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THE STEREOCHEMISTRY OF SUBSTITUENT EFFECTS IN ALPHA-SULFONYL CARBANION FORMATION

by

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GRADUATE PROGRAM

IN

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ABSTRACT

This thesis describes studies designed to cast light on the ways in which the nature and geometry of one part of a molecule may influence reaction in another part of the same molecule. The specific feature examined was the effect that varying the stereochemistry of a substituent group would have on the ease of reaction of a β-substituted sulfone with strong base to form the substituted α-sulfonyl carbanion. King and Rathore in this laboratory first found that the rate of hydroxide-promoted H-D exchange alpha to a sulfonyl group is strongly influenced by the presence of an ether oxygen at the beta position, with acceleration by oxygen varying from 10^2 to 10^4, depending whether the H_α-C_α-C_β-O torsion angle was 60° or 180°. Later King and Guo in this laboratory extended this study to include substrates with other H_α-C_α-C_β-O torsion angles (θ), and the following equation was obtained.

$$\log k_N = 1.6\,(1.7 + \cos 2\theta)$$

Chapter 1 of this thesis gives some related background information about the quantitative study of substituent effects and the anomeric effect (negative hyperconjugation). The details of the previous work mentioned above are also presented.

Chapter 2 describes the continuation of the previous work in this laboratory, leading eventually to the measurement of rates of H-D exchange for nineteen β-alkoxy sulfones believed to have known fixed H_α-C_α-C_β-O torsion angles. In order to get a clear picture about the geometry dependence of the substituent effect, some complicating factors which may increase or decrease the reaction rate, such as the steric effect and the gamma inductive effect, are also explored. This study leads to the conclusion that the

effect of the β-alkoxy substituent cannot be accounted for by the inductive and field effect, but must involve another factor; it is proposed that this factor is the negative hyperconjugation (generalized anomeric effect). The following revised equation is presented.

$$\log k_N \text{ (alkoxy)} = (3.00 \pm 0.08) + (1.31 \pm 0.10) \cos 2\theta$$

$$= (1.70 \pm 0.17) + (2.62 \pm 0.20) \cos^2\theta$$

A new angle dependent feature of the Taft substituent constant (σ_θ^*) is also proposed with the following equation.

$$(\sigma_\theta^*)_{OR} = (0.61 \pm 0.02) + (0.27 \pm 0.02) \cos 2\theta$$

$$= (0.35 \pm 0.03) + (0.54 \pm 0.04) \cos^2\theta$$

This new picture is applied to the interpretation of a long standing mechanistic puzzle, the mechanism of the elimination in β-tosyloxy sulfones originally studied by Pearson, Bordwell, and Hine, et al.

Chapter 3 describes the generalization of the conclusions of Chapter 2. It includes the studies in β-thioalkoxy, β-amino, β-sulfonyl, and β-trialkylammonio systems in addition to the β-alkoxy system. It includes the synthetic and kinetic studies of the β-heteroatom (X) substituted sulfones with a ~60° or ~180° H_α-C_α-C_β-X torsion angle. It is clear that the angle dependence of substituent effect is a general phenomenon. In the case of the β-ammonio systems, which are known to show unusual behavior in the anomeric effect to the point that a 'reverse anomeric effect' has been postulated, our β-ammonio system shows a strong, normal anomeric effect. The origin of the 'reverse anomeric effect' is discussed.

ACKNOWLEDGMENT

I would like to express my sincere appreciation, with deep gratitude and respect, to my supervisor, Professor J. F. King for guidance, constant encouragement, valuable advice, and his endless patience during the course of these studies.

I would like to thank everyone in the Chemistry Department for their cooperation and help throughout the years of my studies. I am also indebted to Professor N. C. Payne for the x-ray crystal structure determinations.

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CHAPTER 1

BACKGROUND

1.1 THE ORIGINAL PROPOSAL

A key procedure for many years in the study of reaction mechanisms has been to examine the influence of a small perturbation in structure - a change of substituent - on properties and reactivity in the substrate. For reactions of non-conjugated systems the electronic effect of a substituent is customarily described as a *polar* effect, itself consisting of an inductive (or electronegativity) effect in which the action of the substituent is propagated along the σ-bond array, and a field (or Coulombic) effect in which the substituent acts directly through space; another effect, polarizability, is sometimes also included.[1, 2a, 3-5] The overall picture has been widely accepted as sufficient for at least three decades.

In 1977, Stirling and Thomas[6, 7] reported that the detritiation of β-substituted acyclic ethyl phenyl sulfones, $PhSO_2CHTCH_2X$, in ethanolic sodium ethoxide depended very strongly on the substituent X (Scheme 1.1.1), showing a good correlation with σ* (of CH_2X, $\rho^* = 4.89$); the effect of changing from CH_3 to OPh, for example, was to increase the exchange rate by about 50,000-fold.

$$PhSO_2CHTCH_2X \xrightarrow{k_{ex}} PhSO_2\overset{\ominus}{C}HCH_2X \xrightarrow{EtOH} PhSO_2CH_2CH_2X$$

Scheme 1.1.1

Such a very large substituent effect raises the question of whether the conventional polar effect terms, i.e. inductive and field effects, are sufficient to account for these observations. This in turn raises the possibility that a third effect, namely the anomeric effect or negative hyperconjugation, might be contributing as well.

The present research is a reinvestigation of the components of a substituent effect,

and a semi-quantitative study, at least, of the significance of the anomeric effect (negative hyperconjugation) of a β-substituent in a carbanion-forming reaction.

To put this work into perspective it is necessary to review (a) earlier work on substituent effects, (b) the anomeric effect and its relation to negative hyperconjugation, and then (c) the stereochemistry of sulfonyl carbanion formation, and finally (d) on the theoretical researches in the literature on the angle dependence of the anomeric effect (negative hyperconjugation). Substituent effects will be discussed first.

1.2 THE QUANTITATIVE STUDY OF SUBSTITUENT EFFECTS — THE HAMMETT EQUATION AND THE TAFT EQUATION

The discovery and improvement of methods for quantitative correlation of rate and equilibrium constants are among the most important developments in the history of physical organic chemistry. It was Hammett[1, 2a] who found that for a large number of reactions of *meta*- and *para*-substituted benzene derivatives. the plot of the logarithms of rate (k) or equilibrium constants (K) for one reaction vs. log k or log K for another reaction gave an acceptable linear relationship (eq 1.2.1). Note that the *ortho*-substituted benzene derivatives are not included because of possible additional influences (steric effect, hydrogen bonding, etc.) from the *ortho*-substituent.

$$\log K = \rho \log K' + \text{constant.} \qquad \text{(eq 1.2.1)}$$

Hammett defined the ionization of the substituted benzoic acids as the reference reaction, i.e. that in which $\rho = 1$. Setting hydrogen as the reference substituent ($\sigma = 0$) he was able to evaluate a substituent constant (σ) for an array of substituent groupings from the relation

$$\log K / K_0 = \sigma \qquad \text{(eq 1.2.2)}$$

Where K is the ionization constant of the substituted benzoic acid and K_0 refers to the ionization of benzoic acid. Hence,

$$\log K/K_0 = \rho \sigma \qquad \text{(eq 1.2.3)}$$

Note a similar equation for the reaction rate (k) may be derived similarly.

$$\log k/k_0 = \rho \sigma \qquad \text{(eq 1.2.4)}$$

Where k_0 refers to the rate constant of the 'unsubstituted' (hydrogen substituted) compound.

Equations 1.2.3 and 1.2.4 are both called the Hammett equation. In the Hammett equation, the substituent constant (σ) is a measure of the electron-withdrawing ability of a substituent, while the reaction constant (ρ) reflects the nature of this reaction and the sensitivity of the substrate to the electronic effect of the substituent in that reaction. An electron-donating substituent has a negative substituent constant ($\sigma < 0$), while an electron-withdrawing substituent has a positive σ value. For example, *p*-MeO group is electron-donating ($\sigma = -0.27$) while *p*-NO_2 ($\sigma = 0.78$) is electron-withdrawing; *p*-methoxybenzoic acid is weaker than benzoic acid while *p*-nitrobenzoic acid is stronger. For a particular reaction, a positive ρ value indicates that an electron-withdrawing group (relative to hydrogen) will increase the reaction rate or equilibrium constant, while a negative ρ value implies an electron-donating group will increase the reaction rate or equilibrium constants; when $\rho > 1$, the ionization or reaction rate is more sensitive to substituent effects than is the ionization of the benzoic acids in water at 25 °C.

A plot of log *k* vs σ is commonly used to study the mechanism of a reaction. Electron demand or release at the reaction centre is signalled by the sign and magnitude of ρ. Change of the slope (ρ value) of the plot is also diagnostic: "concave upwards, is indicative of a change in mechanism, while a discontinuity concave downwards is indicative of a change in the rate-determining step."[8a]

A substituent effect in a benzene system includes at least two physical phenomena, the polar effect (the total of inductive and field effects; sometimes the term "inductive effect" is used to include also the field effect) and the resonance effect. Great effort has been exerted to separate these two, particularly by R. W. Taft[9, 10] and G. Swain.[11, 12] A substituent constant (σ) was considered to have two components: the

universal inductive constant (σ_I) and the resonance constant (σ_R) (eq 1.2.5),[8b]

$$\sigma^0 = \sigma_I + \sigma_R \qquad \text{(eq 1.2.5)}$$

and a rate series would fit into a two-term equation such as:

$$\log k/k_0 = \rho_I \sigma_I + \rho_R \sigma_R \qquad \text{(eq 1.2.6)}$$

The Hammett equation is defined for aromatic systems. In an aliphatic non-conjugated system, the resonance effect (σ_R) may generally be ignored. If the steric effect is also not important, only the polar effect functions and we have the simplest forms of the Taft equation (eq 1.2.7, and eq 1.2.8).

$$\log k_X / k_0 = \rho^* \sigma^*. \qquad \text{(eq 1.2.7)}$$

$$\log K_X / K_0 = \rho^* \sigma^*. \qquad \text{(eq 1.2.8)}$$

Because both σ^* and σ_I are related to the polar effect (or universal inductive effect), eq 1.2.9 has been proposed for most of the substituents.[1, 10]

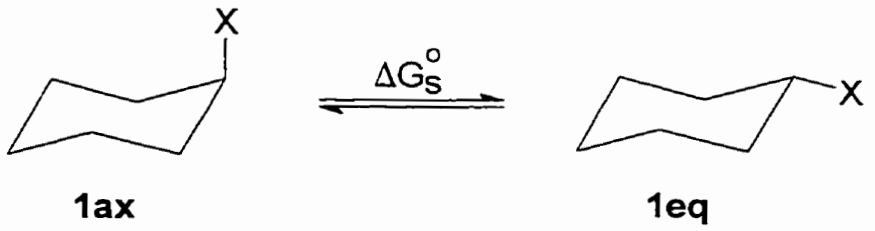
$$\sigma_{I(X)} = 0.45\ \sigma^*_{(XCH2)} \qquad \text{(eq 1.2.9)}$$

As in the Hammett equation (eq 1.2.3 or eq 1.2.4), the value of ρ^* measures the sensitivity of a reaction to a substituent, and the value of σ^* reflects the electron-withdrawing power of the substituents, and Taft plots may be used to probe the mechanism in much the same way as the Hammett equation.

Note that it has been traditional to treat the electronic effect in a saturated system as consisting of only the (traditional) polar effect — i.e. the sum of inductive and field effects. As has been mentioned in section 1.1, it is the contention of this thesis that an anomeric effect or a negative hyperconjugation plays an important role in a substituent effect in the particular case of α-carbanion formation in a saturated β-substituted sulfone system, and hence, by extension, in all saturated reacting systems.

1.3 ANOMERIC EFFECT AND NEGATIVE HYPERCONJUGATION

For the vast majority of cases the more stable chair conformer of a mono-substituted cyclohexane is the one with its substituent (X) equatorial (Scheme 1.3.1).



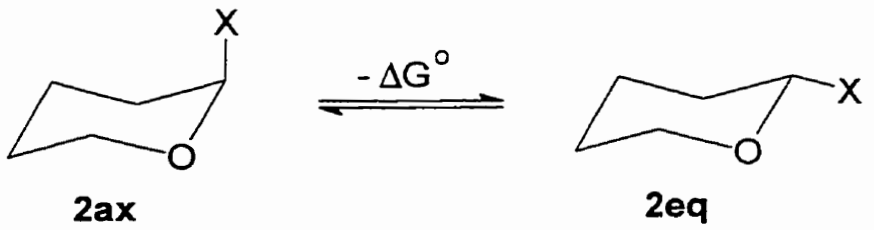
Scheme 1.3.1

When X is axial, as in **1ax**, there are destabilizing steric repulsions. The free-energy difference between axial and equatorial conformers (eq 1.3.1),

$$\Delta G_s^\circ = - RT \ln ([\mathbf{1eq}]/[\mathbf{1ax}]) \qquad (1.3.1)$$

is customarily taken as a quantitative measure of those steric repulsions. The values for $-\Delta G_s^\circ$ are sometimes referred to as "A values".

When a tetrahydropyran ring (Scheme 1.3.2) bears an electronegative substituent X adjacent to oxygen, additional interactions shift the equilibrium so that the axial conformer is commonly the more stable one. This phenomenon is called the *anomeric effect.*[13a]



Scheme 1.3.2

and

$$- \Delta G^\circ = RT \ln ([\mathbf{2eq}]/[\mathbf{2ax}]) \qquad (1.3.2)$$

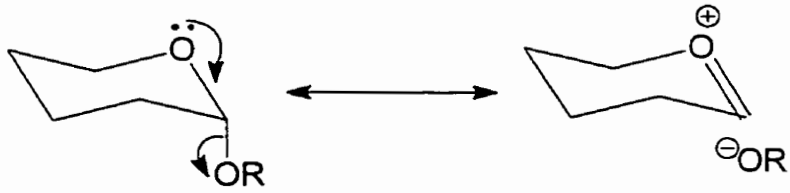
Since the anomeric effect opposes steric repulsion, a quantitative measurement of the anomeric effect is given by eq 1.3.3.

$$\text{anomeric stabilization} = \Delta G^\circ - \Delta G^\circ \text{ (steric)} \qquad (1.3.3)$$

Where, ΔG° (steric) should be the steric preference for equatorial X in a tetrahydropyran, but the ΔG_s° of the eq 1.3.1 is used for simplicity.

The *generalized anomeric effect* "describes the preference for synclinal (sc, gauche) over anti-periplanar (ap, trans) conformations in the molecular fragment W-X-Y-Z, where X possesses one or more pairs of non-bonding electrons, Z is electron-withdrawing and W and Y are of intermediate electronegativity (Y is usually C, P, Si, S)".[14a]

The theoretical basis of the "anomeric effect" has been subject to much discussion. The factor currently believed to account for most of the anomeric effect is *negative (or anionic) hyperconjugation*, i.e. the delocalization of a lone pair of electrons in an orbital on the oxygen into the anti-bonding orbitals of the C_1-OR system, i.e. $n \rightarrow \sigma^*$.



Scheme 1.3.3

Figure 1.3.1a (X = OR for Scheme 1.3.3) shows the stabilization due to the mixing of these two orbitals and creation of a new, lower-energy orbital. The energy of

this new orbital will decrease if the energy of $\sigma^*_{C\text{-}X}$ orbital is lowered. When X is an electronegative element or group (like F), greater stabilization can be expected. On the other hand, there is less stabilization if X is H. In Figure 1.3.1b, the greater stabilization (solid arrow) arises from the lower energy (dashed arrow) of the σ* orbital of $C\text{-}X^-$.

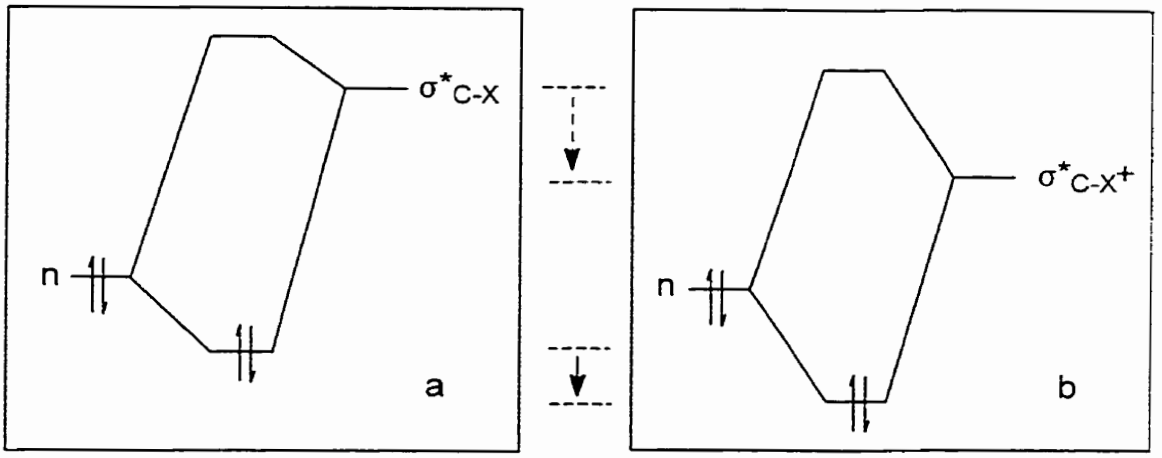
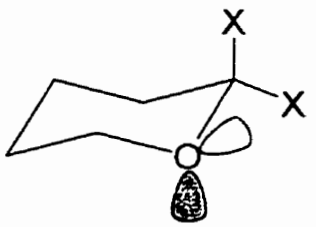


Figure 1.3.1 Filled-vacant stabilizing interaction of long pair (n) with (a) C-X antibonding (σ*) orbital; (b) $C\text{-}X^-$ antibonding (σ*) orbital.[15]

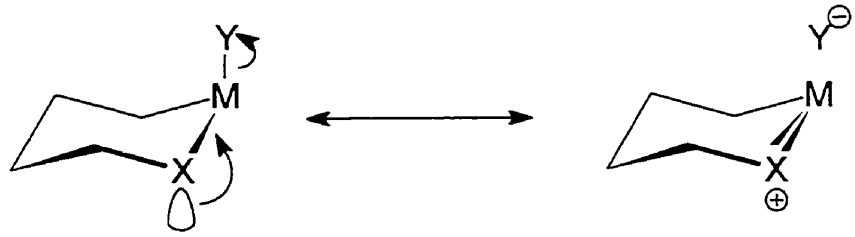
For simplicity, the lone pairs of oxygen are often viewed as sp^3-hybridized (**3**). Delocalization of the (shaded) sp^3 lone pair antiperiplanar to the C-X bond in the axial conformer is considered to provide more stabilization than does delocalization of either lone pair that is synclinal in the equatorial conformer.



3

The *kinetic anomeric effect* is conceptually simple (Scheme 1.3.4): [13b] The

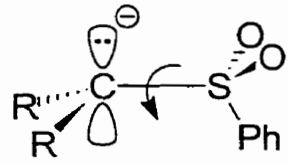
no-bond–double bond hyperconjugative model predicts weakening of the M-Y bond and therefore implies stereoelectronic X-assisted M-Y bond cleavage. Reactivity is therefore controlled by the conformation: if a lone pair orbital is anti-periplanar to the labile M-Y bond, then that bond will be activated for cleavage.



Scheme 1.3.4

1.4 GEOMETRY DEPENDENCE IN β-SUBSTITUTED SULFONES

α-Sulfonyl carbanions have been studied intensively since the observation that α-chiral sulfones undergo base catalysed H-D exchange with retention of chirality.[16, 17] As early as the sixties, Corey and coworkers[18, 19] suggested that this retention of chirality is due to the barrier of rotation of C_α-S bond (see **4**), rather than the tetrahedral configuration at the α-C atom, as would be the case in **5**.



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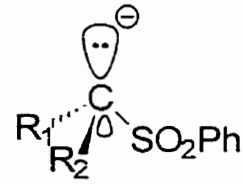
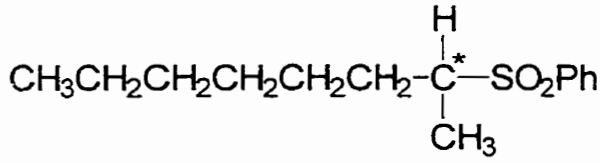
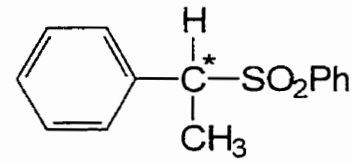


5

Corey and Lowry[19] compared the H-D exchange rate and the racemization rate of **6** and **7**, and found that the exchange rate (k_{exc}) of **7** is much faster than that of **6** (by almost 10^4 times).



6

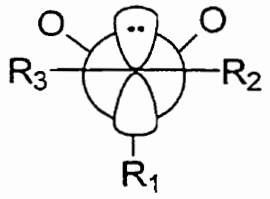


7

It is clear that the benzene ring in **7** is stabilizing the planar form of the intermediate carbanion by *p*-π conjugation. If the retention of chirality is due to the barrier to inversion, then the phenyl group should facilitate the racemization of the carbanion intermediate. However, the ratios of the H-D exchange rate to the racemization rate for **6**

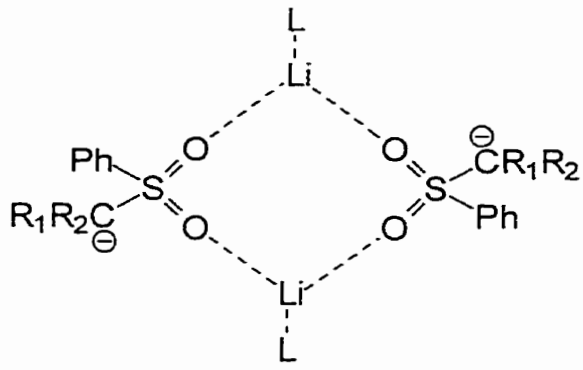
and **7** are almost the same (41 for **6**, 44 for **7**). So, it was concluded that retention of chirality at the α-C is not the source of the barrier to inversion.

Theoretical calculations of the α-sulfonyl carbanion at the 3-21G* level by Wolfe et al.,[20] and by Bors and Streitwieser[21] indicated that the conformation in which the lone electron pair at the α-C is gauche to the two sulfonyl oxygen atoms (**8**), is a thermodynamic minimum on the potential surface that has a rotational barrier of more than 14 kcal mol^{-1}.



8

X-ray structure determinations of the lithium coordinated α-sulfonyl carbanions,[16, 22] such as α-(phenylsulfonyl)benzyllithium-tetra-methylethylenediamine (**9a**), (phenylsulfonyl)-methyllithium-tetra-methylethylenediamine (**9b**), (phenylsulfonyl)isopropyllithium-diglyme (**9c**) and α-(phenylsulfonyl)-α-methylbenzyl-lithium-diglyme (**9d**), shows "in each case a similar dimer with each lithium bridging an oxygen on each of the sulfonyl anions, a short C1–S bond and no C1–Li bond and a conformation of the carbanions with the lone pair electrons at the anionic C-atom bisecting the O–S–O angle".



9a: R_1 = H, R_2 = Ph, L = tmeda

9b: $R_1 = R_2$ = H, L = tmeda

9c: $R_1 = R_2$ = Me, L = diglyme

9d: R_1 = Me, R_2 = Ph, L = diglyme

It has been suggested[20] that the strong stereoelectronic preference for the formation depicted in Figure 1.4.1, may be ascribed to the donation of the lone pair electrons from the anionic α-C atom to the antibonding orbital (σ*) of the S-C_α bond. This is, in fact, negative hyperconjugation; the factor believed to be responsible for most of the *generalized* anomeric effect.

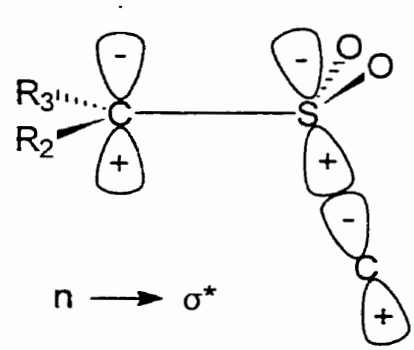


Figure 1.4.1 The conformation preference of α-sulfonyl carbanion.

With $PhSO_2CHTCH_2X$, where X = OPh, or OCH_3 etc., it seems very likely that the carbanion can be stabilized not only by donation into antibonding orbital (σ*) of S-C_α, but also by donation into that of the C_β-O bond (see Figure 1.4.2).

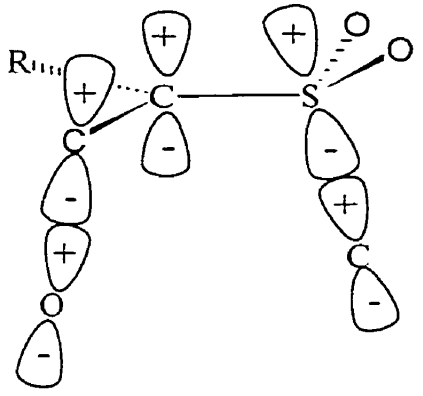
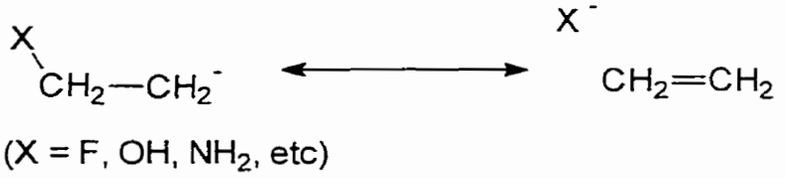


Figure 1.4.2 A second stabilization by the β-substituted oxygen.

That is to say, a third effect (besides inductive and field effects), negative hyperconjugation, or the anomeric effect, may be contributing to such a large substituent effect as well. Obviously, the effectiveness of the anomeric effect (negative hyperconjugation) should depend on the geometry of the β-substituent. The negative hyperconjugation, or anomeric effect, will be greatest in the conformations with a 180° or 0° H_α-C_α-C_β-O torsion angle, while it will be least with a 90° H_α-C_α-C_β-O torsion angle. Therefore, it became the aim of this research to investigate the angle dependence of a substituent effect.

1.5 *AB INITIO* CALCULATIONS OF THE DIFFERENCE BETWEEN 0° AND 90° CONFORMER SUSPECTED OF NEGATIVE HYPERCONJUGATION

Ab initio studies have been carried out on the geometrical dependency of hyperconjugation (anomeric effect). The β-substituted ethyl anion system (Scheme 1.5.1) is one of the most studied theoretically.[23]



Scheme 1.5.1

The high electronegativity of fluorine, oxygen and nitrogen lead to sizable inductive effects. To separate the negative hyperconjugation from the inductive effect, Hoffmann *et al.*[24] compared the energies of β-substituted ethyl anions in different assumed conformations. The inductive effect is not expected to vary with the dihedral angle. On the other hand, the negative hyperconjugation should be maximal in conformation **10**, and disappear in conformation **11** due to the 90° dihedral angle between the carbanion lone pair orbital and the C-X bond. In **10** both negative hyperconjugation and inductive effects involving X can operate, but in **11**, only the inductive effect of X is present.

10 (180°) **11**(90°)

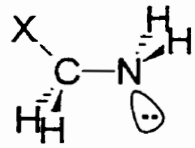
Thus, the energy difference between **10** and **11** gives the negative hyperconjugation

contribution for each substituent X. Theoretical calculations show[23] that it is in the order of 8 - 15 kcal / mol for electronegative substituents like F, OH and NH_2. To evaluate the total stabilization energy, eq 1.5.1 was used.

$$CH_3CH_2^- + XCH_2CH_3 \longrightarrow CH_3CH_3 + XCH_2CH_2^- \qquad \text{(eq 1.5.1)}$$

The net result of eq 1.6.1 is only the transference of the carbanion to the position β to X where negative hyperconjugation (anomeric effect) by the β-X stabilizes the carbanion. The total stabilization is found to be about 10 to 20 kcal/mol allowing the maximum stabilization from hyperconjugation (**10**). It was shown that the contribution from negative hyperconjugation is not only not negligible, but is the major component of the substituent effect.

In neutral systems such as XCH_2NH_2, theoretical calculation also confirms the above conclusion.[23, 25] The 180° torsion angle conformation **12** (X = F) (which permits maximum hyperconjugation) was 8.5 kcal / mol more stable than the 90° torsion angle conformation **13** (X = F) (which lacks hyperconjugation). Furthermore, **12** (X = F) was calculated to have a longer C-F bond and a shorter C-N distance than **13** (X = F).



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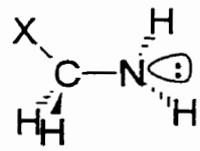
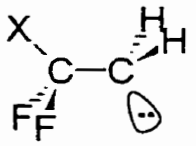


13

Pross *et al* [26] studied the 2,2,2-trifluoroethyl anion system (**14**, X = F). These results reveal a marked lengthening (as compared with **15**), in the anion of the β-CF bond (1.478 Å) which is ideally oriented for hyperconjugation (i.e. in the anion lone pair plane). The other two fluorine atoms in **14** have a 60° dihedral angle to the carbanion

lone pair; these C-F bonds (1.396 Å) are lengthened only slightly relative to the neutral model (**15**, C-F 1.361 Å). The C-C bond is shortened in **14** (1.39 Å) relative to **15** (1.485 Å), as is expected from hyperconjugation.



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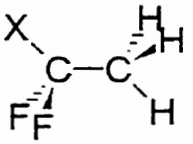


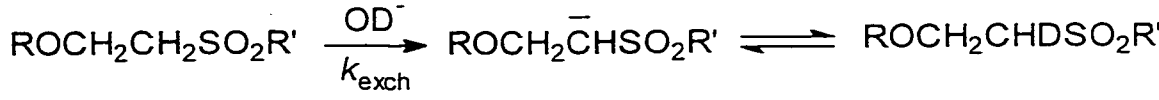
15

It was found[23] that the anomeric effect by the fluorine anti-coplanar to the carbanion lone pair contributes 20 kcal / mol – one half – of the total stabilization energy of the CF_3 group in the 2,2,2-trifluoroethyl anion.

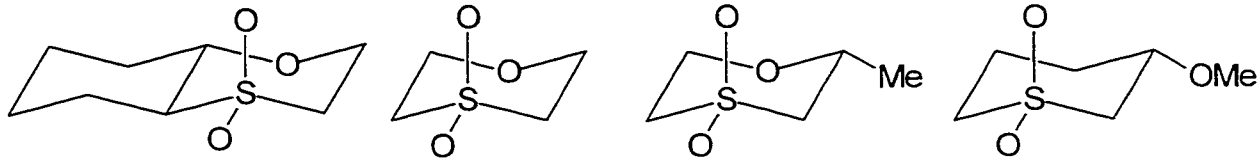
In conclusion, negative hyperconjugation (anomeric effect) has been theoretically shown to be angle dependent, and is conformations oriented for maximum negative hyperconjugation (anomeric effect) in some β-heteroatom substituted systems. Its contribution to the substituent effect is substantial.

1.6 THE FIRST EXPERIMENTAL EVIDENCE

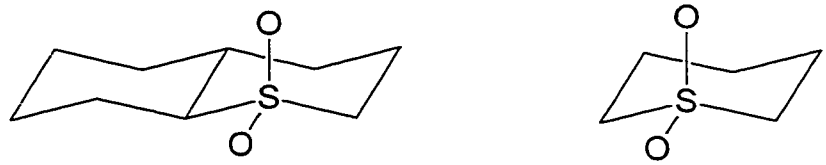
Despite all the theoretical researches on the geometrical dependency of the anomeric effect, the direct experimental evidence on this point is limited. Earlier work from this laboratory[29-32] has lent strong support for this picture. King and Rathore[30, 31] first found that the rate of hydroxide-promoted H-D exchange α to a sulfonyl group (Scheme 1.6.1) is strongly influenced by the presence of an ether oxygen at the β position, with acceleration by oxygen varying from 10^2 to 10^4, depending on the geometry of the molecule (Scheme 1.6.2).



Scheme 1.6.1



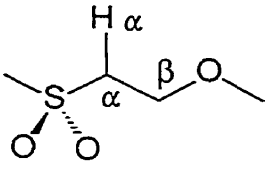
k_{exch} (25 °C, in D_2O):
3.2×10^{-2} 4.3×10^{-2} 1.6×10^{-2} 4.5×10^{-4} (M^{-1} s^{-1})



k_{exch} (25 °C, in D_2O):
$\sim 2 \times 10^{-6}$ 1.2×10^{-6} (M^{-1} s^{-1})

Scheme 1.6.2

Later, King and Guo[29] extended this study to include substrates with other H_α-C_α-C_β-O torsion angles (θ) and conformed that the exchange rates vary with torsion angle (θ) of the alkoxy sulfones (**A**).

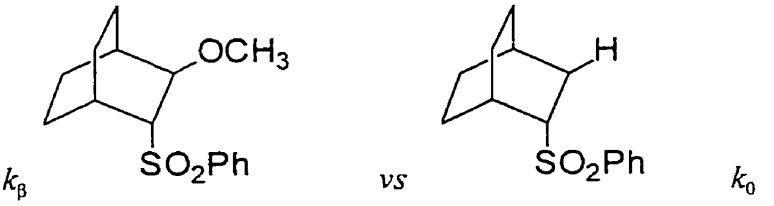


A

The following equation was given:

$$\log k_N = 1.6 (1.7 + \cos (2\theta))$$

where, $k_N = k_\beta / k_0$, k_β refers to k_{exch} for the β-substituted substrate and k_0 to k_{exch} for an analogous model in which the substituent is replaced by hydrogen as, for example:



k_β k_0

Guo's plot of log k_N vs the torsion angles (θ) is shown in Figure 1.6.1. As shown in Figure 1.6.1, some of the points were corrected for a complicating steric effect. This point will be discussed in detail in Chapter 2.

Chapter 2 will present further experiments and also a detailed discussion on the geometry dependence of a substituent effect in a β-oxygen-substituted saturated system.

Chapter 3 describes generalization of the results obtained with the alkoxy group to include the angle dependence of the substituent effect in compounds with sulfur, nitrogen, disulfone, and ammonio substituents. Also, the special feature of the ammonio system will be discussed and a discussion on the 'reverse anomeric effect' will be offered.

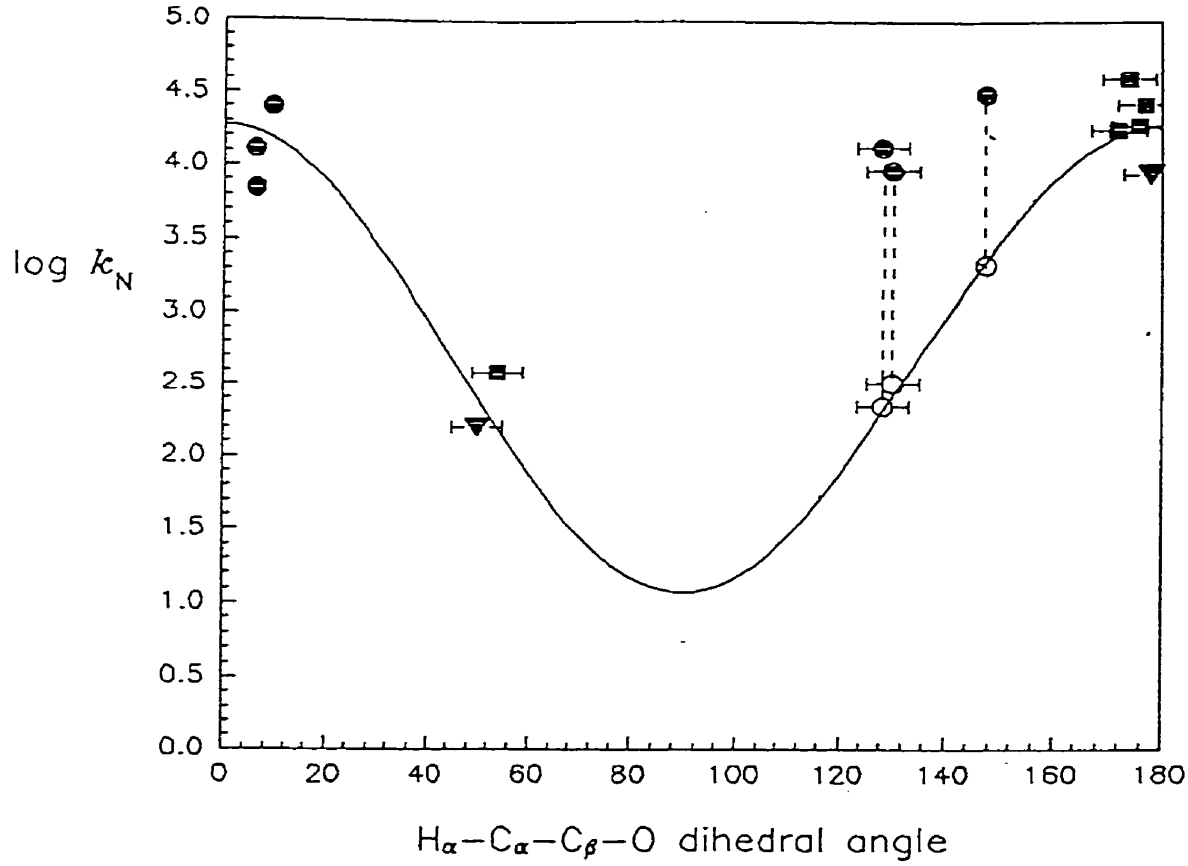


Figure 1.6.1 Guo's plot of log k_N vs. the H_α-C_α-C_β-O torsion angle for the base catalyzed H-D exchange reactions of β-alkoxy sulfones. (The corrections will be discussed in Chapter 2)

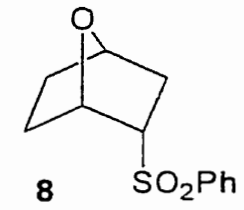
CHAPTER 2

THE GEOMETRY DEPENDENCE OF THE REACTION OF A BETA-ALKOXY SUBSTITUTED SATURATED SYSTEM

2.1 INTRODUCTION

As has been discussed in Chapter 1, there was evidence pointing to the notion that in a saturated system an anomeric effect (negative hyperconjugation) might be contributing to the substituent effect in addition to the traditional inductive and field effects in the specific case of the formation of carbanions in β-substituted sulfones.

The work described in this chapter is a continuation of the study of Rathore and Guo in this laboratory, and leads ultimately to the measurement of rates of H-D exchange for a set of nineteen β-alkoxy sulfones in which there was reason to believe they would have fixed and approximately known H_α-C_α-C_β-O dihedral angles ranging from ~ 0° to ~ 180°. In addition, a sizable number of other sulfones were studied to provide relevant model systems. The aim of this study was to build up as complete a picture as possible of the geometrical dependence of the β-alkoxy substituent effect in α-sulfonyl carbanion formation, and thereby to provide a better understanding of the interaction between substituent and reacting center. To do that, the sulfones shown in Scheme 2.1.1 were synthesized and the rates of hydroxide-promoted H-D exchange alpha to the sulfonyl groups were determined. Also included is the application of the geometry dependent substituent picture to an earlier, only partly solved mechanistic problem.



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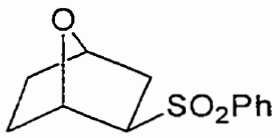

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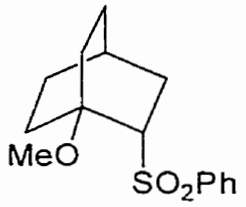
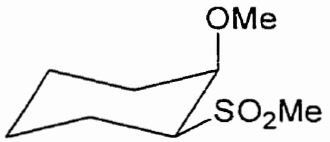


7

5

6a

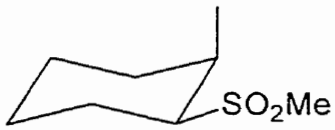


17a

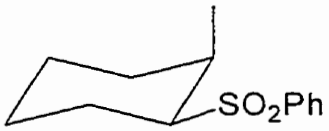
23a

24a

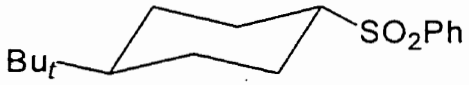
24b



25a



25b



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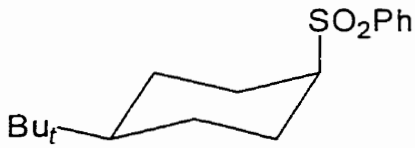

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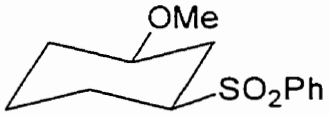

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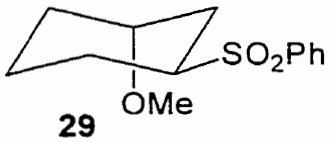


29

32

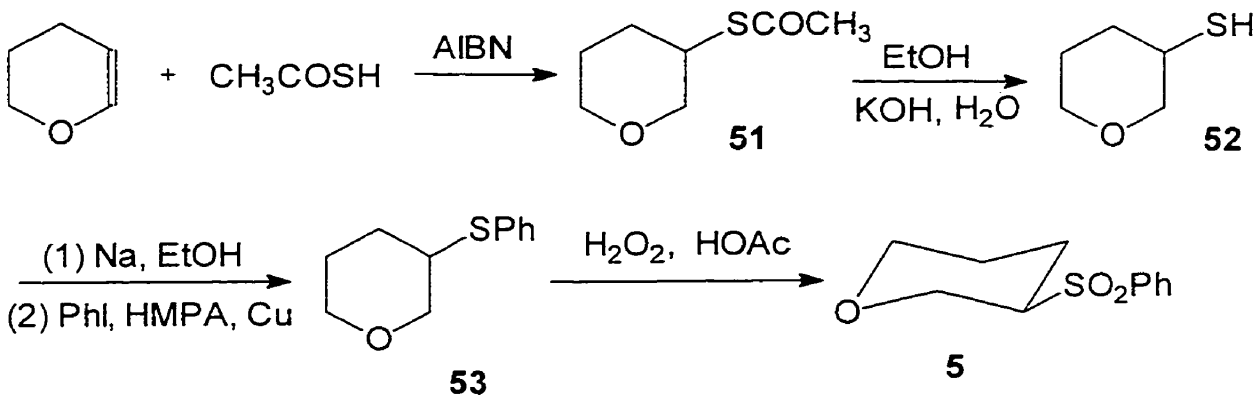
	$PhSO_2(CH_2)_nOMe$	$PhSO_2(CH_2)_nMe$
n = 1		**31a**
n = 2	**30b**	**31b**
n = 3	**30c**	**31c**
n = 4	**30d**	**31d**
n = 5	**30e**	**31e**

Scheme 2.1.1

2.2 RESULTS AND DISCUSSION

2.2.1 PREPARATION OF THE SULFONES

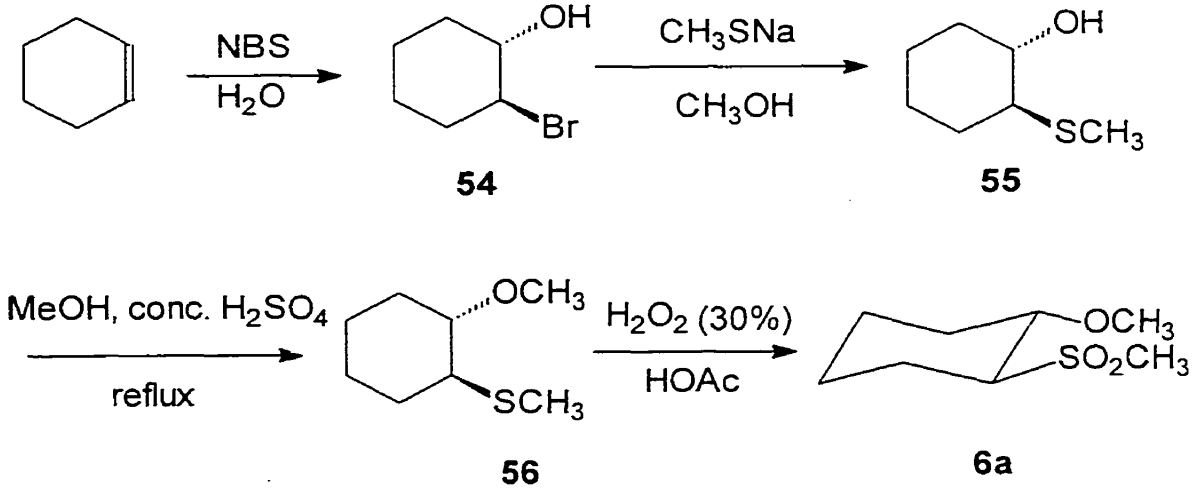
3-(Phenylsulfonyl)tetrahydropyran (**5**) was synthesized as illustrated (Scheme 2.2.1). 3-(Phenylthio)tetrahydropyran (**53**) was prepared according to the procedure of Martin et al.[33] In the first step 3,4-dihydro-2*H*-pyran was treated with thiolacetic acid in the presence of 2,2'-azobisisobutyronitrile (AIBN) to give the 3-(acetylthio)tetrahydropyran (**51**): this was hydrolyzed and the resultant thiol (**52**) was treated with iodobenzene in hexamethylphosphoramide (HMPA) to yield 3-(phenylthio)tetrahydropyran (**53**). Oxidation of **53** gave **5** as a colorless liquid.



Scheme 2.2.1

trans-1-Methoxy-2-(methylsulfonyl)-cyclohexane (**6a**) was prepared following the procedure of Carreno and coworkers[34] as is illustrated in Scheme 2.2.2. Reaction of cyclohexene with *N*-bromosuccinimide (NBS) in water gave *trans*-2-bromocyclohexanol (**54**). The *trans* stereochemistry of **54** can be derived from its ^{1}H NMR spectrum by the coupling of the methine at C1 (ddd, J = 11.7 Hz, 9.3 Hz, 4.4 Hz) and is expected from the rule of diaxial opening. In the next step, reaction of **54** with sodium thiomethoxide gave

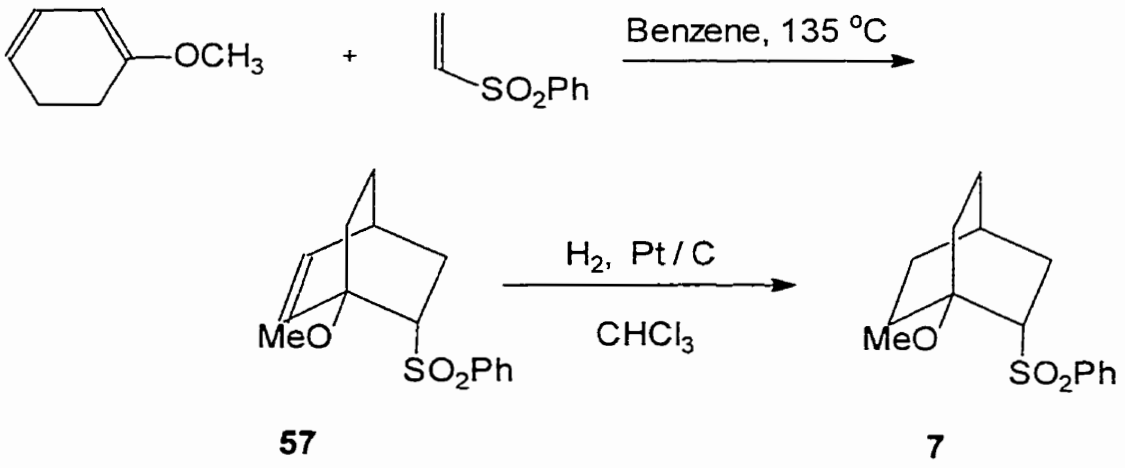
trans-2-(methylthio)cyclo-hexanol (**55**) under very mild conditions. The *trans* stereochemistry can be explained by invoking cyclohexene oxide as the key intermediate.[34] Methanol and concentrated sulfuric acid converted the hydroxy sulfide (**55**) into the methoxy sulfide (**56**), which was then oxidized by hydrogen peroxide (30%) in acetic acid to give the final sulfone (**6a**). The coupling of the methine at C2 in the ^{1}H NMR spectrum of **6a** (ddd, J = 12.6 Hz, 10.0 Hz, 3.9 Hz) is consistent with the *trans* stereochemistry of **6a**.



Scheme 2.2.2

1-Methoxy-2-(phenylsulfonyl)bicyclo[2.2.2]octane (**7**) was obtained by a two-step sequence (Scheme 2.2.3). 1-Methoxy-6-*endo*-(phenylsulfonyl)bicyclo[2.2.2]octa-2-ene (**57**) was synthesized by the method of Paquette and coworkers.[38] Diels-Alder reaction of 1-methoxy-1,3-cyclohexadiene and phenyl vinyl sulfone at 135 °C gave a crude product which was purified by thick-layer chromatography and recrystallization to give 1-methoxy-6-*endo*-(phenylsulfonyl)bicyclo[2.2.2]octa-2-ene (**57**). According to Paquette and coworkers,[38] the crude product might include a small amount of *exo* epimer but only

the pure *endo* (*syn* to the double bond) was separated and identified. The *endo* stereochemistry of **57** was assigned by these authors without further details. Hydrogenation of **57** gave **7** which was characterized unambiguously by x-ray crystallography.

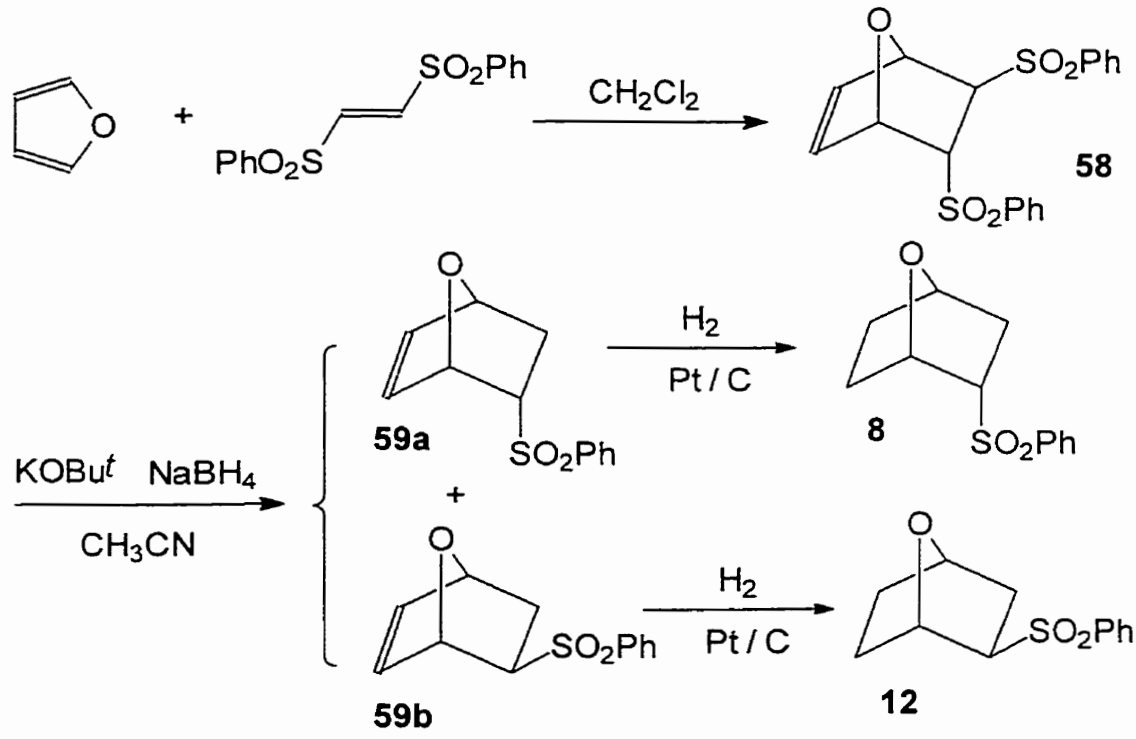


57 **7**

Scheme 2.2.3

Scheme 2.2.4 outlines the preparation of 2-*endo*-(phenylsulfonyl)-7-oxabicyclo-[2.2.1]heptane (**8**) and 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (**12**). 2-*endo*-3-*exo*-Bis(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**58**) was obtained following the method of De Lucchi et al.[39] Diels-Alder reaction of furan and (*E*)-bis(phenyl-sulfonyl)ethylene gave **58** in quantitative yield. The second step, the removal of the phenylsulfonyl group, was carried out in acetonitrile in the presence of potassium *tert*-butoxide (1 equiv.) and sodium borohydride (excess) according to the procedure of Mirsadeghi and Rickborn.[40] The literature[40] described only the major product (**59b**) and referred to it only as a colorless liquid. We separated the products by thick layer chromatography using ether as the developing solvent, and found at least seven bands. One band proved to be the *exo* epimer (**59b**) which, turned out to be crystalline (mp 63.5-

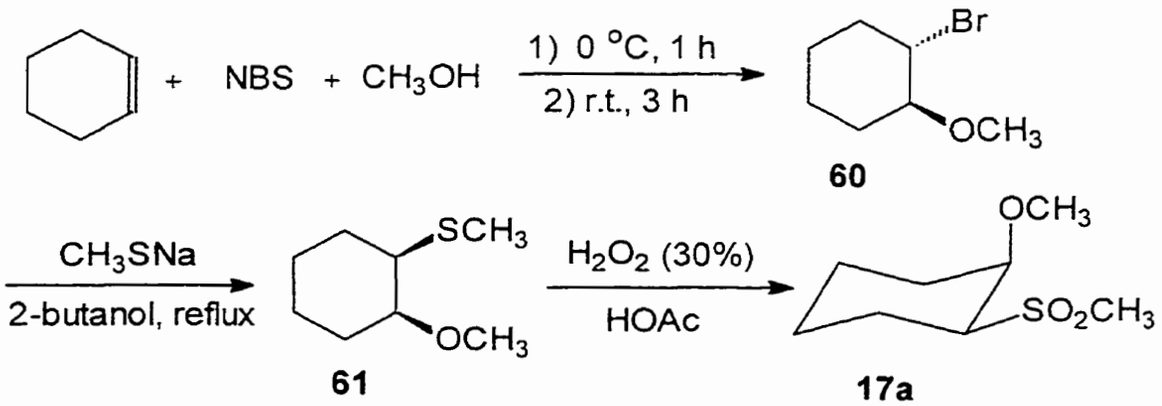
65 °C). Another band evidently contained the *endo* epimer (**59a**) but was still a mixture. After further thick layer chromatography and recrystallization, the *endo* epimer (**59a**) was finally obtained as white crystals (mp 52-53 °C). Hydrogenation of **59a** and **59b** gave **8** and **12**, respectively. The *endo* stereochemistry of **59a** and **8**, the *exo* stereochemistry of **59b** and **12** were clear because equilibration from **8** and from **12** separately in a basic deuterated solvent gave the same mixture with the deuterated form of **12** as the major component. The *exo* stereochemistry of **59b** was originally assigned by Mirsadeghi and Rickborn.[40]



Scheme 2.2.4

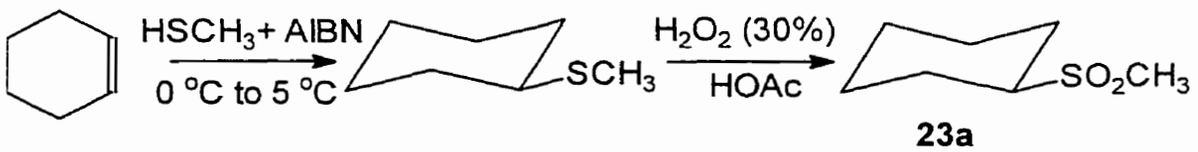
Scheme 2.2.5 shows the synthesis of *cis*-1-methoxy-2-(methylsulfonyl)cyclohexane (**17a**). Reaction of cyclohexene with *N*-bromosuccinimide (NBS) in methanol gave *trans*-1-bromo-2-methoxycyclohexane (**60**).[41] Refluxing of the bromide (**60**) with

sodium thiomethoxide in 2-butanol gave *cis*-2-methoxy-1-(methylthio)cyclohexane (**61**). presumably by way of a S_N2 reaction. Oxidation of the sulfide (**61**) gave the desired sulfone (**17a**). The *cis* stereochemistry of **61** and **17a** can be derived by the ^1H NMR spectrum of **17a** which shows that the signal pattern of the hydrogen at C2 is formed by a large coupling of 12.7 Hz (with the *axial* hydrogen at C3) and two small couplings of 2.9 Hz (with the *equatorial* hydrogens at C1 and C3).



Scheme 2.2.5

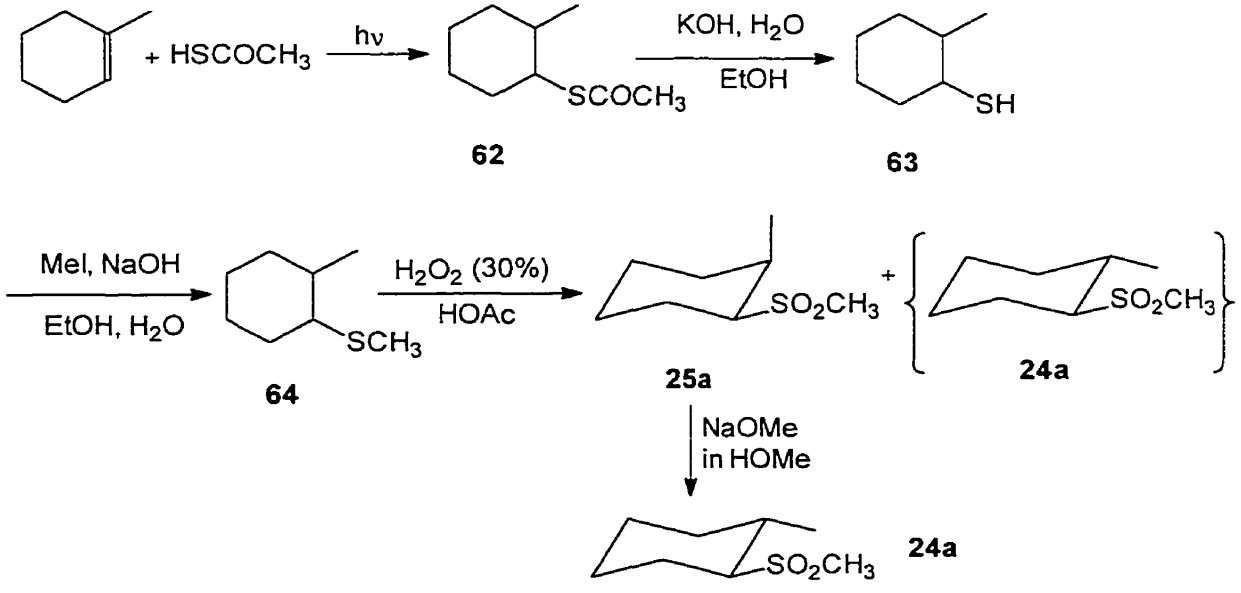
Cyclohexyl methyl sulfone (**23a**)[41] was prepared from oxidation of cyclohexyl methyl sulfide, which was obtained from the addition of methanethiol to cyclohexene (Scheme 2.2.6).



Scheme 2.2.6

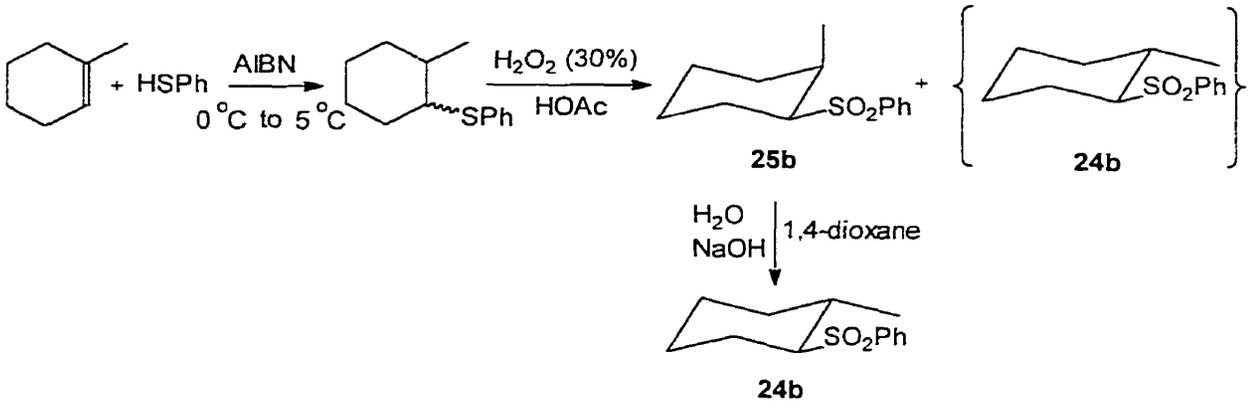
The syntheses of *trans*-2-methyl-1-(methylsulfonyl)cyclohexane (**24a**) and *cis*-2-

methyl-1-(methylsulfonyl)cyclohexane (**25a**) are outlined in Scheme 2.2.7. 2-Methyl-cyclohexanethiol (**63**) was synthesized using the method of Bordwell and Hewett.[42] Addition of thiolacetic acid to 1-methylcyclohexene by irradiating with a 100 watt bulb, followed by hydrolysis of the ester with KOH in aqueous ethanol gave 2-methyl-cyclohexanethiol (**63**). Methylation of the thiol and oxidation of the sulfide to the sulfone gave a mixture of **24a** and **25a** with the *cis* compound (**25a**) as the major component (roughly 75%). Recrystallization from methanol gave pure **25a**. The *cis* stereochemistry of **25a** can be derived by its ^{1}H NMR spectrum which shows that the signal pattern of the hydrogen at C1 is formed by a large coupling of 11.9 Hz (with the *axial* hydrogen at C6) and two small couplings of 3.8 Hz (with the *equatorial* hydrogens at C2 and C6). Refluxing of **25a** in methanol containing sodium methoxide (5%) gave a mixture of **24a** and **25a** with **24a** as the major component. Separation of **24a** and **25a** was unsuccessful; the H-D exchange of **24a** was determined with a mixture of **24a** and **25a** (see Experimental).



Scheme 2.2.7

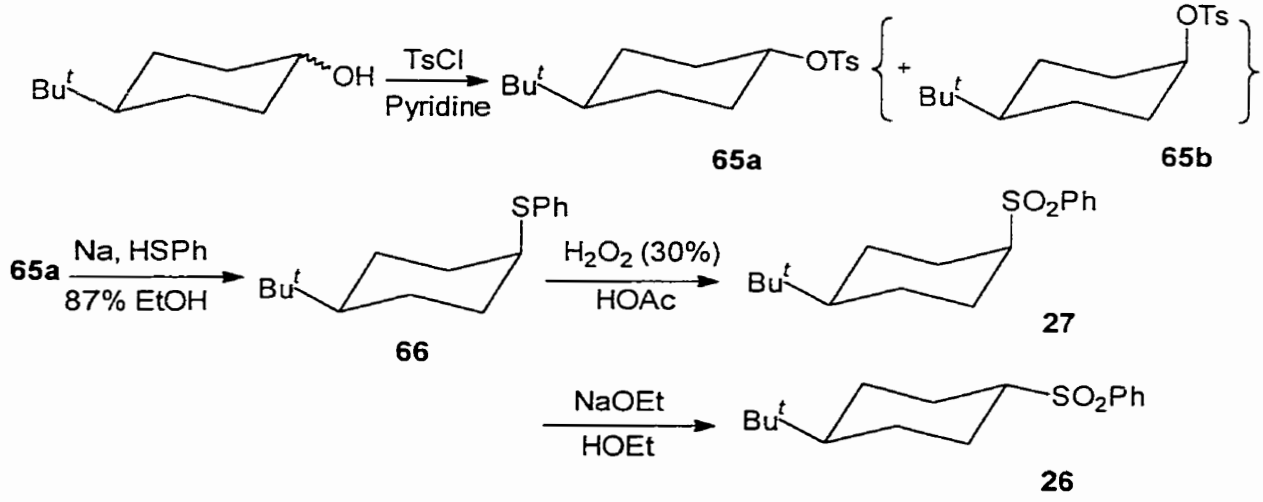
trans-2-Methyl-1-(phenylsulfonyl)cyclohexane (**24b**) and *cis*-2-methyl-1-(phenylsulfonyl)cyclohexane (**25b**) were prepared using the method of Bordwell and Hewett.[42] Reaction of 1-methylcyclohexene with thiophenol in the presence of AIBN gave a mixture of 2-methylcyclohexyl phenyl sulfides (Scheme 2.2.8). Oxidation of the mixture by hydrogen peroxide (30%) in acetic acid and separation by thick layer chromatography gave a mixture of **24b** and **25b** with the *cis* epimer (**25b**) again as the major component (roughly 75%). Recrystallization from hexane : ethyl acetate give pure **25b**. The *cis* epimer (**25b**) was refluxed in 1,4-dioxane and water in the presence of sodium hydroxide and then separation gave a 4:1 mixture of *trans*-2-methyl-1-(phenylsulfonyl)-cyclohexane (**24b**) and **25b**. The *cis* stereochemistry of **25b** can be derived by its ^{1}H NMR spectrum which shows that the signal pattern of the hydrogen at C1 is formed by a large coupling of 12 Hz (with the *axial* hydrogen at C6) and two small couplings of 3.8 Hz (with the *equatorial* hydrogens at C2 and C6). Again, the *trans* methyl sulfone (**24b**) was not obtained free of the *cis* isomer (**25b**) and the H-D exchange rates were obtained from the mixture. The *trans* stereochemistry of **24b** is consistent with ^{1}H NMR spectrum which shows that the signal pattern of the hydrogen at C1 is formed by two large couplings of 11.3 Hz and 9.5 Hz (with the *axial* hydrogens at C2 and C6) and one small coupling of 3.4 Hz (with the *equatorial* hydrogen at C6).



Scheme 2.2.8

cis-4-*tert*-Butylcyclohexyl phenyl sulfone (**27**) and *trans*-4-*tert*-butylcyclohexyl phenyl sulfone (**26**) were prepared using the method of Eliel and Ro[43] as outlined in Scheme 2.2.9. Tosylation of the 4-*tert*-butylcyclohexanol (mixture of *trans* and *cis* epimers) gave the mixture of *trans* and *cis* tosylates (**65a** and **65b**). Recrystallization of the mixture from ether : hexane (1/1) twice gave pure *trans* epimer (**65a**), but the *cis* epimer (**65b**) was always accompanied by approximately 25% of *trans* epimer (**65a**). Therefore, only the pure *trans* epimer (**65a**) was used in the next substitution reaction with $NaSCH_3$ in 90% ethanol, which gave *cis*-4-*tert*-butylcyclohexyl phenyl sulfide (**66**). The sulfide (**66**) was oxidized smoothly by hydrogen peroxide (30%) in acetic acid to give *cis*-4-*tert*-butylcyclohexyl phenyl sulfone (**27**). Epimerization of (**27**) in the presence of sodium ethoxide in ethanol and recrystallization gave *trans*-4-*tert*-butylcyclohexyl phenyl sulfone (**26**) in good yield. The *trans* stereochemistry of **65a** and **26** are consistent with their ^1H NMR spectra which show the signal pattern of the hydrogen at C1 is formed by two large couplings (> 11 Hz, with the *axial* hydrogens at C2 and C6) and two small couplings (< 5 Hz, with the *equatorial* hydrogens at C2 and C6); while the *cis*

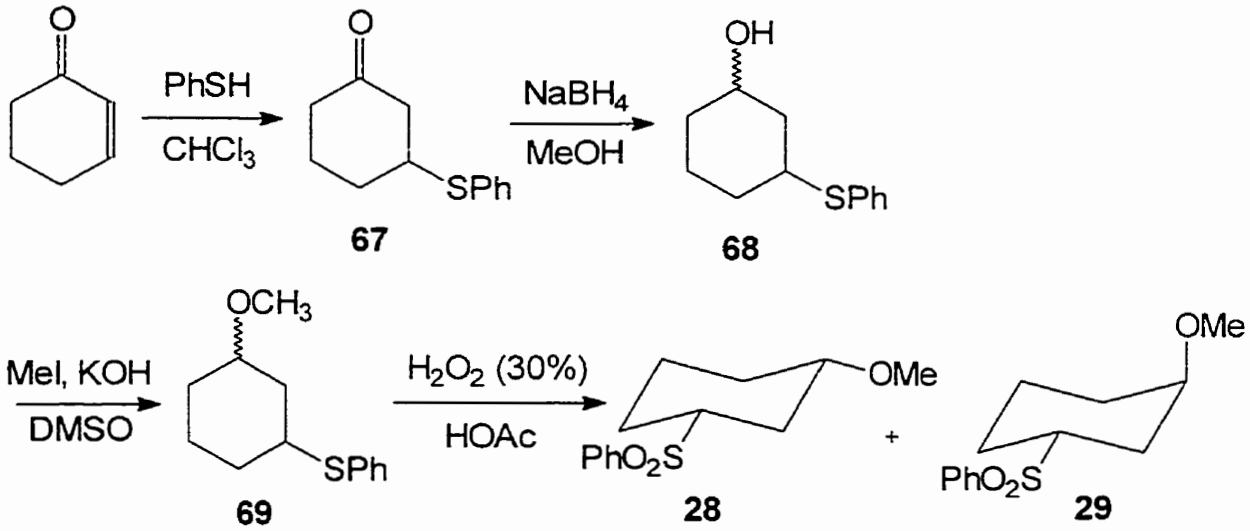
stereochemistry of **27** is consistent with a narrower peak ($w_{1/2}$ = 8.4 Hz) of the hydrogen at C1; the equilibrations between **26** and **27** in deuterated solvent (see Experimental) further support these structures.



Scheme 2.2.9

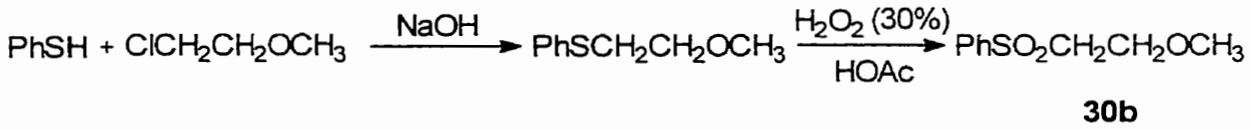
The syntheses of *cis*-1-methoxy-3-(phenylsulfonyl)cyclohexane (**28**) and *trans*-1-methoxy-3-(phenylsulfonyl)cyclohexane (**29**) are shown in scheme 2.2.10. Addition of thiophenol to cyclohexenone gave 3-(phenylthio)cyclohexanone (**67**) in excellent yield.[45] Reduction of the ketone (**67**) by sodium borohydride gave a mixture of *cis* and *trans* epimers (**68a** and **68b**) with the *cis*-3-(phenylthio)cyclohexanol (**68a**) as the major component.[47] The mixture was not separated until after the hydroxy group had been methylated by iodomethane and the sulfides oxidized by hydrogen peroxide to give the mixture of the desired sulfones. The separation by thick layer chromatography led to pure *cis*-1-methoxy-3-(phenylsulfonyl)-cyclohexane (**28,** 88% of mixture) and pure *trans*-1-methoxy-3-(phenylsulfonyl)-cyclohexane (**29,** 12% of mixture). The stereochemistry of **28** can be derived from its ^{1}H NMR spectrum which shows the hydrogen peak at C1 with

two large couplings of 11 Hz (with two *axial* hydrogens) and two small couplings of 4.1 Hz (with two *equatorial* hydrogens): while the stereochemistry of **29** is consistent with a narrower hydrogen signal at C1.



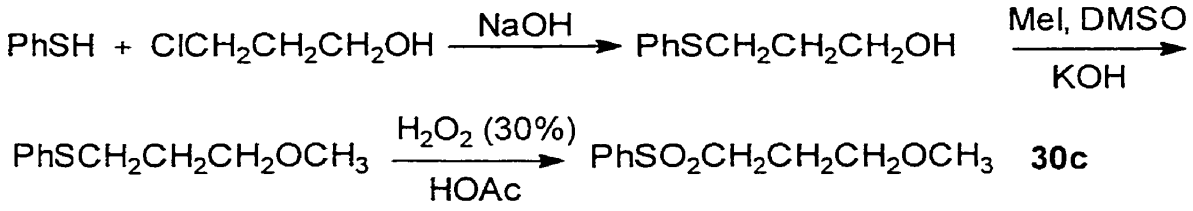
Scheme 2.2.10

A substitution reaction of 2-chloroethyl methyl ether with thiophenol in the presence of sodium hydroxide gave phenyl 2-methoxyethyl sulfide. Oxidation of the sulfide gave the desired phenyl 2-methoxyethyl sulfone (**30b**, Scheme 2.2.11).



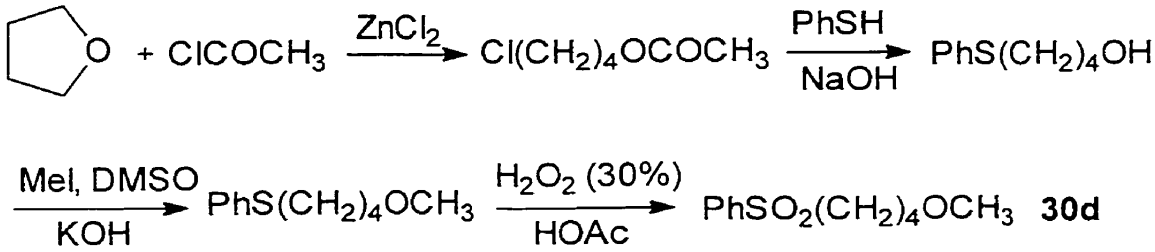
Scheme 2.2.11

Reaction of thiophenol with 3-chloropropanol and sodium hydroxide gave 3-(phenylthio)propanol. Methylation of the alcohol with iodomethane in DMSO gave the methyl ether. Oxidation of the sulfide gave phenyl 3-methoxypropyl sulfone (**30c**, Scheme 2.2.12).

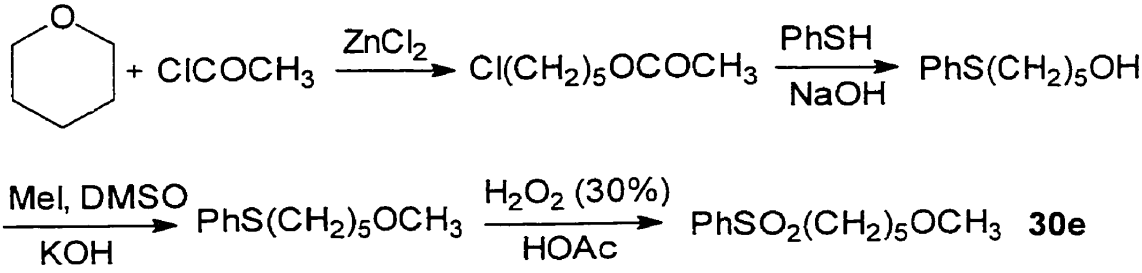


Scheme 2.2.12

Scheme 2.2.13 shows the preparation of phenyl 4-methoxybutyl sulfone (**30d**). Ring-opening of tetrahydrofuran in acetyl chloride gave 4-chlorobutyl acetate, which was treated with PhSNa followed by methylation by iodomethane in DMSO to give phenyl 4-methoxybutyl sulfide. Oxidation of the sulfide gave the desired sulfone (**30d**). A similar procedure starting with tetrahydropyran gave phenyl 5-methoxypentyl sulfone (**30e**, Scheme 2.2.14).

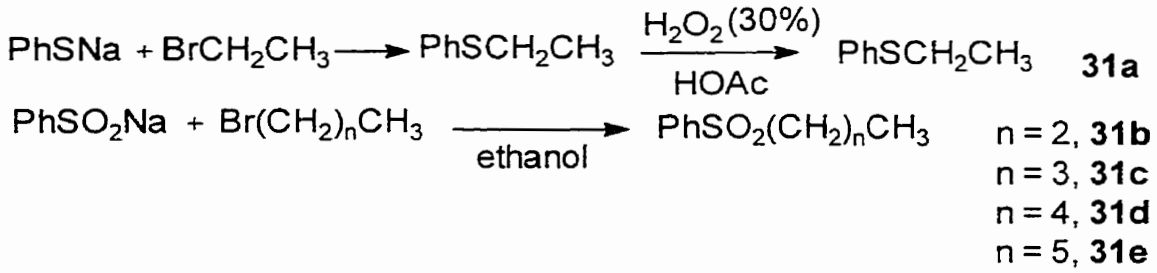


Scheme 2.2.13



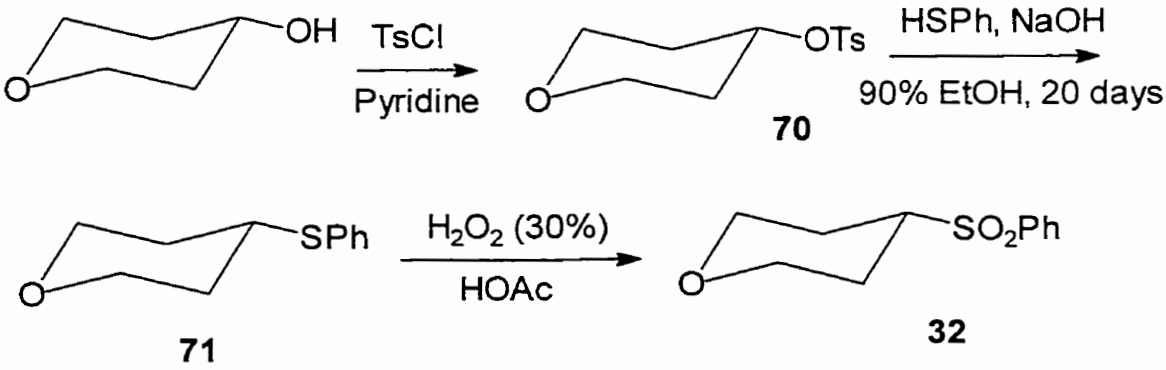
Scheme 2.2.14

The syntheses of other phenyl alkyl sulfones are outlined in scheme 2.2.15. Reaction of PhSNa with ethyl bromide gave phenyl ethyl sulfide, which was oxidized by hydrogen peroxide (30%) to give phenyl ethyl sulfone (**31a**). Refluxing of sodium benzenesulfinate ($PhSO_2Na$) with the appropriate alkyl bromide in ethanol gave the phenyl alkyl sulfone (**31b**, **c**, **d**, and **e**).



Scheme 2.2.15

Tosylation of 4-hydroxytetrahydropyran gave the tosylate (**70**), which was further substituted to give 4-(phenylthio)tetrahydropyran. Oxidation with hydrogen peroxide (30%) in acetic acid gave 4-(phenylsulfonyl)tetrahydropyran (**32**, Scheme 2.1.16).



Scheme 2.2.16

2.2.2 KINETICS AND THERMODYNAMICS OF THE H-D EXCHANGE REACTION

The H-D exchange rates of the sulfones in this study were measured under pseudo-first-order conditions by ^{1}H NMR spectroscopy (or ^{13}C NMR spectroscopy for **30d**, phenyl 4-methoxybutyl sulfone and **31d**, phenyl pentyl sulfone) in sodium deuteroxide using deuterium oxide solution, or a mixed solvent, either dioxane-d_8 and deuterium oxide (1:1 v/v), or acetonitrile-d_3 and deuterium oxide (1:1 v/v) at different temperatures. All our experiments showed that this base-promoted H-D exchange reaction showed first-order kinetics under the pseudo-first-order conditions. The concentration of unreacted starting materials was obtained from the NMR signals by observing the change in area of the α-CH signal relative to an unchanged signal. A plot of the logarithm of the concentration of unreacted starting material vs time gave a linear relationship; the slope of the best-fit line gave the pseudo-first-order rate constant (k_{obs}). The second-order rate constant k_{exch} was obtained as the slope of the straight line from the plot of the pseudo-first-order rate constant (k_{obs}) vs. base concentration.

For the determinations of fast H-D exchange reactions, a low OD^- concentration (pD = 7 to 11) was needed in order to keep the time intervals long enough for the NMR determination. A buffer solution was used instead of deuteroxide solution. The calculation of OD^- concentration was based on the following equations:[58, 59]

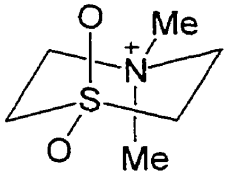
$$pD = \text{pH meter reading} + 0.37 \quad (25°C);$$

$$[\,D_3O^-\,]\,[\,OD^-\,] = 10^{-14.869} \quad (25°C).$$

The H-D exchange rate is not significantly influenced by the concentration of buffer under the conditions used in this research (carbonate for pH 9 to 11, or phosphate

for pH 7 to 10). This is evident from the results in Table 2.2.1 for the determination of exchange in phenyl ethyl sulfone (**30b**) for the carbonate buffers and for the determination of exchange in 4,4-dimethyltetrahydro-1,4-thiazinium iodide (denoted as $(N^+)_{180}$ in Chapter 3) for the phosphate buffer. These observations indicate that the general base catalysis mechanism is not important under the conditions used in these reactions.

Table 2.2.1. The buffer concentration vs. second-order rate constant k_{exch}.

$PhSO_2CH_2CH_2OCH_3$ **30b**	$[CO_3^{2-}]$ (M)	$[OD^-]$ (M)	k_{obs} (s^{-1})	$k_{exch} = k_{obs}/[OD^-]$ ($M^{-1}\ s^{-1}$)
	5.0×10^{-2}	1.62×10^{-4}	8.30×10^{-5}	5.12×10^{-1}
	9.4×10^{-2}	1.35×10^{-5}	6.93×10^{-6}	5.12×10^{-1}
	1.9×10^{-1}	1.45×10^{-5}	7.40×10^{-6}	5.12×10^{-1}
 I^- $(N^+)_{180}$	$[PO_4^{3-}]$ (M)	$[OD^-]$ (M)	k_{obs} (s^{-1})	$k_{exch} = k_{obs}/[OD^-]$ ($M^{-1}\ s^{-1}$)
	3.7×10^{-2}	1.13×10^{-7}	1.69×10^{-4}	1.50×10^{3}
	5.8×10^{-2}	5.90×10^{-8}	8.88×10^{-5}	1.51×10^{3}
	1.4×10^{-1}	3.56×10^{-8}	5.32×10^{-5}	1.50×10^{3}

The equilibrium constants were also determined by ^1H NMR spectroscopy in sodium deuteroxide using the same mixed solvent as for the kinetics. Because the α-H exchanged completely long before the equilibrium was obtained, the equilibrium constants obtained were in fact between the deuterated compounds. The difference between the α-protiated and α-deuterated isotopomers is expected to be very small.

The kinetic data for the β-sulfones with more or less fixed H_α-C_α-C_β-O torsion angles obtained in the present study, together with the previous experiments of Rathore[31] and Guo.[32] are summarized in Table 2.2.2. The corresponding data for all the other sulfones are in Table 2.2.3. The plot of log k_N vs torsion angle (θ) is shown in Figure 2.2.1. All the thermodynamic data are listed in Table 2.2.4.

Table 2.2.2 Rate constants for H-D exchange in β-alkoxy sulfones with 'fixed' H_α-C_α-C_β-O torsion angles (plus model compounds)

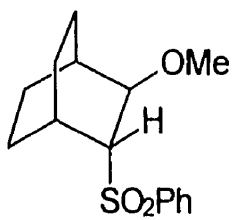
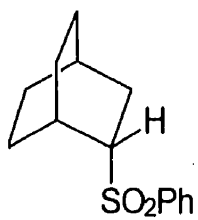
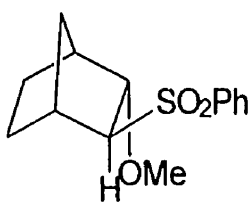
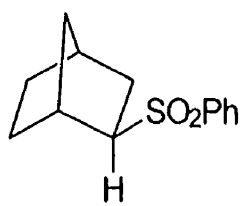
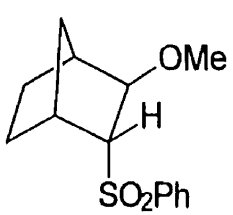
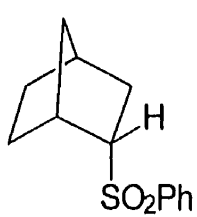
	alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]		model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
1		26.2° (6.2°)	4.9×10^{-4} [k] (A)	**18**		4.2×10^{-8} [k] (A)	4.06
2		7.1° (6.4°)	1.04×10^{-4} [k] (A)	**19**		1.5×10^{-8} [k] (A) 3.1×10^{-4} [k] (B1)	3.84
3		13.9° (9.5°)	1.14×10^{-3} [k] (A)	**20**		(4.5×10^{-8}) [d] (A) 9.2×10^{-4} [k] (B1)	(4.40)

Table 2.2.2 Continued

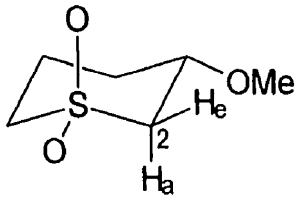
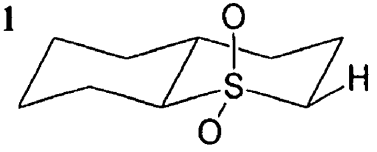
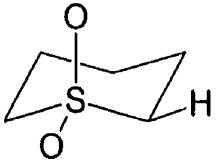
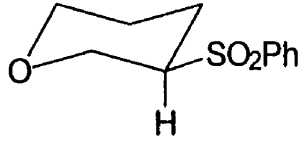
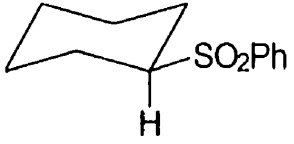
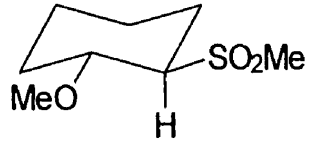
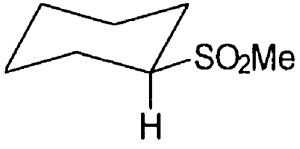
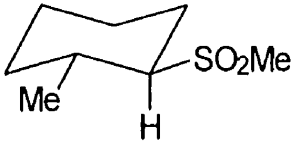
alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
4 	59.3°	C-2H_e: 4.5×10^{-4} [j] (C) C-2H_a: $<1.8\times10^{-5}$ [j] (C)	**21** 	1.2×10^{-6} [j] (C)	2.57
			(22) 	$(\sim2\times10^{-6})$ [e,j] (C)	(~2.35)
5 	60.0°	1.14×10^{-3} (B3)	**23b** 	1.75×10^{-6} (B3)	2.81
6a 	61.3°	3.3×10^{-4} [j] (B2)	**23a** 	3.3×10^{-6} (B2)	2.00
			24a 	1.1×10^{-6} (B2)	2.47

Table 2.2.2 Continued

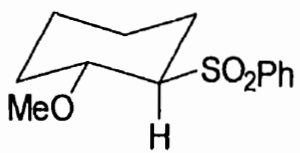
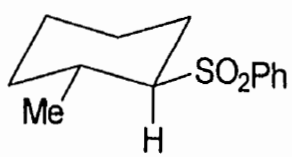
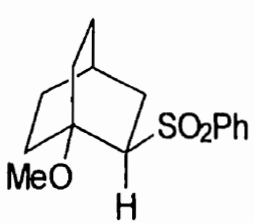
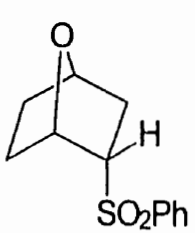
alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
6b 	61.9°	1.12×10^{-4} (B3)	**23b**	1.75×10^{-6} (B3) 1.5×10^{-4} (B2)	1.81
			24b 	(5.25×10^{-7}) [f] (B3) 4.4×10^{-5} (B2)	(2.33)
7 	78.4° (63.9°)	1.06×10^{-3} (B2)	**18**	2.24×10^{-4} [k] (B2)	0.67
8 	74.5°	5.1×10^{-4} (B3)	**20**	(2.07×10^{-7}) [g] (B3) 9.2×10^{-4} [k] (B1)	(3.42)

Table 2.2.2 Continued

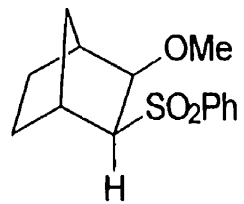
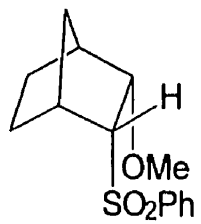
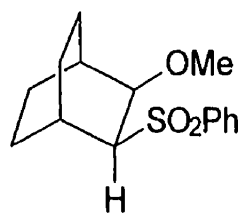
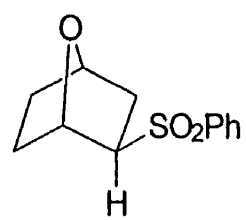
	alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
9		133.0° (128.4°)	2.00×10^{-4} [k] (A)	**19**	1.5×10^{-8} [k] (A)	4.12
10		133.1° (130.3°)	4.13×10^{-4} [k] (A)	**20**	(4.5×10^{-8}) [d] (A)	(3.96)
11		145.0° (147.6°)	1.36×10^{-3} [k] (A)	**18**	4.2×10^{-8} [k] (A)	4.51
12		152.4°	1.1×10^{-3} (B3)	**19**	6.96×10^{-8} (B3) 3.1×10^{-4} [k] (B1)	4.24

Table 2.2.2 Continued

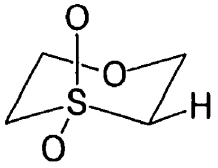
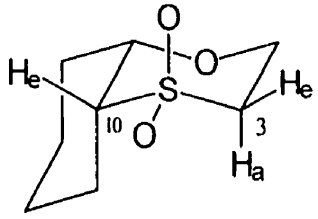
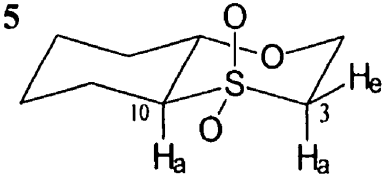
	alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
13		172.9°	(4.30×10^{-2}) [e] (C)	**21**	1.2×10^{-6} [j] (C)	4.55
				(22)	$(\sim2\times10^{-6})$ [e,j] (C)	(~4.33)
14		173.5°	C-3H_e: 4.8×10^{-2} [j] (C) C-3H_a: 1.6×10^{-4} [j] (C) C-10H_e: 3.3×10^{-5} [j] (C)	**21**	1.2×10^{-6} [j] (C)	4.60
15		173.5°	C-3H_e: 3.2×10^{-2} [j] (C) C-3H_a: 1.6×10^{-4} [j] (C) C-10H_a: $<10^{-8}$ [j] (C)	**21**	1.2×10^{-6} [j] (C)	4.43

Table 2.2.2 Continued

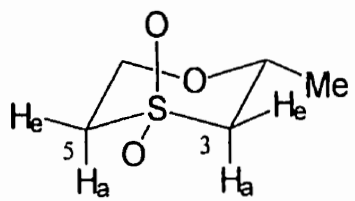
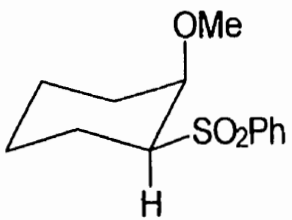
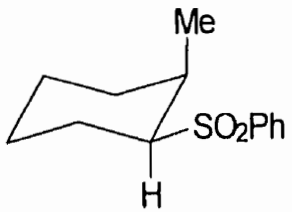
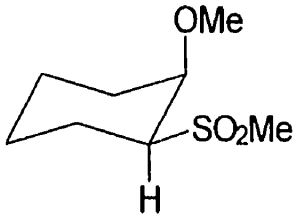
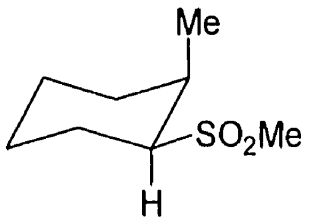
alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
16 	174°	C-3H_e: 1.6×10^{-2} [j] (C) C-3H_a: ~2×10^{-4} [j] (C)	**21**	1.2×10^{-6} [j] (C)	4.12
	173.3°	C-5H_e: 2.3×10^{-2} [j] (C) C-5H_a: ~2×10^{-4} [j] (C)			4.28
17b 	178.0°	9.3×10^{-4} (B3)	**23b**	1.75×10^{-6} (B3) 1.5×10^{-4} (B2)	2.73
			25b 	(8.96×10^{-7}) [h] (B3) 7.5×10^{-5} (B2)	(3.02)

Table 2.2.2 Continued

alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
17a 	179.4°	2.5×10^{-4} (B3)	**23a**	4.2×10^{-8} (B3) 3.3×10^{-6} (B2)	3.77
			25a 	(1.63×10^{-8}) [i] (B3) 1.3×10^{-6} (B2)	(4.19)

[a] The torsion angles (θ) were estimated by calculation using PCMODEL (PCM4), except those in parentheses, which were obtained from X-ray structure determination. [b] Reaction conditions, A: CD_3CN : D_2O (1:1), 21 °C; B1: Dioxane-d_8 : D_2O (1:1), 77 °C; B2: Dioxane-d_8 : D_2O (1:1), 64 °C. B3: Dioxane-d_8 : D_2O (1:1), 25 °C; C: D_2O, 20 °C. Rate constants in parentheses are not directly measured values but are calculated as described in the accompanying footnote. [c] $k_N = k_{exch} / (k_{exch})_{model}$. [d] Estimated value at 21 °C by multiplying the rate constant, k_{exch}, for **19** at 21 °C by the rate constant ratio of **20** to **19** at 77 °C. [e] This rate constant is that for H-D exchange per H, and was obtained by multiplying the experimental value by 2 (see discussion in the text). [f] Estimated value at 25 °C by multiplying the rate constant, k_{exch}, for **23b** at 25 °C by the rate constant ratio of **24b** to **23b** at 64 °C. [g] Estimated value at 25 °C by multiplying the rate constant, k_{exch}, for **19** at 25 °C by the rate constant ratio of **20** to **19** at 77 °C. [h] Estimated value at 25 °C by multiplying the rate constant, k_{exch}, for **23a** at 25 °C by the rate constant ratio of **25a** to **23a** at 64 °C. [i] Estimated value at 25 °C by multiplying the rate constant, k_{exch}, for **23b** at 25 °C by the rate constant ratio of **25b** to **23b** at 64 °C. [j] These data are obtained from Rathore's thesis.[31] [k] These data are obtained from Guo's thesis.[32]

Table 2.2.3 H-D exchange in β-alkoxy sulfones of unfixed conformation and γ-, δ-, ε- alkoxy sulfones [a]

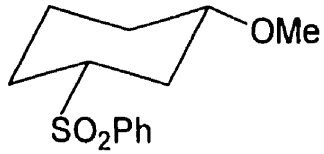
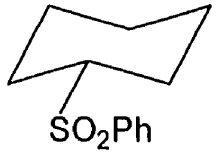
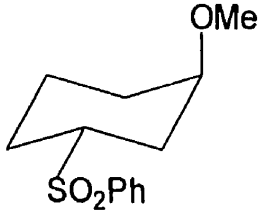
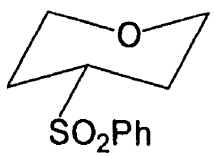
alkoxy sulfone	k_{exch} ($M^{-1}s^{-1}$)	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	k_N
28 	1.83×10^{-3}	**23b** 	1.47×10^{-4}	12.4
29 	1.35×10^{-3}	**23b**	1.47×10^{-4}	9.2
30b $PhSO_2(CH_2)_2OCH_3$ [b]	5.12×10^{-1}	**31a** $PhSO_2CH_2CH_3$	4.14×10^{-4}	1.23×10^{3}
		31b $PhSO_2(CH_2)_2CH_3$	2.3×10^{-4}	2.27×10^{3}
30c $PhSO_2(CH_2)_3OCH_3$	1.68×10^{-3}	**31b**	2.3×10^{-4}	7.5
		31c $PhSO_2(CH_2)_3CH_3$	2.03×10^{-4}	8.3
30d $PhSO_2(CH_2)_4OCH_3$	3.96×10^{-4}	**31c**	2.03×10^{-4}	2.0
		31d $PhSO_2(CH_2)_4CH_3$	1.80×10^{-4}	2.2
30e $PhSO_2(CH_2)_5OCH_3$	4.01×10^{-4}	**31d**	1.80×10^{-4}	2.2
		31e $PhSO_2(CH_2)_5CH_3$	1.80×10^{-4}	2.2

Table 2.2.3 Continued

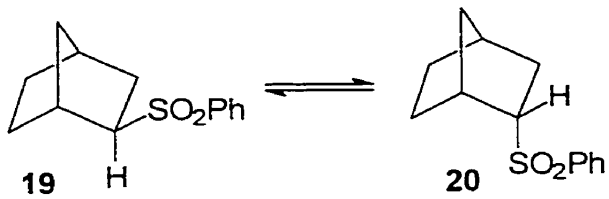
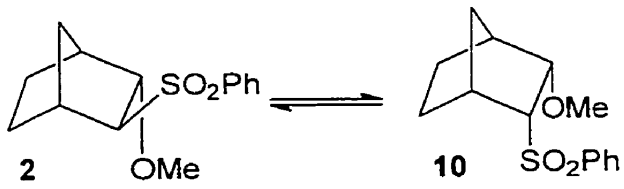
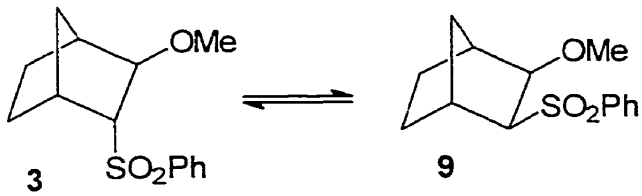
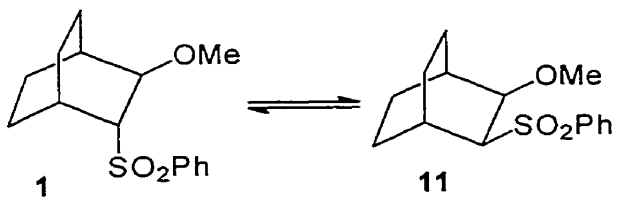
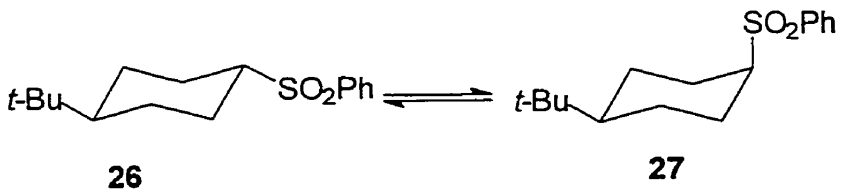
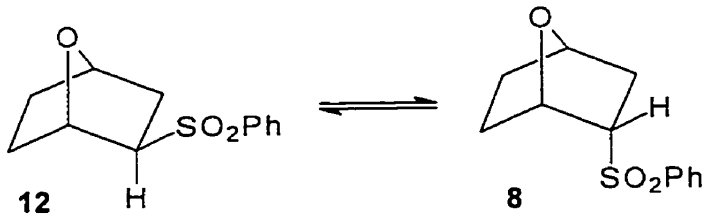
alkoxy sulfone	k_{exch} ($M^{-1}s^{-1}$)	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	k_N
32 	8.6×10^{-3}	**23b**	1.5×10^{-4}	49
33 $CH_3SO_2(CH_2)_2OCH_3$ [b, c]	4.2×10^{-1}	**34** $CH_3SO_2CH_2CH_3$	2.4×10^{-5}	1.79×10^{4}

[a] In D_2O-dioxane-d_8; cyclohexyl sulfones at 64 °C; alkyl sulfones at 25 °C.

[b] For comparison: $PhSO_2CH_3$, $k_{exch} = 2.26 \times 10^{-2}\ M^{-1}\ s^{-1}$; $CH_3SO_2CH_3$, $k_{exch} = 9.95 \times 10^{-4}\ M^{-1}\ s^{-1}$;

[c] Rates refer to the exchange of the methylene hydrogens; for the α-methyl group of **34**: $k_{exch} = 9.9 \times 10^{-4}\ M^{-1}\ s^{-1}$.

Table 2.2.4 The equilibrium constants for sulfone epimerization.

Reaction	K (T, °C)	ΔG° (kcal/mol)
 **19** **20**	0.18 * (77)	1.2 ± 0.3
 **2** **10**	0.003 * (77)	4 ±1
 **3** **9**	0.025 * (77)	2.5 ± 0.3
 **1** **11**	0.030 * (77)	2.4 ± 0.3
 **26** **27**	0.019 (64)	2.66 (lit.[60] 2.5 kcal/mol)
 **12** **8**	0.04 (64)	2.15

* These data are obtained from Guo's thesis.[32]

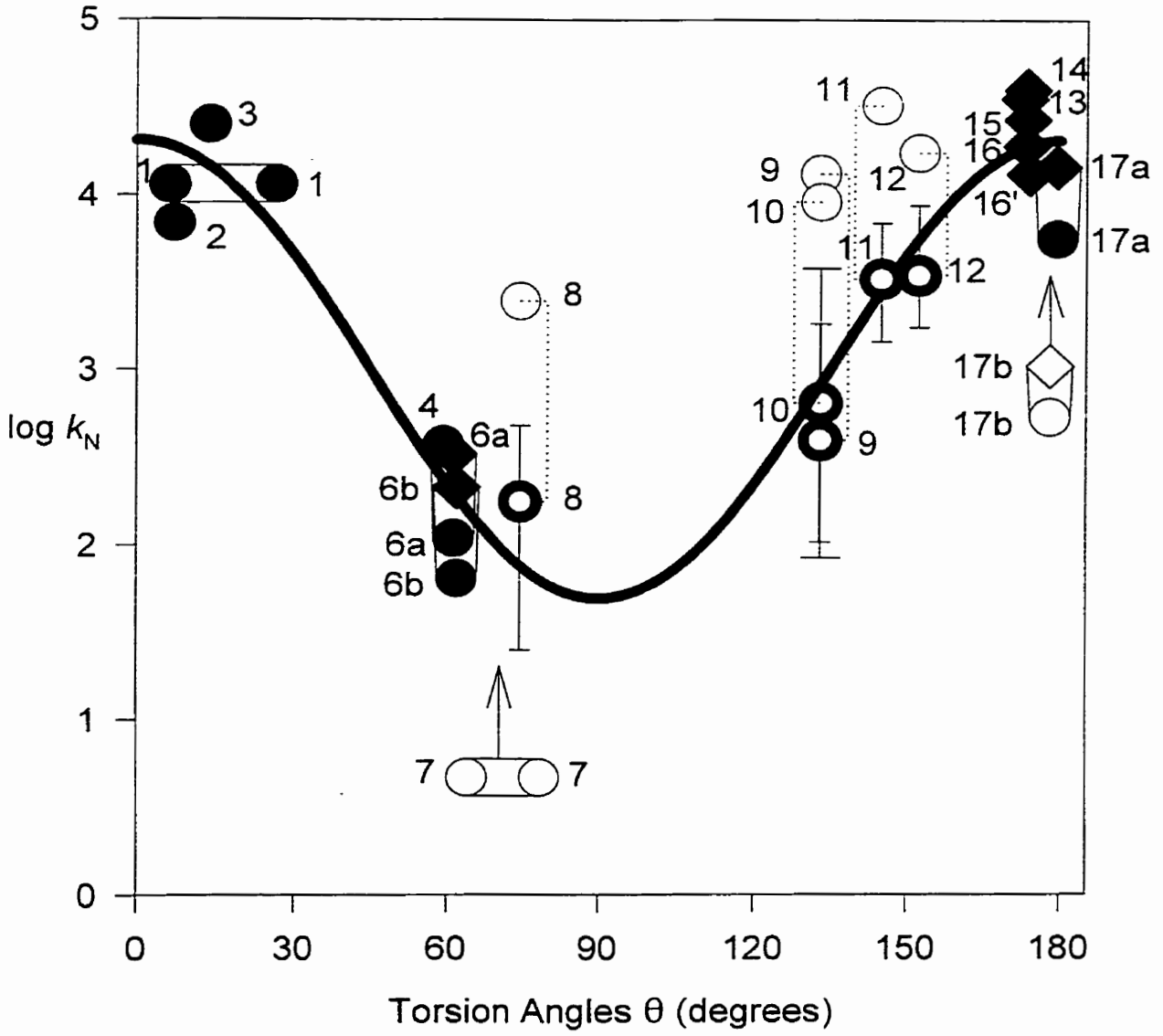


Figure 2.2.1 The torsion angle dependence of the rate of α-hydrogen exchange in β-oxygen substituted sulfones.

2.2.3 GEOMETRIC EFFECTS

2.2.3.1 Geometric Effects: Relation to the Sulfonyl Group

For the majority of the compounds in Table 2.2.2, there is only one hydrogen α to the sulfonyl group and hence there is no ambiguity about which hydrogen is being exchanged. With the compounds carrying a methylsulfonyl group (**6a**, **17a**, **23a-25a**) the exchange of the methyl hydrogens was found to be very much faster than that of the methyne hydrogen on the other side of the sulfonyl groups; it is the common experience that (when otherwise equivalent) methyl groups form a carbanion more readily than a methylene group, which in turn reacts more readily than a methyne. With the substrates and conditions in this study, the results in Table 2.2.3 indicate that the relative rates of hydrogen removal from methyl, methylene, and methyne groups are roughly 10^4:10^2:1.

Seven compounds have the sulfonyl group in a six-membered ring and have at least one methylene group directly attached to the sulfonyl function. In most of these the methylene hydrogens are diastereotopic (i.e. **4**, **14**, **15**, **16**, and **21**), but in two of them (**13** and **22**) the hydrogens of the methylene groups become equivalent by simple chair=chair interconversion; the members of this latter group present no problems in interpreting their spectra but they do require inclusion of a statistical correction factor for comparison with other compounds in this study. The exchange reaction that is being followed is the replacement of all four of the alpha hydrogens; at any time, however, only half of these hydrogens are in the (more reactive) equatorial position and hence the measured rate constant must be multiplied by two for comparison with compounds in which the alpha hydrogen is at all times in the favourable orientation.

In the group of sulfones in which the individual hydrogens of the methylene group

are diastereotopic, the different hydrogens can be expected to exchange at different rates. As has been discussed in the theses of Rathore[31] and Guo,[32] the hydrogens are readily assigned as axial or equatorial (in the most stable conformation) by their ^{1}H NMR signals; the axial hydrogens show the typical large axial-axial coupling (10 - 15 Hz) with each vicinal axial hydrogen and a much smaller axial-equatorial coupling (2 - 4 Hz) with their vicinal equatorial neighbours, whereas the equatorial hydrogens show small couplings with both axial and equatorial neighbours. On observing the exchange reactions by ^{1}H NMR it became evident that in all of the six-membered cyclic sulfones the equatorial hydrogen(s) exchange(s) faster than the epimeric axial hydrogen atom(s). With **21**, for example, the equatorial alpha hydrogen (C-3e) exchanges about 100 times faster than the axial hydrogen of the methylene group (C-3a), and this in turn exchanges much faster than the axial methyne hydrogen (C-10a). Similarly in **4**, it is the equatorial hydrogen which is exchanged more rapidly than the axial, by a factor of more than 25 times. These observations are indeed what was expected on the basis of the known preference for carbanion formation of the α-hydrogen with the anti-periplanar H-C-S-C torsion angle, and would have required little comment had it not been that Katritzky and coworkers[61] have reported that the equatorial : axial rate ratio in a model system of theirs (*cis*-3,5-diphenyl-*trans*-4-hydroxy-3,4,5-trideuterotetrahydrothian 1,1-dioxide) was only 1.6. The origin of the difference between our results and Katritzky's is not immediately apparent, but it is our view that the comparative simplicity of our compounds indicates that our systems describe the general case and it is the Katritzky example which is the exception, being heavily perturbed by the hydroxy and phenyl groups. This is also in agreement with the observation by Fuji, *et al.*[62] that the equatorial α-hydrogens in 6-methyl-1,3-oxathiane

3,3-dioxide exchanges 15 to 25 times more rapidly than the axial α-hydrogens (in $NaOCD_3$-CD_3OD at 20 °C). It could be argued that most of our examples are also perturbed by the presence of an ether oxygen, and it is the basic point of this work that this oxygen and its orientation strongly influence the rate of H-D exchange. In the two simple examples (**21** and **4**) noted above, however, one (**21**) has no ether oxygen at all and the other has the methoxy group symmetrically disposed with respect to the two α-methylene hydrogen atoms, and hence it is most unlikely that the oxygen in **4** is directly responsible for the *difference* between the reactivities of the two hydrogens. In the other three compounds (**14**, **15**, and **16**) the oxygen accelerates the exchange reaction, but in our view it is the orientation of the hydrogen atom with respect to the $C_{\alpha'}$-S bond that is the primary factor which determines which hydrogen is exchanged. The evidence in the present study is fully consistent with the picture that, with the compounds and the conditions used in this investigation at least, exchange of the α-hydrogens *only* takes place when the hydrogen has the anti-periplanar torsion angle around the H-C_α-S-$C_{\alpha'}$ bond. The exchange of hydrogens lacking the favourable H-C_α-S-$C_{\alpha'}$ torsion angle in the major conformation require conformational flip either to the alternative chair conformation (i.e. **4** with the methoxy group axial, **14** with the sulfonyl group axial to the cyclohexane ring, or **16** with the methyl axial), or to the twist conformation of the heterocyclic ring in **15** or **21**. The very slow exchange of the (axial) methyne hydrogen in **15** could conceivably be an exception to this picture, and could be taking place by way of a conformation in which the H-C_α-S-$C_{\alpha'}$ torsion angle is not anti-periplanar; it should be noted, however, that even this hydrogen can come close to achieving the anti-periplanar arrangement when *both* rings are in twist conformations.

2.2.3.2 Geometry Effects: Relation to the Alkoxy Group

(a) Small Steric Effects

The experimental values of log k_N are shown in Figure 2.2.1 as either black filled or fully open circles. With those points shown as black filled circles it is believed that the principal influence on log k_N is the electronic effect of the alkoxy group, i.e. that steric factors have little, or at least a relatively small effect on log k_N; within the context of a range of k_N values spanning more than four orders of magnitude, 'small' may be taken as a factor of three or (more usually) less. Some notion of the result of a small perturbation may be gained by examining the effect of replacing a β-hydrogen by a methyl group, i.e. by comparing the specific rates of H-D exchange either of (a) the α-hydrogens of **23** with those in **24** and **25** or (b) the C-3 and C-5 equatorial hydrogens in **16**. In the case of **24b** and **25b** vs **23b**, the effect of the methyl group is to slow the reaction by factors of 2.0 (with **25b**) and 3.33 (with **24b**). It is customary to assume that part of these rate reductions may arise from a small electronic effect of the methyl group (σ^* of CH_2X for X = H is 0.00 and for X = CH_3 is -0.1)[63a] and hence the steric effect of the methyl group (which must be only a part of the total effect) can not be large. With **16** the effect of the 2-methyl group is to reduce the specific rate of H-D exchange from 3×10^{-2} to 1.6×10^{-2} M^{-1} s^{-1}. Again, in this more reactive system, the steric effect of the methyl group must be small; note that unless the steric effect of the methyl group is to accelerate the reaction (which seems unlikely in these cases) the *maximum* electronic effect of the methyl group is to slow the reaction by a factor of two. Methyl and methoxy groups can often be regarded as of comparable 'size', with a slightly larger Taft E_s values[63b] for OCH_3 vs CH_3 (respectively, for CH_2X, -0.19 and -0.07) and a distinctly lower A value[27a] for methoxy as

compared with methyl (respectively, a range from 0.55 to 0. 75 vs 1.74 kcal mol^{-1}). It is within this framework that the points in Figure 2.2.1 given as filled black circles are regarded as unlikely to be *strongly* influenced by steric factors.

Note that four of the entries in Figure 2.2.1 consist of two points yoked by a pair of parallel lines. For two compounds (**6b** and **17b**) the two circles are yoked by two vertical lines. This reflects the uncertainty as to what is the most appropriate model compound. For example, for **6b** the upper point is obtained by using the "methyl model" (**24b**) and the lower by using the "hydrogen model" (**23b**). With **17b** the upper point arises by division of k_{exch} of **17b** by that of the "methyl model" (**25b**) and the lower from k_{exch} of "hydrogen model" (**23b**). Analogously, the horizontal yoking of points derives from uncertainties in the H-C_α-C_β-O torsion angle. In most instances the angle determined by x-ray crystallography was in fair accord with that estimated with PCModel, but with two compounds, **1** and **7**, the two values differed substantially and both are included in Figure 2.2.1. It should be noted that the PCModel calculations are performed on the conformation corresponding to Figure 2.2.2, i.e. with the sulfonyl group in the conformation with the H-C_α-S-$C_{\alpha'}$ torsion angle at 180 ± 1°.

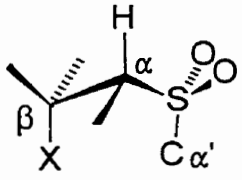


Figure 2.2.2 The conformation used to calculate the H-C_α-S-$C_{\alpha'}$ torsion angle by PCModel.

In the structures obtained from x-ray diffraction of single crystals, none of the

phenylsulfonyl groups are actually in the conformation shown in Figure 2.2.2; a measure of distortion on going to the Figure 2.2.2 arrangement is not unexpected.

The filled and lightly-outlined circles in Figure 2.2.1, taken together, do not justify drawing of the cosine curve (or, indeed, any other curve). We wish to show in the next few subsections (those with "correction" in the titles) that when due allowance is made for either steric assistance or steric hindrance or the "γ-effect", we may, with the aid of arguments totally independent of the generalized anomeric effect, factor out the steric (and γ-effect) contributions to a number of these k_N values leading to the "corrected" log k_N points shown as heavily outlined circles in Figure 2.2.1. In the two remaining examples, lacking sufficient information to make quantitative corrections, we develop an independent argument that indicates that the points should be corrected in the direction shown by the attached arrow in Figure 2.2.1, and that the extent of the change required bring each of these points close to the cosine curve is not beyond reasonable expectation; these latter points are not included in the curve fitting.

(b) Correction for Large Steric Assistance.

In contrast to the examples considered in the previous section in which steric factors are regarded as fairly small, a substantial steric effect was immediately evident from the observation in the reactions of the *cis* methoxy sulfones, **9**, **10**, and **11**, not only of H-D exchange, but also of concomitant isomerization to the equilibration mixture of the *cis* and *trans* α-deuterated isotopomers. That is, **9** gave an equilibrium mixture of the α-D isotopomers of **9** and **3**, with the later predominating. In deuterated media the free energy changes accompanying equilibration ($\Delta G^\circ_{SA} = G^\circ_{syn} - G^\circ_{anti}$) were, respectively,

2.5 ± 0.2 for **3** ⇌ **9** (77 °C), 4 ± 1 for **2** ⇌ **10** (77 °C), and 2.4 ± 0.2 kcal mol^{-1} for **1** ⇌ **11** (77 °C) (Table 2.2.4). The likely source of the clear preference for the *anti* isomer is a strong non-bonding repulsion (probably both steric and Coulombic) between the eclipsed *syn* methoxy and arylsulfonyl groups. In addition to this there is a difference between the $\Delta G°$ values for **3** ⇌ **9** vs **2** ⇌ **10** which is readily assigned to well-known lower energy of *exo* vs *endo* [2.2.1]bicycloheptane systems. This was confirmed by treating **19** and **20** with strong base (at 77 °C) to give mixtures of **19** and **20**, indicating an ultimate equilibrium mixture with 85 ± 5% of **19** and 15 ± 5% of **20**, and corresponding to $\Delta G°_{NX}$ = 1.2 ± 0.3 kcal mol^{-1}. If we label the *cis* interaction energy difference in **9** vs **3** (i.e. *exo-cis*) as $(\Delta G°_C)_X$ and that in **10** vs **2** (i.e. *endo-cis*) as $(\Delta G°_C)_N$, and if we then assign the observed energy differences primarily to the *cis* and *endo* interaction energies, we may write the following.

$$G°_{20} - G°_{19} = \Delta G°_{NX} = 1.2 \pm 0.3 \text{ kcal mol}^{-1}$$

$$G°_{9} - G°_{3} = (\Delta G°_C)_X - \Delta G°_{NX} = 2.5 \pm 0.3 \text{ kcal mol}^{-1}$$

$$G°_{10} - G°_{2} = (\Delta G°_C)_N + \Delta G°_{NX} = 4 \pm 1 \text{ kcal mol}^{-1}$$

From this we readily obtain

$$(\Delta G°_C)_X = 3.7 \pm 0.6 \text{ kcal mol}^{-1} \text{ and } (\Delta G°_C)_N = 2.8 \pm 1.3 \text{ kcal mol}^{-1}.$$

The *exo-* and *endo-cis* isomer interaction energies appear to be somewhat different, though the accumulated error in these estimates precludes precise comparison. Inspection of the S---OMe interaction distances and the O-C-C-S torsion angles (Table 2.2.5), which indicate slightly shorter distances in the *exo* isomer (**9**), are in accord with an apparently higher energy for $(\Delta G°_C)_X$. The energy difference between the *cis* and *trans* [2.2.2]bicyclooctyl sulfones, $G°_{11} - G°_{1}$, was found to be 2.4 ± 0.3 kcal mol^{-1}, i.e. a value

apparently smaller than the other cis interactions, in accord with the larger O-C-C-S torsion angle and S---OMe internuclear distance in **11** vs **10** and **9**.

Table 2.2.5 Comparison of x-ray structures of **9**, **10**, **11**.[32]

	9[a] (*exo*)		**10**[a] (*endo*)				**11**
O-C-C-S torsion angle (°)	11.2	0.7	13.9	17.3	6.2	10.9	30.8
S---O(CH_3) internuclear distance (Å)	2.83	2.9	2.89	2.97	3.01	2.89	2.93

[a] Because **9** and **10** have multiple conformers in the unit cell, multiple values for the torsion angle and internuclear distance are shown in the table.

The abstraction of a proton to form the carbanion from **9**, **10**, or **11** must be accompanied by a change in the O-C-C-S torsion angle which in turn yields a measure of relief of the ground state strain noted above; this well-known phenomenon is often referred to as "steric assistance."[27b] The question that now arises is, what proportion of the observed energies of the *cis* and *endo* interactions is expressed in the transition states leading to the carbanion, i.e. to what extent does ground state strain affect the *rate* of carbanion formation (and hence of H-D exchange) ?

To approach this problem we have looked at the relation between rates and equilibria in two simple sulfonyl systems, **19** ⇌ **20** and **26** ⇌ **27**. An energy diagram for **19** ⇌ **20** is shown in Figure 2.2.3.[32] Note that $\Delta G^{\ddagger}$ is 26.22 kcal mol^{-1} for **19** and 25.46 kcal mol^{-1} for **20**; the difference in free energy of activation, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{19} - \Delta G^{\ddagger}_{20} = 0.76$ kcal cal^{-1} is clearly ascribable to steric acceleration in the reaction of **20**. Of the original 1.2 kcal mol^{-1} of strain energy (in **19** vs **20**) 0.76 kcal mol^{-1} or 63% is released as steric

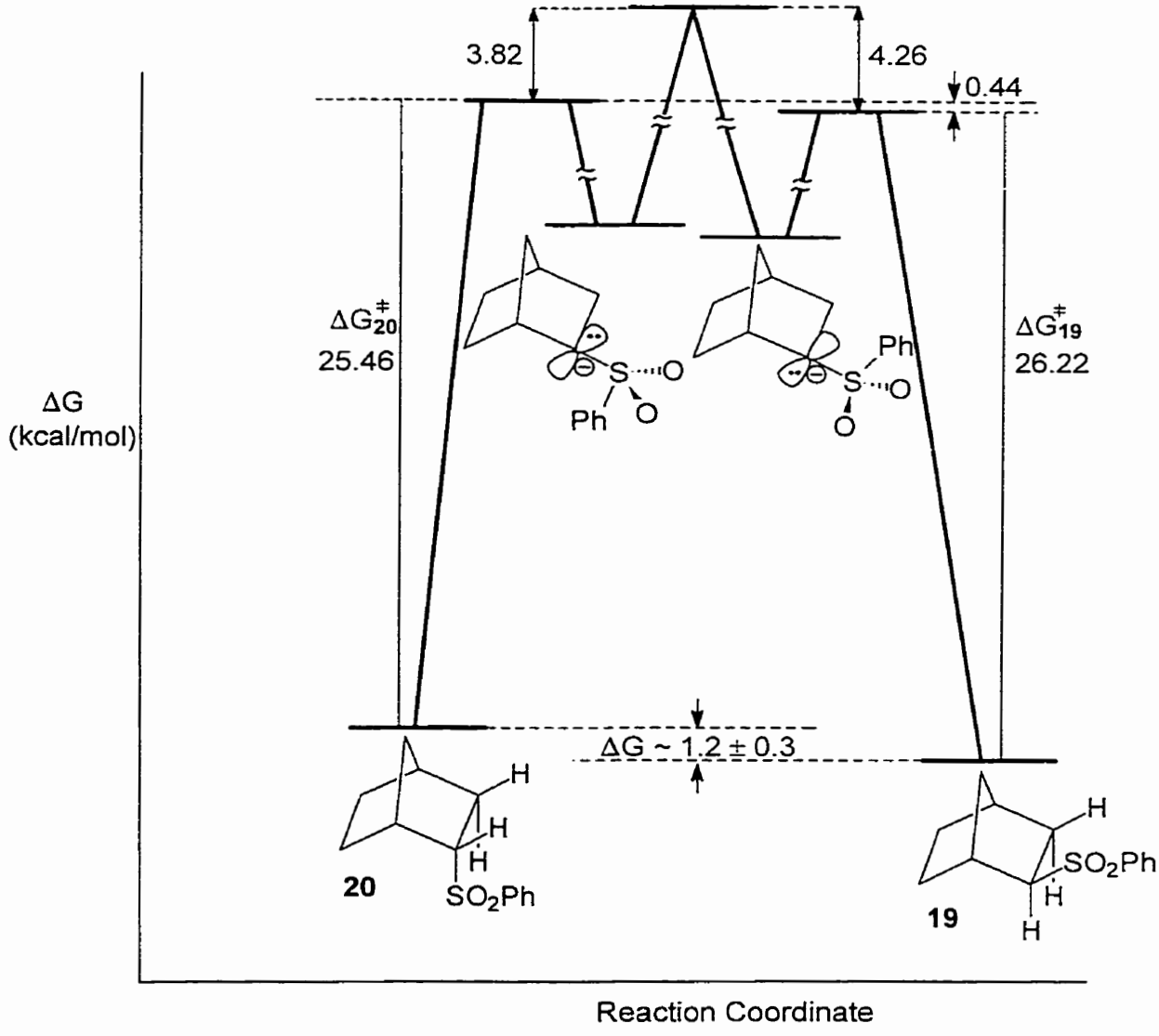


Figure 2.2.3 Energy diagram for the interconversion of **20** and **19**

assistance in the formation of the α-sulfonyl carbanion from the sulfone. In the other system **26** = **27**, the axial isomer was found to be higher in energy by 2.66 kcal mol^{-1}, and the difference in free energies of activation 1.91 kcal mol^{-1} (k_{exch} for **26** is 1.50×10^{-4} M^{-1} s^{-1} and for **27** is 2.60×10^{-3} M^{-1} s^{-1} both under the same conditions: 64°C, dioxane-d_8 : D_2O (1:1)); the release of strain energy is therefore 1.91/2.66 or 72% of the total. The results from the two reactions (an average ratio of strain energy release of 67%) are clearly in general agreement with other work on steric assistance. For example, Rüchardt and Beckhaus find slopes for plots of $\Delta G^{\ddagger}$ vs strain enthalpy for thermal cleavage of hydrocarbons which point to about 40% to 67% of strain energy being released in the reaction.[64] In other instances, strain energy released has been reported to vary from close to 80% to 26%,[65] to little or none.[66]

Returning to the alkoxy systems, the reaction of **9**, we take 67% of 3.7 ± 1 = 2.48 ± 0.7 kcal mol^{-1} as the strain energy released in making the carbanion. To find the electronic effect of the methoxy group we must correct the value of log k_N accordingly, i.e. we must reduce log k_N by the effect of the 2.48 kcal mol^{-1}, which is to say, by $2480/2.303RT = 1.55 \pm 0.44$ (T = 77°C), and the value of log k_N for **9** corrected for steric acceleration becomes 2.57 ± 0.44, the value given by the heavily outlined circle (and error bars) in Figure 2.2.1. In the same way the corrected (heavily outlined circle) values for log k_N for **10** and **11** were also obtained.

(c) Correction for the γ-Effect.

In the light of our observation that an alkoxy substituent in the beta position may accelerate the H-D exchange by more than 10^4-fold, it is evident that due account must be

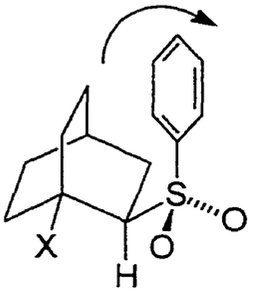
taken of an alkoxy interaction at the *gamma* position and probably at more distant locales as well. Table 2.2.3 indicates the results of a brief look into gamma and more distant effects. From this we see that an alkoxy group connected by a single three-carbon chain to the sulfonyl group increases the rate of H-D exchange (the "γ effect") in four examples by amounts ranging from 7.5 to 12.4 times. With one oxygen connected to the α-carbon by two identical three-carbon chains, as in **32**, the effect of the oxygen is increased to 49-fold. By this same token, we must conclude that in the reactions of the two 7-oxabicyclo-[2.2.1]heptyl sulfones (**8** and **12**), in which the oxygen is beta to the sulfur by one route and gamma by another, the observed rate must be influenced not only by the beta interaction but also by the γ effect, and hence that the magnitude of the gamma effect must be accounted for if we are to estimate the magnitude of the β-effect by itself in these compounds. An *upper* limit of roughly 10- to 12-fold for the γ-effect may be placed by the values in Table 2.2.3. The lower limit is less clear because it would appear reasonable to expect that when one oxygen is interacting by two paths, the total effect will not be as large as if there were two separate oxygen atoms acting independently. That is, to the extent that an oxygen atom acting by, say, a β-effect withdraws charge from the α-carbon in the transition state, then that same oxygen atom acquires an increased negative charge and can be therefore expected to be less electron withdrawing by the other pathway than if this involved another, quite different oxygen atom. In accord with this, we note that the "double γ-effect" via the two pathways (in **32**, 49-fold) is less than that expected for two independent γ-effects. In the absence of any straightforward basis for assigning the γ-effect when the same oxygen also shows a β-effect (as in **8** and **12**), we suggest that the value 5 ● 3 very likely covers the γ-effect range in these substrates. The

corrected point for **12** in Figure 2.2.1 has been obtained using this number: part of the error bars reflects the uncertainty in the γ-effect assignment. For **8**, an additional (steric) correction is required because the strain energy difference **8** and **12** is 2.15 kcal mol^{-1} (or 0.95 kcal mol^{-1} greater than that observed for **19** vs **20**), and hence is not adequately accounted for with **20** as the model. Accordingly a correction corresponding to 67% of the difference in strain energies (i.e. 0.67 × 0.95 kcal mol^{-1}) is applied to **8** in addition to the γ-effect correction.

(d) Correction for Rate Suppression Factors.

Even the most cursory examination of Figure 2.2.1 shows two (unfilled circular) points to be clearly removed from the others, those for (a) *cis*-2-methoxycyclohexyl phenyl sulfone (**17b**), and (b) the bridgehead methoxy sulfone **7**. The k_N value of the latter, 4.6 (log k_N = 0.66), is very low, being much lower than any of the other β-alkoxy sulfones and only about half of the typical γ-effect k_N values (Table 2.2.3). This, in itself, suggests the presence of a rate suppression factor of some kind.

Examination of molecular models suggests that a combination of two factors slows the H-D exchange in **7** relative to its model (**18**). As was noted in the introduction, the preferred (and in the present examples, probably the only) orientation of the α-sulfonyl system for carbanion formation is that shown in **35** as follows:

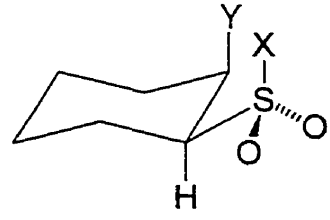


35 a) X = H; b) X = OMe

For **7** (= **35b**) and **18** (= **35a**) this would lead to very strong nonbonding repulsions between the phenyl and the nearest methylene groups. In the model system (**18** = **35a**) this can be alleviated in considerable measure by having the phenyl group move, as shown by the arrow, with concomitant twisting of the [2.2.2]bicyclooctyl system (which presumably also helps to minimize the eclipsing interactions in this array). With **7** (= **35b**), however, such motion leads to a shrinkage of the O-C-C-S torsion angle from its original value of about 60° in the untwisted bicyclo system to a value approaching 0°. This latter extreme would correspond to the eclipsed array, which as has already been seen with **9**, **10**, and **11**, above, would lead to extra energy of the order of about 3 kcal mol^{-1} or so. It would appear that the methoxy group in **7** introduces a steric-cum-electronic effect not adequately factored out by dividing by the rate constant for the model system (**18**), and hence a correction must be applied to increase k_N to find the purely electronic effect of the methoxy group in **7**. Without attempting to assign a numerical correction factor in this case we suggest that some idea of the order of magnitude can be gained from the following. A 1,3-synaxial Ph—CH_3 interaction in a cyclohexane system has been assigned[27b] a $\Delta G°$ (relative to the diequatorial conformer) of 3.4 kcal mol^{-1}. To the extent that a Ph—CH_2 interaction in **35** resembles the cyclohexyl synaxial Ph—CH_3 interaction,

then a comparable amount of energy may be expected to be required to achieve the arrangement in **35a** *with* the phenyl group moved as shown by the curved arrow. Such a movement of the phenyl in **35b** is presumably resisted by the tendency to obtain the eclipsed S-C-C-O array. Within this framework it would be reasonable to expect that the "less relaxed" arrangement in **7** would be of higher energy than the "more relaxed" conformation in **18** by at least 1 kcal mol^{-1} and probably not more than 5 kcal mol^{-1}. In **7** it should be noted that any tendency to involve hyperconjugation (which would be expected to be small because of the unfavourable H-C-C-O torsion angle estimated at 78°, see Table 2.2.2), would probably be accompanied by at least a small change in hybridization (from sp^3 to sp^2) at C-1 and C-2. Such a change would generate angle strain in the bridged structure associated with Bredt's rule, that is "in a small bridged system one cannot, for reasons of excessive strain, have a double bond at the bridgehead position".[27c] The net result could be either (a) no hyperconjugation, or (b) some hyperconjugation, but with little or no energy release because of increased strain.

The other unfilled circle, well removed from the others, is that due to **17b**. Examination of molecular models shows that the appropriate conformation of the H-D exchange is that shown in **36c**.



36

a) X = Ph, Y = H; b) X = Ph, Y = Me;
c) X = Ph, Y = OMe; d) X = Me, Y = OMe

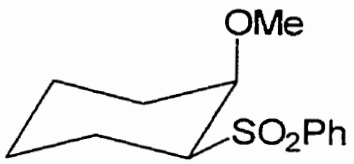
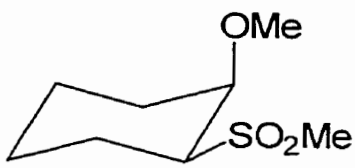
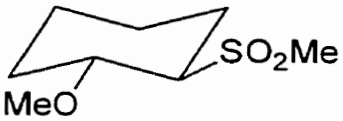
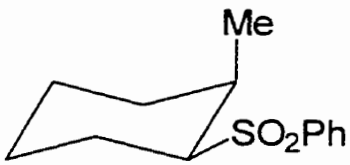
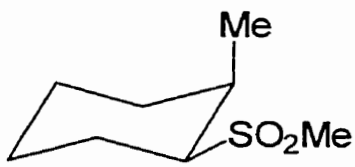
One immediately notes in **36c** what appears to be a substantial "1,3-synaxial-like"

interaction between the methoxy and phenyl groups. Interestingly (as has been noted earlier), however, when *cis*-2-methylcyclohexyl phenyl sulfone (**25b**) was examined, the effect of the "synaxial-like" *methyl*-phenyl interaction was found to be comparatively minor, with the rate constant for H-D exchange in **25b** about one-half of that of cyclohexyl phenyl sulfone (**23a**). One possibility suggested by these results is that there is a substantial MeO—Ph interaction not mimicked by the methyl analogue, i.e. one possibly not primarily steric in origin.

That there is something unusual about the "1,3-synaxial-like" MeO—Ph interaction is suggested by the following evidence which is quite apart from anything related to Figure 2.2.1. Note the effect on relative rates of H-D exchange of changing from a methyl sulfone to the corresponding phenyl sulfone, as shown in Table 2.2.6. For four of these pairs the exchange is substantial, varying from 23- to 58-fold; for the change **17b** to **17a**, however, it is only four-fold.

These results appear to point to a repulsive, possibly Coulombic nonbonding MeO—Ph interaction in **36c** (= **17b**) (and analogous arrays) not compensated for by models such as **23b** or **25b**. Without a clear picture of its origin we are not in a position to make any estimate of its effect on rates of H-D exchange magnitude other than the roughly one order of magnitude change noted in the methyl vs phenyl sulfone series above, Accordingly, we merely indicate by an upward pointing arrow in Figure 2.2.1 that it is likely that the point, when properly corrected, will likely have a distinctly higher log k_N value.

Table 2.2.6 The unusual "1,3-synaxial-like" MeO—Ph interaction in **17b**.

k (Ph) (M^{-1} s^{-1})	k (Me) (M^{-1} s^{-1})	k (Ph) / k (Me)
17b  9.3×10^{-4} [a]	**17a**  2.4×10^{-4} [a]	4
23b  1.75×10^{-6} [a]	**23a**  4.2×10^{-8} [a]	42
CH_3SO_2Ph 2.26×10^{-2} [a]	CH_3SO_2Me 9.95×10^{-4} [a]	23
6b  1.12×10^{-4} [a]	**6a**  $\sim 4.4 \times 10^{-6}$ [a, b]	26
25b  7.5×10^{-5} [c]	**25a**  1.3×10^{-6} [c]	58

[a] reaction conditions: 25°C, Dioxane-d_8 : D_2O (1:1). [b] Estimated value at 25°C, Dioxane-d_8 : D_2O (1:1) by multiplying its rate constant, k_{exch}, at 64 °C (3.7×10^{-4} M^{-1} s^{-1}) by the rate constant ratio of **23b** at 25 °C (1.75×10^{-6} M^{-1} s^{-1}) to that at 64 °C (1.47×10^{-4} M^{-1} s^{-1}). [c] reaction conditions: 64°C, Dioxane-d_8 : D_2O (1:1).

2.2.4 VARIATION OF log k_N WITH THE H-C-C-O TORSION ANGLE

2.2.4.1 Negative Hyperconjugation and the Generalized Anomeric Effect.

Inspection of the filled and heavily outlined circles in Figure 2.2.1 reveals a pattern consistent with variation of log k_N with cos2θ (or $\cos^2\theta$) where θ is the H-C-C-O torsion angle; the line drawn corresponds to the equation

$$\log k_N = (3.00 \pm 0.08) + (1.31 \pm 0.10) \cos 2\theta$$

$$= (1.70 \pm 0.17) + (2.62 \pm 0.20) \cos^2\theta \qquad \text{(eq 2.2.1)}$$

derived from a nonlinear least squares treatment including all of the heavily outlined and filled points in Figure 2.2.1. The three log k_N values not included in the least squares treatment (those for **5**, **7**, and **17b**) are subject to correction of uncertain magnitude, but it is not difficult to imagine that they too, given more information, would also conform to the cosine curve. At present, however, the log k_N values for **7** and **17b** do not, in our view, constitute evidence either for or against the cosine relationship. The case of **5** is discussed in Section 2.2.6.

Experimental free energy relationships in chemistry are always subject to "noise", i.e. to minor deviations from perfect fit to the line. In addition in the present case of log k_N, the problem of imprecision is made worse by the fact noted already that k_N cannot by its very nature always be uniquely and precisely determined. (A similar problem of precise determination appears with some well-known chemical parameters, e.g. resonance energy and effective molarity, or effective concentration; as with these, log k_N can be useful and lack of precision is not in itself grounds for not making use of the idea.) Within this framework we suggest that the results in Figure 2.2.1 constitute a strong case for eq 2.2.1. The variation with θ ranges from log k_N of about 2 to about 4.6, i.e. there is a

torsion angle dependent component of log k_N which appears to constitute more than half of the maximum total effect, and also a component (presumably the inductive and perhaps the field effect) which appears to be (more or less) independent of θ.

The angle dependence, in our view, is in full accord with the presence of negative hyperconjugation (generalized anomeric effect), for which such angle dependence has been predicted. In particularly striking agreement with our experiments are the calculations of Schleyer and Kos[23] who estimated that for the ethyl carbanion, the presence of a β-alkoxy substituent with θ = 180° would stabilizing the carbanion by 23.5 kcal/mol, whereas at 90° the effect would be 10.3 kcal/mol. That is hyperconjugation is responsible for 56% of the maximum total effect of a β-alkoxy group. Our corresponding estimated log k_N for the 180° and 90° conformers are respectively 4.29 and 1.55, pointing to stabilization by hyperconjugation of 64% of the maximum.

2.2.4.2 The Syn-periplanar Lone-pair Stereoelectronic Effect.

One notable feature of Figure 2.2.1 which warrants special mention is the powerful effect of syn-periplanar alkoxy groups, as shown by the large log k_N values for **1**, **2**, and **3**, in which the effect on k_N is close to or as large as that of the anti-periplanar alkoxy groups (e.g. compounds **14**, **15**, and **16**). Padwa and Wannamaker[67] have proposed syn-periplanar $n - \sigma^*$ overlap in connection with carbanion formation from a substituted 2-methoxycyclopropyl *p*-tolyl sulfone. Experimental evidence for the syn-periplanar lone pair effect in the chemistry of acetals has been put forward by Deslongchamps and Kirby and coworkers[68] (who conclude that the syn-periplanar effect is weaker than the anti-periplanar) and supported by calculations.[69] Notwithstanding a

suggestion that "syn-periplanar ... overlap would be disfavoured",[70] the case for the strong syn-periplanar lone pair effect appears established.

2.2.4.3 Angle Dependence of σ*. A New Parameter, σ^*_θ.

The variation of log k_N with the torsion angle may be described in terms of the Taft parameter σ* provided one adds a new feature, namely torsion angle dependence; we shall symbolize the angle dependent σ* as σ^*_θ, where θ implies an unspecified angle and σ^*_{30}, say, refers to the value at θ = 30°. Under the conditions of our experiments (NaOD in D_2O-dioxane-d_8 at 25 °C) or D_2O-organic solvent) the rate constants for H-D exchange of $PhSO_2CH_2CH_2OMe$ (**30b**) and $PhSO_2Et$ (**31a**) were found to be, respectively, 0.51 and 4.2×10^{-4} $M^{-1}s^{-1}$ (ratio = $k_N = 1.2 \times 10^3$). Thomas and Stirling report 0.44 and 3.7×10^{-4} $M^{-1}s^{-1}$ (ratio 1.2×10^3) for their detritiations (in EtO^-/EtOH at 25 °C), and it is clear that our system behaves very similarly to theirs. If we write eq 2.2.1

$$\log k_N = (3.00 \pm 0.08) + (1.31 \pm 0.10) \cos 2\theta$$

$$= (1.70 \pm 0.17) + (2.62 \pm 0.20) \cos^2\theta \qquad \text{(eq 2.2.2)}$$

from our work and take, from Thomas and Stirling's results,[6]

$$\log k_N = 4.89\ (\sigma^*_\theta)_{OR}$$

we get

$$(\sigma^*_\theta)_{OR} = (0.61 \pm 0.02) + (0.27 \pm 0.02) \cos 2\theta$$

$$= (0.35 \pm 0.03) + (0.54 \pm 0.04) \cos^2\theta \qquad \text{(eq 2.2.3)}$$

which gives the σ^*_θ value of the CH_2OR group as a function of the torsion angle, θ. In eq 2.2.3 σ^*_θ for the CH_2OR group may vary from $\sigma^*_{90} = 0.35 \pm 0.03$ to $\sigma^*_0 = \sigma^*_{180} = 0.88 \pm 0.08$. A plot of filled ("uncorrected") and heavily outlined ("corrected") log k_N values vs

σ_θ^* is shown in Figure 2.2.4, and, as expected, gives an approximate straight line with slope (ρ^*) of 4.88 (i.e. very close to 4.89).

Note that $\sigma_{180}^* = 0.88 \pm 0.08$ is distinctly larger than the value of σ^* for CH_2OMe (0.64) used by Thomas and Stirling. This reflects the fact that the maximum value of log k_N in our study is taken as 4.6, whereas in Stirling and Thomas' work log (k_{OMe} / k_H) = 3.08, i.e. in these experiments we are seeing larger k_N values with alkoxy groups in fixed conformations than with the conformationally mobile species (**30b**). Such a situation arises in a conformationally mobile system whenever there is a mixture of conformations of differing reactivity and the system is subject to Winstein-Holness kinetics.[28] In the simplest case of two equimolar conformations, one of which is reactive and the other totally unreactive, for example, the measured k_{obs} is one-half of the specific rate of the reacting conformation; more generally, the measured σ^* is the weighted average of the σ^* values for each conformation present. In the present case of $PhSO_2CH_2CH_2OMe$ the reacting conformer is arranged as in Figure 2.2.2 (X = OMe, $C_{\alpha'}$ = Ph). From the discussion already given in connection with the relatively low reactivity of **17b**, this arrangement is expected to have high energy. The low value of log (k_{OMe} / k_H) is presumably a reflection of a relatively low concentration of the reacting conformer (Figure 2.2.2, X = OMe, $C_{\alpha'}$ = Ph) as compared with that from $PhSO_2CH_2CH_3$ (Figure 2.2.2, X = H, $C_{\alpha'}$ = Ph).

The above discussion suggests that a rigorous treatment of a reaction of conformationally mobile species by the Taft equation would require a full conformational analysis with individual rate constants for conformers taken with a set of σ_θ^* values. Presumably the success of much simpler treatments suggests that (a) some systems are

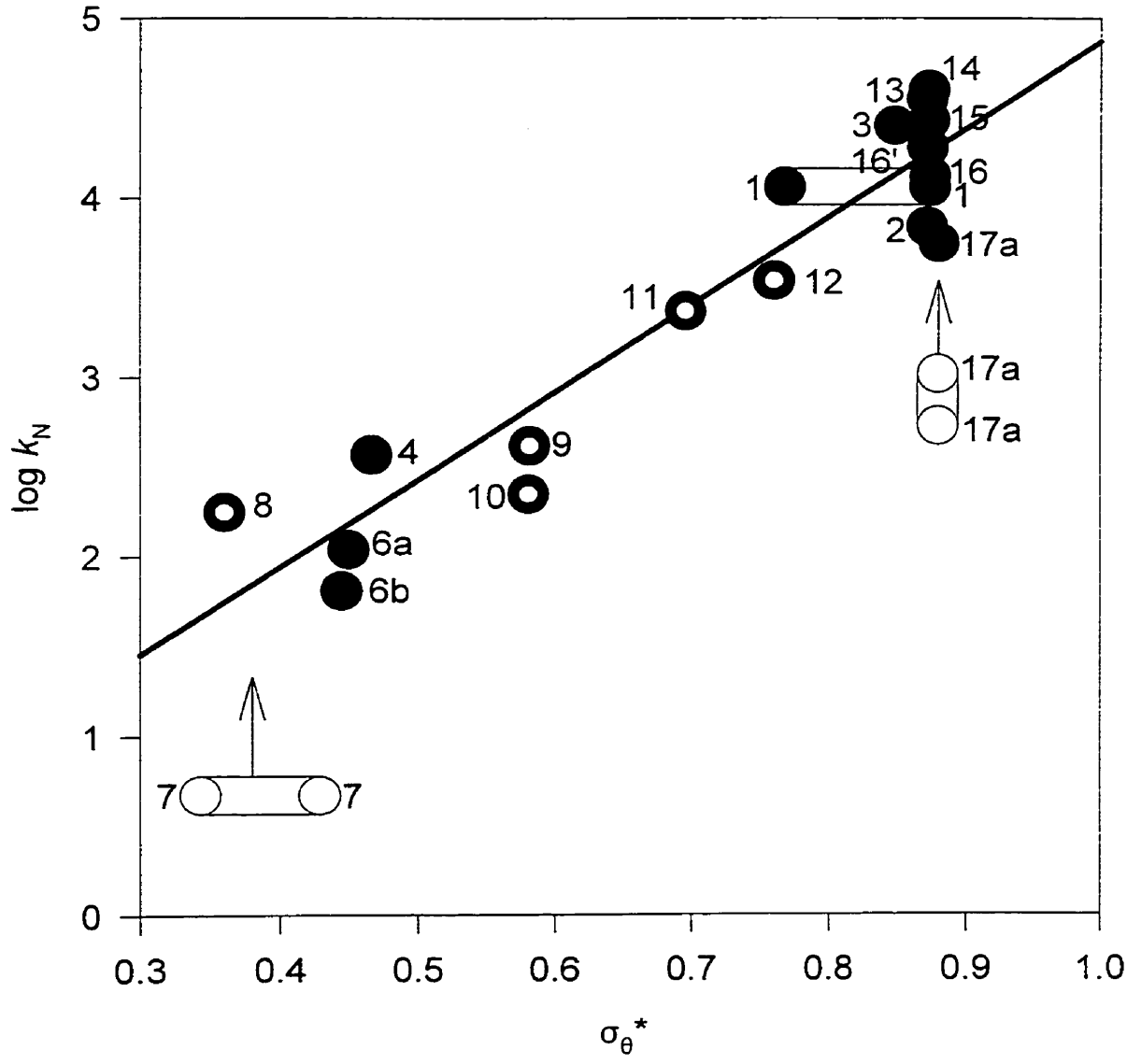


Figure 2.2.4 The angle dependence of σ_θ* term. The equation for the best-fit line is log k_N = -0.010 + 4.88 σ_θ*.

not complex, and (b) we often deal with averaging of conformational populations, rates and σ* values. Observation of experimental "noise" is not surprising.

2.2.5 THE FIELD EFFECT

As has been noted already, nearly half of the effect of alkoxy groups on log k_N appears to be more or less independent of the torsion angle, θ. This is fully consistent with the presence of the inductive effect which operates by successive bond polarizations and is, therefore, uninfluenced by the torsion angle. The field effect, however, is expected to be controlled to some extent by geometry.

In 1938, Kirkwood and Westheimer published their study of the field effect on acidity of a dipolar substituent.[71] An equation, known as Kirkwood-Westheimer equation, was presented:

$$\log (K_X / K_H) = e\,\mu\cos\zeta / (2.3\ RT\ r^2\ D_{eff})$$

where K_X and K_H are the acid dissociation constants of substituted and unsubstituted acids, and μ is the substituent dipole moment; D_{eff} is called to the "effective dielectric constant"; r is the distance between the middle point of bond C-X and hydrogen, ζ is the angle formed by bond C-X and the line which defines r (Figure 2.2.5 (a)).

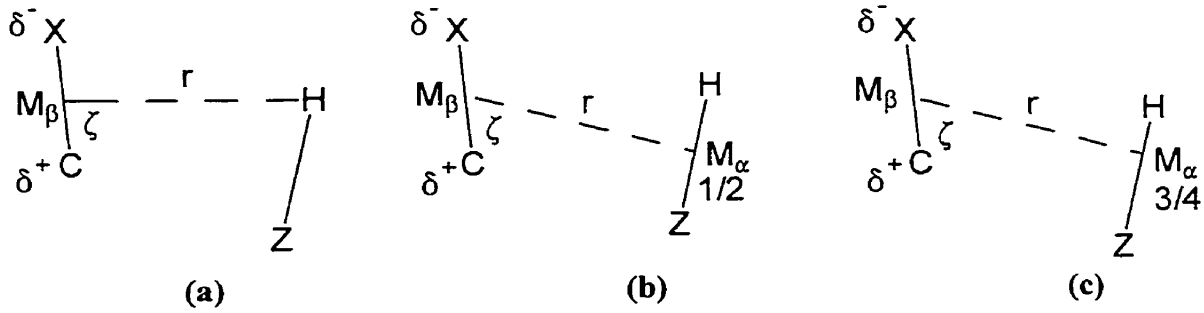


Figure 2.2.5 The definitions of parameters used for Kirkwood-Westheimer equation

This equation indicates that field effect for the same substituent and solvent should vary with (cos ζ) / r^2. However, it is not clear where the charge position at the transition state (the leaving of the H_α) in our situation is. Therefore, two additional pictures (shown in Figure 2.2.5 (b) and (c)) are considered: (b) the charge stays in the middle of the C_α-H; (c) the charge at the 3/4 position, closer to the leaving H.

As is shown in detail in Appendix A, we may calculate the value of (cos ζ) / r^2 (Table 2.2.7) based on the equations above. The plots of log k_N vs. (cos ζ) / r^2 are shown in Figures 2.2.6.

Judging from the Figures 2.2.6 (a), (b) and (c), there is no evident dependence of log k_N on (cos ζ) / r^2. A reasonable conclusion from these is that the field effect is NOT a major factor for the geometry dependence.

In order to have a clearer picture about the geometry dependence of the field effect, ethyl methyl ether was taken as a model (Figure 2.2.7). Table 2.2.8 includes the data obtained from PCModel calculations for this ethyl methyl ether system. The plots of (cos ζ) / r^2 vs. torsion angle θ are shown in Figure 2.2.7.

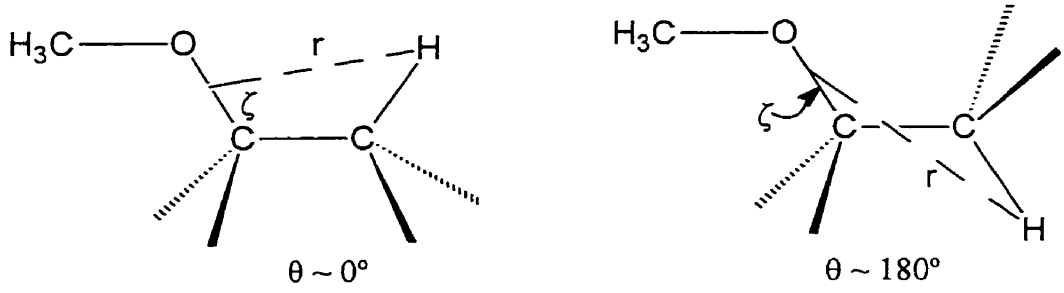


Figure 2.2.7 The conformations of ethyl methyl ether were taken as a model for the field effect.

Table 2.2.7 The torsion angle (θ), the log k_N (after corrections) and estimated parameters of ζ, r, and (cos ζ) / r^2 .

sulfones	torsion angle θ (°)	corrected log k_N	H [a]			1 / 2 [b]			3 / 4 [c]		
			cos ζ	r (Å)	(cos ζ) / r^2	cos ζ	r (Å)	(cos ζ) / r^2	cos ζ	r (Å)	(cos ζ) / r^2
1	26.2	4.06	0.1896	2.185	0.0397	0.4113	1.968	0.1062	0.2970	2.060	0.0700
2	7.1	3.84	0.2489	2.262	0.0487	0.4687	2.035	0.1131	0.3555	2.133	0.0781
3	13.9	4.40	0.1697	2.178	0.0358	0.4058	1.966	0.1050	0.2840	2.056	0.0672
4	59.3	2.57	0.3191	2.317	0.0594	0.4659	2.030	0.1131	0.3901	2.160	0.0836
5	60	2.81	0.3775	2.326	0.0698	0.7034	2.379	0.1242	0.5533	2.306	0.1041
6a	61.3	2.04	0.3603	2.333	0.0662	0.4989	2.053	0.1184	0.4278	2.180	0.0900
6b	61.9	1.81	0.3600	2.341	0.0657	0.4979	2.056	0.1178	0.4270	2.185	0.0894
7	78.4	0.67	0.4574	2.402	0.0793	0.5500	2.091	0.1257	0.5032	2.235	0.1008
8	74.5	3.42	0.3470	2.261	0.0678	0.4558	1.976	0.1168	0.4003	2.105	0.0904
9	133	4.12	0.7705	2.687	0.1067	0.7348	2.267	0.1428	0.7563	2.471	0.1239
10	133.1	3.96	0.8046	2.675	0.1125	0.7701	2.272	0.1493	0.7915	2.465	0.1302
11	145	4.51	0.8107	2.687	0.1123	0.7556	1.787	0.1474	0.7877	2.469	0.1292

Table 2.2.7 Continued.

sulfones	torsion angle θ (°)	corrected log k_N	H [a]			1 / 2 [b]			3 / 4 [c]		
			cos ζ	r (Å)	(cos ζ) / r^2	cos ζ	r (Å)	(cos ζ) / r^2	cos ζ	r (Å)	(cos ζ) / r^2
12	152.4	4.24	0.7507	2.699	0.1031	0.6843	2.237	0.1368	0.7221	2.463	0.1191
13	172.9	4.55	0.8389	2.788	0.1079	0.7703	2.322	0.1429	0.8092	2.551	0.1244
14	173.5	4.60	0.8407	2.799	0.1073	0.7742	2.311	0.1436	0.8119	2.556	0.1242
15	173.5	4.43	0.8425	2.790	0.1083	0.7745	2.322	0.1436	0.8130	2.551	0.1249
16	173.9	4.28	0.8612	2.712	0.1171	0.7857	2.271	0.1523	0.8287	2.486	0.1341
17a	179.4	3.75	0.8547	2.725	0.1151	0.8263	2.208	0.1695	0.8423	2.466	0.1385
17b	178	2.73	0.8749	2.732	0.1172	0.8116	2.306	0.1527	0.8481	2.512	0.1344

[a] Refer to the conformation depicted as Figure 2.2.5 (a);
[b] Refer to the conformation depicted as Figure 2.2.5 (b);
[c] Refer to the conformation depicted as Figure 2.2.5 (c).

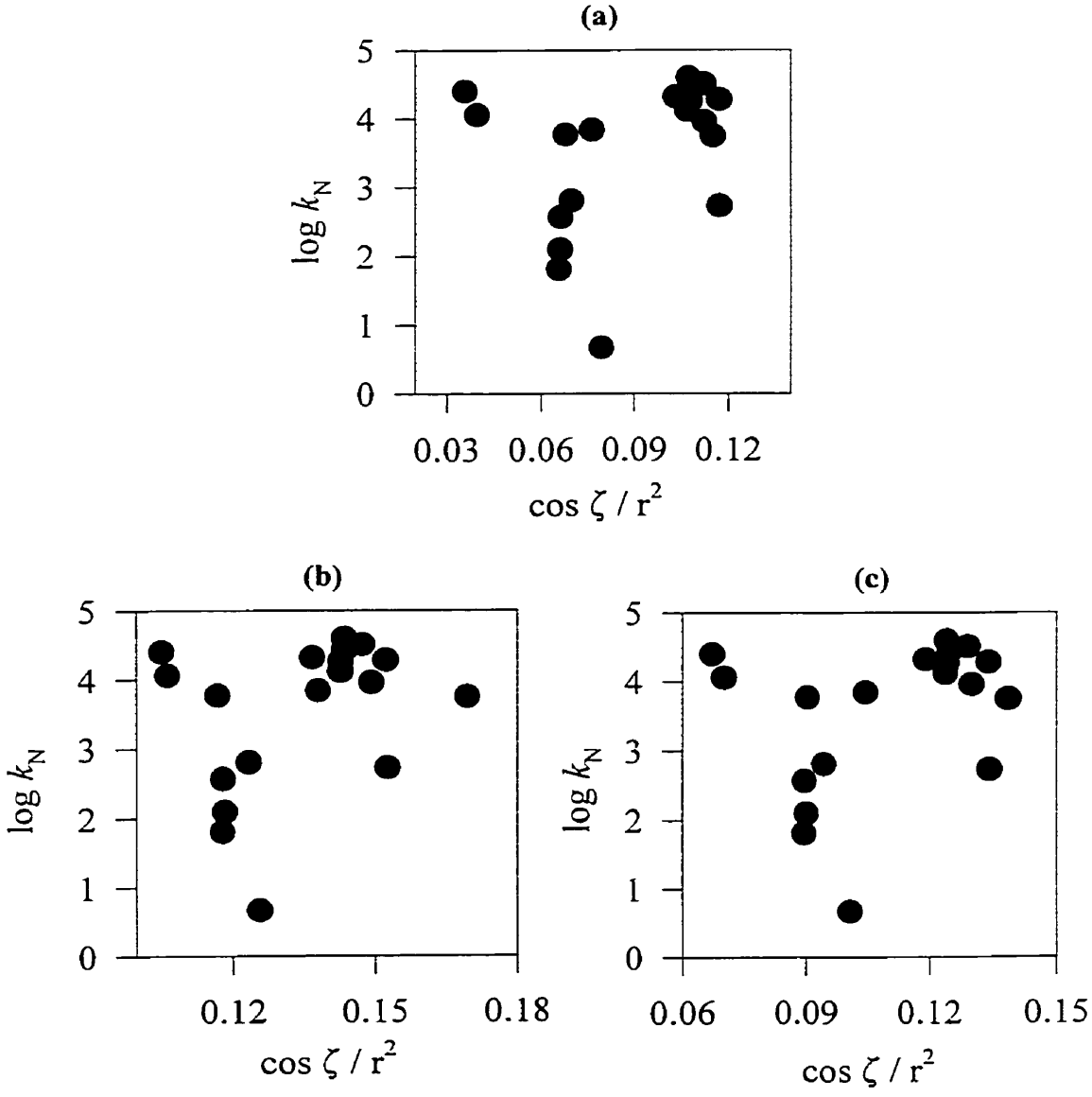


Figure 2.2.6 The lack of any linear dependence of the log k_N (after corrections) on (cos ζ) / r^2 .

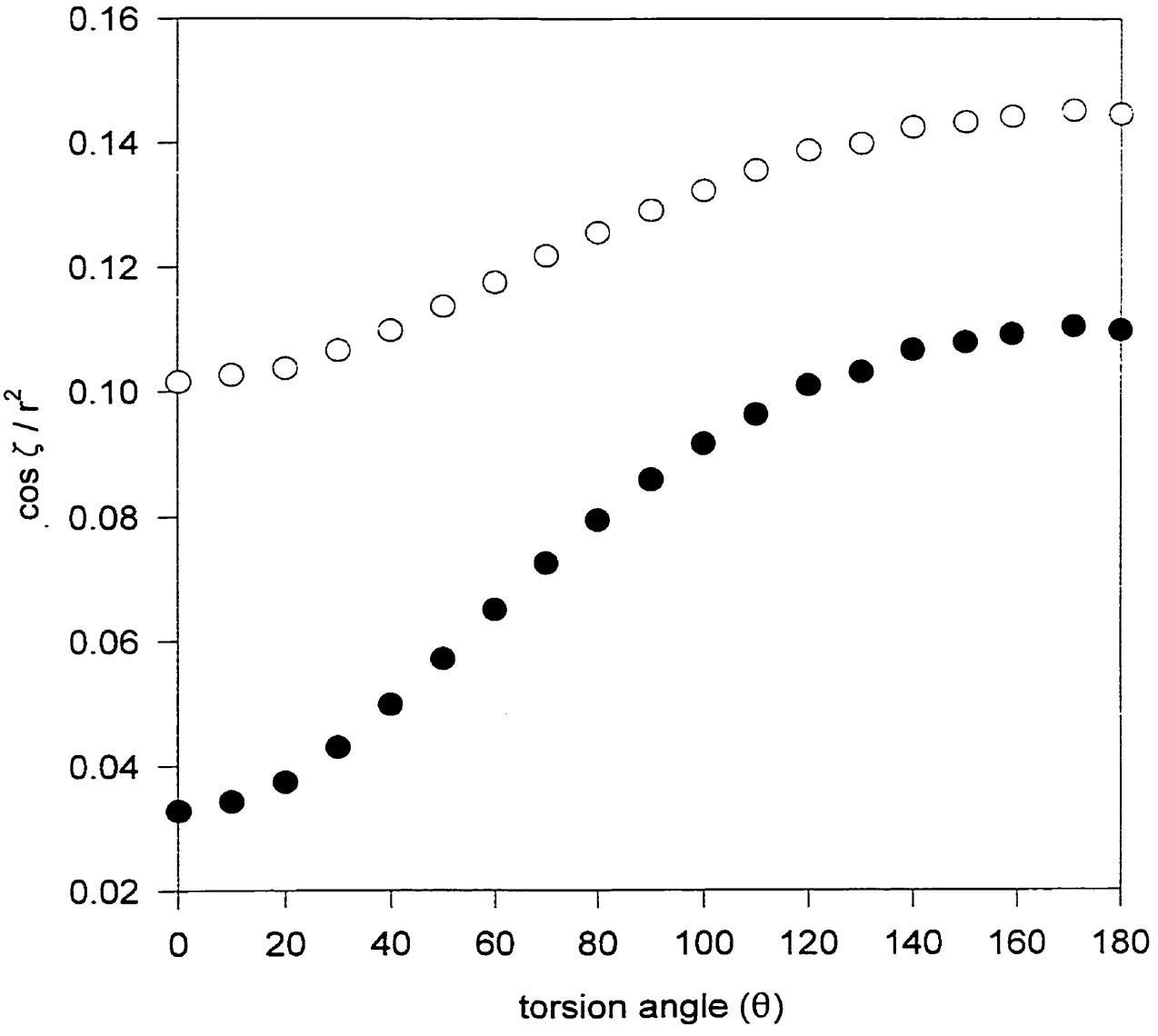


Figure 2.2.8 The field effect vs torsion angle in the ethyl methyl system. The filled circles are for Figure 2.2.5a; the unfilled circles are for Figure 2.2.5b.

Table 2.2.8 The value of (cos ζ) / r^2 vs. torsion angle for the ethyl methyl ether system

torsion angle (θ)	(cos ζ) / r^2 in Figure 2.2.5a	(cos ζ) / r^2 in Figure 2.2.5b
0.1	0.0328	0.1015
10	0.0343	0.1026
20	0.0374	0.1037
30	0.0430	0.1065
40	0.0498	0.1097
50	0.0572	0.1136
60	0.0651	0.1175
70	0.0727	0.1219
80	0.0796	0.1256
90	0.0860	0.1291
100	0.0917	0.1323
110	0.0963	0.1356
120	0.1010	0.1388
130	0.1032	0.1399
140	0.1067	0.1426
150.1	0.1079	0.1434
159	0.1093	0.1443
171	0.1105	0.1453
180	0.1098	0.1447

Figure 2.2.8 indicates that the field effect should be at its minimum when the torsion angle θ is 0 ° and at its maximum when the torsion angle θ is 180°. This is obviously not what we have obtained in Figure 2.2.1, because our results clearly indicate that the substituent effect is higher at either θ = 0° or θ = 180° than at θ ~ 90°. The points around θ = 180° appear to be slightly higher than those around θ = 0°, perhaps by as much

as 0.5 log k_N units, and one conceivable source of this difference — if it is real — could be the field effect.

A more complete evaluation of the Kirkwood-Westheimer equation requires the use of somewhat arbitrary parameters. For a particular substituent (e.g. the alkoxy group) and reaction, the Kirkwood-Westheimer equation may be expressed as

$$\Delta E = q\ \mu \cos\zeta / (D\ r^2)$$

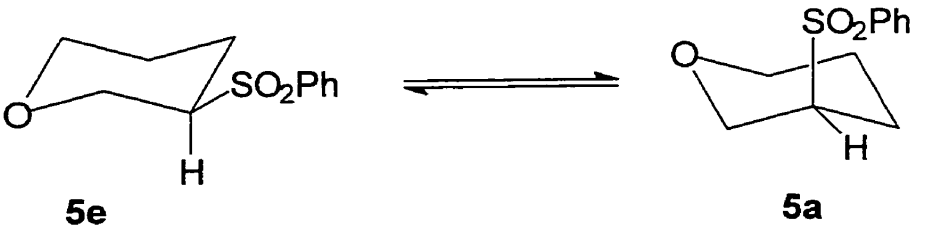
where q is the magnitude of the charge (which we took initially as that of the electron, 1.6×10^{-19} C, see below), μ is the bond moment of the dipolar bond, taken as 0.7 D[88] where 1 D = 3.34×10^{-30} C m, $D = D_E(4\pi\varepsilon_0)$ where D_E is the "effective dielectric constant" (see below) and ε_0 is the permittivity of free space (8.85×10^{-12} C^2 N^{-1} m^{-2}). From this (with Avogadro's number) we obtain $\Delta E = 2.03 \times 10^{-15}$ $(\cos\zeta)/D_E r^2$ J mol^{-1}. As is shown in Table 2.2.8, when θ is 0 ° then $(\cos\zeta)/r^2 = 0.33$ $Å^{-2}$ ($= 3.3 \times 10^{18}$ m^{-2}) and when θ is 180 ° then $(\cos\zeta)/r^2 = 0.11$ $Å^{-2}$ ($= 11 \times 10^{18}$ m^{-2}). At this point we must make a choice of two parameters, D_E and the magnitude of the developing negative charge. Kirkwood and Westheimer[71] have suggested that the effective dielectric constant, D_E, for the space between the charge and a dipole, should be in the range 3 to 10. We find that $D_E = 4$ gives a range of log k_N values consistent with Figure 2.2.1. The developing anionic charge must be less than one, but, from the sensitivity of the reaction to substituent (cf. $\rho^* = 4.89$), we find it difficult to imagine a charge less than 0.5. We used 0.75 in our calculations while noting that the results are not very sensitive to the precise number. These parameters (with 4.184 J/cal) gave ΔE values of 0.3 and 1.00 kcal mol^{-1} for $\theta = 0°$ and 180°, respectively; division by 2.303RT gives log k_N field effect contributions of 0.22 and 0.74 effectively. The results and discussion to this point indicate that the polar effect

of an alkoxy group may be qualitatively analysed as follows: at $\theta = 0°$ and $180°$ the polar effect comprises an anomeric effect, plus a smaller inductive effect, plus a still smaller field effect, and at $\theta = 90°$ the polar effect contains only the inductive effect plus (a smaller) field effect.

2.2.6 REACTION VIA A LESS STABLE CONFORMER: THE CASE OF COMPOUND 5

Although many reactions take place by way of the most stable conformer(s), one must recall that exceptions to this generalization are commonly found when, as in the present study, stereoelectronic requirements are important. It therefore seemed prudent to examine the substrates in Table 2.2.2 to see if any of these might react to a substantial extent via a conformation different from that shown. One likely example, in fact, was found.

As is illustrated in Scheme 2.2.1, Compound **5** in the most stable conformation (**5e**) clearly has the $PhSO_2$ group equatorial and the H-C-C-O torsion angle, θ, close to 60°. The alternative axial conformation (**5a**) must have higher energy than **5e** (*cf.* $\Delta G° = 2.66$ kcal mol^{-1} for **26** ⇌ **27**), but θ in **5a** is close to 180°.



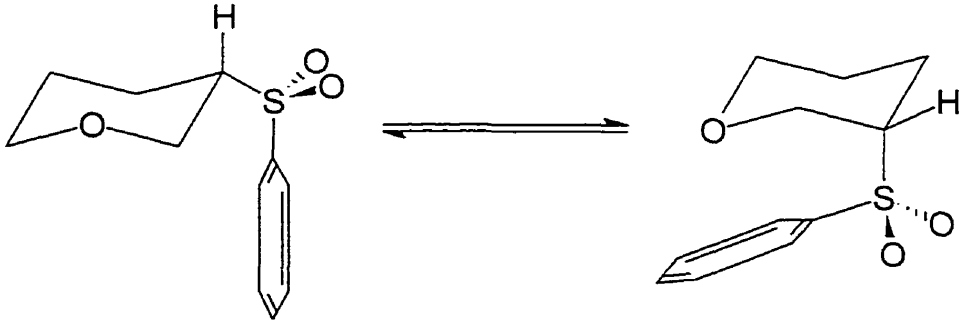
5e **5a**

Scheme 2.2.1

From eq 2.2.1 the rate constant for **5a** must be greater than that for **5e** by about 108 ± 5

times just because of the stereoelectronic factor alone; we therefore use a "θ-factor" of 108-fold. The actual active conformations are illustrated as **5a1** and **5e1** (Scheme 2.2.2).

To estimate the log k_N for **5a1** and **5e1**, we need to evaluate the equilibrium of **5e1** ⇌ **5a1**. As a rough guess for the value of the ΔG° of this equilibrium we suggest about 6 ± 2 kcal mol^{-1} (see Appendix C).



5e1 **5a1**

Scheme 2.2.2

Roughly half of the suggested 6 ± 2 kcal mol^{-1} may be regarded as the energy required to convert **5e** into **5a**, in accord with the 2.66 kcal mol^{-1} observed for **26** ⇌ **27**. The remainder represents the difference in energy used to get to the specific arrangements in **5e1** and **5a1**, each of which will be of higher energy than the other conformers about the C_α-S bond (i.e. those with the phenyl group anti-periplanar to one or the other of the methylene groups). A value in the range of a "syn-axial" conformation (~ 3 kcal mol^{-1}) seems appropriate. Note that using ΔG° = 6 kcal mol^{-1} and a θ-factor of 85, one may estimate that roughly 70% of the reaction of **5** proceeds via **5a1** and about 30% by **5e1**. Note the value of 6 ± 2 kcal mol^{-1} for the ΔG° of the reaction shown in Figure 2.2.2 is given only for illustrative purpose, to show that it is likely that **5** reacts via both the axial and equatorial conformers. Even with values outside the above range, one obtains the

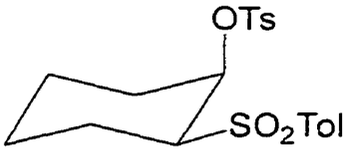
same conclusions: e.g. with $\Delta G° = 3$ kcal mol^{-1}, we would estimate 93% via the axial **5a1**, whereas $\Delta G° = 10$ kcal mol^{-1} predicts 16% via the axial **5a1**.

With **5** and a number of other species in Table 2.2.2, twist forms may be presumed to be present in relatively small concentrations. As is mentioned earlier in the text, these are believed to be the intermediates in the H-D exchange of axial protons in anancomeric (conformationally anchored) systems (**15** and **21**). The 100- to 200-fold slower rates for the axial exchange probably gives a rough idea of the importance of twist forms in the reactions of compounds in Table 2.2.2.

2.3 APPLICATION: A REEXAMINATION OF THE MECHANISM OF THE ELIMINATION IN BETA-TOSYLOXY SULFONES ORIGINALLY STUDIED BY PEARSON, BORDWELL, HINE, AND OTHERS.

2.3.1 Discussion of the Mechanism of Syn and Anti Elimination

Now we apply the results of this study to a question of mechanism which started in the middle 1950's when Bordwell and Pearson and coworkers[72] looked at *syn* and *anti* eliminations in a series of sulfones including **36** and **37**.



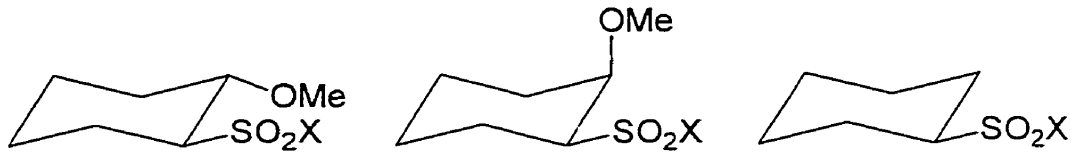
36

37

These authors concluded at that stage that the anti elimination from **36** and the syn elimination from **37** (to form 1-cyclohexenyl *p*-tolyl sulfone in each case) both proceeded by way of a concerted (*E*2) reaction. In 1962 Hine and Ramsay[73] questioned this conclusion and provided evidence that the *syn* elimination, contrary to the contention of Bordwell and Pearson, was not faster than could be expected for a carbanion process. Subsequently, Bordwell, Weinstock, and Sullivan[74] marshalled arguments and evidence to conclude that the *syn* and *anti* eliminations both take place by the carbanion mechanism. Their reasoning invoked two interesting ideas, (a) internal return of the carbanion as a significant reaction in this system, and (b) a "retardation effect" in forming carbanions from 1,2-diequatorially disubstituted cyclohexyl derivatives; in our view, both of these effects need at least some revision.

Returning to Hine and Ramsay's paper, the key piece of evidence was a plot of

log *k* vs σ* in which the reactions were (a) the H-D exchange reactions of cyclohexyl *p*-tolyl sulfone (**23c**) and 2-*cis*-methoxycyclohexyl *p*-tolyl sulfone (**17c**), and (b) the elimination reactions of **36**, **37**, and 2-*cis*-chloro- and 2-*cis*-fluorocyclohexyl *p*-tolyl sulfones (Figure 2.3.1). They commented as follows, "From the best straight line through the unsubstituted, *cis*-2-methoxy and *trans*-2-tosyloxy sulfones [i.e. **23c**, **17c** and **37**], it is seen that the rate of *cis* elimination of the tosyloxy compound [**37**] is not faster but instead rather slower than would be predicted from the σ*-constants of the groups used."



6 **17** **23**

a) X = Me b) X = Ph c) X = *p*-Tol

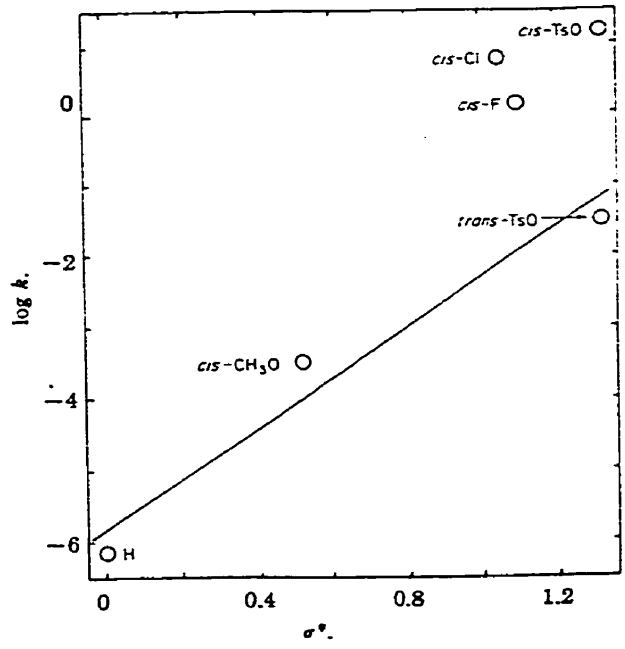


Figure 2.3.1. Rates of proton removal from 2-X-cyclohexyl *p*-tolyl sulfones *vs.* σ* for XCH_2 (copy from Hine and Ramsay's paper[73]).

The agreement between the points and "the best straight line" in the above quote is not very good and the authors discussed possible steric factors for the observation that the point for **37** was below that expected from the σ* value. Hine and Ramsay's plot included *cis*-tosylates (**36**) and two *cis*-halo analogues; the points for these last were well above the best straight line through the other three points, consistent with the idea that these compounds react by an *E*2 reaction. Note that the same σ* value was used for the *cis*- and *trans*-tosylates (**36** and **37**).

Here, we wish to point out that the application of the idea of an angle-dependent σ* parameter alters the picture dramatically.

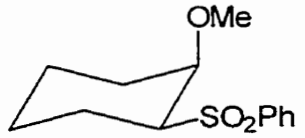
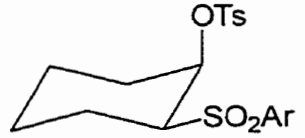
2.3.2 Application of the Angle Dependent σ* term to Hine and Ramsay's plot

Depending on assumptions we may estimate a $(\sigma^*_{60})_{OTs}$ value of roughly 0.63 ± 0.1 (see Appendix B). So, there is a significant difference between the σ* values of the *cis*- and *trans*-tosylates, and this will move the point for **37** in the Hine-Ramsay plot so that it is close to being on the same straight line with *all* of the other points as the scatter of these other points will allow. That is the points for the two H-D exchange reactions and the four elimination processes may be regarded as falling all on the *same* straight line, and from this we may conclude that the transition states for all of these reactions are very similar. Since two of the reactions (the H-D exchange processes) are known to be carbanion reactions, it is reasonable to infer that the eliminations also involve carbanion formation, or, if not, that the transition states are extremely similar to those of carbanions. In other words the reactions are either *E*1cB or very *E*1cB-like *E*2 processes.

In view of the complexity of some of the discussion in this thesis to this point, it

may be helpful to view this topic from a perspective requiring specifically neither σ* values nor "corrected" log k_N values. A simple plot of log *k* for the reactions of **23c** (H-D exchange), **36**, and **37** (both eliminations) (data as presented by Hine and Ramsay[73]) vs our results for H-D exchange in **23b**, **6b**, and **17b** is shown in Figure 2.3.2 (Table 2.3.1 lists the data for Figure 2.3.2). The three points fit a straight line, and we are immediately led to the same conclusions as those drawn in the previous paragraph The point for the *cis*-tosylate (**36**) is slightly above the (projected) line joining **23c** and **37**; this could conceivably permit an *E*1cB mechanism for **37** and an *E*1cB-like *E*2 reaction for **36**.

Table 2.3.1. Comparison of kinetic data obtained by Hine and Ramsay[73] with our results.

Our Results		Hine and Ramsay's Results	
6a 	log *k*: -3.95 (H-D exchange)	**37** 	log *k*: -1.60 (elimination)
17b 	log *k*: -3.03 (H-D exchange)	**36** 	log *k*: 1.24 (elimination)
23b 	log *k*: -5.76 (H-D exchange)	**23c** 	log *k*: -6.18 (H-D exchange)

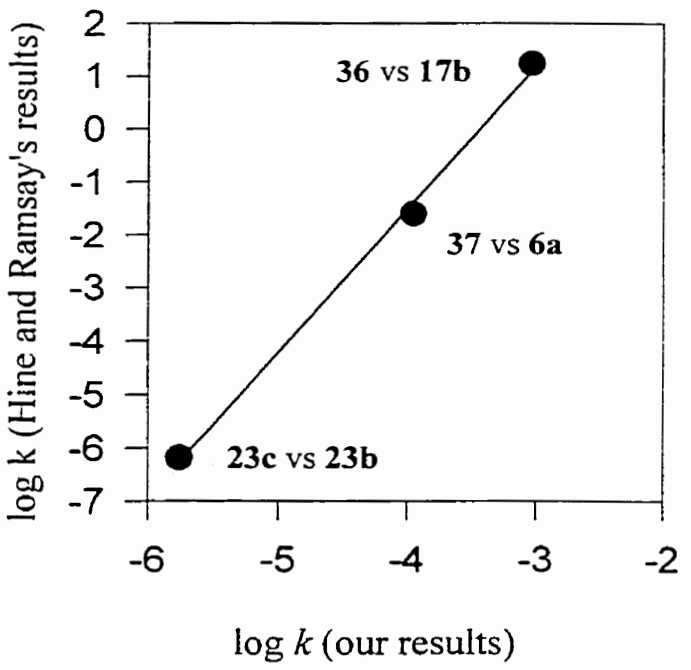


Figure 2.3.2 Comparison of kinetic data obtained by Hine and Ramsay with our results. (For additional information see Table 2.3.1)

Bordwell, *et al.*[74] had already drawn the conclusion that the *anti* and *syn* elimination reactions are probably both carbanion processes, and it is now appropriate to see how the present results relate to their arguments. First we note that the proposal of significant internal return is contradicted by subsequent experiments. The work of Thomas and Stirling,[2a, 75] in particular, clearly establishes that hydrogen exchange alpha to the sulfonyl group is indeed remarkably sensitive to the nature of any β-substituents with $\rho^* = 4.89$ (see above), and they observed a sizable kinetic isotope effect ($k_H/k_T = 7.1$) in good accord with a mechanism in which the hydrogen removal is rate-determining and there is little or no ion-pair return.[2b] The second effect postulated by Bordwell, *et al.* was

the "retardation effect" in carbanion formation in six-membered cyclic compounds. The main reason for calling upon this effect was to account for the observation that syn eliminations in cyclohexyl compounds were invariably slow relative to either (a) the analogous anti eliminations in cyclohexyl or cyclopentyl substrates, or (b) the corresponding syn eliminations in cyclopentyl species. We now look at these results in the light of the present work. The H-C-C-O torsion angle in the cyclohexyl substrates undergoing syn elimination (e.g. **37**) is around 60° and must form, therefore, the carbanion much more slowly than either the *trans*-cyclopentyl compounds (reacting by syn eliminations) in which the torsion angle can readily be close to 0°, or the *cis* substrates in either the cyclopentyl or cyclohexyl systems in which the H-C-C-O torsion angle is close to 180°. The results of the present study *predict* that the syn-cyclohexyl (θ = 60°) reactions will be slower than any of the other reactions (with 0 or 180° torsion angles). It should perhaps be noted that there could also be some sort of (additional) retarding effect in the reactions of cyclohexyl compounds; the log k_N values for **6a** and **6b** (and possibly **17a** and **17b**) may reflect this phenomenon.

2.4 CONCLUSIONS

The angle dependence of the reaction of a β-alkoxy substituted saturated system has been established. The β-effect in the above system has been demonstrated to be not consistent with simple inductive and field effect and it is proposed that there is an additional effect arising from negative hyperconjugation (generalized anomeric effect). It has been shown that the contribution from the negative hyperconjugation (anomeric effect) is the major component, when the substituent is ideally oriented for hyperconjugation.

A new feature, namely the angle dependence, has been added to the Taft parameter σ*, and a new parameter, σ_θ^*, is proposed. This angle dependence feature has been successfully applied to shed light on the question of mechanism of the elimination in β-tosyloxy sulfones originally studied by Pearson, Bordwell, and Hine, et al.

2.5 EXPERIMENTAL

2.5.1 PREPARATION OF SULFONES

Melting points were determined on a Kofler Hot Stage and are uncorrected. Infrared spectra were obtained with a Bruker IFS 32 FTIR spectrometer. ^{1}H NMR spectra were obtained using Varian XL-200, Gemini 200 and Gemini 300 spectrometers. ^{13}C NMR spectra were determined on Gemini 200 and Gemini 300 instruments. Tetramethylsilane (TMS) was used as reference for solvent $CDCl_3$. When D_2O was used as solvent for NMR, the reference was sodium trimethylsilylpropanesulfonate (DSS). Mass spectra were run on a Finnigan 8200 MS data system using low resolution at 70 electron volt ion current and using direct exposure probe. Precise mass determinations were carried out using peak matching with perfluoroalkane. Chemical ionization mass spectra were recorded using isobutane as a moderating gas.

Reagent grade chemicals and solvents were used without additional purification unless otherwise noted. Solvents such as methylene chloride, chloroform, benzene, ethyl acetate, tetrahydrofuran, diethyl ether were distilled before used. Absolute ethanol and methanol were dried by the magnesium alkoxide procedure.

Usual workup of reactions refers to the partition of the reaction mixture between water and an organic solvent (methylene chloride or ether), drying of the organic layer with magnesium sulfate (or sodium sulfate) and then evaporating the solvent using a Buchi rotary evaporator connected to a water aspirator.

Preparation of 3-(Phenylsulfonyl)tetrahydropyran (5)

a) 3-(Phenylthio)tetrahydropyran (53)[33]

To a mixture of thiolacetic acid (2.0 g, 0.026 mol) and 3,4-dihydro-2*H*-pyran (2.2 g, 0.026 mol) at 0 °C, 2,2'-azobisisobutyronitrile (AIBN, 0.020 g, 0.12 mmol) was added. The reaction mixture was stirred for 10 h at 0 °C to 5 °C , then overnight at room temperature. Workup as usual gave 3-(acetylthio)tetrahydropyran (**51**, 2.1 g, 50% yield); bp 54-56 °C/0.3 torr (lit.[33] 56 °C/0.3 torr).

To a solution of 3-(acetylthio)tetrahydropyran (**51**, 2.0 g, 0.013 mol) in ethanol (6.5 mL) was added potassium hydroxide in water (20%, 12.5 mL). After the reaction mixture was refluxed for 1 h, diethyl ether was added and the organic layer was separated. The water layer was neutralized with cold hydrochloric acid (10%), and then extracted three times with diethyl ether. The combined ether layers were washed several times with sodium bicarbonate solution, and then water. Fractional distillation gave 3-mercapto-tetrahydropyran (**52**, 1.0 g, 68% yield); bp 62-64 °C/20-25 torr (lit.[33] 65 °C/21 torr); ^{13}C NMR (CD_3Cl) δ 26.2, 34.3, 35.6, 67.6, 75.1.

To a solution of sodium (0.043 g, 0.0019 mol) in ethanol, 3-mercaptotetrahydro-pyran (0.22 g, 0.0019 mol) was added. After the reaction mixture was stirred at room temperature for 5 min, the solvent was removed completely under reduced pressure. Then hexamethylphosphoramide (HMPA, 2 mL), iodobenzene (0.38 g, 0.0019 mol) and Cu powder (0.6 g) was added. The resulting mixture was heated at 130 °C for 15 h. Water was added and the mixture was extracted three times with methylene chloride. After the combined organic layer was washed three times with saturated sodium chloride solution, the solvent was removed under reduced pressure, and further distillation gave 3-(phenylthio)tetrahydropyran (**53**, 0.290 g, 80% yield); bp 94-96 °C/0.5 torr (lit.[33] 98 °C/0.5 torr).

b) 3-(Phenylsulfonyl)tetrahydropyran (5)

3-(phenylthio)tetrahydropyran (**53**, 0.250 g, 0.0013 mmol) was refluxed with hydrogen peroxide (30%, 3 mL) in acetic acid (1.5 mL) for 20 min. Workup as usual and separation by thick layer chromatography using hexane/ether (4/1) as the developing solvent (developed four times) gave pure **5** as a colorless liquid (0.200 g, 76% yield); ^{1}H NMR ($CDCl_3$) δ 1.45 - 2.25 (m, 4H), 3.05-3.23 (m, 1H), 3.27 (t, J = 11.2 Hz, 1H), 3.47 (t, J = 11.2 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 4.07 (d, J = 11.2 Hz, 1H), 7.50 - 7.90 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.8, 24.6, 60.3, 66.0, 67.6, 128.7, 129.2, 133.9, 137.2. Calcd. exact mass for $C_{11}H_{15}O_3S$ (M+1): 227.0742. Found: 227.0737.

Preparation of *trans*-1-methoxy-2-(methylsulfonyl)cyclohexane (6a)[34]

Cyclohexene (10.27 g, 0.125 mol), N-bromosuccinimide (NBS, 22.25 g, 0.125 mol) and water (100 mL) were mixed and stirred vigorously at room temperature until the solid NBS disappeared. The organic layer was separated and the water layer was washed with ether. Distillation of the combined product gave *trans*-2-bromocyclohexanol (**54**) as a colorless liquid (18.0 g, 80% yield); bp 76-77 °C/ 6 torr (lit.[35] 73-75 °C/5 torr, and lit.[36] 86.6-88.4 °C/10 torr); ^{1}H NMR ($CDCl_3$) δ 1.1-2.4 (m, 8H), 2.85 (br s, 1H), 3.51 (m, 1H), 3.81 (ddd, J = 11.7 Hz, 9.3 Hz, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.8, 26.3, 33.4, 36.0, 61.3, 74.9.

To a solution of *trans*-2-bromocyclohexanol (**54**, 10.0 g, 0.056 mol) in dry methanol (30 mL), sodium thiomethoxide (4.3 g, 0.061 mol) in dry methanol (25 mL) was slowly added. The reaction mixture was stirred overnight at room temperature, quenched with water and extracted with methylene chloride. The extracts were combined

and dried over magnesium sulfate and concentrated to give *trans*-2-(methylthio)cyclohexanol as a colorless liquid (**55**, 6.7 g, 82% yield); bp 85 °C/4.5 torr (lit.[37] 97-98°C/11 torr); ^{1}H NMR ($CDCl_3$) δ 1.0-2.15 (m, 8H), 2.0 (s, 3H), 2.25 (m, 1H), 3.0 (s, 1H), 3.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.26, 24.30, 26.03, 31.30, 33.65, 52.94, 70.91.

To a solution of *trans*-2-(methylthio)-cyclohexanol (5.0 g, 0.034 mol) in methanol (250 mL), conc. sulfuric acid (10 mL) was added. The reaction mixture was refluxed for 24 h. Workup as usual gave *trans*-1-methoxy-2-(methylthio)cyclohexane (**56**, 3.42 g, 59% yield); bp 66 °C/3 torr (lit.[34] 88-90 °C/2 torr); ^{1}H NMR ($CDCl_3$) δ 1.5-2.2 (m, 8H), 2.14 (s, 3H), 2.54 (m, 1H), 3.03 (m, 1H), 3.38(s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.7, 23.6, 25.0, 30.2, 31.1, 49.9, 56.6, 83.0.

To a solution of *trans*-1-methoxy-2-(methylthio)cyclohexane (1.5 g, 9.26 mmol) in acetic acid (6 mL), hydrogen peroxide (30%, 15 mL) was added dropwise at room temperature. The mixture was heated on a steam bath for 20 min. Workup as usual gave *trans*-1-methoxy-2-(methylsulfonyl)cyclohexane (**6a**, 1.66 g, 92% yield); mp 46-47 °C (lit.[34] 46-47 °C); ^{1}H NMR ($CDCl_3$) δ 1.0-2.5 (m, 8H), 2.80 (ddd, J = 12.6 Hz, 10.0 Hz, 3.9 Hz, 1H), 3.00 (s, 3H), 3.36 (s, 3H), 3.43 (symmetric m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 23.7, 24.6, 30.0, 44.3, 56.0, 66.4, 78.9; Calcd. exact mass for $C_8H_{16}O_3S$: 192.0820. Found: 192.0820.

Preparation of 1-Methoxy-2-(phenylsulfonyl)bicyclo[2.2.2]octane (7)

a) 1-Methoxy-6-*endo*-(phenylsulfonyl)bicyclo[2.2.2]oct-2-ene (57)[38]

A mixture of phenyl vinyl sulfone (0.50 g, 0.003 mol), 1-methoxy-1,3-cyclohexadiene (0.66 g, 0.006 mol), benzene (1.4 mL) and hydroquinone (0.005 g) was heated

in an evacuated Carius tube at 135 °C for 18 hours. Workup as usual gave crude 1-methoxy-6-(phenylsulfonyl)bicyclo[2.2.2]-oct-2-ene (**57**, 0.65 g, 78% yield). Separation by thick layer chromatography using hexane : ethyl acetate (3/1) as the developing solvent and recrystallization gave pure 1-methoxy-6-*endo*-(phenylsulfonyl)-bicyclo[2.2.2]-oct-2-ene (**57**, 0.284 g, 34% yield) as a colorless, crystalline solid; mp 86-88 °C (lit.[38] 86-88.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.30-2.03 (m, 6H), 2.62 (symmetric m, 1H), 3.10 (s, 3H), 3.65 (dd, J = 9.2 Hz, 7.0 Hz, 1H), 6.10-6.25 (m, 2H), 7.4-8.0 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.3, 28.8, 29.3, 30.7, 50.3, 66.4, 78.2, 128.3, 129.1, 131.7, 132.0, 132.9, 141.1.

b) 1-Methoxy-2-(phenylsulfonyl)bicyclo[2.2.2]octane (7)

A mixture of 1-methoxy-6-*endo*-(phenylsulfonyl)bicyclo[2.2.2]oct-2-ene (**57**, 0.20 g, 0.72 mmol) and Pt/C (10%, 0.015 g) in chloroform (5 mL) was stirred at room temperature under 1 atm of H_2 for about 6 h and then workup as usual gave a quantitative yield of **7**; mp 91.5-94.0°C; ^{1}H NMR ($CDCl_3$) δ 1.30-2.50 (m, 11H), 2.63 (s, 3H), 3.47 (m, 1H), 7.3-8.0 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.0, 25.9, 26.2, 28.4, 30.0, 48.4, 63.6, 75.0, 128.4, 128.7, 132.8, 141.6; Calcd. exact mass for $C_{15}H_{20}O_3S$: 280.1133. Found: 280.1137. Its x-ray structure is shown in Figure 2.5.1.

Preparation of 2-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (8) and 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (12)

a) 2-*exo*-3-*endo*-Bis(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (58)[39]

Furan (1.2 g, 17.6 mmol) was added with stirring to a solution of (*E*)-1,2-bis-

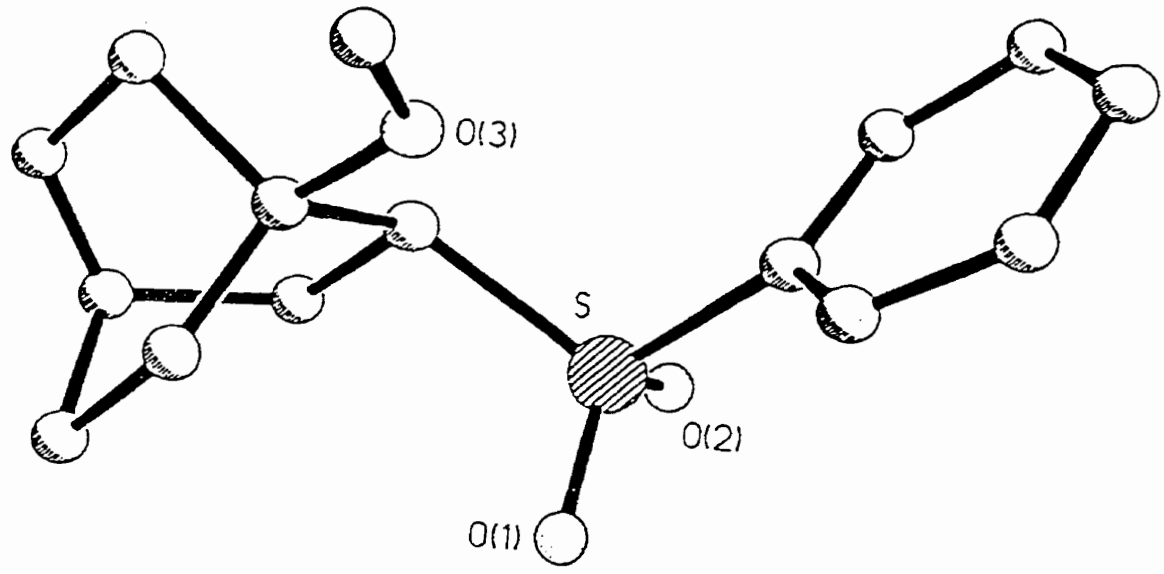


Figure 2.5.1 The x-ray crystal structure of 1-methoxy-2-(phenylsulfonyl)bicyclo[2.2.2]octane (7).

(phenylsulfonyl)ethylene (2.0 g, 6.5 mmol) partially dissolved in methylene chloride (30 mL). The mixture was stirred at room temperature for 6 h until all the white precipitate had dissolved and the reaction mixture was transparent and colorless. Stirring was discontinued and the solution was allowed to stand overnight. Diethyl ether was then added to complete the precipitation and the white solid was filtered, washed with ether and dried to give 2-*exo*-3-*endo*-bis(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**5**·**8**, 2.45 g, 100% yield); mp 231-233 °C (lit.[39] 216-226 °C, lit.[40] 229-230 °C); ^{1}H NMR ($CDCl_3$) δ 3.61 (d, J = 4.5 Hz, 1H), 4.20 (dd, apparent t, J = 4.5 Hz, 1H), 5.24 (dd, J = 4.5 Hz and 1.4 Hz, 1H), 5.40-5.43 (m, 1H), 6.56-6.60 (m, 2H), 7.4-8.0 (m, 10H); ^{13}C NMR

($CDCl_3$) δ 65.5, 67.6, 79.5, 81.9, 128.2, 128.7, 129.5, 134.3, 135.7, 136.6.

b) 2-*endo*-(Phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (59a) and 2-*exo*-(phenylsulfonyl) 7-oxabicyclo[2.2.1]hept-5-ene (59b)[40]

A stirred, ice-bath cooled solution of 2-*exo*-3-*endo*-bis(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**58**, 0.250 g, 0.66 mmol) and $NaBH_4$ (0.166 g, 4.39 mmol) in acetonitrile (16 mL) was treated with potassium *tert*-butoxide (0.074 g, 0.66 mmol). After 4 h, water was added, and most of the solvent removed by rotary evaporation. The residue was taken up in methylene chloride, washed with water three times, and the organic layer dried over magnesium sulfate. The solvent was removed to give an oily liquid (0.220 g). Thick layer chromatography showed at least seven bands using diethyl ether as the developing solvent. One of the seven bands yielded crystalline 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**59b**, ~ 150 mg) from diethyl ether : petroleum ether; mp 63.5-65 °C (reported[40] to be a colorless oil); ^{1}H NMR ($CDCl_3$) δ 1.5-2.4 (m, 2H), 3.10 (dd, J = 8.3 Hz, 4.3 Hz, 1H), 5.06 (m, 1H), 5.32 (m, 1H), 6.37 (m, 2H), 7.4-8.1 (m, 5H). The ^{1}H NMR spectrum is consistent with literature[40] except that the peak for the *endo* methine hydrogen was reported as 3.10 (dd, J = 5, 4 Hz, *endo* methine).

^{1}H NMR showed another band to be a mixture containing the *endo* epimer. It was reapplied to thick layer chromatography using methylene chloride as the developing solvent and developed twice. After recrystallization, the *endo* epimer, was finally obtained as white crystals (**59a**, ~ 20 mg); mp 52-53 °C; ^{1}H NMR ($CDCl_3$) δ 1.6-2.3 (m, 2H), 3.70 (m, 1H), 5.05 (m, 2H), 6.50 (m, 2H), 7.4-8.1 (m, 5H); ^{13}C NMR ($CDCl_3$) δ

28.7, 62.6, 78.2, 79.6, 127.6, 129.4, 131.5, 133.7, 137.2, 140.3. Calcd. exact mass for $C_{12}H_{13}O_3S$ (M+1): 237.0585. Found: 237.0588.

c) 2-*endo*-(Phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (8) and 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (12)

2-*endo*-(Phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**59a**, 40 mg, 0.17 mmol) was dissolved in chloroform, and Pt/C (10%, 15 mg) was added. The mixture was stirred under H_2 (1 atm) for 6 h. The solid was then filtered out and washed with chloroform. The filtrate was dried to give a quantitative yield of 2-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (**8**); mp 75.5-77 °C; ^{1}H NMR ($CDCl_3$) δ 1.6-2.7 (m, 6H), 3.50-3.63 (m, 1H), 4.60-4.70 (m, 2H), 7.50-7.90 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.0, 29.9, 32.9, 65.8, 77.2, 78.3, 127.6, 129.4, 133.7, 140.5; Calcd. exact mass for $C_{12}H_{14}O_3S$: 238.0666. Found 238.0668.

Similar treatment of 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (**59b**, 40 mg, 0.17 mmol) gave a quantitative yield of 2-*exo*-(phenylsulfonyl)-7-oxabicyclo-[2.2.1]heptane (**12**); mp 100-101.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.30-2.25 (m, 6H), 3.29 (dd, J = 8.8 Hz, 5.0 Hz, 1H), 4.63 (t, J = 5.0 Hz, 1H), 4.94 (d, J = 5.0 Hz, 1H), 7.45-8.00 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.9, 33.7, 67.8, 76.4, 76.6, 128.8, 129.2, 133.7, 138.0. Calcd. exact mass for $C_{12}H_{14}O_3S$: 238.0666. Found: 238.0664.

Preparation of *cis*-1-methoxy-2-(methylsulfonyl)cyclohexane (17a)

a) *trans*-1-Bromo-2-methoxy-cyclohexane (60) [41]

Into a 100 mL round-bottomed flask equipped with magnetic stirrer, reflux

condenser and a drying tube was placed anhydrous methanol (30 mL) and N-bromosuccinimide (NBS, 13 g, 0.073 mol). To this mixture was added cyclohexene (6.0 g, 0.073 mol). The resulting mixture was stirred at 0°C for 1 h and then at room temperature for 3 h. The mixture was then poured into ice water, rapidly filtered through a Buchner funnel and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. The ether was removed and the product distilled at reduced pressure to give *trans*-1-bromo-2-methoxycyclohexane (**60**, 60% yield); bp 45-47 °C/3 torr (lit.[41] 45-47 °C/3 torr).

b) *cis*-1-Methoxy-2-(methylthio)cyclohexane (61)

trans-1-Bromo-2-methoxy-cyclohexane (**60**, 10 g, 0.0518 mol) and sodium thiomethoxide (4.0 g, 0.0571 mol) were dissolved in 2-butanol and refluxed for 24 h. Workup as usual gave *cis*-1-methoxy-2-(methylthio)cyclohexane as a colorless liquid (**61**, 4.6 g, 55% yield); ^{1}H NMR ($CDCl_3$) δ 1.0-2.4 (m, 8H), 2.06 (s, 3H), 2.75-2.90 (m, 1H), 3.31 (s, 3H), 3.35-3.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 14.7, 21.4, 23.7, 27.9, 28.5, 49.4, 79.5.

c) *cis*-1-Methoxy-2-(methylsulfonyl)cyclohexane (17a)

The sulfide (**61**) was oxidized by H_2O_2 (30%) in acetic acid to give **17a** (80% yield). White crystals were obtained by recrystallization from ethyl acetate : hexane; mp 44-47 °C; ^{1}H NMR ($CDCl_3$) δ 1.1-2.2 (m, 8H), 2.73 (dt, J = 12.7 Hz and 2.9 Hz, 1H), 2.82 (s, 3H), 3.30 (s, 3H), 4.0 (m, $w_{1/2}$ = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 22.0, 25.1, 27.1, 39.4, 55.9, 67.1, 73.4. Calcd. exact mass for $C_8H_{16}O_3S$: 192.0820. Found: 192.0823

Preparation of cyclohexyl methyl sulfone (23a) [41]

Cyclohexene (2.56 g, 31 mmol) was mixed with methanethiol (1.50 g, 31 mmol) and AIBN (~ 50 mg, 0.3 mmol) at 0 °C to 5 °C. After the resulting mixture was stirred overnight at 0 °C to 5 °C, the solvent was removed carefully. Without further purification, the remaining sulfide was then oxidized by hydrogen peroxide (30%) in acetic acid to give **23a** as a colorless liquid (2.5 g, 50% yield); ^{1}H NMR ($CDCl_3$) δ 1.0-2.5 (m, 10H), 2.78 (s, 3H), 2.72-2.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9 (three carbons), 25.3 (two carbons), 37.1, 62.3.

Preparation of *trans*-2-methyl-1-(methylsulfonyl)cyclohexane (24a) and *cis*-2-methyl-1-(methylsulfonyl)cyclohexane (25a)

a) 2-Methylcyclohexanethiol (63) [42]

Thiolacetic acid (0.75 g, 9.9 mmol) was added slowly to 1-methylcyclohexene (1.15 g, 12 mmol) while irradiating with a 100 watt bulb (tungsten bulb placed about 10 cm from the flask), and the resulting solution was stirred for additional 20 min under the irradiation. Distillation gave 2-methylcyclohexyl thiolacetate (**62**) as a colorless liquid consisting of a mixture of *cis* and *trans* epimers (1.49 g, 97% yield); bp 91-92 °C/8 torr (lit.[42] 110 °C/14 torr). This liquid was used directly for the next step without further purification.

2-Methylcyclohexyl thiolacetate (**62**, 1.2 g, 0.007 mol) was dissolved in a mixture of ethanol (18 mL) and aqueous potassium hydroxide solution (10%, 18 mL). The reaction mixture was refluxed for 1 h, and then neutralized with glacial acetic acid. The

solution was extracted with pentane three times and the pentane layer was dried with sodium sulfate. Careful distillation of the pentane solution gave 2-methylcyclohexane-thiol as a *cis/trans* mixture (**63**, 0.472 g, 52% yield); bp 71-72 °C/23 torr (lit.[42] 71-72 °C /23 torr). No further purification was performed.

b) *cis*-2-Methyl-1-(methylsulfonyl)cyclohexane (25a)

Methyl iodide (1.1 g, 0.0070 mol) was added to a solution of 2-methylcyclohexyl mercaptan (**63**, 0.30 g, 0.0023 mol) and sodium hydroxide (0.0090 g, 0.00023 mol) in aqueous ethanol (1:1, 2 mL). After the resulting mixture was stirred for 30 min, it was poured into water and the sulfide obtained by extraction with petroleum ether. The crude sulfide (**64**) was not purified before it was oxidized by 30% of H_2O_2 in acetic acid to give *cis*-2-methyl-1-(methylsulfonyl)cyclohexane (0.41 g, yield 95% from **63**) as a *cis/trans* mixture. Recrystallization from methanol gave pure *cis* epimer (**25a**, 0.21 g); mp 86-88 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3H), 1.2 - 2.0 (m, 8H), 2.57 (symmetric m, 1H), 2.81 (3H, s), 2.96 (dt, J = 11.9 Hz, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 20.8, 25.5, 27.8, 33.3, 39.4, 65.5; Calcd. exact mass for $C_8H_{17}O_2S$ (M+1): 177.0949. Found: 177.0943.

c) *trans*-2-Methyl-1-(methylsulfonyl)cyclohexane (24a)

cis-2-Methyl-1-(methylsulfonyl)cyclohexane (**25a**, 100 mg) in methanol containing sodium methoxide (5%) was refluxed for 3 days. Workup as usual gave a 3:1 mixture of **24a** and **25a** as a semi solid (100 mg); attempts at separation of the *trans/cis* mixture were not successful, and this mixture was used as such to obtain the rate constant

for **24a**; ^{13}C NMR for **24a** ($CDCl_3$) δ 21.1, 25.0, 25.1, 27.1, 32.8, 35.4, 39.1, 68.7. Calcd. exact mass for $C_8H_{17}O_2S$ (M+1) (the mixture): 177.0949. Found: 177.0946.

Preparation of *trans*-2-methyl-1-(phenylsulfonyl)cyclohexane (24b) and *cis*-2-methyl-1-(phenylsulfonyl)cyclohexane (25b)

a) *cis*-2-Methyl-1-(phenylsulfonyl)cyclohexane (25b)[42]

To a solution of 1-methylcyclohexene (10.0 g, 0.104 mol) and thiophenol (11.9 g, 0.109 mol) in benzene (20 mL) at 0 °C, AIBN (0.87 g, 0.005 mol) was added slowly and the reaction mixture was stirred overnight at less than 5 °C. Workup as usual and then distillation gave 2-methylcyclohexyl phenyl sulfide as a colorless liquid (7.0 g, 32% yield). It was not purified further but was used directly in the next reaction; bp 116-119 °C/~0.9 torr).

2-Methylcyclohexyl phenyl sulfide (5.8 g, 0.028 mol) was refluxed with hydrogen peroxide (30%, 80 mL) in acetic acid (40 mL) for 20 min. Workup as usual gave a *cis/trans* mixture of 2-methyl-1-(phenylsulfonyl)cyclohexane (5.1 g, 76% yield). Recrystalization from hexane : ethyl acetate three times gave pure *cis*-2-methyl-1-(phenylsulfonyl)cyclohexane crystals (**25b**, 2.9 g); mp 73-74 °C (lit.[42] 74-74.5 °C); ^1H NMR ($CDCl_3$) δ 1.00-2.00 (m, 8H), 1.20 (d, J = 7.1 Hz, 3H), 2.45 (symmetric m, 1H), 2.99 (dt, J = 12 Hz, 3.8 Hz, 1H), 7.48-7.93 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 20.2, 25.5, 27.7, 33.4, 66.3, 128.4, 129.0, 133.3, 138.8.

b) *trans*-2-Methyl-1-(phenylsulfonyl)cyclohexane (24b)

cis-2-Methyl-1-(phenylsulfonyl)cyclohexane (**25b**, 1.0 g) was dissolved in

dioxane (20 mL) and sodium hydroxide solution (1 M, 20 mL) was added. The resulting solution was refluxed for five days. Workup as usual gave a *cis/trans* mixture of 2-methyl-1-(phenylsulfonyl)cyclohexane. Recrystallization a number of times using different solvents still gave a mixture of about 4:1 *trans/cis* epimers. Thin layer chromatography using different solvents did not effect separation; mp of the mixture 86-87 °C. The mixture was used directly in the determination of the H-D exchange rate. ^{1}H NMR ($CDCl_3$) for the *trans* epimer (**24b**) δ 0.80-2.20 (m, 9H), 1.22 (d, J = 7.1 Hz, 3H), 2.71 (ddd, J = 11.3 Hz, 9.5 Hz, 3.4 Hz, 1H), 7.45-7.95 (m, 5H); ^{13}C NMR ($CDCl_3$) for the *trans* epimer (**24b**) δ 21.4, 24.8, 25.0, 27.4, 32.3, 35.4, 69.1; the ^{13}C NMR signals for the carbons of benzene ring for the *trans* epimer (**24b**) are not clear because they overlap with the signals of the *cis* epimer (**25b**); Calcd. exact mass for $C_{13}H_{19}O_2S$ (M+1) (the mixture): 239.1106. Found: 239.1100.

Preparation of *trans*-4-*tert*-butylcyclohexyl phenyl sulfone (26) and *cis*-4-*tert*-butylcyclohexyl phenyl sulfone (27)

a) *trans*-4-*tert*-Butylcyclohexyl Tosylate (65a)

Commercially available 4-*tert*-butylcyclohexanol (*cis* and *trans* mixture, 5.0 g, 0.032 mol) dissolved in dry pyridine (20 mL) was added to *p*-toluenesulfonyl chloride (10.0 g, 0.052 mol) in pyridine (20 mL) at 0 °C. The solution was stirred overnight at room temperature, poured into ice-cold 10% hydrochloric acid and extracted with ether three times. The combined ether extract was washed with dilute hydrochloric acid, water, aqueous sodium bicarbonate and again with water, dried over sodium sulfate and then concentrated to give a quantitative yield of 4-*tert*-butylcyclohexyl tosylate as a *cis/trans*

mixture. The crude product was recrystallized from ether : hexane two times to give the pure *trans* epimer as white crystals (**65a**, 6.5 g, 65% yield); mp 89-90 °C (lit.[43] 89-90 °C, lit. [44] 89.4-90 °C); ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 9H), 0.80-2.10 (m, 9H), 2.42 (s, 3H), 4.32 (tt, J = 11.3 Hz, 4.6 Hz, 1H), 7.25-7.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.5, 27.4, 32.1, 32.8, 46.5, 82.6, 127.4, 127.5, 129.7, 134.7.

b) *cis*-4-*tert*-Butylcyclohexyl phenyl sulfone (27)

A solution of NaSPh prepared by addition of thiophenol (2.45 g, 0.022 mol) to a solution of sodium (0.47 g, 0.0204 mol) in ethanol (87%, 36 mL) was added to a solution of *trans*-4-*tert*-butylcyclohexyl tosylate (**65a**, 6.0 g, 0.0193 mol) in 150 mL of the same solvent and allowed to stand for 30 da. Workup as usual gave *cis*-4-*tert*-butylcyclohexyl phenyl sulfide (**66**, 4.1 g, 86% yield). Without further purification, the sulfide was oxidized by 30% hydrogen peroxide in acetic acid. After recrystallization from ethanol : water several times, pure *cis*-4-*tert*-butyl-cyclohexyl phenyl sulfone (**27**, about 1.76 g) was obtained as white crystals; mp 114.5-116 °C (lit.[43] 115-116 °C); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 9H), 0.9-2.5 (m, 9H), 3.1 (m, $w_{1/2}$ = 8.4 Hz, 1H), 7.4-8.0 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.0, 25.0, 27.4, 32.5, 47.0, 58.8, 128.4, 129.0, 133.3, 138.8.

c) *trans*-4-*tert*-Butylcyclohexyl phenyl sulfone (26)

cis-4-*tert*-Butylcyclohexyl phenyl sulfone (**27**, 0.45 g, 1.6 mmol) was boiled for 4 da with ethanolic sodium ethoxide (10%, 30 mL). The solution was poured into water and extracted with ethyl ether which, after drying over sodium sulfate and concentration, left a residue. Separation by thick layer chromatography (developing solvent: ether) gave

the desired *trans*-4-*tert*-butylcyclohexyl phenyl sulfone (**26**, 0.30 g, 67% yield); mp 89-91 °C (lit.[43] 90-91 °C); ^{1}H NMR ($CDCl_3$) δ 0.76 (s, 9H), 0.80-2.22 (m, 9H), 2.82 (tt, J = 12.4 Hz, 3.5 Hz, 1H), 7.45-7.90 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9, 27.3, 32.5, 46.8, 63.4, 128.9 (four carbons), 133.4, 137.0.

Preparation of *cis*-3-methoxy-1-(phenylsulfonyl)cyclohexane (28) and *trans*-3-methoxy-1-(phenylsulfonyl)cyclohexane (29)

a) 3-(Phenylthio)cyclohexanone(67)[45]

Triethylamine (0.3 mL) was added to a solution of 2-cyclohexenone (5.0 g, 0.052 mol) and thiophenol (5.8 g, 0.053 mol) in chloroform (10 mL) at 0 °C. The cooling bath was removed, and the solution was stirred at room temperature for 2 h. Then, it was diluted with ether, and washed twice with saturated sodium chloride solution. After the ether layer was dried over sodium sulfate, the solvent was removed to give 3-(phenylthio)cyclohexanone (**67**, 10.2 g, 95% yield); bp 151-154 °C/0.4 torr (lit.[46] 152-154 °C/0.4 torr); ^{1}H NMR ($CDCl_3$) δ 1.8-3.0 (m, 8H), 3.45-3.80 (m, 1H), 7.3-7.8 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.9, 31.1, 40.8, 46.0, 47.7, 127.7, 129.0, 133.0, 133.1, 208.5.

b) 3-(Phenylthio)cyclohexanol (68)[47]

Sodium borohydride (4.88 g, 0.0129 mol) was added to a solution of 3-(phenylthio)cyclohexanone (**67**, 6.9 g, 0.0334 mol) in methanol (200 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, then hydrolyzed by addition of water, acidified with 10% sulfuric acid, and extracted with ether three times. The combined ether layers were washed with sodium bicarbonate solution and then water. After the solution was dried

over sodium sulfate, the solvent was removed to give 3-(phenylthio)cyclohexanol (**68**, 6.0 g, 86% yield). It was found from its NMR spectrum using literature information[47] to be a mixture of *cis* and *trans* epimers with the *cis* epimer as the major product. No separation was performed before it was used in the next step.

c) 1-Methoxyl-3-(phenylthio)cyclohexane (69)

3-(Phenylthio)cyclohexanol (**68**, 4.84 g, 0.0232 mol) in DMSO (10 mL) was added to potassium hydroxide (5.20 g, 0.093 mol) in DMSO (40 mL) at room temperature and the resulting mixture was stirred for 2 min. Methyl iodide (13.2 g, 0.093 mol) was added and the reaction mixture was stirred 30 min. Water and methylene chloride were then added. The two layers were separated and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed to give 1-methoxyl-3-(phenylthio)-cyclohexane (**69**, 4.8 g, 93% yield). No further separation was performed on **68**.

***d)* *cis*-1-Methoxy-3-(phenylsulfonyl)cyclohexane (28) and *trans*-1-methoxy-3-(phenylsulfonyl)cyclohexane (29)**

Hydrogen peroxide (30%, 25 mL) was added dropwise to 3-methoxy-1-(phenylsulfonyl)cyclohexane (**69**, 2.0 g, 9 mmol) in acetic acid (6 mL) at room temperature. The mixture was refluxed for 20 min, and then water and methylene chloride were added and the two layers were separated. The organic layer was washed with sodium bicarbonate solution and water, and dried over sodium sulfate. The solvent was removed to give 1-methoxy-3-(phenylsulfonyl)cyclohexane as a mixture of *cis* and

trans epimers (2.235 g, 97% yield). It was separated by thick layer chromatography using ether : hexane (3/2) as the developing solvent to give pure *cis*-1-methoxy-3-(phenylsulfonyl)cyclohexane (**28**, ~ 1.3 g, ~ 57% yield) and *trans*-1-methoxy-3-(phenylsulfonyl)-cyclohexane (**29**, ~ 0.17 g, ~ 7.4% yield) separately.

For the *cis* epimer (**28**): mp 95.5-97.5°C; ^{1}H NMR ($CDCl_3$) δ 1.0-2.5 (m, 8H), 2.90 (tt, J = 12.4 Hz, 3.3 Hz, 1H), 3.07 (tt, J = 11.0 Hz, 4.1 Hz, 1H), 3.30 (s, 3H), 7.5-7.9 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.6, 25.1, 31.0 (double intensity), 56.0, 62.0, 78.0, 129.1 (double intensity), 133.7,136.8; Calcd. exact mass for $C_{13}H_{19}O_3S$ (M+1): 255.1055. Found: 255.1056.

For the *trans* epimer (**29**): mp 63.5-64.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.0-2.4 (m, 8H), 3.17 (s, 3H), 3.22 (tt, J = 12.2 Hz and 3.5 Hz, 1H), 3.58 (m, $w_{1/2}$ = 11 Hz, 1H), 7.40-8.0 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.8, 24.8, 28.1, 28.4, 55.7, 58.4, 73.8, 128.8, 128.9, 133.5, 137.2; Calcd. exact mass for $C_{13}H_{19}O_3S$ (M+1): 255.1055. Found: 255.1053.

Preparation of 2-methoxyethyl phenyl sulfone (30b)

A solution of thiophenol (11 g, 0.10 mol), sodium hydroxide (4.0 g, 0.10 mol) and 2-chloroethyl methyl ether (9.5 g, 0.10 mol) in ethanol was refluxed overnight and then workup as usual gave 2-methoxyethyl phenyl sulfide as a yellowish liquid (15 g, 89%). ^{1}H NMR δ 3.10 (t, J = 6.8 Hz, 2H), 3.34 (s, 3H), 3.56 (t, J = 6.8 Hz, 2H), 7.1-7.5 (m, 5H); ^{13}C NMR δ 33.0, 58.6, 70.9, 126.0, 128.8, 129.2, 135.8.

2-Methoxyethyl phenyl sulfide (6 g, 0.036 mol) was oxidized by refluxing with hydrogen peroxide (30%, 50 mL) in acetic acid (20 mL) for 20 min to give, after workup, 2-methoxyethyl phenyl sulfone (**30b**) as a colorless liquid (6.7 g, 97% yield); ^{1}H NMR

($CDCl_3$) δ 3.16 (s, 3H), 3.33 (t, J = 6.2 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 7.4-8.0 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.7, 58.3, 65.3, 127.6, 128.8, 133.5, 139.3.

Preparation of 3-methoxypropyl phenyl sulfone (30c)

Sodium hydroxide (4.25 g, 0.106 mol) was dissolved in water (40 mL), and added to the solution of thiophenol (11.7 g, 0.106 mol) in ethanol (40 mL). Then, 3-chloro-propanol (10 g, 0.106 mol) was added. The resulting solution was stirred for 30 min at room temperature and then refluxed for 10 min. Workup as usual gave 3-hydroxypropyl phenyl sulfide as a colorless liquid (13.5 g, 76% yield).

3-Hydroxypropyl phenyl sulfide (5.0 g, 0.030 mmol) was added to KOH (6.7 g, 0.12 mol) in DMSO (50 mL) and stirred for 2 min at room temperature. Methyl iodide (16.7 g, 0.12 mol) was then added and the resulting solution was stirred for 15 min. Workup as usual gave 3-methoxypropyl phenyl sulfide as a colorless liquid (5.3 g, 98%); ^{13}C NMR ($CDCl_3$) δ 29.5, 30.5, 58.8, 71.1, 126.0, 129.0, 129.2, 136.7.

3-Methoxypropyl phenyl sulfide (1.0 g, 5.5 mmol) was refluxed with hydrogen peroxide (30%, 10 mL) in acetic acid (4 mL) for 20 min. Workup as usual gave 3-methoxypropyl phenyl sulfone (**30c**, 1.06 g, 91% yield) as a colorless oil; ^1H NMR ($CDCl_3$) δ 1.70-2.00 (m, 2H), 3.05-3.15 (m, 2H), 3.16 (s, 3H), 3.32 (t, J = 6.0 Hz, 2H), 7.30-8.00 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.9, 53.2, 58.3, 69.8, 127.7, 129.1, 133.5, 138.9; Calcd. exact mass for $C_{10}H_{15}O_3S$ (M+1): 215.0742. Found: 215.0748.

Preparation of phenyl 4-methoxybutyl sulfone (30d) [48]

a) 4-Chlorobutyl acetate [48]

Refluxing of tetrahydrofuran (3.25 g, 45 mmol) with acetyl chloride (2.5 g, 32 mmol) and zinc chloride (10 mg, 0.07 mmol) for 45 min and then distillation gave 4-chlorobutyl acetate as a yellowish liquid (4.9 g, 72% yield); bp 78-80 °C/10 torr (lit.[48] 92-93 °C/22 torr and lit.[49] 59-60 °C/1.8 torr); ^{1}H NMR ($CDCl_3$) δ 1.6-1.9 (m, 4H), 1.98 (s, 3H), 3.50 (t, J = 6.3 Hz, 2H), 4.02 (t, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 25.9, 29.0, 44.3, 63.4, 170.8.

b) Phenyl 4-methoxybutyl sulfone (30d)

4-Chlorobutyl acetate (1.5 g, 10 mmol) was added to a solution of sodium hydroxide (0.44 g, 11 mmol) and thiophenol (1.2 g, 11 mmol) in water (40 mL). After the resulting mixture was stirred at room temperature for 30 min, sodium hydroxide solution (10%, 100 mL) was added and the solution was refluxed for another 1 h. Workup as usual and distillation gave 4-phenylthiobutanol as a yellowish liquid (1.57 g, 98% yield); bp 148-150 °C / 0.6 torr.

4-Phenylthiobutanol (0.5 g, 0.0027 mmol) was added to KOH (0.67 g, 0.012 mol) in DMSO (5 mL) and stirred for 2 min at room temperature. Methyl iodide (1.7 g, 0.012 mol) was then added and the resulting solution was stirred for 15 min. Workup as usual and distillation gave 4-methoxybutyl phenyl sulfide as a colorless liquid (4.8 g, 89% yield); bp 104-106 °C / 0.6 torr.

The solution of 4-methoxybutyl phenyl sulfide (3.0 g, 0.0153 mol) and hydrogen peroxide (30%, 30 mL) in acetic acid (12 mL) was refluxed for 20 min. Workup as usual gave 4-methoxybutyl phenyl sulfone as a colorless oil (**30d**, 3.4 g, 97% yield); ^{1}H NMR ($CDCl_3$) δ 1.50-1.85 (m, 4H), 3.05-3.15 (m, 2H), 3.23 (s, 3H), 3.30 (t, J = 6.0 Hz, 2H),

7.45-7.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9, 28.1, 56.0, 58.5, 71.7, 128.0, 129.2, 133.6, 139.0; Calcd. exact mass for $C_{11}H_{17}O_3S$ (M+1): 229.0899. Found: 229.0898.

Preparation of phenyl 5-methoxypentyl sulfone (30e)

a) 5-Chloropentyl acetate [50]

Tetrahydropyran (5.0 g, 58 mmol) was mixed with acetyl chloride (4.2 g, 54 mmol) and zinc chloride (0.4 g, 6 mmol) and the resulting mixture was heated in a 100 °C bath for about 45 min. Distillation gave 5-chloropentyl acetate as a colorless liquid (7.5 g, 85% yield); bp 104-106 °C/18-19 torr.

b) 5-Methoxypentyl sulfone (30e)

5-Chloropentyl acetate (2.1 g, 0.013 mol) was mixed with thiophenol (1.5 g, 0.014 mol), and then sodium hydroxide (0.54 g, 0.014 mol) in water (5.5 mL) was added. The reaction mixture was stirred at room temperature for 30 min. More sodium hydroxide solution (10%, 15 mL) was added, and the resulting solution was refluxed for another 70 min. Workup as usual gave 5-hydroxypentyl phenyl sulfide as a colorless oil which became a half solid after 2 da (2.2 g, 86% yield); ^{13}C NMR ($CDCl_3$) δ 24.9, 28.9, 32.2, 33.5, 62.7, 125.7, 128.8, 128.9, 136.7.

Potassium hydroxide powder (2.0 g, 35.6 mmol) was dissolved in dimethyl sulfoxide (DMSO, 15 mL). To this solution, 5-hydroxypentyl phenyl sulfide (1.5 g, 7.6 mmol) in DMSO (5 mL) was added and the resulting solution was stirred for about 2 to 3 min. Methyl iodide (5.1 g, 35.6 mmol) was added and stirring was continued for 15 min. Workup as usual gave 5-methoxypentyl phenyl sulfide as a colorless liquid (1.4 g, 87.5% yield); It was then oxidized by refluxing with hydrogen peroxide (30%, 20 mL) in acetic

acid (10 mL) for 25 min to give 5-methoxypentyl sulfone (**30e**) as a colorless oil (1.4 g, 86% yield): ^{1}H NMR ($CDCl_3$) δ 1.30-1.75 (m, 6H), 2.98-3.10 (m, 2H), 3.24 (s, 3H), 3.28 (t, J = 6.0 Hz, 2H), 7.45-7.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.9, 28.9, 56.1, 58.5, 72.0, 127.9, 129.2, 133.6, 139.0. Calcd. exact mass for $C_{12}H_{19}O_3S$ (M+1): 243.1055. Found: 243.1056.

Preparation of alkyl phenyl sulfones (31a, 31b, 31c, 31d, 31e)

Ethyl phenyl sulfone (**31a**) was prepared from the oxidation of ethyl phenyl sulfide (obtained from Alderich Chemical Company) by hydrogen peroxide (30%) in acetic acid. ^{1}H NMR as reported[51] and ^{13}C NMR as reported.[52]

All the other alkyl phenyl sulfones were obtained by refluxing of sodium benzenesulfinate with the corresponding alkyl bromide. An example is as follows: benzenesulfinic acid (5 g, 30.5 mmol) and propyl bromide (7.5 g, 61 mmol) was dissolved in ethanol and then refluxed for about 6 h. Workup as usual gave phenyl propyl sulfone (**31b**) as a colorless liquid (4.5 g, 80% yield).

Phenyl propyl sulfone (**31b**).[53] ^{13}C NMR ($CDCl_3$) δ 12.9, 16.5, 57.9, 128.0, 129.2, 133.6, 139.1; ^{1}H NMR as reported.[54]

Phenyl butyl sulfone (**31c**).[53] ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 6.0 Hz, 3H), 1.1-1.9 (m, 4H), 3.0 (t, J = 6.0 Hz, 2H), 7.3-7.9 (m, 5H). The ^{1}H NMR spectrum is consistent with literature.[55]

Phenyl pentyl sulfone (**32d**).[54] ^{13}C NMR ($CDCl_3$) δ 13.6, 22.0, 22.2, 30.3, 56.2, 127.9, 129.2, 133.5, 139.1; ^{1}H NMR as reported.[56]

Phenyl hexyl sulfone (**32e**).[57] ^{13}C NMR ($CDCl_3$) δ 13.6, 22.2, 22.5, 27.9, 31.1,

56.3, 128.0, 129.2, 133.5, 139.1; ^{1}H NMR as reported.[54]

Preparation of 4-(phenylsulfonyl)tetrahydropyran (32)

a) Tetrahydro-4*H*-pyran-4-yl tosylate (70)

Commercial available tetrahydro-4*H*-pyran-4-ol (2.5 g, 0.024 mol) dissolved in dry pyridine (16 mL) was added to *p*-toluenesulfonyl chloride (7.7 g, 0.040 mol) in pyridine (16 mL) at 0 °C. The solution was stirred overnight at room temperature, poured into ice-cold 10% hydrochloric acid and extracted with ether three times. The ether extracts were combined and washed with dilute hydrochloric acid, water, and saturated sodium bicarbonate solution. The solvent was removed and then the residue was recrystallized from ether : hexane to give tetrahydro-4*H*-pyran-4-yl tosylate as white crystals (**70**, 5.45 g, 87% yield); mp 56-57 °C; ^{1}H NMR ($CDCl_3$) δ 1.60-1.90 (m, 4H), 3.41 (s, 3H), 3.43 (m, 2H), 3.83 (m, 2H), 4.65 (m, 1H), 7.20-7.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 32.4, 64.7, 77.3, 127.5, 129.8, 134.3, 144.7; exact mass for $C_{12}H_{17}O_4S$ (M+1): found 257.0846, calculated 257.0848.

b) 4-(Phenylsulfonyl)tetrahydropyran (32)

A solution of sodium hydroxide (0.40 g, 0.010 mol) and thiophenol (1.23 g, 0.011 mol) in ethanol (90%, 50 mL) was mixed with tetrahydro-4*H*-pyran-4-yl tosylate (**70**, 2.50 g, 0.0098 mol). The resulting solution was stirred at room temperature for 20 da. Then water was added and the mixture was extracted with methylene chloride three times. The combined organic layer was washed with 5% sodium hydroxide, saturated sodium chloride solution, and dried over magnesium sulfate. Removal of solvent and

distillation of the product gave 4-(phenylthio)tetrahydro-4*H*-pyran as a colorless oil (**71**, 1.45 g, 77% yield).

To a solution of 4-(phenylsulfonyl)-tetrahydropyran (**71**, 1.0 g, 5 mmol) in acetic acid (3 mL), hydrogen peroxide (30%, 8.5 mL) was added. The solution was refluxed for 20 min. Workup as usual and separation by thick layer chromatography (solvent: ether) gave **32** as white crystals (0.89 g, 71% yield); mp 87-89 °C; ^{1}H NMR ($CDCl_3$) δ 1.60-2.00 (m, 4H), 3.11 (tt, J = 11.8 Hz, 4.1 Hz, 1H), 3.30 (td, J = 11.8 Hz, 2.6 Hz, 2H), 4.02 (ddd, J = 11.8 Hz , 4.8 Hz, 1.2 Hz, 2H), 7.5-7.9 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.6, 60.6, 66.5, 129.1, 129.2, 133.9; Calcd. exact mass for $C_{11}H_{14}O_3S$: 226.0664. Found: 226.0666.

2.5.2 KINETIC AND THERMODYNAMIC MEASUREMENTS OF H-D EXCHANGE

2.5.2.1. General procedure

All kinetic measurements were carried out by ^{1}H NMR spectrometry using the Gemini 300 NMR spectrometer. The concentration of unreacted α-hydrogen of the starting material, as determined from its integral relative to that of an inert peak (e.g. the peak of the benzene ring), was monitored with respect to time.

The solutions of sodium deuteroxide (0.05 M to 0.50 M) in deuterium oxide were prepared by dissolving sodium metal in deuterium oxide under nitrogen. These solutions were titrated using 0.01 M hydrochloric acid.

The buffer solutions of sodium carbonate (pH-meter reading from 9 to 11) in deuterium oxide were prepared by dissolving deuterium chloride (37 wt. % in D_2O) and solid sodium carbonate in deuterium oxide.

Sodium phosphate dodecahydrate was dehydrated in a 200 °C oven overnight and cooled down in a desiccator, it was then dissolved in deuterium oxide. Addition of deuterium chloride (37 wt. % in D_2O) gave the sodium phosphate buffer solution (pH-meter readings from 7.0 to 9.0).

A typical kinetic measurement was carried out as follows: A sample (3 mg) was dissolved in dioxane-d_8 (or some other deuterated organic solvents, 0.28 mL) in a NMR tube. Sodium deuteroxide solution or buffer solution (0.28 ml) was added into the NMR tube by a 0.5 mL syringe and the NMR tube was sealed right away and was shaken vigorously. When no organic solvent was used the total volume of the solvent (D_2O) was 0.56 mL. The NMR tube was kept in the NMR instrument at a preset temperature (± 0.2 °C, without calibration), or in a water bath (± 0.2 °C), or in an oil bath (temperature maintained by refluxing a suitable solvent, methanol for 64 °C ± 0.5 °C, methylene chloride for 40 °C ± 0.5 °C, or ethanol for 77 °C ± 0.5 °C). The rate of H-D exchange was then followed by ^{1}H NMR (or by ^{13}C NMR in case of **30c** and **31c**). The amount of unexchanged α-hydrogen (C_t) was obtained from its integral relative to that of an inert peak or set of peaks such as those of the aromatic hydrogens for phenyl sulfones. The slope of ln C_t versus time (t) gave the pseudo-first-order rate constant (k_{obs}) The second-order rate constant (k_{exch}) was obtained from the slope of k_{obs} versus the concentration of sodium deuteroxide ($^-$OD). The kinetic results are listed in Table 2.5.1.

All equilibrium constants were also determined by ^{1}H NMR spectrometry using the Gemini 300 NMR spectrometer. The preparation of the reaction mixture was the same with the rate constants determination described above using dioxane-d_8 : D_2O (1:1) as the solvent. The sample was kept in an oil bath at 64 °C (maintained by refluxing

methanol) for at least 45 da until its NMR spectrum indicated an equilibration reached. To determine the relative concentration in the equilibrated mixture, the ^{1}H NMR peaks were enlarged to the maximum and plotted out on at least four sheets of paper. For each sheet, a peak for each equilibrium component was then cut out manually and the weight gave the relative ratio of the area. An average ratio of the area for all the papers gave the concentration ratio between the equilibrium components. All the equilibrations were determined from both directions.

Table 2.5.1 The results of determination of the H-D Exchange rate of the sulfones.

	T (°C)	solvent	NaOD (M)	k_{obs}, s^{-1}	Calc. k_{exch} ($M^{-1}s^{-1}$)	Mean k_{exch} ($M^{-1}s^{-1}$)
5	25	Dioxane-d_8 : D_2O (1 : 1)	0.1036	1.20×10^{-4}	1.16×10^{-3}	1.14×10^{-3}
			0.1554	1.77×10^{-4}	1.14×10^{-3}	
			0.2072	2.30×10^{-4}	1.10×10^{-3}	
6a	64	Dioxane-d_8 : D_2O (1 : 1)	0.0515	1.91×10^{-5}	3.71×10^{-4}	3.3×10^{-4}
			0.103	3.96×10^{-5}	3.84×10^{-4}	
			0.1545	5.36×10^{-5}	3.47×10^{-4}	
6b	25	Dioxane-d_8 : D_2O (1 : 1)	0.1036	1.13×10^{-5}	1.09×10^{-4}	1.12×10^{-4}
			0.1554	1.74×10^{-5}	1.12×10^{-4}	
7	64	Dioxane-d_8 : D_2O (1 : 1)	0.0536	5.62×10^{-5}	1.05×10^{-3}	1.06×10^{-3}
			0.1036	1.06×10^{-4}	1.02×10^{-3}	
			0.1608	1.70×10^{-4}	1.06×10^{-3}	
8	25	Dioxane-d_8 : D_2O (1 : 1)	0.150	7.49×10^{-5}	4.99×10^{-4}	5.1×10^{-4}
			0.200	1.03×10^{-4}	5.15×10^{-4}	
12	25	Dioxane-d_8 : D_2O (1 : 1)	0.150	1.52×10^{-4}	1.01×10^{-3}	1.1×10^{-3}
			0.200	2.26×10^{-4}	1.13×10^{-3}	
17a	25	Dioxane-d_8 : D_2O (1 : 1)	0.0518	1.10×10^{-5}	2.12×10^{-4}	2.5×10^{-4}
			0.1030	2.63×10^{-5}	2.55×10^{-4}	
			0.1545	3.68×10^{-5}	2.38×10^{-4}	
17b	25	Dioxane-d_8 : D_2O (1 : 1)	0.1036	9.67×10^{-5}	9.33×10^{-4}	9.3×10^{-4}
			0.1554	1.44×10^{-4}	9.27×10^{-4}	

Table 2.5.1 Continued

	T (°C)	solvent	NaOD (M)	k_{obs}, s^{-1}	Calc. k_{exch} ($M^{-1}s^{-1}$)	Mean k_{exch} ($M^{-1}s^{-1}$)
23a	25	Dioxane-d_8 : D_2O (1 : 1)	0.1030	4.90×10^{-9}	4.76×10^{-8}	4.2×10^{-8}
			0.1554	5.73×10^{-9}	3.69×10^{-8}	
	64	Dioxane-d_8 : D_2O (1 : 1)	0.1030	3.65×10^{-8}	3.54×10^{-7}	3.3×10^{-6}
			0.1554	4.85×10^{-8}	3.12×10^{-7}	
23b	64	Dioxane-d_8 : D_2O (1 : 1)	0.075	1.15×10^{-5}	1.53×10^{-4}	1.5×10^{-4}
			0.100	1.39×10^{-5}	1.39×10^{-4}	
			0.200	3.00×10^{-5}	1.50×10^{-4}	
	36	Dioxane-d_8 : D_2O (1 : 1)	0.1036	6.80×10^{-7}	6.56×10^{-6}	7.0×10^{-6}
			0.1554	1.15×10^{-6}	7.40×10^{-6}	
	25	Dioxane-d_8 : D_2O (1 : 1)	0.1036	1.80×10^{-7}	1.74×10^{-6}	1.75×10^{-6}
			0.1554	2.73×10^{-7}	1.76×10^{-6}	
24a	64	Dioxane-d_8 : D_2O (1 : 1)	0.100	9.40×10^{-8}	9.40×10^{-7}	1.1×10^{-6}
			0.150	2.00×10^{-7}	1.33×10^{-6}	
24b	64	Dioxane-d_8 : D_2O (1 : 1)	0.0518	2.11×10^{-6}	4.07×10^{-5}	4.4×10^{-5}
			0.1036	4.92×10^{-6}	4.75×10^{-5}	
25a	64	Dioxane-d_8 : D_2O (1 : 1)	0.100	1.05×10^{-7}	1.05×10^{-6}	1.3×10^{-6}
			0.150	2.31×10^{-7}	1.54×10^{-6}	
25b	64	Dioxane-d_8 : D_2O (1 : 1)	0.0518	3.60×10^{-6}	6.95×10^{-5}	7.5×10^{-5}
			0.1036	8.21×10^{-6}	7.92×10^{-5}	
			0.1545	1.19×10^{-5}	7.70×10^{-5}	
26	64	Dioxane-d_8 : D_2O (1 : 1)	0.0515	9.31×10^{-6}	1.81×10^{-4}	1.5×10^{-4}
			0.1036	1.34×10^{-5}	1.29×10^{-4}	
			0.1545	2.16×10^{-5}	1.40×10^{-4}	

Table 2.5.1 Continued

	T (°C)	solvent	NaOD (M)	k_{obs}, s^{-1}	Calc. k_{exch} ($M^{-1}s^{-1}$)	Mean k_{exch} ($M^{-1}s^{-1}$)
27	64	Dioxane-d_8 : D_2O (1 : 1)	0.0515	1.29×10^{-4}	2.50×10^{-3}	2.60×10^{-3}
			0.1036	2.64×10^{-4}	2.55×10^{-3}	
			0.1545	4.23×10^{-4}	2.74×10^{-3}	
28	64	Dioxane-d_8 : D_2O (1 : 1)	0.0750	1.36×10^{-4}	1.81×10^{-3}	1.83×10^{-3}
			0.100	1.82×10^{-4}	1.82×10^{-3}	
			0.150	2.80×10^{-4}	1.87×10^{-3}	
29	64	Dioxane-d_8 : D_2O (1 : 1)	0.100	1.33×10^{-4}	1.33×10^{-3}	1.35×10^{-3}
			0.125	1.70×10^{-4}	1.36×10^{-3}	
			0.150	2.05×10^{-4}	1.37×10^{-3}	
30b	25	Dioxane-d_8 : D_2O (1 : 1)	1.621×10^{-4} (5.0×10^{-2})[a]	8.303×10^{-5}	5.122×10^{-1}	5.12×10^{-1}
			1.352×10^{-5} (9.4×10^{-2})[a]	6.925×10^{-6}	5.122×10^{-1}	
			1.445×10^{-5} (1.9×10^{-1})[a]	7.396×10^{-6}	5.188×10^{-1}	
30c	25	Dioxane-d_8 : D_2O (1 : 1)	0.100	1.69×10^{-4}	1.69×10^{-3}	1.68×10^{-3}
			0.125	2.07×10^{-4}	1.66×10^{-3}	
			0.150	2.56×10^{-4}	1.68×10^{-3}	
30d	25	Dioxane-d_8 : D_2O (1 : 1)	0.0515	2.09×10^{-5}	4.06×10^{-4}	3.96×10^{-4}
			0.103	4.06×10^{-5}	3.94×10^{-4}	
			0.1545	5.99×10^{-5}	3.88×10^{-4}	
30e	25	Dioxane-d_8 : D_2O (1 : 1)	0.100	4.17×10^{-5}	4.17×10^{-4}	4.01×10^{-4}
			0.150	5.78×10^{-5}	3.85×10^{-4}	

Table 2.5.1 Continued.

	T (°C)	solvent	NaOD (M)	k_{obs}, s^{-1}	Calc. k_{exch} ($M^{-1}s^{-1}$)	Mean k_{exch} ($M^{-1}s^{-1}$)
31a	25	Dioxane-d_8 : D_2O (1 : 1)	0.050	2.09×10^{-5}	4.18×10^{-4}	4.14×10^{-4}
			0.100	4.11×10^{-5}	4.11×10^{-4}	
			0.150	6.20×10^{-5}	4.13×10^{-4}	
31b	25	Dioxane-d_8 : D_2O (1 : 1)	0.050	1.16×10^{-5}	2.32×10^{-4}	2.3×10^{-4}
			0.100	2.12×10^{-5}	2.12×10^{-4}	
			0.200	4.62×10^{-5}	2.31×10^{-4}	
31c	25	Dioxane-d_8 : D_2O (1 : 1)	0.050	1.01×10^{-5}	2.02×10^{-4}	2.03×10^{-4}
			0.100	2.00×10^{-5}	2.00×10^{-4}	
			0.125	2.59×10^{-5}	2.07×10^{-4}	
31d	25	Dioxane-d_8 : D_2O (1 : 1)	0.0515	9.17×10^{-6}	1.78×10^{-4}	1.80×10^{-4}
			0.103	1.84×10^{-5}	1.79×10^{-4}	
			0.1545	2.84×10^{-5}	1.84×10^{-4}	
31e	25	Dioxane-d_8 : D_2O (1 : 1)	0.100	1.82×10^{-5}	1.82×10^{-4}	1.80×10^{-4}
			0.150	2.66×10^{-5}	1.77×10^{-4}	
32	25	Dioxane-d_8 : D_2O (1 : 1)	0.0515	4.36×10^{-6}	8.47×10^{-5}	8.6×10^{-5}
			0.1030	8.98×10^{-6}	8.72×10^{-5}	
			0.1545	1.34×10^{-5}	8.67×10^{-5}	
33	25	Dioxane-d_8 : D_2O (1 : 1)	1.445×10^{-4} ($\sim 1 \times 10^{-1}$)[a]	5.79×10^{-5}	4.01×10^{-1}	4.2×10^{-1}
			1.047×10^{-4} ($\sim 1 \times 10^{-1}$)[a]	4.60×10^{-5}	4.39×10^{-1}	
34	25	Dioxane-d_8 : D_2O (1 : 1)	0.125	3.09×10^{-6} (1.24×10^{-4})[b]	2.47×10^{-5} (9.92×10^{-4})[b]	2.4×10^{-5} (9.92×10^{-4})[b]
			0.200	4.46×10^{-6}	2.23×10^{-5}	

[a] The values shown in parentheses are the concentrations of CO_3^{2-} of the buffer solutions.

[b] The values shown in parentheses are for the H-D exchange of the α-CH_3.

CHAPTER 3

GENERALIZATION OF THE ANGLE DEPENDENCE OF THE BETA-SUBSTITUTED SATURATED SULFONES

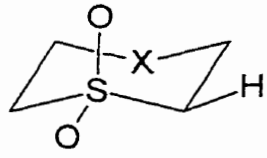
3.1 INTRODUCTION

Chapter 2 presents evidence that the effect of β-alkoxy substituents on the rate of the H-D exchange via α-carbanions ($(k_{exch})_X$) is subject to variation in rate correlating with the H-C-C-O torsion angle (θ). Specifically, defining $k_N = (k_{exch})_X/(k_{exch})_{model}$, we found for a set of β-alkoxy sulfones k_N for carbanion formation is given by

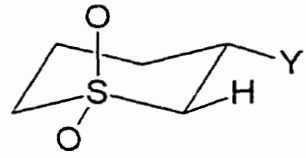
$$\log k_N = a + b \cos 2\theta$$
$$= c + d \cos^2\theta,$$

consistent with the intervention of negative hyperconjugation (the generalized anomeric effect). The values of the parameters *a* and *b* (or *c* and *d*) are such that one may conclude that the maximum anomeric effect of an alkoxy group is greater than the sum of its field and inductive effects. Since the anomeric effect and negative hyperconjugation are not confined to alkoxy groups, the only reasonable construction that we can infer from Chapter 2 is that we must expect the torsion angle dependence to be a general phenomenon, capable of appearing to a greater or lesser measure with *all* substituents. The effect can be expected to be small or negligible with some substituents (e.g. alkyl groups), but with most heteroatomic substituents it should be significant.

This chapter extends our study to additional substituents SR, SO_2R_2, NR_2, and $^+NR_3$ restricting the torsion angle (θ) to either approximately 180° or 60° (Scheme 3.1.1). The angle dependence of these systems is to be discussed in this chapter (together with the β-oxygen substituted compounds presented in Chapter 2).



$X = O, S, SO_2, NMe, {}^{+}NMe_2I^{-}$



$Y = OMe, SMe, SO_2Me, NMe_2, {}^{+}NMe_3I^{-}$

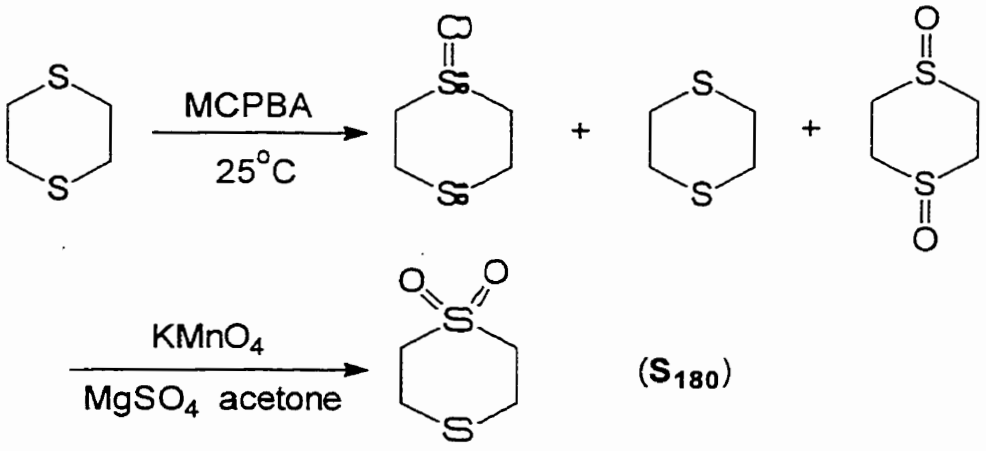
Scheme 3.1.1

In the positively charged ammonio system, the possibility of the so called 'reverse anomeric effect' arises. This chapter will also discuss this point.

3.2 RESULTS AND DISCUSSION

3.2.1 PREPARATION OF THE BETA-HETEROATOM SUBSTITUTED SULFONES

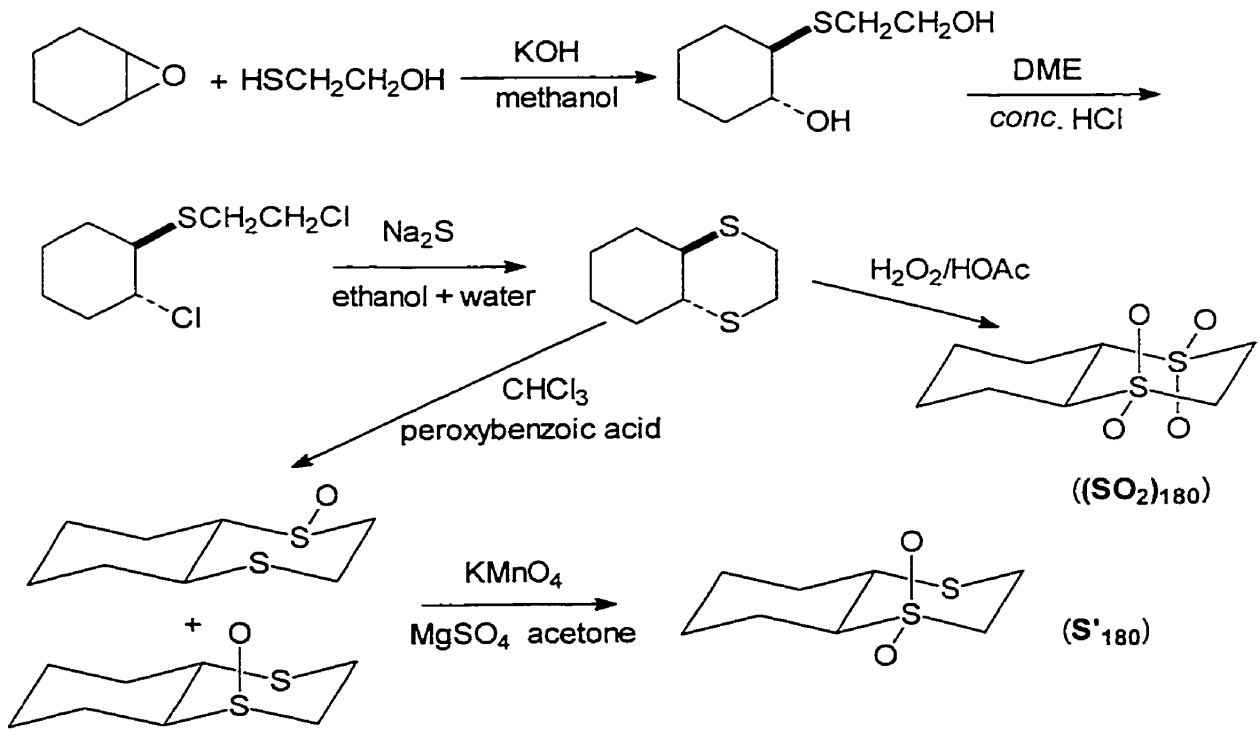
1,4-Dithiane 1,1-dioxide ($\mathbf{S_{180}}$) was synthesized according to the procedure of Clennan and coworkers[76] as illustrated in Scheme 3.2.1. Mild oxidation of 1,4-dithiane by *m*-chloroperoxybenzoic acid at 25°C gave a mixture of starting material (30%), 1,4-dithiane 1-oxide (40%) and 1,4-dithiane 1,4-dioxide (30%). The mixture was further oxidized by potassium permanganate in the presence of magnesium sulfate in acetone to give $\mathbf{S_{180}}$ which could be obtained in pure form after separation by thick layer chromatography and recrystalization.



Scheme 3.2.1

Scheme 3.2.2 illustrates the preparation of *trans*-1,4-dithiadecalin 1,1-dioxide ($\mathbf{S'_{180}}$). Ring-opening reaction of cyclohexene oxide by mercaptoethanol anion gave *trans*-2-(2-hydroxyethylthio)cyclohexanol in 90% yield.[77] This was then treated with concentrated hydrochloric acid in 1,2-dimethoxyethane (DME) to give *trans*-2-chloro-cyclohexyl 2-chloroethyl sulfide as a colorless liquid in quantitative yield.[31] The

stereochemistry of this last reaction presumably results from the intermediate formation of the thiiranium ion. *trans*-1,4-Dithiadecalin was synthesized according to the method of Culvenor and coworkers[78] through the reaction of the dichloride with sodium sulfide. The *trans* stereochemistry about C9 and C10 ring junction of the dithiadecalin has been deduced by Culvenor and coworkers[78] from its synthesis by cyclization of *trans*-2-chloro-ethyl 2-mercaptocyclohexyl sulfide. The stepwise oxidations of *trans*-1,4-dithiadecalin was achieved following the procedure of Rooney and Evans.[79] Oxidation of the *trans*-1,4-dithiadecalin with peroxybenzoic acid gave a mixture containing the axial and equatorial mono sulfoxides, which was not purified before it was oxidized to the desired sulfone ($\mathbf{S'}_{180}$). Pure $\mathbf{S'}_{180}$ was obtained from column chromatographic separation.



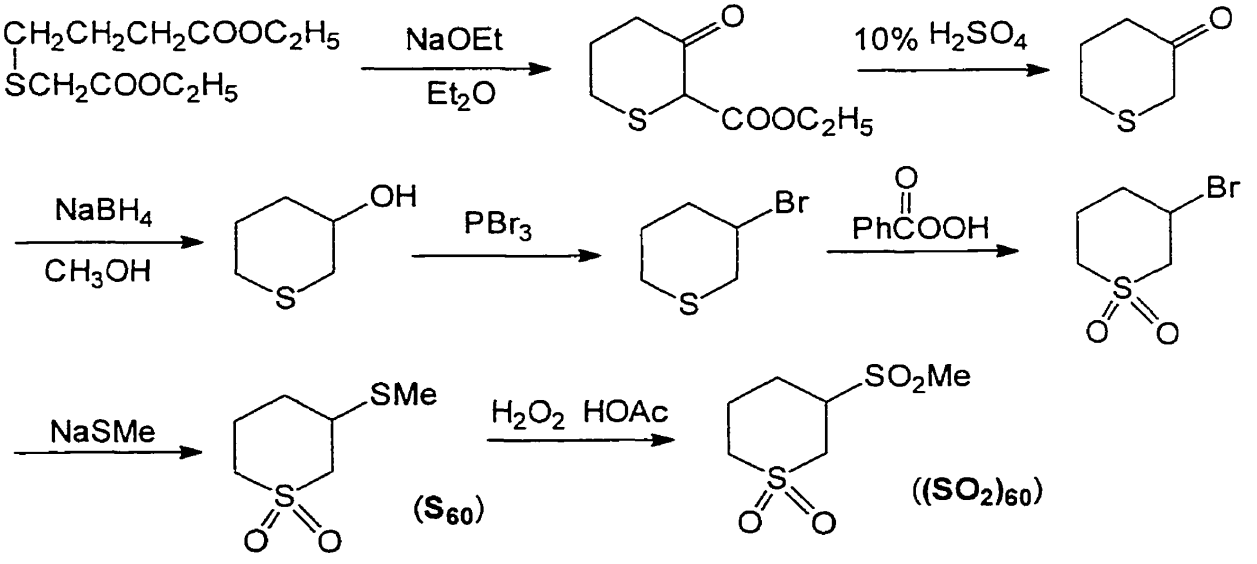
Scheme 3.2.2

Complete oxidation of *trans*-1,4-dithiadecalin by 30% hydrogen peroxide in

acetic acid gave *trans*-1,4-dithiadecalin 1,1,4,4-tetraoxide ($(SO_2)_{180}$, Scheme 3.2.2).

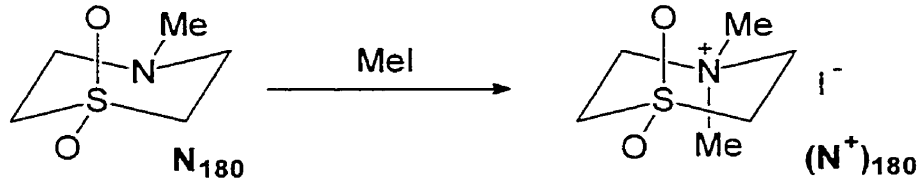
3-(Methylthio)tetrahydrothiapyran 1,1-dioxide (S_{60}) was prepared according to Scheme 3.2.3. 3-Bromotetrahydrothiapyran 1,1-dioxide was prepared according to the procedure of Fenel.[81] Ethyl γ-(carbethoxymethylmercapto)butyrate was treated with alcohol free sodium ethoxide to give 2-carbethoxytetrahydrothiapyran-3-one as a colorless liquid in 80% yield. The β-ketoester was decomposed by 10% sulfuric acid to gave tetrahydrothiapyran-3-one (72% yield). Reduction of the ketone to the alcohol and followed by reaction with phosphorus tribromide gave 3-bromotetrahydrothiapyran as a colorless liquid, which was oxidized to yield 3-bromotetrahydrothiapyran 1,1-dioxide as pale yellow crystals. Substitution of the bromide with sodium thiomethoxide in 2-butanol gave S_{60} as white needles in 71% yield.

Oxidation of 3-(methylthio)tetrahydrothiapyran 1,1-dioxide (S_{60}) by 30% hydrogen peroxide in acetic acid gave 3-(methylsulfonyl)tetrahydrothiapyran 1,1-dioxide ($(SO_2)_{60}$, Scheme 3.2.3).



Scheme 3.2.3

N-Methylthiomorpholine 1,1-dioxide ($\mathbf{N}_{180}$) is commercially available, and its methylation with iodomethane gave 4,4-dimethyltetrahydro-1,4-thiazinium iodide ($(\mathbf{N}^{+})_{180}$, Scheme 3.2.4).

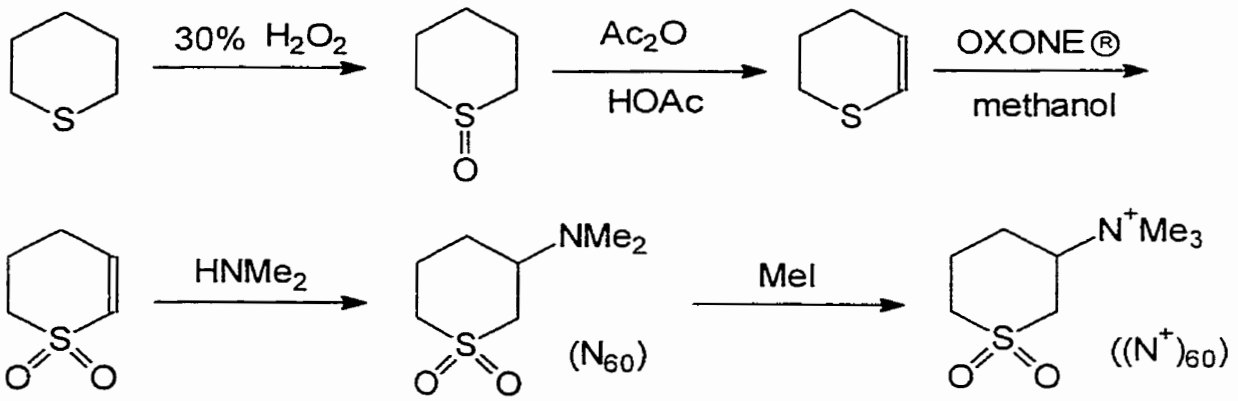


$\mathbf{N}_{180}$ $(\mathbf{N}^{+})_{180}$

Scheme 3.2.4

Scheme 3.2.5 presents the preparation of 3-(dimethylamino)tetrahydrothiapyran 1,1-dioxide ($\mathbf{N}_{60}$). 4*H*-2,3-Dihydrothiapyran 1,1-dioxide was synthesized according to the following procedure of Liebowitz and coworkers.[82] Mild oxidation of tetrahydrothiapyran by 30% hydrogen peroxide gave tetrahydrothiapyran-1-oxide (yield 81%). Pummerer reaction of the sulfoxide with acetic anhydride in acetic acid gave 4*H*-2,3-dihydrothia-pyran, which was selectively oxidized by OXONE® (potassium peroxymonopersulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) to form 4*H*-2,3-dihydrothiapyran 1,1-dioxide. Addition of dimethylamine to the double bond yielded $\mathbf{N}_{60}$ as white crystals in very good yield.

Methylation of 3-(dimethylamino)tetrahydrothiapyran 1,1-dioxide ($\mathbf{N}_{60}$) with iodomethane gave 3-(trimethylammonio)tetrahydrothiapyran 1,1-dioxide ($(\mathbf{N}^{+})_{60}$, Scheme 3.2.5).



Scheme 3.2.5

3.2.2 KINETICS OF THE H-D EXCHANGE REACTION

The H-D exchange rates of the sulfones in this study were measured as outlined in Chapter 2. The solvents used for the NMR kinetic determination included D_2O, dioxane-d_8 : D_2O (1:1, v/v), CD_3CN : D_2O (1:1, v/v). The preparation of buffer solution has also been described in Chapter 2, and the influence of buffer concentration on the H-D exchange rate is believed to be unimportant under the conditions used in this research, see Table 2.2.1 of Chapter 2. The concentration (C_t) of the exchanging hydrogen was followed by ^1H NMR spectroscopy relative to an inert hydrogen in the system. The plot of .ln C_t vs time gave a best-fit line whose slope was the pseudo-first-order rate constant (k_{obs}). The second order rate constant k_{exch} was obtained from the slope of the best-fit line of k_{obs} vs the concentration of OD^- .

The kinetic results obtained in this chapter are summarized in Table 3.2.1.

Table 3.2.1 Kinetic Data for β-Heteroatom Substituted Sulfones.

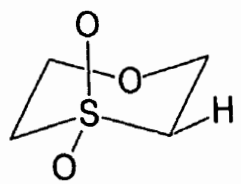
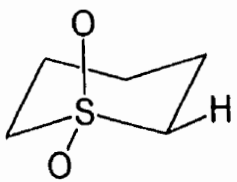
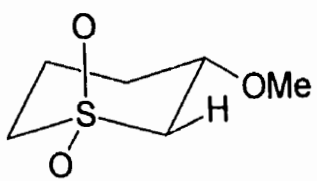
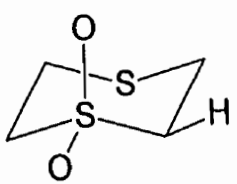
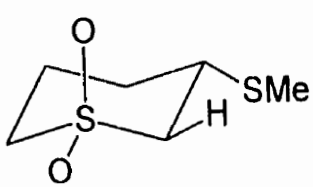
alkoxy sulfone	θ [a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
O_{180} 	173°	2.15×10^{-2} [d] A (4.30×10^{-2}) [f]	**22** 	1.0×10^{-6} [d] A (2.0×10^{-6}) [f]	4.33
O_{60} 	59.3°	4.50×10^{-4} [d] A	**22**	1.0×10^{-6} [d] A (2.0×10^{-6}) [f]	2.35
S_{180} 	172°	2.8×10^{-2} B (5.6×10^{-2}) [f]	**22**	3.09×10^{-6} B (6.2×10^{-6}) [f]	3.96
S_{60} 	56.9°	2.7×10^{-4} B	**22**	3.09×10^{-6} B (6.2×10^{-6}) [f]	1.64

Table 3.2.1 Continued

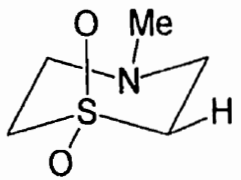
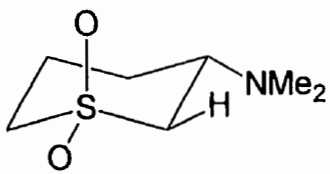
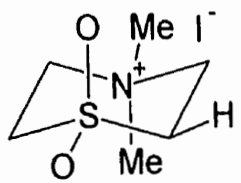
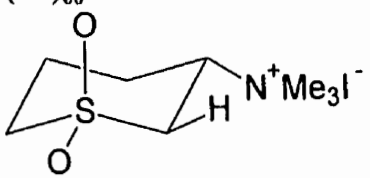
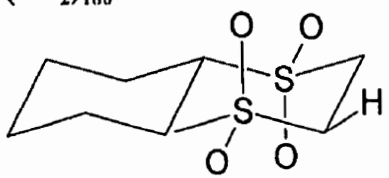
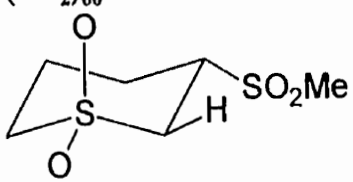
alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
$\mathbf{N_{180}}$ 	175°	2.60×10^{-3} B (5.20×10^{-3}) [f]	**22**	3.1×10^{-6} B (6.2×10^{-6}) [f]	2.93
$\mathbf{N_{60}}$ 	59.4°	1.60×10^{-4} B	**22**	3.1×10^{-6} B (6.2×10^{-6}) [f]	1.41
$\mathbf{(N^+)_{180}}$ 	179°	1.50×10^{3} A (3.00×10^{3}) [f]	**22**	1.0×10^{-6} [d] A (2.0×10^{-6}) [f]	9.18
$\mathbf{(N^+)_{60}}$ 	49.9°	6.3×10^{-1} A	**22**	1.0×10^{-6} [d] A (2.0×10^{-6}) [f]	5.50

Table 3.2.1 Continued

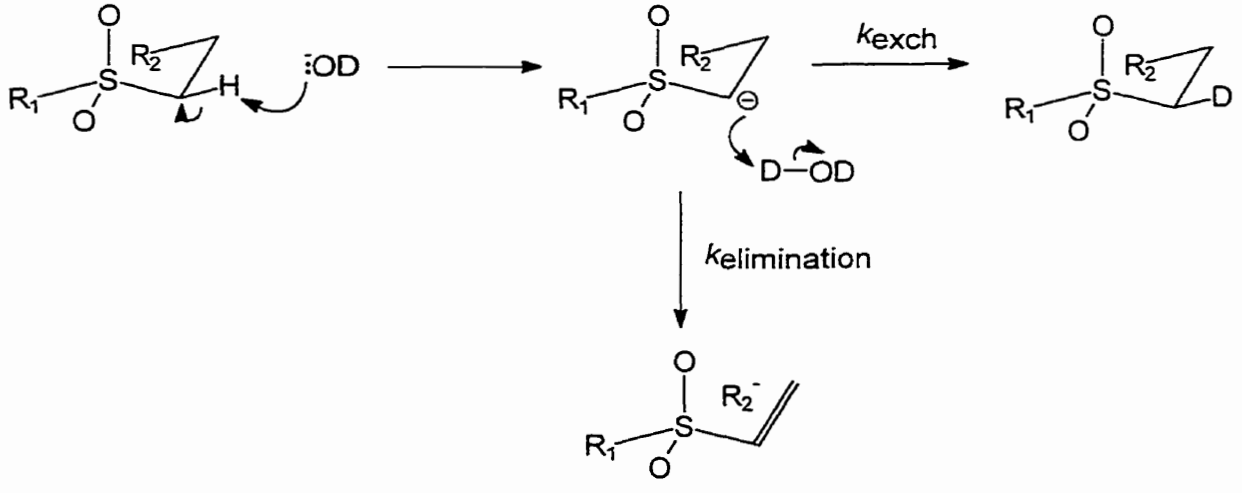
alkoxy sulfone	θ[a]	k_{exch} ($M^{-1}s^{-1}$) (conditions) [b]	model(s)	$(k_{exch})_{model}$ ($M^{-1}s^{-1}$)	log k_N [c]
$(SO_2)_{180}$ 	177°	2.6×10^{2} [c] C	**22**	1.80×10^{-6} [e] C	8.16
$(SO_2)_{60}$ 	53.8°	1.10×10^{-1} A	**22**	1.0×10^{-6} [d] A (2.0×10^{-6}) [f]	4.75

[a] The torsion angles (θ) were estimated by calculation using PCModel (PCM4). [b] Reaction conditions, A: D_2O (20°C); B: D_2O : dioxane-d_8 (1 : 1, 25°C); C: D_2O : CD_3CN (1:1, 21°C). [c] $k_N = k_{exch} / (k_{exch})_{model}$. [d] These data were from the theses of R. Rathore[31] and Zhen Rong Guo[32] [e] Obtained for the conditions C by multiplying the value at conditions B with the converting factor: 0.291. The converting factor was obtained by dividing the rate of 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2,2,1]heptane at conditions C (3.11×10^{-4} $M^{-1}s^{-1}$) by its rate at condition B (1.07×10^{-3} $M^{-1}s^{-1}$). [f] The rate constant in parenthesis is that for H-D exchange per H, and was obtained by multiplying the experimental value by 2.

3.2.3 THE GENERALIZATION OF THE GENERALIZED ANOMERIC EFFECT AS A COMPONENT OF THE POLAR EFFECT

3.2.3.1 The mechanisms of the reactions of heteroatom-substituted sulfones.

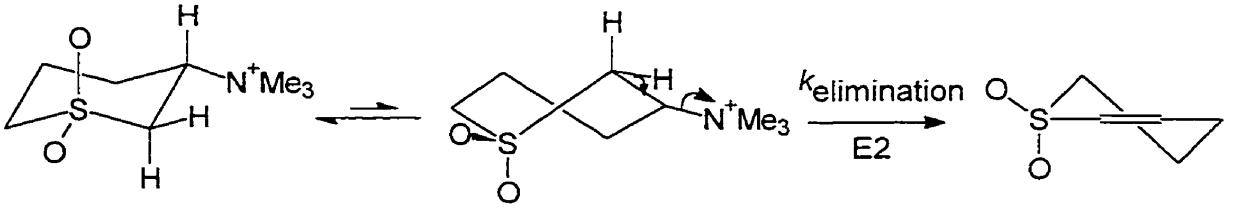
Most sulfones studied in this research gave a H-D exchange (substitution) product under our conditions. In the case of the β-alkoxy substituted sulfones, the H-D exchange of these β-heteroatom substituted sulfones proceeds through the carbanion intermediate as shown in Scheme 3.2.6. In this mechanism, the formation of the carbanion is the slow reaction; the extraction of a proton (D or H) from water (mostly D_2O, with a very small amount of HOD) is much faster. Here the substituent R_2 is OR, a relatively poor leaving group, and the carbanion takes up a proton (to form the exchanged product), rather than eliminate R_2 (to form a double bond by an irreversible E1cB mechanism).



Scheme 3.2.6

One of the ammonium salts, $(N^+)_{60}$, however, did not give the H-D exchange product, but was rapidly converted to the elimination product, and only the elimination rate could be accurately measured. This is exactly what is expected from the irreversible

E1cB mechanism offered above. However, there exist some other possible mechanisms which need to be ruled out. For example, starting from $(N^+)_{60}$, rotation of the six-member ring to a twist boat (Scheme 3.2.7) to make the ammonio group almost *syn* to the leaving hydrogen, and then a *syn* E2 mechanism (Scheme 3.2.7) would result in the same product. So, it is necessary to distinguish the irreversible E1cB mechanism from the other possibilities.



Scheme 3.2.7

To do that, the log k_N values for the β-alkoxy, β-thioalkoxy, β-amine, β-sulfonyl and β-trialkylammonio substituents with different torsion angles were plotted against the σ* values (Table 3.2.2, Figure 3.2.1).

Table 3.2.2 The log k_N values and their corresponding σ* values.

Substituent	Alkoxy	Thioalkoxy	Amine	Sulfonyl	Ammonio
σ*	0.66	0.53	0.11	1.32	1.9
log k_N (~ 60°)	2.35	1.64	1.41	4.75	5.5
log k_N (~ 180°)	4.33	3.96	2.93	8.46	9.18

This gave two roughly straight lines with somewhat different slopes. Except for the point for $(N^+)_{60}$ (the ammonio group at about 60° torsion angle), all the others are the results of

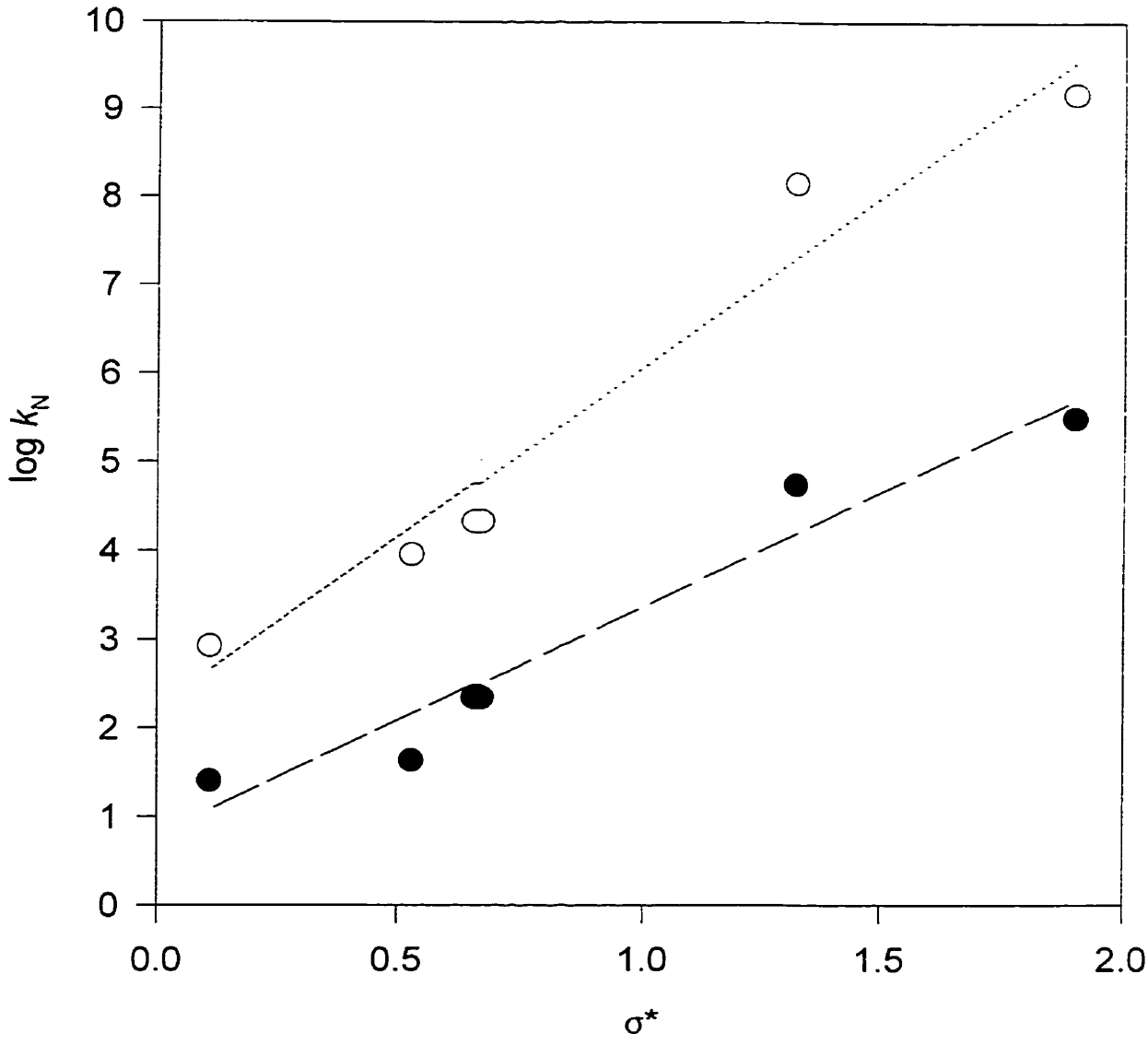


Figure 3.2.1 log k_N vs σ*. The unfilled circles are for the compounds with ~ 60 ° torsion angle; the filled circles are for those with ~ 180 ° torsion angle torsion angle.

H-D exchange which is through a formation of a carbanion intermediate. From the 60° line in Figure 3.2.1, it is easy to find that the elimination rate of $(N^+)_{60}$ is fully consistent with a carbanion intermediate mechanism, and thus, for $(N^+)_{60}$ the irreversible E1cB

mechanism is more likely than the E2 mechanism. If the E2 mechanism were to dominate it would be because it is faster than the irreversible E1cB process, and this would raise the $(N^+)_{60}$ point higher than the 60° line in Figure 3.2.1.

The plot of log k_N (~ 180°) vs log k_N (~ 60°) (Figure 3.2.2) offers another way to investigate the mechanism of the elimination of compound $(N^+)_{60}$. Figure 3.2.2 clearly indicates that the elimination of $(N^+)_{60}$ shares the same kind of transition state.

To summarize, the available evidence indicates that all the points in Figure 3.2.1 (or Figure 3.2.2) are from the same rate determining step — the formation of a carbanion intermediate. It is this conclusion that enables us to include all the points in Figure 3.2.1 into the discussion of the generalization and normalization of the angle dependence of the β-substituent saturated sulfones.

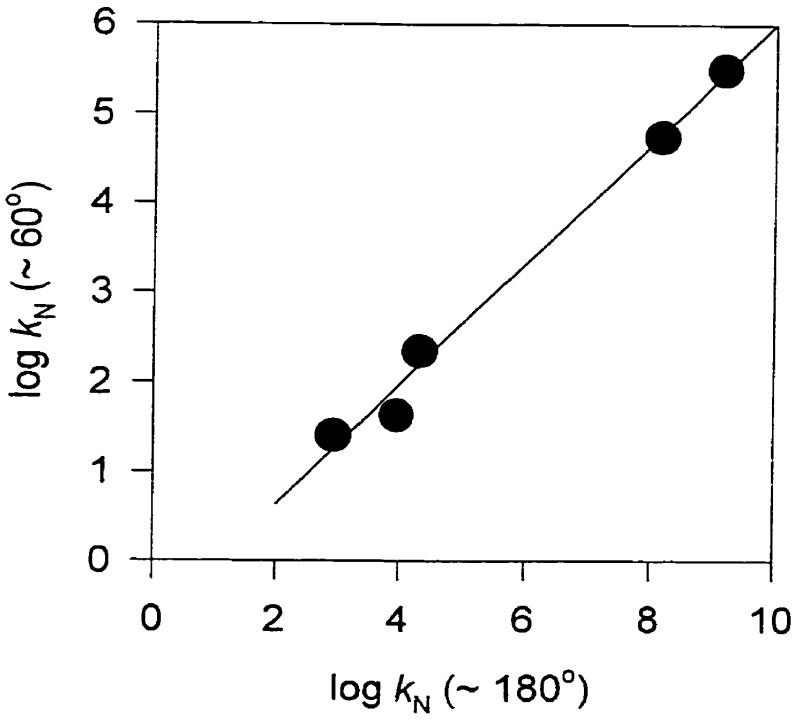


Figure 3.2.2 The log k_N values for the compounds with ~ 60° torsion angle vs those with ~ 180° torsion angle.

3.2.3.2 The generation of the angle dependent term

Chapter 2 presented the evidence for the angle dependence of the rate of formation of α-sulfonyl carbanions of β-alkoxy sulfones, and an equation was given:

$$\log k_N(\text{alkoxy}) = (3.00 \pm 0.08) + (1.31 \pm 0.10)\cos 2\theta$$

$$= (1.70 \pm 0.17) + (2.62 \pm 0.20)\cos^2\theta \qquad \text{eq 3.2.1}$$

The obvious difference of the log k_N values between the ~ 60° torsion angle compound and the ~ 180° torsion angle compound (Table 3.2.2), enables us to extend the angle dependence of the β-alkoxy system to all the β-thioalkoxy, β-amine, β-sulfonyl, and β-ammonio systems studied in this Chapter. To extend eq 3.2.1 to β-thioalkoxy, β-amine, β-sulfonyl and β-ammonio substituents, it is reasonable and also practical to use a minimum set of points (that is, the ~ 60° and ~ 180° sulfones) to find a reasonably accurate equation. For β-oxygen substituted sulfone system, an equation (eq 3.2.2) derived only from the points of the sulfones $\mathbf{O}_{60}$ and $\mathbf{O}_{180}$ is only slightly different from eq 3.2.1.

$$\log k_N(\text{alkoxy}) = 3.00 + 1.37\cos 2\theta$$

$$= 1.63 + 2.74\cos^2\theta \qquad \text{eq 3.2.2}$$

Using the same two-point procedure to find the equations for the other substituent systems, we obtain the following:

$$\log k_N(\text{thioether}) = 2.33 + 1.70\cos 2\theta$$

$$= 0.63 + 3.40\cos^2\theta \qquad \text{eq 3.2.3}$$

$$\log k_N(\text{amine}) = 1.91 + 1.04\cos 2\theta$$

$$= 0.87 + 2.08\cos^2\theta \qquad \text{eq 3.2.4}$$

$$\log k_N(\text{sulfonyl}) = 5.55 + 2.83\cos 2\theta$$

$$= 2.72 + 5.66 \cos^2\theta \qquad \text{eq 3.2.5}$$

$$\log k_N(\text{ammonio}) = 6.04 + 3.15 \cos 2\theta$$

$$= 2.89 + 6.30 \cos^2\theta \qquad \text{eq 3.2.6}$$

These equations (eq 3.2.2 to eq 3.2.6) are used to connect the experimental points in Figure 3.2.3.

Figure 3.2.3 reflects the angle dependence of the substituent effect. It is also possible to estimate the size of hyperconjugative (anomeric) effect and that of a conventional polar effect (Table 3.2.3). Ignoring the angle dependence of the field effect (which may be small judging from our calculation in Section 2.2.4), the maximum electronic effect can be obtained by the log k_N values at 180° (and also at 0°) torsion angle; and the polar effect is given by the log k_N values at 90° torsion angle; their difference gives the maximum contribution from negative hyperconjugation or anomeric effect. The contribution from negative hyperconjugation or the anomeric effect is maximum when the optimal torsion angle (0° or 180°) is allowed.

Table 3.2.3 The Composition of Substituent Electronic Effect

	Maximum hyperconjugative (anomeric) effect	Inductive and field effect
O	2.74 (63%)	1.63 (37%)
S	3.40 (84%)	0.63 (16%)
N	2.08 (71%)	0.87 (29%)
N^+	6.30 (69%) *	2.89 (31%) *
SO_2	5.66 (68%)	2.72 (32%)

* In the ammonio system, the field effect will be much larger than in the uncharged substituents (see discussion in Section 3.2.4). These contributions may be subject to change.

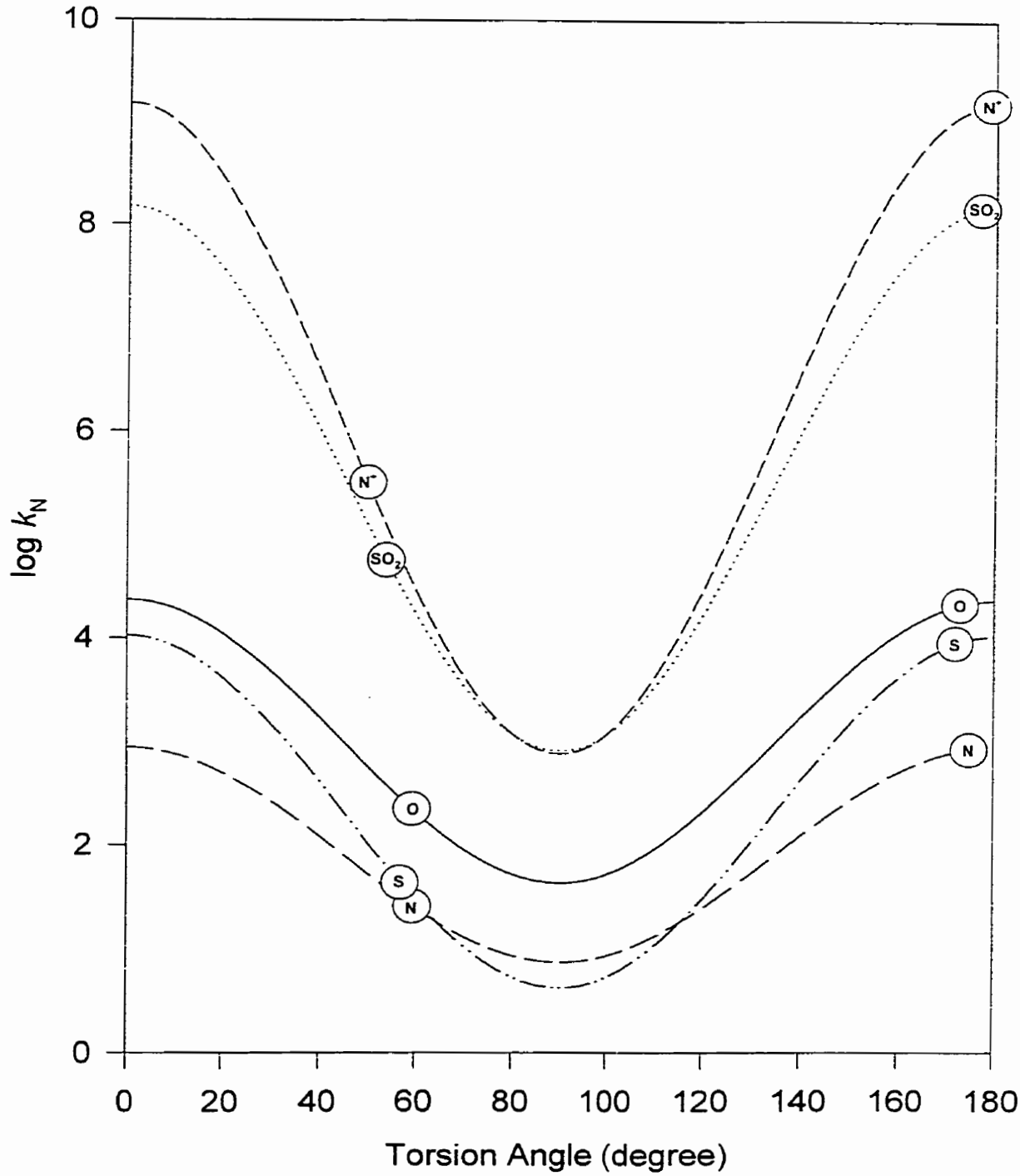


Figure 3.2.3 The torsion angle dependence of β-heteroatom substituted sulfone.

The new feature of the angle dependence of σ^*_θ, introduced in Chapter 2 in β-alkoxy sulfones, can now be extended to β-thioalkoxy, β-amine, β-sulfonyl and β-ammonio substituent system. As has been discussed in the beginning of this Section (Section 3.2.3.1), all the reactions (H-D exchange, and the elimination of $\mathbf{N}^+_{60}$) share the same reaction intermediate and rate-determining step (formation of the carbanion), so we can use the same reaction constant (ρ*) obtained in the alkoxy system by Thomas and Stirling.[6] That is

$$\log k_N = 4.89\ \sigma^*_\theta$$

Combining it with equation 3.2.2 to equation 3.2.6, we get, though eq 3.2.11 is subject to change (see discussion in Section 3.2.4),

$$\sigma^*_\theta(\text{alkoxy}) = 0.61 + 0.28\cos 2\theta$$

$$= 0.33 + 0.56\cos^2\theta \qquad \text{eq 3.2.7}$$

$$\sigma^*_\theta(\text{thioether}) = 0.48 + 0.35\cos 2\theta$$

$$= 0.13 + 0.70\cos^2\theta \qquad \text{eq 3.2.8}$$

$$\sigma^*_\theta(\text{amine}) = 0.39 + 0.21\cos 2\theta$$

$$= 0.18 + 0.43\cos^2\theta \qquad \text{eq 3.2.9}$$

$$\sigma^*_\theta(\text{sulfonyl}) = 1.14 + 0.58\cos 2\theta$$

$$= 0.56 + 1.16\cos^2\theta \qquad \text{eq 3.2.10}$$

$$\sigma^*_\theta(\text{ammonio}) = 1.24 + 0.64\cos 2\theta$$

$$= 0.59 + 1.29\cos^2\theta \qquad \text{eq 3.2.11}$$

Table 3.2.4 lists the σ^*_θ values at 0° (or 180°), 60° (or 120°) and 90° torsion angles for these systems.

Table 3.2.4 The angle dependence feature of σ^*_θ.

	σ^*	$\sigma^*_0 = \sigma^*_{180}$	$\sigma^*_{60} = \sigma^*_{120}$	σ^*_{90}
OR	0.66	0.89	0.47	0.33
SR	0.53	0.83	0.31	0.13
NR_2	0.11	0.61	0.29	0.18
SO_2R	1.32	1.72	0.85	0.56
N^-R_3	1.9*	1.88*	0.91*	0.59*

* refer to the note of Table 3.2.3.

It is obvious that the angle dependent term, σ^*_θ, reaches its maximum at 0° or 180° torsion angle, and drops to its minimum at 90°. The traditional term, σ^*, falls into the range, but the size of the range is not trivial. The angular variation of σ^* may account at least in part for the considerable variation in the σ^* value for a particular substituent that may be found in the literature. Exner,[84] for example, lists six values for the σ_I for the methoxy group; these correspond to σ^* values ranging from 0.51 to 0.76.

The analysis above introduces the angle dependence feature of the substituent constant from the negative hyperconjugation (or anomeric effect). We realize that, for some series, it may not be the only reason; in the ammonio system another factor, the field effect, may change it as well. This will be discussed in the next section.

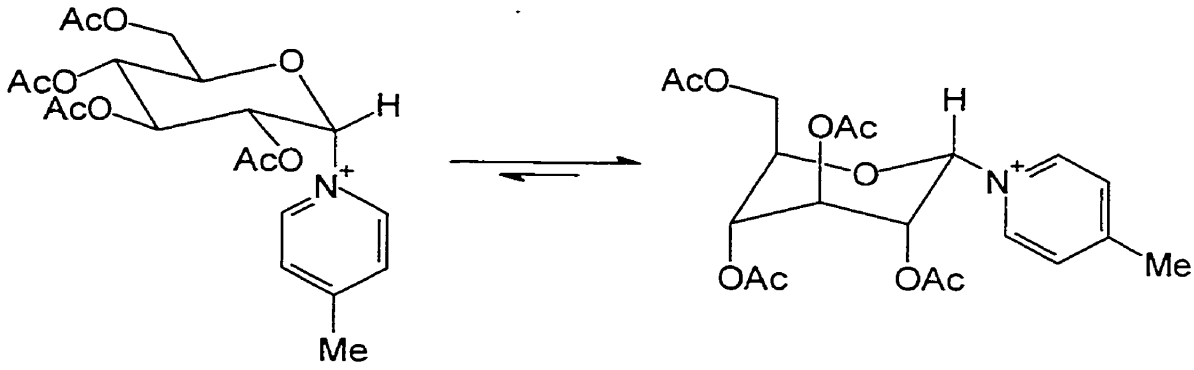
3.2.4 DISCUSSION OF THE TRIALKYLAMMONIO SYSTEM — THE 'REVERSE' ANOMERIC EFFECT

3.2.4.1 A Brief Introduction to 'Reverse Anomeric Effect'

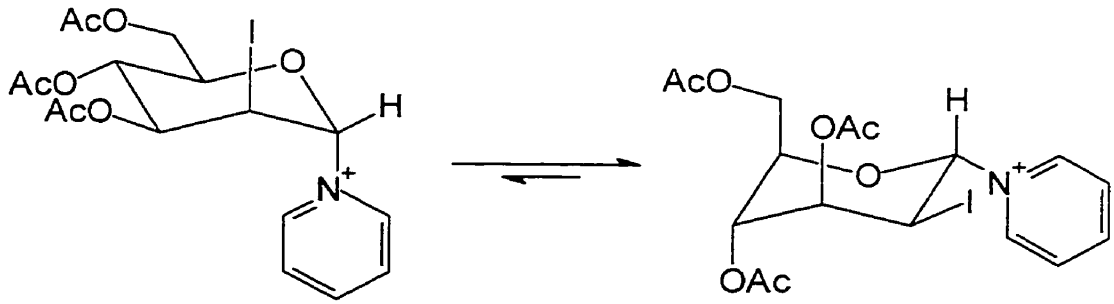
Among the substituents considered in this Chapter is the trialkylammonio group. This substituent is of special interest since positively charged nitrogens are known to show unusual behavior in anomeric effect studies, to the point that a *reverse anomeric effect* has been postulated.

The reverse anomeric effect refers to an apparent preference for the *equatorial* conformation in some systems (Scheme 3.2.8 and 3.2.9), where the anomeric substituent is positively charged such as the ammonio group; such a preference is believed to exist independently of or in addition to steric factors normally favoring the equatorial over the axial conformation. The idea of a reverse anomeric effect was presented by Lemieux and Morgan[83] who studied the conformational equilibria of the N-(tetra-*O*-acetyl-D-gluco-pyranosyl)-4-methylpyridinium ions (Scheme 3.2.8) and the N-(tri-*O*-acetyl-D-2-deoxy-2-iodomannopyranosyl)-4-methylpyridinium ions (Scheme 3.2.9). They concluded that the positively-charged electronegative substituents prefer the equatorial over the axial orientation.

Obviously, the reverse anomeric effect cannot be explained directly by negative hyperconjugation. If a 'normal' anomeric effect functions, as illustrated in Figure 1.3.1 b, a positive charge on the nitrogen should lower the energy of σ^* orbital of C-X^-, and thus enhance the anomeric stabilization.



Scheme 3.2.8



Scheme 3.2.9

Considerable effort has been made to explain the reverse anomeric effect.[15] The first explanation came from Lemieux and Morgan,[83] when they first postulated the phenomenon. Their argument was based on the interpretation of the anomeric effect (Figure 3.2.4) in terms of electrostatic interactions. In the 'normal' anomeric effect (when X is neutral), the dipole-dipole repulsion may destabilize the equatorial conformer, where there is little effect in the axial conformer; in the reverse anomeric effect, however, a positive substituent X is expected to reverse the C-X dipole direction, and thereby to stabilize the equatorial conformer. This theory was criticized by Perrin:[15] "this explanation cannot be valid, since the dipole moment has no intrinsic meaning when

there is net charge". Instead, Perrin suggested[15] that it is more acceptable if the interaction is regarded as between a monopole (X^-) and a dipole. When X^- is equatorial, the positive charge is closer to the negative end of the dipole and thus stabilizes the equatorial conformation, which will lead to a reverse anomeric effect.

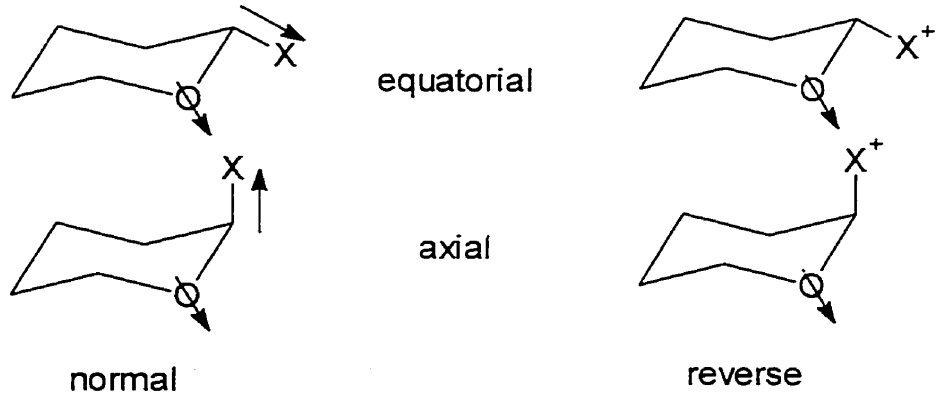
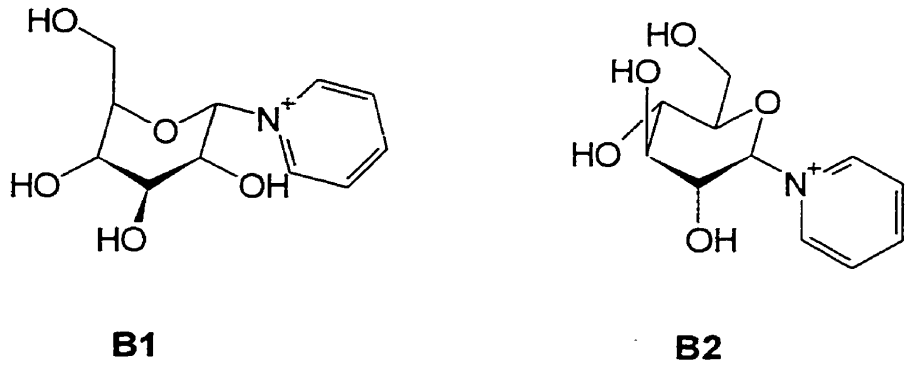


Figure 3.2.4 An electrostatic interpretation of the reverse anomeric effect.

However, Perrin cited an example[15] that a stable "boat form", based on ^{1}H NMR information, for the *N*-(tetrahydroxy-α-D-glucopyranosyl)pyridinium ion (**B1** or **B2**, Scheme 3.2.10) cannot be accounted for by the electrostatic interpretation because **B2** is "apparently stabilized even though the positive charge has moved away from the negative end of the dipole". So, Perrin suggested that "this electrostatic interpretation is not entirely satisfactory". However, the evidence in favour of **B2** does not appear to be conclusive, and in the same paper,[15] Perrin said "the variation with solvent is consistent with a contribution of a reverse anomeric effect arising from monopole-dipole interactions".



B1 **B2**

Scheme 3.2.10

The nature of the reverse anomeric effect is still the topic of controversy. One of the arguments is that in those systems some other complicating factors may be concealing the truth. For example, in a 2-substituted (X) tetrahydropyran system, when X is trimethylammonio group (Scheme 1.3.2), Kirby and Williams[14b] pointed out that the trimethylammonio group is bulky, being sterically equivalent to *t*-butyl group. Such a bulky group will make it impossible to stay axial. Also in a solvent system like water, the high solvation of the positively charged nitrogen may be expected to greatly "enlarge" the size of the substituent. So, the steric effect is an important factor which has to be well understood before the nature of the reverse anomeric effect can be accepted by more people.

A 'normal' anomeric effect has also been found in some positively-charged systems. For example, 2-(trimethylphosphonio)-1,3-dithiane (**2**)[85] was shown to have a 2:1 preference for axial $^{+}PMe_3$ despite a steric repulsion estimated as 1.8 kcal/mol (Scheme 3.2.11).

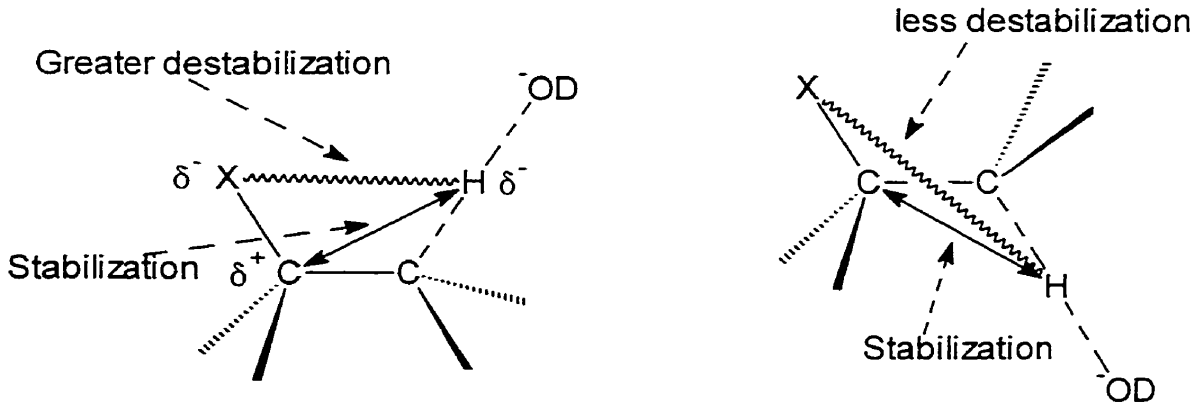
Scheme 3.2.11

Thus, although electrostatic attraction can explain the reverse anomeric effect, this effect simply cannot be explained by the n – σ* delocalization, which is currently the most favoured explanation to account for the anomeric effect in general. In view of the questions and counterexamples, the reverse anomeric effect is under reinvestigation.[15]

3.2.4.2 The Monopole Nature of the C—N^+ Bond and its Influence on the Field Effect

As part of our analysis of electronic effects of a substituent, we have carried out calculations of the variation of field effect with the torsion angle of (a) a dipole-dipole interaction and (b) a dipole-monopole interaction, using the classic treatments of Kirkwood and Westheimer[86] and Bjerrum.[87] We are immediately struck by the result that the variations with torsion angle are reversed (Figure 3.2.5). For a dipole, as mentioned before (see Section 2.2.4), the maximum stabilization by the field effect occurs when the H_α-C_α-C_β-X torsion angle is 0° and the minimum stabilization when the torsion angle is 180°; the partial negative charge on X actually **de**stabilizes the developing negative charge, while the partial positive charge on the carbon stabilizes it. On the other hand, for the monopole, the positive charge on N^+ stabilizes the partial negative charge (developed in the transition state) the most at the 0° H_α-C_α-C_β-X torsion angle while the least at the

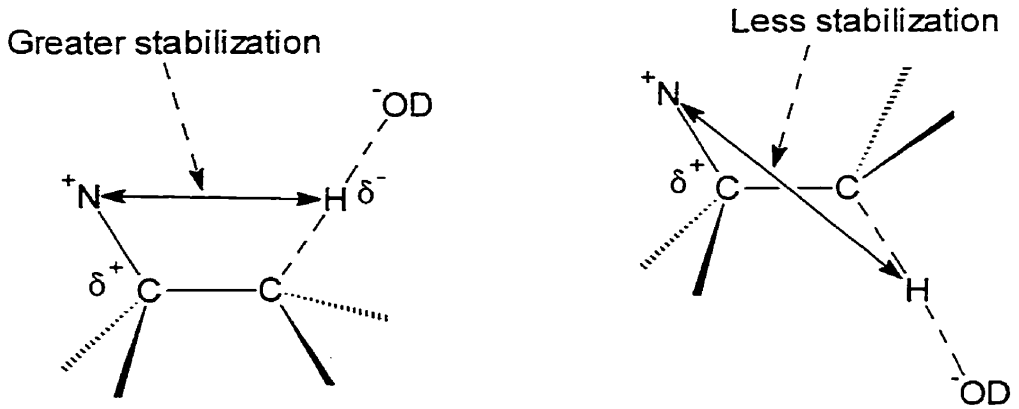
180° H_α-C_α-C_β-N^+ torsion angle. Note, it is by no means obvious where the negative charge is located in the transition state, and in Figure 3.2.5 it is centered on the leaving hydrogen atom only as a reasonable approximation.



DIPOLE

0° torsion angle
Greater **de**stabilization from X

180° torsion angle
Less **de**stabilization from X



MONOPOLE

0° torsion angle
Greater stabilization from N^+

180° torsion angle
Less stabilization from N^+

Figure 3.2.5 The different field effects between monopole and dipole. Note: the influence of the carbon bearing the X or N^+ does not change with the torsion angle.

The question is how much difference in the field effect, in the monopolar system as described above, can be made by changing the H_α-C_α-C_β-X torsion angle. For a monopole, the influence of the charge at the α-C on the negative charge of the reacting center - the position of the α-H for simplicity - stays constant in terms of field effect. Therefore, we can say that the stabilization difference comes from the positive charge at the N^+. One can show[86, 87] that the free energy of charges, q_1 and q_2, separated by a distance r, is equal to $q_1 q_2 / (D_{eff} r)$, where D_{eff} is a parameter related to effective dielectric constant (D_E): $D_{eff} = 4 \pi \varepsilon_0 D_E$; ε_0 is the permittivity of free space. For 1 mol of molecules, we have

$$\Delta E = (N q_1 q_2) / (4 \pi \varepsilon_0 D_E r), \qquad \text{eq 3.2.12}$$

where N is 6.01×10^{23} mol^{-1}, Defining $k_N = k / k_0$, where k_0 is the rate without any influence of the field effect, while k is the rate with the influence from the field effect, for T = 25°C = 298 K, we have

$$\Delta E = RT \ln k_N. \qquad \text{eq 3.2.13}$$

Therefore,

$$\log_{10} k_N = (N q_1 q_2) / (9.212 \pi \varepsilon_0 D_E r RT). \qquad \text{eq 3.2.14}$$

In the present situation, the magnitude of the charge on nitrogen is taken to be equal to that of the electron, 1.60×10^{-19} C. The developing anionic charge can be regarded as approximately 0.75 of an electron charge, or $0.75 \times 1.60 \times 10^{19}$ C, and ε_0 is 8.854×10^{-12} $C^2 N^{-1} m^{-2}$ (see the discussion of the field effect of a dipole in Appendix A). An estimation of the distance (r) between N^+ and the reacting center, depending on the H_α-C_α-C_β-N^+ torsion angle, was obtained by a PCModel calculation on trimethylethylammonium model system (Figure 3.2.5). For different values of D_E, the values of log k_N can be

calculated (Table 3.2.5). The torsion angle dependence of the field effect both in our alkoxy system (as is described in Chapter 2) and in our ammonio system are displayed in Figure 3.2.6.

From Figure 3.2.6, it is clearly shown that in our ammonio system the stabilization due to the field effect will be the smallest at the 180° torsion angle and greatest at the 0° torsion angle; the difference of $\log_{10} k_N$ between them is greatly influenced by the dielectric constant (D_E). For example, if D_E should be equal to 4 (which gives a reasonable value for the evaluation of the field effect in a dipole system in Appendix B), we have $\log_{10} k_N = 4.4$, indicating a huge rate difference due to the field effect. If D_E is 10 on the other hand, we get $\log_{10} k_N = 1.76$ (or $k_N = 57$); and even if D_E is 15, the influence of the field effect on the reaction rate ($k_N = 15$) is still not trivial. It is difficult to obtain an accurate value for the effective dielectric constant (D_E) for the actual space between the N^+ and the reacting center. For a vacuum, D_E is 1; in a solvent system, the maximum value for D_E is presumably to be that of the solvent.

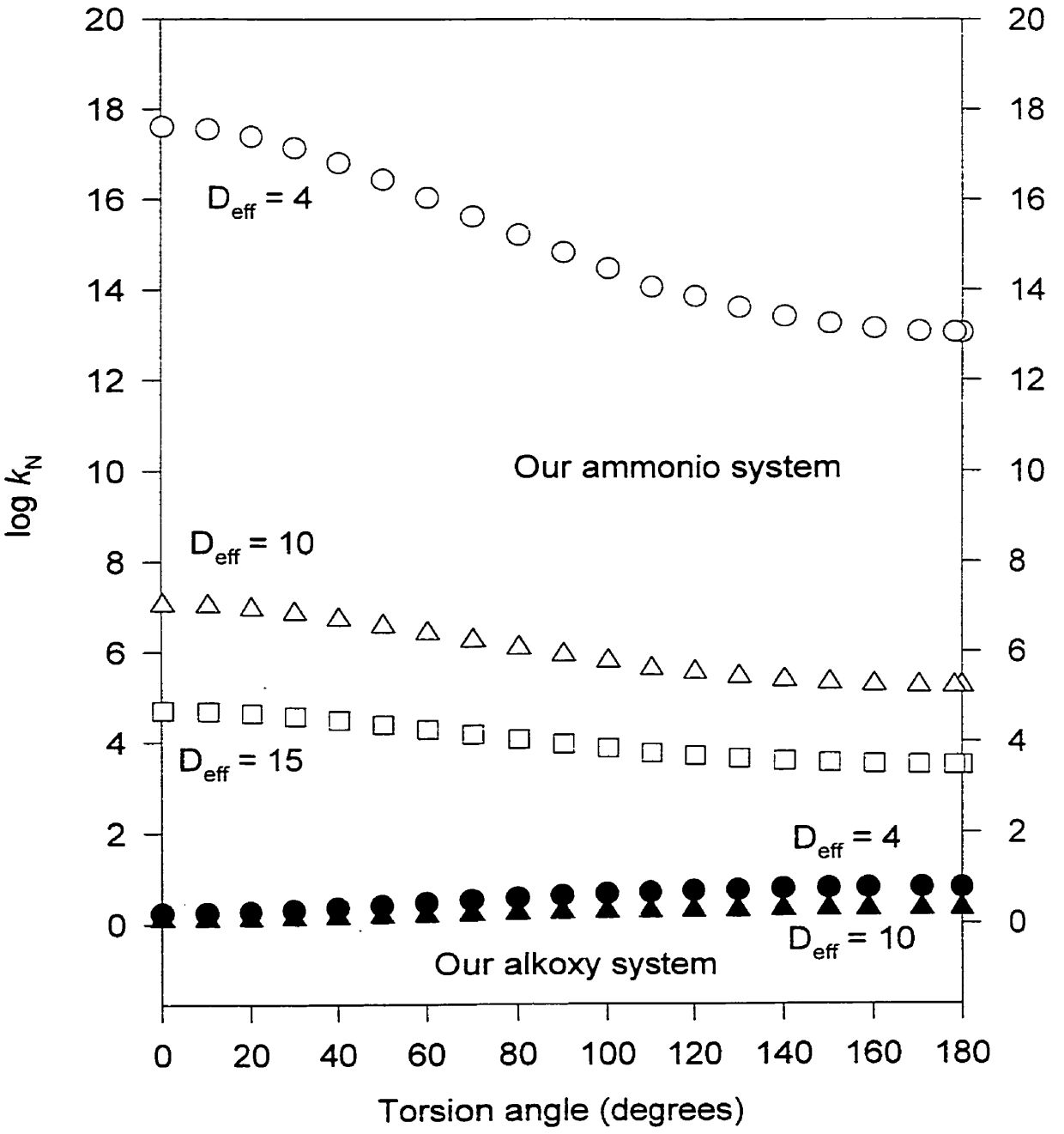


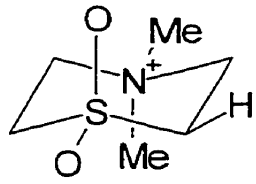
Figure 3.2.6 The angle dependence of the field effect in a dipole-dipole (filled symbols) and a monopole-dipole (unfilled symbols) systems.

Table 3.2.5 The angle dependence of the field effect in the ammonium monopole system.

Torsion angle (°)	R (Å)	log k_N		
		if $D_E = 4$	if $D_E = 10$	if $D_E = 15$
180	3.539	13.06	5.22	3.48
178.28	3.538	13.06	5.22	3.48
170.28	3.533	13.08	5.23	3.49
160.28	3.515	13.15	5.26	3.51
150.28	3.486	13.25	5.30	3.53
140.28	3.445	13.41	5.36	3.58
130.28	3.395	13.61	5.44	3.63
120.28	3.335	13.85	5.54	3.69
110.28	3.286	14.06	5.62	3.75
100.28	3.194	14.467	5.79	3.86
90.28	3.117	14.82	5.93	3.95
80.28	3.037	15.21	6.09	4.06
70.28	2.958	15.62	6.25	4.17
60.28	2.881	16.04	6.42	4.28
50.28	2.81	16.44	6.58	4.38
40.28	2.748	16.81	6.73	4.48
30.28	2.695	17.14	6.86	4.57
20.28	2.656	17.40	6.96	4.64
10.28	2.632	17.56	7.022	4.68
0.28	2.623	17.62	7.046	4.70

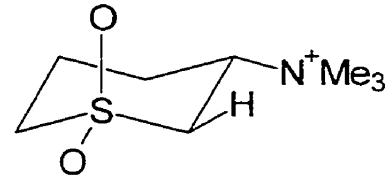
3.2.4.3 The Substituent Effect in the Ammonio System

From Table 3.2.1, we see that the k_N value for the 180° H_α-C_α-C_β-N^- torsion angle compound ($(\mathbf{N^+})_{180}$) reacted much faster than that for the 60° one ($(\mathbf{N^+})_{60}$); this is clearly not a 'reverse anomeric effect'.



$(\mathbf{N^+})_{180}$

$\log k_N = 9.18$



$(\mathbf{N^+})_{60}$

$\log k_N = 5.50$

The observation $(k_N)_{60} << (k_N)_{180}$ is not consistent with a field effect as described in Section 3.2.4.2 (which requires $(k_N)_{60} << (k_N)_{180}$, see Figure 3.2.6). It is also not consistent with the classical inductive effect, which requires $(k_N)_{60} = (k_N)_{180}$. It is, however, fully consistent with the anomeric effect (negative hyperconjugation). That is to say the negative hyperconjugation is the **major** contributor to k_N when $\theta \approx 0$ or 180°. The present results do not allow any decision as to whether the field effect is substantial or negligible. In light of the calculations embodied in Figure 3.2.6, it would seem likely that a substantial variation in field effect would accompany changes in torsion angle in, for example, 1-ammonio sugars.

Comparing our ammonio system with Lemieux and Morgan's system[83] (Scheme 3.2.8 and 3.2.9), or with most examples mentioned under the topic of 'reverse anomeric effect', we realize that the most favorable arrangement for anomeric effect or hyperconjugative stabilization (in $(\mathbf{N^+})_{180}$) does not require placing the ammonio group into an axial conformation. The complicating factor from steric effect (see Kirby and

William's argument in section 3.2.4.1) does not apply to our system. Also our system is much simpler, and thus, decreases the possibility of other complicating factors. As has been mentioned in section 3.2.4.1, Perrin mentioned a stable 'boat' conformation (**B2** in Scheme 3.2.10) that cannot be explained by the 'electrostatic interpretation'. We notice that this example is too complicated to serve as a good counter-example to the electrostatic explanation. The evidence in favor of **B2** over **B1** does not appear to be conclusive. In **B1** an obvious complicating factor may come from the oxygen at C_2. The partially negative charged oxygen at the C_2 may stabilize the positive charge (by the field effect) differently at different conformations. For example, the distance between the partially negative oxygen and the positive ammonio group, in the **B1** conformation, is obviously very close, and extra stabilization may result from this.

In summary, the total polar effect may be described as the sum of three effects: (a) an angle dependent negative hyperconjugation (or generalized anomeric effect) which stabilizes the reacting center to the same extent in the conformation with a 0° H_α-C_α-C_β-N^+ torsion angle and in that with a 180° torsion angle, but with a minimum at the 90° torsion angle; (b) an angle dependent field effect which is expected to yield a higher stabilization for the conformation with a 0° H_α-C_α-C_β-N^+ torsion angle than that with a 180° torsion angle; and (c) an angle independent inductive effect. Based on this, the cosine line for the ammonio system in Figure 3.2.3 may not be appropriate because it ignores the field effect which may be important in a monopole system, as discussed above. A more reasonable plot for the ammonio system should be the addition of the cosine line as shown in Figure 3.2.3 and a pattern similar to what is displayed in Figure 3.2.6. An illustration is shown in Figure 3.2.7.

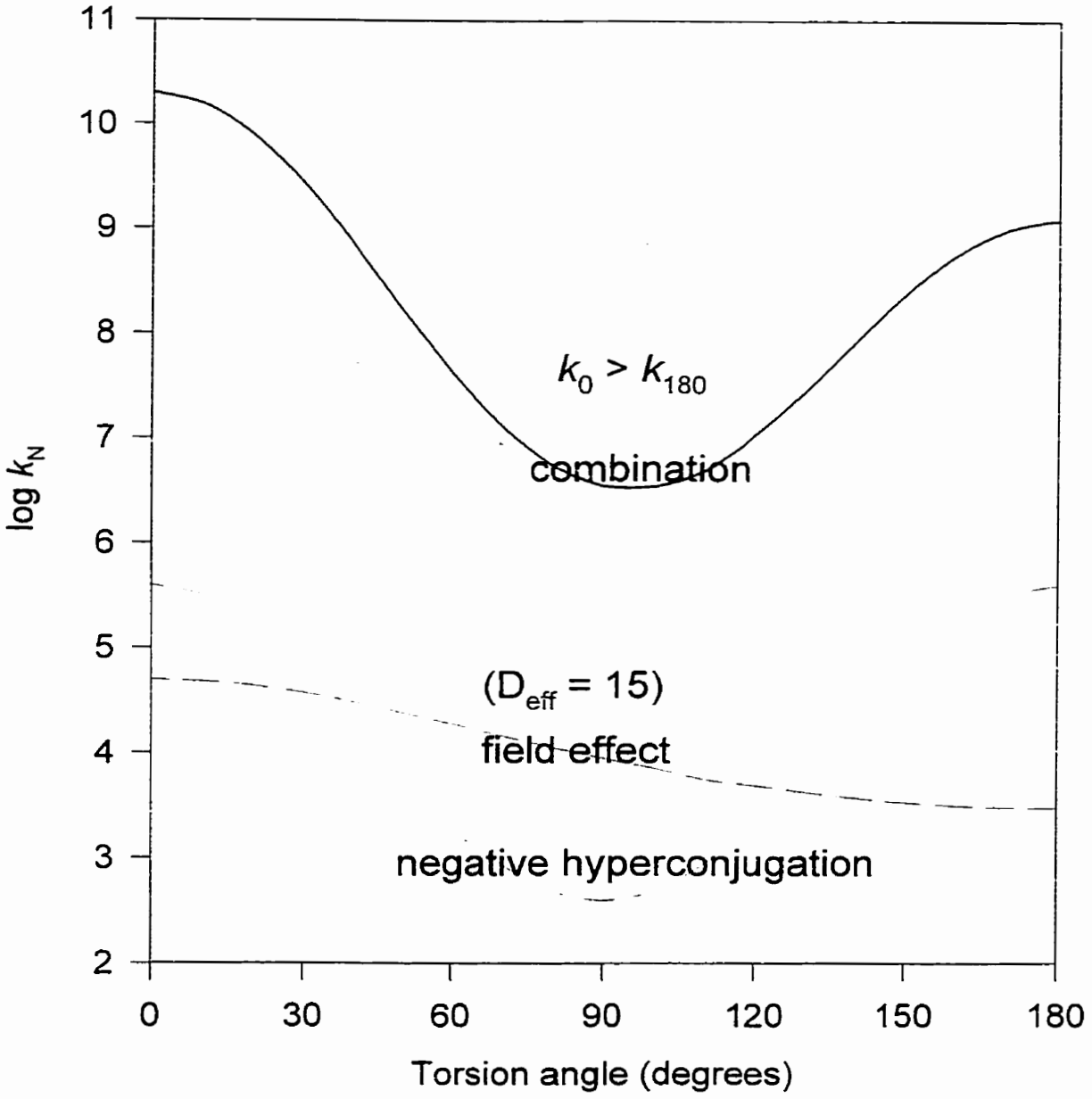


Figure 3.2.7 An illustration of angle dependence of combination of field effect and negative hyperconjugation in ammonio system. Experiments designed to shed light on this matter are currently underway in this laboratory.

3.3 CONCLUSION

A strong dependence on the H-C-C-X torsion angle of a substituent has been found experimentally for beta OR, SR, NR_2, SO_2R, and N^+R_3 substituents. By extension, we can infer from these observations that the torsion angle dependence is a general phenomenon, capable of appearing to a greater or lesser measure with *all* substituents. The effect can be small or negligible with some substituents (e.g. alkyl groups), but with most heteroatomic substituents it must be significant.

Similarly, we can infer that the angle dependence of σ^* is general. The value of σ^*_θ reaches its maximum at 0° or 180° torsion angle, and drops to its minimum at 90°; and the traditional term, σ^*, probably represents a weighted average involving different conformers each with its own torsion angle (θ) and hence, each with different reactivity. This may explain why a different σ^* value is found in different literature sources for the same substituent.

In our positively charged ammonio system, the 180° H_α-C_α-C_β-N^+ torsion angle compound ($(\mathbf{N^+})_{180}$) exchanged much faster than that for the 60° one ($(\mathbf{N^+})_{60}$). This is not consistent with a field effect, and also not consistent with the classic inductive effect. It is clearly not a 'reverse anomeric effect'. It is, however, fully consistent with the normal anomeric effect (negative hyperconjugation), and the negative hyperconjugation is the major contributor to k_N when $\theta \approx 0$ or 180°. Therefore, any discussion on the 'reverse anomeric effect' has to include a strong normal anomeric effect (negative hyperconjugation) as a factor.

3.4 EXPERIMENTAL

3.4.1 PREPARATION OF SULFONES

The general procedure and instrumentation are as described in the experimental part of Chapter 2.

N-Methylthiomorpholine 1,1-dioxide ($\mathbf{N_{180}}$) was obtained directly from Lancaster Synthesis Ltd. Tetrahydrothiapyran was obtained from Aldrich Chemical Company, Inc.

Preparation of 1,4-Dithiane, 1,1-dioxide ($\mathbf{S_{180}}$)[76]

To a rapidly stirred solution of 1,4-dithiane (3.0 g, 25.0 mmol) in chloroform (200 mL) maintained at -20 °C in an dry ice/acetone bath under a nitrogen atmosphere, a solution of 85% *m*-chloroperbenzoic acid (5.58 g, 27.4 mmol) in chloroform (150 mL) was added slowly. The resulting solution was stirred at -20 °C for another 1.5 h and then was warmed slowly to room temperature and then kept there for an additional 2 h. Anhydrous ammonia was bubbled into the reaction mixture, and the resulting white precipitate, ammonium *m*-chlorobenzoate, was removed by filtration. The filtrate was treated with ammonia a few more times, and filtered again. The filtrate was then concentrated under reduced pressure to give a white solid. By comparing its ^{13}C NMR spectrum with reported ^{13}C NMR information,[76] it was concluded that the white solid was a mixture of 1,4-dithiane 1-oxide (~ 40%), 1,4-dithiane 1,4-dioxide (~ 30%) and 1,4-dithiane (~ 30%).

A solution of the mixture obtained above (0.60 g), magnesium sulfate (1.5 g, 12.5 mmol) in acetone (80 mL) in a round-bottom flask was cooled to -30 °C in a dry ice/acetone bath. Potassium permanganate (0.47 g, 3.0 mmol) in acetone (100 mL) was

added slowly with constant stirring. After the addition was complete, the reaction mixture was kept at -30 °C for another 90 min and then warmed to room temperature. Excess sodium metabisulfite ($Na_2S_2O_5$) was then added and the mixture stirred for a few minutes. The solution was filtered and the removal of solvent gave a white solid (400 mg). Thick layer chromatography (4:1 methylene chloride/ethyl acetate, silica gel) and then recrystallization from chloroform gave pure $\mathbf{S_{180}}$ (360 mg); mp 202 - 204 °C; ^{1}H NMR ($CDCl_3$) δ 3.05-3.20 (m, 4H), 3.20-3.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 54.1, 27.7; These data are consistent with the reported values.[76]

Preparation of 1,4-Dithiadecalin 1,1-dioxide ($\mathbf{S'_{180}}$)

a) *trans*-2-(2-Hydroxyethylthio)cyclohexanol[77]

Cyclohexene oxide (12.5 g, 128 mmol) was added dropwise to a solution of mercaptoethanol (10.0 g, 128 mmol) and potassium hydroxide (7.2 g, 128 mmol) in methanol (100 mL). The reaction mixture was stirred at room temperature for 12 h. Workup as usual gave *trans*-2-(2-hydroxyethylthio)-cyclohexanol as a white solid (20.5 g, 90% yield); mp 45-47 °C (lit.[77] 45-48 °C); ^{1}H NMR ($CDCl_3$) δ 1.2-1.5 (m, 4H), 1.6-1.9 (m, 2H), 2.0-2.2 (m, 2H), 2.43 (m, 1H), 2.79 (m, 2H), 3.34 (m, 1H), 3.75 (t, $J = 6$ Hz, 2H), 4.01 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 24.4, 26.3, 33.5, 33.9, 34.3, 53.2, 61.7, 73.4.

b) *trans*-2-Chlorocyclohexyl 2-chloroethyl sulfide[31]

trans-2-(2-Hydroxyethylthio)-cyclohexanol (5 g, 28.4 mmol) in 1,2-dimethoxyethane (DME, 10 mL) was added to concentrated hydrochloric acid (25 mL) and the reaction mixture was stirred overnight. The usual workup gave

trans-2-chloro-cyclohexyl 2-chloroethyl sulfide as a colorless liquid in quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.22-1.85 (m, 6H), 2.16-2.35 (m, 2H), 2.86 (m, 1H), 2.99 (m, 2H), 3.65 (m, 2H), 3.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 24.0, 31.6, 34.4 (double intensity), 43.2, 51.3, 64.0.

c) *trans*-1,4-Dithiadecalin[78]

trans-2-Chlorocyclohexyl 2-chloroethyl sulfide (3.6 g, 20 mmol), $Na_2S{\cdot}9H_2O$ (8.2 g, 34 mmol), ethanol (600 mL), and water (200 mL) were mixed and refluxed for 6 h. Ice-water (600 mL) was added and the precipitate was removed by filtration. The precipitate was recrystallized from ethanol : water and sublimation (70 °C, 1.2 torr) gave *trans*-1,4-dithiadecalin (1.05 g, 60% yield) as white crystals. The *trans* stereochemistry about the C9, C10 ring junction has been determined from the method of synthesis;[78] mp 72-74 °C (lit.[78] mp 77-78 °C, and lit.[79] mp 72-72.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.0-2.0 (m, 8H), 2.5-3.5 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.4, 31.2, 32.7, 47.1 ; these data are consistent with reported values.[79]

d) *trans*-1,4-Dithiadecalin 1-oxide[79]

Peroxybenzoic acid (~ 75%, 460 mg, 2.5 mmol, freshly prepared from benzoic acid and hydrogen peroxide by the literature method[80]) in $CHCl_3$ (15 mL) was added to a solution of *trans*-1,4-dithiadecalin (400 mg, 2.3 mmol) in $CHCl_3$ (20 mL) maintained at -20 °C in an acetone/dry ice bath under a nitrogen atmosphere. The solution was stirred for 1.5 h and then warmed to room temperature for an additional 2 h. Workup as usual gave a white solid (380 mg). Comparison of its ^{13}C NMR spectrum with the information

given by Rooney and Evans.[79] indicated it to be a mixture of *trans*-1,4-dithiadecalin 1-*exo*-oxide (~ 35%), *trans*-1,4-dithiadecalin 1-*endo*-oxide (~ 35%), and an unidentified material. This mixture was used without further separation. ^{13}C NMR for the equatorial isomer ($CDCl_3$) δ 24.9 (C6), 25.1 (C7), 25.4 (C3), 26.8 (C8), 31.4 (C5), 43.2 (C10), 52.4 (C2), 67.9 (C9); ^{13}C NMR for the axial isomer ($CDCl_3$) δ 17.9 (C3), 25.5 (C6), 25.7 (C7), 28.3 (C8), 31.9 (C5), 34.0 (C10), 47.2 (C2), 59.7 (C9); the equatorial and axial configurations and ^{13}C NMR signals were those assigned by Rooney and Evans.[79]

e) *trans*-1,4-Dithiadecalin 1,1-dioxide (S'_{180})[79]

To the solution of acetone (20 mL) containing the mixture obtained above (350 mg, approximately 1.29 mmol of equatorial and axial sulfoxides), magnesium sulfate (625 mg, 5.2 mmol) was added and cooled to -30 °C. $KMnO_4$ (195 mg, 1.23 mmol) in acetone (25 mL) was added slowly with constant stirring. After the addition was complete, the reaction mixture was kept at -30 °C for another 90 min and then warmed to room temperature. Excess sodium metabisulfite ($Na_2S_2O_5$) was then added and the mixture stirred for a few minutes. The solution was filtered and the removal of solvent from the filtrate gave a yellowish solid. This solid was then dissolved in methylene chloride, washed with water, and then the organic layer dried over $MgSO_4$. The solvent was removed to give a white solid. Separation by column chromatography (using alumina as the solid phase and hexane, methylene chloride, and ethyl acetate in sequence as the eluents) gave pure $\mathbf{S'_{180}}$ (178 mg, 0.86 mmol); mp 138-142 °C (lit.[79] mp 138-142 °C); ^1H NMR ($CDCl_3$) δ 1.2-2.4 (m, 8H), 2.79 (symmetric m, 1H), 2.96 (symmetric m, 1H), 3.10-3.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.2 (C8), 24.5 (C6), 25.2

(C7), 26.5 (C3), 31.1 (C5), 44.1 (C10), 53.6 (C2), 68.0 (C9); the ^{13}C NMR assignments are those given by Rooney and Evans.[79]

Preparation of 1,4-dithiadecalin 1,1,4,4-tetraoxide ($(SO_2)_{180}$)

trans-1,4-Dithiadecalin (50 mg) and hydrogen peroxide (30%, 4 mL) in acetic acid (2 mL) was refluxed for 30 min. After the resulting solution was cooled down slowly, white crystals precipitated out. The precipitate was filtered and washed with a large amount of water and dried to give **$(SO_2)_{180}$** (40 mg, 85% yield). mp 195-210 °C (with sublimation), 289 -291 °C (determined in a sealed capillary, lit.[78] 288 °C); ^1H NMR ($CDCl_3$) δ 1.25-1.45 (m, 2H), 1.55-1.75 (m, 2H), 1.88-2.05 (m, 2H), 2.24-2.38 (m, 2H), 3.29-3.42 (m, 2H), 3.40-3.53 (m, 2H), 3.68-3.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2, 23.3, 49.0, 61.6.

Preparation of 3-(methylsulfonyl)tetrahydrothiapyran 1,1-dioxide (S_{60})

(a) 3-Bromotetrahydrothiapyran 1,1-dioxide[81]

A suspension of alcohol-free sodium ethoxide (freshly prepared from 3.34 g of sodium) in dry ether (80 mL) was cooled in an ice bath, while ethyl γ-(carbethoxymethyl-mercapto)butyrate was added dropwise to the mechanically stirred suspension over a 30 min period. The mixture was stirred in the ice bath for another hour, after which it was treated with a mixture of glacial acetic acid (10 mL) and ice water (60 mL). The aqueous solution was separated and extracted with ether (3 × 40 mL). The combined ether layer was washed with aqueous sodium bicarbonate, dried over anhydrous $MgSO_4$ and distilled to give 2-carbethoxytetrahydrothiapyran-3-one as a colorless oil (80% yield); bp 100 -

102 °C / 0.6 - 0.8 torr (lit.[81] bp 117 - 120 °C / 4 torr).

A mixture of 2-carbethoxytetrahydrothiapyran-3-one (8.0 g, 42.5 mmol) and 10% of sulfuric acid (60 mL) was refluxed for 6 h, after which it was cooled and the layers were separated. The aqueous layer was extracted several times with ether and the extracts were added to the original oil layer. The ether solution was washed with sodium bicarbonate solution, water and then dried over magnesium sulfate. Fractional distillation of the ether solution gave tetrahydrothiapyran-3-one as a colorless liquid (72.3% yield); bp 66 - 68 °C / 3.8 torr (lit.[81] bp 101 - 102 °C / 18 torr); ^{1}H NMR ($CDCl_3$) δ 2.35-2.50 (m, 4H), 2.65 - 2.80 (m, 2H), 3.16 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.4, 38.6, 41.8, 203.8.

Sodium borohydride (0.17 g, 4.5 mmol) was added to a solution of tetrahydrothiapyran-3-one (0.5 g, 4.3 mmol) in methanol (15 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, and then 5% of H_2SO_4 was added. The resulting mixture was extracted with methylene chloride three times, and the combined organic layer was washed first with sodium bicarbonate, then with saturated sodium chloride and finally dried over magnesium sulfate. Fractional distillation gave tetrahydrothiapyran-3-ol (0.47 g, 92.4% yield); bp 76 - 78 °C / 2 torr (lit.[81] bp 76 - 78 °C / 2 torr).

Freshly distilled phosphorus tribromide (1.62 g, 6.0 mmol) was added slowly to tetrahydrothiapyran-3-ol (1.77 g, 15.0 mmol) while the mixture was stirred vigorously and cooled to about 10 °C by an ice bath. After that, the viscous mixture was warmed to 70 °C and then allowed to cool to room temperature. Water was added and the resulting mixture was extracted with ether several times. The combined ether layer was washed

with aqueous sodium bicarbonate and dried over magnesium sulfate. Fractional distillation gave 3-bromotetrahydrothiapyran as a colorless liquid (1.90 g, 70% yield): bp 68 - 69 °C / 4 torr (lit.[81] bp 68 - 69 °C / 4 torr).

To a solution of 3-bromotetrahydrothiapyran (1.81 g, 10 mmol) in chloroform (80 mL), was added peroxybenzoic acid (about 75%, 4.65 g, 25 mmol, freshly prepared from benzoic acid and hydrogen peroxide by the literature method[80]) in chloroform (100 mL), while cooling in an ice bath to keep the temperature below 30 °C. The mixture was then stirred at room temperature for 3 h, after which, it was heated slowly to boiling and then allowed to cool to room temperature. The chloroform solution was freed of acid by washing with aqueous sodium bicarbonate several times. Removal of solvent gave a semicrystalline residue, which was then recrystallized from benzene : hexane to give 3-bromotetrahydrothiapyran 1,1-dioxide as pale yellow crystals; mp 89.5 - 91 °C (lit.[81] mp 90-91 °C); ^{13}C NMR ($CDCl_3$) δ 23.0, 35.3, 40.7, 50.4, 60.2.

(b) 3-(Methylthio)tetrahydrothiapyran 1,1-dioxide (S_{60})

The solution of 3-bromotetrahydrothiapyran 1,1-dioxide (350 mg, 1.64 mmol) and sodium thiomethoxide (173 mg, 2.46 mmol) in 2-butanol (30 mL) was refluxed for 1 h under a nitrogen atmosphere. Workup as usual and recrystallization from ethyl acetate : hexane gave **S_{60}** as white needles (210 mg, 71% yield); mp 94 - 95 °C; ^{1}H NMR ($CDCl_3$) δ 1.3-1.5 (m, 1H), 2.0-2.5 (m, 3H), 2.14 (s, 3H), 2.5-3.2 (m, 4H), 3.2-3.5 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 23.1, 30.8, 41.1, 50.8, 56.8; Calcd. exact mass for $C_6H_{12}O_2S_2$: 180.0279. Found: 180.0276.

(c) 3-(Methylsulfonyl)tetrahydrothiapyran 1,1-dioxide ($(SO_2)_{60}$)

3-(Methylthio)tetrahydrothiapyran 1,1-dioxide (230 mg, 1.28 mmol), glacial acetic acid (~1 mL) and hydrogen peroxide (30%, about 2 mL) were mixed and heated to 100°C for 15 min. After the reaction mixture was cooled, water (30 mL) was added and the mixture extracted with methylene chloride (5 × 40 mL). The combined methylene chloride layer was then washed with 5% of aqueous NaOH (2 × 30 mL), saturated NaCl (2 × 60 mL). Removal of the solvent and recrystallization from ethanol gave **$(SO_2)_{60}$** as white crystals (57 mg, 21% yield); mp 210.5 - 212 °C; ^{1}H NMR ($CDCl_3$) δ 1.20-1.30 (m, 1H), 2.05-2.50 (m, 3H), 2.94 (s, 3H), 3.05-3.25 (m, 2H), 3.40-3.60 (m, 2H), 4.0-4.2 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.5, 38.6, 49.8, 50.8, 59.1; exact mass for $C_6H_{13}O_4S_2$ (M+1) : 213.0255. Found: 213.0261.

Preparation of 4,4-dimethyltetrahydro-1,4-thiazinium iodide ($(N^+)_{180}$)

N-Methylthiomorpholine 1,1-dioxide (**N_{180}**, 50 mg, 0.34 mmol) and methyl iodide (238 mg, 1.68 mmol) were mixed in methanol (1 mL) and stirred overnight at room temperature. Ether (~ 5 mL) was added and the precipitate was filtered and washed with ether to give **$(N^+)_{180}$** as a while solid (80 mg, 82% yield); ^{1}H NMR (D_2O) δ 3.2 (s, 6H), 3.5-3.7 (m, 4H), 3.8-4.0 (m, 4H); Calcd. exact mass for $C_6H_{14}NO_2S$ (M^-): 164.0745. Found: 164.0739.

Preparation of 3-(dimethylamino)tetrahydrothiapyran (N_{60})

a) 4*H*-2,3-dihydrothiapyran 1,1-dioxide[82]

Neat tetrahydrothiapyran (5.0 g, 48.9 mmol) was cooled at 0 °C with vigorous

stirring while 30% of hydrogen peroxide was added slowly. After the addition was complete, the mixture was stirred at room temperature overnight. Workup as usual gave tetrahydrothiapyran-1-oxide (4.67 g, 81% yield). ^{1}H NMR ($CDCl_3$) δ 1.2 - 1.8 (m, 4H), 1.9 - 2.4 (m, 2H), 2.5 - 3.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.8, 24.4, 48.7.

A solution of tetrahydrothiapyran 1-oxide (1.5 g, 12.7 mmol) in acetic acid (6 mL) at 110 °C was treated with acetic anhydride (4.5 mL, 38.3 mmol) dropwise with stirring over a period of 45 min. After complete disappearance of the sulfoxide, as detected by thin-layer chromatography, the reaction mixture was diluted with ether (50 mL) and the excess acetic acid and acetic anhydride neutralized with 10% sodium bicarbonate. The ether layer was separated and dried over magnesium sulfate. Fractional distillation gave 4*H*-2,3-dihydrothiapyran (1.14 g, 90% yield); bp 65 - 67 °C / 55 torr (lit.[82] bp 65 - 66 °C / 57 torr); ^{1}H NMR ($CDCl_3$) δ 1.85 - 2.25 (m, 4H), 2.70 - 3.00 (m, 2H), 5.65 - 5.75 (m, 1H), 5.90 - 6.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.6, 26.1, 119.0, 121.1.

OXONE® (potassium peroxymonopersulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 3.68 g, 6.0 mmol) in water (15 mL) was added to a solution of 4*H*-2,3-dihydrothiapyran (0.40 g, 4.0 mmol) in methanol (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and then stirred for 4 h. Workup as usual gave 4*H*-2,3-dihydrothiapyran 1,1-dioxide (0.50 g, 95% yield) as white crystals; mp 44 - 46 °C (lit.[82] mp 45 - 46 °C); ^{1}H NMR ($CDCl_3$) δ 2.20-2.60 (m, 4H), 3.00-3.30 (m, 2H), 6.25-6.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.5, 24.6, 50.5, 129.8, 138.6.

b) 3-(Dimethylamino)tetrahydrothiapyran 1,1-dioxide (N_{60})

4*H*-2,3-Dihydrothiapyran 1,1-dioxide (50 mg, 0.38 mmol) and dimethylamine

(1 mL) were sealed in a NMR tube and kept at room temperature for 2 da. The NMR tube was opened carefully while it was cooled in an ice bath. It was then warmed slowly to room temperature to let the excess dimethylamine evaporate. The residue was then dissolved in methylene chloride and washed with 10% hydrochloric acid, 5% sodium hydroxide, saturated sodium chloride, and then dried over magnesium sulfate. Removal of the solvent gave $\mathbf{N}_{60}$ as a white solid in an almost quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.25-1.50 (m, 1H), 1.80-2.02 (m, 2H), 2.02-2.17 (m, 1H), 2.23 (s, 6H), 2.70-2.85 (m, 2H), 2.90-3.05 (m, 2H), 3.10-3.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 27.3, 40.5, 51.1, 52.2, 60.4.

Preparation of 3-(trimethylammonio)tetrahydrothiapyran 1,1-dioxide ($(\mathbf{N}^+)_{60}$)

Methyl iodide (100 mg, 0.70 mmol) was added to a solution of 3-(dimethyl-amino)tetrahydrothiapyran 1,1-dioxide ($\mathbf{N}_{60}$, 20 mg, 0.11 mmol) in methanol (2 mL) and the reaction mixture was stirred overnight at room temperature. Diethyl ether (5 mL) was added and the precipitate was collected by filtration and rinsed with ether to give $(\mathbf{N}^+)_{60}$ as a white solid (31 mg, 86% yield); ^{1}H NMR ($CDCl_3$) δ 1.50-1.85 (m, 2H), 2.15-2.40 (m, 2H), 2.90 (s, 9H), 2.85-3.20 (m, 2H), 3.36-3.52 (m, 1H), 3.66-3.80 (m, 2H); Calcd. exact mass for $C_8H_{18}NO_2S$ (M^+): 192.1058. Found: 192.1058.

3.4.2 KINETIC MEASUREMENTS OF H-D EXCHANGE

The general procedure are as described in the experimental part (Section 2.5.2.1) of chapter 2. The results are listed in Table 3.4.1

Table 3.4.1 The Pseudo-first-order Rate Constants for H-D Exchange.

	T (°C)	solvent	NaOD (M)	k_{obs} (s^{-1})	calculated k_{exch} ($M^{-1} s^{-1}$)	average k_{exch} ($M^{-1} s^{-1}$)
S_{180}	25	Dioxane-d_8 : D_2O (1 : 1)	0.050	1.5×10^{-3}	3.0×10^{-2}	2.8×10^{-2}
			0.038	1.0×10^{-3}	2.6×10^{-2}	
S_{60}	25	Dioxane-d_8 : D_2O (1 : 1)	0.100	2.3×10^{-5}	2.3×10^{-4}	2.7×10^{-4}
			0.050	1.5×10^{-5}	3.0×10^{-4}	
$(SO_2)_{180}$	21	CD_3CN : D_2O (1 : 1)	6.606×10^{-8} (7.62) [b]	1.9×10^{-5}	2.9×10^{2}	2.6×10^{2}
			5.248×10^{-7} (8.52) [b]	1.2×10^{-4}	2.3×10^{2}	
$(SO_2)_{60}$	21	D_2O	1.002×10^{-4} (10.50) [b]	1.15×10^{-5}	1.15×10^{-1}	1.13×10^{-1}
			3.990×10^{-4} (11.10) [b]	4.39×10^{-5}	1.10×10^{-1}	
N_{180}	25	Dioxane-d_8 : D_2O (1 : 1)	0.150	3.92×10^{-4}	2.61×10^{-3}	2.60×10^{-3}
			0.100	2.59×10^{-4}	2.59×10^{-3}	
N_{60}	25	Dioxane-d_8 : D_2O (1 : 1)	0.200	3.3×10^{-5}	1.7×10^{-4}	1.6×10^{-4}
			0.100	1.5×10^{-5}	1.5×10^{-4}	

Table 3.4.1 Continued

$(N^+)_{180}$	20	D_2O	1.125×10^{-7} (7.55)[b] (3.7×10^{-2} M)[c]	1.69×10^{-4}	1.50×10^{3}	1.50×10^{3}
			5.902×10^{-8} (7.27)[b] (5.8×10^{-2} M)[c]	8.88×10^{-5}	1.50×10^{3}	
			3.556×10^{-8} (7.05)[b] (1.4×10^{-1} M)[c]	5.32×10^{-5}	1.49×10^{3}	
$(N^+)_{60}$	20	D_2O	3.990×10^{-4} (11.10)[b]	2.5×10^{-4}	6.3×10^{-1}	6.3×10^{-1}
			1.002×10^{-6} (8.50)[b]	6.3×10^{-7}	6.3×10^{-1}	
22	25	Dioxane-d_8 : D_2O (1 : 1)	0.100	3.2×10^{-7}	3.2×10^{-6}	3.1×10^{-6}
			0.050	1.5×10^{-7}	3.0×10^{-6}	

Note:

c) The values shown in parentheses are calculated values on a *per-hydrogen* basis.

d) The values shown in parentheses are pH readings for the buffers.

e) The values shown in parentheses are the concentration of phosphate ($[PO_4^{3-}]$).

APPENDIX A

The relative positions of X (O in our cases), (β-) C, (α-) C, (α-) H can be obtained from the calculation results from PCMODEL for the conformation depicted as Figure 2.2.2, and the results are listed in Table A.1. From the x, y, z coordinates, the values of ζ and r are readily obtained as follows.

The coordinates of M_α in case of Figure 2.2.5 (b):

$$x(M_\alpha) = (x_\alpha + x_H) / 2;$$

$$y(M_\alpha) = (y_\alpha + y_H) / 2;$$

$$z(M_\alpha) = (z_\alpha + z_H) / 2.$$

The coordinates of M_α in case of Figure 2.2.5 (c):

$$x(M_\alpha) = [(x_\alpha + x_H) / 2 + x_H] / 2 ;$$

$$y(M_\alpha) = [(y_\alpha + y_H) / 2 + y_H] / 2 ;$$

$$z(M_\alpha) = [(z_\alpha + z_H) / 2 + z_H] / 2.$$

The coordinates of M_β are:

$$x(M_\beta) = (x_\beta + x_O) / 2;$$

$$y(M_\beta) = (y_\beta + y_O) / 2;$$

$$z(M_\beta) = (z_\beta + z_O) / 2.$$

A general formula can be used to obtain the distance, say between point A and B (x and y represent the coordinates):

$$AB=\sqrt{(x_A-x_B)^2+(y_A-y_B)^2+(z_A-z_B)^2}.$$

In case of Figure 2.2.5 (a):

$$r_a=\sqrt{(x(M_\beta)-x_H)^2+(y(M_\beta)-y_H)^2+(z(M_\beta)-z_H)^2};$$

in case of Figure 2.2.5 (b) and (c):

$$r_b(r_c)=\sqrt{(x(M_\beta)-x(M_\alpha))^2+(y(M_\beta)-y(M_\alpha))^2+(z(M_\beta)-z(M_\alpha))^2}.$$

Now the distances can be used to calculate cos ζ. In case of Figure 2.2.5 (a) (see footnote) :

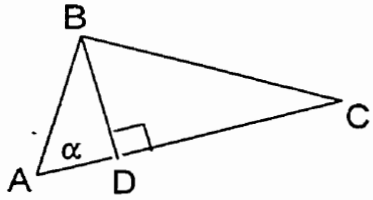
$$\cos\zeta=\frac{(M_\beta C_\beta)^2+(M_\beta H)^2-(C_\beta H)^2}{2(M_\beta C_\beta)(M_\beta H)};$$

while in case of Figure 2.2.5 (b) and (c):

$$\cos\zeta=\frac{(M_\beta C_\beta)^2+(M_\beta M_\alpha)^2-(C_\beta M_\alpha)^2}{2(M_\beta C_\beta)(M_\beta M_\alpha)}.$$

Footnote: the calculation of the cosine value of an angle in a triangle.

In a triangle ,



∵ AD = AB cos α, and DC = AC - AD,

$BD^2 = AB^2 - AD^2$, and $BD^2 = BC^2 - DC^2$

∴ $AB^2 - (AB \cos\alpha)^2 = BC^2 - (AC - AB \cos\alpha)^2$

simplifying the above equation will give:

$BC^2 = AB^2 + AC^2 - 2 \times AB \times AC \cos\alpha.$

Or: $\cos\alpha = (AB^2 + AC^2 - BC^2) / (2 \times AB \times AC).$

Table A.1 Coordinates for the relative positions of X (O in our cases), (β-) C, (α-) C, (α-) H obtained from the calculation results from PC MODEL for the conformation depicted as Figure 2.2.2

sulfone	X (O in our cases)			(β-) C			(α-) C			(α-) H		
	x_o	y_o	z_o	x_β	y_β	z_β	x_α	y_α	z_α	x_H	y_H	z_H
1	1.73	1.91	0.66	0.67	1.23	-0.01	-0.25	0.59	1.05	-0.16	1.18	1.99
2	0.35	-1.61	-2.28	-0.03	-0.61	-1.34	-0.26	-1.14	0.09	-0.20	-2.25	0.11
3	2.40	1.07	-0.60	1.06	0.59	-0.61	0.51	0.57	0.83	1.20	1.17	1.48
4	0.72	0.36	-0.57	0.54	-0.42	0.74	1.21	-0.08	1.56	-1.14	-0.32	1.34
5	-2.30	0.45	1.91	-0.92	0.38	1.57	-0.63	1.23	0.33	-0.90	2.29	0.56
6a	0.61	-0.27	-1.80	-0.34	0.16	-0.82	-0.04	-0.57	0.51	-0.15	-1.67	0.35
6b	0.15	0.18	-2.29	-0.75	-0.09	-1.21	-0.18	-1.26	-0.38	-0.10	-2.17	-1.02
7	0.63	-1.01	1.75	0.88	0.23	1.08	-0.48	0.93	0.83	-0.80	1.40	1.80
8	0.26	2.11	-1.26	0.43	0.71	-1.40	1.40	0.40	-0.24	2.39	0.79	-0.59
9	-0.35	0.43	-1.58	-0.98	-0.77	-1.14	-0.12	-1.48	-0.06	-0.05	-2.57	-0.32
10	1.48	-0.01	-0.18	1.38	1.26	-0.55	0.61	1.25	0.79	1.24	1.84	1.51
11	1.26	-0.21	-0.96	1.23	1.07	-0.33	0.36	1.01	0.95	0.85	1.70	1.69

Table A1 Continued.

sulfone	(β-) C			X (O in our cases)			(α-) C			(α-) H		
	x	y	z	x	y	z	x	y	z	x	y	z
12	-0.78	0.78	0.38	-0.97	-0.60	0.61	0.02	-1.24	-0.39	-0.32	-2.26	-0.71
13	-0.57	0.27	1.76	-1.42	0.70	0.69	-1.31	-0.28	-0.49	-2.04	-0.07	-1.30
14	1.18	0.64	-0.97	2.10	0.91	0.09	1.88	-0.06	1.24	2.64	0.01	2.06
15	1.55	0.04	-1.21	2.51	0.13	-0.15	2.17	-0.87	0.96	2.95	-0.93	1.75
16	0.28	0.04	-1.58	1.14	0.36	-0.50	0.79	-0.49	0.72	1.56	-0.28	1.49
17a	-0.15	0.01	-0.14	0.20	1.34	-0.66	-0.07	-0.90	-0.21	-0.34	-1.93	-0.14
17b	0.09	0.70	-1.53	-0.48	-0.60	-1.60	-0.37	-1.42	-0.30	-0.48	-2.49	-0.60

Note: The unit of length for the x, y, z coordinates is Å.

APPENDIX B

The Quantitative Evaluation of $(\sigma^*_{60})_{OTs}$

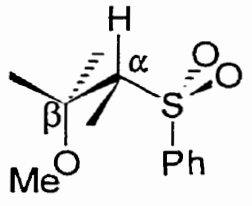
Based on the results we have presented in this thesis, the σ* value shows angle dependence. The tosyloxy group in the *trans*-tosylates (**37**) studied by Hine and Ramsay can be expected to have a different σ* value from that in the *cis*-tosylate (**36**).

If we assume as a first approximation that $(\sigma^*_\theta)_{OTs}$ follows the same basic pattern as $(\sigma^*_\theta)_{OR}$ but requires a scaling factor (*f*) to correct for the greater electronegativity of the tosyloxy group (vs alkoxy) then from eq 2.2.3 we may write

$$(\sigma^*_\theta)_{OTs} = f(0.60 + 0.28 \cos 2\theta)$$

At 180° $(\sigma^*_\theta)_{OTs}$ is maximal. If we assign $(\sigma^*_{180})_{OTs} = 1.31$ (from Hine and Ramsay's $\sigma^* = 1.31$) then $f = 1.31/0.88 = 1.49$ and so $(\sigma^*_\theta)_{OTs} = 0.89 + 0.42 \cos 2\theta$, from which we get $(\sigma^*_{60})_{OTs} = 0.68$. We may note that eq 2.2.3 was based on $\sigma^*_{OMe} = 0.64$ whereas the Hine and Ramsay plot uses $\sigma^*_{OMe} = 0.52$; with correction for this difference $(\sigma^*_{60})_{OTs} = 0.68(0.52/0.64) = 0.55$.

The above assumes that the σ* as measured conventionally (by pK_a' of XCH_2COOH, for example) gives the maximal value. This was not what we found in the H-D exchange reactions; σ^*_{OMe} that was used (by Thomas and Stirling) in the Taft plot was 0.64, whereas we find $(\sigma^*_{180})_{OMe}$ to be 0.88. This could arise because the methoxy-substituted substrate, $PhSO_2CH_2CH_2OMe$, is conformationally mobile and the reactive conformer may be only a small proportion of the total sample, whereas in the **13 - 16**, the reactive conformer constitutes virtually all of the same sample.



A

If, in the Winstein-Holness equation, $k_{obs} = n_a k_a + n_b k_b + \ldots$, only one conformer (subscripted *a*) reacts, then $k_{obs} = n_a k_a$ where k_a is the rate constant for that conformer, i.e. the maximal value for $(\sigma_\theta^*)_{OMe}$ (and *n* refers to the mole fraction of each conformer, reactive or otherwise). From the Taft equation

$$\log(k_{obs})_{OR}/k_H = \sigma^*_{obs}\,\rho^* \quad \text{and} \quad \log(k_a)_{OR}/k_H = \sigma^*_a\rho^*$$

where the subscript "obs" refers to experimental values obtained with the normal mixture of conformers and the subscript "a" to the single conformer. Substituting $(k_a)_{OR} = k_{obs}/n_a$ we get

$$\log(k_{obs})_{OR}/k_H - \log n_a = \sigma^*_a\rho^*$$

and with further substitution

$$\sigma^*_{obs}\,\rho^* - \log n_a = \sigma^*_a\rho^*$$

from which we may obtain

$$-\log n_a = \rho^*(\sigma^*_a - \sigma^*_{obs}) \qquad \text{(i)}$$

and

$$\sigma^*_a = \sigma^*_{obs} - (\log n_a)/\rho^*. \qquad \text{(ii)}$$

From (i) we find $\log n_a = -1.17$ and $n_a = 0.067$, and from (ii) we see that $(\sigma^*_{obs})_{OMe} = 0.64$ is transformed into $(\sigma^*_a)_{OMe} = 0.88$ by adding $1.17/4.89 = 0.24$. If we further assume that the tosylate system behaves in the same way, we get $(\sigma^*_a)_{OTs} = 1.31 + 0.24 = 1.55$. Using 1.55 instead of 1.31 for scaling (as above) we get

$$(\sigma^*_{\theta})_{OTs} = 1.1 + 0.49 \cos 2\theta.$$

from which $(\sigma^*_{60})_{OTs} = 0.86$. Correcting this as before (by 0.52/0.64) we obtain a value of $(\sigma^*_{60})_{OTs} = 0.70$ for use with the Hine-Ramsay equation. Average 0.63 ± 0.1

APPENDIX C

From the Winstein-Holness equation[28]

$$k_{obs} = n_e k_e + n_a k_a + n_x k_x$$

where n refers to mole fractions and the subscripts e and a to **5e1** and **5a1** and x to all non-reacting conformers (i.e. those, mostly equatorial, conformers not arranged as in Figure 2.2.2). Defining $K = n_a/n_e$, then

$$n_e = \frac{1 - n_x}{1 + K}$$

and

$$n_a = \frac{K(1 - n_x)}{1 + K}.$$

For the present case in which $K << 1$, we may then write

$$\frac{k_{obs}}{1 - n_x} \approx k_e + K k_a.$$

From the present text discussion with that of the correction for large steric effects

$$k_a = (\theta\text{-factor})(\text{steric factor}) k_e = 108 k_e \, e^{0.67 \Delta G / RT}$$

which with $K = e^{-\Delta G/RT}$ gives

$$k_{obs}/(1 - n_x) \approx k_e (1 + 108 \, e^{-0.33 \Delta G/RT})$$

from which, using $\Delta G^\circ = 6 \pm 2$ kcal mol^{-1} for **5e1** $\rightleftharpoons$ **5a1**, and assuming that $(1 - n_x)$ is much the same for **5** and **23b**, we find $\log (k_e)_N = 2.33 \pm 0.3$ and $\log (k_a)_N = 4.26 \pm 0.3$. If we assign torsion angles of about 60 and 180°, respectively, we see that they fit well with the filled and heavily outlined circles in Figure 2.2.1; they are not included in the array used for the best fit for eq 2.2.1 because they are not estimated independently of eq 2.2.1.

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