.1		-6.2			-8.1	3.2	-9.4	4.6	13.2	-12.7	-3.5	-2.0	-13.2	-1.6	
			5.7				-8.6									3.2	-7.3		-6.5			-9.1	0.7	-8.6	-0.9	6.6	-12.2	-7.7	-3.3	-12.3	-3.2	
			5.8				-8.2									3.3	-7.7		-6.5			-9.3	-0.9	-7.9	-4.4	2.2	-11.5	-10.1	-4.0	-11.3	-4.0	
			5.9				-7.7									3.4	-7.7		-6.2			-9.1	-2.0	-7.1	-6.4	-0.6	-10.7	-11.3	-4.3	-10.3	-4.4	
			6.0				-7.1									3.5	-7.4		-5.7			-8.6	-2.7	-6.5	-7.5	-2.4	-9.8	-11.7	-4.4	-9.4	-4.5	
																3.6	-6.9		-5.2			-8.0	-3.0	-5.8	-7.9	-3.4	-8.9	-11.6	-4.2		-4.4	
																3.7	-6.3		-4.7			-7.3	-3.2	-5.3	-7.9	-3.9	-8.0	-11.1	-4.0		-4.2	
																3.8	-5.7		-4.2			-6.6	-3.2	-4.7	-7.6	-4.0	-7.2	-10.4	-3.7		-3.9	
																3.9	-5.1		-3.7			-5.9	-3.1	-4.3	-7.1	-3.9	-6.5	-9.7	-3.4		-3.6	
																4.0	-4.5		-3.3			-5.2	-3.0	-3.9	-6.5	-3.7	-5.8	-8.8	-3.1		-3.3	

α	Stacked		Amino Acid Edge T-shaped																Nucleobase Edge T-shaped															
	TYR'	TYR	1	2	3	4	5	6	A	B	C	D	E	F	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H				
0	-24.4	-26.3	-7.1	-15.1	-9.4	-8.9	-9.2	-10.2	-14.7	-11.7	-11.2	-11.1	-11.1	-7.2	-7.7	-6.8	-6.5	-23.2	-13.9	-9.3	-3.2	-12.8	-7.9	-4.0	-12.7	-23.8	-11.7	-4.4	-15.1	-4.5				
30	-26.4	-25.0	-10.1	-15.2	-10.5	-9.6	-9.5	-8.9	-16.4	-13.3	-12.8	-12.5	-11.6	-9.5	-8.1	-6.7	-6.0	-21.8	-13.4	-9.4	-3.9	-13.8	-7.6	-4.1	-11.0	-23.4	-11.0	-5.1	-15.4	-5.5				
60	-22.7	-21.2	-12.1	-16.9	-9.3	-10.1	-10.3	-9.3	-17.5	-14.7	-14.0	-13.8	-12.6	-10.2	-5.2	-7.0	-3.7	-22.7	-12.8	-5.7	-4.6	-15.0	-5.3	-4.2	-6.8	-21.3	-7.7	-4.6	-15.1	-5.4				
90	-18.0	-23.1	-12.5	-16.6	-10.8	-9.9	-10.1	-9.2	-17.9	-14.1	-13.8	-13.9	-12.7	-9.8	-4.5	-7.5	-1.2	-22.9	-12.0	-4.0	-5.5	-16.4	-3.7	-4.6	-3.0	-19.6	-4.9	-4.2	-14.8	-5.6				
120	-21.1	-25.8	-11.8	-14.1	-9.5	-9.2	-9.2	-8.0	-18.0	-12.4	-12.7	-12.9	-11.8	-9.5	-4.8	-7.7	0.9	-22.6	-11.2	-3.5	-6.2	-18.3	-3.0	-5.3	-0.8	-18.4	-3.4	-3.9	-14.5	-5.8				
150	-25.1	-24.4	-10.2	-12.2	-8.7	-8.5	-8.7	-8.0	-17.2	-10.3	-10.9	-11.3	-10.8	-7.4	-6.2	-7.3	0.3	-22.6	-11.3	-5.1	-5.7	-18.1	-3.1	-6.2	-1.4	-18.9	-4.0	-4.7	-14.7	-6.3				
180	-29.3	-22.3	-9.5	-12.6	-8.9	-8.7	-9.2	-9.1	-15.6	-10.9	-10.9	-11.0	-10.8	-7.3	-8.2	-6.7	-6.1	-23.5	-12.8	-8.6	-5.0	-13.6	-3.6	-7.1	-3.7	-21.1	-6.5	-8.7	-15.0	-8.1				
210	-26.6	-20.9	-9.8	-16.1	-10.0	-9.7	-10.3	-10.3	-15.2	-13.5	-12.7	-12.8	-12.4	-7.8	-7.8	-6.6	-7.2	-24.5	-13.8	-9.2	-5.3	-12.9	-3.7	-7.0	-5.2	-21.1	-7.6	-8.9	-15.1	-7.6				
240	-24.2	-24.2	-10.5	-17.6	-11.3	-10.4	-10.7	-10.0	-15.5	-15.3	-14.4	-14.1	-13.3	-9.4	-5.5	-7.1	-4.5	-25.2	-14.0	-6.9	-4.6	-13.7	-3.6	-5.8	-5.6	-20.1	-7.3	-5.4	-15.0	-4.8				
270	-25.4	-24.4	-9.5	-17.0	-11.2	-10.3	-10.4	-10.3	-15.2	-15.5	-14.6	-14.1	-13.4	-9.8	-3.3	-7.6	-3.5	-26.1	-14.2	-4.8	-4.0	-13.4	-4.0	-4.6	-7.2	-19.9	-7.5	-3.3	-14.7	-3.2				
300	-23.1	-24.7	-7.0	-16.8	-10.2	-9.6	-10.2	-11.8	-14.7	-14.5	-13.5	-13.2	-13.2	-8.6	-1.2	-7.8	-3.7	-27.4	-14.4	-2.9	-3.5	-12.8	-4.7	-3.9	-9.9	-20.4	-8.2	-2.4	-14.2	-2.6				
330	-24.2	-28.1	-5.8	-14.8	-9.3	-8.8	-9.4	-11.5	-13.8	-12.5	-11.7	-11.3	-11.6	-7.3	-1.7	-7.4	-4.8	-27.0	-14.4	-3.3	-3.3	-12.6	-6.0	-3.7	-11.7	-21.9	-9.7	-3.0	-14.3	-3.3				

Y ↓ X →	Stacked (TYR' R ₁ =3.4 Å, α=180°)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-19.4	-21.2	-22.5	-22.6	-21.0	-18.2	-15.3
1.0	-20.6	-22.0	-23.0	-23.2	-22.0	-19.8	-17.4
0.5	-22.4	-23.9	-25.5	-26.0	-24.6	-22.2	-19.8
0	-24.4	-26.6	-29.0	-29.3	-26.5	-22.8	-20.3
-0.5	-24.4	-27.1	-30.4	-30.7	-26.8	-21.9	-19.2
-1.0	-22.4	-25.0	-28.8	-29.8	-26.3	-21.7	-18.9
-1.5	-21.5	-23.5	-26.6	-27.8	-25.6	-22.2	-19.5

Y ↓ X →	Amino Acid Edge T-shaped (θ=A, R ₁ =5.0 Å, α=90°)												
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
3.5	-2.7	-3.0	-3.0	-2.9	-3.0	-3.9	-5.7	-7.7	-8.3	-7.0	-5.1	-4.0	-3.9
3.0	-4.5	-5.1	-5.5	-5.6	-5.7	-6.8	-9.1	-11.7	-12.7	-11.3	-9.1	-7.8	-7.4
2.5	-6.7	-7.9	-8.8	-9.2	-9.3	-10.0	-12.0	-14.4	-15.4	-14.2	-12.5	-11.8	-11.6
2.0	-9.2	-11.1	-12.7	-13.4	-13.4	-13.4	-14.1	-15.3	-15.6	-14.9	-14.6	-15.2	-15.5
1.5	-11.4	-14.2	-16.6	-17.8	-17.5	-16.5	-15.8	-15.5	-15.1	-14.8	-15.6	-17.3	-17.8
1.0	-12.9	-16.2	-19.4	-21.0	-20.6	-18.9	-17.3	-16.1	-15.3	-15.1	-16.3	-17.8	-17.9
0.5	-13.0	-16.6	-20.1	-21.9	-21.4	-19.7	-18.2	-17.0	-16.1	-15.7	-16.4	-17.0	-16.2
0	-11.7	-15.3	-18.6	-20.2	-19.8	-18.7	-17.9	-17.3	-16.5	-16.0	-16.1	-15.9	-14.3
-0.5	-9.5	-12.7	-15.5	-16.9	-16.8	-16.5	-16.8	-16.9	-16.4	-16.2	-16.5	-16.0	-13.8
-1.0	-7.0	-9.6	-12.0	-13.4	-14.0	-14.6	-15.6	-16.1	-16.2	-16.8	-17.8	-17.5	-15.0
-1.5	-4.6	-6.6	-8.8	-10.5	-11.9	-13.4	-14.7	-15.4	-15.9	-17.4	-19.1	-19.1	-16.4
-2.0	-2.6	-4.1	-5.8	-7.8	-9.8	-11.6	-12.9	-13.8	-15.0	-17.2	-19.2	-19.3	-16.7
-2.5	-1.0	-1.9	-3.2	-4.8	-6.7	-8.3	-9.6	-10.8	-12.6	-15.2	-17.3	-17.5	-15.3
-3.0	0.3	-0.2	-1.0	-2.0	-3.2	-4.4	-5.6	-7.2	-9.4	-12.0	-13.9	-14.2	-12.6

Y ↓ X →	Nucleobase Edge T-shaped (θ=4, R ₁ =2.3 Å, α=300°)										
	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-7.6	-11.6	-16.0	-19.4	-20.5	-18.2	-13.2	-7.9	-4.0	-1.7	-0.5
2.5	-7.9	-12.6	-17.7	-21.8	-23.4	-21.2	-15.9	-10.3	-6.1	-3.6	-2.1
2.0	-7.9	-12.7	-18.0	-22.2	-23.7	-21.8	-17.6	-12.9	-9.2	-6.4	-4.4
1.5	-7.9	-12.7	-17.8	-21.6	-22.8	-21.5	-18.9	-15.8	-12.8	-9.9	-7.3
1.0	-8.5	-13.2	-18.0	-21.7	-23.1	-22.6	-21.2	-19.1	-16.3	-13.2	-10.1
0.5	-9.5	-14.2	-18.9	-22.7	-24.9	-25.3	-24.2	-22.1	-19.3	-16.0	-12.5
0	-10.3	-15.0	-19.6	-23.6	-26.4	-27.4	-26.5	-24.3	-21.3	-17.9	-14.2
-0.5	-10.3	-15.0	-19.3	-23.2	-26.3	-27.8	-27.3	-25.1	-22.1	-18.6	-14.7
-1.0	-9.3	-13.8	-17.9	-21.6	-24.7	-26.5	-26.5	-24.5	-21.3	-17.7	-13.8
-1.5	-7.7	-11.8	-15.7	-19.1	-22.0	-23.8	-24.0	-22.3	-19.3	-15.7	-12.1
-2.0	-5.6	-9.3	-12.9	-16.1	-18.5	-20.1	-20.4	-19.2	-16.5	-13.3	-10.0
-2.5	-3.3	-6.4	-9.6	-12.4	-14.6	-15.8	-16.2	-15.4	-13.3	-10.6	-7.8
-3.0	-1.5	-3.7	-6.3	-8.7	-10.6	-11.7	-12.1	-11.5	-9.9	-7.9	-5.8

Adenine–Tryptophan Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped																
R_1	TRP'	TRP	R_1	1	2	3	A	B	C	D	E	F	G	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
3.4	-24.8	-26.8	4.0				96.0							2.0		6.6		-26.6	-5.7		92.8	-5.1				8.7				34.5
3.5	-25.5	-26.9	4.1				59.3							2.1		0.4		-29.4	-11.2		66.4	-10.2				-6.3				14.7
3.6	-25.0	-26.1	4.2				33.2							2.2		-3.7		-30.5	-14.6		46.3	-13.3				-16.1				1.1
			4.3				15.0								2.3		-6.2		-30.4	-16.5		31.1	-15.0				-22.2			-7.8
			4.4				2.6								2.4		-7.6		-29.6	-17.3		19.8	-15.6				-25.6			-13.5
4.5				-5.6	60.9				9.5	65.8		63.8	2.5		-8.2		-28.3	-17.3		11.5	-15.6				-27.1				-16.8	
4.6				-10.7	33.8				0.7	40.2			38.4	2.6		-8.3		-26.7	-16.9		5.5	-15.1				-27.4				-18.4
4.7				-13.7	14.9				-5.1	22.1			20.5	2.7		-8.1		-24.9	-16.2		1.3	-14.4				-26.9				-18.9
4.8				-15.2	2.0				-8.6	9.6			8.3	2.8		-7.7		-23.1	-15.4		-1.7	-13.5				-25.8				-18.7
4.9				-15.6	-6.4				-10.5	1.1			0.1	2.9		-7.2		-21.4	-14.4		-3.6	-12.5				-24.4				-18.0
5.0				-15.4	-11.8	10.3	-11.4	-4.4	53.5	-5.1	3.0	-4.7	-6.6	-4.9	-19.7	-13.4	-7.6	-4.9	-11.5	17.0	17.8	-9.9	-22.8	3.1	-2.3	-17.1	-2.0			
5.1				-14.8	-14.9	0.8	-11.6	-7.7	31.3	-8.3	3.1	-6.3		-6.0					-8.8	-5.6	-10.5	7.9	8.8	-10.7		-3.5	-3.9	-15.9	-3.6	
5.2				-14.0	-16.4	-5.2	-11.3	-9.6	15.8	-10.0	3.2	-7.1		-6.5					-9.2	-5.9	-9.6	1.8	2.8	-11.0		-7.6	-4.7	-14.8	-4.6	
5.3				-13.0	-16.9	-8.9	-10.8	-10.5	5.2	-10.8	3.3	-7.2		-6.5					-9.1	-5.9	-8.7	-2.2	-1.2	-10.8		-10.0	-5.1	-13.6	-5.0	
5.4				-12.0	-16.7	-11.0	-10.1	-10.7	-1.7	-10.9	3.4	-7.0		-6.3					-8.7	-5.8	-7.9	-4.7	-3.6	-10.4		-11.3	-5.1	-12.4	-5.0	
5.5	2.2	-1.5	-1.6	-11.0	-16.1	-11.9	-9.3	-10.5	-6.1	-10.5	3.5	-6.6		-5.9					-8.1	-5.6	-7.1	-6.1	-5.0	-9.8		-11.8	-5.0	-11.4	-4.9	
5.6	-3.1	-5.0	-5.0				-12.0				-8.7		3.6	-6.0		-5.4				-7.5		-6.4	-6.8	-5.7	-9.1		-11.7	-4.7		-4.6
5.7	-6.6	-7.0	-7.0				-11.7				-10.1		3.7	-5.4		-4.9				-6.8		-5.8	-6.9	-5.9	-8.4		-11.3	-4.4		-4.2
5.8	-8.6	-8.1	-8.0				-11.1				-10.5		3.8	-4.8		-4.4				-6.1		-5.2	-6.8	-5.8	-7.7		-10.7	-4.0		-3.8
5.9	-9.7	-8.5	-8.4				-10.4				-10.5		3.9	-4.2		-3.9				-5.4		-4.7	-6.4	-5.5	-7.1		-10.0	-3.6		-3.4
6.0	-10.1	-8.5	-8.4				-9.5				-10.1		4.0	-3.6		-3.5				-4.8		-4.2	-5.9	-5.1	-6.5		-9.2	-3.3		-3.0
6.1	-10.0	-8.2	-8.1																											
6.2	-9.7	-7.8	-7.6																											
6.3	-9.2	-7.2	-7.1																											
6.4	-8.6	-6.6	-6.5																											
6.5	-8.0	-6.1	-5.9																											

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped															
	TRP'	TRP	1	2	3	A	B	C	D	E	F	G	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
0	-25.5	-26.9	-10.1	-8.5	-8.4	-15.6	-16.9	-12.0	-11.6	-10.7	-10.5	-10.9	-7.2	-8.3	-6.5	-30.5	-17.3	-9.2	-5.9	-15.6	-6.9	-5.9	-11.0	-27.4	-11.8	-5.1	-18.9	-5.0
30	-26.5	-26.6	-10.6	-9.7	-9.5	-20.8	-19.5	-13.0	-12.9	-12.3	-12.4	-13.3	-11.7	-7.5	-9.7	-28.0	-16.9	-13.5	0.1	-13.3	-7.7	-7.2	-10.3	-31.4	-12.8	-8.3	-21.3	-7.8
60	-25.5	-26.5	-11.0	-10.2	-10.7	-22.7	-18.7	-15.1	-14.4	-12.0	-13.9	-15.6	-13.7	-7.2	-10.0	-26.6	-15.8	-14.5	0.2	-15.2	-8.1	-8.2	-9.3	-32.4	-12.5	-10.3	-21.6	-10.4
90	-22.9	-28.4	-10.2	-9.9	-10.7	-22.5	-17.4	-14.4	-14.2	-11.3	-14.1	-15.4	-12.8	-7.6	-5.8	-25.0	-14.2	-12.0	-5.5	-19.8	-7.6	-8.2	-6.0	-30.1	-10.0	-9.5	-20.7	-11.2
120	-24.3	-28.2	-8.7	-9.4	-9.8	-22.9	-17.9	-11.7	-13.0	-11.6	-13.1	-13.9	-9.6	-8.3	-1.8	-24.8	-13.3	-7.8	-7.9	-21.9	-6.4	-7.3	-3.1	-26.7	-7.3	-6.9	-19.2	-9.6
150	-25.6	-25.3	-7.8	-8.6	-8.9	-19.3	-16.3	-9.7	-11.1	-10.6	-11.3	-12.1	-6.8	-8.7	-1.3	-26.4	-13.8	-5.2	-11.6	-22.2	-5.5	-6.6	-3.3	-24.5	-6.3	-6.1	-17.9	-8.4
180	-27.2	-21.9	-8.7	-8.6	-8.9	-17.7	-16.5	-10.5	-11.1	-10.7	-10.8	-11.9	-7.5	-8.2	-5.1	-27.5	-15.2	-7.6	-6.7	-18.3	-6.0	-6.6	-6.2	-26.9	-8.6	-6.9	-19.0	-7.8
210	-29.3	-19.8	-10.8	-9.1	-9.8	-19.0	-18.2	-14.0	-13.4	-11.9	-12.2	-13.2	-11.5	-7.5	-9.8	-27.3	-16.8	-13.5	-1.3	-14.2	-7.7	-7.3	-10.1	-31.2	-12.7	-8.7	-21.3	-8.3
240	-30.5	-24.2	-12.3	-9.9	-10.0	-22.2	-20.6	-15.0	-14.4	-13.6	-13.4	-13.0	-12.5	-7.3	-12.1	-29.0	-17.8	-15.4	0.3	-13.0	-8.9	-7.6	-14.8	-33.2	-15.7	-8.9	-21.5	-7.6
270	-28.6	-28.8	-12.4	-9.7	-9.5	-21.6	-19.6	-14.6	-14.4	-13.1	-13.4	-11.9	-8.8	-7.7	-11.4	-32.4	-18.5	-11.8	1.7	-11.6	-8.7	-7.1	-17.0	-32.5	-15.8	-6.9	-20.3	-5.5
300	-24.7	-29.8	-11.6	-8.8	-8.9	-17.5	-17.3	-14.4	-14.3	-11.7	-12.3	-11.2	-4.6	-8.4	-8.5	-34.0	-18.5	-7.2	-1.0	-12.0	-7.5	-6.2	-15.6	-29.7	-13.7	-4.6	-18.7	-3.7
330	-24.0	-28.4	-10.4	-8.2	-8.1	-14.5	-15.9	-12.3	-12.2	-10.4	-10.6	-10.0	-3.7	-8.8	-5.9	-33.2	-17.9	-5.8	-5.5	-14.9	-6.8	-5.5	-13.4	-26.6	-12.0	-3.5	-17.5	-3.1

Stacked (TRP' $R_1=3.5 \text{ \AA}$, $\alpha=240^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-23.2	-25.7	-28.3	-28.9	-26.5	-23.1	-21.2
1.0	-25.3	-27.1	-29.5	-30.0	-26.9	-22.8	-20.7
0.5	-26.9	-27.9	-29.7	-30.0	-27.4	-24.0	-21.8
0	-29.2	-30.0	-30.9	-30.5	-28.6	-26.2	-23.8
-0.5	-31.9	-33.3	-33.3	-31.7	-29.2	-27.0	-24.5
-1.0	-32.8	-34.9	-35.0	-32.3	-28.8	-26.0	-23.4
-1.5	-31.2	-33.8	-34.4	-31.9	-28.1	-25.1	-22.3

Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=120^\circ$)													
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
3.5	-1.0	-1.9	-3.0	-4.0	-4.4	-4.3	-4.0	-4.0	-4.6	-5.3	-6.0	-6.3	-6.3
3.0	-2.8	-4.3	-6.2	-7.8	-8.4	-8.2	-7.6	-7.2	-7.3	-7.7	-8.2	-8.4	-8.3
2.5	-5.3	-7.5	-10.2	-12.4	-13.3	-12.9	-12.1	-11.4	-10.9	-10.6	-10.4	-10.3	-10.0
2.0	-8.4	-10.9	-13.9	-16.3	-17.3	-17.0	-16.3	-15.5	-14.8	-13.9	-12.9	-11.9	-11.0
1.5	-11.7	-13.9	-16.3	-18.3	-19.2	-19.3	-19.1	-18.9	-18.5	-17.5	-15.8	-13.6	-11.5
1.0	-14.8	-16.1	-17.4	-18.4	-19.2	-20.2	-21.1	-21.5	-21.4	-20.5	-18.3	-14.9	-11.7
0.5	-17.3	-17.5	-17.7	-18.1	-19.0	-20.8	-22.5	-23.1	-22.8	-21.6	-19.1	-15.3	-11.6
0	-18.5	-18.2	-17.8	-18.0	-19.0	-21.1	-22.9	-23.2	-22.1	-20.5	-18.0	-14.6	-11.2
-0.5	-18.1	-17.8	-17.6	-17.8	-18.7	-20.3	-21.7	-21.6	-20.2	-18.3	-16.1	-13.4	-10.8
-1.0	-16.1	-16.5	-16.8	-17.2	-17.9	-18.9	-19.9	-19.8	-18.7	-16.9	-14.8	-12.6	-10.5
-1.5	-13.5	-14.6	-15.6	-16.3	-16.9	-17.9	-18.9	-19.0	-18.1	-16.3	-14.2	-12.1	-10.1
-2.0	-11.2	-12.7	-14.1	-15.1	-16.2	-17.7	-18.8	-19.0	-17.9	-15.9	-13.6	-11.3	-9.4
-2.5	-9.1	-10.7	-12.1	-13.5	-15.3	-17.3	-18.7	-18.7	-17.3	-15.0	-12.5	-10.2	-8.2
-3.0	-6.6	-8.1	-9.5	-11.2	-13.4	-15.8	-17.3	-17.3	-15.8	-13.4	-10.9	-8.7	-6.9

Nucleobase Edge T-shaped ($\theta=4$, $R_1=2.2 \text{ \AA}$, $\alpha=300^\circ$)													
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
2.5	-11.1	-14.3	-17.6	-20.3	-21.7	-21.4	-20.1	-18.1	-15.3	-11.7	-7.9	-4.6	-2.1
2.0	-13.4	-17.4	-21.3	-24.6	-26.3	-26.1	-24.7	-22.7	-19.6	-15.6	-11.1	-7.0	-4.0
1.5	-15.3	-19.9	-24.5	-28.3	-30.3	-30.2	-28.7	-26.6	-24.0	-20.2	-15.4	-10.7	-6.9
1.0	-16.1	-21.4	-26.6	-30.9	-33.2	-33.2	-31.6	-29.7	-27.8	-24.9	-20.5	-15.3	-10.7
0.5	-16.0	-21.7	-27.2	-31.8	-34.5	-34.8	-33.5	-32.2	-30.9	-28.7	-24.7	-19.4	-14.3
0	-15.6	-21.2	-26.5	-30.8	-33.7	-34.5	-34.0	-33.5	-32.9	-30.8	-27.0	-21.8	-16.6
-0.5	-15.0	-20.3	-24.7	-28.4	-31.0	-32.2	-32.8	-33.3	-33.4	-31.7	-28.0	-22.9	-17.6
-1.0	-13.4	-18.0	-21.6	-24.7	-27.3	-29.0	-30.4	-31.8	-32.6	-31.4	-28.0	-23.0	-17.5
-1.5	-10.1	-14.0	-17.1	-20.0	-22.8	-25.1	-27.1	-28.9	-30.1	-29.4	-26.5	-21.9	-16.6
-2.0	-6.4	-9.5	-12.1	-14.6	-17.3	-19.9	-22.2	-24.2	-25.3	-25.1	-23.0	-19.3	-14.7
-2.5	-3.5	-5.6	-7.6	-9.4	-11.5	-13.7	-16.1	-18.1	-19.4	-19.6	-18.3	-15.6	-12.1

Cytosine–Histidine Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped														
R_1	HIS'	HIS	R_1	1	2	3	4	5	A	B	C	D	E	R_1	1	2	3	4	5	6	7	A	B	C	D	E	F	G
3.3	-24.1		4.0	0.3										2.0	-20.2			9.3	1.6	-5.1	-2.2							
3.4	-24.5	-7.4	4.1	-6.0				16.3						2.1	-23.8			3.5	-6.0	-11.5	-7.9							
3.5	-24.1	-7.9	4.2	-10.0				7.1						2.2	-25.5			-0.2	-10.8	-15.4	-11.3					-10.2		-9.5
3.6		-7.8	4.3	-12.3	-0.7	-3.4	1.8	0.8	-10.8	-12.6	-6.8	-4.4	-7.7	2.3	-26.0			-2.4	-13.6	-17.5	-13.3					-14.8		-15.6
			4.4	-13.4	-3.6	-3.6	-2.2	-3.4	-12.1	-13.1	-7.3	-5.4	-9.3	2.4	-25.5			-3.6	-15.1	-18.4	-14.1					-17.4		-19.1
			4.5	-13.8	-5.4	-3.5	-4.7	-6.0	-12.6	-12.9	-7.2	-5.8	-10.0	2.5	-24.5			-4.1	-15.6	-18.4	-14.3	2.5			-10.1	-18.5	-9.9	-20.8
			4.6	-13.6	-6.3	-3.2	-6.1	-7.6	-12.5	-12.4	-6.8	-5.8	-10.1	2.6	-23.2			-4.1	-15.5	-18.0	-13.9	-4.1			-11.9	-18.7	-11.9	-21.3
			4.7	-13.1	-6.7	-2.9	-6.9	-8.4	-12.1	-11.6	-6.2	-5.6	-9.8	2.7	-21.8			-3.9	-14.9	-17.1	-13.3	-8.2			-12.7	-18.3	-12.8	-21.0
			4.8	-12.4	-6.7	-2.4	-7.2	-8.7	-11.4	-10.7	-5.5	-5.2	-9.4	2.8	-20.3			-3.5	-14.2	-16.1	-12.6	-10.6			-12.7	-17.6	-13.0	-20.2
			4.9	-11.7	-6.4	-2.4	-7.2	-8.7	-10.7	-9.8	-4.8	-4.8	-8.8	2.9	-18.8			-3.0	-13.3	-15.1	-11.7	-11.9			-12.2	-16.6	-12.8	-19.1
			5.0	-10.8		-1.6	-7.0	-8.5	-9.9	-9.0	-4.2	-4.3	-8.1	3.0	-17.4		15.1	-2.5	-12.3	-13.9	-10.9	-12.3			-11.5	-15.5	-12.2	-17.9
														3.1			9.9					-12.2			-10.7	-14.3	-11.6	-16.6
														3.2			6.5					-11.8			-9.7	-13.2	-10.8	-15.4
														3.3			4.4					-11.2			-8.8		-10.0	
														3.4			3.0					-10.5			-7.9		-9.2	
														3.5			2.2					-9.8			-7.1		-8.5	
													3.6			1.9												
													3.7			1.8												
													3.8			1.8												
													3.9			1.9												
													4.0			2.1												
													...															
													5.0		0.7							4.8	4.7					
													5.1		0.6							4.6	4.6					
													5.2		0.6							4.5	4.5					
													5.3		0.6							4.3	4.4					
													5.4		0.6							4.2	4.3					
													5.5		0.6							4.0	4.2					
													5.6		0.6							3.9	4.1					
													5.7		0.5							3.8	4.0					
													5.8		0.5							3.7	3.8					
													5.9		0.5							3.5	3.7					
													6.0		0.5							3.4	3.6					

α	Stacked		Amino Acid Edge T-shaped											Nucleobase Edge T-shaped													
	HIS'	HIS	1	2	3	4	5	A	B	C	D	E	1	2	3	4	5	6	7	A	B	C	D	E	F	G	
0	-24.5	-7.9	-13.8	-6.7	-3.6	-7.2	-8.7	-12.6	-13.1	-7.3	-5.8	-10.1	-26.0		1.8	-4.1	-15.6	-18.4	-14.3	-12.3				-12.7	-18.7	-13.0	-21.3
30	-24.1	-11.9	-14.6	-2.8	-4.4	-10.2	-12.4	-15.9	-10.9	-2.7	-9.4	-13.6	-19.0		-5.4	-13.6	-16.3	-13.6	-13.5	-3.7				-13.6	-15.4	-10.8	-18.4
60	-21.4	-16.2	-15.6	-0.8	-5.5	-11.9	-15.0	-19.8	-12.0	0.5	-11.8	-16.4	-13.5		-10.9	-21.1	-16.1	-10.9	-12.7	3.3				-14.6	-13.6	-9.6	-16.0
90	-19.0	-20.1	-15.7	-0.8	-5.3	-11.8	-14.9	-21.0	-12.7	2.3	-12.4	-16.5	-9.0		-15.5	-26.4	-16.9	-9.5	-12.5	8.3				-16.3	-13.6	-9.8	-14.5
120	-15.7	-23.2	-14.7	-2.2	-4.2	-10.4	-12.5	-18.8	-11.4	2.2	-11.6	-14.1	-3.4		-21.1	-28.7	-20.3	-9.8	-13.4	11.3				-18.4	-15.6	-11.6	-14.9
150	-9.7	-24.2	-13.8	-5.1	-3.4	-8.0	-9.3	-15.2	-11.5	-1.6	-9.2	-10.5	-1.1		-23.0	-26.3	-22.3	-12.2	-14.3	10.4				-19.5	-17.8	-13.2	-16.0
180	-3.7	-22.0	-14.3	-9.4	-4.4	-5.1	-7.1	-12.8	-14.1	-7.3	-6.4	-8.0	-7.7		-16.1	-21.6	-20.2	-13.6	-13.9	3.8				-18.0	-18.0	-12.5	-15.6
210	-0.2	-16.1	-15.9	-14.2	-6.5	-2.2	-6.1	-12.1	-18.1	-13.1	-3.4	-6.6	-17.7		-6.7	-15.7	-16.4	-14.1	-13.0	-5.2				-14.8	-17.1	-10.8	-15.2
240	-1.3	-9.1	-17.3	-17.1	-8.2	-0.7	-6.1	-13.8	-22.3	-17.0	-1.3	-6.6	-25.4		0.1	-11.0	-14.9	-13.9	-12.4	-12.9				-11.6	-16.5	-9.7	-16.4
270	-6.0	-3.8	-17.2	-17.0	-8.0	-0.9	-5.9	-14.4	-23.9	-17.8	-0.1	-6.8	-30.8		5.2	-6.8	-13.9	-14.4	-12.5	-17.9				-9.8	-16.6	-10.1	-18.9
300	-12.9	-2.4	-15.7	-14.7	-6.1	-2.1	-5.6	-12.4	-21.8	-16.2	-0.1	-6.6	-33.4		8.5	-1.0	-13.8	-18.3	-13.3	-20.4				-10.0	-18.8	-12.3	-21.8
330	-20.2	-4.6	-14.1	-10.9	-4.1	-4.3	-6.3	-11.2	-17.1	-11.9	-2.4	-7.4	-31.7		7.2	1.5	-15.5	-21.5	-14.3	-19.1				-11.4	-20.8	-14.0	-22.9

Stacked (HIS R ₁ =3.5 Å, α=150°)							
Y ↓ X →	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-20.4	-20.4	-19.7	-18.7	-17.6	-16.3	-14.3
1.0	-22.5	-22.2	-21.3	-20.7	-20.1	-18.6	-15.9
0.5	-24.3	-23.9	-23.2	-23.1	-22.6	-20.5	-16.9
0	-24.6	-24.4	-24.1	-24.2	-23.4	-20.8	-16.9
-0.5	-23.5	-24.3	-24.9	-25.0	-23.6	-20.6	-16.7
-1.0	-22.4	-24.7	-26.2	-26.1	-24.1	-20.9	-17.2
-1.5	-21.9	-25.0	-26.9	-26.5	-24.3	-21.3	-17.7

Amino Acid Edge T-shaped (θ=B, R ₁ =4.4 Å, α=270°)											
Y ↓ X →	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-4.8	-7.4	-8.8	-8.9	-8.1	-7.0	-6.3	-6.4	-6.8	-6.8	-6.1
2.5	-7.1	-9.9	-11.7	-12.3	-12.0	-11.3	-10.4	-10.1	-10.1	-9.7	-8.7
2.0	-8.8	-11.3	-13.3	-14.7	-15.6	-15.7	-15.0	-14.2	-13.6	-12.7	-11.4
1.5	-10.2	-12.2	-14.2	-16.3	-18.4	-19.6	-19.5	-18.3	-16.7	-15.3	-13.9
1.0	-11.6	-13.3	-15.3	-17.7	-20.4	-22.6	-23.2	-21.9	-19.5	-17.5	-16.0
0.5	-12.7	-14.4	-16.4	-18.5	-21.1	-24.1	-25.6	-24.6	-21.8	-19.3	-17.6
0	-12.6	-14.5	-16.3	-18.0	-20.5	-23.9	-26.4	-26.0	-23.4	-20.6	-18.5
-0.5	-11.6	-13.6	-15.2	-16.8	-19.2	-22.9	-26.0	-26.4	-24.4	-21.4	-18.9
-1.0	-10.1	-12.4	-14.1	-15.9	-18.6	-22.2	-25.3	-26.3	-25.0	-22.1	-19.2
-1.5	-8.6	-11.0	-13.0	-15.4	-18.5	-22.0	-24.7	-25.8	-25.0	-22.5	-19.5
-2.0	-6.6	-9.0	-11.3	-14.2	-17.7	-21.0	-23.3	-24.3	-23.8	-21.7	-19.1

Nucleobase Edge T-shaped (θ=1, R ₁ =2.3 Å, α=300°)									
Y ↓ X →	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.0	-14.3	-18.2	-22.3	-26.0	-28.7	-29.5	-27.5	-21.8	-13.7
1.5	-16.3	-20.9	-25.4	-29.2	-31.8	-32.8	-31.1	-25.8	-17.4
1.0	-17.9	-23.1	-27.9	-31.4	-33.3	-33.5	-31.8	-26.8	-18.5
0.5	-18.5	-24.2	-29.1	-32.5	-33.6	-32.9	-30.3	-25.1	-17.3
0	-17.6	-23.5	-28.7	-32.2	-33.4	-32.1	-28.8	-23.2	-15.8
-0.5	-15.6	-21.5	-26.8	-30.6	-32.3	-31.3	-27.8	-22.2	-15.5
-1.0	-13.1	-18.6	-23.8	-27.7	-29.7	-29.2	-26.2	-21.5	-15.9
-1.5	-10.9	-15.7	-20.2	-23.5	-25.3	-25.2	-23.2	-19.7	-15.5
-2.0	-8.9	-12.7	-16.1	-18.6	-19.9	-20.0	-18.9	-16.7	-13.8

Cytosine–Phenylalanine Dimers

	<u>Stacked</u>		<u>Amino Acid Edge T-shaped</u>				<u>Nucleobase Edge T-shaped</u>																		
R_1	PHE	R_1	1	A	R_1	1	2	3	4	5	6	7	A	B	C	D	E	F	G						
3.4	-14.4	4.7	-4.4	-7.2	2.0	-14.8			-7.8	0.3	-0.2	-5.4													
3.5	-15.1	4.8	-6.2	-8.4	2.1	-18.7			-12.7	-7.9	-7.3	-10.3													
3.6	-15.2	4.9	-7.2	-8.9	2.2	-20.7			-15.7	-13.3	-12.0	-13.4					-5.6		-3.3						
		5.0	-7.6	-8.8	2.3	-21.4			-17.3	-16.5	-14.8	-15.1					-11.9		-11.0						
		5.1	-7.6	-8.5	2.4	-21.3			-17.8	-18.2	-16.2	-15.8					-15.8		-15.8						
		5.2	-7.4	-8.1	2.5	-20.5			-17.7	-18.9	-16.8	-15.8	14.4			-12.8	-17.9	-7.5	-18.5						
		5.3	-7.0	-7.5	2.6	-19.5			-17.1	-18.9	-16.7	-15.4	6.5			-15.0	-18.8	-10.4	-19.8						
					2.7	-18.2			-16.2	-18.4	-16.2	-14.8	1.4			-16.1	-18.9	-12.1	-20.0						
					2.8	-16.9			-15.2	-17.6	-15.4	-13.9	-1.9			-16.3	-18.4	-12.8	-19.6						
					2.9	-15.5			-14.1	-16.6	-14.5	-13.0	-3.8			-15.9	-17.6	-12.9	-18.8						
					3.0	-14.2		5.9	-13.0	-15.6	-13.5	-12.1	-4.8		1.6	-15.2	-16.6	-12.6	-17.7						
					3.1				0.3					-5.2		-2.0	-14.3	-15.5	-12.1	-16.5					
					3.2				-3.2					-5.2		-4.3	-13.3	-14.4	-11.4	-15.2					
					3.3				-5.4					-4.9		-5.6	-12.3		-10.6						
					3.4				-6.6					-4.5		-6.2	-11.2		-9.8						
					3.5				-7.1					-4.1		-6.4	-10.3		-9.0						
					3.6				-7.2							-6.3									
					3.7				-7.0							-5.9									
					3.8				-6.6							-5.5									
					3.9				-6.1							-5.0									
					4.0				-5.6							-4.5									
					...																				
			5.0			2.2																			
			5.1			2.1																			
			5.2			2.0																			
			5.3			2.0																			
			5.4			1.9																			
			5.5			1.8																			
			5.6			1.8																			
			5.7			1.7																			
			5.8			1.6																			
			5.9			1.6																			
			6.0			1.5																			

α	<u>Stacked</u>	<u>Amino Acid Edge T-shaped</u>		<u>Nucleobase Edge T-shaped</u>													
	PHE	1	A	1	2	3	4	5	6	7	A	B	C	D	E	F	G
0	-15.1	-7.6	-8.9	-21.4		-7.2	-17.8	-18.9	-16.8	-15.8	-5.2		-6.4	-16.3	-18.9	-12.9	-20.0
30	-15.1	-7.5	-9.0	-21.5		-7.4	-17.7	-19.5	-16.9	-15.8	-5.2		-7.0	-16.3	-19.0	-13.0	-20.1
60		-8.3	-10.0														
90		-9.3	-11.1														
120		-9.4	-11.0														
150		-8.6	-9.7														

Stacked ($R_1=3.5 \text{ \AA}$, $\alpha=0^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-14.2	-14.1	-14.0	-13.6	-12.8	-11.5	-10.0
1.0	-16.3	-15.5	-14.8	-14.7	-14.5	-13.3	-11.3
0.5	-18.0	-16.7	-15.4	-15.4	-15.7	-14.5	-11.7
0	-18.4	-16.7	-15.1	-15.1	-15.4	-14.0	-11.0
-0.5	-17.8	-16.7	-15.5	-15.1	-14.7	-12.8	-10.0
-1.0	-17.3	-17.5	-17.1	-16.2	-14.5	-12.2	-9.5
-1.5	-17.1	-18.3	-18.3	-16.9	-14.3	-11.7	-9.3

Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=90^\circ$)											
$Y \downarrow$ $X \rightarrow$	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-3.9	-4.3	-4.4	-4.3	-4.2	-4.0	-3.7	-3.5	-3.3	-3.1	-2.5
2.5	-5.0	-5.5	-5.7	-5.9	-6.1	-6.0	-5.6	-5.1	-4.8	-4.4	-3.8
2.0	-5.8	-6.4	-6.9	-7.4	-7.9	-8.1	-7.6	-6.9	-6.4	-5.8	-5.0
1.5	-6.2	-7.0	-7.7	-8.4	-9.2	-9.7	-9.4	-8.6	-8.8	-6.9	-6.2
1.0	-6.5	-7.6	-8.5	-9.2	-9.8	-10.6	-10.8	-10.1	-8.8	-7.8	-7.1
0.5	-6.7	-8.2	-9.3	-9.6	-10.0	-11.1	-11.8	-11.2	-9.7	-8.4	-7.7
0	-6.8	-8.5	-9.5	-9.6	-9.9	-11.1	-12.1	-11.8	-10.2	-8.8	-7.9
-0.5	-6.6	-8.1	-9.0	-9.1	-9.5	-10.7	-11.8	-11.6	-10.3	-8.8	-7.8
-1.0	-6.1	-7.3	-8.0	-8.5	-9.2	-10.2	-10.9	-10.8	-10.0	-8.6	-7.5
-1.5	-5.5	-6.3	-7.1	-8.0	-8.9	-9.6	-9.9	-9.9	-9.5	-8.4	-7.4
-2.0	-4.7	-5.4	-6.2	-7.3	-8.3	-8.8	-8.9	-8.9	-8.6	-7.9	-7.0

Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.3 \text{ \AA}$, $\alpha=30^\circ$)									
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	5.1	3.1	1.1	-0.1	-1.0	-2.7	-4.4	-5.4	-5.3
2.0	2.4	-0.9	-3.8	-4.9	-5.2	-6.2	-7.6	-8.2	-7.6
1.5	-0.6	-4.4	-7.8	-9.3	-9.6	-10.3	-11.2	-11.2	-10.1
1.0	-3.4	-6.9	-10.5	-12.8	-14.0	-14.8	-15.1	-14.4	-12.6
0.5	-6.5	-9.5	-13.1	-16.2	-18.3	-19.1	-18.7	-17.3	-15.0
0	-9.4	-12.4	-16.0	-19.4	-21.5	-21.9	-20.9	-19.0	-16.5
-0.5	-11.4	-14.6	-18.0	-20.9	-22.5	-22.4	-21.1	-19.2	-16.8
-1.0	-11.9	-15.2	-18.3	-20.6	-21.5	-21.3	-20.3	-18.5	-16.1
-1.5	-11.3	-14.5	-17.3	-19.1	-19.8	-19.8	-19.1	-17.5	-15.0
-2.0	-9.9	-12.8	-15.3	-16.8	-17.5	-17.7	-17.3	-15.8	-13.4
-2.5	-8.0	-10.4	-12.5	-13.8	-14.6	-14.9	-14.5	-13.3	-11.3

Cytosine–Tyrosine Dimers

Stacked			Amino Acid Edge T-shaped														Nucleobase Edge T-shaped													
R_1	TYR'	TYR	R_1	1	2	3	4	5	6	A	B	C	D	E	F	R_1	1	2	3	4	5	6	7	A	B	C	D	E	F	G
3.4		-17.3	4.5		-11.2				-5.6							2.3	-17.6			-13.3	-14.1	-18.2	-15.2					-15.3		-17.0
3.5	-14.0	-18.3	4.6		-12.5				-7.4							2.4	-18.1			-14.6	-17.1	-19.1	-15.9					-18.1		-20.3
3.6	-14.1	-18.2	4.7		-13.0				-8.3	-10.6	-0.3			-4.6	-3.3	2.5	-17.8			-15.0	-18.6	-19.1	-15.9	17.0			-13.5	-19.4	-13.7	-21.8
3.7	-13.6		4.8		-12.9				-8.6	-13.2	-3.9			-6.9	-5.1	2.6	-17.1			-14.8	-19.1	-18.5	-15.5	9.2			-15.5	-19.7	-15.3	-22.2
			4.9		-12.4				-8.5	-14.5	-6.1			-8.1	-5.9	2.7	-16.2			-14.3	-19.0	-17.6	-14.8	4.0			-16.4	-19.4	-15.9	-21.8
			5.0		-11.7	-5.1		-5.1	-8.1	-14.9	-7.3	-3.2	-3.4	-8.5	-6.2	2.8	-15.1			-13.5	-18.4	-16.6	-14.0	0.7			-16.5	-18.6	-15.8	-20.9
			5.1	-2.4	-10.9	-6.6		-6.7	-7.6	-14.7	-7.8	-6.1	-6.2	-8.5	-6.1	2.9	-13.9			-12.6	-17.5	-15.4	-13.1	-1.4			-16.0	-17.6	-15.3	-19.7
			5.2	-4.3		-7.3		-7.5		-14.2	-7.8	-7.6	-7.8	-8.2	-5.8	3.0	-12.8		7.7	-11.6	-16.5	-14.2	-12.1	-2.5		27.7	-15.3	-16.5	-14.5	-18.4
			5.3	-5.4		-7.6	-6.2	-7.8		-13.4	-7.6	-8.3	-8.5	-7.8	-5.3	3.1			-0.4					-3.0		17.5	-14.4	-15.3	-13.6	-17.0
			5.4	-5.8		-7.5	-7.0	-7.7				-8.5	-8.7			3.2			-5.6				-3.2		10.4	-13.3	-14.2	-12.7	-15.6	
			5.5	-5.9		-7.2	-7.4	-7.4				-8.3	-8.5			3.3			-8.8				-3.1		5.5	-12.3		-12.7		
			5.6	-5.7		-6.8	-7.3	-7.0				-7.8	-8.0			3.4			-10.5				-2.8		2.2	-11.3		-10.7		
			5.7	-5.4			-7.1									3.5			-11.3				-2.6		0.1	-10.3		-9.8		
			5.8				-6.7									3.6			-11.3							-1.2				
																3.7			-11.0							-2.0				
																3.8			-10.4							-2.4				
																3.9			-9.6							-2.5				
																4.0			-8.7					2.4	-2.5					
																4.1									1.7					
																4.2									1.2					
																4.3									1.0					
																4.4									1.0					
																4.5									1.0					
																4.6									1.1					
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																5.0		2.0												
																5.1		2.0												
																5.2		1.9												
																5.3		1.9												
																5.4		1.8												
																5.5		1.8												
																5.6		1.7												
																5.7		1.7												
																5.8		1.6												
																5.9		1.5												
																6.0		1.5												

α	Stacked		Amino Acid Edge T-shaped												Nucleobase Edge T-shaped												
	TYR'	TYR	1	2	3	4	5	6	A	B	C	D	E	F	1	2	3	4	5	6	7	A	B	C	D	E	F
0	-14.1	-18.3	-5.9	-13.0	-7.6	-7.4	-7.8	-8.6	-14.9	-7.8	-8.5	-8.7	-8.5	-6.2	-18.1	-11.3	-15.0	-19.1	-19.1	-15.9	-3.2	1.0	-2.5	-16.5	-19.7	-15.9	-22.2
30	-15.8	-19.0	-10.0	-12.4	-8.4	-8.2	-8.3	-6.8	-15.6	-8.0	-9.2	-9.1	-8.0	-9.1	-19.8	-8.9	-11.7	-19.5	-19.4	-16.3	-5.0	2.1	-0.3	-16.1	-20.2	-16.3	-22.6
60	-16.4	-16.7	-14.0	-13.5	-9.2	-9.0	-9.0	-5.8	-16.9	-8.8	-10.4	-10.1	-8.2	-9.9	-21.3	-7.2	-14.0	-18.7	-16.0	-15.7	-6.5	2.6	-2.9	-15.2	-18.8	-14.0	-21.5
90	-16.0	-17.1	-15.5	-13.2	-8.7	-8.9	-9.1	-5.8	-16.8	-9.1	-10.6	-10.2	-8.3	-6.9	-23.6	-5.2	-14.6	-17.8	-15.3	-14.9	-8.4	3.2	-3.3	-14.4	-18.0	-12.1	-20.8
120	-18.2	-19.1	-14.0	-10.2	-7.7	-8.0	-8.5	-6.2	-15.4	-8.3	-9.7	-9.3	-8.1	-3.5	-26.4	-2.0	-14.7	-16.6	-15.5	-14.0	-10.4	3.7	-2.9	-13.8	-17.8	-11.5	-20.4
150	-20.0	-16.7	-10.3	-9.0	-7.2	-7.3	-7.9	-7.1	-14.2	-7.5	-8.7	-8.6	-8.2	-2.3	-26.0	-1.5	-14.7	-16.7	-17.1	-13.9	-10.9	3.7	-2.7	-14.4	-18.9	-12.7	-20.5
180	-21.7	-13.1	-6.8	-10.6	-8.2	-7.7	-8.2	-8.6	-12.2	-8.2	-9.0	-8.9	-9.0	-4.1	-19.3	-9.2	-15.2	-20.2	-18.8	-15.1	-8.9	2.7	-3.2	-16.2	-21.2	-15.1	-20.5
210	-20.1	-11.0	-4.8	-15.2	-9.9	-9.0	-9.6	-11.1	-10.2	-10.5	-10.2	-10.1	-10.5	-4.9	-17.2	-10.5	-16.5	-21.4	-18.9	-15.4	-6.7	2.0	-4.8	-17.2	-21.5	-15.2	-19.4
240	-15.6	-13.6	-4.5	-18.9	-11.4	-10.0	-10.6	-12.3	-11.0	-12.4	-11.5	-11.5	-12.0	-5.6	-18.2	-8.8	-18.2	-19.2	-17.0	-14.8	-4.8	1.6	-6.5	-17.2	-19.6	-13.5	-18.5
270	-13.6	-18.1	-3.9	-18.5	-11.4	-9.9	-10.1	-11.7	-14.0	-12.3	-11.5	-11.6	-12.1	-6.0	-17.9	-10.4	-20.4	-18.4	-14.8	-14.4	-2.9	0.9	-8.6	-16.7	-18.0	-11.9	-18.3
300	-13.2	-20.5	-2.8	-16.4	-9.9	-8.7	-8.9	-11.1	-16.0	-10.5	-10.2	-10.5	-11.1	-5.3	-17.1	-12.9	-23.9	-18.1	-12.0	-14.2	-1.4	-0.3	-11.7	-16.2	-16.7	-11.2	-18.6
330	-14.4	-20.6	-3.2	-13.2	-8.2	-7.5	-7.8	-10.0	-15.7	-8.6	-8.8	-9.1	-9.6	-5.0	-17.0	-14.0	-24.3	-18.7	-11.7	-14.7	-1.4	-0.5	-12.5	-16.1	-17.2	-12.6	-19.9

Stacked (TYR $R_1=3.5 \text{ \AA}$, $\alpha=330^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-20.4	-20.3	-19.6	-19.0	-18.5	-17.2	-14.9
1.0	-22.5	-22.0	-20.7	-20.2	-20.4	-19.3	-16.4
0.5	-23.5	-22.5	-20.9	-20.3	-20.6	-19.4	-16.2
0	-23.7	-22.8	-21.3	-20.6	-20.2	-18.5	-15.2
-0.5	-23.8	-23.6	-22.8	-21.8	-20.2	-17.6	-14.4
-1.0	-23.6	-24.2	-23.9	-22.5	-19.9	-16.7	-13.5
-1.5	-23.0	-23.7	-23.3	-21.5	-18.5	-15.2	-12.2

Amino Acid Edge T-shaped ($\theta=1$, $R_1=5.5 \text{ \AA}$, $\alpha=90^\circ$)												
$Y \downarrow$ $X \rightarrow$	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
3.0	-6.7	-8.8	-9.9	-9.2	-7.1	-5.0	-3.8	-3.6	-3.7	-3.6	-3.0	-2.2
2.5	-8.2	-10.3	-11.4	-10.9	-9.0	-6.9	-5.5	-4.9	-4.5	-3.9	-3.0	-2.0
2.0	-9.2	-10.8	-11.8	-11.8	-10.8	-9.4	-8.1	-6.9	-5.7	-4.2	-2.9	-1.7
1.5	-9.9	-10.7	-11.4	-12.1	-12.4	-12.0	-10.9	-9.1	-6.8	-4.6	-2.8	-1.4
1.0	-10.5	-10.5	-11.0	-12.2	-13.6	-14.1	-13.1	-10.9	-8.0	-5.2	-2.9	-1.2
0.5	-10.9	-10.6	-10.9	-12.4	-14.3	-15.3	-14.6	-12.3	-9.2	-6.1	-3.3	-1.2
0	-10.9	-10.6	-11.0	-12.4	-14.3	-15.5	-15.3	-13.5	-10.6	-7.2	-3.9	-1.3
-0.5	-10.5	-10.7	-11.2	-12.4	-13.9	-15.2	-15.6	-14.5	-11.8	-8.1	-4.3	-1.3
-1.0	-10.0	-10.9	-11.7	-12.6	-13.8	-15.1	-16.0	-15.3	-12.6	-8.5	-4.4	-1.2
-1.5	-9.3	-10.8	-12.0	-12.8	-13.8	-15.3	-16.3	-15.7	-12.7	-8.4	-4.1	-1.0
-2.0	-8.3	-10.1	-11.4	-12.4	-13.6	-15.2	-16.1	-15.2	-12.1	-7.8	-3.8	-0.8
-2.5	-6.8	-8.6	-10.1	-11.4	-12.9	-14.4	-15.1	-13.9	-10.9	-7.0	-3.3	-0.7

Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.4 \text{ \AA}$, $\alpha=120^\circ$)											
$Y \downarrow$ $X \rightarrow$	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-5.3	-9.4	-14.2	-18.5	-20.7	-19.6	-15.9	-11.4	-7.8	-5.3	-3.7
2.5	-4.7	-9.3	-15.0	-20.4	-23.4	-22.7	-18.8	-14.0	-10.1	-7.3	-5.4
2.0	-3.9	-8.6	-14.7	-20.6	-24.0	-23.9	-20.8	-16.7	-13.0	-10.1	-7.7
1.5	-3.7	-8.4	-14.4	-20.2	-23.6	-24.0	-22.3	-19.5	-16.3	-13.2	-10.4
1.0	-4.5	-9.2	-14.9	-20.4	-23.8	-24.9	-24.1	-22.2	-19.5	-16.3	-13.0
0.5	-5.4	-10.3	-15.8	-20.9	-24.6	-26.1	-25.8	-24.3	-21.8	-18.7	-15.1
0	-5.4	-10.5	-15.9	-20.7	-24.4	-26.4	-26.7	-25.4	-23.1	-20.1	-16.4
-0.5	-4.4	-9.8	-14.9	-19.3	-22.8	-25.3	-26.2	-25.4	-23.3	-20.4	-16.6
-1.0	-2.8	-8.3	-13.3	-17.2	-20.4	-23.1	-24.6	-24.2	-22.2	-19.2	-15.6
-1.5	-0.8	-5.9	-10.7	-14.3	-17.3	-20.0	-21.8	-21.7	-19.9	-17.0	-13.6
-2.0	1.5	-2.7	-7.0	-10.6	-13.6	-16.3	-18.1	-18.3	-16.8	-14.2	-11.3
-2.5	3.4	0.4	-3.1	-6.5	-9.7	-12.4	-14.2	-14.5	-13.4	-11.2	-8.9
-3.0	4.1	2.3	-0.4	-3.4	-6.4	-8.9	-10.5	-10.9	-10.1	-8.5	-6.7

Cytosine–Tryptophan Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped														
R_1	TRP ⁱ	TRP	R_1	1	2	3	A	B	C	D	E	F	G	R_1	1	2	3	4	5	6	7	A	B	C	D	E	F	G
3.3	-17.7		4.6				-9.5							2.2	-20.6			-21.1	-21.0	-15.9	-16.1					-13.4		-15.0
3.4	-18.5	-23.4	4.7				-12.4							2.3	-21.3			-22.7	-23.3	-18.7	-17.9					-18.7		-20.5
3.5	-18.3	-23.6	4.8				-13.9			-5.5				2.4	-21.0			-23.2	-24.3	-20.0	-18.6					-21.8		-23.6
3.6		-22.9	4.9				-14.4			-7.7				2.5	-20.2			-22.9	-24.3	-20.3	-18.6	15.4			-19.5	-23.2	-16.6	-25.0
			5.0				-14.3	-7.6		-8.8				2.6	-19.1			-22.1	-23.8	-20.0	-18.2	7.9			-21.0	-23.5	-18.0	-25.2
			5.1				-13.8	-10.9		-9.2	-4.2		-7.7	2.7	-17.8			-21.0	-22.9	-19.3	-17.4	3.1			-21.4	-23.2	-18.5	-24.6
			5.2				-13.1	-12.7		-9.1	-6.4		-9.3	2.8	-16.4			-19.8	-21.7	-18.3	-16.4	0.0			-21.1	-22.3	-18.3	-23.5
			5.3					-13.5	-5.5	-8.7	-7.6		-10.1	2.9	-15.0			-18.5	-20.4	-17.2	-15.4	-1.8			-20.4	-21.2	-17.6	-22.2
			5.4				-13.5	-7.5	-8.2	-8.0			-10.2	3.0	-13.6		-4.3	-17.2	-19.1	-16.1	-14.3	-2.7		-2.4	-19.3	-19.9	-16.7	-20.7
			5.5				-13.2	-8.5		-8.1	-3.1	-10.0	3.1				-8.4					-3.0		-6.6	-18.1	-18.6	-15.7	-19.1
			5.6		-4.9	-5.4		-12.5	-8.9		-7.8	-6.0	-9.5	3.2			-10.9					-3.0		-9.1	-16.9	-17.2	-14.6	-17.6
			5.7	-5.2	-6.4	-6.9			-8.7		-7.4	-7.7	-8.9	3.3			-12.2					-2.7		-10.4	-15.6		-13.6	
			5.8	-6.7	-7.1	-7.6			-8.3			-8.5		3.4			-12.6					-2.4		-11.0	-14.4		-12.5	
			5.9	-7.4	-7.4	-7.9			-7.7			-8.7		3.5			-12.5					-1.9		-11.0	-13.3		-11.5	
			6.0	-7.6	-7.3	-7.8						-8.5		3.6			-12.1							-10.6				
			6.1	-7.5	-7.0	-7.5						-8.1		3.7			-11.4							-10.1				
			6.2	-7.2	-6.6	-7.1								3.8			-10.7							-9.4				
			6.3	-6.8										3.9			-9.8							-8.6				
														4.0			-9.0											
														4.1														
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													5.3		3.3													
													5.4		3.2													
													5.5		3.1													
													5.6		3.0													
													5.7		2.9													
													5.8		2.8													
													5.9		2.7													

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped												
	TRP'	TRP	1	2	3	A	B	C	D	E	F	G	1	2	3	4	5	6	7	A	B	C	D	E	F
0	-18.5	-23.6	-7.6	-7.4	-7.9	-14.4	-13.5	-8.9	-9.2	-8.1	-8.7	-10.2	-21.3	-12.6	-23.2	-24.3	-20.3	-18.6	-3.0	2.1	-11.0	-21.4	-23.5	-18.5	-25.2
30	-19.1	-21.6	-7.2	-8.7	-9.6	-18.3	-16.0	-7.9	-9.4	-9.9	-9.9	-13.0	-20.2	-11.9	-16.8	-22.3	-24.6	-20.2	-6.5	3.8	-3.3	-23.3	-27.0	-22.2	-29.4
60	-19.8	-19.4	-7.4	-9.8	-11.0	-22.6	-18.0	-8.1	-10.1	-11.5	-11.3	-14.8	-23.3	-10.0	-14.8	-21.9	-26.0	-20.4	-10.9	4.9	2.2	-22.7	-28.6	-24.0	-31.8
90	-15.7	-19.3	-7.1	-9.4	-10.9	-24.5	-17.3	-8.2	-10.2	-11.1	-11.4	-14.5	-29.8	-5.0	-12.9	-21.8	-25.1	-19.2	-14.7	5.9	5.0	-20.2	-27.6	-22.4	-31.6
120	-18.6	-17.0	-6.4	-8.2	-9.5	-23.1	-15.4	-7.4	-9.4	-9.9	-10.1	-12.4	-32.7	-1.1	-12.6	-20.1	-22.6	-18.1	-15.6	6.1	2.4	-17.9	-25.1	-19.2	-29.6
150	-25.1	-15.5	-6.6	-7.2	-7.7	-18.3	-13.6	-6.8	-8.7	-8.8	-8.6	-9.5	-32.4	-1.5	-15.9	-21.9	-20.1	-17.8	-13.6	5.4	-2.1	-16.8	-23.0	-16.9	-26.9
180	-27.9	-17.5	-8.6	-7.2	-6.9	-15.0	-14.0	-8.5	-9.4	-9.1	-8.1	-7.9	-26.9	-6.0	-17.4	-21.7	-21.0	-18.8	-10.1	4.6	-5.2	-19.3	-24.0	-18.4	-27.2
210	-27.4	-18.0	-11.8	-7.9	-7.5	-13.8	-15.0	-13.2	-11.6	-9.7	-8.6	-8.8	-21.4	-11.1	-15.6	-22.3	-24.9	-20.1	-7.3	4.0	-0.7	-23.2	-27.3	-22.1	-29.3
240	-25.3	-21.5	-14.2	-8.8	-8.2	-15.7	-16.3	-16.8	-13.3	-10.3	-9.6	-10.0	-18.9	-15.3	-19.1	-22.8	-25.6	-20.1	-4.7	2.4	-1.1	-24.8	-28.4	-23.9	-29.8
270	-21.3	-27.3	-14.2	-8.8	-7.9	-16.1	-16.8	-16.4	-13.2	-10.2	-9.8	-9.7	-16.3	-19.1	-27.3	-22.0	-21.8	-19.1	-1.3	0.5	-12.8	-24.3	-26.3	-22.0	-28.4
300	-17.4	-28.2	-12.0	-8.0	-7.1	-13.4	-15.8	-13.5	-11.7	-9.3	-8.9	-8.6	-16.0	-19.0	-30.8	-21.7	-18.0	-18.0	0.7	-0.3	-20.0	-22.7	-23.2	-18.6	-26.0
330	-18.2	-26.0	-9.3	-7.2	-6.8	-12.7	-14.1	-10.2	-9.8	-8.1	-8.3	-8.3	-19.3	-15.5	-29.6	-22.8	-17.0	-17.6	-0.1	0.3	-19.7	-20.8	-21.6	-16.7	-23.7

$\gamma \downarrow$ $X \rightarrow$	Stacked (TRP $R_1=3.5 \text{ \AA}$, $\alpha=300^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-28.9	-28.5	-29.2	-30.0	-28.5	-24.4	-19.3
1.0	-29.9	-29.1	-28.9	-28.8	-27.1	-23.4	-18.7
0.5	-30.9	-30.4	-29.3	-27.9	-25.8	-22.6	-18.4
0	-32.4	-32.6	-30.8	-28.2	-25.7	-22.9	-18.8
-0.5	-33.3	-33.4	-30.9	-27.9	-25.6	-23.0	-18.7
-1.0	-32.0	-31.7	-29.0	-26.2	-24.3	-21.8	-17.6
-1.5	-29.3	-29.1	-26.9	-24.7	-22.8	-20.2	-16.1

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=90^\circ$)												
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
3.5	-0.6	-2.5	-4.6	-5.8	-5.7	-4.7	-3.6	-2.9	-2.9	-3.1	-3.3	-3.1	-2.8
3.0	-3.0	-5.6	-8.4	-10.0	-9.8	-8.5	-7.0	-6.0	-5.6	-5.6	-5.5	-5.1	-4.5
2.5	-5.5	-8.5	-11.4	-13.3	-13.5	-12.6	-11.4	-10.3	-9.5	-9.0	-8.4	-7.6	-6.6
2.0	-7.9	-10.5	-12.9	-14.8	-16.0	-16.4	-16.3	-15.4	-14.1	-12.8	-11.6	-10.4	-9.1
1.5	-10.1	-12.1	-13.8	-15.6	-17.7	-19.7	-20.7	-20.3	-18.6	-16.5	-14.6	-13.0	-11.4
1.0	-12.3	-13.9	-15.2	-16.8	-19.3	-22.1	-23.9	-24.1	-22.4	-19.7	-17.2	-15.2	-13.5
0.5	-13.7	-15.2	-16.5	-18.1	-20.3	-22.9	-25.2	-26.2	-25.1	-22.4	-19.4	-16.9	-15.0
0	-13.5	-15.1	-16.7	-18.1	-19.7	-21.8	-24.5	-26.6	-26.6	-24.3	-21.0	-18.1	-15.8
-0.5	-11.8	-13.8	-15.7	-17.0	-18.0	-19.8	-22.9	-26.1	-27.1	-25.4	-22.1	-18.8	-16.2
-1.0	-9.6	-12.1	-14.4	-15.8	-16.8	-18.8	-22.3	-25.9	-27.4	-26.1	-22.8	-19.2	-16.4
-1.5	-7.6	-10.3	-12.9	-14.7	-16.4	-19.0	-22.7	-25.9	-27.1	-25.9	-22.9	-19.3	-16.5
-2.0	-5.5	-8.0	-10.5	-12.7	-15.2	-18.6	-22.2	-24.9	-25.6	-24.4	-21.7	-18.6	-15.9
-2.5	-3.3	-5.2	-7.3	-9.8	-12.8	-16.4	-19.8	-22.0	-22.4	-21.3	-19.2	-16.7	-14.4

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.3 \text{ \AA}$, $\alpha=120^\circ$)												
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
2.5	-9.8	-13.6	-17.6	-21.2	-23.6	-24.4	-24.0	-22.5	-19.9	-16.5	-12.7	-9.3	-6.5
2.0	-10.4	-15.1	-20.1	-24.7	-27.8	-29.0	-28.7	-27.3	-24.6	-20.7	-16.3	-12.1	-8.7
1.5	-10.0	-15.5	-21.5	-27.0	-30.7	-32.2	-32.2	-31.1	-28.9	-25.3	-20.6	-15.8	-11.7
1.0	-9.0	-15.1	-21.8	-27.9	-32.0	-33.8	-33.9	-33.4	-32.2	-29.5	-25.1	-20.0	-15.3
0.5	-8.1	-14.7	-21.5	-27.5	-31.7	-33.6	-34.0	-34.2	-34.1	-32.5	-28.7	-23.7	-18.6
0	-7.7	-14.6	-20.7	-25.9	-29.8	-31.9	-32.7	-33.7	-34.5	-33.6	-30.5	-25.8	-20.7
-0.5	-6.8	-13.5	-18.7	-23.1	-26.9	-29.3	-30.8	-32.3	-33.7	-33.5	-30.9	-26.6	-21.6
-1.0	-3.9	-9.9	-14.7	-18.8	-22.8	-25.7	-27.8	-30.0	-31.9	-32.3	-30.3	-26.3	-21.2
-1.5	0.2	-4.7	-9.0	-13.0	-17.0	-20.3	-23.0	-25.8	-28.4	-29.4	-28.1	-24.5	-19.8
-2.0	3.2	-0.3	-3.7	-7.0	-10.1	-13.0	-16.1	-19.6	-22.9	-24.6	-24.1	-21.3	-17.3
-2.5	4.2	2.0	-0.1	-2.1	-4.0	-6.2	-9.2	-13.1	-16.8	-19.0	-19.1	-17.2	-14.2

Guanine–Histidine Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped																	
R_1	HIS'	HIS	R_2	1	2	3	4	5	A	B	C	D	E	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H	
3.2		-22.2	4.0			-6.5								2.0	4.7	-18.2	-8.4		-12.0	-7.6											
3.3	-10.1	-23.0	4.1			-8.7			-8.7	-16.2	-11.2			2.1	-2.9	-22.5	-13.1		-15.4	-12.1											
3.4	-10.5	-22.7	4.2	-15.0		-9.7			-12.5	-19.0	-13.3	-5.6	-5.2	2.2	-7.7	-24.6	-15.7		-17.1	-14.7			-18.0								
3.5	-10.0		4.3	-17.1		-10.1			-14.5	-20.3	-14.2	-6.9	-7.8	2.3	-10.5	-25.3	-17.0		-17.7	-16.0			-20.8				-14.8				
			4.4	-18.1	-12.2	-9.9			-15.4	-20.5	-14.4	-7.3	-9.0	2.4	-11.9	-24.9	-17.3		-17.5	-16.4			-21.9				-18.6				
			4.5	-18.2	-13.9	-9.5	-0.4	-5.6	-15.4	-20.2	-14.1	-7.2	-9.5	2.5	-12.3	-24.0	-17.0		-16.8	-16.2			-21.8	-16.1			-20.5				
			4.6	-17.8	-14.8	-8.8	-2.1	-7.3	-14.9	-19.4	-13.5	-6.7	-9.4	2.6	-12.1	-22.6	-16.3		-15.8	-15.6			-21.0	-17.6			-21.1				
			4.7	-17.0	-14.9		-3.1	-8.1	-14.2	-18.4	-12.7	-6.1	-8.9	2.7	-11.5	-21.1	-15.4		-14.7	-14.8	9.1		-19.8	-18.0			-20.9				8.9
			4.8	-16.1	-14.7		-3.6	-8.4				-5.4	-8.3	2.8	-10.6	-19.4	-14.4		-13.6	-14.0	2.5		-18.3	-17.7			-20.1				5.9
			4.9		-14.2		-3.7	-8.3						2.9	-9.6	-17.8	-13.3		-12.5	-13.0	-1.8		-16.8	-17.0			-19.1				4.1
			5.0		-13.6		-3.5	-7.9						3.0	-8.6	-16.3	-12.3	-11.0	-11.4	-12.1	-4.4		-15.2	-16.1			-17.9				3.1
			5.1				-3.3	-7.5						3.1				-12.4			-5.9		-13.7	-14.9			-16.6				2.6
														3.2				-13.0			-6.6		-12.2	-13.8	-0.1	-7.4	-15.3				2.4
														3.3				-12.9			-6.9			-12.7	-1.6	-8.2	-14.1	-12.1		2.4	
														3.4				-12.5			-6.8			-11.6	-2.6	-8.5		-13.2			2.6
														3.5				-11.8			-6.5			-10.6	-3.2	-8.5		-13.6	1.8		2.7
														3.6				-11.1			-6.1				-3.5	-8.3		-13.4	1.4		2.9
														3.7				-10.3			-5.7				-3.7	-8.1		-13.0	1.1		3.1
														3.8				-9.4							-3.7	-7.7		-12.3	1.0		
														3.9				-8.6							-3.6	-7.3		-11.6	0.9		
														4.0				-7.9							-3.4	-6.9		-10.8	0.8		
														4.1											-3.2	-6.5		-10.0	0.8		
														4.2											-3.0	-6.1		-9.2	0.8		
														4.3														-8.5	0.9		
														...																	
														5.0												3.2					
														5.1												3.1					
														5.2												3.0					
														5.3												2.9					
														5.4												2.8					
														5.5												2.7					
														5.6												2.6					
														5.7												2.5					
														5.8												2.5					
														5.9												2.4					
														6.0												2.3					

α	Stacked		Amino Acid Edge T-shaped											Nucleobase Edge T-shaped													
	HIS'	HIS	1	2	3	4	5	A	B	C	D	E	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G
0	-10.5	-23.0	-18.2	-14.9	-10.1	-3.7	-8.4	-15.4	-20.5	-14.4	-7.3	-9.5	-12.3	-25.3	-17.3	-13.0	-17.7	-16.4	-6.9	-21.9	-18.0	-3.7	-8.5	-21.1	-13.6	0.8	2.4
30	-10.6	-15.4	-19.7	-16.9	-12.0	-2.8	-8.7	-17.8	-25.2	-17.2	-6.6	-10.8	-22.6	-22.0	-13.9	-6.1	-20.2	-12.2	-2.2	-26.5	-15.5	-3.2	-3.8	-16.2	-6.3	1.3	-5.3
60	-15.1	-11.5	-19.2	-16.9	-11.5	-2.7	-8.0	-16.1	-25.6	-18.6	-4.8	-10.1	-30.1	-21.6	-11.2	-2.8	-22.0	-8.3	1.4	-30.2	-13.2	-1.7	-3.8	-12.7	-0.4	1.6	-12.2
90	-23.7	-11.2	-17.1	-14.8	-8.8	-3.8	-7.0	-13.3	-21.8	-17.3	-4.3	-9.1	-35.8	-21.7	-9.5	-1.6	-23.3	-5.0	4.2	-34.4	-12.4	-1.8	-2.7	-11.5	3.8	2.2	-17.3
120	-29.5	-13.9	-15.1	-10.8	-6.0	-5.9	-7.2	-12.3	-16.6	-13.3	-6.0	-9.4	-42.5	-22.1	-8.0	-6.1	-24.2	-3.3	9.3	-39.1	-13.5	-7.3	-2.1	-12.8	6.3	3.0	-20.5
150	-29.7	-18.7	-15.2	-6.9	-6.0	-8.5	-10.0	-14.1	-13.5	-9.5	-8.1	-11.9	-44.4	-24.1	-7.2	-13.4	-23.9	-3.7	12.4	-39.7	-15.3	-12.0	-6.1	-14.9	5.7	3.4	-19.9
180	-27.8	-20.7	-16.9	-4.5	-8.1	-10.5	-13.8	-18.9	-14.1	-7.4	-10.4	-16.3	-35.4	-24.4	-10.2	-10.8	-22.3	-6.4	6.6	-35.3	-15.9	-8.3	-4.1	-16.1	1.6	3.0	-14.2
210	-26.8	-22.3	-18.1	-3.5	-9.6	-11.5	-15.9	-23.3	-15.9	-6.4	-12.1	-19.6	-23.8	-24.3	-14.2	-6.4	-20.2	-10.1	-1.2	-28.8	-15.3	-3.2	-2.3	-16.9	-4.6	1.9	-6.2
240	-25.8	-25.4	-17.7	-3.1	-9.0	-11.6	-15.3	-23.1	-14.3	-4.2	-13.6	-19.2	-16.4	-22.7	-17.6	-3.6	-18.6	-13.8	-6.5	-24.1	-14.6	-2.0	0.2	-18.0	-10.7	0.8	0.8
270	-22.8	-29.8	-16.1	-3.9	-7.0	-10.5	-12.5	-19.2	-12.3	-3.7	-13.7	-16.1	-10.3	-21.5	-19.8	-2.7	-17.3	-16.8	-11.3	-20.9	-15.2	-0.6	0.9	-19.6	-15.7	0.1	6.2
300	-18.3	-32.4	-14.8	-6.7	-5.5	-8.2	-9.2	-14.8	-12.8	-6.2	-11.4	-11.9	-4.8	-24.3	-20.8	-8.8	-16.0	-18.9	-13.8	-18.5	-17.1	-0.5	-5.4	-22.4	-19.3	-0.1	9.1
330	-13.1	-30.0	-15.8	-11.0	-6.9	-5.6	-7.8	-13.4	-15.5	-10.1	-8.8	-9.2	-5.2	-27.5	-20.4	-16.7	-15.8	-19.0	-11.5	-18.7	-18.8	-3.6	-11.5	-24.2	-19.0	0.2	8.1

$\gamma \downarrow$ $X \rightarrow$	Stacked (HIS $R_1=3.3 \text{ \AA}$, $\alpha=300^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-17.5	-21.4	-25.4	-29.0	-32.0	-33.7	-33.6
1.0	-22.4	-26.2	-29.2	-31.5	-33.8	-33.4	-35.3
0.5	-25.3	-29.8	-32.6	-33.0	-32.8	-32.9	-32.2
0	-23.9	-29.2	-32.9	-32.4	-29.8	-28.0	-26.7
-0.5	-20.6	-25.7	-30.2	-30.3	-27.5	-25.0	-23.2
-1.0	-19.9	-23.5	-27.2	-27.8	-26.3	-24.5	-22.2
-1.5	-21.6	-23.2	-24.6	-24.9	-24.6	-23.7	-21.3

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=B$, $R_1=4.4 \text{ \AA}$, $\alpha=60^\circ$)														
	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
2.5	-13.4	-15.1	-16.7	-17.9	-18.9	-20.3	-22.2	-23.6	-23.5	-22.2	-20.0	-16.9	-12.9	-8.8	-5.3
2.0	-14.6	-16.3	-18.0	-19.5	-20.6	-21.9	-23.5	-24.3	-23.7	-22.3	-20.3	-17.1	-12.8	-8.4	-4.7
1.5	-15.0	-17.1	-19.4	-21.2	-22.5	-23.8	-24.7	-24.4	-23.1	-21.6	-19.7	-16.6	-12.4	-8.0	-4.3
1.0	-14.6	-17.6	-20.8	-23.1	-24.6	-25.8	-26.2	-24.8	-22.6	-20.8	-19.0	-16.0	-12.0	-8.1	-4.5
0.5	-13.8	-17.8	-21.9	-24.5	-26.2	-27.4	-27.4	-25.4	-22.7	-20.7	-18.6	-15.6	-12.1	-8.7	-5.5
0	-12.5	-17.1	-21.6	-24.3	-26.2	-27.7	-27.7	-25.6	-22.9	-20.9	-18.6	-15.3	-12.1	-9.4	-6.7
-0.5	-10.8	-15.0	-19.1	-22.0	-24.3	-26.3	-26.6	-24.9	-22.9	-21.2	-18.6	-15.0	-11.9	-9.8	-7.8
-1.0	-8.5	-11.7	-15.1	-18.3	-21.4	-23.8	-24.3	-23.2	-22.0	-20.8	-18.3	-15.0	-12.1	-10.2	-8.8
-1.5	-6.0	-8.2	-11.1	-14.5	-18.0	-20.5	-21.1	-20.6	-20.1	-19.4	-17.8	-15.4	-13.1	-11.2	-9.6
-2.0	-3.7	-5.1	-7.5	-10.7	-14.1	-16.5	-17.4	-17.5	-17.5	-17.3	-16.8	-15.8	-14.2	-12.2	-9.8

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=A$, $R_1=2.5 \text{ \AA}$, $\alpha=30^\circ$)								
	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.0	-14.1	-20.3	-26.7	-32.5	-36.9	-39.7	-40.1	-36.7	-29.7
1.5	-14.1	-21.3	-29.1	-36.3	-41.5	-43.9	-42.9	-38.3	-30.9
1.0	-13.4	-21.0	-29.8	-38.1	-44.0	-46.4	-44.9	-39.7	-32.3
0.5	-12.3	-19.8	-28.6	-37.1	-43.3	-46.0	-44.7	-39.8	-32.8
0	-11.1	-18.1	-26.2	-34.0	-39.7	-42.3	-41.4	-37.3	-31.1
-0.5	-10.0	-16.4	-23.4	-29.9	-34.6	-36.6	-35.8	-32.5	-27.4
-1.0	-8.7	-14.4	-20.2	-25.5	-29.3	-30.6	-29.6	-26.7	-22.6
-1.5	-7.0	-12.0	-16.8	-21.2	-24.2	-25.0	-23.7	-21.1	-17.6
-2.0	-5.2	-9.5	-13.5	-17.1	-19.5	-19.8	-18.4	-16.0	-13.3

Guanine–Phenylalanine Dimers

<u>Stacked</u>		<u>Amino Acid Edge T-shaped</u>										<u>Nucleobase Edge T-shaped</u>									
<i>R_i</i>	PHE	<i>R_i</i>	1	A	<i>R_i</i>	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
3.3	-24.1	4.7	-7.4	-11.6	2.0	-13.4	-16.3	-5.6		-19.7	-2.0										
3.4	-24.5	4.8	-9.3	-12.4	2.1	-20.5	-22.2	-10.6		-22.4	-7.1			-19.3							
3.5	-23.9	4.9	-10.2	-12.5	2.2	-24.8	-25.7	-13.7		-23.5	-10.3			-26.0							
		5.0	-10.5	-12.1	2.3	-27.0	-27.4	-15.4		-23.7	-12.1			-29.7							
		5.1	-10.4	-11.5	2.4	-27.7	-27.8	-16.0		-23.1	-13.0			-31.4							
		5.2	-10.0	-10.8	2.5	-27.5	-27.4	-16.0		-22.0	-13.2			-31.6	-14.5			-17.6			
		5.3	-9.4	-10.0	2.6	-26.6	-26.4	-15.6		-20.7	-13.0			-30.9	-16.6			-19.1			
					2.7	-25.2	-25.1	-14.9		-19.3	-12.5			-29.5	-17.5			-19.5			-1.4
					2.8	-23.7	-23.6	-14.0		-17.8	-11.8			-27.8	-17.7			-19.2			-4.5
					2.9	-22.0	-22.0	-13.0		-16.4	-11.0			-26.0	-17.2			-18.5			-6.2
					3.0	-20.3	-20.4	-12.0	-2.3	-15.0	-10.2	5.0		-24.1	-16.4	8.2		-17.5			-7.1
					3.1				-5.7			2.4		-22.1	-15.5	3.6		-16.3			-7.3
					3.2				-7.7			0.8			-14.4	0.4	-1.2	-15.1			-7.2
					3.3				-8.8			-0.2			-13.3	-1.8	-3.0	-13.9	-2.3		-6.8
					3.4				-9.2			-0.7			-12.2	-3.3	-4.1	-12.7	-4.7		-6.3
					3.5				-9.2			-1.0			-11.1	-4.2	-4.7	-11.6	-6.0	3.2	-5.7
					3.6				-9.0			-1.0				-4.8	-5.1		-6.7	2.6	-5.2
					3.7				-8.5			-0.9				-5.0	-5.2		-6.8	2.3	-4.6
					3.8				-8.0			-0.8				-5.1	-5.1		-6.6	2.0	
					3.9				-7.4			-0.6				-5.0	-4.9		-6.3	1.9	
					4.0				-6.8			-0.4				-4.8	-4.7		-5.8	1.8	
					4.1												-4.4		-5.3	1.8	
					4.2												-4.1		-4.8	1.8	
					4.3														-4.3	1.8	
					4.4															1.8	
					4.5																1.9
					...																
					7.0								0.9								
					7.1								0.9								
					7.2								0.8								
					7.3								0.8								
					7.4								0.8								
					7.5								0.7								
					7.6								0.7								
					7.7								0.7								
					7.8								0.7								
					7.9								0.7								
					8.0								0.6								

α	Stacked	Amino Acid Edge T-shaped										Nucleobase Edge T-shaped									
	PHE	1	A	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H		
0	-24.5	-10.5	-12.5	-27.7	-27.8	-16.0	-9.2	-23.7	-13.2	-1.0		-31.6	-17.7	-5.1	-5.2	-19.5	-6.8	1.8	-7.3		
30	-24.4	-11.5	-14.2	-28.2	-28.1	-16.3	-9.4	-23.7	-13.2	-1.1		-31.6	-17.7	-5.4	-5.5	-19.6	-6.8	1.8	-7.4		
60		-11.1	-13.7																		
90		-9.6	-12.1																		
120		-8.3	-10.7																		
150		-8.8	-10.7																		

$\gamma \downarrow$ $X \rightarrow$	Stacked ($R_1=3.4 \text{ \AA}$, $\alpha=0^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-12.8	-14.9	-16.9	-18.7	-20.5	-22.3	-22.9
1.0	-16.6	-18.9	-20.8	-21.8	-22.9	-24.5	-24.7
0.5	-18.8	-22.1	-24.1	-23.9	-23.3	-23.7	-23.4
0	-18.2	-22.4	-25.3	-24.5	-22.4	-21.4	-20.6
-0.5	-17.0	-21.1	-24.5	-24.2	-22.0	-20.3	-18.7
-1.0	-18.0	-21.0	-23.5	-23.4	-22.0	-20.4	-18.0
-1.5	-20.7	-21.9	-22.3	-21.7	-20.9	-19.6	-17.0

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=30^\circ$)																	
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	
2.5	-5.7	-6.8	-7.5	-8.1	-8.6	-9.0	-9.2	-9.5	-9.6	-9.3	-8.4	-7.2	-5.9	-4.6	-3.3	-2.2	-1.5	
2.0	-5.9	-7.1	-8.0	-8.8	-9.5	-10.1	-10.6	-10.9	-11.0	-10.6	-9.7	-8.7	-7.5	-5.9	-4.2	-2.8	-1.9	
1.5	-5.8	-7.1	-8.3	-9.5	-10.5	-11.3	-11.9	-12.4	-12.5	-11.9	-11.1	-10.2	-8.8	-6.8	-4.8	-3.2	-2.2	
1.0	-5.5	-7.0	-8.7	-10.5	-12.0	-12.7	-13.3	-13.8	-13.7	-13.0	-12.0	-10.9	-9.3	-7.2	-5.1	-3.5	-2.4	
0.5	-5.2	-7.0	-9.2	-11.5	-13.1	-13.7	-14.1	-14.5	-14.3	-13.4	-12.2	-10.9	-9.2	-7.2	-5.3	-3.9	-2.8	
0	-4.9	-6.9	-9.3	-11.5	-13.0	-13.7	-14.2	-14.4	-14.2	-13.3	-12.2	-10.8	-9.1	-7.3	-5.7	-4.3	-3.0	
-0.5	-4.6	-6.5	-8.6	-10.5	-11.9	-12.9	-13.7	-14.1	-13.9	-13.4	-12.6	-11.3	-9.5	-7.7	-6.1	-4.6	-3.2	
-1.0	-4.2	-5.9	-7.5	-9.1	-10.6	-12.1	-13.4	-13.8	-13.6	-13.4	-12.8	-11.5	-9.6	-7.8	-6.1	-4.5	-3.1	
-1.5	-3.7	-5.0	-6.3	-7.7	-9.3	-11.2	-12.6	-13.0	-12.9	-12.7	-12.2	-10.9	-9.1	-7.4	-5.8	-4.4	-3.2	
-2.0	-3.1	-4.1	-5.1	-6.4	-8.0	-9.6	-10.8	-11.3	-11.3	-11.2	-10.7	-9.7	-8.4	-7.0	-5.7	-4.5	-3.5	
-2.5	-2.5	-3.3	-4.2	-5.2	-6.4	-7.6	-8.4	-9.0	-9.4	-9.5	-9.3	-8.7	-7.9	-6.9	-5.7	-4.5	-3.5	

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=A$, $R_1=2.5 \text{ \AA}$, $\alpha=30^\circ$)								
	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-13.0	-15.1	-16.4	-17.0	-16.9	-15.8	-13.6	-11.0	-8.2
2.0	-15.1	-17.7	-19.6	-20.8	-21.0	-19.9	-17.6	-14.5	-11.2
1.5	-17.2	-20.4	-23.0	-24.7	-25.2	-24.1	-21.7	-18.4	-14.4
1.0	-18.9	-22.8	-26.0	-28.1	-28.6	-27.6	-25.2	-21.8	-17.4
0.5	-19.8	-24.3	-27.9	-30.2	-30.8	-29.8	-27.5	-24.0	-19.6
0	-19.8	-24.6	-28.3	-30.7	-31.6	-30.8	-28.5	-24.9	-20.3
-0.5	-19.0	-23.8	-27.5	-29.9	-31.0	-30.4	-27.9	-24.1	-19.6
-1.0	-17.3	-21.9	-25.5	-27.8	-28.7	-28.0	-25.6	-21.8	-17.4
-1.5	-14.8	-18.9	-22.2	-24.2	-24.8	-24.1	-21.9	-18.6	-14.3
-2.0	-11.9	-15.3	-18.0	-19.5	-19.8	-19.2	-17.8	-15.1	-11.2
-2.5	-9.1	-11.7	-13.6	-14.6	-14.4	-13.9	-13.2	-11.4	-7.9

Guanine–Tyrosine Dimers

Stacked			Amino Acid Edge T-shaped														Nucleobase Edge T-shaped																
R_i	TYR'	TYR	R_i	1	2	3	4	5	6	A	B	C	D	E	F	R_i	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H	
3.3	-28.1	-19.5	4.5		-15.7				-9.3							2.0	-2.2	-19.0	3.0		-14.5	3.6											
3.4	-28.4	-20.3	4.6		-17.1				-11.0							2.1	-14.0	-24.7	-3.9		-18.7	-2.9											
3.5	-27.6	-20.0	4.7		-17.6				-11.8	-6.6	-7.2			-9.6	-4.3	2.2	-21.5	-27.7	-8.5		-21.0	-7.2			-22.5								
			4.8		-17.4				-12.0	-9.4	-10.6			-11.4	-6.1	2.3	-25.8	-28.9	-11.2		-21.9	-9.8			-26.2				-13.2				
			4.9		-16.8				-11.7	-11.0	-12.5			-12.2	-7.1	2.4	-27.9	-28.8	-12.7		-21.9	-11.2			-28.0				-17.1				
			5.0		-16.0	-9.8		-9.2	-11.2	-11.6	-13.4	-9.6	-8.7	-12.4	-7.4	2.5	-28.5	-27.9	-13.4		-21.2	-11.8			-28.3	-15.1			-19.2				
			5.1	-6.7	-15.0	-11.3		-10.6	-10.6	-11.6	-13.6	-11.8	-11.0	-12.1	-7.3	2.6	-28.2	-26.6	-13.4		-20.2	-11.9			-27.8	-17.0			-20.0				
			5.2	-8.1		-11.9		-11.3		-11.2	-13.3	-12.9	-12.2	-11.6	-7.0	2.7	-27.1	-24.9	-13.1		-19.0	-11.6			-26.7	-17.7			-19.9			-10.1	
			5.3	-8.6		-12.0	-9.9	-11.4		-10.7	-12.8	-13.2	-12.5	-10.9	-6.5	2.8	-25.7	-23.2	-12.5		-17.6	-11.0			-25.2	-17.7			-19.2			-11.8	
			5.4	-8.5		-11.7	-10.7	-11.1				-13.0	-12.4			2.9	-24.0	-21.5	-11.8		-16.3	-10.4			-23.6	-17.1			-18.3			-12.5	
			5.5	-8.1		-11.2	-10.9	-10.6				-12.4	-11.9			3.0	-22.3	-19.7	-11.0	-14.5	-15.0	-9.7	12.5	2.1	-21.9	-16.3	18.5	-11.3	-17.1			-12.5	
			5.6	-7.5		-10.6	-10.7	-10.0				-11.7	-11.2			3.1				-17.2			7.7	1.4	-20.1	-15.3	9.6	-14.7	-15.9			-12.0	
			5.7	-6.8			-10.3									3.2				-18.2			4.4	1.0	-18.5	-14.2	3.3	-16.4	-14.6			-11.2	
			5.8				-9.7									3.3				-18.3			2.3	0.9		-13.1	-1.0	-17.1	-13.4	-3.8		-10.4	
			5.9				-9.1									3.4				-17.7			1.0	0.9		-12.1	-4.0	-17.0		-5.3		-9.4	
																3.5				-16.8			0.2	1.0		-11.1	-5.9	-16.4		-6.1	0.8	-8.5	
																3.6				-15.6			-0.2	1.0			-7.1	-15.5		-6.4	0.7	-7.6	
																3.7				-14.4			-0.4	1.1			-7.7	-14.4		-6.3	0.7	-6.8	
																3.8				-13.2			-0.4	1.2			-8.0	-13.3		-5.9	0.7		
																3.9				-11.9			-0.4	1.3			-7.9	-12.2		-5.5	0.8		
																4.0				-10.8			-0.2	1.3			-7.7	-11.1		-5.0	1.0		
																4.1														-4.5	1.1		
																4.2														-4.0	1.2		
																4.3														-3.5	1.4		
																4.4																1.5	
																4.5																1.6	

α	Stacked		Amino Acid Edge T-shaped												Nucleobase Edge T-shaped															
	TYR'	TYR	1	2	3	4	5	6	A	B	C	D	E	F	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
0	-28.4	-20.3	-8.6	-17.6	-12.0	-10.9	-11.4	-12.0	-11.6	-13.6	-13.2	-12.5	-12.4	-7.4	-28.5	-28.9	-13.4	-18.3	-21.9	-11.9	-0.4	0.9	-28.3	-17.7	-8.0	-17.1	-20.0	-6.4	0.7	-12.5
30	-24.4	-23.3	-9.1	-19.9	-13.6	-12.0	-12.2	-12.0	-12.7	-16.1	-15.4	-14.4	-13.8	-9.9	-25.9	-26.7	-14.4	-17.8	-22.2	-13.1	-1.4	1.8	-26.6	-18.5	-8.5	-19.1	-20.5	-7.8	0.6	-9.7
60	-20.9	-24.7	-6.9	-20.5	-13.0	-11.6	-11.9	-12.6	-14.0	-15.5	-14.6	-14.0	-13.9	-10.4	-25.3	-24.5	-15.3	-11.5	-22.5	-13.6	-2.3	2.3	-28.2	-18.0	-6.8	-7.2	-19.7	-8.5	0.9	-6.6
90	-18.3	-28.1	-4.3	-18.0	-10.9	-9.9	-10.5	-12.3	-15.2	-12.6	-12.3	-12.5	-13.1	-9.0	-23.7	-25.5	-16.2	-8.7	-22.0	-14.0	-3.5	2.6	-28.8	-17.2	-5.2	-3.8	-19.6	-9.8	0.7	-3.0
120	-21.8	-29.8	-4.2	-13.6	-8.8	-8.4	-9.0	-10.9	-16.0	-9.8	-10.4	-10.9	-11.6	-7.2	-20.7	-26.7	-16.8	-6.3	-21.1	-14.3	-5.5	2.8	-28.4	-16.5	-2.1	-0.7	-20.0	-11.4	0.1	-0.3
150	-25.7	-27.6	-6.8	-12.8	-9.0	-8.6	-8.9	-9.4	-16.5	-8.9	-10.1	-10.5	-10.2	-9.0	-20.0	-28.6	-16.2	-8.2	-20.9	-13.9	-5.7	2.4	-28.8	-16.9	-0.6	-3.3	-21.3	-12.0	0.2	-0.3
180	-28.0	-24.8	-11.4	-15.4	-10.6	-10.1	-10.1	-8.7	-17.3	-10.2	-11.8	-12.0	-10.7	-12.5	-28.7	-29.9	-15.4	-18.4	-21.4	-12.8	0.3	1.2	-31.5	-18.1	-14.2	-2.7	-22.9	-10.5	1.5	-4.8
210	-24.4	-24.8	-15.3	-18.4	-11.3	-11.0	-11.1	-8.6	-18.0	-11.5	-13.5	-13.8	-12.0	-12.9	-30.0	-30.1	-16.0	-18.0	-22.2	-11.7	1.7	0.4	-32.6	-18.3	-15.0	-6.1	-22.1	-8.2	2.2	-7.2
240	-24.6	-27.4	-16.4	-16.7	-10.8	-10.6	-10.8	-8.2	-17.2	-10.9	-13.0	-13.2	-11.5	-11.0	-27.8	-28.8	-15.1	-11.4	-22.5	-11.0	-0.1	0.1	-32.5	-17.6	-6.8	-3.6	-19.7	-6.3	2.0	-7.7
270	-26.2	-28.8	-13.8	-13.1	-9.3	-9.2	-9.6	-8.5	-15.8	-9.6	-11.7	-11.5	-10.4	-8.4	-29.8	-27.2	-14.0	-8.4	-23.1	-10.4	-0.4	-0.1	-33.0	-16.4	-4.8	-4.5	-17.7	-4.8	1.5	-9.8
300	-31.4	-26.4	-9.9	-10.4	-8.3	-8.2	-8.7	-9.4	-14.4	-8.9	-10.6	-10.2	-10.0	-6.0	-33.2	-25.4	-13.2	-6.1	-23.9	-9.9	0.0	-0.3	-34.4	-15.4	-4.7	-2.4	-16.5	-3.7	1.2	-13.2
330	-33.4	-21.6	-8.1	-12.4	-9.5	-9.0	-9.6	-10.9	-12.4	-10.2	-10.9	-10.5	-10.7	-5.5	-34.1	-25.5	-13.1	-7.8	-23.7	-10.2	0.1	-0.1	-34.7	-15.8	-6.6	-0.1	-17.3	-4.1	1.0	-14.8

$\gamma \downarrow$ $X \rightarrow$	Stacked (TYR' $R_1=3.4 \text{ \AA}$, $\alpha=330^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-16.7	-20.4	-23.9	-26.1	-27.3	-28.5	-29.0
1.0	-19.7	-24.1	-28.6	-30.6	-30.3	-29.9	-29.3
0.5	-21.0	-25.6	-31.0	-33.2	-31.8	-29.7	-27.9
0	-22.2	-26.0	-31.1	-33.4	-32.1	-29.9	-27.3
-0.5	-25.1	-27.6	-30.8	-32.1	-31.4	-30.0	-27.5
-1.0	-28.6	-30.1	-30.8	-30.2	-29.4	-28.7	-26.6
-1.5	-29.7	-30.9	-30.2	-28.3	-26.8	-25.7	-23.7

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=A$, $R_1=5.1 \text{ \AA}$, $\alpha=90^\circ$)					
	-2.5	-2.0	-1.5	-1.0	-0.5	0
2.5	-15.2	-16.6	-17.3	-17.4	-17.0	-16.2
2.0	-17.3	-18.8	-19.0	-18.2	-16.6	-14.7
1.5	-19.1	-20.8	-20.7	-19.0	-16.5	-13.6
1.0	-19.9	-21.8	-21.6	-19.6	-16.8	-13.8
0.5	-19.3	-21.2	-21.0	-19.2	-17.0	-14.6
0	-17.2	-18.9	-18.8	-17.6	-16.4	-15.2
-0.5	-14.2	-15.8	-15.8	-15.3	-15.2	-14.9
-1.0	-11.0	-12.5	-13.1	-13.5	-14.0	-14.2
-1.5	-7.8	-9.5	-10.8	-11.9	-12.8	-13.2
-2.0	-4.8	-6.5	-8.1	-9.6	-10.6	-11.3

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=A$, $R_1=2.4 \text{ \AA}$, $\alpha=300^\circ$)										
	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-9.1	-12.4	-15.8	-18.4	-19.3	-18.0	-14.7	-10.4	-6.3	-3.3	-10.4
2.5	-10.5	-14.7	-18.8	-21.6	-22.1	-19.8	-15.9	-11.9	-8.7	-6.1	-11.9
2.0	-11.8	-16.9	-21.9	-25.2	-25.5	-22.7	-18.5	-14.7	-11.9	-9.4	-14.7
1.5	-12.6	-18.4	-24.2	-28.2	-28.9	-26.3	-22.3	-18.6	-15.6	-12.8	-18.6
1.0	-12.7	-18.9	-25.0	-29.6	-31.3	-29.8	-26.6	-23.1	-19.7	-16.2	-23.1
0.5	-12.4	-18.4	-24.6	-29.6	-32.3	-32.5	-30.7	-27.5	-23.5	-19.1	-14.6
0	-12.1	-17.9	-24.0	-29.3	-33.1	-34.7	-33.9	-31.0	-26.5	-21.2	-31.0
-0.5	-12.4	-18.1	-24.2	-29.8	-34.1	-36.2	-35.7	-32.7	-28.0	-22.2	-16.4
-1.0	-12.8	-18.5	-24.5	-30.1	-34.3	-36.2	-35.5	-32.6	-27.9	-22.0	-32.6
-1.5	-12.4	-17.9	-23.7	-28.8	-32.5	-34.0	-33.2	-30.5	-26.1	-20.5	-30.5
-2.0	-10.5	-15.8	-21.2	-25.6	-28.5	-29.6	-29.0	-26.7	-22.8	-18.0	-26.7
-2.5	-7.6	-12.6	-17.6	-21.2	-23.2	-23.9	-23.6	-21.8	-18.7	-14.8	-21.8
-3.0	-4.2	-9.0	-13.4	-16.1	-17.3	-17.8	-17.8	-16.8	-14.5	-11.6	-16.8

Guanine–Tryptophan Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped																	
R_1	TRP'	TRP	R_1	1	2	3	A	B	C	D	E	F	G	R_1	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H	
3.3	-35.6	-24.8	4.6				-13.5							2.0	-22.5	-22.3	-7.4		-23.0	2.2											
3.4	-36.7	-25.8	4.7				-16.0							2.1	-29.4	-28.8	-12.4		-26.2	-4.5											
3.5	-36.2	-25.4	4.8				-17.1			-11.7				2.2	-33.3	-32.4	-15.4		-27.5	-8.9			-35.9								
			4.9				-17.3			-13.4				2.3	-35.2	-34.1	-17.0		-27.7	-11.5			-38.7								
			5.0				-16.8	-15.2		-14.1				2.4	-35.5	-34.4	-17.5		-27.0	-12.8			-39.6								
			5.1				-16.0	-17.6		-14.1	-10.8		-10.6	2.5	-34.9	-33.7	-17.4		-25.9	-13.3			-39.2	-20.1			-24.4				
			5.2				-15.0	-18.6		-13.7	-12.2		-11.8	2.6	-33.6	-32.4	-16.8		-24.4	-13.3			-38.0	-21.5			-24.7				
			5.3					-18.8	-14.4	-13.0	-12.7		-12.2	2.7	-31.9	-30.8	-16.0		-22.9	-12.8			-36.2	-21.9			-24.3				-9.0
			5.4				-18.4	-16.0		-12.2	-12.6		-12.0	2.8	-30.1	-29.0	-15.1		-21.2	-12.2			-34.1	-21.5			-23.3				-11.5
			5.5				-17.6	-16.6			-12.2	-7.2	-11.5	2.9	-28.1	-27.1	-14.0		-19.6	-11.4			-31.9	-20.7			-22.0				-12.8
			5.6		-7.6	-7.6	-16.6	-16.5			-11.5	-9.7	-10.7	3.0	-26.1	-25.2	-13.0	-8.7	-18.0	-10.6	2.7		-29.7	-19.6	-0.8		-20.6				-13.2
			5.7	-11.6	-9.1	-9.0			-15.9		-10.8	-11.0	-9.9	3.1				-11.9			0.9	1.1	-27.4	-18.4	-3.9		-19.1				-13.0
			5.8	-13.0	-9.8	-9.6			-15.0			-11.4		3.2			-13.6			-0.1	0.8	-25.3	-17.1	-5.9	-5.7	-17.6					-12.5
			5.9	-13.6	-9.9	-9.7			-14.1			-11.3		3.3			-14.3			-0.5	0.7		-15.8	-7.2	-7.5	-16.2	-4.8				-11.7
			6.0	-13.7	-9.7	-9.4						-10.8		3.4			-14.4			-0.6	0.8		-14.6	-7.9	-8.5	-14.8	-6.2				-10.8
			6.1	-13.4	-9.2	-8.9						-10.2		3.5			-14.0			-0.4	0.9		-13.4	-8.3	-9.0	-13.5	-6.8	3.4			-10.0
			6.2	-12.8	-8.7	-8.3								3.6			-13.3			-0.2	1.1			-8.4	-9.1		-6.8	3.1			-9.1
			6.3	-12.2										3.7			-12.5			0.2	1.2			-8.2	-8.9		-6.6	3.0			-8.3
														3.8			-11.6			0.5	1.4			-8.0	-8.6		-6.1	2.9			
														3.9			-10.7			0.9	1.5			-7.7	-8.2		-5.5	2.9			
														4.0			-9.8			1.2	1.6			-7.3	-7.7		-4.9	3.0			
														4.1							1.7				-7.1		-4.2	3.1			
														4.2											-6.6		-3.6	3.1			
														4.3													-3.0	3.2			
														4.4																	3.3
														4.5																	3.3

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped																
	TRP'	TRP	1	2	3	A	B	C	D	E	F	G	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H	
0	-36.7	-25.8	-13.7	-9.9	-9.7	-17.3	-18.8	-16.6	-14.1	-12.7	-11.4	-12.2	-35.5	-34.4	-17.5	-14.4	-27.7	-13.3	-0.6	0.7	-39.6	-21.9	-8.4	-9.1	-24.7	-6.8	2.9	-13.2	
30	-35.4	-30.8	-15.8	-10.9	-10.3	-20.7	-21.8	-20.0	-16.3	-14.1	-13.0	-14.0	-33.5	-37.4	-15.1	-23.8	-26.3	-15.4	3.1	1.9	-40.2	-25.5	-13.1	-13.2	-29.8	-10.6	3.5	-11.2	
60	-29.3	-37.6	-15.2	-10.6	-9.8	-17.9	-20.7	-19.7	-16.0	-12.9	-12.5	-13.4	-31.5	-38.1	-15.5	-27.0	-25.5	-17.2	2.4	3.5	-39.6	-26.3	-14.2	-13.9	-32.5	-14.3	2.8	-8.7	
90	-25.5	-39.0	-12.4	-9.2	-8.6	-14.6	-17.9	-16.1	-14.2	-10.8	-11.1	-11.4	-26.3	-37.0	-18.7	-22.1	-24.6	-18.5	-5.0	4.8	-36.7	-25.0	-10.3	-11.5	-32.3	-16.8	1.6	-3.6	
120	-26.2	-35.7	-9.4	-8.0	-7.9	-13.9	-14.6	-11.8	-11.7	-8.7	-10.1	-10.2	-22.6	-34.5	-19.9	-14.9	-24.2	-18.9	-9.0	5.5	-34.1	-23.1	-2.8	-9.0	-29.7	-16.7	0.9	-0.2	
150	-28.2	-31.2	-8.5	-8.8	-9.1	-15.8	-15.9	-9.4	-10.6	-9.9	-10.5	-11.9	-24.8	-32.3	-21.9	-10.5	-25.4	-18.0	-8.7	5.1	-33.2	-21.4	-5.0	-6.4	-26.3	-14.5	0.9	-1.3	
180	-28.7	-28.1	-9.5	-10.7	-11.6	-21.1	-19.2	-11.3	-12.3	-12.8	-12.7	-16.4	-29.0	-33.8	-19.6	-14.9	-26.3	-16.7	-3.1	3.9	-36.0	-22.7	-8.7	-8.2	-26.6	-12.1	2.2	-5.7	
210	-28.9	-26.0	-10.2	-11.6	-13.1	-25.6	-21.0	-13.5	-14.2	-14.7	-14.7	-19.0	-32.1	-37.9	-16.1	-23.8	-25.6	-15.5	2.0	2.3	-39.3	-25.6	-13.7	-13.0	-29.9	-10.8	3.5	-10.7	
240	-26.9	-29.8	-9.4	-11.2	-12.6	-26.5	-20.3	-11.8	-13.4	-14.6	-14.1	-17.6	-37.0	-40.0	-14.8	-26.6	-25.6	-13.8	4.5	0.6	-42.3	-25.7	-14.3	-14.2	-30.4	-8.9	3.6	-16.4	
270	-29.6	-29.0	-7.9	-9.7	-10.5	-22.9	-17.6	-9.0	-11.9	-12.8	-12.2	-13.9	-42.7	-38.8	-13.4	-21.9	-27.4	-11.8	6.3	-0.7	-46.6	-23.6	-11.8	-10.9	-27.5	-6.3	3.3	-20.5	
300	-32.2	-26.6	-7.6	-8.2	-8.4	-17.1	-15.1	-7.4	-10.7	-10.9	-10.3	-9.9	-43.4	-35.9	-13.6	-14.8	-28.3	-10.8	4.5	-1.0	-47.1	-21.2	-10.0	-4.9	-23.8	-4.4	3.1	-20.4	
330	-35.9	-24.5	-10.0	-8.4	-8.3	-15.0	-14.8	-10.8	-11.4	-10.3	-9.9	-9.7	-40.3	-33.2	-16.4	-10.1	-28.8	-11.5	0.9	-0.1	-42.7	-19.8	-6.5	-6.0	-21.8	-4.3	2.6	-17.2	

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped															
	TRP'	TRP	1	2	3	A	B	C	D	E	F	G	1	2	3	4	5	6	7	8	A	B	C	D	E	F	G	H
0	-36.7	-25.8	-13.7	-9.9	-9.7	-17.3	-18.8	-16.6	-14.1	-12.7	-11.4	-12.2	-35.5	-34.4	-17.5	-14.4	-27.7	-13.3	-0.6	0.7	-39.6	-21.9	-8.4	-9.1	-24.7	-6.8	2.9	-13.2
30	-35.4	-30.8	-15.8	-10.9	-10.3	-20.7	-21.8	-20.0	-16.3	-14.1	-13.0	-14.0	-33.5	-37.4	-15.1	-23.8	-26.3	-15.4	3.1	1.9	-40.2	-25.5	-13.1	-13.2	-29.8	-10.6	3.5	-11.2
60	-29.3	-37.6	-15.2	-10.6	-9.8	-17.9	-20.7	-19.7	-16.0	-12.9	-12.5	-13.4	-31.5	-38.1	-15.5	-27.0	-25.5	-17.2	2.4	3.5	-39.6	-26.3	-14.2	-13.9	-32.5	-14.3	2.8	-8.7
90	-25.5	-39.0	-12.4	-9.2	-8.6	-14.6	-17.9	-16.1	-14.2	-10.8	-11.1	-11.4	-26.3	-37.0	-18.7	-22.1	-24.6	-18.5	-5.0	4.8	-36.7	-25.0	-10.3	-11.5	-32.3	-16.8	1.6	-3.6
120	-26.2	-35.7	-9.4	-8.0	-7.9	-13.9	-14.6	-11.8	-11.7	-8.7	-10.1	-10.2	-22.6	-34.5	-19.9	-14.9	-24.2	-18.9	-9.0	5.5	-34.1	-23.1	-2.8	-9.0	-29.7	-16.7	0.9	-0.2
150	-28.2	-31.2	-8.5	-8.8	-9.1	-15.8	-15.9	-9.4	-10.6	-9.9	-10.5	-11.9	-24.8	-32.3	-21.9	-10.5	-25.4	-18.0	-8.7	5.1	-33.2	-21.4	-5.0	-6.4	-26.3	-14.5	0.9	-1.3
180	-28.7	-28.1	-9.5	-10.7	-11.6	-21.1	-19.2	-11.3	-12.3	-12.8	-12.7	-16.4	-29.0	-33.8	-19.6	-14.9	-26.3	-16.7	-3.1	3.9	-36.0	-22.7	-8.7	-8.2	-26.6	-12.1	2.2	-5.7
210	-28.9	-26.0	-10.2	-11.6	-13.1	-25.6	-21.0	-13.5	-14.2	-14.7	-14.7	-19.0	-32.1	-37.9	-16.1	-23.8	-25.6	-15.5	2.0	2.3	-39.3	-25.6	-13.7	-13.0	-29.9	-10.8	3.5	-10.7
240	-26.9	-29.8	-9.4	-11.2	-12.6	-26.5	-20.3	-11.8	-13.4	-14.6	-14.1	-17.6	-37.0	-40.0	-14.8	-26.6	-25.6	-13.8	4.5	0.6	-42.3	-25.7	-14.3	-14.2	-30.4	-8.9	3.6	-16.4
270	-29.6	-29.0	-7.9	-9.7	-10.5	-22.9	-17.6	-9.0	-11.9	-12.8	-12.2	-13.9	-42.7	-38.8	-13.4	-21.9	-27.4	-11.8	6.3	-0.7	-46.6	-23.6	-11.8	-10.9	-27.5	-6.3	3.3	-20.5
300	-32.2	-26.6	-7.6	-8.2	-8.4	-17.1	-15.1	-7.4	-10.7	-10.9	-10.3	-9.9	-43.4	-35.9	-13.6	-14.8	-28.3	-10.8	4.5	-1.0	-47.1	-21.2	-10.0	-4.9	-23.8	-4.4	3.1	-20.4
330	-35.9	-24.5	-10.0	-8.4	-8.3	-15.0	-14.8	-10.8	-11.4	-10.3	-9.9	-9.7	-40.3	-33.2	-16.4	-10.1	-28.8	-11.5	0.9	-0.1	-42.7	-19.8	-6.5	-6.0	-21.8	-4.3	2.6	-17.2

$\gamma \downarrow$ $X \rightarrow$	Stacked (TRP' $R_1=3.4 \text{ \AA}$, $\alpha=0^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-19.1	-23.0	-27.4	-31.8	-35.2	-36.8	-37.7
1.0	-24.8	-28.4	-32.8	-37.8	-40.9	-40.7	-39.4
0.5	-30.9	-32.6	-35.2	-39.6	-42.5	-41.3	-38.3
0	-34.9	-34.5	-34.0	-36.7	-39.4	-38.5	-36.1
-0.5	-36.1	-35.1	-33.2	-34.3	-36.1	-35.6	-34.5
-1.0	-35.6	-35.9	-34.9	-35.3	-35.3	-34.0	-33.1
-1.5	-34.1	-35.5	-36.1	-36.3	-34.8	-32.1	-30.2

$\gamma \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=240^\circ$)																
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
3.0	-9.5	-11.2	-12.8	-14.2	-15.3	-16.2	-17.4	-19.1	-20.5	-20.9	-20.3	-18.8	-16.4	-13.2	-9.7	-6.6	-4.2
2.5	-11.0	-12.7	-14.4	-15.8	-16.9	-17.8	-19.1	-21.0	-22.6	-23.2	-22.7	-21.1	-18.3	-14.4	-10.3	-6.7	-3.9
2.0	-12.1	-13.9	-15.7	-17.3	-18.7	-19.9	-21.3	-22.9	-23.9	-24.0	-23.4	-21.8	-18.8	-14.7	-10.3	-6.4	-3.4
1.5	-12.4	-14.4	-16.6	-18.8	-20.7	-22.4	-23.9	-24.8	-24.7	-23.9	-22.6	-20.8	-18.0	-14.2	-10.0	-6.2	-3.1
1.0	-11.9	-14.3	-17.4	-20.4	-23.0	-25.1	-26.6	-26.8	-25.5	-23.4	-21.3	-19.2	-16.7	-13.6	-10.1	-6.6	-3.4
0.5	-10.7	-13.7	-17.9	-21.9	-24.9	-27.1	-28.5	-28.3	-26.2	-23.4	-20.8	-18.4	-16.0	-13.5	-10.8	-7.7	-4.6
0	-9.2	-12.6	-17.3	-21.8	-25.1	-27.4	-28.7	-28.5	-26.5	-23.9	-21.4	-18.8	-16.2	-13.9	-11.6	-9.1	-6.3
-0.5	-7.7	-10.8	-15.0	-19.4	-22.9	-25.6	-27.2	-27.2	-25.9	-24.2	-22.1	-19.5	-16.6	-14.1	-12.0	-10.2	-8.1
-1.0	-6.1	-8.5	-11.8	-15.5	-19.1	-22.3	-24.3	-24.8	-24.3	-23.4	-22.1	-19.9	-17.1	-14.5	-12.5	-11.1	-9.8
-1.5	-4.5	-6.1	-8.4	-11.4	-14.9	-18.3	-20.7	-21.7	-21.8	-21.5	-20.8	-19.6	-17.9	-15.8	-13.8	-12.1	-10.9
-2.0	-3.0	-4.0	-5.5	-7.9	-11.0	-14.2	-16.7	-18.1	-18.7	-18.8	-18.8	-18.8	-18.5	-17.3	-15.2	-12.8	-10.7
-2.5	-1.7	-2.3	-3.3	-5.0	-7.4	-10.0	-12.4	-14.1	-15.2	-15.7	-16.3	-17.2	-17.9	-17.5	-15.5	-12.4	-9.5
-3.0	-0.7	-1.0	-1.5	-2.6	-4.2	-6.1	-7.9	-9.5	-10.8	-11.9	-13.0	-14.5	-15.8	-15.9	-14.1	-11.0	-7.7

$\gamma \downarrow$ $X \rightarrow$	Nucleobase Edge T-shaped ($\theta=A$, $R_1=2.4 \text{ \AA}$, $\alpha=300^\circ$)												
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
2.5	-24.8	-20.7	-23.7	-25.8	-26.9	-26.8	-25.4	-22.5	-18.8	-15.0	-11.2	-7.6	-4.4
2.0	-21.3	-26.2	-30.1	-32.7	-33.9	-33.6	-31.4	-27.6	-23.2	-18.7	-14.6	-10.9	-7.5
1.5	-24.8	-30.9	-35.7	-38.7	-40.2	-39.8	-37.2	-32.8	-27.6	-22.7	-18.4	-14.8	-11.3
1.0	-26.9	-34.0	-39.5	-43.0	-44.8	-44.6	-42.3	-37.9	-32.5	-27.2	-22.7	-18.7	-15.0
0.5	-27.7	-35.3	-41.2	-45.0	-46.9	-47.2	-45.8	-42.4	-37.4	-32.1	-27.1	-22.4	-18.0
0	-27.5	-35.0	-40.9	-44.6	-46.6	-47.3	-47.1	-45.1	-41.1	-36.1	-31.0	-25.8	-20.7
-0.5	-26.5	-33.1	-38.5	-42.1	-44.1	-45.5	-46.3	-45.5	-42.5	-38.3	-33.4	-28.1	-22.6
-1.0	-24.0	-29.7	-34.7	-38.2	-40.4	-42.4	-44.1	-44.2	-42.0	-38.2	-33.5	-28.3	-22.7
-1.5	-19.4	-24.6	-29.4	-33.1	-35.8	-38.3	-40.5	-41.2	-39.5	-35.9	-31.2	-26.0	-20.7
-2.0	-13.2	-17.9	-22.4	-26.1	-29.2	-32.3	-35.0	-36.2	-35.1	-31.7	-27.2	-22.3	-17.4
-2.5	-7.2	-10.8	-14.3	-17.4	-20.7	-24.4	-27.8	-29.5	-29.0	-26.2	-22.2	-17.9	-13.7

Thymine–Histidine Dimers

Stacked			Amino Acid Edge T-shaped												Nucleobase Edge T-shaped											
R_1	HIS'	HIS	R_1	1	2	3	4	5	A	B	C	D	E	R_1	1	2	3	4	5	6	A	B	C	D	E	F
3.3	-18.0	-9.9	4.0			-12.1								2.0	-22.1		-5.8			-3.6						
3.4	-18.8	-11.2	4.1			-13.9			-1.0		-14.7			2.1	-25.2		-10.3			-9.3						
3.5	-18.7	-11.5	4.2			-14.7			-4.9	-11.7	-16.4	-7.5	-2.9	2.2	-26.5		-12.9			-12.7						-11.4
3.6		-11.2	4.3	-6.6		-14.8			-7.1	-13.0	-17.0	-8.9	-5.6	2.3	-26.6		-14.1			-14.6					-1.5	-17.1
			4.4	-8.1	-8.0	-14.5			-8.2	-13.4	-16.9	-9.4	-7.1	2.4	-26.0		-14.4			-15.4					-5.8	-20.3
			4.5	-8.7	-9.7	-13.8	-0.7	-1.4	-8.5	-13.2	-16.3	-9.4	-7.7	2.5	-24.8		-14.1			-15.4					-8.4	-21.8
			4.6	-8.8	-10.5	-13.0	-2.4	-3.1	-8.4	-12.7	-15.4	-9.0	-7.7	2.6	-23.4		-13.5			-15.0	-4.4	10.6	1.3		-9.8	-22.1
			4.7	-8.5	-10.8		-3.4	-4.1	-7.9	-11.9	-14.5	-8.4	-7.4	2.7	-21.9		-12.6			-14.3	-8.6	5.7	-3.2		-10.4	-21.6
			4.8	-8.0	-10.7		-3.9	-4.6				-7.7	-6.9	2.8	-20.3		-11.7			-13.5	-11.1	2.5	-6.0		-10.4	-20.7
			4.9		-10.3		-4.0	-4.7						2.9	-18.8		-10.7			-12.5	-12.3	0.6	-7.5		-10.1	-19.5
			5.0		-9.8		-3.9	-4.6						3.0	-17.3	1.3	-9.7	1.8	6.9	-11.6	-12.8	-0.5	-8.2	4.7	-9.6	-18.2
			5.1				-3.7	-4.3						3.1		0.6		1.1	2.3		-12.7	-1.0	-8.3	3.3	-9.0	-16.9
														3.2		0.2		0.8	-0.7		-12.3	-1.2	-8.1	2.5	-8.3	-15.5
														3.3		0.0		0.6	-2.4		-11.7	-1.1	-7.7	2.1	-7.6	
														3.4		-0.1		0.6	-3.4		-11.0	-1.0	-7.2	1.8		
														3.5		-0.1		0.7	-3.8		-10.2	-0.8	-6.7	1.7		
														3.6		0.0		0.7	-3.8		-9.5	-0.5	-6.1	1.7		
														3.7		0.0		0.8	-3.7					1.7		
														3.8		0.1		0.9	-3.4					1.7		
														3.9		0.2		1.0	-3.1					1.8		
														4.0		0.2		1.0	-2.7					1.8		

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped											
	HIS'	HIS	1	2	3	4	5	A	B	C	D	E	1	2	3	4	5	6	A	B	C	D	E	F
0	-18.8	-11.5	-8.8	-10.8	-14.8	-4.0	-4.7	-8.5	-13.4	-17.0	-9.4	-7.7	-26.6	-0.1	-14.4	0.6	-3.8	-15.4	-12.8	-1.2	-8.3	1.7	-10.4	-22.1
30	-21.9	-10.5	-8.8	-7.7	-14.7	-6.2	-6.7	-9.1	-10.9	-14.7	-10.7	-9.4	-21.2	0.9	-16.6	0.6	-5.9	-15.1	-4.9	-5.8	-4.0	-1.6	-11.7	-20.4
60	-23.6	-14.2	-8.4	-4.7	-13.9	-8.3	-8.0	-9.1	-8.5	-10.7	-11.1	-10.3	-17.0	1.9	-18.6	0.5	-7.6	-15.6	1.3	-9.6	-0.8	-4.9	-13.0	-19.1
90	-25.2	-18.7	-7.6	-3.1	-12.7	-9.1	-8.0	-8.8	-7.2	-7.3	-10.7	-10.1	-13.5	2.4	-19.1	0.1	-9.0	-16.4	5.4	-11.6	1.2	-7.3	-14.6	-18.5
120	-25.5	-22.0	-6.9	-1.9	-11.6	-9.5	-7.9	-8.6	-5.5	-5.5	-11.4	-10.1	-9.2	2.4	-16.4	-0.2	-9.9	-17.6	7.8	-12.2	2.9	-8.0	-17.0	-19.6
150	-21.4	-23.5	-7.2	-1.2	-12.2	-9.9	-8.4	-10.2	-5.5	-6.3	-13.4	-11.5	-7.7	2.1	-12.9	-0.2	-9.7	-18.6	7.0	-11.0	2.9	-7.0	-18.0	-20.8
180	-16.1	-24.3	-8.0	-2.7	-13.6	-9.1	-8.6	-12.1	-7.7	-9.0	-14.4	-12.2	-12.9	1.8	-13.8	0.0	-8.4	-17.1	1.2	-7.7	-0.8	-5.1	-15.7	-19.6
210	-12.6	-22.9	-8.7	-6.2	-14.5	-7.0	-7.5	-10.7	-8.9	-11.4	-13.0	-10.3	-20.5	1.4	-16.7	0.4	-6.7	-15.2	-6.6	-4.1	-6.2	-2.6	-12.0	-17.8
240	-12.1	-20.0	-8.9	-9.4	-14.7	-5.1	-5.9	-9.1	-9.7	-12.5	-10.2	-7.8	-26.2	0.9	-19.2	0.8	-5.3	-13.4	-13.0	-1.3	-10.5	-0.1	-9.3	-17.5
270	-13.1	-17.2	-8.5	-10.4	-14.2	-4.3	-4.1	-7.9	-10.1	-12.2	-8.0	-5.7	-30.2	0.2	-20.0	0.9	-3.9	-12.7	-17.2	0.6	-12.8	1.9	-7.9	-18.9
300	-11.8	-15.8	-7.9	-10.9	-13.5	-3.6	-3.0	-6.3	-10.4	-13.1	-6.9	-4.6	-32.4	-0.4	-17.6	0.8	-2.6	-13.9	-19.6	2.1	-13.4	3.4	-7.9	-21.4
330	-13.6	-14.9	-8.2	-11.7	-14.0	-3.2	-3.2	-6.5	-12.1	-15.7	-7.6	-5.5	-31.1	-0.6	-14.2	0.6	-2.5	-15.3	-18.8	2.0	-12.2	3.6	-9.1	-22.9

$\Upsilon \downarrow$ $X \rightarrow$	Stacked (HIS' $R_1=3.4 \text{ \AA}$, $\alpha=120^\circ$)						
	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-17.8	-18.1	-19.2	-20.4	-21.0	-20.6	-19.1
1.0	-19.7	-20.9	-21.7	-22.5	-23.5	-23.7	-22.1
0.5	-22.0	-24.4	-24.6	-24.6	-25.7	-26.1	-24.0
0	-24.1	-26.8	-26.3	-25.5	-25.9	-25.8	-23.4
-0.5	-24.2	-26.4	-25.8	-24.7	-24.2	-23.2	-20.6
-1.0	-22.1	-23.8	-24.2	-23.7	-22.4	-20.3	-17.8
-1.5	-19.4	-21.3	-22.9	-23.2	-21.4	-18.4	-15.9

$\Upsilon \downarrow$ $X \rightarrow$	Amino Acid Edge T-shaped ($\theta=C$, $R_1=4.3 \text{ \AA}$, $\alpha=0^\circ$)										
	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-6.7	-7.5	-9.7	-12.0	-13.4	-13.7	-13.1	-12.1	-10.9	-9.7	-8.5
2.0	-6.3	-7.2	-9.9	-13.2	-15.9	-17.3	-17.2	-15.8	-13.8	-11.8	-9.9
1.5	-5.2	-5.3	-8.3	-12.5	-16.1	-18.3	-18.8	-17.5	-15.1	-12.6	-10.2
1.0	-2.2	-1.2	-5.0	-10.7	-15.4	-18.2	-19.1	-18.2	-16.0	-13.0	-9.9
0.5	-0.9	0.5	-3.9	-10.5	-15.5	-17.9	-18.7	-18.2	-16.3	-12.9	-8.8
0	-4.4	-3.9	-7.7	-12.9	-16.1	-17.1	-17.0	-16.5	-14.7	-11.1	-6.5
-0.5	-9.7	-10.4	-12.7	-15.2	-16.2	-15.7	-14.7	-13.7	-11.7	-8.1	-3.8
-1.0	-12.6	-13.9	-15.1	-15.8	-15.8	-15.2	-14.0	-12.4	-9.8	-6.3	-2.6
-1.5	-12.8	-14.3	-15.1	-15.4	-15.6	-15.7	-14.8	-12.6	-9.6	-6.2	-3.1
-2.0	-11.5	-12.9	-13.9	-14.6	-15.2	-15.5	-14.7	-12.4	-9.4	-6.4	-4.1
-2.5	-9.5	-10.9	-12.1	-13.0	-13.6	-13.6	-12.7	-10.8	-8.5	-6.3	-4.8

	Nucleobase Edge T-shaped ($\theta=1, R_1=2.3 \text{ \AA}, \alpha=300^\circ$)								
$\Upsilon \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.0	-12.3	-16.5	-21.0	-25.3	-28.8	-30.5	-29.4	-24.7	-17.4
1.5	-14.2	-19.1	-24.0	-28.5	-31.9	-33.6	-32.7	-28.2	-20.5
1.0	-15.7	-21.1	-26.3	-30.5	-33.2	-34.2	-33.0	-28.6	-21.0
0.5	-16.2	-22.0	-27.3	-31.2	-33.1	-33.1	-31.1	-26.5	-19.4
0	-15.3	-21.3	-26.7	-30.5	-32.4	-32.0	-29.3	-24.3	-17.6
-0.5	-13.4	-19.3	-24.7	-28.7	-31.0	-30.8	-27.9	-22.9	-16.8
-1.0	-11.0	-16.6	-21.8	-25.8	-28.3	-28.4	-25.9	-21.5	-16.3
-1.5	-8.8	-13.6	-18.1	-21.7	-23.8	-24.0	-22.3	-19.0	-15.0
-2.0	-6.7	-10.6	-14.1	-16.8	-18.3	-18.5	-17.5	-15.4	-12.7

Thymine–Phenylalanine Dimers

Stacked		Amino Acid Edge T-shaped				Nucleobase Edge T-shaped											
R_1	PHE	R_1	1	A	R_1	1	2	3	4	5	6	A	B	C	D	E	F
3.4	-20.0	4.7	-4.5	-8.7	2.0	-19.2		-11.2			-2.6						
3.5	-20.6	4.8	-6.4	-9.6	2.1	-22.4		-15.4			-9.4						
3.6	-20.2	4.9	-7.4	-9.8	2.2	-24.0		-17.7			-13.7						-7.6
		5.0	-7.8	-9.6	2.3	-24.3		-18.8			-16.2						-14.9
		5.1	-7.8	-9.2	2.4	-23.9		-18.9			-17.5						-19.3
		5.2	-7.6	-8.6	2.5	-22.9		-18.4			-17.9	16.0	15.3			-10.6	-21.6
		5.3	-7.2	-7.9	2.6	-21.6		-17.5			-17.7	7.6	7.0			-12.6	-22.5
					2.7	-20.2		-16.5			-17.1	2.0	1.5			-13.6	-22.5
					2.8	-18.7		-15.2			-16.3	-1.6	-1.9			-13.9	-21.9
					2.9	-17.2		-14.0			-15.3	-3.7	-4.0			-13.7	-20.9
					3.0	-15.7		-12.8	2.7	6.0	-14.3	-6.4	-4.9	-5.2	0.0	-13.2	-19.6
					3.1				1.8	0.6		-6.8	-5.5	-5.6	-1.5	-12.5	-18.3
					3.2				1.3	-2.9		-6.8	-5.6	-5.7	-2.3	-11.7	-16.9
					3.3				1.0	-5.0		-6.5	-5.4	-5.5	-2.7	-10.9	
					3.4				0.9	-6.3		-6.1	-5.1	-5.2	-2.8	-10.1	
					3.5				0.9	-6.8		-5.6	-4.6	-4.7	-2.7	-9.3	
					3.6				0.9	-6.9		-5.0			-2.5		
					3.7				0.9	-6.8		-4.5			-2.3		
					3.8				0.9	-6.5		-4.0			-2.0		
					3.9				1.0	-6.1		-3.6			-1.7		
					4.0				1.0	-5.6		-3.2			-1.5		
					...												
					5.0		1.2										
					5.1		1.2										
					5.2		1.1										
					5.3		1.1										
					5.4		1.1										
					5.5		1.0										
					5.6		1.0										
					5.7		0.9										
					5.8		0.9										
					5.9		0.9										
					6.0		0.8										

α	Stacked	Amino Acid Edge T-shaped				Nucleobase Edge T-shaped										
	PHE	1	A	1	2	3	4	5	6	A	B	C	D	E	F	
0	-20.6	-7.8	-9.8	-24.3		-18.9	0.9	-6.9	-17.9	-6.8	-5.6	-5.7	-2.8	-13.9	-22.5	
30	-20.8	-8.1	-9.8	-24.4		-18.9	0.9	-6.9	-18.2	-6.9	-5.6	-5.7	-2.8	-13.9	-22.7	
60		-8.0	-8.9													
90		-7.4	-7.8													
120		-6.9	-7.4													
150		-7.2	-8.4													

Stacked ($R_1=3.5 \text{ \AA}$, $\alpha=30^\circ$)							
$\gamma \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-13.9	-14.3	-15.4	-16.3	-16.3	-15.6	-14.5
1.0	-15.5	-16.6	-17.7	-18.5	-19.0	-18.9	-17.5
0.5	-18.1	-19.8	-20.2	-20.4	-21.1	-21.3	-19.6
0	-20.8	-22.1	-21.5	-20.8	-21.2	-21.3	-19.5
-0.5	-21.7	-22.4	-21.3	-20.2	-20.0	-19.6	-17.8
-1.0	-20.8	-21.5	-21.0	-20.2	-19.3	-17.9	-16.0
-1.5	-19.3	-20.4	-21.0	-20.7	-19.1	-16.9	-14.7

Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=0^\circ$)										
$\gamma \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
2.5	0.4	0.0	-2.8	-6.1	-8.1	-8.6	-8.3	-7.8	-7.2	-6.1
2.0	-1.9	-2.7	-5.0	-7.5	-9.1	-9.6	-9.4	-8.8	-7.9	-6.8
1.5	-2.4	-3.1	-5.2	-7.5	-9.3	-10.2	-10.2	-9.5	-8.5	-7.4
1.0	-0.9	-1.1	-3.6	-6.7	-9.1	-10.5	-10.7	-10.2	-9.1	-8.1
0.5	0.0	0.0	-2.7	-6.3	-9.1	-10.4	-10.8	-10.3	-9.5	-8.6
0	-1.2	-1.5	-3.8	-6.8	-8.8	-9.7	-9.8	-9.5	-9.0	-8.3
-0.5	-3.2	-3.8	-5.3	-7.0	-8.1	-8.5	-8.5	-8.4	-8.1	-7.8
-1.0	-4.3	-5.0	-5.9	-6.6	-7.2	-7.7	-7.9	-7.9	-7.7	-7.6
-1.5	-4.3	-5.0	-5.6	-6.0	-6.6	-7.3	-7.6	-7.7	-7.5	-7.5
-2.0	-3.8	-4.5	-5.0	-5.5	-6.0	-6.6	-6.9	-6.9	-6.8	-6.9
-2.5	-3.2	-3.7	-4.3	-4.7	-5.1	-5.4	-5.5	-5.6	-5.7	-5.9

Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.3 \text{ \AA}$, $\alpha=30^\circ$)									
$\gamma \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	1.6	-0.6	-2.7	-3.9	-4.6	-5.6	-6.6	-6.8	-6.2
2.0	-1.3	-4.8	-7.6	-8.7	-8.9	-9.5	-10.2	-10.0	-8.7
1.5	-4.3	-8.2	-11.6	-13.1	-13.5	-13.9	-14.1	-13.3	-11.4
1.0	-7.0	-10.7	-14.3	-16.6	-17.8	-18.3	-18.0	-16.6	-14.1
0.5	-9.8	-13.3	-16.9	-19.9	-21.7	-22.2	-21.5	-19.4	-16.6
0	-12.3	-15.8	-19.5	-22.6	-24.4	-24.5	-23.3	-21.1	-18.1
-0.5	-13.6	-17.3	-20.9	-23.7	-25.0	-24.7	-23.4	-21.2	-18.3
-1.0	-13.6	-17.3	-20.7	-23.0	-23.8	-23.6	-22.4	-20.4	-17.6
-1.5	-12.5	-16.1	-19.2	-21.1	-21.8	-21.8	-21.0	-19.1	-16.3
-2.0	-10.7	-13.9	-16.6	-18.4	-19.2	-19.4	-18.8	-17.1	-14.4
-2.5	-8.5	-11.1	-13.4	-15.0	-15.9	-16.2	-15.7	-14.3	-12.1

Thymine–Tyrosine Dimers

Stacked			Amino Acid Edge T-shaped														Nucleobase Edge T-shaped													
R_1	TYR'	TYR	R_1	1	2	3	4	5	6	A	B	C	D	E	F	R_1	1	2	3	4	5	6	A	B	C	D	E	F		
3.3	-14.8	-17.0	4.5		-10.6				-8.7							2.0	-13.3		-2.0			-0.3								
3.4	-17.4	-19.5	4.6		-12.0				-10.3							2.1	-17.8		-8.2			-8.7								
3.5	-18.5	-20.5	4.7		-12.6				-11.0	-0.9	-3.8			-7.5	-7.3	2.2	-20.2		-12.0			-14.0					-15.7			
3.6	-18.5	-20.4	4.8		-12.5				-11.1	-3.9	-7.0			-9.3	-8.9	2.3	-21.2		-14.1			-17.1				-8.6	-21.0			
3.7	-17.9	-19.7	4.9		-12.1				-10.9	-5.7	-8.8			-10.1	-9.6	2.4	-21.3		-15.0			-18.6				-12.6	-23.8			
			5.0		-11.5	-6.0		-6.4	-10.4	-6.5	-9.7	-5.7	-6.1	-10.3	-9.8	2.5	-20.7		-15.1			-19.1				-14.9	-25.1			
			5.1	-4.4	-10.7	-7.5		-7.8	-9.7	-6.8	-9.9	-8.2	-8.4	-10.1	-9.5	2.6	-19.7		-14.7			-18.9	-1.9	9.5		-16.0	-25.1			
			5.2	-5.9		-8.3		-8.5		-6.7	-9.8	-9.5	-9.6	-9.7	-9.0	2.7	-18.5		-14.0			-18.2	-5.7	4.0		-16.3	-24.5			
			5.3	-6.5		-8.6	-6.9	-8.7		-6.4	-9.3	-10.0	-10.1	-9.0	-8.4	2.8	-17.2		-13.0			-17.3	-8.0	0.5		-16.0	-23.3			
			5.4	-6.7		-8.5	-7.8	-8.6				-10.0	-10.0			2.9	-15.9		-12.0			-16.2	-9.1	-1.6		-15.4	-21.9			
			5.5	-6.5		-8.1	-8.1	-8.2				-9.6	-9.6			3.0	-14.6	2.1	-11.0	0.6	2.9	-15.1	-4.3	-9.4	-2.9	-4.2	-14.6	-20.4		
			5.6	-6.1		-7.7	-8.0	-7.7				-9.1	-9.1			3.1		1.3		-0.1	-1.7		-4.8	-9.2	-3.5	-5.0	-13.7	-18.9		
			5.7	-5.5			-7.8									3.2		0.8		-0.4	-4.5		-4.9	-8.8	-3.7	-5.3	-12.7	-17.3		
			5.8				-7.3									3.3		0.6		-0.5	-6.2		-4.8	-8.1	-3.6	-5.3	-11.7			
			5.9				-6.9									3.4		0.5		-0.4	-7.1		-4.5	-7.4	-3.4	-5.0				
																3.5		0.5		-0.3	-7.4		-4.2	-6.7	-3.1	-4.6				
																3.6		0.5		-0.2	-7.4		-3.8	-6.0	-2.8	-4.2				
																3.7		0.6		-0.1	-7.1		-3.4			-3.7				
																3.8		0.6		0.1	-6.7		-3.0			-3.3				
																3.9		0.7		0.2	-6.3		-2.7			-2.9				
																4.0		0.8		0.3	-5.8		-2.4			-2.5				

α	Stacked		Amino Acid Edge T-shaped												Nucleobase Edge T-shaped											
	TYR'	TYR	1	2	3	4	5	6	A	B	C	D	E	F	1	2	3	4	5	6	A	B	C	D	E	F
0	-18.5	-20.5	-6.7	-12.6	-8.6	-8.1	-8.7	-11.1	-6.8	-9.9	-10.0	-10.0	-9.7	-9.6	-21.3	0.5	-15.1	-0.5	-7.4	-19.1	-4.9	-9.4	-3.7	-5.3	-16.3	-25.1
30	-17.7	-25.4	-7.7	-11.0	-8.9	-8.2	-8.3	-9.3	-9.0	-9.4	-9.9	-9.8	-8.8	-13.2	-22.6	0.1	-14.3	-0.5	-6.6	-19.5	-6.5	-7.9	-4.1	-4.1	-15.7	-25.2
60	-20.3	-24.6	-8.7	-9.5	-8.5	-8.0	-7.8	-7.9	-11.1	-7.8	-8.8	-8.8	-7.7	-13.8	-23.7	0.3	-16.4	0.0	-6.7	-17.7	-7.7	-6.3	-5.3	-3.1	-14.1	-23.7
90	-21.3	-25.1	-9.4	-8.7	-7.0	-7.2	-7.6	-8.3	-11.8	-6.1	-7.3	-7.8	-7.3	-9.7	-25.3	0.6	-18.5	0.4	-6.8	-16.6	-9.3	-4.5	-7.2	-2.2	-12.4	-22.7
120	-22.4	-25.8	-9.8	-6.8	-6.1	-6.6	-7.2	-7.9	-11.3	-5.0	-6.6	-7.3	-6.9	-7.5	-27.6	0.8	-20.4	0.4	-6.6	-15.5	-11.2	-3.2	-9.4	-2.2	-11.3	-22.2
150	-23.8	-23.7	-10.4	-6.8	-6.7	-6.9	-7.1	-6.8	-11.1	-5.6	-7.8	-8.1	-7.1	-10.3	-27.3	0.7	-19.8	0.0	-6.8	-15.8	-11.9	-2.6	-10.2	-2.3	-12.0	-22.5
180	-24.6	-19.1	-10.9	-8.6	-8.0	-7.7	-7.6	-6.9	-10.4	-7.3	-9.6	-9.4	-7.9	-13.1	-22.1	0.4	-15.2	-0.3	-7.5	-17.3	-10.5	-2.5	-8.9	-2.2	-15.0	-23.2
210	-24.2	-17.4	-10.2	-9.9	-8.5	-8.2	-8.5	-9.3	-7.9	-8.6	-9.8	-9.7	-8.7	-10.9	-20.5	0.5	-14.2	-0.4	-8.0	-18.1	-8.7	-2.8	-7.5	-2.8	-15.9	-22.5
240	-20.6	-20.5	-9.2	-10.5	-8.5	-8.2	-8.9	-10.9	-6.6	-8.6	-8.9	-9.2	-9.0	-7.0	-21.5	1.0	-16.4	-0.3	-8.2	-17.5	-6.8	-4.1	-6.3	-4.1	-14.6	-21.8
270	-21.3	-25.4	-8.0	-9.0	-8.5	-7.7	-8.0	-10.1	-7.2	-7.7	-7.9	-8.3	-8.4	-5.0	-21.2	1.4	-18.3	0.0	-8.6	-17.5	-4.8	-6.4	-5.1	-5.2	-14.0	-21.7
300	-24.5	-23.8	-6.6	-8.0	-8.0	-7.2	-7.4	-9.8	-7.1	-7.2	-7.5	-7.8	-8.1	-4.2	-20.4	1.6	-20.0	0.1	-9.1	-17.5	-3.2	-9.3	-4.2	-6.5	-14.7	-21.8
330	-23.4	-20.0	-5.9	-10.3	-8.1	-7.5	-8.0	-10.9	-6.3	-8.5	-8.6	-8.8	-8.9	-6.1	-20.2	1.2	-19.4	-0.1	-8.8	-18.2	-3.2	-10.7	-3.8	-6.8	-15.8	-23.0

Stacked (TYR R ₁ =3.5 Å, α=120°)							
Y ↓ X →	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-16.2	-18.0	-18.8	-17.8	-16.3	-15.6	-15.9
1.0	-17.9	-20.0	-21.3	-21.1	-19.8	-18.6	-18.0
0.5	-20.3	-22.1	-23.5	-24.3	-23.8	-22.1	-19.9
0	-23.1	-23.9	-24.6	-25.8	-26.1	-24.0	-20.4
-0.5	-24.4	-24.1	-23.8	-24.8	-25.3	-23.3	-19.5
-1.0	-23.7	-23.2	-22.6	-22.9	-22.9	-21.2	-18.0
-1.5	-21.9	-22.2	-22.0	-21.6	-20.5	-18.8	-16.5

Amino Acid Edge T-shaped (θ=F, R ₁ =4.9 Å, α=60°)										
Y ↓ X →	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
2.5	-1.1	-3.4	-3.8	-3.1	-2.6	-3.1	-4.4	-6.0	-7.3	-8.0
2.0	-1.4	-3.8	-4.6	-4.8	-5.2	-6.1	-7.0	-8.1	-9.2	-9.8
1.5	-3.3	-4.3	-4.7	-5.7	-7.2	-8.2	-8.6	-9.2	-10.2	-10.7
1.0	-4.8	-4.2	-4.5	-6.5	-8.8	-9.9	-9.9	-10.2	-10.8	-10.7
0.5	-5.3	-4.3	-5.0	-7.8	-10.6	-11.8	-11.8	-11.7	-11.3	-10.1
0	-5.6	-5.2	-6.6	-9.4	-12.1	-13.5	-13.8	-13.1	-11.2	-8.6
-0.5	-6.5	-6.9	-8.2	-10.2	-12.2	-13.9	-14.5	-13.1	-9.8	-6.3
-1.0	-7.6	-8.4	-9.2	-10.0	-11.4	-13.2	-13.7	-11.6	-7.6	-3.9
-1.5	-8.3	-9.1	-9.5	-9.8	-10.8	-12.1	-12.1	-9.6	-5.6	-2.3
-2.0	-8.3	-9.2	-9.7	-10.0	-10.7	-11.3	-10.5	-7.9	-4.4	-1.8
-2.5	-7.8	-8.9	-9.6	-10.1	-10.5	-10.4	-9.0	-6.5	-3.8	-1.8

Nucleobase Edge T-shaped (θ=1, R ₁ =2.4 Å, α=120°)											
Y ↓ X →	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-6.6	-10.5	-15.0	-18.8	-20.5	-19.2	-15.2	-10.6	-6.9	-4.4	-2.7
2.5	-6.4	-10.9	-16.2	-21.0	-23.4	-22.3	-18.1	-13.2	-9.2	-6.4	-4.5
2.0	-6.0	-10.7	-16.3	-21.5	-24.2	-23.5	-20.1	-16.0	-12.3	-9.3	-7.0
1.5	-6.0	-10.7	-16.3	-21.3	-24.0	-23.8	-21.8	-19.0	-15.9	-12.8	-9.9
1.0	-6.9	-11.6	-17.0	-21.8	-24.6	-25.1	-24.0	-22.1	-19.4	-16.1	-12.7
0.5	-7.8	-12.7	-18.0	-22.7	-25.7	-26.8	-26.3	-24.6	-22.1	-18.8	-15.0
0	-8.1	-13.2	-18.4	-22.8	-26.0	-27.6	-27.5	-26.1	-23.7	-20.4	-16.5
-0.5	-7.4	-12.7	-17.7	-21.7	-24.9	-26.9	-27.4	-26.3	-24.0	-20.8	-16.7
-1.0	-6.0	-11.4	-16.1	-19.9	-22.8	-25.1	-26.1	-25.3	-23.0	-19.6	-15.7
-1.5	-4.1	-9.1	-13.7	-17.2	-20.0	-22.3	-23.5	-23.0	-20.7	-17.4	-13.7
-2.0	-1.8	-6.0	-10.1	-13.5	-16.3	-18.6	-19.8	-19.5	-17.5	-14.5	-11.3
-2.5	0.4	-2.7	-6.2	-9.4	-12.2	-14.4	-15.6	-15.4	-13.8	-11.4	-8.7
-3.0	1.6	-0.4	-3.0	-5.8	-8.4	-10.4	-11.5	-11.4	-10.2	-8.4	-6.4

Thymine–Tryptophan Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped												
R_1	TRP'	TRP	R_1	1	2	3	A	B	C	D	E	F	G	R_1	1	2	3	4	5	6	A	B	C	D	E	F
3.2	-32.4		4.6				-5.5							2.0	-18.0		-12.4			-3.1						
3.3	-33.4	-29.7	4.7				-8.3							2.1	-21.4		-17.0			-11.5						
3.4	-32.9	-31.0	4.8				-9.7			-9.7				2.2	-22.9		-19.5			-16.9						-20.2
3.5		-30.9	4.9				-10.2			-11.4				2.3	-23.2		-20.5			-20.1						-25.3
			5.0				-10.1	-0.4		-12.1				2.4	-22.6		-20.6			-21.8						-28.1
			5.1				-9.7	-4.9		-12.1	-4.9		-8.7	2.5	-21.5		-20.0			-22.3	9.4	13.1		-18.0	-29.2	
			5.2				-9.0	-7.5		-11.8	-7.5		-9.8	2.6	-20.1		-19.1			-22.1	1.6	5.5		-19.2	-29.1	
			5.3					-8.9	-12.2	-11.2	-8.8		-10.1	2.7	-18.6		-17.9			-21.5	-3.4	0.5		-19.5	-28.2	
			5.4					-9.5	-13.5	-10.4	-9.4		-10.0	2.8	-17.0		-16.6			-20.5	-6.4	-2.6		-19.2	-26.9	
			5.5				-9.5	-13.9			-9.5	-5.6	-9.6	2.9	-15.4		-15.2			-19.4	-8.1	-4.4		-18.5	-25.4	
			5.6		-5.6	-6.0		-9.2	-13.7		-9.2	-8.1	-8.9	3.0	-13.8	2.9	-13.9	0.6	-7.1	-18.1	-5.7	-8.8	-5.4	-6.4	-17.7	-23.7
			5.7	-6.7	-7.2	-7.4			-13.2		-8.7	-9.5	-8.2	3.1		2.1		0.0	-10.0	-6.0	-9.0	-5.7	-7.0	-16.6	-22.0	
			5.8	-8.2	-7.9	-8.1			-12.4			-10.0		3.2		1.7		-0.3	-11.6	-5.9	-8.7	-5.6	-7.1	-15.6	-20.3	
			5.9	-8.9	-8.2	-8.2			-11.5			-9.9		3.3		1.5		-0.3	-12.3	-5.5	-8.2	-5.3	-6.9	-14.5		
			6.0	-9.1	-8.1	-8.0						-9.6		3.4		1.5		-0.2	-12.3	-5.1	-7.6	-4.9	-6.4	-13.4		
			6.1	-8.9	-7.8	-7.7						-9.0		3.5		1.5		0.0	-12.0	-4.5	-6.9	-4.4	-5.9	-12.4		
			6.2	-8.6	-7.3	-7.2								3.6		1.6		0.2	-11.4	-4.0			-5.3			
			6.3	-8.1										3.7		1.6		0.4	-10.7	-3.5			-4.7			
														3.8		1.7		0.5	-9.9	-3.0			-4.2			
														3.9		1.8		0.7	-9.1	-2.5			-3.7			
														4.0		1.9		0.9	-8.4	-2.1			-3.2			

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped											
	TRP'	TRP	1	2	3	A	B	C	D	E	F	G	1	2	3	4	5	6	A	B	C	D	E	F
0	-33.4	-31.0	-9.1	-8.2	-8.2	-10.2	-9.5	-13.9	-12.1	-9.5	-10.0	-10.1	-23.2	1.5	-20.6	-0.3	-12.3	-22.3	-6.0	-9.0	-5.7	-7.1	-19.5	-29.2
30	-28.9	-36.0	-8.4	-8.9	-8.8	-11.7	-11.2	-11.6	-11.5	-10.5	-10.2	-11.0	-22.4	0.6	-15.3	-0.5	-11.3	-23.1	-9.2	-7.4	-7.0	-4.3	-21.0	-33.8
60	-25.1	-34.9	-7.0	-9.1	-9.0	-12.0	-12.0	-7.7	-9.7	-10.8	-9.5	-9.7	-24.8	0.0	-15.4	-0.6	-10.5	-23.2	-13.1	-6.6	-9.7	-3.3	-21.8	-36.1
90	-19.7	-31.6	-5.4	-8.2	-9.1	-10.8	-9.7	-7.1	-8.7	-9.3	-8.5	-10.8	-29.7	0.0	-19.3	-0.3	-9.7	-21.5	-16.4	-5.3	-12.7	-2.7	-19.6	-35.0
120	-21.8	-25.6	-4.2	-7.6	-8.7	-10.1	-8.2	-5.7	-7.6	-8.3	-8.1	-10.1	-32.0	0.4	-22.2	0.1	-9.5	-20.0	-16.9	-4.4	-13.3	-2.5	-16.4	-32.0
150	-31.8	-23.3	-4.5	-8.1	-8.8	-12.8	-9.9	-5.7	-8.5	-9.8	-9.2	-10.6	-31.5	0.7	-24.1	0.4	-9.9	-20.3	-14.9	-4.6	-11.9	-3.0	-15.5	-28.8
180	-36.4	-26.0	-5.9	-8.9	-9.0	-15.4	-11.4	-7.4	-10.2	-11.2	-10.6	-10.8	-27.2	0.7	-20.8	0.1	-10.6	-22.1	-11.9	-5.5	-9.3	-3.4	-17.5	-29.9
210	-30.8	-28.9	-7.6	-8.8	-9.2	-13.5	-10.3	-10.3	-11.3	-10.7	-10.3	-11.1	-23.1	0.6	-15.4	-0.6	-11.2	-22.9	-9.9	-6.7	-7.7	-3.9	-20.7	-33.5
240	-28.7	-29.1	-8.6	-8.4	-8.7	-11.5	-8.5	-12.0	-11.1	-9.3	-9.1	-10.4	-21.3	0.8	-15.3	-1.0	-12.1	-23.8	-7.9	-9.3	-6.8	-6.4	-23.5	-35.2
270	-27.0	-30.5	-8.4	-8.1	-7.3	-10.3	-9.8	-10.1	-9.7	-9.7	-7.6	-7.8	-19.0	1.4	-18.8	-0.9	-13.3	-24.5	-4.7	-12.1	-5.5	-9.1	-24.0	-34.2
300	-27.5	-30.5	-8.0	-7.6	-6.3	-7.9	-9.2	-9.2	-8.9	-9.2	-7.0	-6.1	-18.6	2.0	-21.6	-0.5	-14.0	-23.4	-2.6	-12.8	-4.4	-9.8	-22.1	-31.3
330	-33.4	-28.2	-8.6	-7.6	-7.0	-7.8	-9.0	-11.9	-10.5	-9.1	-8.2	-7.8	-21.4	2.1	-23.6	-0.2	-13.5	-22.8	-3.2	-11.5	-4.6	-9.5	-19.9	-28.1

Stacked (TRP' $R_1=3.3 \text{ \AA}$, $\alpha=180^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-19.5	-17.7	-16.6	-18.3	-21.1	-23.0	-23.0
1.0	-18.7	-19.0	-21.1	-24.2	-26.2	-27.2	-27.6
0.5	-21.8	-24.4	-29.1	-32.0	-31.2	-29.7	-29.7
0	-27.3	-30.5	-35.3	-36.4	-33.0	-29.5	-28.5
-0.5	-30.4	-32.6	-35.7	-35.6	-32.1	-28.8	-27.1
-1.0	-30.8	-32.1	-33.2	-32.9	-31.3	-29.5	-27.4
-1.5	-31.1	-32.2	-32.0	-31.5	-31.2	-30.3	-27.4

Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=180^\circ$)										
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
2.5	2.2	1.1	-4.5	-10.7	-14.7	-16.1	-16.0	-15.5	-14.2	-12.1
2.0	-1.9	-3.5	-7.8	-12.6	-16.3	-18.2	-18.5	-17.6	-15.7	-13.0
1.5	-3.9	-5.4	-8.8	-12.9	-16.8	-19.6	-20.5	-19.3	-16.7	-13.7
1.0	-2.7	-3.5	-6.9	-11.5	-16.0	-19.5	-20.9	-19.7	-16.8	-13.8
0.5	-0.7	-0.7	-4.4	-9.6	-14.3	-17.6	-18.9	-18.0	-15.6	-13.0
0	-1.0	-1.0	-4.3	-8.9	-12.6	-14.7	-15.4	-14.9	-13.6	-11.9
-0.5	-3.2	-3.9	-6.5	-9.6	-11.7	-12.4	-12.4	-12.4	-12.2	-11.5
-1.0	-5.0	-6.4	-8.5	-10.5	-11.5	-11.4	-10.9	-11.1	-11.6	-11.5
-1.5	-5.1	-7.0	-9.0	-10.7	-11.3	-10.9	-10.2	-10.3	-10.9	-11.3
-2.0	-4.1	-6.0	-8.0	-9.7	-10.3	-10.0	-9.4	-9.2	-9.6	-10.4
-2.5	-2.5	-4.1	-5.9	-7.4	-8.3	-8.4	-8.2	-8.0	-8.2	-9.5

Nucleobase Edge T-shaped ($\theta=F$, $R_1=2.5 \text{ \AA}$, $\alpha=60^\circ$)													
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
2.5	-17.1	-19.5	-20.7	-20.9	-19.9	-18.1	-15.7	-12.9	-9.7	-6.5	-3.6	-1.4	0.3
2.0	-19.8	-22.1	-23.6	-24.2	-23.5	-21.9	-19.8	-17.4	-14.3	-10.7	-7.2	-4.0	-1.5
1.5	-21.7	-24.1	-25.8	-26.5	-25.8	-24.5	-23.4	-21.9	-19.2	-15.5	-11.4	-7.4	-3.9
1.0	-23.2	-25.8	-27.5	-27.9	-27.4	-27.0	-27.2	-26.4	-23.7	-19.9	-15.5	-10.8	-6.5
0.5	-23.8	-26.6	-28.3	-28.7	-29.1	-30.5	-31.9	-30.9	-27.4	-23.1	-18.7	-13.9	-9.2
0	-23.1	-26.0	-27.8	-28.8	-30.7	-34.0	-36.1	-34.3	-29.9	-25.4	-21.4	-16.7	-11.9
-0.5	-20.9	-23.8	-26.0	-27.8	-30.9	-34.9	-37.0	-35.0	-30.8	-27.2	-23.7	-18.9	-13.8
-1.0	-17.8	-20.7	-23.2	-25.6	-28.7	-32.2	-33.9	-32.7	-30.0	-27.6	-24.4	-19.5	-14.3
-1.5	-14.4	-17.3	-19.9	-22.3	-25.0	-27.6	-29.0	-28.7	-27.4	-25.7	-22.5	-18.0	-13.6
-2.0	-11.1	-13.7	-16.2	-18.4	-20.6	-22.7	-24.2	-24.6	-23.8	-22.1	-19.3	-15.8	-12.9
-2.5	-8.3	-10.4	-12.5	-14.4	-16.3	-18.2	-19.7	-20.4	-19.9	-18.4	-16.2	-14.0	-12.4

Uracil–Histidine Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped												
R_1	HIS'	HIS	R_1	1	2	3	4	5	A	B	C	D	E	R_1	1	2	3	4	5	6	A	B	C	D	E	F
3.3	-15.1	-9.1	3.9			-8.4			18.0	7.6	-4.5			2.0	-22.4		-6.3		6.6	-4.9						
3.4	-16.0	-10.3	4.0	9.3		-11.8			8.1	-0.7	-10.3	2.7	12.3	2.1	-25.5		-10.8		1.1	-9.5						
3.5	-15.9	-10.6	4.1	2.6		-13.6			1.6	-6.1	-13.8	2.7	4.7	2.2	-26.8		-13.3		-2.4	-12.2						-11.5
3.6	-15.3	-10.3	4.2	-1.8		-14.5			-2.5	-9.2	-15.6	-5.3	-0.2	2.3	-26.9		-14.5		-4.4	-13.6					1.7	-17.2
			4.3	-4.6	-4.0	-14.6			-4.9	-10.9	-16.3	-6.9	-3.3	2.4	-26.2		-14.8		-5.5	-14.0					-3.9	-20.4
			4.4	-6.2	-7.0	-14.2	3.6	3.1	-6.2	-11.6	-16.2	-7.6	-5.0	2.5	-25.1		-14.5		-5.9	-13.9					-7.3	-21.8
			4.5	-6.9	-8.8	-13.6	0.8	0.1	-6.7	-11.6	-15.7	-7.8	-5.8	2.6	-23.6		-13.9		-5.9	-13.3	-4.5	10.0	1.2		-9.3	-22.1
			4.6	-7.1	-9.7	-12.8	-1.0	-1.8	-6.8	-11.3	-14.9	-7.5	-6.0	2.7	-22.1		-13.0		-5.6	-12.6	-8.7	5.1	-3.4		-10.2	-21.7
			4.7	-7.0	-10.0	-11.9	-2.1	-2.9	-6.5	-10.7	-14.0	-7.1	-5.9	2.8	-20.5		-12.0		-5.1	-11.8	-11.2	2.0	-6.1		-10.4	-20.7
			4.8	-6.7	-10.0	-11.0	-2.6	-3.4	-6.0	-10.0	-13.1	-6.5	-5.5	2.9	-18.9		-11.0		-4.6	-10.9	-12.4	0.1	-7.7		-10.2	-19.5
			4.9	-6.2	-9.7	-10.1	-2.8	-3.6	-5.5	-9.2	-12.1	-5.9	-5.1	3.0	-17.5		-10.0		-4.1	-10.0	-12.9	-1.0	-8.4	4.0	-9.7	-18.2
			5.0	-5.7	-9.3		-2.8	-3.6				-5.3	-4.6	3.1						-12.8	-1.5	-8.5	3.1	-9.1	-16.9	
			5.1		-8.8		-2.7	-3.4						3.2						-12.4	-1.6	-8.3	2.5	-8.3	-15.5	
			5.2		-8.3		-2.5	-3.2						3.3						-11.8	-1.5	-7.9	2.2	-7.6		
			5.3		-7.7		-2.2	-2.9						3.4						-11.1	-1.4	-7.4	2.1			
			5.4				-1.9	-2.5						3.5						-10.4	-1.1	-6.9	2.0			
														3.6						-9.6	-0.9	-6.3	2.0			
														3.7									2.1			
														3.8									2.1			
														3.9									2.2			
														4.0									2.2			
														...												
														5.0		0.2		1.1								
														5.1		0.2		1.1								
														5.2		0.2		1.0								
														5.3		0.2		1.0								
														5.4		0.2		1.0								
														5.5		0.2		1.0								
														5.6		0.2		0.9								
														5.7		0.2		0.9								
														5.8		0.1		0.9								
														5.9		0.1		0.8								
														6.0		0.1		0.8								

α	Stacked		Amino Acid Edge T-shaped										Nucleobase Edge T-shaped											
	HIS'	HIS	1	2	3	4	5	A	B	C	D	E	1	2	3	4	5	6	A	B	C	D	E	F
0	-16.0	-10.6	-7.1	-10.0	-14.6	-2.8	-3.6	-6.8	-11.6	-16.3	-7.8	-6.0	-26.9		-14.8		-5.9	-14.0	-12.9	-1.6	-8.5	2.0	-10.4	-22.1
30	-18.9	-8.7	-7.6	-7.4	-15.2	-4.7	-5.9	-8.4	-10.8	-14.1	-9.2	-8.3	-21.5		-16.8		-10.9	-14.8	-5.1	-6.1	-4.0	-2.4	-11.5	-20.6
60	-21.3	-10.9	-7.2	-4.3	-14.5	-6.7	-7.2	-9.3	-9.6	-10.4	-10.2	-9.8	-17.3		-18.5		-15.0	-15.5	1.1	-9.7	-0.6	-6.4	-13.2	-19.3
90	-24.4	-15.6	-5.9	-2.2	-12.5	-7.8	-6.9	-8.3	-7.1	-6.8	-10.3	-9.3	-13.8		-19.0		-18.3	-16.6	5.2	-11.6	1.6	-9.2	-15.5	-18.9
120	-24.9	-20.0	-4.8	-0.7	-10.9	-8.5	-6.5	-7.3	-3.8	-4.2	-11.1	-8.8	-9.6		-16.2		-20.0	-18.1	7.5	-12.1	3.3	-10.6	-17.9	-20.1
150	-20.7	-22.6	-5.1	0.0	-11.4	-8.9	-7.2	-8.5	-3.7	-4.7	-12.7	-10.0	-8.2		-12.8		-19.3	-19.0	6.6	-10.9	3.2	-9.9	-18.7	-21.3
180	-14.6	-23.0	-6.3	-1.2	-13.3	-8.3	-8.0	-10.3	-5.7	-7.0	-13.3	-11.1	-13.4		-13.7		-16.3	-17.6	0.7	-7.7	-0.7	-6.8	-16.3	-19.9
210	-10.4	-21.3	-7.4	-4.5	-14.8	-6.4	-7.5	-10.5	-7.9	-9.8	-11.9	-10.1	-20.9		-16.8		-12.3	-15.2	-7.0	-4.1	-6.3	-2.8	-12.6	-18.1
240	-10.4	-18.6	-7.5	-7.5	-15.0	-4.5	-5.7	-10.0	-9.7	-11.6	-9.8	-8.1	-26.5		-19.4		-8.9	-13.1	-13.4	-1.5	-10.8	0.7	-9.6	-17.7
270	-11.3	-16.1	-6.6	-8.7	-13.7	-3.4	-3.4	-7.5	-9.6	-11.6	-7.9	-5.3	-30.5		-20.5		-5.9	-11.9	-17.5	0.3	-13.2	3.3	-8.0	-19.0
300	-10.9	-15.2	-5.8	-9.5	-12.6	-2.7	-1.7	-4.5	-9.2	-12.7	-6.5	-3.2	-32.6		-18.1		-3.1	-12.0	-19.9	1.7	-13.9	5.2	-8.2	-21.4
330	-12.5	-14.1	-6.1	-10.4	-13.2	-2.3	-1.8	-4.7	-10.6	-15.1	-6.7	-3.8	-31.3		-14.7		-2.6	-13.1	-19.0	1.6	-12.6	5.0	-9.4	-22.8

Stacked (HIS' $R_1=3.4 \text{ \AA}$, $\alpha=120^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-18.3	-18.9	-19.8	-20.9	-21.5	-20.8	-18.9
1.0	-21.6	-22.0	-22.2	-23.3	-24.5	-24.0	-21.2
0.5	-24.7	-24.7	-24.1	-25.1	-26.4	-25.5	-22.0
0	-25.8	-25.6	-24.6	-24.9	-25.6	-24.2	-20.5
-0.5	-24.3	-24.5	-24.0	-23.7	-23.1	-21.2	-18.0
-1.0	-21.7	-23.1	-23.7	-23.0	-21.0	-18.6	-16.0
-1.5	-19.7	-22.0	-23.4	-22.5	-19.6	-16.8	-14.5

Amino Acid Edge T-shaped ($\theta=C$, $R_1=4.3 \text{ \AA}$, $\alpha=0^\circ$)									
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
3.5	-3.9	-3.4	-2.8	-2.4	-2.5	-2.9	-3.4	-3.8	-4.0
3.0	-7.1	-7.4	-7.7	-7.7	-7.7	-7.6	-7.4	-7.1	-6.5
2.5	-9.7	-11.0	-12.2	-13.0	-12.9	-12.1	-10.9	-9.7	-8.4
2.0	-11.0	-12.9	-15.0	-16.4	-16.2	-14.8	-12.9	-11.0	-9.2
1.5	-11.5	-13.5	-16.0	-17.7	-17.7	-16.1	-13.8	-11.4	-9.0
1.0	-12.3	-14.2	-16.5	-18.2	-18.4	-17.1	-14.6	-11.3	-8.0
0.5	-14.0	-15.5	-17.0	-18.0	-18.2	-17.2	-14.4	-10.3	-6.1
0	-15.5	-16.4	-16.6	-16.5	-16.3	-15.2	-12.3	-7.9	-3.5
-0.5	-16.0	-16.3	-15.8	-15.0	-14.1	-12.5	-9.4	-5.3	-1.5
-1.0	-15.7	-15.9	-15.8	-15.1	-13.7	-11.3	-8.0	-4.4	-1.3
-1.5	-15.1	-15.7	-16.1	-15.8	-14.1	-11.2	-7.9	-4.9	-2.4
-2.0	-14.1	-14.8	-15.3	-15.0	-13.3	-10.6	-7.7	-5.3	-3.6
-2.5	-12.1	-12.9	-13.1	-12.5	-11.2	-9.2	-7.2	-5.7	-4.8

Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.3 \text{ \AA}$, $\alpha=300^\circ$)									
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.0	-12.3	-16.6	-21.3	-25.7	-29.3	-31.0	-29.9	-25.2	-17.8
1.5	-14.3	-19.2	-24.3	-28.9	-32.4	-34.2	-33.2	-28.7	-20.9
1.0	-15.7	-21.2	-26.6	-30.9	-33.6	-34.7	-33.5	-29.0	-21.4
0.5	-16.2	-22.1	-27.5	-31.5	-33.5	-33.6	-31.6	-26.9	-19.7
0	-15.2	-21.4	-26.8	-30.7	-32.6	-32.3	-29.7	-24.7	-18.0
-0.5	-13.1	-19.2	-24.8	-28.9	-31.2	-31.1	-28.3	-23.3	-17.2
-1.0	-10.7	-16.4	-21.7	-25.9	-28.4	-28.6	-26.2	-21.8	-16.6
-1.5	-8.3	-13.3	-18.0	-21.6	-23.8	-24.2	-22.5	-19.2	-15.2
-2.0	-6.2	-10.2	-13.9	-16.7	-18.2	-18.5	-17.5	-15.4	-12.7

Uracil–Phenylalanine Dimers

Stacked		Amino Acid Edge T-shaped				Nucleobase Edge T-shaped											
R_1	PHE	R_1	1	A	R_1	1	2	3	4	5	6	A	B	C	D	E	F
3.3	-16.4	4.4		5.4	2.0	-19.6		-11.3		-3.9	-10.5						
3.4	-18.2	4.5		-0.7	2.1	-22.8		-15.5		-8.5	-14.4						
3.5	-18.7	4.6		-4.5	2.2	-24.4		-17.9		-11.3	-16.7						-7.9
3.6	-18.4	4.7	-3.2	-6.7	2.3	-24.7		-18.9		-12.8	-17.7					2.0	-15.1
		4.8	-5.1	-7.9	2.4	-24.2		-19.0		-13.4	-18.0					-5.1	-19.5
		4.9	-6.2	-8.3	2.5	-23.2		-18.6		-13.4	-17.7					-9.6	-21.8
		5.0	-6.7	-8.3	2.6	-23.2		-17.7		-13.0	-17.0	4.9	7.5	7.1		-12.3	-22.8
		5.1	-6.8	-8.0	2.7	-20.5		-16.6		-12.4	-16.1	-0.4	1.8	1.6		-13.7	-22.7
		5.2	-6.7	-7.6	2.8	-19.0		-15.4		-11.6	-15.1	-3.8	-1.7	-1.9		-14.2	-22.1
		5.3	-6.4	-7.0	2.9	-17.4		-14.1		-10.8	-14.0	-5.7	-3.9	-4.0		-14.1	-21.0
		5.4	-6.0	-6.4	3.0	-16.0		-12.9		-10.0	-13.0	-6.8	-5.1	-5.1	-1.6	-13.7	-19.8
		5.5	-5.5		3.1							-7.1	-5.6	-5.6	-2.6	-13.0	-18.4
		5.6	-5.1		3.2							-7.1	-5.7	-5.7	-3.1	-12.2	-17.0
					3.3							-6.8	-5.6	-5.5	-3.3	-11.3	
					3.4							-6.3	-5.2	-5.2	-3.2		
					3.5							-5.8	-4.8	-4.7	-3.0		
					3.6							-5.3	-4.4	-4.3	-2.8		
					3.7										-2.5		
					3.8										-2.2		
					3.9										-2.0		
					4.0										-1.7		
					...												
					5.0		1.1		1.2								
					5.1		1.0		1.2								
					5.2		1.0		1.2								
					5.3		1.0		1.1								
					5.4		0.9		1.1								
					5.5		0.9		1.1								
					5.6		0.9		1.0								
					5.7		0.8		1.0								
					5.8		0.8		1.0								
					5.9		0.8		0.9								
					6.0		0.7		0.9								

α	Stacked	Amino Acid Edge T-shaped				Nucleobase Edge T-shaped									
	PHE	1	A	1	2	3	4	5	6	A	B	C	D	E	F
0	-18.7	-6.8	-8.3	-24.7		-19.0		-13.4	-18.0	-7.1	-5.7	-5.7	-3.3	-14.2	-22.8
30	-18.7	-7.4	-8.8	-24.7		-19.1		-13.4	-18.0	-7.2	-5.8	-5.7	-3.3	-14.3	-22.8
60		-7.2	-8.4												
90		-6.3	-7.0												
120		-5.6	-6.0												
150		-5.9	-7.0												

Stacked ($R_1=3.5 \text{ \AA}$, $\alpha=0^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-12.3	-13.1	-14.0	-14.8	-15.1	-14.8	-13.9
1.0	-15.3	-15.6	-16.1	-17.2	-18.2	-18.0	-16.3
0.5	-18.4	-17.9	-17.6	-18.7	-20.1	-19.8	-17.4
0	-19.8	-18.9	-18.0	-18.7	-19.8	-19.3	-16.8
-0.5	-19.5	-18.9	-18.1	-18.3	-18.5	-17.6	-15.4
-1.0	-18.6	-19.1	-19.1	-18.7	-17.7	-16.1	-14.2
-1.5	-17.9	-19.4	-20.0	-19.2	-17.2	-15.0	-13.1

Amino Acid Edge T-shaped ($\theta=A$, $R_1=4.9 \text{ \AA}$, $\alpha=30^\circ$)										
$Y \downarrow$ $X \rightarrow$	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-4.4	-5.2	-5.8	-6.6	-7.4	-7.8	-7.6	-6.9	-6.0	-4.9
2.0	-4.3	-5.2	-6.3	-7.3	-8.1	-8.4	-8.2	-7.7	-7.0	-6.0
1.5	-4.2	-5.2	-6.7	-8.0	-8.7	-8.7	-8.6	-8.6	-8.1	-7.1
1.0	-4.1	-5.4	-7.2	-8.6	-9.1	-9.0	-9.1	-9.4	-9.1	-7.9
0.5	-4.2	-5.7	-7.4	-8.6	-9.0	-9.0	-9.4	-9.7	-9.4	-8.3
0	-4.4	-5.7	-7.0	-7.8	-8.3	-8.8	-9.3	-9.4	-9.1	-8.2
-0.5	-4.3	-5.3	-6.0	-6.6	-7.7	-8.7	-9.2	-9.2	-8.8	-8.2
-1.0	-4.1	-4.7	-5.2	-6.0	-7.5	-8.9	-9.3	-9.1	-8.7	-8.2
-1.5	-3.6	-4.2	-4.7	-5.8	-7.3	-8.5	-8.8	-8.6	-8.2	-7.8
-2.0	-3.1	-3.6	-4.3	-5.2	-6.3	-7.1	-7.4	-7.3	-7.1	-6.7
-2.5	-2.5	-3.0	-3.7	-4.3	-4.9	-5.4	-5.7	-5.9	-5.9	-5.7

Nucleobase Edge T-shaped ($\theta=1$, $R_1=2.3 \text{ \AA}$, $\alpha=30^\circ$)									
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	1.4	-0.9	-3.0	-4.2	-4.9	-5.9	-6.8	-7.0	-6.3
2.0	-1.6	-5.1	-8.0	-9.1	-9.3	-9.9	-10.5	-10.2	-8.9
1.5	-4.6	-8.6	-12.0	-13.5	-13.9	-14.3	-14.4	-13.6	-11.6
1.0	-7.3	-11.1	-14.7	-17.1	-18.2	-18.7	-18.4	-16.9	-14.4
0.5	-10.1	-13.7	-17.3	-20.3	-22.1	-22.6	-21.8	-19.8	-16.8
0	-12.6	-16.2	-19.9	-23.0	-24.7	-24.9	-23.7	-21.4	-18.3
-0.5	-13.9	-17.6	-21.3	-24.1	-25.3	-25.1	-23.7	-21.5	-18.5
-1.0	-13.8	-17.6	-21.0	-23.3	-24.2	-23.9	-22.7	-20.7	-17.7
-1.5	-12.7	-16.3	-19.4	-21.4	-22.1	-22.1	-21.3	-19.3	-16.4
-2.0	-10.8	-14.0	-16.8	-18.6	-19.4	-19.6	-19.0	-17.2	-14.5
-2.5	-8.5	-11.2	-13.5	-15.1	-16.0	-16.3	-15.8	-14.3	-12.1

Uracil–Tyrosine Dimers

Stacked			Amino Acid Edge T-shaped														Nucleobase Edge T-shaped													
R_1	TYR'	TYR	R_1	1	2	3	4	5	6	A	B	C	D	E	F	R_1	1	2	3	4	5	6	A	B	C	D	E	F		
3.3	-14.8	-14.4	4.2		6.7											2.0	-13.7		-2.1		1.8	-8.4								
3.4	-17.1	-16.7	4.3		-0.7				0.9							2.1	-18.2		-8.3		-4.3	-13.3								
3.5	-18.0	-17.7	4.4		-5.5				-3.9						9.1	2.2	-20.6		-12.1		-8.3	-16.1					-15.6			
3.6	-17.9	-17.7	4.5		-8.5				-6.9						1.2	2.3	-21.6		-14.2		-10.6	-17.6				-6.6	-20.9			
			4.6		-10.2				-8.7	6.3	4.3				-3.8	2.4	-21.6		-15.1		-11.8	-18.1				-11.6	-23.8			
			4.7		-10.9				-9.5	1.3	-1.4			-5.1	-6.8	2.5	-21.0		-15.2		-12.2	-18.0				-14.5	-25.0			
			4.8		-11.0	2.2		2.1	-9.8	-1.9	-5.0	8.1		-7.2	-8.5	2.6	-20.0		-14.8		-12.2	-17.4	7.2	-2.0	9.6	-16.0	-25.1			
			4.9	5.1	-10.8	-2.2		-2.2	-9.7	-3.8	-7.2	1.0	0.8	-8.3	-9.2	2.7	-18.8		-14.1		-11.7	-16.5	1.9	-5.9	4.2	-16.5	-24.5			
			5.0	0.3	-10.3	-4.9	3.5	-4.9	-9.3	-4.8	-8.3	-3.6	-3.6	-8.7	-9.3	2.8	-17.5		-13.2		-11.1	-15.5	-1.5	-8.1	0.7	-16.3	-23.4			
			5.1	-2.6	-9.6	-6.5	-1.0	-6.5	-8.8	-5.2	-8.7	-6.4	-6.3	-8.7	-9.1	2.9	-16.2		-12.2		-10.4	-14.5	-3.5	-9.2	-1.5	-15.8	-22.0			
			5.2	-4.3	-8.9	-7.4	-4.0	-7.3	-8.2	-5.2	-8.7	-7.9	-7.8	-8.4	-8.6	3.0	-14.8		-11.1		-9.6	-13.4	-4.6	-9.5	-2.8	-6.4	-14.9	-20.5		
			5.3	-5.2		-7.7	-5.7	-7.6	-7.6	-5.0	-8.5	-8.6	-8.4	-8.0	-8.1	3.1						-5.1	-9.4	-3.4	-6.6	-14.0	-18.9			
			5.4	-5.4		-7.7	-6.7	-7.6		-4.6	-8.0	-8.7	-8.6	-7.4	-7.4	3.2						-5.2	-8.9	-3.6	-6.5	-13.0	-17.4			
			5.5	-5.3		-7.4	-7.1	-7.3		-4.2	-7.5	-8.5	-8.4	-6.9		3.3						-5.1	-8.3	-3.6	-6.2	-12.0				
			5.6	-5.0		-7.0	-7.1	-6.9		-3.8	-6.9	-8.1	-8.0	-6.3		3.4						-4.8	-7.6	-3.4	-5.7					
			5.7	-4.6		-6.6	-6.9	-6.5				-7.6	-7.4	-5.7		3.5						-4.4	-6.9	-3.1	-5.2					
			5.8	-4.1		-6.1	-6.6	-6.0				-7.0	-6.9			3.6						-4.0	-6.1	-2.8	-4.6					
			5.9	-3.7			-6.2						-6.3			3.7									-4.1					
			6.0				-5.7									3.8									-3.6					
																3.9									-3.2					
																...														
																5.0		0.8		1.1										
																5.1		0.8		1.1										
																5.2		0.8		1.0										
																5.3		0.8		1.0										
																5.4		0.8		1.0										
																5.5		0.8		1.0										
																5.6		0.8		0.9										
																5.7		0.7		0.9										
																5.8		0.7		0.9										
																5.9		0.7		0.9										
																6.0		0.7		0.8										

α	<u>Stacked</u>		<u>Amino Acid Edge T-shaped</u>												<u>Nucleobase Edge T-shaped</u>											
	TYR'	TYR	1	2	3	4	5	6	A	B	C	D	E	F	1	2	3	4	5	6	A	B	C	D	E	F
0	-18.0	-17.7	-5.4	-11.0	-7.7	-7.1	-7.6	-9.8	-5.2	-8.7	-8.7	-8.6	-8.7	-9.3	-21.6		-15.2		-12.2	-18.1	-5.2	-9.5	-3.6	-6.6	-16.5	-25.1
30	-16.6	-22.5	-7.2	-11.1	-8.3	-7.6	-7.7	-8.2	-6.3	-8.6	-9.2	-8.8	-8.0	-12.6	-23.0		-14.5		-10.7	-17.9	-6.9	-8.2	-4.1	-5.0	-15.5	-25.2
60	-18.0	-23.9	-8.6	-10.1	-7.7	-7.2	-7.2	-6.8	-8.1	-7.3	-8.7	-8.2	-6.8	-13.1	-24.0		-16.7		-11.1	-17.0	-8.0	-6.5	-5.4	-3.3	-13.8	-23.8
90	-19.3	-24.0	-8.9	-8.2	-5.8	-6.1	-6.4	-6.8	-8.8	-5.1	-7.0	-6.9	-5.8	-9.3	-25.6		-18.7		-11.1	-16.0	-9.6	-4.7	-7.4	-1.5	-12.5	-22.8
120	-22.5	-25.2	-9.1	-5.3	-4.5	-5.3	-5.8	-6.6	-8.6	-3.4	-5.7	-6.0	-5.4	-6.7	-27.8		-20.6		-10.6	-15.0	-11.5	-3.4	-9.5	-0.3	-12.1	-22.2
150	-23.8	-21.9	-9.9	-5.3	-5.2	-5.6	-5.9	-5.9	-8.8	-4.0	-6.5	-6.7	-5.9	-8.7	-27.7		-20.0		-10.7	-15.1	-12.2	-2.8	-10.2	-0.5	-13.4	-22.5
180	-24.3	-17.2	-10.8	-7.4	-6.8	-6.6	-6.6	-5.8	-8.0	-5.8	-8.1	-8.0	-6.8	-11.7	-22.5		-15.3		-12.0	-16.9	-10.8	-2.7	-8.8	-1.8	-16.0	-23.2
210	-22.1	-14.6	-10.7	-9.9	-7.8	-7.4	-7.7	-7.4	-6.2	-7.5	-8.7	-8.8	-7.9	-10.8	-21.0		-14.4		-13.1	-17.7	-9.0	-3.0	-7.4	-2.9	-16.6	-22.7
240	-17.3	-17.1	-9.8	-10.7	-7.8	-7.4	-7.9	-8.5	-5.4	-7.9	-8.5	-8.8	-8.7	-7.8	-21.8		-16.4		-13.7	-17.3	-7.2	-4.2	-6.2	-3.6	-15.6	-22.0
270	-17.9	-21.6	-7.7	-8.0	-7.2	-6.6	-6.7	-8.1	-5.8	-6.9	-7.4	-7.6	-7.8	-5.6	-21.6		-18.3		-14.7	-17.2	-5.1	-6.5	-5.0	-5.1	-15.0	-21.9
300	-21.8	-20.9	-5.0	-6.3	-6.6	-5.9	-5.9	-8.4	-5.8	-6.2	-6.7	-6.5	-7.0	-4.8	-20.7		-20.0		-15.9	-17.2	-3.5	-9.4	-4.1	-7.4	-15.1	-22.0
330	-22.4	-17.5	-4.3	-8.1	-6.9	-6.2	-6.5	-9.5	-5.4	-7.4	-7.5	-7.4	-8.0	-6.4	-20.5		-19.5		-15.5	-17.5	-3.4	-10.8	-3.6	-8.4	-15.9	-23.2

Stacked (TYR' R ₁ =3.5 Å, α=180°)							
Y ↓ X →	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-15.3	-16.3	-17.3	-18.2	-18.5	-17.9	-16.3
1.0	-17.9	-18.4	-18.9	-19.9	-20.7	-20.4	-18.3
0.5	-20.5	-20.7	-20.9	-22.2	-23.5	-23.1	-20.5
0	-22.8	-22.8	-22.9	-24.3	-25.7	-25.1	-21.8
-0.5	-23.4	-23.4	-23.3	-24.4	-25.5	-24.6	-21.4
-1.0	-22.0	-22.6	-22.7	-23.2	-23.4	-22.1	-19.4
-1.5	-20.3	-21.8	-22.5	-22.3	-21.2	-19.5	-17.4

Amino Acid Edge T-shaped (θ=F, R ₁ =5.0 Å, α=60°)										
Y ↓ X →	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-2.3	-2.2	-2.5	-3.3	-4.3	-5.5	-6.7	-7.6	-7.6	-6.9
2.0	-2.8	-3.7	-5.1	-6.2	-6.9	-7.5	-8.4	-9.1	-8.9	-7.8
1.5	-2.7	-4.6	-7.0	-8.3	-8.6	-8.8	-9.4	-9.9	-9.3	-7.9
1.0	-2.6	-5.3	-8.3	-9.9	-10.2	-10.2	-10.4	-10.1	-9.0	-7.2
0.5	-3.4	-6.4	-9.6	-11.4	-12.0	-11.9	-11.2	-9.8	-7.9	-5.9
0	-5.3	-7.8	-10.6	-12.5	-13.4	-13.1	-11.4	-8.7	-6.2	-4.3
-0.5	-7.2	-8.8	-10.7	-12.6	-13.7	-12.9	-10.2	-6.8	-4.2	-2.6
-1.0	-8.3	-9.1	-10.3	-11.9	-12.7	-11.5	-8.3	-4.8	-2.5	-1.4
-1.5	-8.8	-9.2	-10.0	-11.1	-11.3	-9.7	-6.6	-3.5	-1.5	-0.7
-2.0	-8.8	-9.3	-9.9	-10.4	-9.9	-8.0	-5.3	-2.8	-1.3	-0.7
-2.5	-8.5	-9.2	-9.6	-9.5	-8.5	-6.7	-4.4	-2.5	-1.3	-0.8

Nucleobase Edge T-shaped (θ=1, R ₁ =2.4 Å, α=120°)											
Y ↓ X →	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5
3.0	-6.6	-10.5	-15.0	-18.9	-20.7	-19.4	-15.5	-10.7	-6.8	-4.1	-2.4
2.5	-6.4	-10.8	-16.2	-21.0	-23.6	-22.5	-18.4	-13.3	-9.1	-6.2	-4.2
2.0	-6.0	-10.7	-16.3	-21.5	-24.3	-23.7	-20.4	-16.1	-12.2	-9.1	-6.7
1.5	-6.2	-10.8	-16.4	-21.4	-24.2	-24.1	-22.0	-19.1	-15.8	-12.6	-9.6
1.0	-7.1	-11.8	-17.2	-22.0	-24.8	-25.3	-24.2	-22.2	-19.4	-16.0	-12.5
0.5	-8.1	-13.0	-18.3	-23.0	-26.0	-27.1	-26.5	-24.8	-22.2	-18.8	-14.9
0	-8.4	-13.6	-18.7	-23.2	-26.3	-27.8	-27.7	-26.3	-23.8	-20.5	-16.4
-0.5	-7.7	-13.1	-18.1	-22.1	-25.2	-27.2	-27.7	-26.6	-24.2	-20.8	-16.7
-1.0	-6.4	-11.8	-16.6	-20.3	-23.2	-25.5	-26.4	-25.6	-23.2	-19.7	-15.7
-1.5	-4.5	-9.5	-14.1	-17.6	-20.4	-22.7	-23.9	-23.2	-20.9	-17.5	-13.7
-2.0	-2.1	-6.4	-10.5	-13.9	-16.7	-19.0	-20.2	-19.8	-17.7	-14.6	-11.3
-2.5	0.1	-3.0	-6.5	-9.7	-12.5	-14.7	-15.9	-15.7	-14.0	-11.4	-8.7
-3.0	1.4	-0.6	-3.3	-6.1	-8.7	-10.7	-11.7	-11.6	-10.3	-8.4	-6.4

Uracil–Tryptophan Dimers

Stacked			Amino Acid Edge T-shaped											Nucleobase Edge T-shaped													
R_1	TRP'	TRP	R_1	1	2	3	A	B	C	D	E	F	G	R_1	1	2	3	4	5	6	A	B	C	D	E	F	
3.2	-28.7	-21.7	4.4				11.5							2.0	-21.2		-11.9		-4.6	-11.7							
3.3	-30.1	-24.9	4.5				3.3							2.1	-24.6		-16.6		-10.4	-16.9							
3.4	-30.0	-26.2	4.6				-1.9			1.8				2.2	-26.1		-19.2		-14.0	-19.9						-20.7	
3.5	-28.8	-26.1	4.7				-5.2			-3.8				2.3	-26.3		-20.3		-16.0	-21.5					-13.0	-25.9	
3.6	-27.1	-25.3	4.8				-6.9	15.3		-7.3				2.4	-25.8		-20.4		-16.9	-22.0						-17.5	-28.6
			4.9				-7.8	5.8		-9.2	5.6		0.0	2.5	-24.7		-19.9		-17.0	-21.8						-20.0	-29.6
			5.0				-8.0	-0.5		-10.2	-0.4		-4.2	2.6	-23.3		-19.0		-16.7	-21.1	4.2	1.7	5.7		-21.1	-29.5	
			5.1				-7.8	-4.4	-2.0	-10.4	-4.3		-6.6	2.7	-21.7		-17.8		-16.0	-20.1	-0.7	-3.3	0.7		-21.2	-28.6	
			5.2				-7.3	-6.7	-7.1	-10.3	-6.6		-8.0	2.8	-20.1		-16.5		-15.1	-19.0	-3.8	-6.4	-2.5		-20.8	-27.3	
			5.3				-6.8	-8.0	-10.2	-9.8	-7.9	9.1	-8.5	2.9	-18.5		-15.2		-14.1	-17.8	-5.5	-8.1	-4.3		-20.0	-25.7	
			5.4		2.6	2.1	-6.1	-8.4	-11.8	-9.3	-8.4	1.7	-8.5	3.0	-16.9		-13.9		-13.1	-16.6	-6.3	-8.9	-5.2	-6.3	-18.9	-24.0	
			5.5	1.2	-1.6	-1.9		-8.4	-12.4	-8.6	-8.5	-3.0	-8.2	3.1							-6.6	-9.0	-5.6	-6.8	-17.7	-22.3	
			5.6	-2.9	-4.3	-4.5		-8.2	-12.4	-7.9	-8.3	-5.9	-7.7	3.2							-6.4	-8.8	-5.5	-6.9	-16.5	-20.6	
			5.7	-5.6	-5.9	-6.0		-7.7	-12.0		-7.9	-7.5	-7.1	3.3							-6.1	-8.3	-5.2	-6.7	-15.3		
			5.8	-7.1	-6.8	-6.7		-7.1	-11.3		-7.4	-8.2	-6.4	3.4							-5.6	-7.7	-4.8	-6.3			
			5.9	-7.9	-7.1	-7.0			-10.6		-6.8	-8.4	-5.8	3.5							-5.0	-7.0	-4.3	-5.8			
			6.0	-8.2	-7.1	-6.9			-9.8			-8.2		3.6							-4.4	-6.3	-3.8	-5.3			
			6.1	-8.2	-6.9	-6.7			-9.0			-7.8		3.7										-4.8			
			6.2	-7.9	-6.5	-6.3						-7.3		3.8										-4.3			
			6.3	-7.5	-6.1	-5.8						-6.7		3.9										-3.8			
			6.4	-7.1	-5.6	-5.3								...													
			6.5	-6.6										5.0		2.9		1.8									
														5.1		2.8		1.7									
														5.2		2.8		1.7									
														5.3		2.8		1.6									
														5.4		2.7		1.6									
														5.5		2.7		1.5									
														5.6		2.6		1.5									
														5.7		2.6		1.5									
														5.8		2.5		1.4									
														5.9		2.5		1.4									
														6.0		2.4		1.3									

α	<u>Stacked</u>		1	2	3	<u>Amino Acid Edge T-shaped</u>							1	2	3	4	5	6	<u>Nucleobase Edge T-shaped</u>						
	TRP'	TRP				A	B	C	D	E	F	G													
0	-30.1	-26.2	-8.2	-7.1	-7.0	-8.0	-8.4	-12.4	-10.4	-8.5	-8.4	-8.5	-26.3		-20.4		-17.0	-22.0	-6.6	-9.0	-5.6	-6.9	-21.2	-29.6	
30	-26.9	-30.4	-8.1	-8.1	-8.0	-10.3	-10.6	-10.9	-10.3	-10.0	-9.1	-9.9	-25.4		-15.3		-14.8	-23.0	-9.8	-7.6	-7.0	-4.9	-23.1	-34.1	
60	-24.7	-31.7	-6.6	-8.1	-8.2	-11.4	-11.1	-7.5	-8.9	-10.3	-9.0	-9.6	-27.8		-15.9		-13.1	-22.4	-13.7	-6.9	-9.9	-3.5	-23.4	-36.0	
90	-16.6	-30.9	-4.4	-6.9	-7.7	-9.6	-8.3	-4.6	-7.0	-8.5	-8.0	-8.5	-32.8		-19.8		-11.5	-20.6	-16.9	-5.7	-12.9	-1.6	-21.2	-34.8	
120	-18.5	-25.1	-2.7	-6.0	-7.3	-8.5	-6.0	-3.2	-5.8	-7.0	-7.1	-8.3	-35.0		-22.7		-11.0	-19.2	-17.2	-4.8	-13.4	-0.4	-18.2	-31.8	
150	-27.9	-20.8	-2.9	-6.6	-7.5	-10.8	-7.3	-3.7	-6.9	-8.2	-8.0	-9.2	-34.6		-24.4		-12.2	-19.0	-15.2	-5.0	-11.9	-1.1	-16.7	-28.8	
180	-30.6	-23.6	-4.7	-7.8	-8.1	-13.2	-9.4	-6.1	-8.6	-9.8	-9.2	-10.3	-30.4		-20.8		-13.6	-20.7	-12.2	-5.9	-9.3	-2.7	-18.8	-30.2	
210	-28.0	-24.3	-6.8	-8.1	-8.6	-12.7	-9.4	-10.2	-10.0	-9.7	-9.4	-11.3	-26.4		-15.4		-14.4	-22.8	-10.3	-7.1	-7.5	-4.5	-22.9	-33.8	
240	-26.7	-25.7	-7.7	-7.7	-7.9	-11.6	-8.3	-12.3	-10.1	-8.6	-8.8	-10.3	-24.6		-15.6		-16.2	-23.6	-8.2	-9.7	-6.6	-7.6	-25.8	-35.2	
270	-26.0	-29.9	-7.1	-6.8	-6.1	-9.3	-7.5	-10.0	-8.4	-7.6	-7.2	-7.2	-22.4		-18.9		-19.1	-23.4	-5.0	-12.3	-5.1	-10.5	-25.9	-34.2	
300	-26.0	-28.0	-6.5	-6.1	-4.8	-5.6	-7.1	-7.8	-7.3	-7.3	-6.1	-4.7	-22.0		-21.7		-20.4	-22.5	-2.9	-12.9	-4.1	-11.0	-23.8	-31.4	
330	-30.3	-24.9	-7.2	-6.3	-5.4	-5.7	-7.5	-10.2	-8.9	-7.7	-6.9	-6.0	-24.7		-23.5		-19.5	-21.7	-3.7	-11.5	-4.4	-9.6	-21.3	-28.3	

Stacked (TRP $R_1=3.4 \text{ \AA}$, $\alpha=60^\circ$)							
$Y \downarrow$ $X \rightarrow$	-1.5	-1.0	-0.5	0	0.5	1.0	1.5
1.5	-22.5	-24.9	-25.3	-24.8	-25.0	-25.6	-24.9
1.0	-27.3	-29.5	-29.1	-27.4	-26.8	-27.7	-27.2
0.5	-30.4	-32.1	-31.4	-29.3	-27.9	-27.9	-26.9
0	-31.9	-33.2	-33.3	-31.7	-29.7	-28.0	-25.7
-0.5	-32.2	-33.3	-34.5	-33.9	-31.3	-28.0	-24.6
-1.0	-31.3	-32.4	-33.6	-33.1	-30.4	-26.6	-22.9
-1.5	-29.8	-30.8	-31.0	-29.8	-27.2	-23.9	-20.5

Amino Acid Edge T-shaped ($\theta=A$, $R_1=5.0 \text{ \AA}$, $\alpha=180^\circ$)									
$Y \downarrow$ $X \rightarrow$	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0
2.5	-10.4	-12.6	-14.3	-15.1	-15.0	-14.2	-12.5	-10.2	-7.9
2.0	-10.7	-13.3	-15.7	-17.1	-17.0	-15.7	-13.5	-10.9	-8.5
1.5	-10.6	-13.5	-16.5	-18.3	-18.3	-16.6	-14.0	-11.4	-9.0
1.0	-10.2	-13.1	-16.1	-18.0	-18.0	-16.3	-13.8	-11.3	-9.2
0.5	-9.9	-12.3	-14.6	-16.0	-16.0	-14.6	-12.6	-10.7	-9.0
0	-9.7	-11.5	-12.7	-13.2	-13.2	-12.6	-11.5	-10.1	-8.8
-0.5	-9.8	-11.0	-11.3	-11.1	-11.1	-11.2	-10.8	-10.0	-8.9
-1.0	-9.6	-10.6	-10.5	-9.9	-9.8	-10.3	-10.5	-10.1	-9.4
-1.5	-8.8	-9.8	-9.5	-8.9	-8.8	-9.3	-9.8	-10.1	-10.0
-2.0	-7.1	-8.0	-8.0	-7.7	-7.6	-7.9	-8.7	-9.9	-10.7
-2.5	-4.6	-5.6	-6.2	-6.3	-6.4	-6.7	-7.9	-9.9	-11.6

Nucleobase Edge T-shaped ($\theta=F$, $R_1=2.5 \text{ \AA}$, $\alpha=60^\circ$)													
$Y \downarrow$ $X \rightarrow$	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0	1.5	2.0	2.5	3.0
2.5	-17.5	-19.9	-21.1	-21.1	-20.1	-18.2	-15.6	-12.6	-9.3	-5.9	-3.0	-0.7	1.0
2.0	-20.3	-22.6	-24.1	-24.6	-23.8	-22.0	-19.9	-17.2	-13.9	-10.1	-6.4	-3.2	-0.6
1.5	-22.2	-24.6	-26.3	-27.0	-26.2	-24.8	-23.6	-21.8	-18.8	-14.9	-10.6	-6.4	-2.8
1.0	-23.6	-26.3	-28.0	-28.4	-27.8	-27.4	-27.4	-26.3	-23.3	-19.2	-14.6	-9.7	-5.3
0.5	-24.3	-27.1	-28.8	-29.2	-29.5	-30.9	-32.0	-30.7	-26.8	-22.3	-17.6	-12.7	-7.9
0	-23.6	-26.5	-28.3	-29.2	-31.1	-34.2	-36.0	-33.9	-29.0	-24.4	-20.1	-15.4	-10.5
-0.5	-21.4	-24.4	-26.5	-28.3	-31.2	-23.8	-36.7	-34.3	-29.8	-25.9	-22.3	-17.5	-12.3
-1.0	-18.2	-21.2	-23.8	-26.1	-29.0	-32.3	-33.6	-31.9	-28.9	-26.2	-22.9	-17.9	-12.6
-1.5	-14.7	-17.6	-20.3	-22.7	-25.2	-27.6	-28.7	-28.0	-26.3	-24.2	-21.0	-16.3	-11.9
-2.0	-11.3	-13.9	-16.4	-18.6	-20.7	-22.6	-23.8	-23.8	-22.7	-20.7	-17.8	-14.2	-11.2
-2.5	-8.4	-10.5	-12.5	-14.4	-16.1	-17.8	-19.1	-19.5	-18.7	-17.0	-14.7	-12.5	-10.7

Appendix C

Summary of the Strongest MP2/6-31G*(0.25) Interactions (kJ mol⁻¹) for All Nucleobase–Amino Acid Dimers as Determined from Potential Energy Surface Scans that Vary R₁ (Å), α (°), and R₂ (X-axis Shift (Å), Y-axis Shift (Å))

	Page
Stacked Dimers	C-2–C-3
T-shaped Dimers	C-4–C17
Adenine Dimers	C-4
Cytosine Dimers	C-6
Guanine Dimers	C-8
Thymine Dimers	C-10
Uracil Dimers	C-12
1,N ⁶ -ethenoadenine and 3-methyladenine Dimers	C-14

Stacked Dimers

Adenine								
Dimer	R_1	ΔE	α	ΔE	$\Delta(\alpha-R_1)$	R_2	ΔE	$\Delta(R_2-\alpha)$
A:HIS'	3.3	-24.3	120	-27.0	-2.7	0, -0.5	-27.2	-0.2
A:HIS	3.3	-18.1	180	-28.3	-10.2	0, -1.0	-29.7	-1.4
A:PHE	3.4	-24.3	0	-24.3	—	0, 0	-24.3	—
A:TYR'	3.4	-24.4	180	-29.3	-4.9	0, -0.5	-30.7	-1.4
A:TYR	3.4	-26.3	330	-28.1	-1.8	0, 0.5	-28.9	-0.8
A:TRP'	3.5	-25.5	240	-30.5	-5.0	-0.5, -1.0	-35.0	-4.5
A:TRP	3.5	-26.9	300	-29.8	-2.9	-0.5, -1.0	-32.0	-2.2

Cytosine								
Dimer	R_1	ΔE	α	ΔE	$\Delta(\alpha-R_1)$	R_2	ΔE	$\Delta(R_2-\alpha)$
C:HIS'	3.4	-24.5	0	-24.5	—	-1.5, 0	-26.0	-1.5
C:HIS	3.5	-7.9	150	-24.2	-16.3	-0.5, -1.5	-26.9	-2.7
C:PHE	3.5	-15.1	0	-15.1	—	-1.5, 0	-18.4	-3.3
C:TYR'	3.6	-14.1	180	-21.7	-7.6	-1.5, 0	-22.7	-1.0
C:TYR	3.5	-18.3	330	-20.6	-2.3	-1.0, -1.0	-24.2	-3.6
C:TRP'	3.4	-18.5	180	-27.9	-9.4	-1.0, 0	-32.9	-5.0
C:TRP	3.5	-23.6	300	-28.2	-4.6	-1.0, -0.5	-33.4	-5.2

Guanine								
Dimer	R_1	ΔE	α	ΔE	$\Delta(\alpha-R_1)$	R_2	ΔE	$\Delta(R_2-\alpha)$
G:HIS'	3.4	-10.5	150	-29.7	-19.2	-0.5, 0	-31.4	-1.7
G:HIS	3.3	-23.0	300	-32.4	-9.4	1.5, 1.0	-35.3	-2.9
G:PHE	3.4	-24.5	0	-24.5	—	-0.5, 0	-25.3	-0.8
G:TYR'	3.4	-28.4	330	-33.4	-5.0	0, 0	-33.4	—
G:TYR	3.4	-20.3	120	-29.8	-9.5	1.0, 0.5	-32.8	-3.0
G:TRP'	3.4	-36.7	0	-36.7	—	0.5, 0.5	-42.5	-5.8
G:TRP	3.4	-25.8	90	-39.0	-13.2	-1.0, -1.0	-42.4	-3.4

Thymine								
Dimer	R_1	ΔE	α	ΔE	$\Delta(\alpha-R_1)$	R_2	ΔE	$\Delta(R_2-\alpha)$
T:HIS'	3.4	-18.8	120	-25.5	-6.7	-1.0, 0	-26.8	-1.3
T:HIS	3.5	-11.5	180	-24.3	-12.8	-1.0, 0	-25.0	-0.7
T:PHE	3.5	-20.6	30	-20.8	-0.2	-1.0, -0.5	-22.4	-1.6
T:TYR'	3.6	-18.5	180	-24.6	-6.1	-0.5, -0.5	-25.5	-0.9
T:TYR	3.5	-20.5	120	-25.8	-5.3	0.5, 0	-26.1	-0.3
T:TRP'	3.3	-33.4	180	-36.4	-3.0	0, 0	-36.4	—
T:TRP	3.4	-31.0	30	-36.0	-5.0	0, 0	-36.0	—

Uracil								
Dimer	R ₁	ΔE	α	ΔE	Δ(α-R ₁)	R ₂	ΔE	Δ(R ₂ -α)
U:HIS'	3.4	-16.2	240	-24.7	-8.5	1.0, 90	-26.4	-1.7
U:HIS	3.5	-10.4	180	-23.1	-12.7	0.5, 90	-24.6	-1.5
U:PHE	3.5	-18.7	0	-18.7	—	1.0, 45	-19.9	-1.2
U:TYR'	3.5	-17.8	180	-24.4	-6.6	0.5, 180	-25.2	-0.8
U:TYR	3.5	-17.7	240	-25.2	-7.5	0, 0	-25.2	—
U:TRP'	3.3	-30.4	30	-30.9	-0.5	0.5, 225	-32.6	-1.7
U:TRP	3.5	-25.7	300	-30.6	-4.9	1.0, 90	-33.0	-2.4

1,N ⁶ -ethenoadenine								
Dimer	R ₁	ΔE	α	ΔE	Δ(α-R ₁)	R ₂	ΔE	Δ(R ₂ -α)
εA:HIS'	3.4	-15.3	120	-35.5	-20.2	-0.5, -0.5	-36.5	-1.0
εA:HIS	3.3	-26.2	300	-37.4	-11.2	0, 0	-37.4	—
εA:PHE	3.3	-31.3	0	-31.3	—	0, 0	-31.3	—
εA:TYR'	3.4	-33.1	330	-35.8	-2.7	0, -0.5	-36.4	-0.6
εA:TYR	3.4	-27.8	120	-37.7	-9.9	0.5, 0	-38.0	-0.3
εA:TRP'	3.4	-46.8	0	-46.8	—	0.5, 0	-49.2	-2.4
εA:TRP	3.4	-34.1	60	-43.7	-9.6	0.5, -0.5	-47.5	-3.8

3-methyladenine								
Dimer	R ₁	ΔE	α	ΔE	Δ(α-R ₁)	R ₂	ΔE	Δ(R ₂ -α)
3MeA:HIS'	3.3	-32.9	180	-52.3	-19.4	-0.5, 0	-52.7	-0.4
3MeA:HIS	3.3	-38.1	240	-51.7	-13.6	0, 0	-51.7	—
3MeA:PHE	3.3	-47.2	0	-47.2	—	0, -0.5	-48.6	-1.4
3MeA:TYR'	3.3	-51.6	240	-53.6	-2.0	-0.5, -0.5	-55.0	-1.4
3MeA:TYR	3.3	-52.0	180	-52.5	-0.5	0, -0.5	-53.9	-1.4
3MeA:TRP'	3.4	-62.1	270	-68.5	-6.4	0.5, 0	-69.7	-1.2
3MeA:TRP	3.4	-64.3	120	-69.9	-5.6	-0.5, -0.5	-71.5	-1.6

Adenine T-shaped Dimers

Histidine													
Adenine (face)							Adenine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	4.5	-16.4	240	-18.4	(-2, 0.5)	-21.6	1	3.3	-7.6	330	-10.2	—	—
2	4.8	-10.2	300	-12.7	—	—	2	2.6	-6.4	90	-7.4	—	—
3	4.4	-6.1	240	-8.8	—	—	3	3.4	-0.6	150	-9.4	—	—
4	4.9	-6.1	120	-9.2	—	—	4	2.3	-16.2	120	-29.5	(0.5, 1.0)	-33.6
5	4.9	-8.5	90	-12.5	—	—	5	2.5	-9.2	150	-17.2	—	—
							6	3.3	-5.6	150	-7.0	—	—
							7	3.2	-7.7	300	-13.4	—	—
							8	2.4	-17.6	300	-22.5	(0, 0.5)	-22.6
A	4.4	-15.0	90	-21.8	(0, 1.0)	-22.3	A	3.8	-3.7	150	-6.3	—	—
B	4.4	-17.2	270	-22.2	(0, 0.5)	-22.5	B	3.7	-5.0	330	-6.4	—	—
C	4.4	-11.6	300	-15.0	(-0.5, -2.5)	-18.7	C	3.5	0.0	120	-13.8	—	—
D	4.5	-6.9	120	-11.8	—	—	D	2.6	-18.6	150	-22.6	(0.5, 0.5)	-25.3
E	4.5	-10.8	90	-16.8	—	—	E	3.7	-3.5	150	-13.3	—	—
							F	3.4	-4.8	330	-6.8	—	—
							G	2.7	-14.7	330	-15.0	(0.5, 0.5)	-17.2
							H	3.4	-6.7	330	-9.5	—	—

Phenylalanine													
Adenine (face)							Adenine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.1	-8.9	60	-10.3	(0.5, 0)	-10.6	1	3.5	-3.8	0	-3.8	—	—
							2	2.5	-7.9	0	-7.9	—	—
							3	3.4	-2.4	0	-2.4	—	—
							4	2.2	-25.6	0	-25.6	(0, 0)	-25.6
							5	2.4	-14.1	0	-14.1	—	—
							6	3.4	-4.2	0	-4.2	—	—
							7	3.4	-5.5	30	-5.8	—	—
							8	2.5	-15.3	0	-15.3	(0, -0.5)	-16.0
A	4.9	-11.3	90	-14.1	(0, 0)	-14.1	A	3.9	-4.4	0	-4.4	—	—
							B	3.9	-4.3	0	-4.3	—	—
							C	3.4	-5.7	0	-5.7	—	—
							D	2.7	-20.6	30	-20.7	(-0.5, -0.5)	-21.7
							E	3.7	-6.8	30	-6.9	—	—
							F	3.5	-3.5	30	-3.6	—	—
							G	2.8	-15.3	0	-15.3	(0, 0)	-15.3
							H	3.5	-4.0	30	-4.1	—	—

Tyrosine													
Adenine (face)							Adenine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.4	-7.1	90	-12.5	(0, -1.5)	-14.7	1	3.3	-7.7	180	-8.2	—	—
2	4.8	-15.1	240	-17.6	(0.5, -0.5)	-18.1	2	2.6	-6.8	300	-7.8	—	—
3	5.3	-9.4	240	-11.3	—	—	3	3.2	-6.5	210	-7.2	—	—
4	5.6	-8.9	240	-10.4	—	—	4	2.3	-23.2	300	-27.4	(0, -0.5)	-27.8
5	5.3	-9.2	240	-10.7	—	—	5	2.5	-13.9	330	-14.4	—	—
6	4.8	-10.2	300	-11.8	—	—	6	3.3	-9.3	30	-9.4	—	—
							7	3.8	-3.2	120	-6.2	—	—
							8	2.5	-12.8	120	-18.3	(0.5, 0)	-18.4
A	5.0	-14.7	90	-17.9	(-1.5, 0.5)	-21.9	A	3.6	-7.9	0	-7.9	—	—
B	5.0	-11.7	270	-15.5	—	—	B	3.8	-4.0	180	-7.1	—	—
C	5.3	-11.2	270	-14.6	—	—	C	3.1	-12.7	0	-12.7	—	—
D	5.3	-11.1	240	-14.1	—	—	D	2.6	-23.8	0	-23.8	(-0.5, 0.5)	-25.5
E	5.0	-11.1	270	-13.4	—	—	E	3.5	-11.7	0	-11.7	—	—
F	5.0	-7.2	60	-10.2	—	—	F	3.5	-4.4	210	-8.9	—	—
							G	2.8	-15.1	30	-15.4	(0, -0.5)	-15.5
							H	3.5	-4.5	180	-8.1	—	—

Tryptophan													
Adenine (face)							Adenine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	6.0	-10.1	270	-12.4	—	—	1	3.3	-7.2	60	-13.7	—	—
2	5.9	-8.5	60	-10.2	—	—	2	2.6	-8.3	330	-8.8	—	—
3	5.9	-8.4	60	-10.7	—	—	3	3.3	-6.5	240	-12.1	—	—
							4	2.2	-30.5	300	-34.0	(-0.5, 0.5)	-34.8
							5	2.5	-17.3	300	-18.5	—	—
							6	3.2	-9.2	240	-15.4	—	—
							7	3.3	-5.9	150	-11.6	—	—
							8	2.4	-15.6	150	-22.2	(1.0, 0)	-23.1
A	4.9	-15.6	120	-22.9	(0.5, 0)	-23.2	A	3.7	-6.9	240	-8.9	—	—
B	5.3	-16.9	240	-20.6	(0.5, -1.0)	-22.9	B	3.7	-5.9	90	-8.2	—	—
C	5.6	-12.0	60	-15.1	(0, -0.5)	-15.6	C	3.2	-11.0	270	-17.0	—	—
D	5.1	-11.6	240	-14.4	(-0.5, 0)	-15.0	D	2.6	-27.4	240	-33.2	(0, 0)	-33.2
E	5.4	-10.7	240	-13.6	—	—	E	3.5	-11.8	270	-15.8	—	—
F	5.8	-10.5	90	-14.1	—	—	F	3.4	-5.1	60	-10.3	—	—
G	5.4	-10.9	60	-15.6	—	—	G	2.7	-18.9	60	-21.6	(0, -0.5)	-21.7
							H	3.4	-5.0	90	-11.2	—	—

Cytosine T-shaped Dimers

Histidine													
Cytosine (face)							Cytosine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	4.5	-13.8	240	-17.3	—	—	1	2.3	-26.0	300	-33.4	(0, 0.5)	-33.6
2	4.8	-6.7	240	-17.1	—	—	2	—	—	—	—	—	—
3	4.4	-3.6	240	-8.2	—	—	3	3.7	1.8	150	-23.0	—	—
4	4.8	-7.2	60	-11.9	—	—	4	2.6	-4.1	120	-28.7	(0.5, 1)	-31.2
5	4.8	-8.7	60	-15.0	—	—	5	2.5	-15.6	150	-22.3	—	—
							6	2.5	-18.4	330	-21.5	—	—
							7	2.5	-14.3	330	-14.3	—	—
A	4.5	-12.6	90	-21.0	(0.5, 0)	-23.1	A	3.0	-12.3	300	-20.4	—	—
B	4.4	-13.1	270	-23.9	(1, -0.5)	-26.4	B	—	—	—	—	—	—
C	4.4	-7.3	270	-17.8	(-0.5, -2)	-20.0	C	—	—	—	—	—	—
D	4.6	-5.8	90	-12.4	—	—	D	2.8	-12.7	150	-19.5	—	—
E	4.6	-10.1	90	-16.5	—	—	E	2.6	-18.7	330	-20.8	—	—
							F	2.8	-13.0	330	-14.0	—	—
							G	2.6	-21.3	330	-22.9	—	—

Phenylalanine													
Cytosine (face)							Cytosine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.1	-7.6	60	-9.4	—	—	1	2.3	-21.4	30	-21.5	(0, -0.5)	-22.5
							2	—	—	—	—	—	—
							3	3.6	-7.2	30	-7.4	—	—
							4	2.4	-17.8	0	-17.8	—	—
							5	2.5	-18.9	30	-19.5	(0, 0)	-19.5
							6	2.5	-16.8	30	-16.9	—	—
							7	2.5	-15.8	30	-15.8	—	—
A	4.9	-8.9	90	-11.1	(0.5, 0)	-12.1	A	3.1	-5.2	30	-5.2	—	—
							B	—	—	—	—	—	—
							C	3.5	-6.4	30	-7.0	—	—
							D	2.8	-16.3	30	-16.3	—	—
							E	2.7	-18.9	30	-19.0	(0, 0)	-19.0
							F	2.9	-12.9	30	-13.0	—	—
							G	2.7	-20.0	30	-20.1	(-0.5, 0.5)	-20.2

Tyrosine													
Cytosine (face)							Cytosine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.5	-5.9	90	-15.5	(0.5, -1.5)	-16.3	1	2.4	-18.1	120	-26.4	(0.5, 0)	-26.7
2	4.7	-13.0	240	-18.9	(1.5, 0)	-19.9	2	—	—	—	—	—	—
3	5.3	-7.6	240	-11.4	—	—	3	3.6	-11.3	330	-14.0	—	—
4	5.5	-7.4	240	-10.0	—	—	4	2.5	-15.0	330	-24.3	(0.5, -0.5)	-25.3
5	5.3	-7.8	240	-10.6	—	—	5	2.6	-19.1	210	-21.4	(0, -0.5)	-22.1
6	4.8	-8.6	240	-12.3	—	—	6	2.4	-19.1	30	-19.4	—	—
							7	2.5	-15.9	30	-16.3	—	—
A	5.0	-14.9	240	-11.0	(1.5, -1)	-22.5	A	3.2	-3.2	150	-10.9	—	—
B	5.2	-7.8	240	-12.4	—	—	B	4.4	1.0	330	-0.5	—	—
C	5.4	-8.5	270	-11.5	—	—	C	3.9	-2.5	330	-12.5	—	—
D	5.4	-8.7	270	-11.6	—	—	D	2.8	-16.5	210	-17.2	—	—
E	5.1	-8.5	270	-12.1	—	—	E	2.6	-19.7	30	-20.2	(-0.5, 0.5)	-21.1
F	5.0	-6.2	60	-9.9	—	—	F	2.7	-15.9	30	-16.3	—	—
							G	2.6	-22.2	30	-22.6	(-0.5, 0.5)	-23.7

Tryptophan													
Cytosine (face)							Cytosine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	6.0	-7.6	240	-14.2	—	—	1	2.3	-21.3	120	-32.7	(1, 0)	-34.5
2	5.9	-7.4	60	-9.8	—	—	2	—	—	—	—	—	—
3	5.9	-7.9	60	-11.0	—	—	3	3.4	-12.6	270	-19.1	—	—
							4	2.4	-23.2	300	-30.8	(-0.5, 0.5)	-32.2
							5	2.4	-24.3	0	-24.3	—	—
							6	2.5	-20.3	60	-26.0	—	—
							7	2.4	-18.6	60	-20.4	—	—
A	4.9	-14.4	90	-24.5	(1, -1)	-27.4	A	3.1	-3.0	60	-10.9	—	—
B	5.4	-13.5	60	-18.0	—	—	B	4.5	2.1	300	-0.3	—	—
C	5.6	-8.9	240	-16.8	—	—	C	3.5	-11.0	300	-20.0	—	—
D	5.1	-9.2	240	-13.3	—	—	D	2.7	-21.4	240	-24.8	—	—
E	5.5	-8.1	60	-11.5	—	—	E	2.6	-23.5	60	-28.6	—	—
F	5.9	-8.7	60	-11.3	—	—	F	2.7	-18.5	60	-24.0	—	—
G	5.4	-10.2	60	-14.8	—	—	G	2.6	-25.2	60	-31.8	(0, -0.5)	-32.4

Guanine T-shaped Dimers

Histidine													
Guanine (face)							Guanine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	4.5	-18.2	30	-19.7	—	—	1	2.5	-12.3	150	-44.4	(0, 0)	-44.4
2	4.7	-14.9	60	-16.9	—	—	2	2.3	-25.3	330	-27.5	—	—
3	4.3	-10.1	30	-12.0	—	—	3	2.4	-17.3	300	-20.8	—	—
4	4.9	-3.7	240	-11.6	—	—	4	3.2	-13.0	330	-16.7	—	—
5	4.8	-8.4	210	-16.4	—	—	5	2.3	-17.7	120	-24.2	(0.5, 1)	-26.7
							6	2.4	-16.4	330	-19.0	—	—
							7	3.3	-6.9	300	-13.8	—	—
							8	—	—	—	—	—	—
A	4.5	-15.4	210	-23.3	(-1.5, 0)	-25.1	A	2.4	-21.9	150	-39.7	(0.5, 1)	-46.4
B	4.4	-20.5	60	-25.6	(-0.5, 0)	-27.7	B	2.7	-18.0	330	-18.8	—	—
C	4.4	-14.4	60	-18.6	(2, 2)	-21.8	C	3.8	-3.7	150	-12.0	—	—
D	4.4	-7.3	270	-13.7	—	—	D	3.4	-8.5	330	-11.5	—	—
E	4.5	-9.5	210	-19.6	—	—	E	2.6	-21.1	330	-24.2	(0.5, 0.5)	-26.4
							F	3.5	-13.6	300	-19.3	—	—
							G	4.2	0.8	300	-0.1	—	—
							H	3.3	2.4	120	-20.5	—	—

Phenylalanine													
Guanine(face)							Guanine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.0	-10.5	30	-11.5	—	—	1	2.4	-27.7	30	-28.2	(-0.5, 1)	-31.1
A	4.9	-12.5	30	-14.2	(-0.5, 0.5)	-14.5	2	2.4	-27.8	30	-28.1	(0.5, -1)	-31.3
							3	2.4	-16.0	30	-16.3	—	—
							4	3.5	-9.2	30	-9.4	—	—
							5	2.3	-23.7	30	-23.7	(0, 0)	-23.7
							6	2.5	-13.2	0	-13.2	—	—
							7	3.5	-1.0	30	-1.1	—	—
							8	—	—	—	—	—	—
							A	2.5	-31.6	30	-31.6	(0, 0)	-31.6
							B	2.8	-17.7	30	-17.7	—	—
							C	3.8	-5.1	30	-5.4	—	—
D	3.7	-5.2	30	-5.5	—	—							
E	2.7	-19.5	30	-19.6	(0.5, -1)	-21.0							
F	3.7	-6.8	30	-6.8	—	—							
G	4.1	1.8	0	1.8	—	—							
H	3.1	-7.3	30	-7.4	—	—							

Tyrosine													
Guanine (face)							Guanine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.3	-8.6	240	-16.4	(1.5, 2.5)	-18.5	1	2.5	-28.5	330	-34.1	(0.5, 0)	-36.1
2	4.7	-17.6	60	-20.5	(-1, 0)	-20.9	2	2.3	-28.9	210	-30.1	(-1, 1.5)	-32.8
3	5.3	-12.0	30	-13.6	—	—	3	2.6	-13.4	120	-16.8	—	—
4	5.5	-10.9	30	-12.0	—	—	4	3.3	-18.3	180	-18.4	—	—
5	5.3	-11.4	30	-12.2	—	—	5	2.3	-21.9	300	-23.9	(0, -0.5)	-24.3
6	4.8	-12.0	60	-12.6	—	—	6	2.6	-11.9	120	-14.3	—	—
							7	3.8	-0.4	150	-5.7	—	—
							8	3.4	0.9	300	-0.3	—	—
A	5.1	-11.6	90	-15.2	(-2, 1)	-21.8	A	2.5	-28.3	330	-34.7	(0, -0.5)	-36.2
B	5.1	-13.6	30	-16.1	—	—	B	2.7	-17.7	30	-18.5	—	—
C	5.3	-13.2	30	-15.4	—	—	C	3.8	-8.0	210	-15.0	—	—
D	5.3	-12.5	30	-14.4	—	—	D	3.3	-17.1	30	-19.1	—	—
E	5.0	-12.4	60	-13.9	—	—	E	2.6	-20.0	180	-22.9	(-0.5, 0.5)	-24.6
F	5.0	-7.4	210	-12.9	—	—	F	3.6	-6.4	150	-12.0	—	—
							G	3.7	0.7	120	0.1	—	—
							H	2.9	-12.5	330	-14.8	—	—

Tryptophan													
Guanine (face)							Guanine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	6.0	-13.7	30	-15.8	—	—	1	2.4	-35.5	300	-43.4	(0.5, 1)	-46.8
2	5.9	-9.9	210	-11.6	—	—	2	2.4	-34.4	240	-40.0	—	—
3	5.9	-9.7	210	-13.1	—	—	3	2.4	-17.5	150	-21.9	—	—
							4	3.4	-14.4	60	-27.0	—	—
							5	2.3	-27.7	330	-28.8	(-0.5, 0.5)	-29.4
							6	2.5	-13.3	120	-18.9	—	—
							7	3.4	-0.6	120	-9.0	—	—
							8	3.3	0.7	300	-1.0	—	—
A	4.9	-17.3	240	-26.5	(-1, 0)	-28.7	A	2.4	-39.6	300	-47.1	(-0.5, 0)	-47.3
B	5.3	-18.8	30	-21.8	—	—	B	2.7	-21.9	60	-26.3	—	—
C	5.5	-16.6	30	-20.0	—	—	C	3.6	-8.4	240	-14.3	—	—
D	5.1	-14.1	30	-16.3	—	—	D	3.6	-9.1	60	-13.9	—	—
E	5.3	-12.7	210	-14.7	—	—	E	2.6	-24.7	60	-32.5	(0, 0)	-32.5
F	5.8	-11.4	210	-14.7	—	—	F	3.6	-6.8	90	-16.8	—	—
G	5.3	-12.2	210	-19.0	—	—	G	3.8	2.9	120	0.9	—	—
							H	3.0	-13.2	270	-20.5	—	—

Thymine T-shaped Dimers

Histidine													
Thymine (face)							Thymine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	4.6	-8.8	240	-8.9	—	—	1	2.3	-26.6	300	-32.4	(0.5, 0.5)	-34.2
2	4.7	-10.8	330	-11.7	—	—	2	3.4	-0.1	330	-0.6	—	—
3	4.3	-14.8	0	-14.8	(-1.5, -2.5)	-16.7	3	2.4	-14.4	270	-20.0	(1, 1)	-22.5
4	4.9	-4.0	150	-9.9	—	—	4	3.4	0.6	150	-0.2	—	—
5	4.9	-4.7	180	-8.6	—	—	5	3.6	-3.8	120	-9.9	—	—
A	4.5	-8.5	180	-12.1	—	—	6	2.5	-15.4	150	-18.6	—	—
B	4.4	-13.4	0	-13.4	(0, 1.5)	-18.7	A	3.0	-12.8	300	-19.6	—	—
C	4.3	-17.0	0	-17.0	(0, 1)	-19.1	B	3.2	-1.2	120	-12.2	—	—
D	4.4	-9.4	180	-14.4	(0, 1)	-15.9	C	3.1	-8.3	300	-13.4	—	—
E	4.6	-7.7	180	-12.2	—	—	D	3.6	1.7	120	-8.0	—	—
							E	2.8	-10.4	150	-18.0	—	—
							F	2.6	-22.1	330	-22.9	(1, 1)	-28.8

Phenylalanine													
Thymine (face)							Thymine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.1	-7.8	30	-8.1	—	—	1	2.3	-24.3	30	-24.4	(0.5, -0.5)	-24.7
							2	—	—	—	—	—	—
							3	2.4	-18.9	30	-18.9	(0, 0)	-18.9
							4	3.5	0.9	0	0.9	—	—
							5	3.6	-6.9	30	-6.9	—	—
							6	2.5	-17.9	30	-18.2	—	—
A	4.9	-9.8	0	-9.8	(0, 0.5)	-10.8	A	3.1	-6.8	30	-6.9	—	—
							B	3.2	-5.6	30	-5.6	—	—
							C	3.2	-5.7	30	-5.7	—	—
							D	3.4	-2.8	30	-2.8	—	—
							E	2.8	-13.9	30	-13.9	—	—
							F	2.6	-22.5	30	-22.7	(-0.5, 0.5)	-23.1

Tyrosine													
Thymine (face)							Thymine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.4	-6.7	180	-10.9	(0, 1.5)	-15.2	1	2.4	-21.3	120	-27.6	(0, 0)	-27.6
2	4.7	-12.6	0	-12.6	(-0.5, 2)	-13.7	2	3.5	0.5	30	0.1	—	—
3	5.3	-8.6	30	-8.9	—	—	3	2.5	-15.1	120	-20.4	(0, -0.5)	-20.6
4	5.5	-8.1	240	-8.2	—	—	4	3.3	-0.5	0	-0.5	—	—
5	5.3	-8.7	240	-8.9	—	—	5	3.5	-7.4	300	-9.1	—	—
6	4.8	-11.1	0	-11.1	(0, -0.5)	-11.5	6	2.5	-19.1	30	-19.5	—	—
A	5.1	-6.8	0	-14.0	(0, 2)	-15.7	A	3.2	-4.9	150	-11.9	—	—
B	5.1	-9.9	0	-9.9	—	—	B	3.0	-9.4	330	-10.7	—	—
C	5.3	-10.0	0	-10.0	—	—	C	3.2	-3.7	150	-10.2	—	—
D	5.4	-10.0	0	-10.0	—	—	D	3.3	-5.3	330	-6.8	—	—
E	5.2	-9.7	0	-9.7	—	—	E	2.7	-16.3	0	-16.3	—	—
F	4.9	-9.6	60	-13.8	(0, -0.5)	-14.5	F	2.6	-25.1	0	-25.1	(-0.5, 0.5)	-26.3

Tryptophan													
Thymine (face)							Thymine (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	6.0	-9.1	0	-9.1	—	—	1	2.3	-23.2	120	-32.0	(0, 0.5)	-32.6
2	5.9	-8.2	60	-9.1	—	—	2	3.4	1.5	60	0.0	—	—
3	5.9	-8.2	210	-9.2	—	—	3	2.4	-20.6	150	-24.1	(1, -1)	-25.4
							4	3.3	-0.3	240	-1.0	—	—
							5	3.4	-12.3	300	-14.0	—	—
							6	2.5	-22.3	270	-24.5	—	—
A	4.9	-10.2	180	-15.4	(0, 1)	-20.9	A	3.1	-6.0	120	-16.9	—	—
B	5.5	-9.5	60	-12.0	—	—	B	3.1	-9.0	300	-12.8	—	—
C	5.5	-13.9	0	-13.9	—	—	C	3.1	-5.7	120	-13.3	—	—
D	5.1	-12.1	0	-12.1	—	—	D	3.2	-7.1	300	-9.8	—	—
E	5.5	-9.5	180	-11.2	—	—	E	2.7	-19.5	60	-21.8	—	—
F	5.8	-10.0	180	-10.6	—	—	F	2.5	-29.2	60	-36.1	(0, -0.5)	-37.0
G	5.3	-10.1	210	-11.1	—	—							

Uracil T-shaped Dimers

Histidine													
Uracil (face)							Uracil (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	4.6	-7.1	30	-7.6	—	—	1	2.3	-26.9	300	-32.6	(0.5, 1)	-34.7
2	4.7	-10.0	330	-10.4	—	—	2	—	—	—	—	—	—
3	4.3	-14.6	30	-15.2	(-2, -2.5)	-18.0	3	2.4	-14.8	270	-20.5	(1, 1)	-23.0
4	4.9	-2.8	150	-8.9	—	—	4	—	—	—	—	—	—
5	4.9	-3.6	180	-8.0	—	—	5	2.5	-5.9	120	-20.0	—	—
							6	2.4	-14.0	150	-19.0	—	—
A	4.6	-6.8	210	-10.5	—	—	A	3.0	-12.9	300	-19.9	—	—
B	4.5	-11.6	0	-11.6	(-1, 2)	-17.3	B	3.2	-1.6	120	-12.1	—	—
C	4.3	-16.3	0	-16.3	(0, 1)	-18.4	C	3.1	-8.5	300	-13.9	—	—
D	4.5	-7.8	180	-13.3	(-0.5, 0.5)	-14.5	D	3.5	2.0	120	-10.6	—	—
E	4.6	-6.0	180	-11.1	—	—	E	2.8	-10.4	150	-18.7	—	—
							F	2.6	-22.1	330	-22.8	(1, 1)	-29.3

Phenylalanine													
Uracil (face)							Uracil (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.1	-6.8	30	-7.4	—	—	1	2.3	-24.7	30	-24.7	(0, -0.5)	-25.3
							2	—	—	—	—	—	—
							3	2.4	-19.0	30	-19.1	(0, 0)	-19.1
							4	—	—	—	—	—	—
							5	2.5	-13.4	0	-13.4	—	—
							6	2.4	-18.0	0	-18.0	—	—
A	4.9	-8.3	30	-8.8	(1, 0.5)	-9.7	A	3.1	-7.1	30	-7.2	—	—
							B	3.2	-5.7	30	-5.8	—	—
							C	3.2	-5.7	30	-5.7	—	—
							D	3.3	-3.3	30	-3.3	—	—
							E	2.8	-14.2	30	-14.3	—	—
							F	2.6	-22.8	30	-22.8	(-0.5, 0.5)	-23.4

Tyrosine													
Uracil (face)							Uracil (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	5.4	-5.4	60	-8.6	(1, -1)	-14.9	1	2.4	-21.6	120	-27.8	(0, 0)	-27.8
2	4.8	-11.0	30	-11.1	(0.5, 1.5)	-13.5	2	—	—	—	—	—	—
3	5.3	-7.7	30	-8.3	—	—	3	2.5	-15.2	120	-20.6	(0, -0.5)	-20.8
4	5.6	-7.1	30	-7.6	—	—	4	—	—	—	—	—	—
5	5.3	-7.6	240	-7.9	—	—	5	2.5	-12.2	300	-15.9	—	—
6	4.8	-9.8	0	-9.8	(-0.5, -0.5)	-10.6	6	2.4	-18.1	0	-18.1	—	—
A	5.2	-5.2	90	-8.8	(0, 2.5)	-13.1	A	3.2	-5.2	150	-12.2	—	—
B	5.1	-8.7	0	-8.7	—	—	B	3.0	-9.5	330	-10.8	—	—
C	5.4	-8.7	30	-9.2	(1, 0.5)	-9.9	C	3.2	-3.6	150	-10.2	—	—
D	5.4	-8.6	240	-8.8	—	—	D	3.1	-6.6	330	-8.4	—	—
E	5.0	-8.7	0	-8.7	—	—	E	2.7	-16.5	210	-16.6	—	—
F	5.0	-9.3	60	-13.1	(-0.5, -0.5)	-13.7	F	2.6	-25.1	30	-25.2	(-0.5, 0.5)	-26.2

Tryptophan													
Uracil (face)							Uracil (edge)						
θ	R_1	ΔE	α	ΔE	R_2	ΔE	θ	R_1	ΔE	α	ΔE	R_2	ΔE
1	6.0	-8.2	0	-8.2	—	—	1	2.3	-26.3	120	-35.0	(-0.5, 0.5)	-35.7
2	5.9	-7.1	210	-8.1	—	—	2	—	—	—	—	—	—
3	5.9	-7.0	210	-8.6	—	—	3	2.4	-20.4	150	-24.4	(1, -1)	-25.7
							4	—	—	—	—	—	—
							5	2.5	-17.0	300	-20.4	—	—
							6	2.4	-22.0	240	-23.6	—	—
A	5.0	-8.0	180	-13.2	(-0.5, 1.5)	-18.3	A	3.1	-6.6	120	-17.2	—	—
B	5.5	-8.4	60	-11.1	—	—	B	3.1	-9.0	300	-12.9	—	—
C	5.5	-12.4	0	-12.4	—	—	C	3.1	-5.6	120	-13.4	—	—
D	5.1	-10.4	0	-10.4	—	—	D	3.2	-6.9	300	-11.0	—	—
E	5.5	-8.5	60	-10.3	—	—	E	2.7	-21.2	270	-25.9	—	—
F	5.9	-8.4	210	-9.4	—	—	F	2.5	-29.6	60	-36.0	(0, -0.5)	-36.7
G	5.4	-8.5	210	-11.3	—	—							

1,N⁶-ethenoadenine and 3-methyladenine T-shaped Dimers

Histidine (edge)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	4.5	-17.5	30	-18.2	—	—	4.7	15.6	90	13.8	—	—
2	4.7	-15.7	30	-16.7	—	—	4.7	-14.7	30	-15.4	—	—
3	4.2	-14.7	30	-15.5	—	—	4.2	-53.3	90	-55.9	(0.5, -1.5)	-61.6
4	4.9	-4.2	210	-11.8	—	—	4.8	-18.2	210	-27.2	—	—
5	4.8	-8.5	210	-17.8	—	—	5.0	8.1	240	0.4	—	—
A	4.4	-17.0	210	-25.2	(0, 0.5)	-26.7	4.7	16.1	240	6.8	—	—
B	4.3	-24.5	30	-26.9	(0, 1)	-29.0	4.5	2.8	60	-0.3	—	—
C	4.2	-21.3	30	-23.8	(0, 0.5)	-25.5	4.2	-48.2	60	-50.0	(-0.5, -1.0)	-53.4
D	4.4	-6.8	210	-17.8	—	—	4.3	-40.1	240	-51.8	(-0.5, -1.0)	-55.7
E	4.5	-12.0	210	-20.6	—	—	4.5	-7.8	120	-16.4	—	—

Phenylalanine (edge)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	5.0	-11.4	30	-11.9	—	—	5.0	-11.0	90	-12.6	(0.5, 0)	-13.5
1+5°	—	—	—	—	—	—	5.0	-11.0	270	-13.2	—	—
1+10°	—	—	—	—	—	—	5.0	-11.3	270	-14.0	—	—
1+15°	—	—	—	—	—	—	5.0	-11.8	270	-14.7	—	—
1+20°	—	—	—	—	—	—	4.9	-12.5	270	-16.1	—	—
1+25°	—	—	—	—	—	—	4.9	-13.2	270	-16.5	—	—
A	4.8	-14.9	30	-16.0	(0, 0.5)	-16.2	4.8	-13.7	90	-16.8	(0, 0)	-16.8

Tyrosine (edge)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	5.3	-7.9	210	-19.2	(0.5, 1)	-21.0	5.3	-10.0	240	-23.8	(-1.0, 0)	-26.1
2	4.7	-21.2	30	-21.7	(0.5, 1)	-22.4	4.8	-3.5	60	-6.5	—	—
3	5.3	-12.9	30	-13.9	—	—	5.3	-9.2	60	-10.5	—	—
4	5.5	-11.8	30	-12.4	—	—	5.5	-11.7	90	-13.3	—	—
5	5.3	-12.2	30	-12.3	—	—	5.3	-13.9	300	-15.4	—	—
6	4.7	-13.6	60	-13.8	—	—	4.7	-27.4	30	-28.1	(0, -0.5)	-28.8
A	5.0	-14.2	150	-17.7	(-2, 1)	-25.9	5.1	-0.4	210	-5.2	—	—
B	5.0	-15.1	30	-17.1	(0,0)	-17.1	5.0	-7.7	60	-9.9	—	—
C	5.2	-15.1	30	-16.7	—	—	5.2	-13.4	300	-16.1	—	—
D	5.2	-15.0	30	-16.1	—	—	5.3	-14.8	90	-17.9	—	—
E	4.9	-15.2	30	-15.7	—	—	5.0	-18.7	90	-20.5	—	—
F	4.9	-12.2	30	-15.3	—	—	4.8	-28.6	120	-33.1	(0, -0.5)	-33.9

Tryptophan (edge)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	5.9	-14.5	30	-16.0	—	—	6.0	-4.9	60	-6.5	—	—
2	5.9	-11.1	210	-12.1	—	—	5.8	-21.9	90	-23.4	—	—
3	5.8	-10.7	210	-13.7	—	—	5.8	-16.6	240	-21.0	—	—
A	4.8	-18.5	210	-28.7	(0, 1)	-31.7	5.0	3.9	240	-9.6	—	—
B	5.3	-19.7	30	-21.5	—	—	5.3	1.0	60	-0.4	—	—
C	5.5	-19.2	30	-20.9	—	—	5.6	-15.8	60	-19.9	(0, 0)	-19.9
D	5.0	-16.8	30	-18.0	—	—	5.0	-23.1	60	-26.1	(-0.5, 0)	-26.6
E	5.3	-14.2	210	-15.8	—	—	5.2	-26.5	240	-27.0	(0.5, 0)	-28.0
F	5.8	-13.8	210	-16.1	—	—	5.8	-22.7	270	-26.6	—	—
G	5.3	-14.0	210	-19.3	—	—	5.4	-9.7	240	-17.9	—	—

Histidine (face)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	2.5	-12.7	150	-19.2	(0, 0)	-19.2	3.2	-18.1	330	-22.0	—	
2	2.4	-18.6	330	-21.6	(0, 0)	-21.6	2.6	-22.0	120	-41.5	(0.5, 0.5)	-42.1
3	3.3	-4.7	150	-17.3	—	—	3.3	-21.1	150	-27.6	—	
4	2.3	-18.7	120	-27.4	(1, 1.5)	-31.7	2.3	-48.5	330	-51.8	(1.0, 1.0)	-64.5
5	2.5	-8.0	150	-19.7	—	—	2.3	-21.5	150	-34.9	(1.0, 1.5)	-36.4
6	3.8	4.2	—	—	—	—	3.1	-18.5	330	-21.4	—	
7	3.3	-5.9	300	-12.3	—	—	3.1	-10.1	120	-17.5	—	
8	2.6	-5.2	120	-13.9	(0, 0)	-13.9	2.3	-27.2	210	-29.7	—	
A	2.6	-16.1	330	-17.3	(0.5, 1)	-20.5	3.6	-15.9	150	-29.2	—	
B	3.6	-11.3	330	-14.3	—	—	2.5	-29.8	150	-33.9	(1.0, 1.0)	-43.1
C	3.4	-3.7	150	-11.9	(-0.5, -1)	-14.5	2.6	-37.2	150	-40.7	(0.5, 1.0)	-46.2
D	2.6	-18.0	150	-25.2	(0.5, 0.5)	-27.8	2.5	-34.3	150	-51.5	(0.5, 0.5)	-55.8
E	3.8	-0.5	120	-17.9	—	—	3.5	-14.8	150	-24.4	—	
F	3.9	2.1	—	—	—	—	3.2	-11.4	150	-17.4	—	
G	3.6	-10.9	330	-15.0	—	—	2.5	-33.0	330	-33.3	(1.5, 2.0)	-40.0
H	2.8	-8.9	150	-16.0	(0.5, 0.5)	-16.5	3.3	-10.4	150	-22.9	—	

Phenylalanine (face)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	2.5	-16.7	30	-16.8	(0, 0.5)	-17.0	3.2	-20.2	0	-20.2	—	
2	2.5	-17.1	30	-17.4	(1, -2)	-17.5	2.5	-33.4	30	-34.0	(-1.0, 2.0)	-34.4
3	3.3	-7.2	30	-7.3	—	—	3.3	-27.2	0	-27.2	—	
4	2.2	-26.3	30	-26.3	(0, 0)	-26.3	2.6	-40.0	30	-40.1	(0, 0.5)	-41.9
5	2.4	-14.7	0	-14.7	—	—	2.2	-31.3	0	-31.3	—	
6	3.5	-2.3	30	-2.6	—	—	3.2	-16.9	0	-16.9	—	
7	3.6	-1.4	30	-1.6	—	—	3.2	-14.7	30	-15.4	—	
8	2.5	-10.1	0	-10.1	(0, 0)	-10.1	2.3	-33.1	30	-33.3	—	
A	2.7	-17.1	30	-17.3	(0.5, -0.5)	-17.3	3.6	-22.2	0	-22.2	—	
B	3.7	-8.5	30	-8.6	—	—	2.6	-34.6	0	-34.6	(0, -0.5)	-34.8
C	3.4	-6.6	30	-6.7	(-1, 1.5)	-11.9	2.7	-41.0	0	-41.0	(0, 1.0)	-41.7
D	2.7	-21.2	30	-21.3	(-0.5, 0.5)	-22.5	2.5	-43.5	0	-43.5	(0, 1.0)	-46.4
E	3.7	-8.1	0	-8.1	—	—	3.5	-19.0	0	-19.0	—	
F	3.9	1.1	—	—	—	—	3.3	-14.4	30	-14.5	—	
G	3.7	-5.8	0	-5.8	—	—	2.6	-37.1	30	-37.2	(0, 0)	-37.2
H	2.9	-11.7	30	-11.7	(-0.5, 1)	-13.5	3.3	-16.1	30	-16.3	—	

Tyrosine (face)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	2.5	-17.9	0	-17.9	(-0.5, 2)	-19.3	3.1	-27.0	210	-28.4	—	
2	2.5	-17.7	30	-18.6	(0, -0.5)	-20.3	2.6	-34.6	210	-37.1	(0, -0.5)	-38.4
3	3.3	-13.1	210	-14.0	—	—	3.2	-29.4	210	-30.2	—	
4	2.3	-24.1	300	-26.9	(0, -0.5)	-27.4	2.7	-40.5	30	-47.2	(-0.5, -0.5)	-48.6
5	2.5	-14.3	300	-15.8	—	—	2.3	-31.1	330	-31.5	—	
6	3.9	-0.5	—	—	—	—	3.2	-24.2	30	-24.5	—	
7	3.8	-0.6	150	-5.2	—	—	3.5	-12.1	210	-18.4	—	
8	2.6	-9.5	300	-11.1	(0, -0.5)	-11.4	2.4	-30.1	240	-34.0	—	
A	2.6	-18.9	0	-18.9	(-0.5, 0.5)	-20.1	3.4	-30.7	0	-30.7	—	
B	3.6	-8.7	180	-13.2	—	—	2.5	-35.9	210	-37.5	(-0.5, 0.5)	-39.2
C	3.0	-14.5	0	-14.5	(1.5, 1)	-17.7	2.6	-47.4	0	-47.4	(-0.5, 0.5)	-49.6
D	2.6	-24.6	0	-24.6	(-0.5, 0.5)	-26.4	2.4	-49.3	0	-49.3	(-0.5, 0.5)	-54.1
E	3.5	-12.1	330	-13.6	—	—	3.4	-26.5	0	-26.5	—	
F	3.9	-0.1	—	—	—	—	3.3	-16.2	210	-23.7	—	
G	3.7	-5.4	150	-10.0	—	—	2.6	-36.0	30	-36.3	(0, -0.5)	-37.3
H	2.8	-14.5	0	-14.5	(0, 0.5)	-16.1	3.3	-18.9	210	-26.2	—	

Tryptophan (face)												
θ	1,N ⁶ -ethenoadenine						3-methyladenine					
	R ₁	ΔE	α	ΔE	R ₂	ΔE	R ₁	ΔE	α	ΔE	R ₂	ΔE
1	2.5	-21.0	240	-23.6	(1, -0.5)	-25.9	3.1	-32.5	240	-43.3	—	
2	2.5	-19.6	90	-22.5	(1.5, 0)	-26.7	2.4	-46.7	0	-46.7	(-1, 0.5)	-49.3
3	3.2	-13.0	240	-21.7	—	—	3.1	-43.8	240	-45.9	—	
4	2.2	-31.0	300	-33.2	(-0.5, 0.5)	-34.0	2.6	-48.7	180	-57.0	(-1.0, 0)	-60.6
5	2.4	-18.5	300	-20.6	—	—	2.3	-39.5	270	-41.6	—	
6	3.5	-4.6	300	-10.1	—	—	3.1	-27.9	60	-38.7	—	
7	3.4	-1.8	150	-8.2	—	—	3.0	-22.8	0	-22.8	—	
8	2.5	-12.4	300	-14.2	(0, 0)	-15.6	2.2	-41.8	0	-41.8	—	
A	2.6	-22.5	240	-26.9	(0, 0)	-26.9	3.4	-35.1	240	-43.3	—	
B	3.6	-11.7	60	-17.1	—	—	2.5	-46.6	240	-52.0	(0, -0.5)	-52.6
C	3.2	-11.9	270	-17.0	(2, 0.5)	-18.0	2.6	-57.6	240	-63.7	(-0.5, -0.5)	-64.7
D	2.6	-28.9	240	-34.8	(0, 0)	-34.8	2.4	-60.7	240	-72.0	(0, 0)	-72.0
E	3.5	-14.2	270	-19.7	—	—	3.4	-29.6	240	-36.0	—	
F	3.8	0.9	—	—	—	—	3.2	-22.3	240	-29.1	—	
G	3.6	-6.0	90	-14.2	—	—	2.5	-46.1	210	-50.1	(-0.5, 0)	-51.2
H	2.7	-17.3	240	-22.9	(0, 0)	-22.9	3.2	-25.6	240	-33.2	—	

Appendix D

Higher-level (MP2 and CCSD(T)) Interaction Energies (kJ mol⁻¹) for All Nucleobase–Amino
Acid Dimers

Dimers	Page
Adenine	D-2
Cytosine	D-3
Guanine	D-4
Thymine	D-5
Uracil	D-6
1,N ⁶ -ethenoadenine	D-7
3-methyladenine	D-8

Adenine							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-29.7	-35.7	-37.7	-38.5	-20.9	-29.8
HIS' stacked		-27.2	-33.5	-35.6	-36.4	-18.5	-27.8
PHE stacked		-24.3	-31.5	-33.7	-34.6	-13.0	-23.3
TYR stacked		-28.9	-36.2	-38.4	-39.3	-18.0	-28.4
TYR' stacked		-30.7	-38.2	-40.2	-41.1	-19.6	-30.0
TRP stacked		-32.0	-39.9	-41.7	-42.4	-20.2	-30.6
TRP' stacked		-35.0	-42.4	-44.1	-44.8	-23.6	-33.5
HIS edge	B	-22.5	-23.8	-25.1	-25.7	-19.2	-22.4
PHE edge	A	-14.1	-17.1	-18.1	-18.5	-10.8	-15.2
TYR edge	A	-21.9	-22.9	-23.7	-24.1	-20.3	-22.4
TRP edge	A	-23.2	-25.3	-26.6	-27.2	-18.9	-22.9
HIS face	4	-33.6	-34.4	-35.8	-36.4	-30.5	-33.3
	(8)	(-22.6)	(-23.8)	(-25.2)	(-25.9)	(-20.3)	(-23.6)
PHE face	4	-25.6	-27.5	-30.3	-31.5	-20.5	-26.4
	(8)	(-16.0)	(-17.8)	(-19.3)	(-20.0)	(-13.5)	(-17.4)
TYR face	4	-27.8	-29.8	-31.9	-32.8	-23.3	-28.3
	(8)	(-18.4)	(-20.5)	(-21.8)	(-22.4)	(-16.0)	(-20.0)
TRP face	4	-34.8	-37.5	-39.8	-40.8	-28.8	-34.8
	(8)	(-23.1)	(-25.3)	(-26.6)	(-27.1)	(-20.0)	(-24.0)

Cytosine							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-26.9	-31.4	-32.4	-32.8	-23.6	-29.5
HIS' stacked		-26.0	-30.3	-31.8	-32.5	-22.6	-29.1
PHE stacked		-18.4	-24.1	-25.7	-26.4	-12.6	-20.6
TYR stacked		-24.2	-29.7	-31.2	-31.8	-19.5	-27.1
TYR' stacked		-22.7	-28.0	-29.3	-29.8	-17.8	-25.0
TRP stacked		-33.4	-40.8	-42.5	-43.2	-25.6	-35.4
TRP' stacked		-32.9	-41.2	-43.4	-44.3	-24.0	-35.4
HIS edge	B	-26.4	-28.0	-29.1	-29.6	-24.3	-27.5
PHE edge	A	-12.1	-14.8	-15.7	-16.2	-10.0	-14.0
TYR edge	A	-22.5	-23.6	-24.3	-24.6	-21.6	-23.7
TRP edge	A	-27.4	-29.7	-30.5	-30.9	-25.3	-28.8
HIS face	1 (4)	-33.6 (-31.2)	-35.6 (-33.8)	-37.5 (-34.7)	-38.3 (-35.0)	-31.5 (-29.8)	-36.1 (-33.7)
PHE face	1 (5)	-22.5 (-19.5)	-25.2 (-21.4)	-27.7 (-22.8)	-28.7 (-23.4)	-19.1 (-17.8)	-25.4 (-21.8)
TYR face	1 (4)	-26.7 (-25.3)	-29.3 (-28.5)	-31.1 (-30.0)	-31.9 (-30.7)	-23.9 (-22.8)	-29.1 (-28.2)
TRP face	1 (4)	-34.5 (-32.2)	-37.5 (-34.6)	-39.2 (-36.3)	-40.0 (-37.1)	-31.1 (-29.0)	-36.6 (-33.9)

Guanine							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6-31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-35.3	-40.3	-42.0	-42.7	-30.3	-37.8
HIS' stacked		-31.4	-37.1	-38.7	-39.3	-24.8	-32.7
PHE stacked		-25.3	-32.4	-34.6	-35.5	-15.1	-25.3
TYR stacked		-32.8	-39.5	-41.6	-42.4	-25.6	-35.2
TYR' stacked		-33.4	-40.7	-43.0	-43.9	-23.6	-34.1
TRP stacked		-42.4	-51.0	-53.0	-53.9	-30.6	-42.1
TRP' stacked		-42.5	-51.4	-53.8	-54.8	-30.8	-43.1
HIS edge	B	-27.7	-29.1	-30.2	-30.7	-24.2	-27.2
PHE edge	A	-14.5	-17.7	-18.5	-18.9	-11.5	-16.0
TYR edge	A	-21.8	-22.6	-23.0	-23.2	-20.4	-21.8
TRP edge	A	-28.7	-31.3	-32.3	-32.8	-24.8	-28.9
HIS face	5	-26.7	-27.5	-29.0	-29.6	-23.8	-26.7
	(A)	(-46.4)	(-47.7)	(-49.5)	(-50.3)	(-44.5)	(-48.4)
PHE face	5	-23.7	-25.4	-27.6	-28.6	-19.4	-24.3
	(A)	(-31.6)	(-33.0)	(-35.4)	(-36.5)	(-28.4)	(-33.2)
TYR face	E	-24.6	-26.0	-27.6	-28.3	-21.2	-24.9
	(A)	(-36.2)	(-37.7)	(-40.1)	(-41.1)	(-33.0)	(-37.8)
TRP face	E	-32.5	-34.4	-36.2	-37.0	-27.9	-32.4
	(A)	(-47.3)	(-50.2)	(-52.9)	(-54.1)	(-42.8)	(-49.5)

Thymine							
	θ	MP2/ 6-31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-25.0	-29.3	-30.8	-31.4	-20.7	-27.1
HIS' stacked		-26.8	-31.8	-33.5	-34.2	-22.0	-29.3
PHE stacked		-22.4	-28.1	-30.0	-30.8	-16.1	-24.5
TYR stacked		-26.1	-31.1	-32.7	-33.4	-21.0	-28.3
TYR' stacked		-25.5	-30.6	-32.3	-33.0	-20.0	-27.5
TRP stacked		-36.0	-43.8	-46.4	-47.5	-26.3	-37.8
TRP' stacked		-36.4	-45.0	-48.2	-49.5	-25.4	-38.5
HIS edge	C	-19.1	-22.6	-23.8	-24.2	-18.1	-23.3
PHE edge	A	-10.8	-13.2	-14.1	-14.5	-8.5	-12.3
TYR edge	A	-15.7	-16.8	-17.3	-17.5	-14.7	-16.6
TRP edge	A	-20.9	-23.2	-24.3	-24.8	-18.2	-22.1
HIS face	1	-34.2	-34.7	-36.6	-37.4	-30.1	-34.2
	(3)	(-22.5)	(-23.8)	(-24.9)	(-25.4)	(-21.6)	(-24.4)
PHE face	1	-24.7	-24.6	-27.0	-28.0	-18.9	-22.2
	(3)	(-18.9)	(-21.2)	(-23.5)	(-24.5)	(-16.1)	(-21.6)
TYR face	1	-27.6	-29.6	-31.4	-32.2	-24.8	-29.4
	(3)	(-20.6)	(-22.7)	(-24.4)	(-25.2)	(-18.3)	(-22.9)
TRP face	F	-37.0	-39.0	-41.3	-42.3	-32.6	-37.9
	(3)	(-25.4)	(-27.6)	(-29.4)	(-30.1)	(-22.4)	(-27.2)

Uracil							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-23.6	-27.1	-28.3	-28.8	-20.8	-26.0
HIS' stacked		-26.4	-30.6	-32.1	-32.7	-22.8	-29.1
PHE stacked		-20.1	-24.5	-26.2	-26.9	-14.9	-21.7
TYR stacked		-25.2	-30.1	-31.8	-32.5	-20.3	-27.6
TYR' stacked		-25.7	-30.3	-32.0	-32.7	-20.8	-27.7
TRP stacked		-34.5	-41.3	-43.7	-44.7	-26.6	-36.8
TRP' stacked		-34.0	-41.6	-44.5	-45.8	-24.4	-36.1
HIS edge	C	-18.4	-21.9	-23.0	-23.5	-17.8	-22.8
PHE edge	A	-9.7	-11.8	-12.6	-12.9	-8.5	-11.7
TYR edge	1	-14.9	-16.6	-17.3	-17.6	-15.3	-18.0
TRP edge	A	-18.3	-20.1	-20.9	-21.3	-16.3	-19.2
HIS face	1	-34.7	-36.4	-38.0	-38.7	-32.8	-36.9
	(3)	(-23.0)	(-24.3)	(-25.4)	(-25.9)	(-22.0)	(-24.9)
PHE face	1	-25.3	-27.3	-29.7	-30.8	-22.2	-27.6
	(3)	(-19.1)	(-21.3)	(-23.7)	(-24.6)	(-16.2)	(-21.7)
TYR face	1	-27.8	-29.9	-31.7	-32.5	-25.1	-29.7
	(3)	(-20.8)	(-22.9)	(-24.7)	(-25.4)	(-18.4)	(-23.1)
TRP face	F	-36.7	-38.5	-40.8	-41.8	-32.7	-37.7
	(3)	(-25.7)	(-27.8)	(-29.7)	(-30.4)	(-22.6)	(-27.4)

1,N⁶-ethenoadenine							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-37.4	-44.3	-46.2	-47.0	-27.6	-37.3
HIS' stacked		-36.5	-42.3	-43.8	-44.4	-28.0	-35.9
PHE stacked		-31.3	-39.9	-42.7	-43.8	-16.2	-28.8
TYR stacked		-38.0	-45.4	-47.8	-48.8	-25.3	-36.2
TYR' stacked		-36.4	-43.7	-46.0	-47.0	-24.1	-34.7
TRP stacked		-47.5	-56.6	-59.1	-60.2	-31.0	-43.7
TRP' stacked		-49.2	-59.5	-62.9	-64.2	-30.0	-45.1
HIS edge	B	-29.0	-31.2	-32.5	-33.0	-24.4	-28.4
PHE edge	A	-16.2	-20.0	-21.1	-21.5	-11.7	-17.0
TYR edge	A	-25.9	-27.2	-27.9	-28.3	-24.2	-26.6
TRP edge	A	-31.7	-35.1	-36.2	-36.7	-26.1	-31.2
HIS face	4	-31.7	-32.6	-33.4	-33.8	-29.0	-31.2
	(2)	(-21.6)	(-23.6)	(-25.2)	(-25.8)	(-19.3)	(-23.5)
PHE face	4	-26.3	-27.9	-30.7	-31.8	-21.0	-26.6
	(2)	(-17.5)	(-19.8)	(-21.5)	(-22.3)	(-13.8)	(-18.6)
TYR face	4	-27.4	-29.1	-31.2	-32.0	-22.8	-27.4
	(2)	(-20.3)	(-23.0)	(-24.5)	(-25.2)	(-17.2)	(-22.1)
TRP face	D	-34.8	-36.4	-38.1	-38.9	-29.9	-34.1
	(A)	(-26.9)	(-30.1)	(-31.9)	(-32.6)	(-22.7)	(-28.4)

3-methyladenine							
	θ	MP2/ 6- 31G*(0.25)	MP2/ aug-cc- pVDZ	MP2/ aug-cc- pVTZ	MP2/ CBS	CCSD(T)/ 6- 31G*(0.25)	CCSD(T)/ CBS
HIS stacked		-51.7	-54.4	-56.6	-57.6	-42.6	-48.4
HIS' stacked		-52.7	-55.2	-57.4	-58.3	-43.6	-49.3
PHE stacked		-48.6	-52.8	-56.1	-57.5	-35.3	-44.2
TYR stacked		-53.9	-57.8	-61.0	-62.4	-41.1	-49.6
TYR' stacked		-55.0	-59.0	-62.3	-63.7	-42.2	-50.9
TRP stacked		-71.5	-75.5	-78.6	-79.9	-57.1	-65.5
TRP' stacked		-69.7	-73.6	-76.9	-78.3	-55.7	-64.2
HIS edge	3	-61.6	-63.2	-64.2	-64.6	-58.7	-61.6
PHE edge	A	-16.8	-20.0	-21.2	-21.7	-13.0	-17.8
TYR edge	F	-33.9	-35.2	-36.5	-37.0	-32.2	-35.2
TRP edge	E	-28.0	-31.4	-32.7	-33.1	-23.0	-28.2
HIS face	4	-64.5	-63.6	-66.6	-67.9	-61.6	-65.1
	(B)	(-43.1)	(-43.1)	(-44.5)	(-45.1)	(-41.4)	(-43.5)
PHE face	D	-46.4	-47.1	-49.3	-50.3	-41.7	-45.6
	(G)	(-37.2)	(-36.0)	(-38.2)	(-39.2)	(-33.3)	(-35.4)
TYR face	D	-54.1	-54.6	-57.2	-58.3	-48.7	-52.9
	(B)	(-39.2)	(-40.8)	(-42.9)	(-43.8)	(-36.2)	(-40.8)
TRP face	D	-72.0	-72.8	-75.8	-77.2	-64.8	-70.1
	(B)	(-52.6)	(-54.6)	(-57.0)	(-58.1)	(-48.4)	(-53.9)

Appendix E

Computational Details for Crystal Structure Overlay Calculations

In chapter 2, three crystal structures containing representative examples of stacking,¹ amino acid edge T-shaped,² and nucleobase edge T-shaped³ contacts were examined to determine the interaction energies between the relevant monomers in the crystal structure geometries. In these calculations, the crystal structures were initially reduced to contain only the nucleobase and amino acid of interest (DG109 and F37 in the stacked orientation,¹ ATP1500 and H1223 in the amino acid edge orientation,² and DC11 (chain B) and Y424 (chain M) in the nucleobase edge orientation³). Next, the (C_s symmetry) MP2/6-31G(d) optimized amino acids and nucleobases were individually overlaid (according to maximum atomic overlap of all heavy atoms) onto the corresponding molecule in the crystal structure. In the case of HIS, the two tautomeric forms were considered (i.e., a hydrogen atom bonded to N_{δ1} or N_{ε2}). In the case of TYR, two orientations of the OH group were considered. Once the calculated monomer geometries were overlaid onto the crystal structures, the MP2/6-31G*(0.25) dimer interaction energies were calculated and compared to the interaction energies predicted from our potential energy surface scans as explained in section 2.3.4.

¹ Ohndorf, U. M.; Rould, M. A.; He, Q.; Pabo, C. O.; Lippard, S. J. *Nature* **1999**, 399, 708–712.

² Schmitt, E.; Moulinier, L.; Fujiwara, S.; Imanaka, T.; Thierry, J. C.; Moras, D. *EMBO J.* **1998**, 17, 5227–5237.

³ Giffin, M. J.; Stroud, J. C.; Bates, D. L.; von Koenig, K. D.; Hardin, J.; Chen, L. *Nat. Struct. Biol.* **2003**, 10, 800–806.

Appendix F

Computational Details for DFT-SAPT Calculations and A or 3MeA–Histidine Hydrogen-Bonded Structures

DFT-SAPT Calculations

DFT-SAPT is a unique theoretical method that uses monomer properties, as well as electronic densities from DFT in order to compute interaction energies using the symmetry adapted perturbation theory (SAPT).¹ In DFT-SAPT, the total interaction energy (E_{int}) is dissected into physically meaningful components as follows:

$$E_{int} = E_{pol}^1 + E_{ex}^1 + E_{ind}^2 + E_{ex-ind}^2 + E_{disp}^2 + E_{ex-disp}^2 + \delta HF$$

Some of these terms can be combined to define commonly understood physical quantities. The electrostatic (E_{elec}), induction (E_{ind}), dispersion (E_{disp}) and exchange-repulsion (E_{exch}) can further be defined as:

$$\begin{aligned} E_{elec} &= E_{pol}^1 \\ E_{ind} &= E_{ind}^2 + E_{ex-ind}^2 + \delta HF \\ E_{disp} &= E_{disp}^2 + E_{ex-disp}^2 \\ E_{exch} &= E_{ex}^1 \end{aligned}$$

All DFT-SAPT calculations have been carried out using the PBE0 functional with the aug-cc-pVDZ basis set within MolPro.²

Hydrogen-Bonded Structures

Hydrogen-bonded structures involving histidine and adenine or 3-methyladenine were freely optimized using MP2/6-31+G(d,p). Specifically, only the nucleobase model was chosen for adenine and 3-methyladenine, where histidine was modeled as imidazole. All structures were verified to be minima through frequency calculations at the same level of theory. Since histidine and adenine are able to accept and donate hydrogen bonds, only the combinations which resembled the T-shaped orientations were examined to provide a more relevant comparison. Additionally, since (cationic) 3-methyladenine is not able to accept a hydrogen-bond, the hydrogen-bonded structures determined in this study correspond to 3MeA donating a hydrogen bond from the most acidic sites of this nucleobase. All calculations were completed in Gaussian09.³

¹ Heßelmann, A.; Jansen, G.; Schutz, M. *J. Chem. Phys.* **2005**, *122*, 014103.

² Werner, H.-J.; Knowles, P. J.; Lindh, R.; Manby, F. R.; Schütz, M.; Celani, P.; Korona, T.; Rauhut, G.; Amos, R. D.; Bernhardsson, A.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert, F.; Hampel, C.; Hetzer, G.; Lloyd, A. W.; McNicholas, S. J.; Meyer, W.; Mura, M. E.; Nicklass, A.; Palmieri, P.; Pitzer, R.; Schumann, U.; Stoll, H.; Stone, A. J.; Tarroni, R.; Thorsteinsson, T. *MolPro*, Version 2006.1; University College Cardiff Consultants Ltd.: Cardiff, UK, 2006.

³ Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Jr., J. A. M.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford CT, 2009.

Appendix G

Full MP2/6-31G*(0.25) Potential Energy Surface Scans for HIS_A_HIS(edge) and HIS'_3MeA_HIS' Trimers, Geometric Variables (R_1 , α , R_2) Used to Construct All Trimers, and Molecular Graphs of All 18 Trimers

	Page
Potential Energy Surface Scans	G-2–G-4
HIS_A_HIS(edge)	G-2
HIS'_3MeA_HIS'	G-3
Geometric Variables Used to Construct All Trimers	G-5–G-6
Molecular Graphs for All Trimers	G-7–G-9
His_A_His	G-7
His_A_His ⁺	G-8
His_3MeA_His	G-9

MP2/6-31G*(0.25) Interaction Energies (kJ mol⁻¹) Determined from Potential Energy Surface Scans of the HIS_A_HIS(edge) Trimer that Varies R₁ (Å), α (°) and R₂ (X-axis Shift (Å), Y-axis Shift (Å)) Simultaneously.

R ₁		HIS(edge)				
		4.3	4.4	4.5	4.6	4.7
HIS	3.0	-27.7	-28.9	-29.3	-28.9	-28.2
	3.1	-32.2	-33.5	-33.8	-33.5	-32.8
	3.2	-34.4	-35.7	-36.0	-35.7	-35.0
	3.3	-35.0	-36.3	-36.7	-36.3	-35.6
	3.4	-34.6	-35.9	-36.2	-35.9	-35.2
	3.5	-33.6	-34.9	-35.2	-34.9	-34.2

α		HIS(edge)											
		0	30	60	90	120	150	180	210	240	270	300	330
HIS	0	-36.7	-37.5	-38.1	-37.7	-36.7	-35.9	-36.3	-37.7	-38.6	-38.4	-37.5	-36.6
	30	-37.8	-38.7	-39.4	-38.9	-37.8	-37.0	-37.4	-38.7	-39.6	-39.4	-38.6	-37.7
	60	-38.1	-39.1	-39.8	-39.4	-38.2	-37.3	-37.7	-39.0	-40.0	-39.8	-38.9	-38.0
	90	-38.4	-39.4	-40.2	-39.8	-38.7	-37.7	-38.0	-39.3	-40.3	-40.1	-39.2	-38.3
	120	-41.2	-42.2	-43.1	-42.8	-41.7	-40.7	-41.0	-42.2	-43.2	-43.0	-42.1	-41.1
	150	-45.4	-46.4	-47.3	-47.0	-46.0	-45.1	-45.4	-46.5	-47.4	-47.2	-46.3	-45.4
	180	-46.6	-47.6	-48.4	-48.1	-47.1	-46.3	-46.6	-47.9	-48.7	-48.4	-47.5	-46.5
	210	-43.3	-44.4	-45.2	-44.9	-43.9	-43.1	-43.5	-44.7	-45.6	-45.2	-44.2	-43.2
	240	-39.3	-40.4	-41.2	-40.9	-39.9	-39.0	-39.5	-40.8	-41.7	-41.4	-40.3	-39.3
	270	-38.0	-39.0	-39.9	-39.6	-38.5	-37.7	-38.1	-39.5	-40.5	-40.2	-39.1	-38.0
	300	-37.9	-38.8	-39.6	-39.3	-38.3	-37.5	-37.9	-39.2	-40.2	-40.0	-39.0	-37.9

R ₂	-2.5				-2.0				-1.5			
Y ↓ X →	HIS(edge) fixed at (-2.5, 0) HIS scanned:				HIS(edge) fixed at (-2.0, 0) HIS scanned:				HIS(edge) fixed at (-1.5, 0) HIS scanned:			
0	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5
	-1.5	-49.4	-49.3	-46.8	-1.5	-50.6	-50.6	-48.1	-1.5	-50.5	-50.5	-48.0
	-1.0	-49.2	-50.3	-47.5	-1.0	-50.4	-51.6	-48.8	-1.0	-50.3	-51.6	-48.8
	-0.5	-49.4	-50.1	-46.0	-0.5	-50.7	-51.5	-47.4	-0.5	-50.6	-51.4	-47.5
	HIS(edge) fixed at (-2.5, 0.5) HIS scanned:				HIS(edge) fixed at (-2.0, 0.5) HIS scanned:				HIS(edge) fixed at (-1.5, 0.5) HIS scanned:			
0.5	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5
	-1.5	-51.5	-51.4	-48.9	-1.5	-52.3	-52.2	-49.8	-1.5	-51.3	-51.3	-48.9
	-1.0	-51.2	-52.4	-49.6	-1.0	-52.1	-53.3	-50.6	-1.0	-51.1	-52.4	-49.7
	-0.5	-51.5	-52.2	-48.2	-0.5	-52.3	-53.2	-49.2	-0.5	-51.4	-52.3	-48.4
	HIS(edge) fixed at (-2.5, 1.0) HIS scanned:				HIS(edge) fixed at (-2.0, 1.0): HIS scanned:				HIS(edge) fixed at (-1.5, 1.0) HIS scanned:			
1.0	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5	Y ↓ X →	-0.5	0	0.5
	-1.5	-50.6	-50.5	-48.1	-1.5	-51.1	-51.1	-48.7	-1.5	-50.0	-50.0	-47.7
	-1.0	-50.3	-51.6	-48.8	-1.0	-50.9	-52.2	-49.4	-1.0	-49.8	-51.1	-48.4
	-0.5	-50.5	-51.4	-47.4	-0.5	-51.1	-52.0	-48.0	-0.5	-50.0	-51.0	-47.1

MP2/6-31G*(0.25) Interaction Energies (kJ mol⁻¹) Determined from Potential Energy Surface Scans of the HIS'_3MeA_HIS' Trimer that Varies R₁ (Å), α (°) and R₂ (X-axis Shift (Å), Y-axis Shift (Å)) Simultaneously.

R ₁		HIS'				
HIS'		3.1	3.2	3.3	3.4	3.5
	3.1	-57.4	-60.1	-60.9	-60.4	-59.1
	3.2	-60.1	-62.7	-63.5	-63.0	-61.6
	3.3	-60.9	-63.5	-64.2	-63.7	-62.4
	3.4	-60.4	-63.0	-63.7	-63.2	-61.8
	3.5	-59.1	-61.6	-62.4	-61.8	-60.5
	3.6	-57.3	-59.8	-60.5	-60.0	-58.7

α		HIS'											
HIS'		0	30	60	90	120	150	180	210	240	270	300	330
	0	-64.2	-65.0	-70.6	-76.8	-81.4	-85.8	-86.2	-80.9	-72.4	-64.2	-61.7	-62.8
	30	-65.0	-65.2	-70.5	-76.6	-81.3	-85.9	-86.5	-81.6	-73.3	-65.4	-63.0	-63.9
	60	-70.6	-70.6	-75.5	-81.3	-85.8	-90.4	-91.3	-86.6	-78.6	-70.9	-68.7	-69.8
	90	-76.8	-76.6	-81.3	-86.6	-90.7	-95.2	-96.0	-91.5	-83.9	-76.5	-74.6	-75.9
	120	-81.4	-81.3	-85.8	-90.7	-94.4	-98.5	-99.2	-94.7	-87.3	-80.3	-78.7	-80.3
	150	-85.8	-85.9	-90.4	-95.2	-98.5	-102.0	-102.2	-97.7	-90.4	-83.7	-82.5	-84.4
	180	-86.2	-86.5	-91.3	-96.0	-99.2	-102.2	-101.9	-97.1	-89.8	-83.2	-82.2	-84.5
	210	-80.9	-81.6	-86.6	-91.5	-94.7	-97.7	-97.1	-92.0	-84.3	-77.4	-76.5	-78.9
	240	-72.4	-73.3	-78.6	-83.9	-87.3	-90.4	-89.8	-84.3	-76.0	-68.8	-67.7	-70.1
	270	-64.2	-65.4	-70.9	-76.5	-80.3	-83.7	-83.2	-77.4	-68.8	-61.0	-59.6	-61.8
	300	-61.7	-63.0	-68.7	-74.6	-78.7	-82.5	-82.2	-76.5	-67.7	-59.6	-57.6	-59.5

Refined α		HIS'								
HIS'		153	156	159	162	165	168	171	174	177
	153	-102.5	-102.7	-102.8	-102.9	-103.0	-103.0	-102.9	-102.8	-102.6
	156	-102.7	-102.9	-103.0	-103.1	-103.1	-103.1	-103.1	-102.9	-102.8
	159	-102.8	-103.0	-103.1	-103.2	-103.3	-103.3	-103.2	-103.1	-102.9
	162	-102.9	-103.1	-103.2	-103.3	-103.3	-103.3	-103.2	-103.1	-102.9
	165	-103.0	-103.1	-103.3	-103.3	-103.4	-103.3	-103.3	-103.1	-102.9
	168	-103.0	-103.1	-103.3	-103.3	-103.3	-103.3	-103.2	-103.1	-102.9
	171	-102.9	-103.1	-103.2	-103.2	-103.3	-103.2	-103.1	-103.0	-102.8
	174	-102.8	-103.0	-103.1	-103.1	-103.1	-103.1	-103.0	-102.8	-102.6
	177	-102.6	-102.8	-102.9	-102.9	-102.9	-102.9	-102.8	-102.6	-102.4

R_2	-1.0				-0.5				0			
$Y \downarrow X \rightarrow$	HIS' fixed at (-1.0, -0.5) HIS' scanned:				HIS' fixed at (-0.5, -0.5) HIS' scanned:				HIS' fixed at (0, -0.5) HIS' scanned:			
-0.5	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0
	-0.5	-91.3	-95.9	-97.2	-0.5	-95.9	-100.4	-101.4	-0.5	-97.2	-101.4	-102.3
	0	-93.1	-97.0	-97.0	0	-97.8	-101.5	-101.3	0	-99.1	-102.6	-102.1
	0.5	-94.1	-96.2	-95.1	0.5	-98.8	-100.8	-99.4	0.5	-100.0	-101.8	-100.3
0	HIS' fixed at (-1.0, 0) HIS' scanned:				HIS' fixed at (-0.5, 0) HIS' scanned:				HIS' fixed at (0, 0) HIS' scanned:			
	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0
	-0.5	-93.1	-97.8	-99.1	-0.5	-97.0	-101.5	-102.6	-0.5	-97.0	-101.3	-102.1
	0	-94.9	-98.8	-98.8	0	-98.8	-102.6	-102.3	0	-98.8	-102.3	-101.9
	0.5	-95.8	-97.9	-96.8	0.5	-99.7	-101.7	-100.4	0.5	-99.7	-101.5	-100.0
0.5	HIS' fixed at (-1.0, 0.5) HIS' scanned:				HIS' fixed at (-0.5, 0.5) HIS' scanned:				HIS' fixed at (0, 0.5) HIS' scanned:			
	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0	$Y \downarrow X \rightarrow$	-1.0	-0.5	0
	-0.5	-94.1	-98.8	-100.0	-0.5	-96.2	-100.8	-101.8	-0.5	-95.1	-99.4	-100.3
	0	-95.8	-99.7	-99.7	0	-97.9	-101.7	-101.5	0	-96.8	-100.4	-100.0
	0.5	-96.6	-98.7	-97.6	0.5	-98.7	-100.7	-99.5	0.5	-97.6	-99.5	-98.0

Geometric Variables (R_1 (Å), α (°) and R_2 (X-axis Shift (Å), Y-axis Shift (Å))) Used to Construct the Dimer and Trimer Geometries Investigated in this Study.

Adenine and Histidine

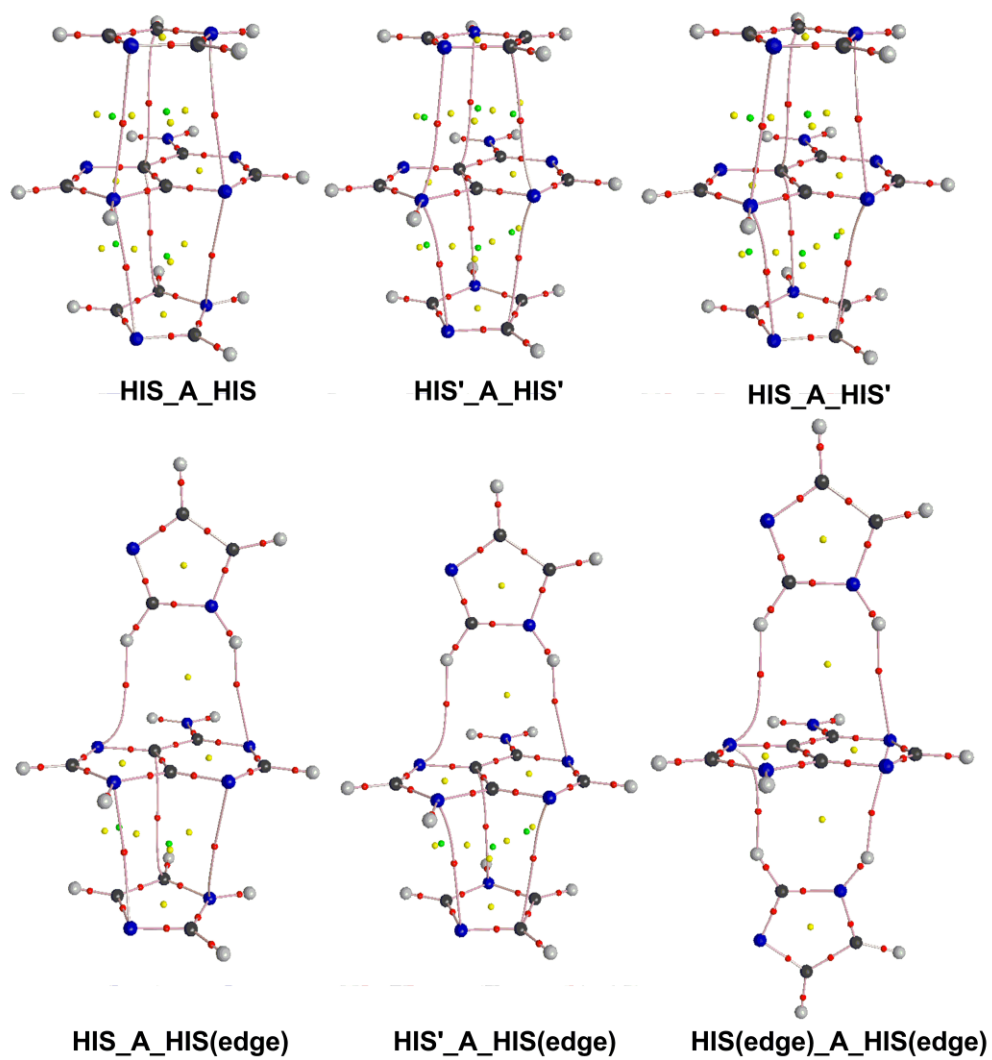
Dimer		R_1	α	R_2
A_HIS		3.3	180	(0, -1.0)
A_HIS'		3.3	120	(0, -0.5)
A_HIS(edge)		4.4	270	(0, 0.5)
Trimer		R_1	α	R_2
HIS_A_HIS	I	3.3	180	(0, -1.0)
	II	3.3	180	(0, -1.0)
HIS'_A_HIS'	I	3.3	120	(0, -0.5)
	II	3.3	120	(0, -0.5)
HIS_A_HIS'	I	3.3	180	(0, -1.0)
	II	3.3	120	(0, -0.5)
HIS_A_HIS(edge)	I	3.3	180	(0, -1.0)
	II	4.4	270	(0, 0.5)
HIS'_A_HIS(edge)	I	3.3	120	(0, -0.5)
	II	4.4	270	(0, 0.5)
HIS(edge)_A_HIS(edge)	I	4.4	270	(0, 0.5)
	II	4.4	270	(0, 0.5)

Adenine and Histidine (Protonated and Neutral)

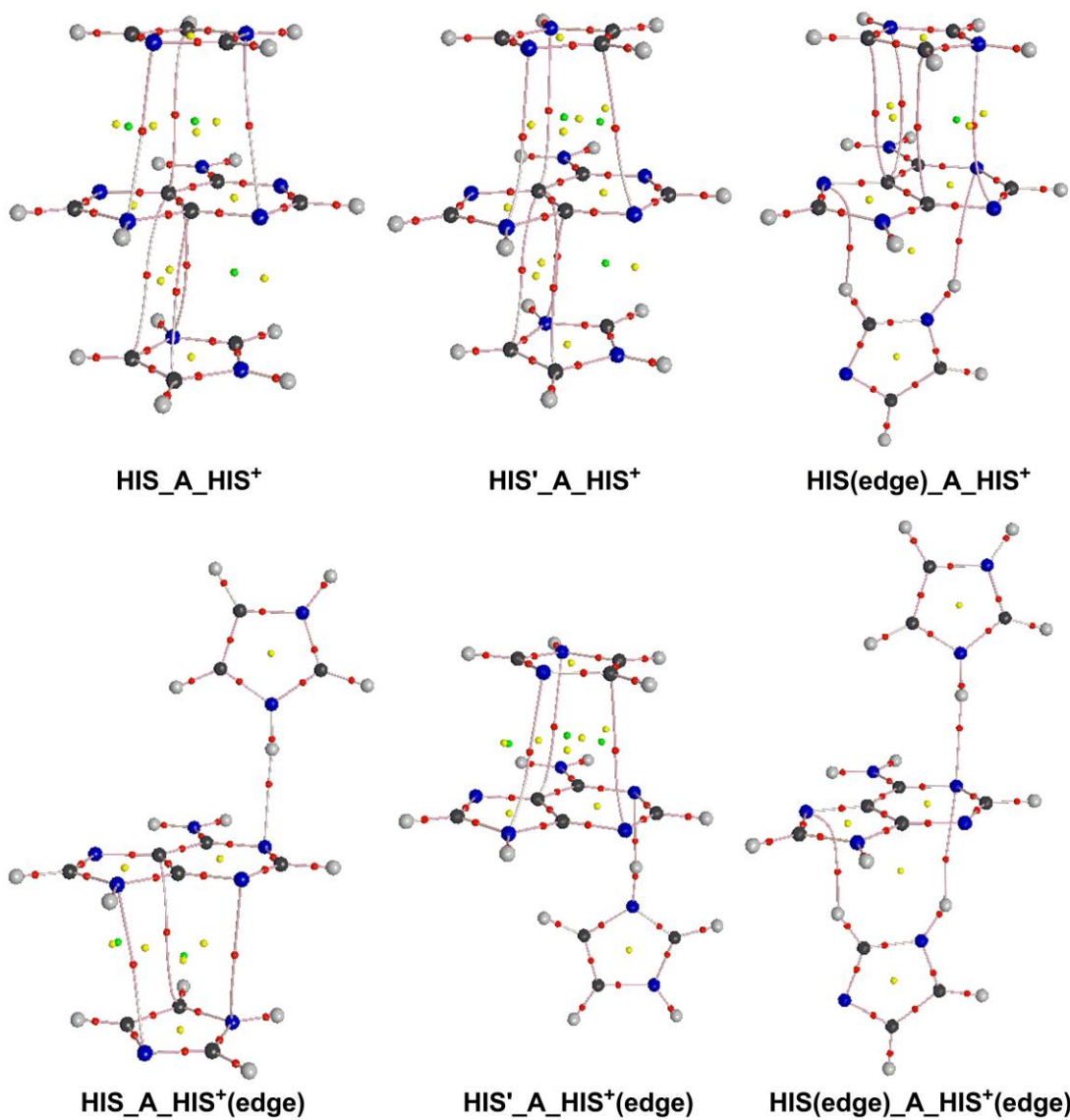
Dimer		R_1	α	R_2
A_HIS		3.3	180	(0, -1.0)
A_HIS'		3.3	120	(0, -0.5)
A_HIS edge		4.4	270	(0, 0.5)
A_HIS ⁺		3.2	270	(0, 0)
A_HIS ⁺ edge		4.2	90	(2, 1.5)
Trimer		R_1	α	R_2
HIS_A_HIS ⁺	I	3.3	180	(0, -1.0)
	II	3.2	270	(0, 0)
HIS'_A_HIS ⁺	I	3.3	120	(0, -0.5)
	II	3.2	270	(0, 0)
HIS(edge)_A_HIS ⁺	I	4.4	270	(0, 0.5)
	II	3.2	270	(0, 0)
HIS_A_HIS ⁺ (edge)	I	3.3	180	(0, -1.0)
	II	4.2	90	(2, 1.5)
HIS'_A_HIS ⁺ (edge)	I	3.3	120	(0, -0.5)
	II	4.2	90	(2, 1.5)
HIS(edge)_A_HIS ⁺ (edge)	I	4.4	270	(0, 0.5)
	II	4.2	90	(2, 1.5)

3-methyladenine and Histidine

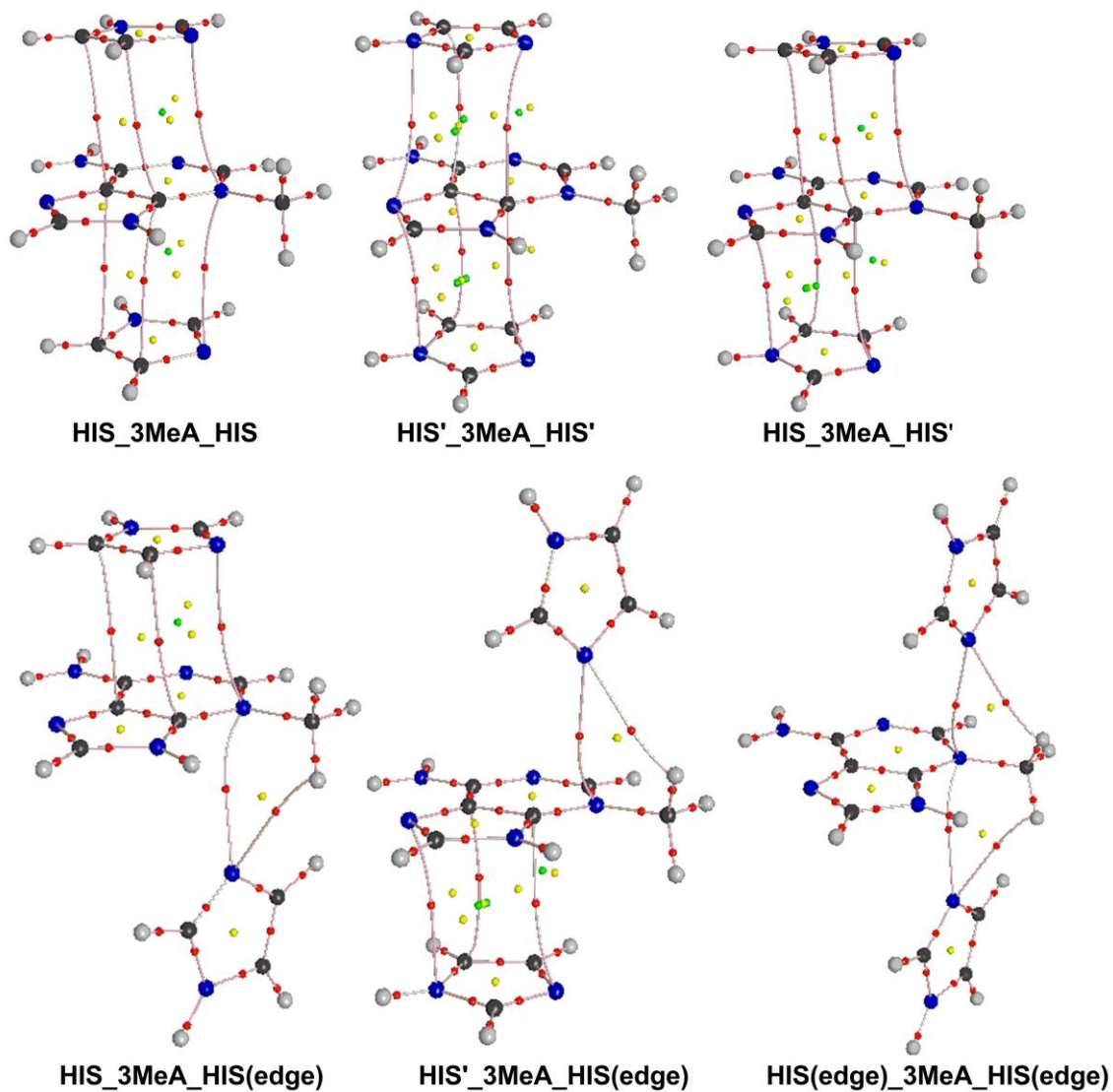
Dimer		R_1	α	R_2
3MeA_HIS		3.3	240	(0, 0)
3MeA_HIS'		3.3	180	(-0.5, 0)
3MeA_HIS(edge)		4.2	90	(0.5, -1.5)
Trimer		R_1	α	R_2
HIS_3MeA_HIS	I	3.3	240	(0, 0)
	II	3.3	240	(0, 0)
HIS'_3MeA_HIS'	I	3.3	180	(-0.5, 0)
	II	3.3	180	(-0.5, 0)
HIS_3MeA_HIS'	I	3.3	240	(0, 0)
	II	3.3	180	(-0.5, 0)
HIS_3MeA_HIS(edge)	I	3.3	240	(0, 0)
	II	4.2	90	(0.5, -1.5)
HIS'_3MeA_HIS(edge)	I	3.3	180	(-0.5, 0)
	II	4.2	90	(0.5, -1.5)
HISedge_3MeA_HIS(edge)	I	4.2	90	(0.5, -1.5)
	II	4.2	90	(0.5, -1.5)



Molecular graphs of all His:A:His trimers examined in this study.



Molecular graphs of all His:A:His⁺ trimers examined in this study.

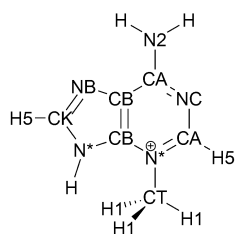


Molecular graphs of all His:3MeA:His trimers examined in this study.

Appendix H

AMBER Atom Types and Parameters, Interaction Energy Analysis for Neutral and Cationic Systems, and Full Potential Energy Surface Scan Data for the Three Stacked and Three T-shaped Dimers

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AMBER Atom Types Used for 3-Methyladenine (3MeA) as Defined using ANTECHAMBER.

Additional Parameters Used for the 129 Nucleobase–Amino Acid Dimers in this Study.

Bond	K_r	r_{eq}	Derived from:
CA N*	411.10	1.391	na-c2 in GAFF
CA H5	344.30	1.087	c2-ha in GAFF
CC H4	367.00	1.080	CA-H4, CA-HA, CM-H4, CM-H5, CM-HA, CQ-H5, CR-H5, CV-H4, CW-H4 in AMBER
C* H4	367.00	1.080	CA-H4, CA-HA, CM-H4, CM-H5, CM-HA, CQ-H5, CR-H5, CV-H4, CW-H4 in AMBER
Angle	K_θ	θ_{eq}	Derived from:
N* CA NC	71.7	123.62	n2-c2-na in GAFF
NC CA H5	52.4	120.54	n2-c2-ha in GAFF
CA NC CA	70.7	109.95	ca-nc-ca in GAFF
CA N* CB	67.8	110.37	c2-na-c2 in GAFF
CA N* CT	64.2	117.20	c2-na-c3 in GAFF
N* CA H5	51.2	112.42	na-c2-ha in GAFF
N* CB N*	73.7	109.33	na-c2-na in GAFF
CW C* H4	35.00	120.00	C-CA-HA, C*-CW-H4, CA-CA-H4, CA-CA-HA, CB-CA-H4, CB-CA-HA, etc in AMBER
CB C* H4	35.00	120.00	C-CA-HA, C*-CW-H4, CA-CA-H4, CA-CA-HA, CB-CA-H4, CB-CA-HA, etc in AMBER
CW CC H4	35.00	120.00	C-CA-HA, C*-CW-H4, CA-CA-H4, CA-CA-HA, CB-CA-H4, CB-CA-HA, etc in AMBER
NB CC H4	35.00	120.00	NB-CM-H4, NA-CW-H4 in AMBER
NA CC H4	35.00	120.00	NB-CM-H4, NA-CW-H4 in AMBER

Mean unsigned error (MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 47 nucleobase–amino acid stacked dimers.^a

Method	Basis Set	MUE			MSE			MAX			MAX %		
MP2 ^b	6-31G*(0.25)	2.2	(1.8)	[3.4]	0.3	(1.4)	[-3.1]	6.0	(3.1)	[6.0]	11.4	(-10.7)	[11.4]
	6-31G(d)	12.7	(13.3)	[11.1]	12.7	(13.3)	[11.1]	19.4	(19.4)	[13.8]	-58.0	(-58.0)	[-30.0]
	6-31G(d,p)	12.2	(12.7)	[10.7]	12.2	(12.7)	[10.7]	18.2	(18.2)	[13.0]	-54.8	(-54.8)	[-27.8]
	cc-pVDZ	8.8	(9.2)	[7.4]	8.8	(9.2)	[7.4]	12.8	(12.8)	[9.4]	-39.2	(-39.2)	[-20.4]
	6-31+G(d,p)	4.5	(4.4)	[4.8]	4.5	(4.4)	[4.8]	7.5	(7.5)	[6.7]	-22.8	(-22.8)	[-15.4]
B3LYP	aug-cc-pVDZ	5.0	(4.8)	[5.8]	-5.0	(-4.8)	[-5.8]	10.0	(9.3)	[10.0]	35.2	(35.2)	[19.5]
	6-31G(d)	26.8	(26.4)	[28.0]	26.8	(26.4)	[28.0]	39.9	(39.1)	[39.9]	-133.2	(-133.2)	[-82.3]
	6-31G(d,p)	26.8	(26.4)	[28.0]	26.8	(26.4)	[28.0]	39.9	(38.9)	[39.9]	-132.5	(-132.5)	[-82.1]
	cc-pVDZ	27.5	(27.1)	[28.8]	27.5	(27.1)	[28.8]	42.9	(39.8)	[42.9]	-135.3	(-135.3)	[-89.4]
	6-31+G(d,p)	31.1	(30.3)	[33.5]	31.1	(30.3)	[33.5]	47.2	(44.7)	[47.2]	-156.2	(-156.2)	[-96.6]
PBE	aug-cc-pVDZ	30.3	(29.8)	[31.9]	30.3	(29.8)	[31.9]	45.3	(42.9)	[45.3]	-149.1	(-149.1)	[-90.9]
	6-31G(d)	20.9	(21.1)	[20.2]	20.9	(21.1)	[20.2]	30.4	(30.4)	[29.8]	-100.7	(-100.7)	[-61.0]
	6-31G(d,p)	20.8	(21.0)	[20.2]	20.8	(21.0)	[20.2]	30.1	(30.1)	[29.8]	-99.8	(-99.8)	[-60.8]
	cc-pVDZ	20.5	(20.6)	[20.1]	20.5	(20.6)	[20.1]	31.4	(29.7)	[31.4]	-97.3	(-97.3)	[-65.3]
	6-31+G(d,p)	23.3	(23.1)	[24.1]	23.3	(23.1)	[24.1]	34.8	(33.5)	[34.8]	-114.6	(-114.6)	[-70.7]
PBE-D	6-31G(d)	3.0	(2.1)	[5.8]	-3.0	(-2.1)	[-5.8]	8.4	(4.1)	[8.4]	21.5	(11.5)	[21.5]
	6-31G(d,p)	3.1	(2.2)	[5.8]	-3.1	(-2.2)	[-5.8]	8.6	(4.3)	[8.6]	21.3	(11.8)	[21.3]
	cc-pVDZ	3.1	(2.2)	[5.8]	-3.1	(-2.2)	[-5.8]	8.6	(4.3)	[8.6]	21.3	(11.8)	[21.3]
	6-31+G(d,p)	0.9	(0.6)	[1.9]	-0.6	(-0.1)	[-1.9]	4.2	(1.5)	[4.2]	14.0	(-5.3)	[14.0]
	6-31G(d)	32.3	(32.0)	[32.9]	32.3	(32.0)	[32.9]	46.7	(46.0)	[46.7]	-152.2	(-152.2)	[-97.2]
BLYP	6-31G(d,p)	32.2	(32.0)	[32.9]	32.2	(32.0)	[32.9]	46.6	(45.8)	[46.6]	-151.4	(-151.4)	[-97.0]
	cc-pVDZ	33.1	(32.9)	[33.7]	33.1	(32.9)	[33.7]	50.0	(47.0)	[50.0]	-156.0	(-156.0)	[-104.7]
	6-31+G(d,p)	38.1	(37.5)	[40.1]	38.1	(37.5)	[40.1]	55.9	(53.2)	[55.9]	-181.4	(-181.4)	[-114.7]
	6-31G(d)	6.0	(5.1)	[8.8]	-6.0	(-5.1)	[-8.8]	12.3	(9.1)	[12.3]	25.1	(23.7)	[25.1]
	6-31G(d,p)	6.1	(5.2)	[8.8]	-6.1	(-5.2)	[-8.8]	12.4	(9.3)	[12.4]	24.8	(24.2)	[24.8]
TPSS	cc-pVDZ	5.2	(4.2)	[8.0]	-5.2	(-4.2)	[-8.0]	11.0	(8.1)	[11.0]	25.3	(21.0)	[25.3]
	6-31+G(d,p)	1.0	(0.8)	[1.7]	-0.2	(0.3)	[-1.6]	3.7	(2.0)	[3.7]	9.3	(-9.0)	[9.3]
	6-31G(d)	26.8	(26.8)	[26.8]	26.8	(26.8)	[26.8]	38.9	(37.8)	[38.9]	-127.4	(-127.4)	[-78.2]
	6-31G(d,p)	26.7	(26.7)	[26.8]	26.7	(26.7)	[26.8]	38.8	(37.6)	[38.8]	-126.7	(-126.7)	[-78.0]
	cc-pVDZ	26.1	(26.0)	[26.4]	26.1	(26.0)	[26.4]	39.9	(36.7)	[39.9]	-122.2	(-122.2)	[-81.3]
TPSS-D	6-31+G(d,p)	29.2	(28.9)	[30.4]	29.2	(28.9)	[30.4]	43.4	(40.8)	[43.4]	-141.1	(-141.1)	[-86.5]
	6-31G(d)	5.1	(4.2)	[7.9]	-5.1	(-4.2)	[-7.9]	11.2	(8.1)	[11.2]	23.7	(21.0)	[23.7]
	6-31G(d,p)	5.2	(4.3)	[7.9]	-5.2	(-4.3)	[-7.9]	11.4	(8.3)	[11.4]	23.5	(21.6)	[23.5]
	cc-pVDZ	5.8	(4.9)	[8.3]	-5.8	(-4.9)	[-8.3]	11.9	(9.3)	[11.9]	25.5	(24.0)	[25.5]
	6-31+G(d,p)	2.7	(2.1)	[4.4]	-2.7	(-2.1)	[-4.4]	7.1	(5.2)	[7.1]	16.5	(13.4)	[16.5]
B97-D	6-31G(d)	4.7	(3.9)	[7.1]	-4.7	(-3.9)	[-7.1]	10.1	(6.3)	[10.1]	23.8	(16.6)	[23.8]
	6-31G(d,p)	4.8	(4.0)	[7.2]	-4.8	(-4.0)	[-7.2]	10.2	(6.6)	[10.2]	23.6	(17.3)	[23.6]
	cc-pVDZ	4.8	(4.0)	[7.0]	-4.8	(-4.0)	[-7.0]	9.2	(6.7)	[9.2]	24.6	(19.0)	[24.6]
	6-31+G(d,p)	1.1	(0.8)	[2.2]	-1.0	(-0.6)	[-2.2]	4.1	(1.6)	[4.1]	13.8	(5.6)	[13.8]
	aug-cc-pVDZ	2.2	(1.6)	[4.0]	-2.2	(-1.6)	[-4.0]	5.8	(4.4)	[5.8]	18.4	(12.0)	[18.4]
MPWB1K	6-31G(d)	10.4	(10.5)	[10.0]	10.4	(10.5)	[10.0]	15.9	(15.9)	[14.9]	-52.8	(-52.8)	[-27.0]
	6-31G(d,p)	10.3	(10.4)	[10.0]	10.3	(10.4)	[10.0]	15.8	(15.8)	[14.8]	-52.5	(-52.5)	[-26.7]
	cc-pVDZ	9.5	(9.4)	[9.7]	9.5	(9.4)	[9.7]	14.9	(13.7)	[14.9]	-46.4	(-46.4)	[-30.6]
	6-31+G(d,p)	11.3	(11.1)	[11.8]	11.3	(11.1)	[11.8]	17.2	(16.7)	[17.2]	-61.2	(-61.2)	[-32.8]
	aug-cc-pVDZ	10.1	(10.0)	[10.4]	10.1	(10.0)	[10.4]	15.0	(14.6)	[15.0]	-49.9	(-49.9)	[-26.6]
M05-2X	6-31G(d)	4.5	(4.9)	[3.2]	4.4	(4.9)	[3.1]	8.8	(8.8)	[6.3]	-30.4	(-30.4)	[-10.6]
	6-31G(d,p)	4.4	(4.8)	[3.1]	4.3	(4.8)	[2.9]	8.7	(8.7)	[5.9]	-29.9	(-29.9)	[-10.1]
	cc-pVDZ	3.6	(3.9)	[2.9]	3.5	(3.9)	[2.6]	6.7	(6.7)	[6.6]	-25.4	(-25.4)	[-14.1]
	6-31+G(d,p)	4.0	(4.1)	[3.7]	3.9	(4.1)	[3.5]	8.0	(8.0)	[6.5]	-31.3	(-31.3)	[-12.4]
	aug-cc-pVDZ	2.5	(2.7)	[1.8]	2.3	(2.7)	[1.3]	5.5	(5.5)	[3.4]	-19.1	(-19.1)	[9.0]
M06-2X	6-31G(d)	1.9	(1.4)	[3.3]	-1.5	(-0.8)	[-3.3]	5.2	(4.1)	[5.2]	13.1	(13.1)	[12.6]
	6-31G(d,p)	1.9	(1.4)	[3.4]	-1.5	(-0.9)	[-3.4]	5.1	(4.2)	[5.1]	13.5	(13.5)	[12.4]
	cc-pVDZ	2.5	(2.1)	[3.7]	-2.5	(-2.1)	[-3.7]	6.2	(5.0)	[6.2]	15.1	(14.3)	[15.1]
	6-31+G(d,p)	2.2	(1.9)	[3.1]	-2.1	(-1.8)	[-3.0]	4.4	(4.4)	[4.4]	14.3	(13.3)	[14.3]
	aug-cc-pVDZ	3.3	(2.8)	[4.8]	-3.3	(-2.8)	[-4.8]	7.0	(6.8)	[7.0]	17.8	(17.6)	[17.8]
M06-L	6-31G(d)	2.8	(3.0)	[2.3]	2.7	(3.0)	[2.1]	5.1	(5.1)	[3.6]	-17.0	(-17.0)	[-6.7]
	6-31G(d,p)	2.6	(2.8)	[2.2]	2.6	(2.8)	[2.0]	4.9	(4.9)	[3.8]	-15.8	(-15.8)	[-7.0]
	cc-pVDZ	2.3	(2.3)	[2.3]	2.2	(2.3)	[2.1]	4.4	(3.3)	[4.4]	-12.2	(-12.2)	[-9.9]
	6-31+G(d,p)	2.0	(1.9)	[2.1]	1.9	(1.9)	[1.8]	4.1	(4.1)	[3.6]	-13.6	(-13.6)	[-6.6]
	aug-cc-pVDZ	1.3	(1.3)	[1.3]	1.1	(1.2)	[0.8]	3.5	(3.5)	[2.4]	-12.6	(-12.6)	[7.3]
B2PLYP	6-31G(d)	26.4	(25.8)	[28.2]	26.4	(25.8)	[28.2]	40.0	(38.9)	[40.0]	-135.8	(-135.8)	[-83.0]
	6-31G(d,p)	26.4	(25.7)	[28.1]	26.4	(25.7)	[28.1]	39.9	(38.7)	[39.9]	-135.2	(-135.2)	[-82.8]
	cc-pVDZ	27.2	(26.6)	[29.1]	27.2	(26.6)	[29.1]	43.0	(39.7)	[43.0]	-139.4	(-139.4)	[-90.7]
	6-31+G(d,p)	30.8	(29.8)	[33.4]	30.8	(29.8)	[33.4]	47.4	(44.7)	[47.4]	-160.5	(-160.5)	[-98.3]
	aug-cc-pVDZ	29.7	(29.0)	[31.7]	29.7	(29.0)	[31.7]	45.0	(42.4)	[45.0]	-151.7	(-151.7)	[-91.7]
B2PLYP-D	6-31G(d)	9.3	(9.4)	[9.1]	9.3	(9.4)	[9.1]	14.7	(14.7)	[13.2]	-55.6	(-55.6)	[-29.2]
	6-31G(d,p)	9.3	(9.3)	[9.0]	9.3	(9.3)	[9.0]	14.5	(14.5)	[13.1]	-55.1	(-55.1)	[-29.0]
	cc-pVDZ	10.2	(10.2)	[10.0]	10.2	(10.2)	[10.0]	16.3	(14.7)	[16.3]	-59.3	(-59.3)	[-36.9]
	6-31+G(d,p)	13.7	(13.4)	[14.3]	13.7	(13.4)	[14.3]	20.6	(19.9)	[20.6]	-80.3	(-80.3)	[-44.5]
	aug-cc-pVDZ	12.6	(12.6)	[12.6]	12.6	(12.6)	[12.6]	18.6	(18.6)	[18.2]	-71.5	(-71.5)	[-37.9]
mPW2PLYP	6-31G(d)	21.0	(20.5)	[22.5]	21.0	(20.5)	[22.5]	32.6	(31.8)	[32.6]	-111.5	(-111.5)	[-68.2]
	6-31G(d,p)	21.0	(20.5)	[22.4]	21.0	(20.5)	[22.4]	32.5	(31.6)	[32.5]	-111.0	(-111.0)	[-67.9]
	cc-pVDZ	22.0	(21.5)	[23.6]	22.0	(21.5)	[23.6]	35.8	(32.9)	[35.8]	-116.2	(-116.2)	[-76.5]
	6-31+G(d,p)	25.7	(24.8)	[28.1]	25.7	(24.8)	[28.1]	40.6	(38.1)	[40.6]	-138.2	(-138.2)	[-84.7]
	aug-cc-pVDZ	24.7	(24.1)	[26.4]	24.7	(24.1)	[26.4]	38.2	(35.8)	[38.2]	-129.7	(-129.7)	[-78.2]
mPW2PLYP-D	6-31G(d)	8.6	(8.6)	[8.6]	8.6	(8.6)	[8.6]	14.2	(14.2)	[13.1]	-53.3	(-53.3)	[-29.0]
	6-31G(d,p)	8.5	(8.5)	[8.5]	8.5	(8.5)	[8.5]	14.0	(14.0)	[13.0]	-52.7	(-52.7)	[-28.8]
	cc-pVDZ	9.6	(9.6)	[9.7]	9.6	(9.6)	[9.7]	16.5	(14.5)	[16.5]	-57.9	(-57.9)	[-37.4]
	6-31+G(d,p)	13.2	(12.9)	[14.2]	13.2	(12.9)	[14.2]	21.1	(19.9)	[21.1]	-80.0	(-80.0)	[-45.6]
	aug-cc-pVDZ	12.3	(12.2)	[12.5]	12.3	(12.2)	[12.5]	18.8	(18.7)	[18.8]	-71.4	(-71.4)	[-39.1]
AM1		42.3	(39.9)	[49.4]	42.3	(39.9)	[49.4]	66.1	(59.0)	[66.1]	-184.4	(-184.4)	[-130.2]
PM3		41.8	(38.1)	[52.6]	41.8	(38.1)	[52.6]	69.3	(55.0)	[69.3]	-177.1	(-177.1)	[-130.2]
PM6		21.2	(18.9)	[27.7]	21.2	(18.9)	[27.7]	37.5	(27.8)	[37.5]	-86.7	(-86.7)	[-68.0]
AMBER		3.2	(1.8)	[7.3]	2.5	(0.9)	[7.3]	12.4	(5.1)	[12.4]	-29.5	(-13.8)	[-29.5]

^a Values reported are for all 47 stacked dimer interaction energies, where values in parentheses correspond to the 35 neutral dimer interactions, and the values in square brackets correspond to the 12 cationic dimer interactions. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Mean unsigned error (MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 82 nucleobase–amino acid T-shaped dimers.^a

Method	Basis Set	MUE			MSE			MAX			MAX %		
MP2 ^b	6-31G*(0.25)	1.5	(1.5)	[1.5]	1.2	(1.4)	[0.8]	5.7	(4.4)	[5.7]	-19.3	(-19.3)	[-7.8]
	6-31G(d)	6.2	(6.2)	[6.3]	6.2	(6.2)	[6.3]	12.1	(9.5)	[12.1]	-46.1	(-46.1)	[-44.5]
	6-31G(d,p)	6.1	(6.1)	[6.1]	6.1	(6.1)	[6.1]	11.6	(9.3)	[11.6]	-42.1	(-42.1)	[-38.2]
	cc-pVDZ	5.9	(5.7)	[6.2]	5.9	(5.7)	[6.2]	11.8	(9.1)	[11.8]	-40.3	(-40.3)	[-26.0]
	6-31+G(d,p)	4.4	(4.3)	[4.9]	4.4	(4.3)	[4.9]	8.4	(7.1)	[8.4]	-31.1	(-31.1)	[-18.9]
B3LYP	aug-cc-pVDZ	1.0	(0.9)	[1.5]	-0.4	(-0.6)	[0.1]	4.2	(2.7)	[4.2]	12.5	(12.5)	[12.4]
	6-31G(d)	9.5	(9.6)	[9.4]	9.4	(9.6)	[9.1]	19.1	(15.9)	[19.1]	-99.2	(-87.4)	[-99.2]
	6-31G(d,p)	9.7	(9.8)	[9.3]	9.6	(9.8)	[9.0]	19.2	(16.0)	[19.2]	-98.0	(-86.6)	[-98.0]
	cc-pVDZ	10.5	(10.7)	[9.8]	10.4	(10.7)	[9.6]	24.0	(19.6)	[24.0]	-98.4	(-90.2)	[-98.4]
	6-31+G(d,p)	14.3	(14.3)	[14.3]	14.3	(14.3)	[14.3]	25.1	(21.4)	[25.1]	-112.3	(-112.3)	[-101.4]
PBE	aug-cc-pVDZ	13.8	(13.9)	[13.5]	13.8	(13.9)	[13.5]	24.1	(21.3)	[24.1]	-101.6	(-101.6)	[-89.6]
	6-31G(d)	5.9	(5.7)	[6.5]	5.5	(5.7)	[5.2]	13.7	(11.2)	[13.7]	-73.6	(-59.6)	[-73.6]
	6-31G(d,p)	5.9	(5.8)	[6.3]	5.6	(5.8)	[5.0]	13.3	(11.2)	[13.3]	-71.8	(-58.3)	[-71.8]
	cc-pVDZ	6.4	(6.4)	[6.5]	6.0	(6.3)	[5.2]	16.1	(14.4)	[16.1]	-71.1	(-59.7)	[-71.1]
	6-31+G(d,p)	9.5	(9.4)	[9.7]	9.5	(9.4)	[9.7]	16.5	(14.3)	[16.5]	-75.4	(-75.4)	[-71.1]
PBE-D	6-31G(d)	7.2	(7.0)	[7.6]	-7.2	(-7.0)	[-7.6]	12.8	(12.1)	[12.8]	47.2	(47.2)	[30.1]
	6-31G(d,p)	7.1	(6.9)	[7.8]	-7.1	(-6.9)	[-7.8]	12.9	(11.7)	[12.9]	46.9	(46.9)	[29.5]
	cc-pVDZ	6.6	(6.3)	[7.6]	-6.6	(-6.3)	[-7.6]	13.7	(10.0)	[13.7]	42.8	(42.8)	[21.4]
	6-31+G(d,p)	3.2	(3.3)	[3.2]	-3.2	(-3.3)	[-3.1]	6.7	(6.7)	[6.4]	23.9	(23.9)	[17.1]
	6-31G(d)	12.1	(12.2)	[11.7]	12.0	(12.2)	[11.6]	24.3	(21.0)	[24.3]	-114.6	(-102.5)	[-114.6]
BLYP	6-31G(d,p)	12.2	(12.4)	[11.7]	12.2	(12.4)	[11.6]	24.5	(21.2)	[24.5]	-113.6	(-102.5)	[-113.6]
	cc-pVDZ	13.1	(13.4)	[12.0]	13.1	(13.4)	[12.0]	29.5	(25.3)	[29.5]	-115.4	(-106.6)	[-115.4]
	6-31+G(d,p)	18.2	(18.2)	[18.3]	18.2	(18.2)	[18.3]	31.8	(27.5)	[31.8]	-135.2	(-135.2)	[-119.7]
	6-31G(d)	8.3	(8.1)	[8.9]	-8.3	(-8.1)	[-8.9]	13.7	(13.6)	[13.7]	50.1	(50.1)	[31.9]
	6-31G(d,p)	8.1	(7.8)	[8.9]	-8.1	(-7.8)	[-8.9]	13.6	(13.1)	[13.6]	49.2	(49.2)	[31.2]
TPSS	cc-pVDZ	7.3	(6.8)	[8.5]	-7.3	(-6.8)	[-8.5]	15.7	(10.7)	[15.7]	46.0	(46.0)	[27.7]
	6-31+G(d,p)	2.2	(2.1)	[2.3]	-2.1	(-2.1)	[-2.2]	5.1	(5.1)	[5.0]	21.5	(16.8)	[21.5]
	6-31G(d)	9.4	(9.4)	[9.3]	9.3	(9.4)	[9.2]	18.2	(15.8)	[18.2]	-96.7	(-85.5)	[-96.7]
	6-31G(d,p)	9.4	(9.4)	[9.1]	9.3	(9.4)	[9.0]	17.8	(15.7)	[17.8]	-94.7	(-84.7)	[-94.7]
	cc-pVDZ	9.8	(10.0)	[9.3]	9.8	(10.0)	[9.3]	21.4	(18.6)	[21.4]	-93.5	(-86.0)	[-93.5]
TPSS-D	6-31+G(d,p)	13.0	(13.0)	[13.2]	13.0	(13.0)	[13.2]	21.6	(19.7)	[21.6]	-105.0	(-105.0)	[-95.3]
	6-31G(d)	7.6	(7.5)	[7.9]	-7.6	(-7.5)	[-7.9]	13.0	(12.5)	[13.0]	49.7	(49.7)	[31.0]
	6-31G(d,p)	7.6	(7.4)	[8.1]	-7.6	(-7.4)	[-8.1]	13.2	(12.3)	[13.2]	49.6	(49.6)	[30.4]
	cc-pVDZ	7.1	(6.9)	[7.8]	-7.1	(-6.9)	[-7.8]	13.5	(10.9)	[13.5]	42.3	(42.3)	[25.1]
	6-31+G(d,p)	3.9	(3.9)	[3.9]	-3.9	(-3.9)	[-3.9]	8.9	(7.4)	[8.9]	27.5	(27.5)	[22.4]
B97-D	6-31G(d)	6.9	(7.0)	[6.8]	-6.8	(-7.0)	[-6.5]	11.9	(11.9)	[11.4]	44.4	(44.4)	[26.4]
	6-31G(d,p)	6.9	(6.9)	[6.9]	-6.8	(-6.9)	[-6.7]	11.6	(11.6)	[11.5]	44.1	(44.1)	[26.0]
	cc-pVDZ	6.0	(6.0)	[6.1]	-6.0	(-6.0)	[-6.1]	11.7	(9.5)	[11.7]	45.1	(45.1)	[23.7]
	6-31+G(d,p)	2.7	(2.7)	[2.6]	-2.5	(-2.7)	[-1.8]	5.8	(5.8)	[5.3]	20.3	(20.3)	[20.1]
	aug-cc-pVDZ	3.1	(3.1)	[3.3]	-2.9	(-3.1)	[-2.5]	6.6	(6.1)	[6.6]	31.5	(26.4)	[31.5]
MPWB1K	6-31G(d)	3.8	(3.8)	[3.7]	3.5	(3.7)	[3.0]	11.4	(9.3)	[11.4]	-57.9	(-44.6)	[-57.9]
	6-31G(d,p)	3.7	(3.7)	[3.6]	3.5	(3.7)	[2.8]	10.9	(9.1)	[10.9]	-55.6	(-42.4)	[-55.6]
	cc-pVDZ	4.0	(4.0)	[4.0]	3.8	(4.0)	[3.2]	9.8	(8.3)	[9.8]	-53.3	(-43.5)	[-53.3]
	6-31+G(d,p)	6.2	(6.4)	[5.8]	6.2	(6.4)	[5.8]	11.6	(11.6)	[11.3]	-54.6	(-54.6)	[-53.9]
	aug-cc-pVDZ	5.4	(5.5)	[5.2]	5.4	(5.5)	[5.2]	10.2	(10.2)	[9.3]	-45.3	(-45.3)	[-42.8]
M05-2X	6-31G(d)	1.6	(1.3)	[2.6]	-0.6	(-0.4)	[-1.1]	7.5	(4.9)	[7.5]	-31.8	(18.0)	[-31.8]
	6-31G(d,p)	1.7	(1.3)	[2.9]	-0.8	(-0.6)	[-1.5]	8.0	(4.9)	[8.0]	-29.6	(18.5)	[-29.6]
	cc-pVDZ	1.7	(1.2)	[2.9]	-0.5	(-0.3)	[-1.1]	9.3	(4.4)	[9.3]	-27.1	(14.7)	[-27.1]
	6-31+G(d,p)	1.4	(1.4)	[1.4]	1.1	(1.1)	[0.9]	5.0	(5.0)	[4.7]	-21.8	(-21.8)	[-21.8]
	aug-cc-pVDZ	1.1	(1.0)	[1.4]	-0.2	(-0.2)	[-0.3]	3.7	(3.7)	[3.3]	16.4	(16.4)	[-9.5]
M06-2X	6-31G(d)	1.9	(1.5)	[2.9]	-1.5	(-1.1)	[-2.4]	10.1	(5.4)	[10.1]	22.2	(22.2)	[-17.5]
	6-31G(d,p)	2.0	(1.6)	[3.0]	-1.6	(-1.3)	[-2.6]	10.4	(5.6)	[10.4]	22.1	(22.1)	[-14.5]
	cc-pVDZ	1.7	(1.4)	[2.7]	-1.4	(-1.1)	[-2.2]	11.3	(5.4)	[11.3]	15.5	(15.5)	[-12.9]
	6-31+G(d,p)	1.2	(1.1)	[1.3]	0.4	(0.6)	[-0.2]	4.9	(3.9)	[4.9]	-17.0	(-17.0)	[-6.6]
	aug-cc-pVDZ	1.3	(1.2)	[1.6]	-0.7	(-0.6)	[-1.1]	4.2	(4.2)	[3.9]	18.8	(18.8)	[7.1]
M06-L	6-31G(d)	2.1	(2.0)	[2.2]	2.0	(2.0)	[2.1]	4.9	(4.9)	[4.8]	-23.0	(-22.5)	[-23.0]
	6-31G(d,p)	1.9	(1.9)	[2.1]	1.8	(1.8)	[1.8]	4.5	(4.5)	[4.5]	-20.0	(-20.0)	[-19.5]
	cc-pVDZ	2.8	(2.6)	[3.2]	2.6	(2.6)	[2.7]	8.6	(6.5)	[8.6]	-27.5	(-27.5)	[-20.9]
	6-31+G(d,p)	3.1	(3.1)	[3.3]	3.1	(3.1)	[3.3]	6.0	(5.4)	[6.0]	-24.3	(-24.3)	[-17.0]
	aug-cc-pVDZ	2.9	(2.9)	[3.0]	2.9	(2.9)	[2.9]	6.1	(4.7)	[6.1]	-19.8	(-19.8)	[-13.0]
B2PLYP	6-31G(d)	9.5	(9.5)	[9.5]	9.5	(9.5)	[9.3]	20.3	(15.6)	[20.3]	-101.8	(-88.4)	[-101.8]
	6-31G(d,p)	9.7	(9.7)	[9.4]	9.6	(9.7)	[9.2]	20.0	(15.9)	[20.0]	-100.8	(-88.2)	[-100.8]
	cc-pVDZ	10.4	(10.6)	[10.0]	10.4	(10.6)	[9.8]	23.3	(18.1)	[23.3]	-100.3	(-90.6)	[-100.3]
	6-31+G(d,p)	13.8	(13.8)	[13.6]	13.8	(13.8)	[13.6]	24.4	(21.3)	[24.4]	-111.9	(-111.9)	[-104.8]
	aug-cc-pVDZ	13.2	(13.3)	[13.0]	13.2	(13.3)	[13.0]	22.7	(20.9)	[22.7]	-101.0	(-101.0)	[-93.3]
B2PLYP-D	6-31G(d)	1.7	(1.3)	[2.9]	0.2	(0.3)	[-0.1]	7.1	(4.0)	[7.1]	-37.1	(-26.2)	[-37.1]
	6-31G(d,p)	1.7	(1.3)	[2.8]	0.3	(0.5)	[-0.2]	7.1	(3.9)	[7.1]	-36.1	(-25.3)	[-36.1]
	cc-pVDZ	2.4	(2.0)	[3.6]	1.1	(1.3)	[0.4]	7.6	(4.7)	[7.6]	-35.5	(-26.9)	[-35.5]
	6-31+G(d,p)	4.5	(4.6)	[4.3]	4.5	(4.6)	[4.2]	8.4	(7.8)	[8.4]	-43.4	(-43.4)	[-40.1]
	aug-cc-pVDZ	3.9	(4.0)	[3.7]	3.9	(4.0)	[3.6]	6.4	(6.2)	[6.4]	-32.5	(-32.5)	[-28.6]
mPW2PLYP	6-31G(d)	6.3	(6.2)	[6.8]	6.0	(6.1)	[5.7]	16.4	(11.7)	[16.4]	-81.8	(-66.6)	[-81.8]
	6-31G(d,p)	6.5	(6.4)	[6.8]	6.2	(6.4)	[5.6]	16.1	(12.0)	[16.1]	-80.7	(-65.7)	[-80.7]
	cc-pVDZ	7.3	(7.3)	[7.2]	7.0	(7.2)	[6.3]	18.5	(13.9)	[18.5]	-80.4	(-67.3)	[-80.4]
	6-31+G(d,p)	10.4	(10.5)	[10.2]	10.4	(10.5)	[10.2]	19.7	(16.7)	[19.7]	-86.4	(-86.4)	[-84.7]
	aug-cc-pVDZ	9.8	(9.9)	[9.6]	9.8	(9.9)	[9.6]	17.9	(16.2)	[17.9]	-76.1	(-76.1)	[-73.6]
mPW2PLYP-D	6-31G(d)	1.8	(1.4)	[3.0]	-0.7	(-0.6)	[-1.1]	8.3	(4.9)	[8.3]	-34.7	(-21.8)	[-34.7]
	6-31G(d,p)	1.8	(1.3)	[3.0]	-0.6	(-0.4)	[-1.2]	8.3	(4.4)	[8.3]	-33.6	(-20.8)	[-33.6]
	cc-pVDZ	2.4	(1.9)	[3.8]	0.2	(0.5)	[-0.6]	8.8	(4.6)	[8.8]	-33.4	(-22.5)	[-33.4]
	6-31+G(d,p)	3.7	(3.8)	[3.7]	3.6	(3.8)	[3.3]	8.1	(7.4)	[8.1]	-37.6	(-37.3)	[-37.6]
	aug-cc-pVDZ	3.2	(3.2)	[3.3]	3.1	(3.2)	[2.8]	6.3	(5.7)	[6.3]	-28.0	(-28.0)	[-26.6]
AM1		22.5	(21.1)	[26.3]	22.5	(21.1)	[26.3]	45.4	(31.5)	[45.4]	-128.0	(-128.0)	[-121.0]
PM3		22.5	(20.3)	[28.5]	22.5	(20.3)	[28.5]	46.4	(36.0)	[46.4]	-125.6	(-125.6)	[-121.5]
PM6		14.1	(12.4)	[18.6]	14.1	(12.4)	[18.6]	34.2	(19.4)	[34.2]	-79.1	(-79.1)	[-74.2]
AMBER		4.7	(2.3)	[11.2]	2.2	(-1.1)	[11.2]	18.7	(7.5)	[18.7]	-82.3	(19.5)	[-82.3]

^a Values reported are for all 82 T-shaped dimer interaction energies, where values in parentheses correspond to the 60 neutral dimer interactions, and the values in square brackets correspond to the 22 cationic dimer interactions. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Mean unsigned error (MUE, kJ mol⁻¹), mean signed error (MSE, kJ mol⁻¹), maximum absolute difference (MAX, kJ mol⁻¹) and maximum percent error (MAX %) between various methods and the CCSD(T)/CBS benchmark interaction energies for 129 nucleobase–amino acid noncovalent dimers.^a

Method	Basis Set	MUE			MSE			MAX			MAX %		
MP2 ^b	6-31G*(0.25)	1.8	(1.6)	[2.2]	0.9	(1.4)	[-0.6]	6.0	(4.4)	[6.0]	-19.3	(-19.3)	[11.4]
	6-31G(d)	8.6	(8.8)	[8.0]	8.6	(8.8)	[8.0]	19.4	(19.4)	[13.8]	-58.0	(-58.0)	[-44.5]
	6-31G(d,p)	8.3	(8.5)	[7.7]	8.3	(8.5)	[7.7]	18.2	(18.2)	[13.0]	-54.8	(-54.8)	[-38.2]
	cc-pVDZ	6.9	(7.0)	[6.6]	6.9	(7.0)	[6.6]	12.8	(12.8)	[11.8]	-40.3	(-40.3)	[-26.0]
	6-31+G(d,p)	4.5	(4.3)	[4.9]	4.5	(4.3)	[4.9]	8.4	(7.5)	[8.4]	-31.1	(-31.1)	[-18.9]
B3LYP	aug-cc-pVDZ	2.5	(2.3)	[3.0]	-2.1	(-2.1)	[-2.0]	10.0	(9.3)	[10.0]	35.2	(35.2)	[19.5]
	6-31G(d)	15.8	(15.8)	[16.0]	15.8	(15.8)	[15.8]	39.9	(39.1)	[39.9]	-133.2	(-133.2)	[-99.2]
	6-31G(d,p)	15.9	(15.9)	[15.9]	15.8	(15.9)	[15.7]	39.9	(38.9)	[39.9]	-132.5	(-132.5)	[-98.0]
	cc-pVDZ	16.7	(16.8)	[16.5]	16.7	(16.8)	[16.4]	42.9	(39.8)	[42.9]	-135.3	(-135.3)	[-98.4]
	6-31+G(d,p)	20.4	(20.2)	[21.0]	20.4	(20.2)	[21.0]	47.2	(44.7)	[47.2]	-156.2	(-156.2)	[-101.4]
PBE	aug-cc-pVDZ	19.8	(19.8)	[20.0]	19.8	(19.8)	[20.0]	45.3	(42.9)	[45.3]	-149.1	(-149.1)	[-90.9]
	6-31G(d)	11.2	(11.1)	[11.3]	10.9	(11.1)	[10.5]	30.4	(30.4)	[29.8]	-100.7	(-100.7)	[-73.6]
	6-31G(d,p)	11.1	(11.1)	[11.2]	10.9	(11.1)	[10.4]	30.1	(30.1)	[29.8]	-99.8	(-99.8)	[-71.8]
	cc-pVDZ	11.3	(11.4)	[11.3]	11.1	(11.3)	[10.5]	31.4	(29.7)	[31.4]	-97.3	(-97.3)	[-71.1]
	6-31+G(d,p)	14.3	(14.1)	[14.8]	14.3	(14.1)	[14.8]	34.8	(33.5)	[34.8]	-114.6	(-114.6)	[-71.1]
PBE-D	6-31G(d)	5.6	(5.2)	[7.0]	-5.6	(-5.2)	[-7.0]	12.8	(12.1)	[12.8]	47.2	(47.2)	[30.1]
	6-31G(d,p)	5.6	(5.1)	[7.1]	-5.6	(-5.1)	[-7.1]	12.9	(11.7)	[12.9]	46.9	(46.9)	[29.5]
	cc-pVDZ	5.5	(4.9)	[7.0]	-5.5	(-4.9)	[-7.0]	13.7	(10.0)	[13.7]	42.8	(42.8)	[23.3]
	6-31+G(d,p)	2.4	(2.3)	[2.7]	-2.3	(-2.1)	[-2.7]	6.7	(6.7)	[6.4]	23.9	(23.9)	[17.1]
	6-31G(d)	19.1	(19.1)	[19.2]	19.1	(19.1)	[19.1]	46.7	(46.0)	[46.7]	-152.2	(-152.2)	[-114.6]
BLYP	6-31G(d,p)	19.2	(19.2)	[19.2]	19.2	(19.2)	[19.1]	46.6	(45.8)	[46.6]	-151.4	(-151.4)	[-113.6]
	cc-pVDZ	20.0	(20.2)	[19.7]	20.0	(20.2)	[19.7]	50.0	(47.0)	[50.0]	-156.0	(-156.0)	[-115.4]
	6-31+G(d,p)	25.1	(24.8)	[26.0]	25.1	(24.8)	[26.0]	55.9	(53.2)	[55.9]	-181.4	(-181.4)	[-119.7]
	6-31G(d)	7.4	(6.9)	[8.8]	-7.4	(-6.9)	[-8.8]	13.7	(13.6)	[13.7]	50.1	(50.1)	[31.9]
	6-31G(d,p)	7.3	(6.8)	[8.9]	-7.3	(-6.8)	[-8.9]	13.6	(13.1)	[13.6]	49.2	(49.2)	[31.2]
TPSS	cc-pVDZ	6.5	(5.8)	[8.3]	-6.5	(-5.8)	[-8.3]	15.7	(10.7)	[15.7]	46.0	(46.0)	[27.7]
	6-31+G(d,p)	1.7	(1.6)	[2.1]	-1.4	(-1.2)	[-2.0]	5.1	(5.1)	[5.0]	21.5	(16.8)	[21.5]
	6-31G(d)	15.4	(15.4)	[15.5]	15.4	(15.4)	[15.4]	38.9	(37.8)	[38.9]	-127.4	(-127.4)	[-96.7]
	6-31G(d,p)	15.4	(15.4)	[15.4]	15.4	(15.4)	[15.3]	38.8	(37.6)	[38.8]	-126.7	(-126.7)	[-94.7]
	cc-pVDZ	15.5	(15.5)	[15.3]	15.5	(15.5)	[15.3]	39.9	(36.7)	[39.9]	-122.2	(-122.2)	[-93.5]
TPSS-D	6-31+G(d,p)	18.7	(18.4)	[19.3]	18.7	(18.4)	[19.3]	43.4	(40.8)	[43.4]	-141.1	(-141.1)	[-95.3]
	6-31G(d)	6.6	(6.2)	[7.9]	-6.6	(-6.2)	[-7.9]	13.0	(12.5)	[13.0]	49.7	(49.7)	[31.0]
	6-31G(d,p)	6.7	(6.2)	[8.0]	-6.7	(-6.2)	[-8.0]	13.2	(12.3)	[13.2]	49.6	(49.6)	[30.4]
	cc-pVDZ	6.6	(6.1)	[8.0]	-6.6	(-6.1)	[-8.0]	13.5	(10.9)	[13.5]	42.3	(42.3)	[25.5]
	6-31+G(d,p)	3.4	(3.2)	[4.0]	-3.4	(-3.2)	[-4.0]	8.9	(7.4)	[8.9]	27.5	(27.5)	[22.4]
B97-D	6-31G(d)	6.1	(5.8)	[6.9]	-6.1	(-5.8)	[-6.7]	11.9	(11.9)	[11.4]	44.4	(44.4)	[26.4]
	6-31G(d,p)	6.1	(5.8)	[7.0]	-6.1	(-5.8)	[-6.9]	11.6	(11.6)	[11.5]	44.1	(44.1)	[26.0]
	cc-pVDZ	5.6	(5.3)	[6.4]	-5.6	(-5.3)	[-6.4]	11.7	(9.5)	[11.7]	45.1	(45.1)	[24.6]
	6-31+G(d,p)	2.1	(2.0)	[2.5]	-1.9	(-1.9)	[-1.9]	5.8	(5.8)	[5.3]	20.3	(20.3)	[20.1]
	aug-cc-pVDZ	2.8	(2.5)	[3.6]	-2.7	(-2.5)	[-3.0]	6.6	(6.1)	[6.6]	31.5	(26.4)	[31.5]
MPWB1K	6-31G(d)	6.2	(6.2)	[6.0]	6.0	(6.2)	[5.5]	15.9	(15.9)	[14.9]	-57.9	(-52.8)	[-57.9]
	6-31G(d,p)	6.1	(6.2)	[5.9]	6.0	(6.2)	[5.4]	15.8	(15.8)	[14.8]	-55.6	(-52.5)	[-55.6]
	cc-pVDZ	6.0	(6.0)	[6.0]	5.9	(6.0)	[5.5]	14.9	(13.7)	[14.9]	-53.3	(-46.4)	[-53.3]
	6-31+G(d,p)	8.1	(8.1)	[7.9]	8.1	(8.1)	[7.9]	17.2	(16.7)	[17.2]	-61.2	(-61.2)	[-53.9]
	aug-cc-pVDZ	7.1	(7.1)	[7.1]	7.1	(7.1)	[7.1]	15.0	(14.6)	[15.0]	-49.9	(-49.9)	[-42.8]
M05-2X	6-31G(d)	2.7	(2.6)	[2.8]	1.2	(1.5)	[0.4]	8.8	(8.8)	[7.5]	-31.8	(-30.4)	[-31.8]
	6-31G(d,p)	2.7	(2.6)	[2.9]	1.1	(1.4)	[0.1]	8.7	(8.7)	[8.0]	-29.9	(-29.9)	[-29.6]
	cc-pVDZ	2.4	(2.2)	[2.9]	1.0	(1.3)	[0.2]	9.3	(6.7)	[9.3]	-27.1	(-25.4)	[-27.1]
	6-31+G(d,p)	2.3	(2.4)	[2.2]	2.1	(2.2)	[1.8]	8.0	(8.0)	[6.5]	-31.3	(-31.3)	[-21.8]
	aug-cc-pVDZ	1.6	(1.6)	[1.5]	0.7	(0.9)	[0.3]	5.5	(5.5)	[3.4]	-19.1	(-19.1)	[-9.5]
M06-2X	6-31G(d)	1.9	(1.5)	[3.0]	-1.5	(-1.0)	[-2.7]	10.1	(5.4)	[10.1]	22.2	(22.2)	[-17.5]
	6-31G(d,p)	1.9	(1.5)	[3.2]	-1.6	(-1.1)	[-2.9]	10.4	(5.6)	[10.4]	22.1	(22.1)	[-14.5]
	cc-pVDZ	2.0	(1.6)	[3.1]	-1.8	(-1.4)	[-2.7]	11.3	(5.4)	[11.3]	15.5	(15.5)	[15.1]
	6-31+G(d,p)	1.6	(1.4)	[1.9]	-0.5	(-0.3)	[-1.2]	4.9	(4.4)	[4.9]	-17.0	(-17.0)	[14.3]
	aug-cc-pVDZ	2.0	(1.8)	[2.7]	-1.7	(-1.4)	[-2.4]	7.0	(6.8)	[7.0]	18.8	(18.8)	[17.8]
M06-L	6-31G(d)	2.3	(2.3)	[2.3]	2.2	(2.3)	[2.1]	5.1	(5.1)	[4.8]	-23.0	(-22.5)	[-23.0]
	6-31G(d,p)	2.2	(2.2)	[2.1]	2.1	(2.1)	[1.9]	4.9	(4.9)	[4.5]	-20.0	(-20.0)	[-19.5]
	cc-pVDZ	2.6	(2.4)	[2.9]	2.4	(2.4)	[2.5]	8.6	(6.5)	[8.6]	-27.5	(-27.5)	[-20.9]
	6-31+G(d,p)	2.7	(2.6)	[2.9]	2.7	(2.6)	[2.8]	6.0	(5.4)	[6.0]	-24.3	(-24.3)	[-17.0]
	aug-cc-pVDZ	2.3	(2.3)	[2.4]	2.2	(2.2)	[2.2]	6.1	(4.7)	[6.1]	-19.8	(-19.8)	[-13.0]
B2PLYP	6-31G(d)	15.7	(15.5)	[16.1]	15.6	(15.5)	[16.0]	40.0	(38.9)	[40.0]	-135.8	(-135.8)	[-101.8]
	6-31G(d,p)	15.7	(15.6)	[16.0]	15.7	(15.6)	[15.9]	39.9	(38.7)	[39.9]	-135.2	(-135.2)	[-100.8]
	cc-pVDZ	16.6	(16.5)	[16.7]	16.5	(16.5)	[16.6]	43.0	(39.7)	[43.0]	-139.4	(-139.4)	[-100.3]
	6-31+G(d,p)	20.0	(19.7)	[20.6]	20.0	(19.7)	[20.6]	47.4	(44.7)	[47.4]	-160.5	(-160.5)	[-104.8]
	aug-cc-pVDZ	19.2	(19.1)	[19.6]	19.2	(19.1)	[19.6]	45.0	(42.4)	[45.0]	-151.7	(-151.7)	[-93.3]
B2PLYP-D	6-31G(d)	4.5	(4.3)	[5.1]	3.5	(3.6)	[3.1]	14.7	(14.7)	[13.2]	-55.6	(-55.6)	[-37.1]
	6-31G(d,p)	4.5	(4.3)	[5.0]	3.6	(3.7)	[3.1]	14.5	(14.5)	[13.1]	-55.1	(-55.1)	[-36.1]
	cc-pVDZ	5.3	(5.0)	[5.9]	4.4	(4.6)	[3.8]	16.3	(14.7)	[16.3]	-59.3	(-59.3)	[-36.9]
	6-31+G(d,p)	7.8	(7.8)	[7.9]	7.8	(7.8)	[7.8]	20.6	(19.9)	[20.6]	-80.3	(-80.3)	[-44.5]
	aug-cc-pVDZ	7.1	(7.2)	[6.8]	7.1	(7.2)	[6.8]	18.6	(18.6)	[18.2]	-71.5	(-71.5)	[-37.9]
mPW2PLYP	6-31G(d)	11.7	(11.4)	[12.4]	11.5	(11.4)	[11.6]	32.6	(31.8)	[32.6]	-111.5	(-111.5)	[-81.8]
	6-31G(d,p)	11.7	(11.6)	[12.3]	11.6	(11.6)	[11.6]	32.5	(31.6)	[32.5]	-111.0	(-111.0)	[-80.7]
	cc-pVDZ	12.6	(12.5)	[13.0]	12.5	(12.5)	[12.4]	35.8	(32.9)	[35.8]	-116.2	(-116.2)	[-80.4]
	6-31+G(d,p)	16.0	(15.8)	[16.5]	16.0	(15.8)	[16.5]	40.6	(38.1)	[40.6]	-138.2	(-138.2)	[-84.7]
	aug-cc-pVDZ	15.3	(15.2)	[15.5]	15.3	(15.2)	[15.5]	38.2	(35.8)	[38.2]	-129.7	(-129.7)	[-78.2]
mPW2PLYP-D	6-31G(d)	4.3	(4.1)	[5.0]	2.7	(2.8)	[2.3]	14.2	(14.2)	[13.1]	-53.3	(-53.3)	[-34.7]
	6-31G(d,p)	4.2	(4.0)	[4.9]	2.7	(2.9)	[2.2]	14.0	(14.0)	[13.0]	-52.7	(-52.7)	[-33.6]
	cc-pVDZ	5.0	(4.7)	[5.9]	3.6	(3.8)	[3.0]	16.5	(14.5)	[16.5]	-57.9	(-57.9)	[-37.4]
	6-31+G(d,p)	7.2	(7.1)	[7.4]	7.1	(7.1)	[7.2]	21.1	(19.9)	[21.1]	-80.0	(-80.0)	[-45.6]
	aug-cc-pVDZ	6.5	(6.5)	[6.5]	6.4	(6.5)	[6.2]	18.8	(18.7)	[18.8]	-71.4	(-71.4)	[-39.1]
AM1		29.7	(28.0)	[34.4]	29.7	(28.0)	[34.4]	66.1	(59.0)	[66.1]	-184.4	(-184.4)	[-130.2]
PM3		29.6	(26.9)	[37.0]	29.6	(26.9)	[37.0]	69.3	(55.0)	[69.3]	-177.1	(-177.1)	[-130.2]
PM6		16.7	(14.8)	[21.8]	16.7	(14.8)	[21.8]	37.5	(27.8)	[37.5]	-86.7	(-86.7)	[-74.2]
AMBER		4.1	(2.1)	[9.8]	2.3	(-0.4)	[9.8]	18.7	(7.5)	[18.7]	-82.3	(19.5)	[-82.3]

^a Values reported are for all 129 dimer interaction energies, where values in parenthesis correspond to the 95 neutral dimer interactions, and the values in square brackets correspond to the 34 cationic dimer interactions. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Interaction Energies (kJ mol⁻¹) between Adenine and Histidine Potential Energy Surface Scans that Vary R₁ (Å), and α (°)^a

Stacked						
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
3.0	-10.2	-18.5	-18.8	-16.2	-18.4	-13.6
3.1	-14.9	-22.2	-21.7	-19.9	-21.4	-17.0
3.2	-17.3	-23.7	-22.2	-21.0	-22.2	-18.4
3.3	-18.1	-23.8	-21.5	-20.9	-21.7	-18.5
3.4	-17.8	-23.0	-19.3	-19.2	-20.5	-17.8
3.5	-16.9	-21.6	-16.4	-16.8	-19.0	-16.7
3.6	-15.6	-19.9	-13.8	-14.5	-17.2	-15.5
3.7	-14.1	-18.0	-11.3	-12.3	-15.4	-14.3
3.8	-12.6	-16.2	-8.9	-10.2	-13.7	-13.0
3.9	-11.1	-14.4	-6.8	-8.2	-12.0	-11.8
4.0	-9.7	-12.7	-5.1	-6.5	-10.4	-10.7

Stacked									
α	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
	R ₁ =3.3	R ₁ =3.3	R ₁ =3.2	R ₁ =3.3	R ₁ =3.2	R ₁ =3.2	R ₁ =3.2	R ₁ =3.3	R ₁ =3.3
0	-18.1	-23.8	-22.2	-21.5	-21.0	-20.9	-22.2	-21.7	-18.5
30	-19.2	-24.9	-24.3	-23.5	-22.3	-22.2	-24.3	-23.7	-19.9
60	-19.7	-25.3	-24.0	-23.1	-22.7	-22.4	-23.7	-23.2	-20.1
90	-20.0	-25.6	-23.6	-22.9	-22.0	-22.1	-23.8	-23.6	-20.1
120	-22.8	-28.7	-27.1	-26.3	-25.2	-25.2	-27.2	-26.7	-23.1
150	-27.0	-33.5	-31.7	-30.5	-31.5	-30.8	-30.9	-30.0	-27.6
180	-28.3	-34.6	-33.0	-31.8	-31.9	-31.4	-32.9	-31.9	-29.1
210	-25.1	-31.3	-29.1	-28.0	-28.3	-27.8	-28.4	-27.8	-25.2
240	-21.1	-26.9	-25.1	-24.3	-23.6	-23.4	-24.7	-24.3	-20.9
270	-19.7	-25.9	-24.5	-23.7	-23.4	-23.3	-23.8	-23.1	-20.1
300	-19.4	-25.7	-24.1	-23.2	-23.8	-23.5	-23.4	-22.8	-20.3
330	-18.0	-23.7	-21.8	-21.2	-20.2	-20.3	-22.4	-22.1	-18.5

HIS(edge) (θ=B)						
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
4.0	-8.1	-10.7	-10.8	-9.0	-18.1	-14.0
4.1	-12.9	-15.0	-14.8	-13.4	-22.0	-18.2
4.2	-15.7	-17.4	-16.7	-15.7	-23.8	-20.4
4.3	-16.9	-18.5	-17.2	-16.4	-24.1	-21.1
4.4	-17.2	-18.6	-16.8	-16.3	-23.5	-20.8
4.5	-16.9	-18.1	-15.9	-15.6	-22.2	-19.9
4.6	-16.1	-17.3	-14.7	-14.6	-20.7	-18.8
4.7	-15.2	-16.3	-13.5	-13.5	-19.2	-17.5
4.8	-14.1	-15.2	-12.3	-12.4	-17.6	-16.2
4.9	-13.1	-14.0	-11.2	-11.4	-16.1	-15.0
5.0	-12.0	-12.9	-10.2	-10.5	-14.6	-13.8

HIS(edge) ($\theta=B$)										
α	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)	PBE-D/ 6-31+G(d,p)
	R ₁ =4.4	R ₁ =4.4	R ₁ =4.3	R ₁ =4.4	R ₁ =4.3	R ₁ =4.4	R ₁ =4.3	R ₁ =4.4	R ₁ =4.3	R ₁ =4.4
0	-17.2	-18.6	-17.2	-16.8	-16.4	-16.3	-24.1	-23.5	-21.1	-20.8
30	-18.2	-19.7	-19.6	-18.8	-18.2	-17.7	-26.2	-25.1	-22.5	-21.9
60	-20.1	-21.5	-22.8	-21.4	-21.0	-20.0	-28.9	-27.3	-24.8	-23.7
90	-19.2	-20.4	-21.9	-20.4	-20.0	-18.9	-28.0	-26.4	-23.9	-22.7
120	-16.0	-17.0	-17.5	-16.5	-15.9	-15.2	-24.1	-22.9	-20.2	-19.4
150	-13.8	-14.8	-13.8	-13.4	-12.7	-12.6	-20.6	-20.1	-17.3	-17.1
180	-15.2	-16.4	-15.5	-15.1	-14.2	-14.1	-22.6	-22.0	-19.0	-18.8
210	-19.3	-20.6	-20.8	-19.8	-19.2	-18.5	-27.7	-26.4	-23.7	-22.9
240	-21.8	-23.3	-23.8	-22.5	-22.0	-21.0	-30.5	-29.0	-26.3	-25.3
270	-22.2	-23.5	-23.9	-22.7	-22.2	-21.3	-30.5	-29.0	-26.5	-25.4
300	-21.6	-22.7	-23.1	-21.7	-21.9	-20.7	-29.4	-27.9	-26.0	-24.8
330	-18.9	-20.1	-19.0	-18.3	-18.4	-17.9	-25.6	-24.7	-22.7	-22.1

^a See Figure 2.2 for the definition of R₁ and α. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Interaction Energies (kJ mol⁻¹) between 3-methyladenine and Histidine Potential Energy Surface Scans that Vary R₁ (Å), and α (°)^a

Stacked										
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)				
3.0	-24.4	-28.6	-30.6	-26.8	-33.1	-26.2				
3.1	-29.7	-33.0	-34.0	-31.1	-36.0	-29.9				
3.2	-32.2	-34.9	-34.7	-32.7	-36.6	-31.2				
3.3	-32.9	-35.1	-33.7	-32.6	-35.7	-31.1				
3.4	-32.4	-34.3	-31.2	-30.8	-34.0	-30.1				
3.5	-31.0	-32.7	-28.0	-28.3	-31.8	-28.7				
3.6	-29.2	-30.8	-24.8	-25.6	-29.5	-27.1				
3.7	-27.1	-28.7	-21.8	-23.1	-27.1	-25.4				
3.8	-24.9	-26.5	-18.8	-20.5	-24.7	-23.7				
3.9	-22.7	-24.4	-16.2	-18.1	-22.4	-22.1				
4.0	-20.6	-22.4	-13.9	-16.1	-20.2	-20.6				

Stacked										
α	MP2 ^b / 6-31G*(0.25) R ₁ =3.3	MP2 ^b / aug-cc-pVDZ R ₁ =3.3	M06-2X/ 6-31G(d) R ₁ =3.2	M06-2X/ 6-31G(d) R ₁ =3.3	M06-2X/ 6-31+G(d,p) R ₁ =3.2	M06-2X/ 6-31+G(d,p) R ₁ =3.3	PBE-D/ 6-31G(d) R ₁ =3.2	PBE-D/ 6-31G(d) R ₁ =3.3	PBE-D/ 6-31+G(d,p) R ₁ =3.2	PBE-D/ 6-31+G(d,p) R ₁ =3.3
0	-32.9	-35.1	-34.7	-33.7	-32.7	-32.6	-36.6	-35.7	-31.2	-31.1
30	-33.5	-35.6	-34.1	-33.5	-32.6	-32.8	-37.2	-36.6	-32.0	-32.1
60	-38.7	-41.2	-40.7	-39.6	-39.0	-38.7	-42.4	-41.5	-37.2	-36.9
90	-44.3	-47.2	-46.7	-45.6	-46.0	-45.5	-48.0	-46.6	-43.7	-43.0
120	-48.3	-51.0	-51.2	-49.7	-50.2	-49.5	-51.7	-50.3	-47.6	-46.9
150	-52.2	-54.8	-56.1	-53.9	-54.9	-53.6	-55.5	-53.6	-51.2	-50.0
180	-52.3	-54.7	-55.7	-53.5	-54.0	-52.8	-56.3	-54.3	-51.3	-50.1
210	-47.2	-49.9	-50.9	-48.7	-49.7	-48.4	-50.9	-49.0	-46.4	-45.2
240	-39.1	-41.5	-41.2	-39.9	-40.2	-39.6	-42.7	-41.3	-38.0	-37.3
270	-31.5	-33.5	-32.0	-31.5	-30.3	-30.5	-33.9	-33.5	-28.7	-29.0
300	-29.7	-31.8	-30.2	-29.4	-28.4	-28.4	-31.9	-31.4	-26.6	-26.8
330	-31.4	-33.5	-32.1	-31.5	-29.6	-29.9	-34.5	-33.9	-28.7	-28.9

HIS(edge) (θ=3)						
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
4.0	-51.7	-55.0	-53.3	-52.6	-56.2	-52.8
4.1	-53.1	-56.0	-53.9	-53.5	-57.0	-54.0
4.2	-53.3	-55.9	-53.1	-53.0	-56.5	-54.0
4.3	-52.6	-55.0	-51.6	-51.8	-55.1	-53.2
4.4	-51.4	-53.6	-49.6	-50.2	-53.3	-52.0
4.5	-49.8	-51.8	-47.4	-48.3	-51.1	-50.4
4.6	-48.0	-49.9	-44.9	-46.2	-48.8	-48.7
4.7	-46.0	-47.8	-42.4	-44.0	-46.4	-46.9
4.8	-44.0	-45.8	-40.1	-42.0	-44.0	-45.2
4.9	-42.1	-43.8	-38.0	-40.2	-41.7	-43.4
5.0	-40.1	-41.9	-36.0	-38.5	-39.5	-41.7

HIS(edge) (θ=3)										
α	MP2 ^b / 6-31G*(0.25) R ₁ =4.2	MP2 ^b / aug-cc-pVDZ R ₁ =4.2	M06-2X/ 6-31G(d) R ₁ =4.1	M06-2X/ 6-31G(d) R ₁ =4.2	M06-2X/ 6-31+G(d,p) R ₁ =4.1	M06-2X/ 6-31+G(d,p) R ₁ =4.2	PBE-D/ 6-31G(d) R ₁ =4.1	PBE-D/ 6-31G(d) R ₁ =4.2	PBE-D/ 6-31+G(d,p) R ₁ =4.1	PBE-D/ 6-31+G(d,p) R ₁ =4.2
0	-53.3	-55.9	-53.9	-53.1	-53.5	-53.0	-57.0	-56.5	-54.0	-54.0
30	-53.7	-56.3	-54.4	-53.6	-54.0	-53.5	-57.5	-57.0	-54.6	-54.6
60	-55.6	-58.2	-57.0	-55.9	-56.7	-56.0	-59.5	-58.7	-56.7	-56.5
90	-55.9	-58.4	-56.7	-55.8	-56.6	-56.0	-59.4	-58.8	-56.8	-56.7
120	-54.8	-57.3	-55.1	-54.4	-54.9	-54.4	-58.1	-57.6	-55.4	-55.4
150	-52.8	-55.4	-53.1	-52.3	-52.8	-52.4	-56.1	-55.6	-53.3	-53.3
180	-50.9	-53.4	-50.7	-50.2	-50.3	-50.0	-54.2	-53.9	-51.3	-51.4
210	-51.3	-53.7	-51.1	-50.5	-50.7	-50.4	-54.7	-54.2	-51.8	-51.8
240	-53.8	-56.3	-54.4	-53.4	-54.0	-53.4	-57.3	-56.7	-54.4	-54.3
270	-55.2	-57.7	-55.6	-54.7	-55.4	-54.9	-58.5	-58.0	-55.9	-55.8
300	-55.4	-58.0	-55.8	-55.0	-55.6	-55.1	-58.8	-58.2	-56.1	-56.1
330	-54.5	-57.2	-55.1	-54.4	-54.9	-54.4	-58.0	-57.4	-55.2	-55.2

^a See Figure 2.2 for the definition of R₁ and α. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Interaction Energies (kJ mol⁻¹) between Adenine and Protonated Histidine Potential Energy Surface Scans that Vary R₁ (Å), and α (°)^a

Stacked						
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
3.0	-51.1	-53.0	-54.6	-52.4	-57.4	-51.4
3.1	-53.7	-55.3	-55.4	-54.2	-57.9	-52.8
3.2	-54.0	-55.3	-54.1	-53.7	-56.4	-52.2
3.3	-52.6	-53.9	-51.6	-52.0	-53.8	-50.4
3.4	-50.3	-51.6	-47.8	-48.9	-50.6	-48.0
3.5	-47.4	-48.9	-43.5	-45.0	-47.1	-45.3
3.6	-44.3	-45.8	-39.4	-41.3	-43.7	-42.5
3.7	-41.0	-42.8	-35.7	-38.0	-40.3	-39.8
3.8	-37.9	-39.8	-32.2	-34.7	-37.2	-37.3
3.9	-34.9	-36.9	-28.9	-31.6	-34.2	-34.8
4.0	-32.1	-34.2	-26.2	-28.9	-31.4	-32.6

Stacked											
α	MP2 ^b / 6-31G*(0.25) R ₁ =3.2	MP2 ^b / aug-cc-pVDZ R ₁ =3.1	MP2 ^b / aug-cc-pVDZ R ₁ =3.2	M06-2X/ 6-31G(d) R ₁ =3.1	M06-2X/ 6-31G(d) R ₁ =3.2	M06-2X/ 6-31+G(d,p) R ₁ =3.1	M06-2X/ 6-31+G(d,p) R ₁ =3.2	PBE-D/ 6-31G(d) R ₁ =3.1	PBE-D/ 6-31G(d) R ₁ =3.2	PBE-D/ 6-31+G(d,p) R ₁ =3.1	PBE-D/ 6-31+G(d,p) R ₁ =3.2
0	-54.0	-55.3	-55.3	-55.4	-54.1	-54.2	-53.7	-57.9	-56.4	-52.8	-52.2
30	-54.4	-55.6	-55.4	-57.9	-56.0	-55.1	-54.2	-60.6	-58.5	-54.0	-53.0
60	-52.8	-54.1	-54.2	-55.1	-53.8	-53.3	-52.9	-57.5	-55.9	-52.0	-51.4
90	-54.4	-55.5	-55.7	-55.5	-54.4	-53.8	-53.6	-58.9	-57.4	-53.4	-52.8
120	-56.3	-57.6	-57.3	-58.5	-56.7	-55.9	-55.2	-62.3	-60.3	-56.1	-55.0
150	-55.2	-56.5	-56.3	-56.9	-55.5	-55.6	-55.0	-60.0	-58.2	-54.6	-53.7
180	-55.5	-56.2	-56.3	-58.0	-56.5	-55.2	-54.7	-61.8	-60.0	-55.2	-54.3
210	-54.0	-55.0	-55.3	-55.2	-54.3	-53.6	-53.6	-58.0	-56.7	-52.7	-52.3
240	-57.2	-58.5	-58.4	-59.4	-57.9	-57.0	-56.5	-62.3	-60.5	-56.3	-55.5
270	-58.4	-60.2	-59.8	-61.1	-59.3	-59.1	-58.3	-64.0	-61.9	-58.3	-57.2
300	-57.7	-59.3	-59.2	-59.2	-58.1	-58.4	-58.0	-62.1	-60.4	-57.3	-56.4
330	-57.2	-58.4	-58.4	-59.2	-57.7	-57.0	-56.4	-63.0	-61.1	-57.0	-56.1

HIS(edge) (θ=1)						
R ₁	MP2 ^b / 6-31G*(0.25)	MP2 ^b / aug-cc-pVDZ	M06-2X/ 6-31G(d)	M06-2X/ 6-31+G(d,p)	PBE-D/ 6-31G(d)	PBE-D/ 6-31+G(d,p)
4.0	-42.9	-42.8	-39.8	-35.8	-54.9	-47.9
4.1	-47.1	-46.4	-43.5	-39.8	-57.2	-50.5
4.2	-48.7	-47.6	-44.9	-41.5	-57.4	-51.2
4.3	-48.6	-47.3	-44.7	-41.8	-56.1	-50.5
4.4	-47.3	-45.9	-43.3	-41.0	-53.9	-48.9
4.5	-45.3	-44.0	-41.1	-39.4	-51.1	-46.8
4.6	-42.9	-41.7	-38.6	-37.4	-47.9	-44.3
4.7	-40.3	-39.2	-35.9	-35.2	-44.5	-41.5
4.8	-37.7	-36.7	-33.3	-33.0	-41.1	-38.7
4.9	-35.1	-34.3	-30.8	-30.8	-37.9	-36.0
5.0	-32.6	-32.0	-28.5	-28.7	-34.9	-33.4

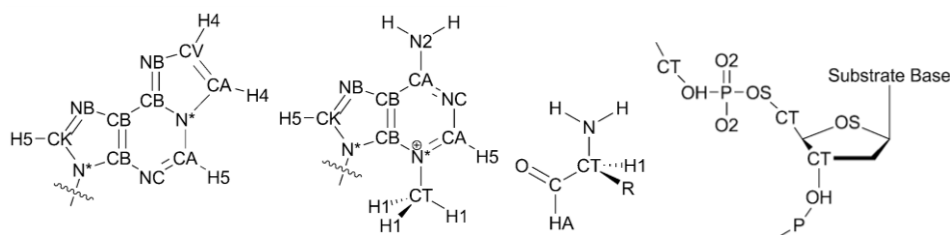
HIS(edge) (θ=1)							
α	MP2 ^b / 6-31G*(0.25) R ₁ =4.2	MP2 ^b / aug-cc-pVDZ R ₁ =4.2	M06-2X/ 6-31G(d) R ₁ =4.2	M06-2X/ 6-31+G(d,p) R ₁ =4.2	M06-2X/ 6-31+G(d,p) R ₁ =4.3	PBE-D/ 6-31G(d) R ₁ =4.2	PBE-D/ 6-31+G(d,p) R ₁ =4.2
0	-48.7	-47.6	-44.9	-41.8	-41.5	-57.4	-51.2
30	-51.7	-50.8	-48.2	-44.9	-44.9	-60.3	-54.3
60	-53.7	-52.6	-50.4	-46.9	-46.9	-62.5	-56.3
90	-52.9	-51.6	-49.5	-45.9	-45.8	-61.9	-55.4
120	-50.8	-49.4	-47.2	-43.8	-43.5	-59.6	-53.2
150	-48.8	-47.6	-45.1	-42.2	-41.9	-57.3	-51.3
180	-49.3	-48.2	-45.7	-42.7	-42.4	-57.8	-51.9
210	-51.4	-50.6	-48.0	-44.9	-44.9	-60.1	-54.2
240	-52.8	-51.8	-49.4	-46.0	-46.0	-61.7	-55.6
270	-51.7	-50.4	-48.0	-44.5	-44.3	-60.7	-54.2
300	-49.4	-48.0	-45.6	-42.1	-41.8	-58.4	-51.8
330	-47.6	-46.4	-43.7	-40.6	-40.2	-56.2	-50.0

^a See Figure 2.2 for the definition of R₁ and α. ^b MP2 interaction energies were calculated using the BSSE-corrected dimer energies.

Appendix I

AMBER Atom Types and Parameters, Tables of Energies for the PES Plots, and Important Structural Information for Constrained Stationary Points for ϵ A and 3MeA

	Page
AMBER Atom Types	I-2
AMBER and GAFF Parameters	I-2
Relative Energies for PES Plots	I-3-I-4
ϵ A (Wat502 and Wat517 nucleophile)	I-3
3MeA	I-4
A	I-4
Important Structural Information for Constrained Stationary Points	I-5
ϵ A	I-5
3MeA	I-5



AMBER atom types used in the present study (as determined through ANTECHAMBER).

AMBER and GAFF bond and angle parameters used in the present study.

Bond	K_r	r_{eq}	Derived from:
N* CA	411.10	1.391	Same as na-c2
CA H5	344.30	1.087	Same as c2-ha
CA CV	411.70	1.434	Same as ca-cc
CA N*	411.10	1.391	Same as na-c2
CA H5	344.30	1.087	Same as c2-ha
C HA	325.1	1.101	Same as c-ha
Angle	K_θ	θ_{eq}	Derived from:
N* CA CV	69.8	121.38	Same as na-c2-c2
N* CA NC	71.7	123.62	Same as n2-c2-na
N* CA H5	51.2	112.42	Same as na-c2-ha
N* CB NB	71.7	123.62	Same as n2-c2-na
N* CA H4	51.2	122.42	Same as na-c2-ha
CA N* CB	67.8	110.37	Same as c2-na-c2
CA N* CA	67.8	110.37	Same as c2-na-c2
NC CA H5	52.4	120.54	Same as n2-c2-ha
CB CB CB	67.9	110.70	Same as cc-cc-cc
CB NB CV	68.6	110.19	Same as cc-nc-cc
NB CV CA	70.0	113.42	Same as nc-cc-cc
CA CV H4	50.0	120.94	Same as c2-c2-ha
CV CA H4	50.0	120.94	Same as c2-c2-ha
N* CA NC	71.7	123.62	Same as n2-c2-na
NC CA H5	52.4	120.54	Same as n2-c2-ha
CA NC CA	70.7	109.95	Same as ca-nc-ca
CA N* CB	67.8	110.37	Same as c2-na-c2
CA N* CT	64.2	117.20	Same as c2-na-c3
N* CA H5	51.2	112.42	Same as na-c2-ha
N* CB N*	73.7	109.33	Same as na-c2-na
CT C HA	46.0	115.22	Same as c3-c-ha
O C HA	55.4	120.00	Same as o-c-hc
CT C CT	63.0	117.00	From parm99.dat
P OH CT	100.0	120.50	Same as P-OS-CT

ONIOM(M06-2X/6-31G(d):AMBER) Relative (Optimization) Energies (kJ mol⁻¹) for the εA PES where Wat502 is Considered as the Nucleophile.

		C1'-N9 Glycosidic Bond Length (Å)												
		1.300	1.500	1.700	1.900	2.100	2.300	2.500	2.700	2.900	3.100	3.300	3.500	3.700
C1'-O _{Wat502} Nucleophile-C1' Distance (Å)	1.200					376.5	294.3	251.0	221.0	209.3	196.5	185.1	214.0	208.3
	1.400				354.9	256.4	192.9	141.6	126.1	115.6	117.0	65.9	57.4	98.7
	1.600		351.7	295.8	242.4	223.4	168.2	156.1	127.9	116.0	101.2	111.8	95.4	104.1
	1.800	327.3	212.6	203.2	182.9	158.5	144.6	122.8	124.9	125.0	107.7	115.7	101.4	119.8
	2.000	194.1	100.4	132.6	141.6	150.0	135.3	121.3	125.4	128.1	133.1	131.6	118.1	120.2
	2.200	114.5	59.0	81.0	114.2	127.8	139.6	129.2	136.5	136.8	152.2	127.1	143.1	147.0
	2.400	100.0	29.8	57.5	94.8	115.4	132.1	136.3	144.8	147.1	150.9	153.0	176.0	170.0
	2.600	68.6	14.6	37.5	79.3	108.9	138.9	143.7	144.9	159.0	160.6	155.5	167.4	201.2
	2.800	68.2	0.7	34.7	74.5	110.5	121.4	128.8	143.4	160.9	161.9	141.5	209.1	181.8
	3.000	55.8	10.1	31.9	76.1	113.2	129.0	154.8	162.0	162.0	166.4	140.2	224.5	207.5
	3.200	58.5	0.0	54.1	94.6	128.3	153.1	163.5	177.5	184.4	177.2	211.7	211.8	225.0
	3.400	70.0	19.3	59.0	96.2	132.4	156.4	161.5	173.0	182.4	189.7	182.3	213.8	201.1
	3.600	76.6	34.9	60.0	119.1	132.8	148.9	166.9	168.1	186.7	198.6	185.5	215.4	218.6

ONIOM(M06-2X/6-31G(d):AMBER) Relative (Optimization) Energies (kJ mol⁻¹) for the εA PES where Wat517 is Considered as the Nucleophile.

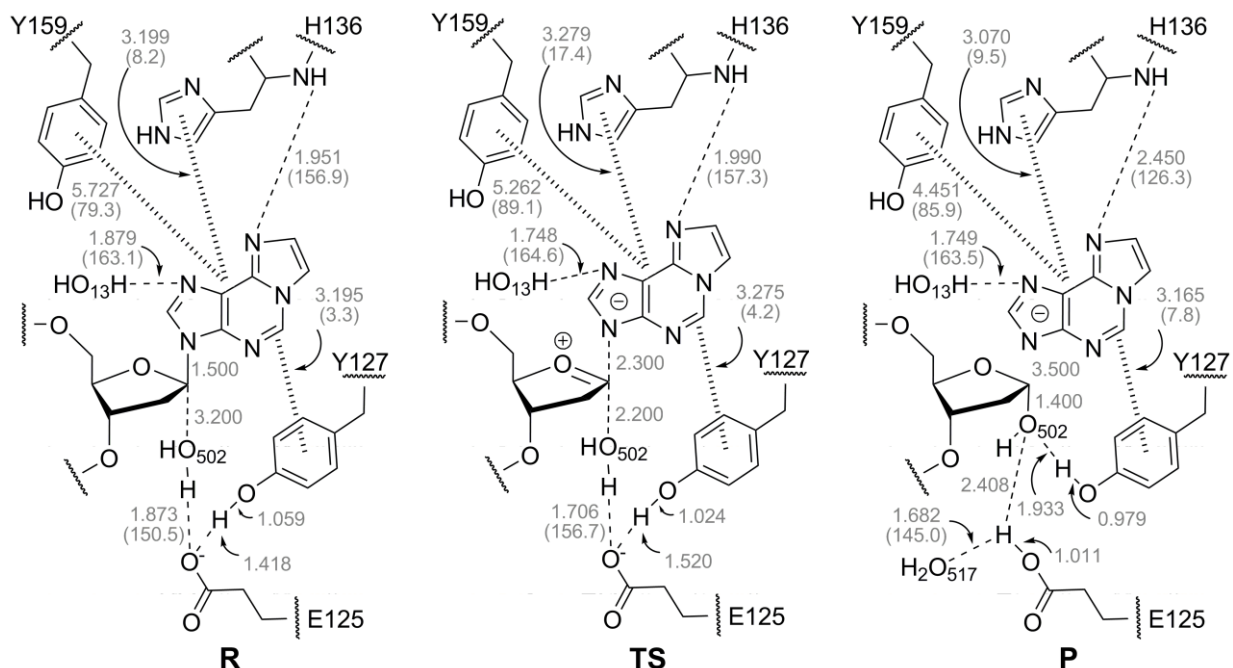
		C1'-N9 Glycosidic Bond Length (Å)												
		1.300	1.500	1.700	1.900	2.100	2.300	2.500	2.700	2.900	3.100	3.300	3.500	3.700
C1'-O _{Wat517} Nucleophile-C1' Distance (Å)	1.200													
	1.400													
	1.600													
	1.800	350.9	323.5	346.2	377.2	375.4	415.7	333.5	275.8	205.8	193.8	190.6	176.4	172.5
	2.000	243.6	185.8	221.7	265.3	300.7	314.7	317.4	314.4	274.1	225.3	197.4	208.6	196.5
	2.200	159.9	101.3	133.3	174.3	207.4	217.9	229.0	251.9	256.5	248.1	266.1	232.8	215.5
	2.400	108.0	54.9	73.7	120.2	157.8	187.6	189.2	193.9	197.9	216.1	264.8	235.1	247.2
	2.600	83.6	22.9	57.5	80.2	131.1	162.1	169.3	182.1	189.3	200.1	214.6	220.5	219.3
	2.800	69.4	17.5	45.8	80.7	112.5	149.7	152.3	162.8	173.0	177.4	197.7	198.2	221.1
	3.000	65.8	0.0	47.8	79.2	113.8	145.7	150.7	159.5	167.1	189.6	190.7	183.9	211.2
	3.200	56.3	10.4	39.7	96.0	125.1	156.5	164.2	162.7	166.3	207.0	200.1	185.1	197.6
	3.400	71.8	5.9	43.4	99.2	139.4	161.6	173.1	179.0	168.3	171.3	204.6	219.5	194.3

ONIOM(M06-2X/6-31G(d):AMBER) Relative (Optimization) Energies (kJ mol⁻¹) for the 3MeA PES where Wat502 is Considered as the Nucleophile.

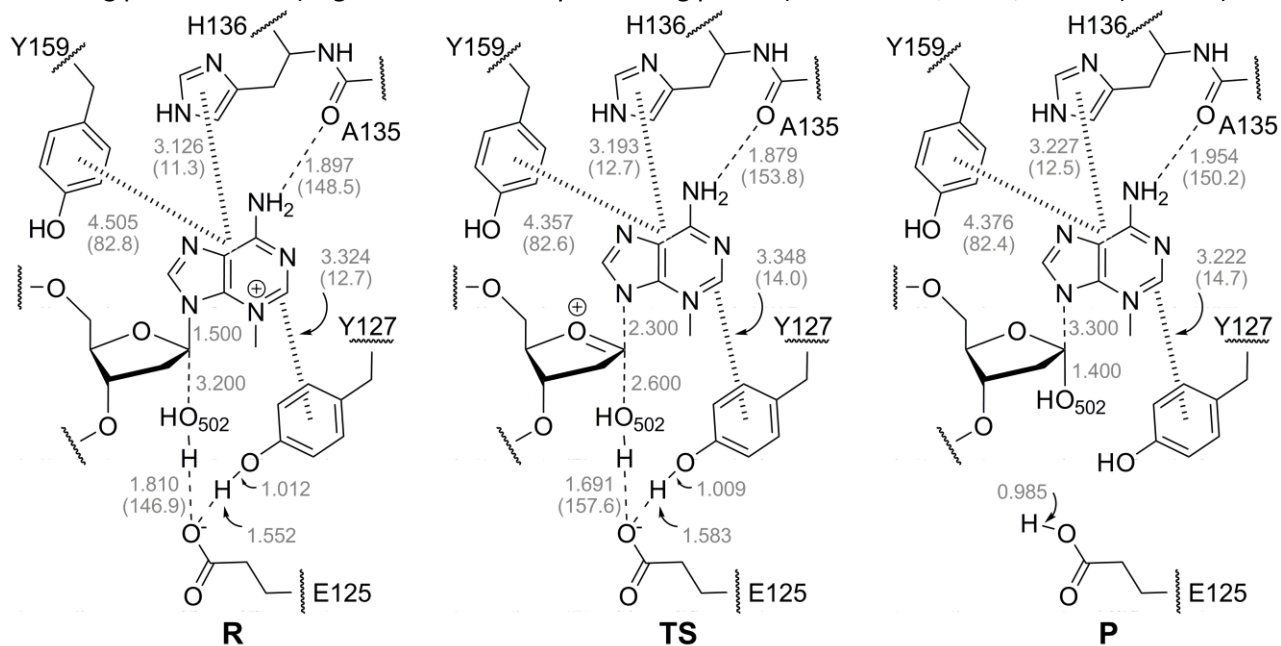
		C1'-N9 Glycosidic Bond Length (Å)											
		1.300	1.500	1.700	1.900	2.100	2.300	2.500	2.700	2.900	3.100	3.300	3.500
C1'-O _{wat502} Nucleophile-C1' Distance (Å)	1.200						198.4	140.7	121.6	118.7	101.2	117.2	102.3
	1.400						109.9	48.0	10.4	7.4	5.2	-12.6	-3.0
	1.600					201.7	125.0	59.6	62.3	14.8	9.0	7.8	19.9
	1.800			205.5	183.6	158.7	106.4	64.1	77.5	44.5	72.0	86.0	81.2
	2.000	264.1	143.2	113.4	115.0	121.7	82.7	69.4	68.1	56.9	85.4	85.3	86.2
	2.200	181.7	29.9	51.3	82.9	108.6	95.8	68.3	78.2	50.2	59.9	66.8	65.2
	2.400	127.5	28.0	49.2	70.0	83.4	79.2	77.5	62.9	48.8	50.7	77.9	67.8
	2.600	107.8	27.3	39.1	51.1	80.1	80.9	76.8	101.1	64.9	60.1	53.8	46.3
	2.800	77.1	11.2	26.6	49.1	65.8	80.8	90.6	101.4	95.3	76.3	79.2	74.4
	3.000	64.8	0.4	22.8	52.3	64.6	78.1	87.5	96.4	94.6	87.6	92.6	86.8
	3.200	67.9	0.0	16.9	39.3	55.9	74.2	88.8	100.1	92.7	87.8	90.5	92.7
	3.400	69.0	1.3	2.1	29.5	59.1	75.0	92.7	100.4				
	3.600	72.5	0.0	18.0	44.1	58.8	74.1	101.0					

ONIOM(M06-2X/6-31G(d):AMBER) Relative (Optimization) Energies (kJ mol⁻¹) for the A PES where Wat502 is Considered as the Nucleophile.

		C1'-N9 Glycosidic Bond Length (Å)											
		1.300	1.500	1.700	1.900	2.100	2.300	2.500	2.700	2.900	3.100	3.300	
C1'-O _{wat502} Nucleophile-C1' Distance (Å)	1.300						230.2	137.8	132.0	86.8	79.7	70.5	
	1.500					225.2	166.7	118.7	62.1	23.1	7.3	43.2	
	1.700				239.7	202.8	194.0	144.5	123.4	110.7	127.5	85.3	
	1.900	310.4	206.7	204.6	202.9	199.6	176.0	148.6	145.8	130.6	130.0	137.4	
	2.100	200.3	119.6	134.1	156.7	171.4	160.8	134.8	150.0	135.0	161.4	165.0	
	2.300	131.5	66.1	95.6	127.5	141.6	138.2	136.0	152.4	145.3	140.0	181.2	
	2.500	96.2	38.0	61.7	106.2	125.8	127.6	138.0	96.3	116.2	130.1	127.8	
	2.700	80.5	8.7	42.6	91.9	111.6	122.8	106.5	100.6	119.5	138.9	135.0	
	2.900	68.2	1.5	36.3	82.7	100.6	113.7	115.3	120.0	121.8	140.2	138.7	
	3.100	67.6	0.0	40.2	82.0	107.5	113.0	116.1	121.0	155.3	164.7		
	3.300	62.2	6.8	42.7	89.1	112.0	121.0	123.6	124.0	153.5			
	3.500	60.4	6.9	28.6	74.9	115.0	122.3						



Important ONIOM(M06-2X/6-31G(d):AMBER) structural information (hydrogen-bond distances in Å (angles in °)) for the constrained stationary points found when considering the ϵ A substrate. Stacking and T-shaped interactions are indicated through wide dashed lines (distances measured between heavy atom ring centroids (Y127, H136, and Y159) and the ϵ A heavy atom ring plane are in Å (angles between heavy atom ring planes (ϵ A and Y127, H136, or Y159) are in °).



Important ONIOM(M06-2X/6-31G(d):AMBER) structural information (hydrogen-bond distances in Å (angles in °)) for the constrained stationary points found when considering the 3MeA substrate. Stacking and T-shaped interactions are indicated through wide dashed lines (distances measured between heavy atom ring centroids (Y127, H136, and Y159) and the 3MeA heavy atom ring plane are in Å (angles between heavy atom ring planes (3MeA and Y127, H136, or Y159) are in °).