α - LITHIO SULFOXIDES AND SULFONES

by

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ABSTRACT

In this work we examined the effects of various factors such as solvent, temperature, time, etc. on the reactions of a number of acyclic lithio sulfoxides and of some cyclic lithio sulfones in an attempt to test experimentally the findings suggested by extensive non-empirical calculations on the hypothetical hydrogen methyl sulfinyl (14) and sulfonyl carbanions; we also attempted to evaluate the synthetic potential of α - sulfinyl carbanions as suggested by the preliminary work of Durst (19) and McClory (20).

The conditions (temperature, carbanion equilibration time, side reactions) under which α - sulfinyl and sulfonyl carbanions can best be generated and trapped with electrophiles have been defined. A series of acyclic sulfoxide carbanions were generated and quenched with a number of electrophiles and the diastereomeric product ratios and stereochemistry of the reactions determined in each case. The diastereomeric product ratio is constant for each lithio sulfoxide regardless of the electrophile used (CH_3I, D_2O, acetone). A critical evaluation of a hypothesis (20) to explain the variations in diastereomer ratios with change in sulfoxide structure is made. The deuteration and hydroxyalkylation reactions were shown to proceed with retention of the carbanion stereochemistry, the alkylation reactions with inversion. An interpretation of the stereochemistry of the reactions and a mechanism to support this interpretation is proposed.

An investigation of the stereochemistry of the deuteration and methylation reactions of the carbanions of two conformationally fixed sulfones was carried out. Preliminary conclusions concerning the stereochemistry of these reactions and those of other sulfur stabilized carbanions are drawn.

The sulfone stabilized carbanions in a conformationally fixed six-membered ring system were found to exhibit a strong preference for the equatorial orientation. Several other sulfur stabilized carbanions exhibit similar behaviour (33, 39, 41, 42). This phenomenon was examined and a new determination of the lithium A value (α to a sulfone) in T.H.F. was made.

The effect of solvent on the conformational preference of the benzyl methyl sulfoxide carbanion was studied. In high dielectric constant solvents the R, S lithio sulfoxide was preferred, in low dielectric constant solvents the S, S lithio sulfoxide predominated. The effect of solvent on α - sulfonyl carbanions was also investigated, the carbanion on the O-S-O bisector was the preferred one in T.H.F.

The relationship between the kinetic and thermodynamic preference in the lithiation of benzyl methyl and benzyl t-butyl sulfoxide was determined. For benzyl methyl sulfoxide the kinetic preference for the removal of the pro S hydrogen in the S sulfoxide was 1.7:1 while the thermodynamic preference for the S, S vs R, S carbanion was 15:1.

For benzyl t-butyl sulfoxide the values were 117 ± 20:1 and 10^{10}:1 in favour of the pro S (in S) proton and the S, S carbanion respectively. The implications arising from these results are discussed.

The benzene and trifluroracetic acid solvent effects on proton shifts in a number of acyclic sulfoxides were measured. These effects were compared with the downfield shifts resulting from the addition of $Eu(DPM)_3$. For the acyclic sulfoxides studied none of the methods produced effects which show any correlation with sulfoxide stereochemistry.

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LIST OF ABBREVIATIONS

T.H.F.	-	tetrahydrofuran
DMSO	-	dimethylsulfoxide
n.m.r.	-	nuclear magnetic resonance
T.L.C.	-	thin layer chromatography
T	-	temperature
inv.	-	inversion
B.T.A.-OH	-	benzyltrimethylamine hydroxide
I.R.	-	infra red
b.p.	-	boiling point
m.p.	-	melting point
Fig.	-	Figure
pet. ether	-	petroleum ether
eq.	-	equivalent
lit.	-	literature
mmoles	-	millimoles
MPBA	-	meta-chloroperbenzoic acid
DMF	-	dimethylformamide
s	-	singlet
d	-	doublet
t	-	triplet
q.	-	quartet

LIST OF ABBREVIATIONS

m.	-	multiplet
b	-	broad
ax	-	axial
eq	-	equitorial

CHAPTER 1

GENERAL INTRODUCTION

Interest in sulfur stabilized carbanions† arose from the initial work of Cram and co-workers (1) on α- sulfonyl carbanions ($R-SO_2-\bar{C}(R)_2$) in the early 1960's. The novelty of this work was the remarkable asymmetry demonstrated by this reactive species. Similar observations were soon after reported by two other groups of workers (2, 3). A controversy regarding the structure and preferred conformation of α- sulfonyl carbanions arose and this problem received a great deal of attention during the subsequent years (4).

The development of α- sulfinyl carbanion chemistry was much slower. This may be attributed to the initial conclusion of Cram and Pine (5) that α- sulfinyl carbanions were intrinsically symmetric, and thus less interesting than the α- sulfonyl carbanions. Cram and Pine based their conclusions on the base catalyzed exchanges of optically active 2-octyl phenyl sulfoxides (see Scheme 1).

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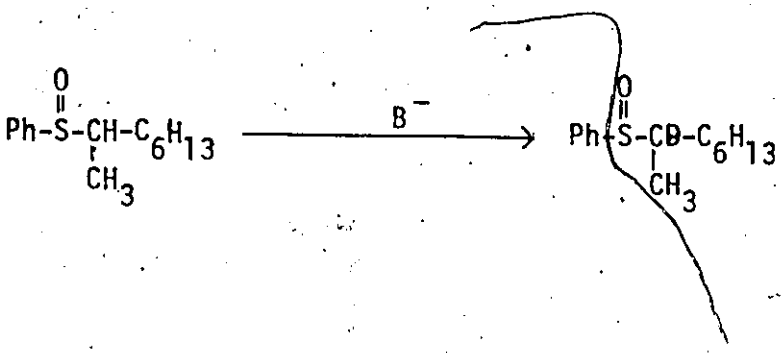
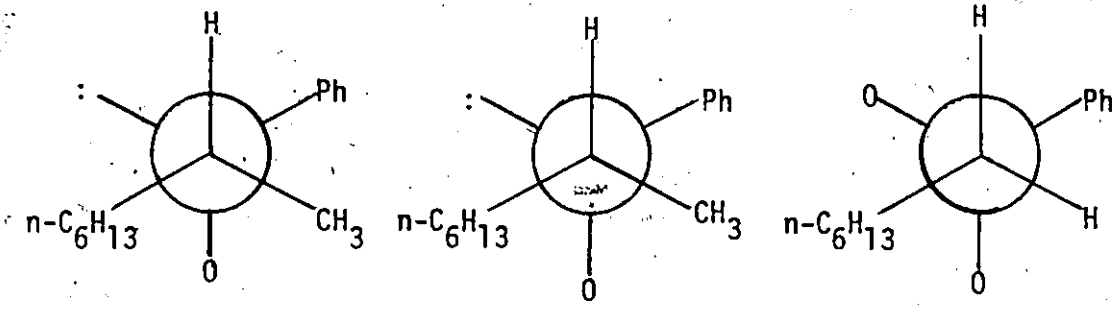
† The term carbanion will in general be used to denote the metal salt of a carbon acid e.g.: an α- lithio sulfoxide R-CH(Li)-SO-R will be called an α- sulfinyl carbanion.

The rate of exchange at carbon, k_e, and the rate of racemization at carbon, k_α, were measured by removing aliquots of sulfoxide at various times from the reaction mixture and oxidizing the sulfoxides of sulfone. The sulfones were then examined for their optical purity and deuterium content. The stereochemical results were then expressed in terms of a k_e/k_α ratio. As k_e/k_α approaches infinity the steric course of the reaction approaches complete retention of configuration at carbon. Complete racemization is expressed by a ratio equal to one, whereas complete inversion requires a ratio of 0.5. The sulfoxides were stable to racemization at sulfur under the reaction conditions employed. Values of k_e/k_α were measured in t-BuOD with t-BuOK as base at 60° and in DMSO 1.2 M in MeOH with MeOK as base at 60 . In t-BuOH, sulfoxide 1 (R, S) had k_e/k_α = 1.2 and 2 (S, S) had k_e/k_α = 3.6. In DMSO 1 had k_e/k_α = 0.6 and 2 had k_e/k_α = 1.4. In contrast to these results sulfone 3 had k_e/k_α = 73 - 1980 in t-BuOH at 25° and k_e/k_α = 10 in DMSO at 25 .

These results demonstrated that the sulfoxide carbanion was generated and consumed with considerable racemization at carbon in contrast to high retention of the carbanion configuration demonstrated by the sulfone.





(R,S)[c] (S,S)[c] (S)

solvent / base			
t-BuOH / t-BuOK	$\frac{k_e^a}{k_\alpha^b}$ = 1.2	$\frac{k_e^a}{k_\alpha^b}$ = 3.6	$\frac{k_e^a}{k_\alpha^b}$ = 73-1980
DMSO-CH_3OD / CH_3OK	$\frac{k_e^a}{k_\alpha^b}$ = 0.6	$\frac{k_e^a}{k_\alpha^b}$ = 1.4	$\frac{k_e^a}{k_\alpha^b}$ = 10

Scheme 1

a) k_e = rate of exchange at carbon

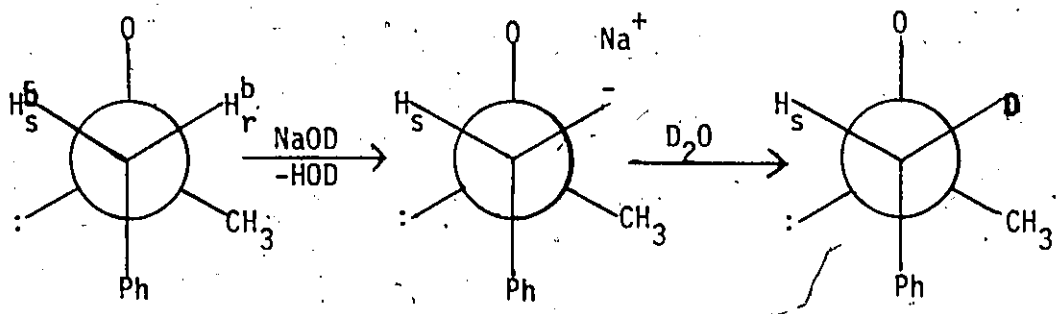
b) k_α = rate of racemization at carbon

c) The original absolute configurations at sulfur assigned by Cram have been reversed (6) and are corrected here. This in no way changes the major conclusions of the author

Cram explained the differences in the sterochemical behaviour of the sulfonyl and sulfinyl carbanions on the basis of intrinsic symmetry properties of the ions themselves. He suggested that α- sulfonyl carbanions were asymmetric and were consumed faster than they racemized, but that α- sulfinyl carbanions were either symmetric or equilibrating asymmetric but enantiomeric species. The small variations in k_e/k_α from unity were attributed to asymmetric solvation due to the sulfur asymmetry.

In 1965, Wolfe and co-workers (7) reported that the diastereotopic protons of benzyl methyl sulfoxide exchanged at significantly different rates in D_2O/NaOD at 15°; one proton exchanging 14 times faster than the other. This showed that for the more rapidly exchanging hydrogen, an α- sulfinyl carbanion was formed and consumed with high selectivity. The only reasonable process for the exchange was one involving retention of configuration in each step. The stereochemistry of the exchange for the slower proton could not be determined from these results (see Scheme 2).

The following year Wolfe et al (8) reported that the faster exchanging proton in benzyl methyl sulfoxide was the pro S hydrogen. This assignment has since been shown to be in error and it is the pro R hydrogen which is the most rapidly exchanged in D_2O/NaOD (9)



$k_{H_r} = 13.7\ k_{H_s}$

Scheme 2

a) The conformation depicted for the exchange is not necessarily the one involved

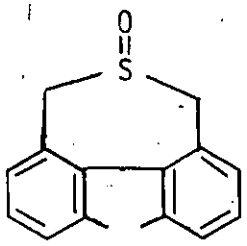
b) H_s = pro S hydrogen

H_r = pro R hydrogen

(see Scheme 2). In addition the authors pointed out that the structure and stability of α- sulfinyl carbanions appeared to be strongly influenced by the nature of the solvent in which they are generated.

Several other examples of stereoselective base - catalyzed exchanges next to the sulfinyl group in acyclic systems have since been reported (10). These results showed that benzyl methyl sulfoxide was not a unique system, but they did not contribute any further information concerning the preferred carbanion conformations or the stereochemistry of the exchange process.

Kinetic exchanges using conformationally fixed, or strongly biased sulfoxides, (see Fig. 1), have yielded much more useful information (11 - 13). In 4, Fig. 1, the relative rates of exchange varied from 1 for H_1 to 7500 for H_3 in CH_3OD - CH_3OK and from 1 for H_1 to 1200 for H_4 in t-BuOH - t-BuOK. In 5 and 6, Fig. 1, the relative rates in D_2O - NaOD and MeOD - MeONa were Ha>He $He^1>Ha^1$. In t-BuOH - t-BuOK and DMSO 1M CH_3OH - CH_3OK the exchange was non-stereoselective. In 7 $k_{hx}/k_{hn} \geq$ 12/1 and in 8 k_{hx}/k_{hn} = 1/2.5 in CD_3OD - CD_3ONa. A qualitative discussion of the rate differences for 9 was given (13) and will be discussed later in the thesis.



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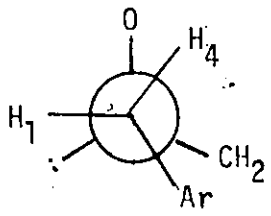

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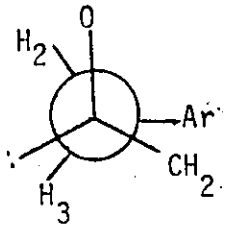

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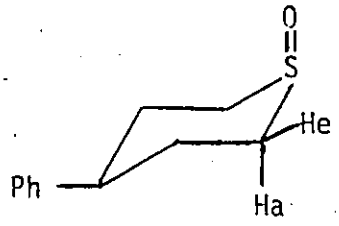

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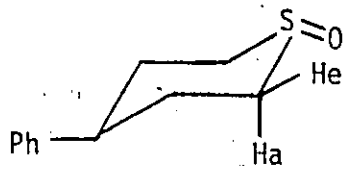

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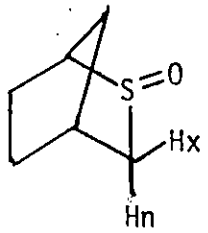

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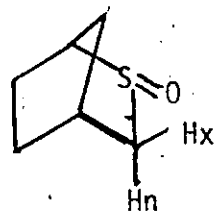

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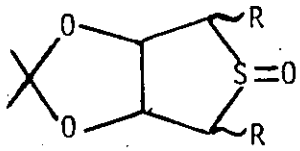

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R = H, CH_3

Figure 1

These results demonstrated two things: 1) A significant solvent effect exists on the relative rates of exchange of a set of diastereotopic protons having fixed relationship to the sulfoxide asymmetry, in other words, on the relative stability of carbanions in various conformations. 2) Small changes in the dihedral angle, θ, cause large changes in the relative exchange rates, i.e. carbanion stability is greatly affected by change in θ. These results will be discussed at greater lengths in the appropriate section of the thesis.

To gain further insights as to the nature of α- sulfinyl carbanions and their stereochemical behaviour, Wolfe and co-workers carried out extensive non-empirical calculations on the hypothetical hydrogen methyl sulfinyl carbanion ($\bar{C}H_2$-S(O)H) (14). These calculations were carried out within the Hartree - Fock framework and are of the L.C.A.O. - M.O. - S.C.F. type.† They were used to examine the following points:

1) The hybridization of the carbanion (i.e. is it tetrahedral or planar).

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† A discussion of the background, the terminology and limitations of this type of calculation is beyond the scope of this thesis. For a brief review of the above points see Ref. 15.

2) The involvement of d - orbitals on sulfur (i.e. d - orbital conjugation with the carbanion).
3) The variations in carbanion energy and in the barrier to carbanion inversion as a function of rotation about the carbon sulfur bond.
4) The effect of substituting an alkyl group (methyl) for hydrogen at sulfur.

The calculations suggested the following:

1) A pyramidal carbanion is preferred* (i.e. sp^3 hybridization).
2) d - orbital conjugation is not a significant factor in determining the properties of these carbanions.
3) The variation in carbanion stability as a function of rotation about the C - S bond showed two maxima and two minima (see Fig. 2). The barrier to carbanion inversion is low or non-existent and any carbanion generated in a high energy conformation should spontaneously convert to one of lower energy by inversion, rotation or both.
4) The calculated properties were virtually unaffected when the S - H bond was replaced by a C - S bond.

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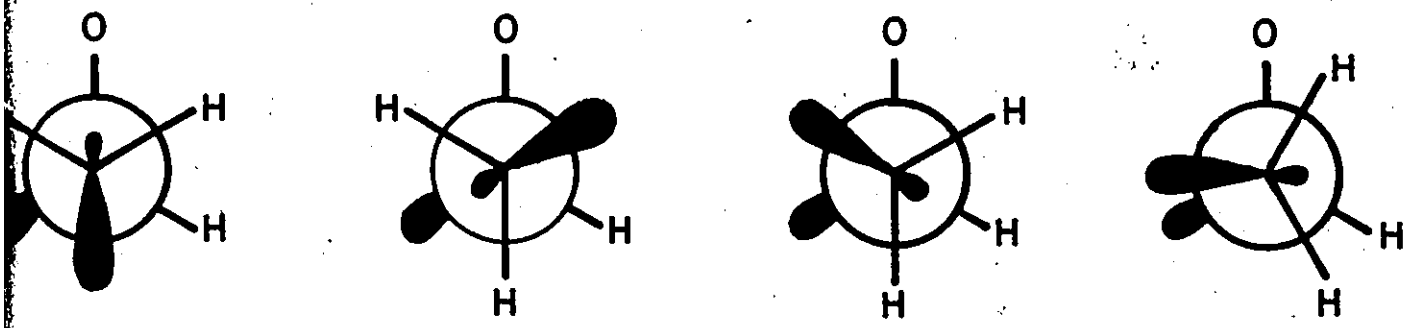
* Subsequent calculations (16) have suggested that sp^3 hybridization is also favoured in α- sulfonyl carbanions.


O
H
H
A
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H
H
H
B
O
H
H
H
C
O
H
H
H
D

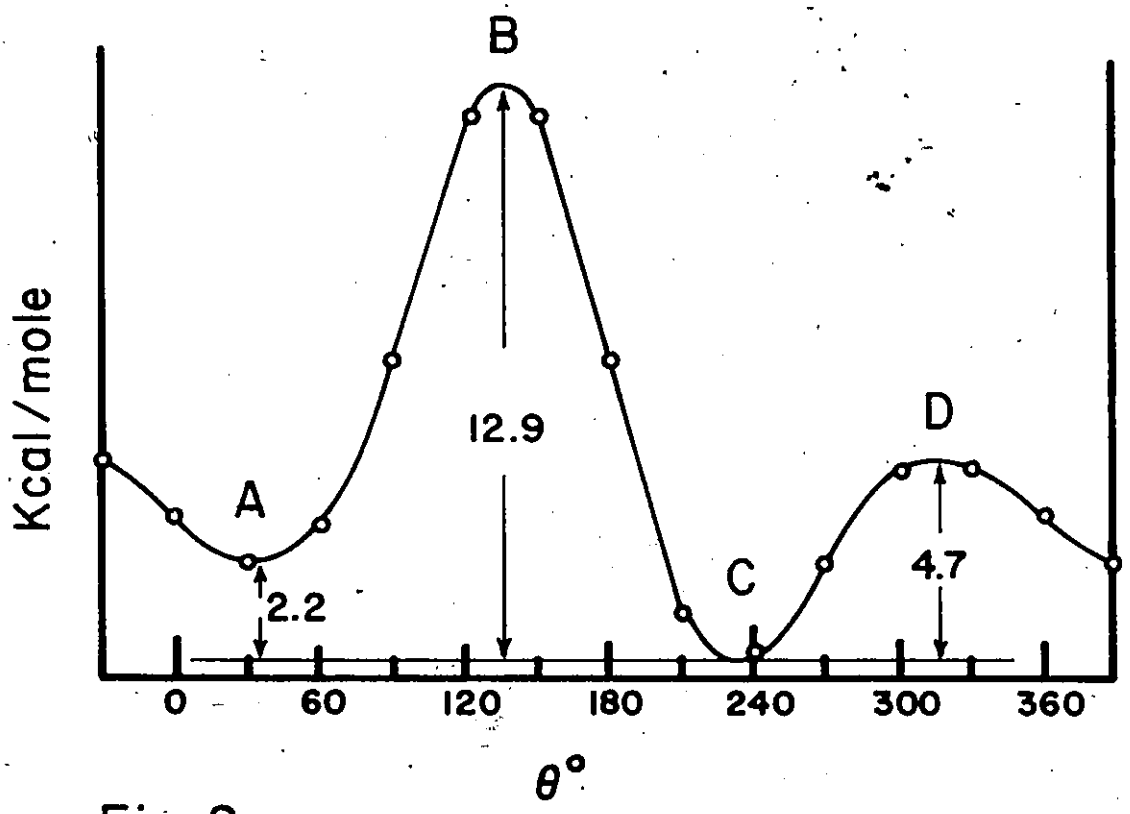
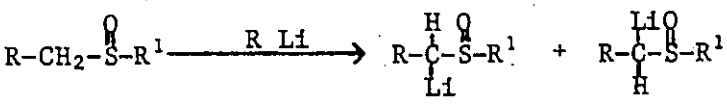
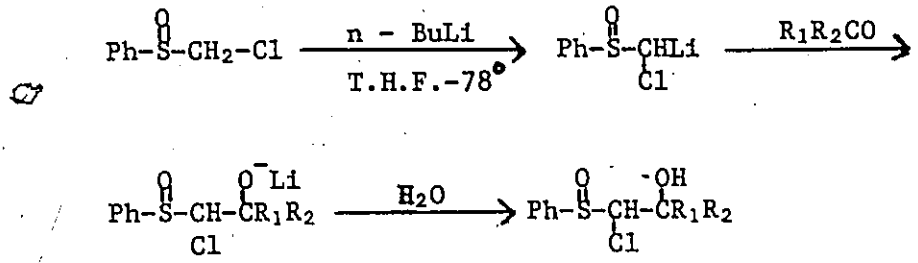

B
D
A
C
12.9
4.7
2.2
Kcal/mole
0
60
120
180
240
300
360
θ°

Fig. 2

Most studies of the properties of sulfur stabilized carbanions and in particular ∝- sulfinyl carbanions have involved base catalyzed hydrogen - deuterium exchanges (5, 7, 10 - 13). By contrast, work on the synthetic applications of ∝- sulfinyl carbanions (17), e.g. methyl sulfinyl carbanion, has required the production of the carbanion in high yield under irreversible conditions. The carbanion can then be reacted with an electrophile to give the desired product. One of the methods to produce these carbanions is to react sulfoxides bearing ∝- hydrogens with alkyllithiums in tetrahydrofuran (T.H.F.) (17a, 18). When applied to sulfoxides of the type $R-CH_2S(O)-R^1$ this method should give rise to a mixture of diastereomeric lithio sulfoxides. e.g.



The first example of this type was reported by Durst in 1969 (19). He reacted chloromethylphenyl sulfoxide with n - butyllithium at - 78 in T.H.F. to give soluble ∝- lithio salts. These salts were reacted with a series of symmetrical ketones (see Scheme 3), followed by hydrolysis. An analysis of the products showed that one diastereomeric adduct was produced in greater than 98:2 proportion. The unusually high stereoselectivity in the formation of the adducts was attributed to an energy difference of at least 2 kcal/mole between the 2 possible diastereomeric lithio derivatives.



$R_1R_2=(CH_2)_5$

$R_1=R_2=CH_3$, Ph

SCHEME 3

A study of the metallation of sulfoxides of the type $R\text{-}S(O)\text{-}CH_2\text{-}R^1$ (R or R^1 = alkyl or aryl) followed by reaction with symmetrical ketones was then carried out McClory (20). He found that the diastereomeric ratios of the products varied from 60:40 for benzyl phenyl sulfoxide to greater than 95:5 for benzyl t - butyl sulfoxide.†

In order to continue and expand this work we decided to study the chemistry of ∝ - sulfinyl carbanions from two points of view:

1) To attempt to test experimentally the findings suggested by Wolfe et al's calculations.

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† A more complete description of this work will be given in Chapter 3 of the thesis.

2) To evaluate the synthetic potential of α- sulfinyl carbanions as intermediates in the synthesis of compounds having asymmetry at carbon related to that at sulfur.

In order to achieve our aims it was necessary for us to determine the following:

1) The possible effects of solvents on the configuration and stability of these carbanions.
2) The diastereomer product ratios obtained by reacting lithio salts of sulfoxides having diastereotopic protons with a variety of electrophiles.
3) The variation in these product ratios with variations in sulfoxide structure.
4) The stereochemical course of the reactions of the lithio salts, with various electrophiles, producing the major diastereomers.

CHAPTER 2

PRODUCTION AND STABILITY OF ∝- LITHIO SULFOXIDES

Introduction:

In order to study ∝- sulfinyl carbanions a good method for their preparation was required. One possible method was via the reaction of the sulfoxide with an alkyllithium in T.H.F. (17 - 20). Durst and McClory (19, 20) have both pointed out that lithio sulfoxides of the type R-CHLi-S(0)-R are produced almost instantaneously on reaction of the sulfoxide with alkyllithiums in T.H.F. at - 78°. This was indicated by the appearance of a yellow colour after the addition of the first drops of alkyllithium.† Reactions of the lithio salts with ketones were also rapid as evidenced by the loss of colour† (20). From a preparative point of view this appeared to be a rapid and easy way of obtaining ∝- sulfinyl carbanions.

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† Colour has previously been used as a diagnostic tool to detect the presence of carbanions in solution (21). N.B. Not all ∝- sulfinyl carbanions are coloured, so that appearance and loss of colour cannot always be used as a criterion for their formation and reaction (see experimental) (25).

The thermal stability of ∝- lithio chloromethyl sulfoxide has been examined (19, 26). In T.H.F. at - 78° this salt was stable for at least 2 hours, but decomposed rapidly above - 20°. Decomposition via ∝- elimination of form either phenyl sulfinyl carbene or chlorocarbene was suggested (19). Tin has since shown that this reaction does not occur; a complex mixture of products is obtained (26). McClory (20) also noted that some benzylic carbanions decomposed at 0°. He found that methyllithium was in general a better base than n-butyllithium.

Franzen (22) has reported that DMSO reacts with alkyllithiums in the following manner:

$$CH_3\text{-}SO\text{-}CH_3 \xrightarrow{RLi} CH_3\text{-}SO\text{-}R \pm CH_3Li$$

Jacobus and Mislow (23) investigated the reactions of aryl methyl sulfoxides with methyl and phenyllithium in which they also claim to have observed displacement. The generality and mechanism of this displacement reaction has recently been studied in some detail in this laboratory (24).

Since it was our desire to produce cleanly relatively stable ∝ - lithio salts of sulfoxides bearing diastereotopic hydrogens by reaction with alkyllithiums, experimental conditions in which the above mentioned displacements and decompositions are minimized were required.

Thermal Stability of α- Lithiobenzyl Methyl Sulfoxide

α - Lithiobenzyl methyl sulfoxide was generated at - 60°† in T.H.F. by reaction with a 10% excess of MeLi.* The reaction mixture was allowed to warm to room temperature, 24°, over half an hour and the carbanion quenched with a large excess of water (greater than 10 fold excess). The nuclear magnetic resonance (n.m.r.) spectrum of the total crude reaction mixture showed about 50% regenerated sulfoxide and 50% other materials. When the lithio salt was generated at - 60° and kept for four hours at this temperature, then quenched with excess H_2O, a mixture of 50% sulfoxide and 50% other materials was again obtained. (The percentages are based on the n.m.r. spectrum of the total crude reaction products). These other materials were attributed to decomposition of the lithio sulfoxide and could be separated from the

† The lithio sulfoxide precipitated out of solution at - 78°. When the solution was warmed to - 60° it completely disolved. We felt that reaction under homogeneous conditions would lead to simpler interpretations, therefore - 60° was preferred to the lower temperature mentioned in the previous work.

* A 10% excess of MeLi was used to account for any residual traces of water in the reaction solvent or reaction vessel. On large scale reactions a smaller excess was often used.

recovered sulfoxide by chromatography on silica gel. They constituted of the faster moving fractions and appeared as a smear on thin layer chromatography (T.L.C.). They also exhibited a complex n.m.r. spectrum in $CDCl_3$ with broad multiplets at 2.75 - 3.65, 3.60 - 4.20, 6.80 - 7.60 ppm downfield from TMS.† The infrared spectrum in $CHCl_3$ exhibited a strong peak at 1035 cm^{-1}.

From the above data we concluded that the α- lithio sulfoxide had probably decomposed to give a complex mixture of products. We made no further attempt to determine the nature of these products. We felt that the 1:1 ratio of decomposition products to recovered sulfoxide was due to the formation of a decomposition product or products which completely quenched the carbanion after 50% decomposition. Therefore the same percentage decomposition occurred irregardless of the reaction conditions.

When the α - lithio salt was generated at - 60° and quenched after five minutes, less than 5% decomposition was observed.

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† The delta (δ) scale will be used throughout this thesis unless otherwise indicated.

When the anions were quenched after 1 minute† virtually no decomposition could be detected. Recovered yields of sulfoxide were >90% under these conditions.

Displacement Reactions at Sulfur:

α - Lithio benzyl methyl sulfoxide was generated at - 60° in T.H.F. using n-BuLi as base and quenched after one minute with excess water. Analysis of the total reaction mixture by n.m.r. indicated the presence of 60% starting sulfoxide and 40% of another material. The peaks corresponding to this material were at 0.7 - 2.0 and 2.2 - 3.0. We attributed these peaks to methyl n-butyl sulfoxide which we assumed arose from the following displacement.

$$PH\text{-}CH_2\text{-}SO\text{-}CH_3 \xrightarrow[THF,-60^\circ]{n\text{-}BuLi} CH_3\text{-}SO\text{-}n\text{-}Bu$$

A more careful examination of this reaction has confirmed this assignment (24b).

When α - lithio benzyl phenyl sulfoxide was generated in T.H.F. at - 60° using MeLi and quenched after one minute with excess H_2O, analysis of the n.m.r. spectrum of the total crude reaction pro-

† Other implications of this rapid quench time will be discussed in Chapter 3.

ducts showed about 98% regenerated sulfoxide. Peaks corresponding to about 2% of the total crude were identical with those of phenyl methyl sulfoxide. This product could arise as follows:

$$PH\text{-}CH_2\text{-}SO\text{-}Ph \xrightarrow[THF,\ -60^{0}]{MeLi} Ph\text{-}SO\text{-}CH_3$$

An independant study (24b) has confirmed that this reaction occurs under the above conditions with comparable yields. Our results are also in agreement with those of Le Belle (24) which indicated that $Ph\text{-}CH_2^-$ is a preferred leaving group in these substitution reaction (e.g. preferred over CH_3^- and Ph^-).

In all other cases where MeLi was used as base no significant displacement products were noted. This was further confirmed by generally high recovered yields of products (>90%). Le Belle (24) has also observed that the amount of displacement increases in the order MeLi < n-BuLi ~ t-BuLi.

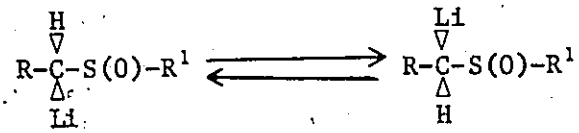
Therefore the general procedure adopted for the generation of α - lithio sulfoxides was to react the appropriate sulfoxide with 10% excess MeLi at -60°C. After one minute an excess of the desired electrophile was added.

CHAPTER 3

PREFERRED CONFORMATION OF ACYCLIC α- SULFINYL CARBANIONS

Introduction:

As pointed out in Chapters 1 and 2, sulfoxides bearing alpha hydrogens react rapidly with alkyllithiums to give carbanions and if the alpha hydrogens are diastereotopic then diastereomeric lithio sulfoxides could be produced. Durst (19) and McClory (20) have generated a number of carbanions of sulfoxides of the type $R-S(O)-CH_2-R^1$ in T.H.F. Both assumed that the diastereomeric lithio salts thus produced rapidly equilibrated by the carbanion inversion mechanism (27).



They noted that the reaction of these carbanions with ketones were very rapid even at - 78°. They both felt that the reaction of these carbanions with ketones were fast enough to trap the above mentioned carbanion equilibrium. If this is so, then a mixture of diastereomeric adducts should be obtained and the ratio of these products should be a measure of the carbanion equilibrium in solution (e.g. a measure of the relative stability of the two equilibrating carbanions). Both observed some unusually high stereoselectivity in the formation of adducts and

they attributed this to a significant energy difference between the two possible diastereomeric lithio salts in solution. Durst's results were summarized in Chapter 1, McClory's are listed in Table 1.

The latter (20) observed significant variations in diastereomer product ratios with changes in sulfoxide structure. He interpreted these variations as a balance between two competing factors affecting the carbanion equilibrium : one factor being electronic, the other steric in origin.

McClory (20) assumed that the relative stereochemistry at carbon and sulfur of the predominant adduct of benzyl methyl and phenyl ethyl sulfoxide was opposite to that of the predominant adduct for t-butyl ethyl and t-butyl benzyl sulfoxides. This assumption was based on the results obtained from some benzene induced n.m.r. solvent shifts of α-d-benzyl methyl and α-d-benzyl t-butyl sulfoxides obtained by quenching the respective lithio sulfoxides with D_2O and of the non deuterated parent compounds*.

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* We will demonstrate later in the thesis that this method is not very reliable for assigning stereochemistry in acyclic sulfoxides.

TABLE 1

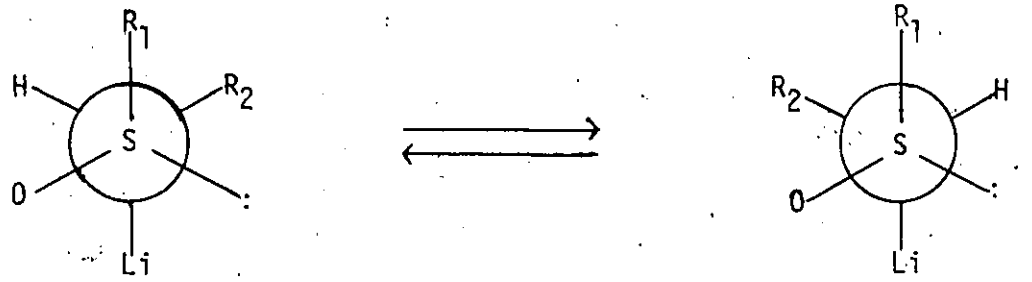
Diastereomeric product ratios from the reaction of lithio sulfoxides with ketones. (20)

Lithio Sulfoxide	Ketone	Adduct Yield (%)	Diastereomic Product Ratio[a]
Ph-CHLi-S(O)-CH_3	cyclohexanone	49	>90:10
Ph-CHLi-S(O)-Ph	acetone	50	60:40
	cyclohexanone	85	60:40
	benzophenone	59	50:50
Ph-CHLi-S(O)-t-Bu	acetone	77	< 5:95
	benzophenone	40	15:85
Ph-S(O)-CHLi-CH_3	acetone	81	93:7
	benzophenone	73	92:8
CH_3-CHLi-S(O)-t-Bu	acetone	78	<10:90
	cyclohexanone	86	<10:90
	benzophenone	67	<10:90

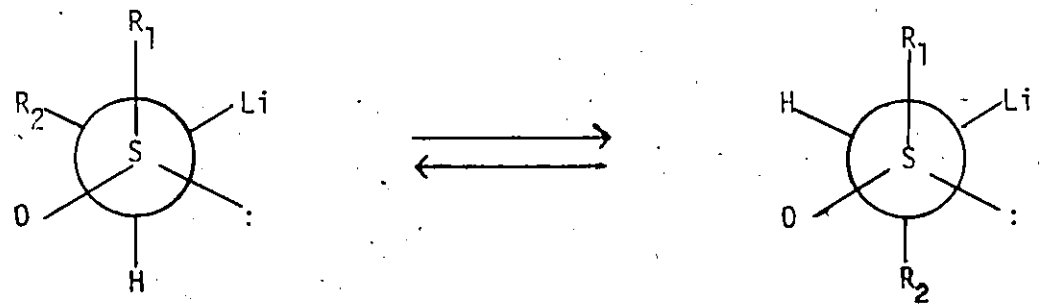
(a) The diastereomeric ratio of products were measured either spectrometrically (n.m.r.) or via separation of the diastereomers by chromatography.

There exist 3 possible sets of staggered conformations for the equilibrating carbanions of the sulfoxides he studied (see Fig. 3). An interpretation of McClory's (20) arguments concerning the prefered carbanion configurations follows: Assuming A and B (Fig. 3) are electronically favoured with A sterically favoured due to the R_2-lone pair gauche interaction in A < the R_2-oxygen gauche interaction in B. As R_1 and R_2 increase in size A becomes disfavoured sterically. Therefore in A the electronic and steric effects oppose each other and one could expect a change in the relative configurations at carbon and sulfur of the major diastereomer as the size of R_1 and/or R_2 is greatly increased.

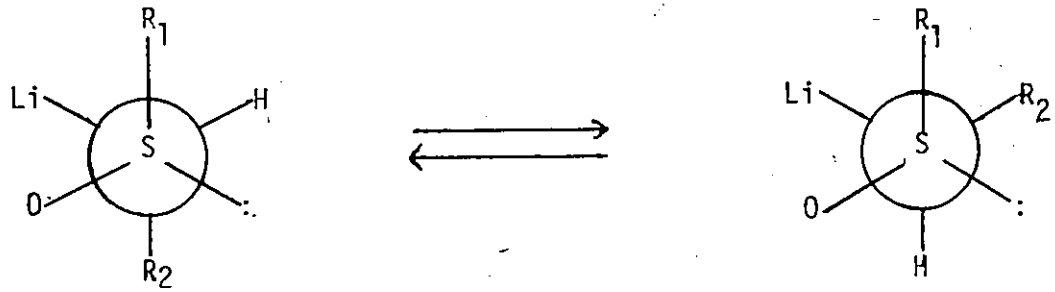
If C and D are electronically the most favoured conformations, D should be more stable than C (e.g. R_1-R_2 gauche interaction > R_1-H gauche interaction). In this case the steric and electronic factors should reinforce each other. Therefore no change in the relative carbon and sulfur stereochemistry would be expected with changes in the size of R_1 and R_2. This is inconsistent with the assumption made by McClory based on the benzene induced solvent shifts. This possibility was therefore eliminated.



A ⇌ B



C ⇌ D



E ⇌ F

Figure 3

If E and F are assumed to be the most electronically favoured carbanion conformations with E the more stable (R_1-R_2 + hydrogen - oxygen gauche interactions > R_1-hydrogen + R_2-oxygen gauche interaction) then the steric and electronic factors again should reinforce each other and the same conclusion regarding the relative sulfur and carbon stereochemistry as for C and D holds.

From these arguments McClory concluded that the carbanion on the bisector of the oxygen - sulfur - lone pair angle (A) must be electronically the most favoured one. When the steric interactions in A become prohibitive (e.g. as R_1 and/or R_2 become large), these unfavourable interactions can be relieved by either rotation to E or rotation and inversion to D. Since simple rotation to E does not give rise to a new diastereomer (e.g. opposite relative stereochemistry at sulfur and carbon of the major adduct), the preferred pathway for relieving the steric interaction must be conversion to D. Therefore the carbanion D trans to oxygen and gauche to the lone pair is electronically preferred to the one which is trans to the lone pair and gauche to oxygen (E). These conclusions are in agreement with the order for carbanion stability proposed by Wolfe et al (14) on the basis of their ab initio calculations.

The validity of McClory's conclusions regarding the preferred conformations for acyclic sulfoxide carbanions depends on the following 3 points:

1) Opposite relative stereochemistry at sulfur and carbon is obtained for the reaction of the carbanions of benzyl methyl and benzyl t-butyl sulfoxides. The same relative stereochemistry at carbon and sulfur is obtained for benzyl methyl and phenyl ethyl sulfoxides.
2) Carbanion equilibration occurs rapidly under the reaction conditions used.
3) Reactive electrophiles such as ketones trap the carbanion equilibrium.

In order to verify McClory's conclusions the above 3 points had to be verified.

Diastereomer Product Ratios From The Reactions Of The Lithio Salts Of Sulfoxides With Electrophiles

For our study we chose to first re-examine the reactions of the lithio salts of benzyl methyl, benzyl phenyl and benzyl t-butyl sulfoxides with a number of different electrophiles, mainly D_2O, CH_3I, acetone. We then examined the variations in the diastereomer ratios by systematically increasing the size of R in $Ph-CH_2-S(O)-R$: R =

methyl, ethyl, iso-propyl, phenyl, t-butyl. The reactions of α-lithio-p-tolyl ethyl sulfoxide were also examined. The effect of temperature on the diastereomer product ratios for α- lithiobenzyl methyl sulfoxide was also noted. The results are listed in Table 2.

Measurement of Diastereomer Product Ratios

The diastereomer product ratios in Table 2 were obtained spectrometrically by n.m.r. integration of a signal from each diastereomer. An average of at least 8 integrals obtained with a Varian HA-100 Spectrometer were taken for each measurement. The accuracy of this method can be taken as better than ±5% for each integral. The n.m.r. integration method has been shown to compare favourably with results obtained by mass spectrometry (accurate to > 2%) when the kinetics for the exchange of benzyl methyl sulfoxide in D_2O/NaOD were measured by both methods (28). We have also noted a similar good agreement (see Chapter 6).

The benzylic sulfoxides in Table 2 gave well resolved AB spectra (n.m.r.) for the diastereotopic protons in DMSO-d_6 or $CDCl_3$. The diastereomer product ratios of the deuterated adducts of these sulfoxides were obtained by integration of the relative heights of the two singlets due to the unexchanged protons during deuterium decoupling.

TABLE 2

Products obtained from the reaction of various lithio sulfoxides with electrophiles in T.H.F. at - 60°.

Lithio Sulfoxide	Electrophile	Products	Yields(%)	Diastereomic Product Ratio(a),(b)
	D_2O	$Ph-CHD-S(O)-CH_3$	92	15.5:1
		" "		12.4:1 (c)
		" "		7.7:1 (d)
	CH_3I	$Ph-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-S(O)-CH_3$	96	14.5:1
	CH_3Br	" "	80	15:1
$Ph-CHLi-S(O)-CH_3$	$CH_3-CO-CH_3$	$Ph-\underset{\displaystyle HO-\overset{\displaystyle \vert}{C}-(CH_3)_2}{\underset{\vert}{CH}}-S(O)-CH_3$	94	14.9:1
	$CH_2=CH-CH_2-Br$	$Ph-\underset{\displaystyle CH_2-CH=CH_2}{\underset{\vert}{CH}}-S(O)-CH_3$	92	14-15:1
	$CH_2=CH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-Br$ (f)	$Ph-\underset{\displaystyle CH_2-CH=CH-CH_3}{\underset{\vert}{CH}}-S(O)-CH_3$	88	14-15:1
$Ph-CHLi-S(O)-Et$	D_2O	$Ph-CHD-S(O)-Et$	98	9.9:1
$Ph-CHLi-S(O)-\underline{i}-prop.$	D_2O	$Ph-CHD-S(O)-\underline{i}-prop.$	90	13.1:1

TABLE 2 (Cont'd)

Ph-CHLi-S(0)-t-Bu	D_2O	Ph-CHD-S(0)-t-Bu	94	> 99:1
	CH_3I	Ph-CH(CH$_3$)-S(0)-t-Bu	95	> 99:1
Ph-CHLi-S(0)-Ph	D_2O	Ph-CHD-S(0)-Ph	91	1.50:1
	CH_3I	Ph-CH(CH$_3$)-S(0)-Ph	94	1.53:1
p-Tol-S(0)-CHLi-CH_3	CH_2=CH-CH_2-Br	p-Tol-S(0)-CH(CH$_3$)-CH_2-CH=CH_2	92	2.40:1
	CH_2=CH-CH(Br)-CH_3 [f]	p-Tol-S(0)-CH(CH$_3$)-CH_2-CH_2=CH-CH_3	95	2.70:1
	CH_3-CO-CH_3	p-Tol-S(0)-CH(CH$_3$)-C(OH)-$(CH_3)_2$	100	5:1 [e]

(a) All ratios are the average of 2 or more independent determinations.

(b) Ratios measured by n.m.r. integration, with each integral accurate to ±5%.

(c) Measured at - 20°

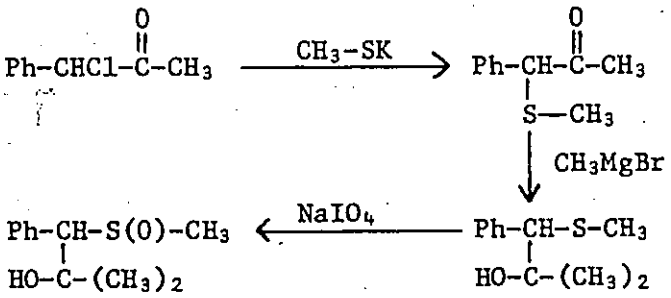
(d) Measured at - 24°

(e) Obtained from optical rotation data, see Chapter 5

(f) This material contained 10% of 1-bromo-2-butene, see footnote, page 32

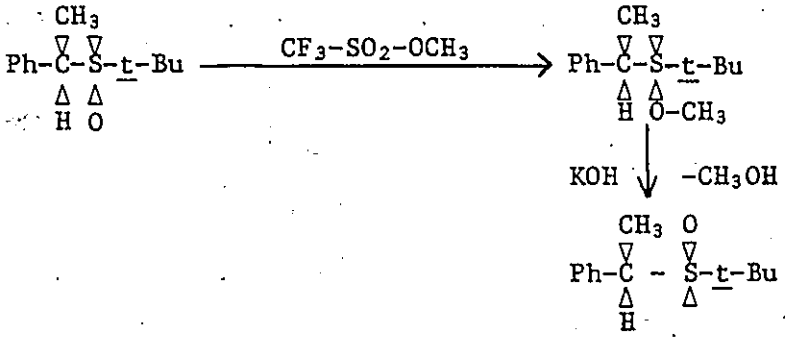
The diastereomer ratios for the alkylation reactions of α- lithiobenzyl methyl sulfoxide were measured by integration of the two singlets obtained for the methyl group bonded to sulfur. An authentic sample of the major diastereomer for the methylation reaction was obtained via synthesis from α- phenethyl alcohol (see Chapter 5).

The hydroxyalkylation of benzyl methyl sulfoxide with acetone gave two products, the major isomer having a methine singlet at δ = 3.94 and methyl singlets at δ = 1.07, 1.64, and 2.37. The minor isomer had the methine singlet at δ = 3.22 and methyl singlets at δ = 1.21, 1.62 and 2.09. Integrals of the methine singlets were used to determine the product ratio. The gross structures of the two isomers were proven as follows: (See Scheme 4 and Experimental Section for details).



SCHEME 4

The alkylation of benzyl t-butyl sulfoxide with CH_3I yielded only one diastereomer in >99% as evidenced by n.m.r. spectrometry. In this compound the methyl doublet appeared at $\delta = 1.63$, $J = 7.2$ Hz. To verify the absence of the other diastereomer it was necessary to prepare this product. This was accomplished via oxygen - methylation of the above adduct with methyl trifluoromethanesulfonate followed by treatment with 2N KOH. This sequence is known to cause inversion at sulfur (29). (Scheme 5). The new diastereomer had it's methyl doublet at $\delta = 1.72$, $J = 7.2$ Hz. One percent of this product in the original reaction mixture would have been detected by n.m.r.



SCHEME 5

The methylation of benzyl phenyl sulfoxide with CH_3I yielded the two known isomers of α- methylbenzyl phenyl sulfoxide (30). The methine protons of the two isomers appear as quartets at δ =3.91 and 3.66 in CCl_4 as solvent. In $CDCl_3$ the methyl groups of the two isomers appear as doublets at δ = 4.00 and 3.85, J = 7.2 Hz. Both sets of signals were used as probes for the product ratios and yielded identical values.

Alkylation of p-tolyl ethyl sulfoxide with allyl bromide gave 4-pent-1-enyl p-tolyl sulfoxide. In $CDCl_3$ the alkyl methyl groups of the two isomers appear as two doublets at δ = 0.93 and 1.09, J = 6.6 Hz, and were used to measure the product ratios. When 3-bromo-1-butene was the alkylating agent, 5-hex-2-enyl p-tolyl sulfoxide* was obtained. The non allylic methyl group appears as four doublets due to the formation of 4 isomers (e.g. each diastereomer may be obtained as a

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* It has recently been shown that 1-bromo-2-butene also reacts to give this product (35). The allylic bromide used in these reactions contained 10% of the 1-bromo and 90% of the 3-bromo compound; since a >10 fold excess of electrophile was used, the carbanion may have reacted exclusively with the 1-bromo compound. Further investigation of this point is currently underway (35).

mixture of cis and trans isomers about the double bond). The major isomer's doublets appear at δ = 1.10 and 1.06 and those of the minor isomer at 0.92 and 0.90 (J = 6.8 Hz for all 4 doublets). The cis/trans ratio was 2.42 to 1, but it was not possible to determine from spectroscopic data whether the cis or trans isomers are dominant.

Effect of Time and Temperature on the Carbanion Equilibrium

McClory (20) in his work assumed that carbanion equilibration was rapid and that equilibrium was attained in less than 15 minutes, even when the carbanion was generated at -78°. To test this assumption we examined the variations in diastereomer product ratios with the time allowed for carbanion equilibration. We chose α-lithiobenzyl methyl sulfoxide as our model carbanion.

When this metal salt was allowed to equilibrate for 15 minutes at - 60°, then reacted with a large excess of D_2O* (>10 fold molar excess) the diastereomer ratio was 15.5:1. When the equilibration time was reduced successively to 10, 5 and 1 minutes, product ratios identical with that for the 15 minute equilibration were obtained.

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* When DCl or acetic acid-O-d was used to trap the carbanion in T.H.F. no changes in diastereomer product ratios were observed.

This diastereomer product ratio could be due to either a carbanion equilibrium (K = 15) or a kinetic selectivity with one proton being removed 15 times as fast as the other, there being no subsequent equilibration. (e.g. the product ratio would reflect the kinetic selectivity of the proton removal reaction).

In order to verify which of the above two possibilities was the correct one we prepared samples of α-d-benzyl methyl sulfoxide specifically deuterated in the pro R or pro S positions and of known deuterium content. These samples were then reacted with CH_3Li at -60° in T.H.F. and the carbanions quenched with CH_3I. In all experiments a 15:1 ratio of methylated adducts (by n.m.r.) was obtained. By measuring the proportions of deuterated and non deuterated products we were able to determine the kinetic selectivity. The kinetic selectivity was 1.7 ± 0.3 favouring the pro S over the pro R proton for (S)-benzyl methyl sulfoxide. A more detailed description of this work will be presented in Chapter 6.

From these experiments we concluded that carbanion equilibration does occur in acyclic sulfoxide carbanions and that equilibrium is reached in less than 1 minute. In light of this we decided to quench all our carbanions 1 minute after their formation. All the

data listed in Table 2 was obtained using these reaction conditions. A further point which supports our conclusion is the constancy of the product ratios and the good agreement with McClory's results. The applicability of our conclusion regarding carbon equilibration to other sulfur stabilized carbanions will be shown later in this Chapter.

At least 10 fold molar excesses of electrophile were used to trap the carbanion equilibria. When equimolar amounts or slight excesses of electrophiles were used diastereomeric ratios other than those recorded in Table 2 were observed in some cases. This may be explained as follows: When no excess of electrophile is used, the adduct initially formed by reaction with the electrophile may itself react with unquenched carbanion; this new adduct carbanion could then epimerize before being reprotonated. In such a situation the product ratio may not reflect the parent carbanion equilibrium. When a large excess of electrophile is added all at once with rapid stirring to the carbanion mixture, the carbanion equilibrium is more likely to be trapped.

When our model carbanion was generated in T.H.F. at various temperatures and quenched with D_2O, changes in selectivity were observed (Table 2). A plot of log k (k = product ratio) vs 1/T (T = temperature ^{o}K) gave a straight line (see Fig. 4). This behaviour, consistent

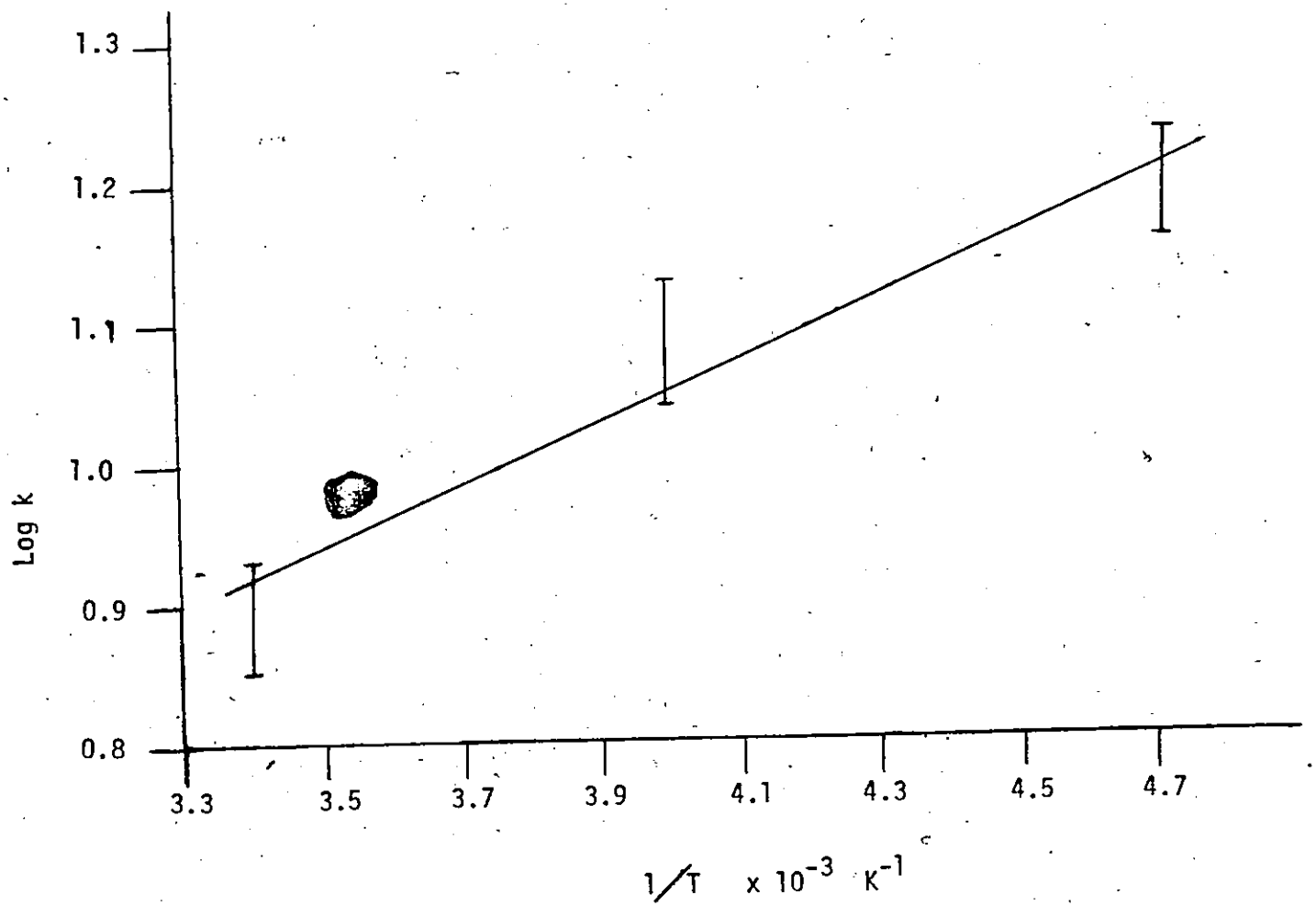

Figure 4

with a temperature dependent equilibrium, further supports the idea that α- sulfinyl carbanions readily undergo equilibration.

One of our principal aims as outlined in the general introduction was to test experimentally the findings suggested by Wolfe et al's calculations. One of these was that both α- sulfinyl and sulfonyl carbanions have low barriers to inversion (14, 16). We felt that we could establish an upper limit for the barrier to carbanion inversion ($\Delta G^{\ddagger}$) if an estimate of the maximum time for inversion could be made.

When 3-phenyl-2-thia-trans-decalin-2, 2-dioxide, (1), was reacted with CH_3Li in T.H.F. at - 60 and the carbanion quenched with excess H_2O after 1 minute, the axial isomer 2 was obtained in 92% yield* (>98% purity by n.m.r.) (see Scheme 6). The isomers 1 and 2 were distinguished from each other by n.m.r.: 1 shows a doublet of doublets at $\delta = 4.06$, Jax-ax = 12.5 Hz Jax-eq. = 3.8 Hz for the methine proton; 2 had a broad singlet at $\delta = 4.24$ for this proton.

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* This rather surprising equitorial to axial equilibration will be discussed in greater detail in Chapter 4.

An estimate of the upper limit for the free energy of inversion ($\Delta G^{\ddagger}$) of the carbanions $\underline{\underline{3}}$ and $\underline{\underline{4}}$ can be arrived at by the following line of reasoning: Assuming that deprotonation and reprotonation occur with the same stereochemistry[†] (most likely retention in both steps) and since $\underline{\underline{2}}$ was the only product (>98% purity) isolated from the carbanion reaction, one can estimate that the carbanion equilibration process has proceeded through at least 10 half lives in 1 minute. The maximum half life for this reaction is thus 6 seconds. The rate constant for a first order reaction (such as this one) is related to half life by eq. 1 (31).

$$t_{\frac{1}{2}} = \frac{0.69}{ki} \qquad \text{.....1)}$$

where $t_{\frac{1}{2}}$ = half life and ki = rate. From eq. 1 we get ki = 0.115 seconds $^{-1}$ for the inversion process. The free energy of inversion $\Delta G^{\ddagger}$ can now be obtained from the Eyring equation (32), eq. 2.

$$ki = \frac{kT}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}} \qquad \text{.....2)}$$

where k = Boltzman's constant, T = temperature, h = Planck's constant, R = gas constant. Substitution of ki in eq. 2 gives a value of 13 kcal per mole as the upper limit for $\Delta G^{\ddagger}$ at - 60°. Via a similar line of reasoning Durst (33) has arrived at a value of 12 kcal per mole for

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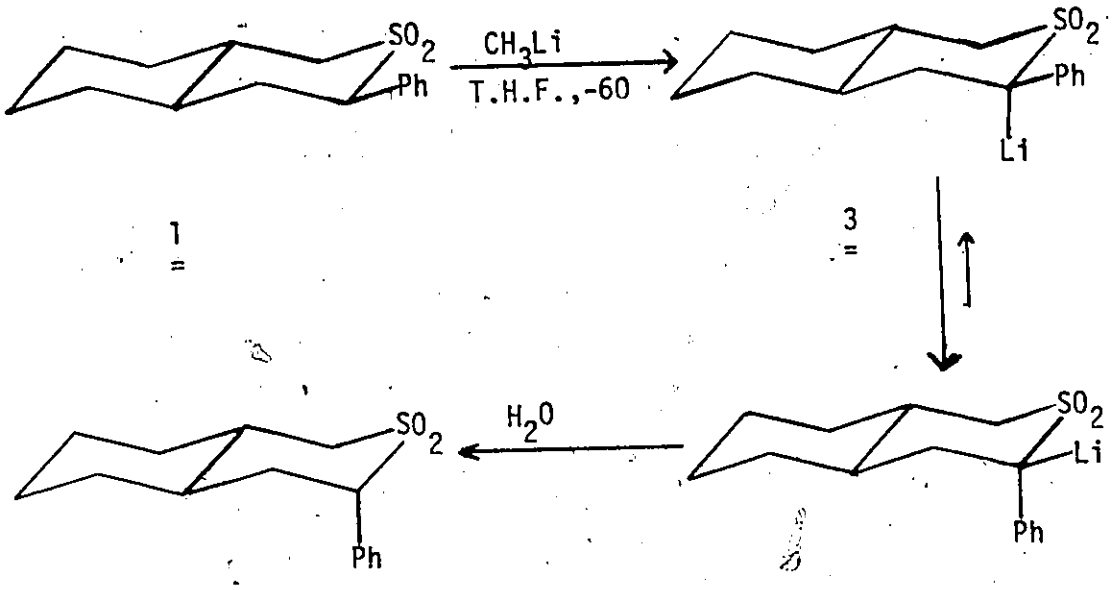
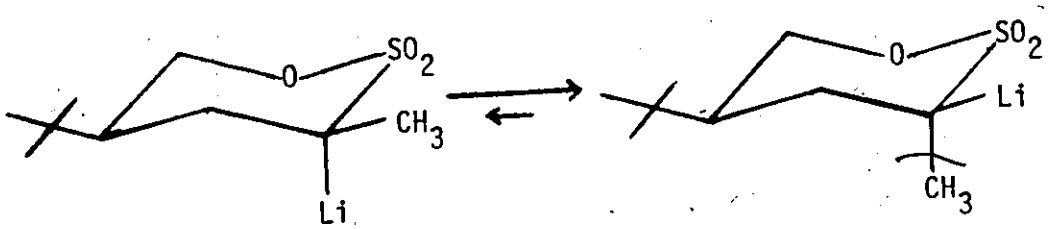
[†] We will show this is so for at least one sulfoxide (Chapter 6).



Scheme 6



Scheme 7

$\Delta G^{\ddagger}$ for the equilibration of the sultone carbanions 5 and 6 at - 78° (Scheme 7).

These results demonstrate that some sulfur stabilized carbanions rapidly equilibrate even at low temperature. In going from sultone carbanions to sulfone carbanions there is a decrease of one oxidation level at sulfur, nevertheless both types of carbanions have demonstrated similar behaviour and similar values for $\Delta G^{\ddagger}$. It therefore seems reasonable to assume that a further decrease of one oxidation level at sulfur (e.g. going from sulfone to sulfoxide carbanions) should not greatly affect the behaviour of the carbanion. α-Sulfinyl carbanions should therefore also have similar low barriers to carbanion inversion (e.g. $\Delta G^{\ddagger} \sim 13$ kcal/mole).

Conclusions:

We have shown that α-sulfinyl carbanions equilibrate rapidly under the reaction conditions employed. We have also shown that reactive electrophiles in general act as carbanion traps. Two free energy diagrams can be drawn to explain these results (see Fig. 5)

a) Carbanion equilibration is slower than the reaction of the carbanion with the electrophile i.e.: $\Delta G^{\ddagger}_{inv} > \Delta G^{\ddagger}$ (curve a), the electrophile therefore will trap the carbanion equilibrium;

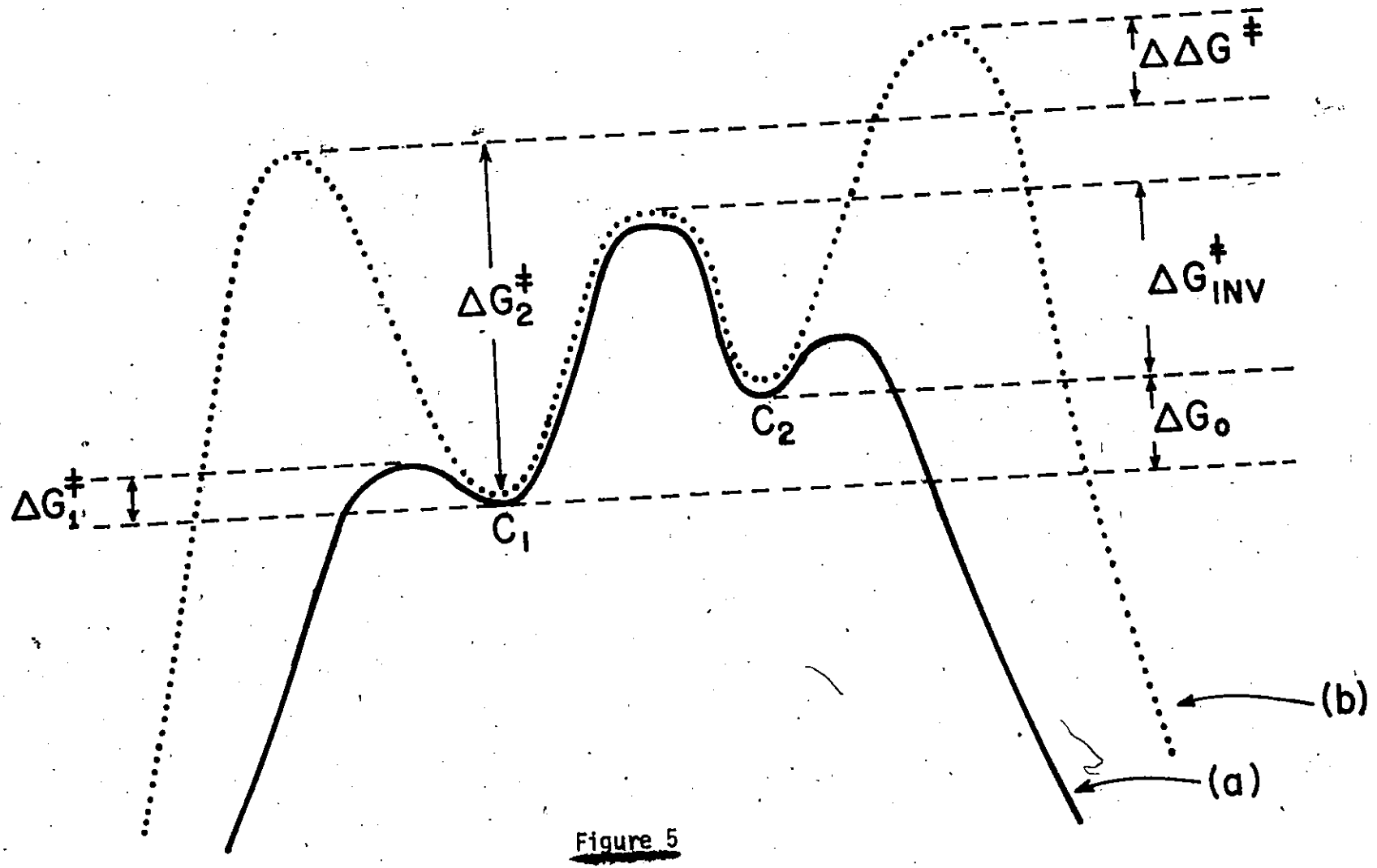

$\Delta\Delta G^{\ddagger}$
$\Delta G_2^{\ddagger}$
$\Delta G_{INV}^{\ddagger}$
ΔG_o
$\Delta G_1^{\ddagger}$
C_1
C_2
(b)
(a)

Figure 5

b) Carbanion equilibration is faster than carbanion reaction i.e.: $\Delta G^{\ddagger}_{1}$ inv. $< \Delta G^{\ddagger}_{2}$ (curve b), but since the reaction between the carbanion and electrophile is a rapid exothermic reaction, according to Hammond's postulate (45) the transition states for both carbanions should reflect their respective ground states i.e.: $\Delta\Delta G^{\ddagger} \propto \Delta G$. Unless the barrier to carbanion inversion is extremely small as suggested by the theoretical calculations, then explanation a) should be the more likely one. When carbanions are exposed to less reactive electrophiles, diastereomer ratios other than those observed with reactive ones would not be unexpected. This has been observed in some cases (34, 50).

We have shown that α- sulfinyl carbanions equilibrate rapidly and that reactive electrophiles serve as traps for this equilibrium. This is a verification of points 2) and 3) on which McClory's conclusions were based. The principal point (point 1) on which McClory's explanation for the preferred conformations for acyclic carbanions was based will be treated in Chapter 5 and conclusions regarding this theory will be given at that time.

Implicit in all the previous arguments and conclusions in this Chapter was the assumption that α- sulfinyl and sulfonyl carbanions are sp^3 hybridized. Although the sp^2 carbanion model

cannot be eliminated we at present feel that the sp^3 representation for both α- sulfinyl and sulfonyl carbanions is probably the correct one. There are several points which favour this latter representation: 1) The ab initio calculations of Wolfe and co-workers (14, 16) predict an sp^3 hybridized carbanion for both sulfoxides and sulfones. 2) The variations of product ratios with temperature indicate a temperature dependent equilibrium process (i.e. either inversion for sp^3 carbanions, or rotation for sp^2 carbanions). 3) The effects of solvents on some α- sulfonyl carbanions are more consistent with an sp^3 hybridized model (see Chapter 4) 4) The stereochemistry of electrophile attack on α- sulfinyl carbanions is more readily explained on the basis of an sp^3 model (see Chapter 5).

CHAPTER 4

SOLVENT EFFECTS ON THE CONFORMATIONAL PREFERENCE OF α- SULFINYL AND α- SULFONYL CARBANIONS

Introduction:

The effect of solvent on the stereochemical fate of base - catalysed exchanges involving carbanion intermediates has been extensively studied by Cram and co-workers (36). Four qualitatively different kinds of solvents for carbanions have been recognized (21): a) protic polar solvents such as water, the lower alcohols and polyols; b) aprotic polar solvents such as dimethyl sulfoxide (DMSO), sulfolane, dimethyl formamide (DMF); c) protic apolar solvents such as the butanols and aniline; d) aprotic non-polar solvents such as T.H.F., ether, dioxane, benzene and cyclohexane. These divisions are somewhat arbitrary since a continuity of changes in the properties of carbanions are observed as the solvent is varied (21).

Cram (36) has also characterized the solvents as being racemization, retention, or inversion solvents. The polar protic solvents give exchange with predominant inversion, the polar aprotic solvents with racemization, and the other two types give exchange with predominent retention of configuration (see Table 3). Cram has also

TABLE 3

Cram's classification of carbanion solvent-base systems.[a]

Solvent	Base	Type of System
CH_3OH	CH_3OK	Inversion
$HO-(CH_2)_2OH$	$HO-(CH_2)_2-OK$	Inversion
DMSO	t-BuOK	Racemization
B.T.A.-OH[b]	KOH	Racemization
t-BuOH	$(CH_3)_4NOH$	Racemization
$Ph-NHCH_3$	$Ph-NKCH_3$	Retention
Benzene	t-BuOK	Retention
Dioxane	t-BuOK or KOH	Retention
t-BuOH	t-BuOK	Retention

a) Data taken from reference 36.

b) B.T.A.-OH = Benzyltrimethylamine hydroxide.

shown that the base has a considerable effect on the stereochemical course of such exchanges (Table 3). The most striking example of this occurred when tetramethyl ammonium t-butoxide was substituted for potassium t-butoxide as base in t-butanol; the steric course of the exchange went from retention to racemization. It has also been noted that the metal cation plays a minor but detectible role in controlling the stereochemical course of the exchange reactions (37). Lithium salts tend to give somewhat higher retention in retention solvents than do potassium or sodium salts, the latter two giving similar results. In inversion solvents lithium salts often gives less inversion than potassium salts.

When Cram and co-workers (38) studied the base - catalysed exchange of phenyl 2-octyl sulfone in a variety of solvent - base systems, they found that in all systems the exchange proceeded with retention of configuration at carbon (see Table 4 and also Chapter 1 for significance of k_e/k_α ratios). Although all systems gave exchange with retention, the stereoselectivity was nevertheless quite sensitive to base and medium. The polar and protic solvents (inversion and racemization solvents) provided lower net retention for sulfone exchanges than did the non-polar protic (retention) solvents. The base also displayed an important role in the stereochemistry of the exchange.

TABLE 4

Cram's results for the base-catalysed exchange of 2-octyl phenyl sulfone in various solvents.

Solvent	Base	k_e a)/k_α b)
CH_3OH	CH_3OK	10
$HO-(CH_2)_2OH$	$HO-(CH_2)_2OK$	14.5-32 c)
DMSO	CH_3OK	10
t-BuOH	$(CH_3)_4NOH$	22-64 c)
t-BuOH	t-BuOK	73-1980 c)

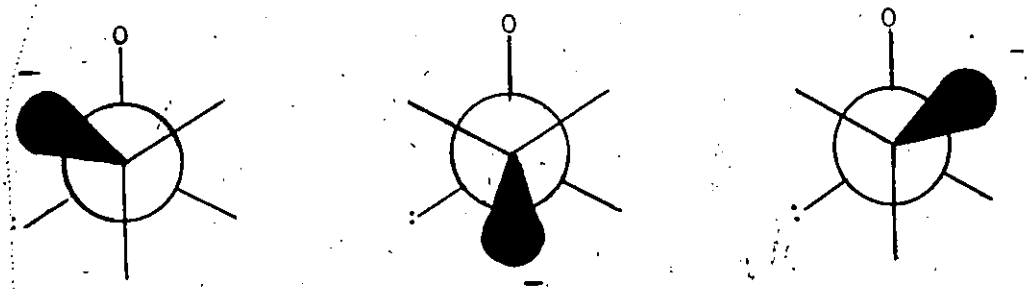
a) k_e = rate of exchange at carbon.

b) k_α = rate of racemization at carbon.

c) Ratio varies with concentration of base employed.

When tetramethylammonium hydroxide was substituted for potassium t-butoxide in t-butanol, the amount of retention decreased by factors of 3.5 to 31 depending on the base-substrate concentrations. This is reminiscent of the previously observed effect of tetraalkylammonium salts. From these results Cram et al concluded that carbanions stabilized by a sulfonyl group had different stereochemical capabilities than those stabilized by any other group studied up to that time.

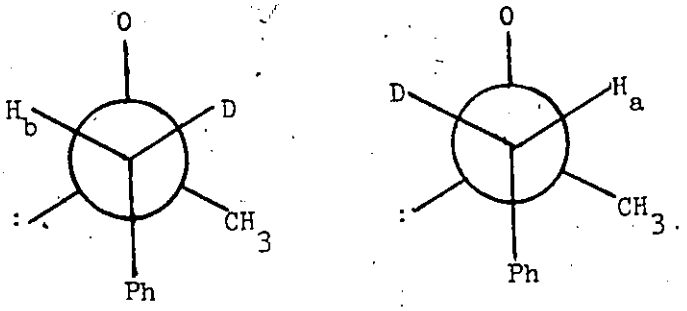
Little selectivity was observed by Cram and Pine (15) in the base-catalysed exchanges of optically active 2-octyl phenyl sulfoxides whether the solvent was t-butanol or DMSO. The first study in which any significant effect of solvent was observed was that of Katritzky and co-workers (12). They examined the base-catalysed exchanges of cis and trans 4 - phenylthiane-1-oxides in D_2O-NaOD, CH_3OD-CH_3ONa, t-BuOH-t-BuOK, DMSO 1M CH_3OD-CH_3OK (see Fig. 1, Chapter 1). In both D_2O - NaOD and CH_3OD-CH_3ONa the exchanges were stereoselective, the relative rates of exchange being Ha>He and He′>Ha′ (see Fig. 1). The exchanges in the other two solvent-base systems were nonstereoselective. From this the authors concluded that in polar protic solvents, water and methanol, the order of carbanion stability was B>A>C (See Fig. 6). For the exchanges in t-butanol and DMSO they suggested that "the non-stereoselectivity probably arises from fast inversion of the carbanions in these solvents".



A B C

Newman projection formulas of the staggered conformations of an ∝-sulfinyl carbanion

Figure 6



1 2

$Ph-CH_2-S(O)-CH_3$ $Ph-CHLi-S(O)-CH_3$

3 4

Figure 7

The Effect of Solvent on the Conformational Preference of Carbanions Derived From Benzyl Methyl Sulfoxide

The well documented effects of solvent and base on the stereochemistry of acyclic α- sulfonyl carbanions suggested that acyclic α- sulfinyl carbanions should also demonstrate some solvent-base dependence in their reactions. The preliminary results of Katritzky et al (12) in cyclic systems further supported this idea. We therefore decided to investigate the effects of solvent on the stereoselectivity of formation of diastereomeric monodeuterated sulfoxides 1 and 2 (Fig. 7) produced from benzyl methyl sulfoxide, (3), by competitive base-catalysed exchange* in deuterated protic solvents and by rapid quench of the α- lithiosulfoxide 4 in aprotic media.

The relative rates of exchange of the two diastereotopic protons of 3 are given in Table 5. The rates in D_2O/NaOD were obtained by measuring the deuterium uptake by mass spectrometry and are accurate to ± 2% (28); they compare favourably with those obtained by n.m.r. integration of the benzylic AB quartet as the exchange proceeded.

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* This work was carried out in collaboration with R.R. Fraser, R.B. Swingle, Y.Y. Wigfield who did the base-catalysed exchange experiments. We carried out the rapid quench experiments.

This latter method was used to obtain the data in CD_3OD/CD_3ONa. In t-BuOD the relative rates were obtained by quenching the reaction after partial exchange and analysing the n.m.r. spectrum of the products, the accuracy being ± 15%.

The lithio derivative 4 was generated at 24° in DMSO, T.H.F. and benzene by reaction of benzyl methyl sulfoxide with CH_3Li. The carbanion in T.H.F. was quenched with excess D_2O. In benzene and DMSO an excess of D_2O/DOAC (acetic acid-O-d) was used to quench the carbanion. It was noted in these solvents that the LiOD produced on quenching of the carbanion catalysed further exchange of the sulfoxide unless it was immediately neutralized on formation. Similar occurrences have been observed by others (21) when DMSO was used as solvent. The results from the quenching experiments are listed in Table 6.

These results can be rationalized on the basis of either a single planar carbanion intermediate which protonates preferentially from one side in high dielectric solvents D_2O, CD_3OD and DMSO and from the opposite side in low dielectric solvents T.H.F., t-BuOD and benzene or two isomeric pyramidal carbanions in which the relative energies of the diastereomers vary greatly with solvent.* We prefer

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* The question of planar vs pyramidal carbanion structure was discussed in Chapter 3.

TABLE 5

Relative Rates of Exchange of the Diastereotopic Protons in Benzyl Methyl Sulfoxide at 24°.

Solvent / Base	Relative Rates HA	HB
D_2O / NaOD	14.2	1
CD_3OD / CD_3ONa	5.5	1
t-BuOD / t-BuONa	0.50	1
t-BuOD / t-BuOLi	0.22	1

TABLE 6

Relative Amounts of Monodeuterated Species 1 and 2 Formed Upon Quenching of 4 at 24°.

Solvent	Relative Amounts 1	2
DMSO	1.7	1
Benzene	0.11	1
T.H.F.	0.13	1

the latter view at this time. On this basis the above experiments provide evidence that the relative stability of diastereomeric carbanions derived from 3 are markedly dependent on solvation. The kinetic results provide the relative stabilities of the transition states leading to carbanions. A theoretical discussion of the validity of the relative rates of exchange as a measure of carbanion stability has recently been published (11b). The quenching experiments give the relative stabilities of the carbanion themselves (see Chapter 3).

Under both sets of experimental conditions the diastereomer 1 having R configuration at carbon and S at sulfur (9) is preferentially formed in solvents having a high dielectric constant while 2 having S configuration at carbon and S at sulfur (9) predominates in solvents of low dielectric constant. The metal cation also seems to exert some effect (Table 5) on the stereochemical course of the exchange. When the cation was changed from sodium to lithium in t-BuOH as solvent, a different stereoselectivity was observed. This observation is analogous to those of Cram et al (37) for carbanion exchange reactions in t-BuOH.

Effect of Solvent on Some Sulfone Carbanions

As pointed out above the effect of solvent on base-catalysed exchange next to sulfone has been well studied. However, no data

involving the effect of solvent on quenching experiments of α-sulfonyl carbanions has appeared in the literature. We therefore decided to study the effect of solvent on the quenching reactions of sulfone carbanions.

When the equitorial phenyl sulfone 5 (Scheme 8, see Chapter 3) was treated with CH_3Li in T.H.F. at - 60° and the carbanion quenched after 1 minute with a large excess of H_2O, only axial sulfone 6 was recovered. When 6 was reacted with CH_3Li in DMSO-d_6 at 24° and the carbanion quenched after 1 minute with excess H_2O a 90% yield of 5 (>98% pure by n.m.r.) was recovered. Integration of the methine relative to the aromatic protons showed that essentially no deuterium incorporation had occured (e.g. <5%). This demonstrates that the conversion of axial 6 to equitorial 5 is not a rapid solvent carbanion exchange process leading to the thermodymically more stable product.*

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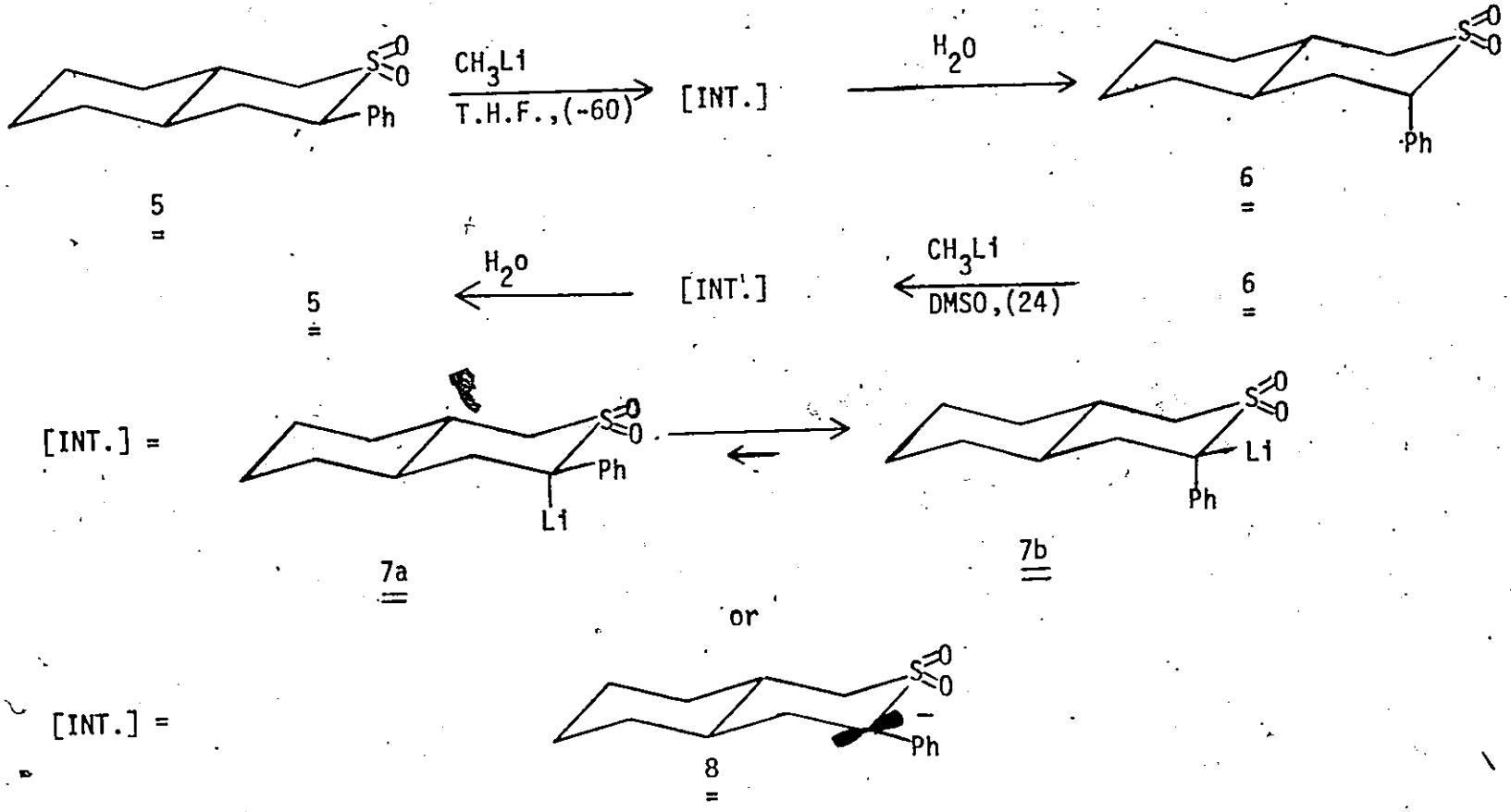
* Eliel et al (39) have observed that conformationally fixed 2 - lithiodithianes undergo rapid base solvent exchange in DMSO-d_6 to give 2,2 dideuterated dithianes under similar conditions.


CH3Li
T.H.F.,(-60)
[INT.]
H2O
Ph
5
6
H2O
[INT.]
CH3Li
DMSO,(24)
[INT.] =
Li
7a
7b
or
[INT.] =
8

Scheme 8

The results in T.H.F. may be interpreted in terms of either equilibrating sp^3 hybridized carbanion intermediates 7a and 7b or in terms of a single sp^2 hybridized intermediate 8. If one assumes the first explanation to be correct then 7b is favoured in T.H.F. whereas 7a is favoured in DMSO. Both carbanions are assumed to reprotonate with retention of configuration. If the second interpretation is correct then in T.H.F. the high stereospecificity may be accounted for on the basis of preferential equitorial attack on the carbanion 8. To account for the result in DMSO the attack by the electrophile must occur from the more hindered axial direction.

If our interpretation of the results on the basis of an sp^3 hybridized carbanion is correct, lithium (the carbanion) exhibits a strong preference for the equitorial position in T.H.F.; i.e. the carbanion on the bisector of the oxygen - sulfur - oxygen angle is preferred to the one gauche to one oxygen and trans to the other. In T.H.F. it appears that the preferred conformation for α- sulfonyl carbanions as was the case for α- sulfinyl carbanions is in agreement with the theoretical calculations (16).

An estimate of the minimum energy difference for lithium equitorial vs lithium axial (7a vs 7b) may be arrived at as follows: The ratio of 5 to 6 obtained upon quenching is a measure of the equilibrium between 7a and 7b (see Chapter 3). Since less than 2% of 5 was obtained, 7b is more stable than 7a by at least 1.7 kcal per mole. To this must be added the phenyl A value, 3.0 kcal/mole (40), to compensate for the unfavourable axial phenyl interaction in 7b. The minimum energy difference for equitorial lithium vs axial lithium is thus 1.7 + 3.0 = 4.7 kcal per mole.

The observed high thermodynamic preference for the equitorial vs axial orientation of the lithium in T.H.F. is not unique to α- lithiosulfones. Durst (33) has observed that in conformationally biased six-membered ring sultone carbanions in T.H.F., lithium also shows a high equitorial vs axial preference. The estimated preference for the equitorial orientation was $\geq$ 2.7 kcal /mole. A similar equitorial preference for lithium in some conformationally fixed six-membered ring dithiane carbanions in T.H.F. has been reported by Eliel and co-workers (39, 41, 42). They estimated this preference to be at least 4 to 5 kcal per mole.

The general preference for the equitorial orientation of sulfur stabilized carbanions in T.H.F. could be attributed to a stereoelectronic effect. For the sulfone carbanions the calculated conformation of lowest energy corresponds to the carbanion in the equitorial position (16). Explanations for the preferred equatorial orientation in dithianes have also been advanced (43, 44). Even though an explanation for our results consistent with the theoretical calculations was at hand, we felt that the estimated preference for the equitorial vs axial orientation of the carbanion was remarkably high. In addition the above three estimates neglected the A value for lithium in T.H.F.; in all cases it was assumed to be relatively small. The limited data available seemed to support this assumption. Glaze (46) found that in dimethyl ether at - 78 °menthyllithium had a 5.7:1 ratio of equitorial to axial lithium, i.e. an A value of about 0.7 kcal per mole. The related cyclohexyl Grignard and dicyclohexyl magnessium derivatives show A values between 0.25 and 0.78 kcal/mole in ether solvents (47). We however decided to verify this assumption experimentally.

cis-4-t-Butylcyclohexyl phenyl sulfone 9 was prepared as described by Eliel and Ro (48). The sulfur methine proton in the n.m.r. spectrum of this compound appeared as a broad singlet at

δ = 3.11. trans-4-t-Butylcyclohexyl phenyl sulfone 10 was prepared by equilibration of 9 in refluxing CH_3ONa/CH_3OH (44) (see Scheme 9). The sulfur methine proton of 10 appeared as a triplet of triplets at δ = 2.86, Jax-ax = 12.5 Hz, Jax-eq. = 3.5 Hz.

When 9 was treated with either a 10 or 50% excess of CH_3Li in T.H.F. at - 60° and the carbanion quenched after 1 minute with a large excess of H_2O a 99% yield of a 23 to 77% mixture of 9 to 10 was obtained.* The ratio of 9 to 10 was obtained by n.m.r. integration of the sulfur methine protons. When 10 was treated with a 50% excess of MeLi under identical conditions a 96% yield of a 23 to 77% mixture of 9 to 10 was again obtained. Since water traps the carbanion equilibrium (Chapter 3), the above results reflect the thermodynamic equilibrium between 11 and 12. At - 60° the 77:23 ratio corresponds to an energy difference of 0.5 kcal/mole favouring 12 over 11. (see Scheme 9). Sterically 12 is favoured over 11 by the SO_2-Ph A value which is 2.5 kcal per mole (40). Assuming that both the axial and equitorial carbanions are stabilized to the same extent by the sulfone group, then the A value for lithium in T.H.F. is 2.5 - 0.5 = 2 kcal per mole.

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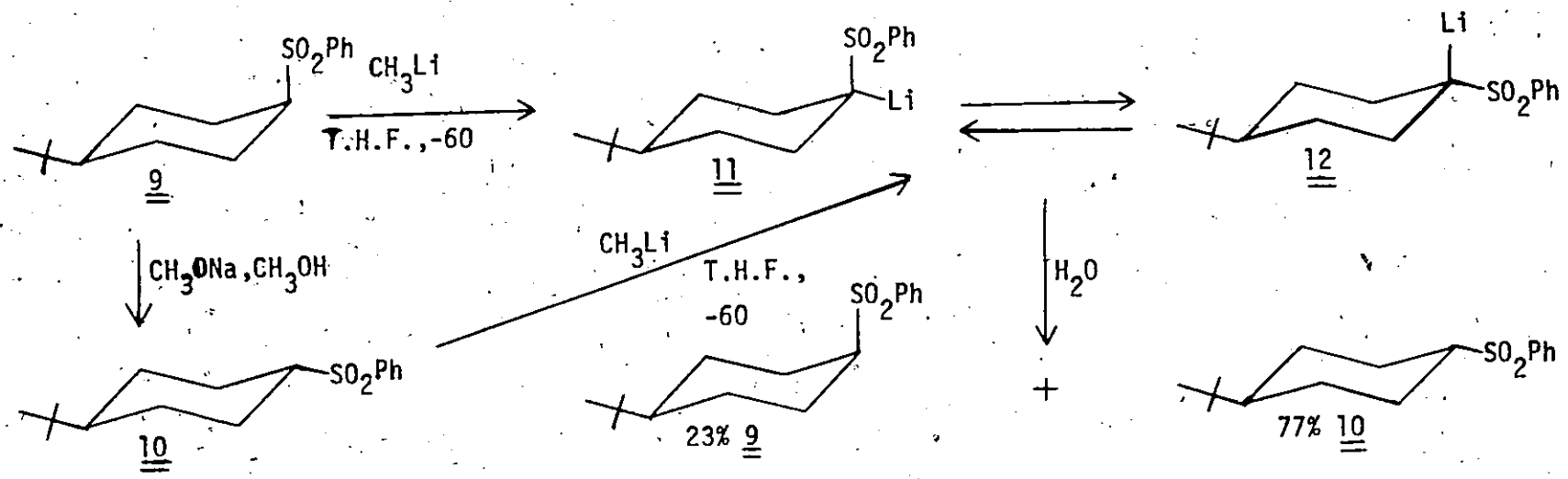
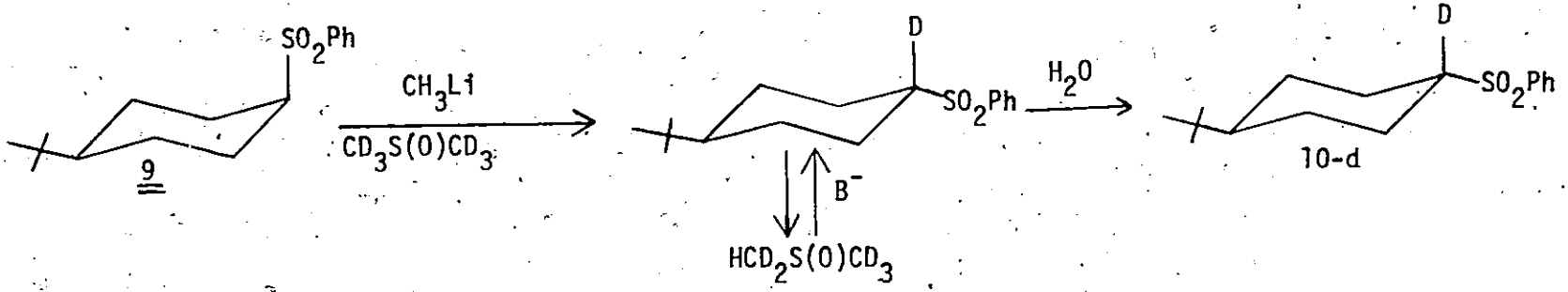
* These results are an average of at least 2 or more duplicate experiments.



Scheme 9



Scheme 10

In light of this result it seems that the previously estimated minima for the equitorial preference of lithium in six membered ring sulfur stabilized carbanions are all about 2 kcal/mole too high. Even when corrected for this, the equitorial preference for these sulfur stabilized carbanions remains surprisingly high.

When 9 was treated with a 50% excess of MeLi at 24° in DMSO-d_6 as solvent and the carbanion quenched with H_2O after 1 minute a 93% yield of product totally deuterated at the sulfur methine position was recovered. Comparison of the high field n.m.r. signals for the ring together with the t-butyl protons of the product with those of 9 and 10* indicated that the product was mainly deuterated 10. The conversion of 9 to 10 in DMSO can be attributed to a rapid solvent carbanion exchange leading to the thermodynamically more stable product. This is analogous to the behaviour of dithianes in DMSO (39).

An alternate explanation for the results in T.H.F. on the basis of an sp^2 hybridized carbanion can be invoked (see Scheme 11). As in the case of 8 equitorial attack should be favoured since the steric

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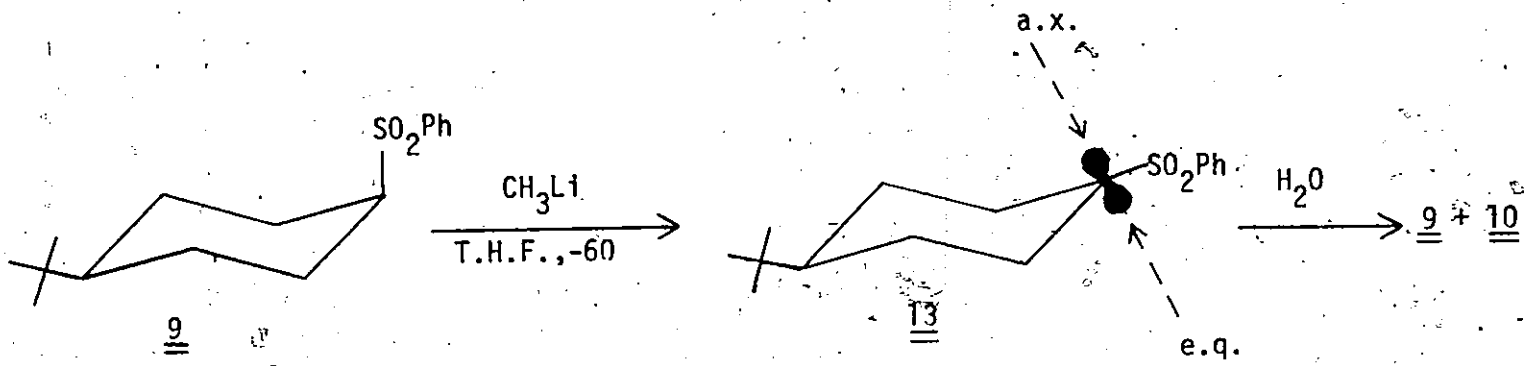
* These signals in 9 and 10 are quite different due to the effect of the axial SO_2-Ph group in 9.



Scheme 11

hindrance by the ring protons is similar in both 8 and 13 and since the SO_2-Ph group (A value = 2.5 kcal/mole) and the phenyl group (A value = 3.0 kcal/mole) are of comparable size. Therefore mainly axial sulfone 9 should be obtained; but only 23% of 9 is obtained. According to the sp^2 model, this means that 77% of the attack by the electrophile on the carbanion must have occurred from the more hindered axial side. It would seem that for two carbanions of the same type, in the same solvent, experiencing similar steric effects two different courses for the attack of H_2O on these carbanions predominate. We feel that the sp^2 carbanion model leads to an explanation inconsistent with the experimental observations, and that the behaviour of the above α-sulfonyl carbanions is more readily interpreted on the basis of an sp^3 hybridized model.

Effect of Solvent on Some Conformationally Fixed α- Sulfinyl Carbanions: (Literature Survey)

Several papers dealing with the conformational preference of α- sulfinyl carbanions in conformationally fixed systems and the effect of solvent on this preference have recently appeared (11, 13)*.

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* In all these papers the results were discussed in terms of an sp^3 hybridized carbanion.

A good summary of the work in this area has most recently been presented by Fraser et al (11). The results from these papers are summarized in Table 7 (the compound numbering in this section will refer to that of Fig. 1, Chapter 1).

The relative rates of exchanges of the protons in 4 were $H_1 = 1$, $H_2 = 1100$, $H_3 = 300$, $H_4 = 1300$ in t-BuOD/t-BuOK; and $H_1 = 1$, $H_2 = 200$, $H_3 = 7600$, $H_4 = 30$ in $CD_3OD/NaOCD_3$. Proper evaluation of the results requires a comparison of H_1 vs H_2 and H_3 vs H_4 only, since these pairs of protons reside in identical environments with respect to the asymmetric biaryl system. Any differences in reactivity within either pair can thus be attributed to the influence of the sulfoxide group on the stability of the carbanions and this difference is a reflection of the stabilizing effect of the sulfoxide group.

In t-BuOD the rate of exchange of H_4 is approximately 3 times that of H_3. Therefore in this solvent carbanion C>B. But in CD_3OD the rate of exchange of H_3>200 times that of H_4, therefore carbanion B>>C in this solvent. This latter result is similar to one obtained by Lett and Marquet (13) in D_2O and by Katritzky (12) in D_2O and CD_3OD (12). (compounds 5, 6 and 9 in Table 7).

TABLE 7

Effect of Solvent on the Stability of Conformationally Fixed Sulfoxide Carbanions

Compound[a]	Solvent / Base	Order of Carbanion Stability[b]	Ref.
4	t-BuOD/t-BuOK	C>B	11a
4	CD_3OD/CD_3ONa	B>C	11a
	CD_3OD/CD_3ONa	B>A>C	12
	$D_2O/NaOD$	B>A>C	12
5 and 6	$DMSO-CD_3OD/CD_3ONa$	B≳C≳A	12
	t-BuOD/t-BuOK	B≳C≳A	12
9	$D_2O/NaOD$	B>C, B>A	13
7	CD_3OD/CD_3ONa		11a
8	CD_3OD/CD_3ONa		11a
Theory	Gas Phase	A>B>C	14

a) See Fig. 1, Chapter 1 for compound numbering, p. 7.

b) See Fig. 6, p. 49.

Apart from the remarkable solvent effect noted above a rather large angular dependence of carbanion orientation was observed. Exchange of protons H_1 and H_2 in 4 lead to type A carbanion in both cases. In spite of only a 40^{o} difference in their orientation with respect to the sulfur asymmetry H_2 exchanged 200 and 1100 times faster than H_1 depending on the solvent. The exchange which produces the carbanion closer to the lone pair on sulfur occurs more slowly in both solvents.

Exchange experiments in CD_3OD/CD_3ONa for compounds 7 and 8 showed that $k_{h_x}/k_{h_n} \geq 12:1$ in 7 and $k_{h_x}/k_{h_n} = 1:2.5$ in 8. These results indicate that abstraction of the proton syn to the sulfur - oxygen bond is greatly prefered (5.4 times) to that syn to the sulfur lone pair.

From these results Fraser and co-workers concluded that the molecular orbital calculations of Wolfe et al (14) concur with experimental findings in that large variations in carbanion stability vs dihedral angle do occur. From the fact that a change in solvent completely reversed the relative reactivities of protons H_3 and H_4 they concluded that the role of solvent dominates over that of the dihedral angular relationship of the carbanion to the sulfoxide in determining the ultimate stereochemical influence on reactivity.

These authors also re-examined the results from the kinetic exchanges of benzyl methyl sulfoxide and suggested that the high selectivity in D_2O (16:1) might be best explained on the basis of non-staggered carbanion conformers.

CHAPTER 5

STEREOCHEMICAL COURSE OF THE REACTION OF α- SULFINYL AND α- SULFONYL CARBANION WITH ELECTROPHILES

Introduction:

One of the main objectives in our study of α- sulfinyl carbanions was to evaluate their synthetic potential as intermediates in the synthesis of compounds having asymmetry at carbon. In order to do this it was necessary to determine the stereochemical course of the reactions of the lithio salts of sulfoxides, with various electrophiles, which produce the major diastereomeric products. This was accomplished in the following manner: Sulfoxides of known absolute configuration (6, 49) were reacted with methyllithium and the α- lithio sulfoxides thus formed were treated with electrophiles. The asymmetry at sulfur in the products was then removed by either oxydation to sulfones or reduction to sulfides. The absolute configuration at the alpha-carbon was then determined by comparison of the rotation of these products with compounds having known configuration at carbon.

The stereochemical behaviour of α- lithio benzyl methyl, benzyl t-butyl, and p-tolyl ethyl sulfoxides was stuided in greatest detail. These lithio sulfoxides were chosen because they would also

enable us to examine the major assumption on which McClory's arguments (20) concerning the prefered conformations of acyclic sulfoxides carbanions were based (point 1), Chapter 3).

The Stereochemical Behaviour of α- Lithio Sulfoxides

The optically active sulfoxides of known configuration were prepared by reaction of the appropriate Grignard reagent with either l-menthyl phenylmethane sulfinate or l-menthyl p-tolyl sulfinate, both of known configuration at sulfur (6, 49, 51).

When (S) - benzyl methyl sulfoxide (1), $[\alpha]_D$ + 97.7 (C = 0.8 EtOH)*, lit. (52) $[\alpha]_D$ + 96, was treated with CH_3Li at - 60° in T.H.F. and the carbanion quenched with a > 10 fold excess of D_2O, monodeuterated sulfoxide 2, $[\alpha]_D$ + 92 * (C = 0.7, EtOH) was obtained (Scheme 12). This result demonstrated that no significant loss in sulfoxide asymmetry occurred under the reaction conditions used. Similar observations have previously been made by Jacobus and Mislow (53). A sample

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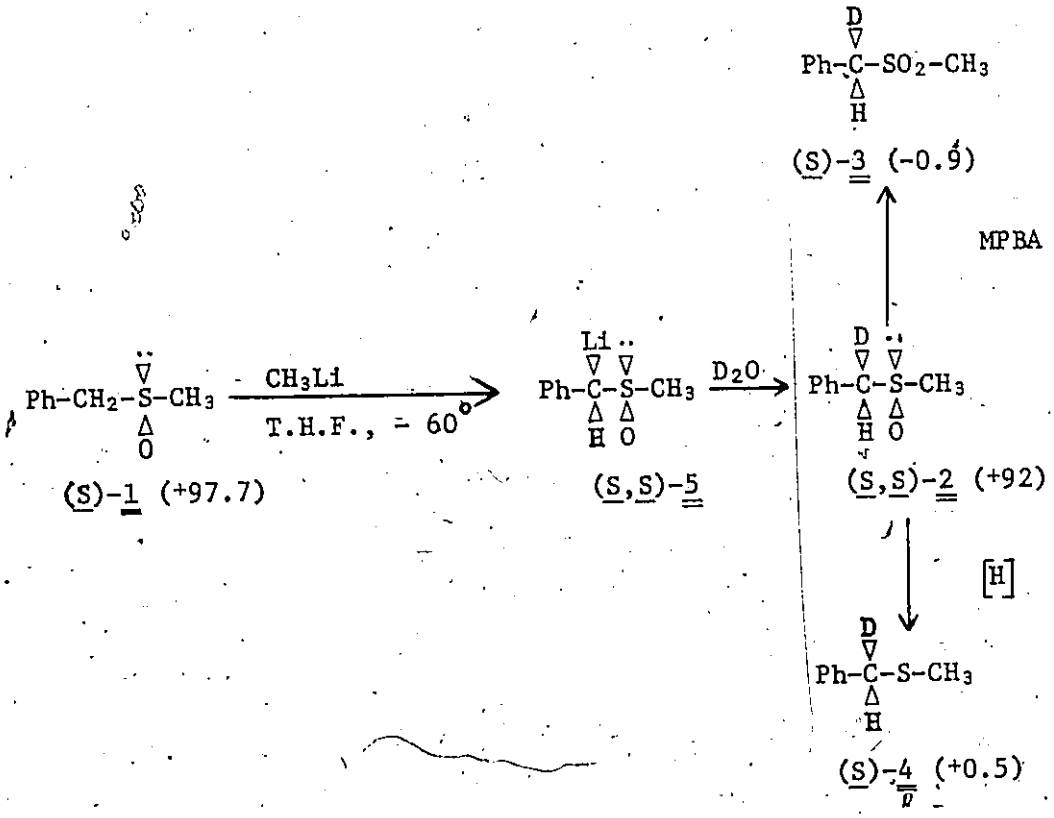
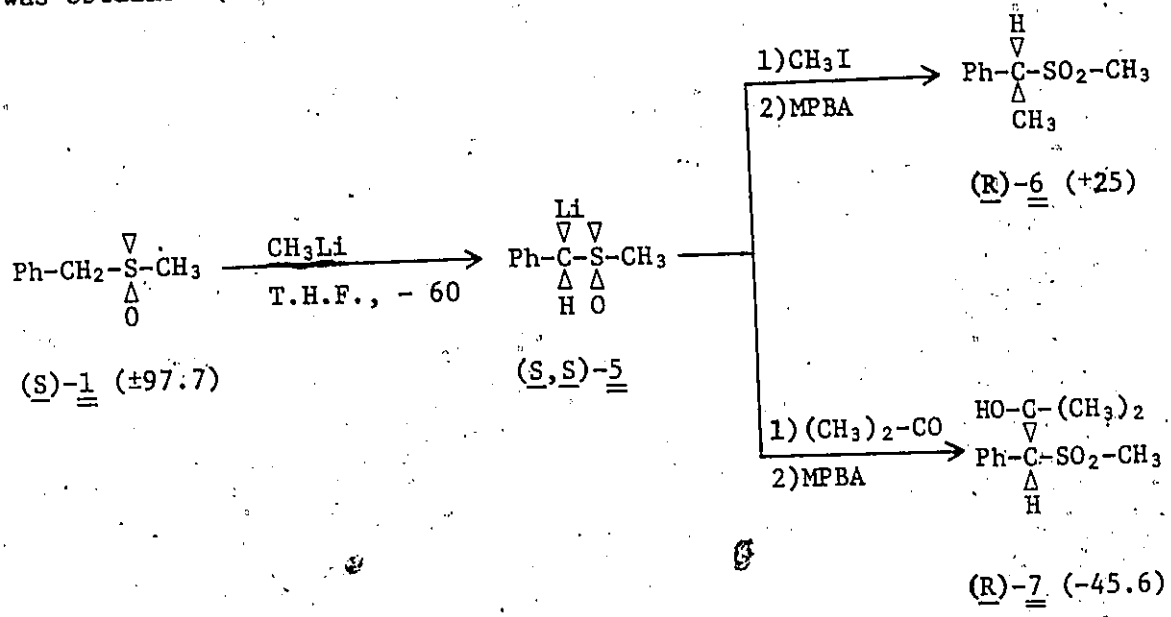
* The rotation of this sulfoxide was slightly higher than any previously reported since we were able to obtain l-menthyl phenylmethane sulfinate, its precursor, of a higher rotation than previously reported (51). In addition, variations in the rotation of this sulfoxide were noted due to its extreme hydroscopic nature.

of 2 was oxidized to the sulfone 3, $[\alpha]_D$ - 0.9 (C = 1.2, $CHCl_3$) using excess m-chloroperbenzoic acid (MPBA). A second portion of 2 was reduced to the sulfide 4, $[\alpha]_D$ + 0.5 (C = 11.5, $CHCl_3$) using $SnCl_2$-CH_3COCl in DMF/CH_3CN (53). (S) - α - Deuteriobenzyl methyl sulfone, $[\alpha]_D$ - 0.6 (C = 6, $CHCl_3$) and (S) - α - deuteriobenzyl methyl sulfide, $[\alpha]_D$ + 0.73 (C = 12, EtOH) have previously been described (9a). The major isomer produced on deuteration of the lithio salt of (S) - benzyl methyl sulfoxide thus has S configuration at carbon.



SCHEME 12

When the lithio sulfoxide 5 was reacted with CH_3I and the product oxidized with excess MPBA, the sulfone 6, $[\alpha]_D$ + 25 (C = 7, EtOH) was obtained (Scheme 13).



(S)-1 (±97.7)

(S,S)-5

(R)-6 (+25)

(R)-7 (-45.6)

SCHEME 13

The configuration at carbon in 6 was determined by the sequence of reactions shown in Scheme 14. (S)-α-Phenethyl alcohol, $[\alpha]_D$ - 43.2 (neat) 99% optically pure, reported $[\alpha]_D$ - 43.6 (neat) (54), was converted to (S)-α-methylbenzyl phenylmethane sulfonate 8* by reaction with α - toluene sulfonyl chloride and $(Et)_3N$ in CH_2Cl_2 (56). The

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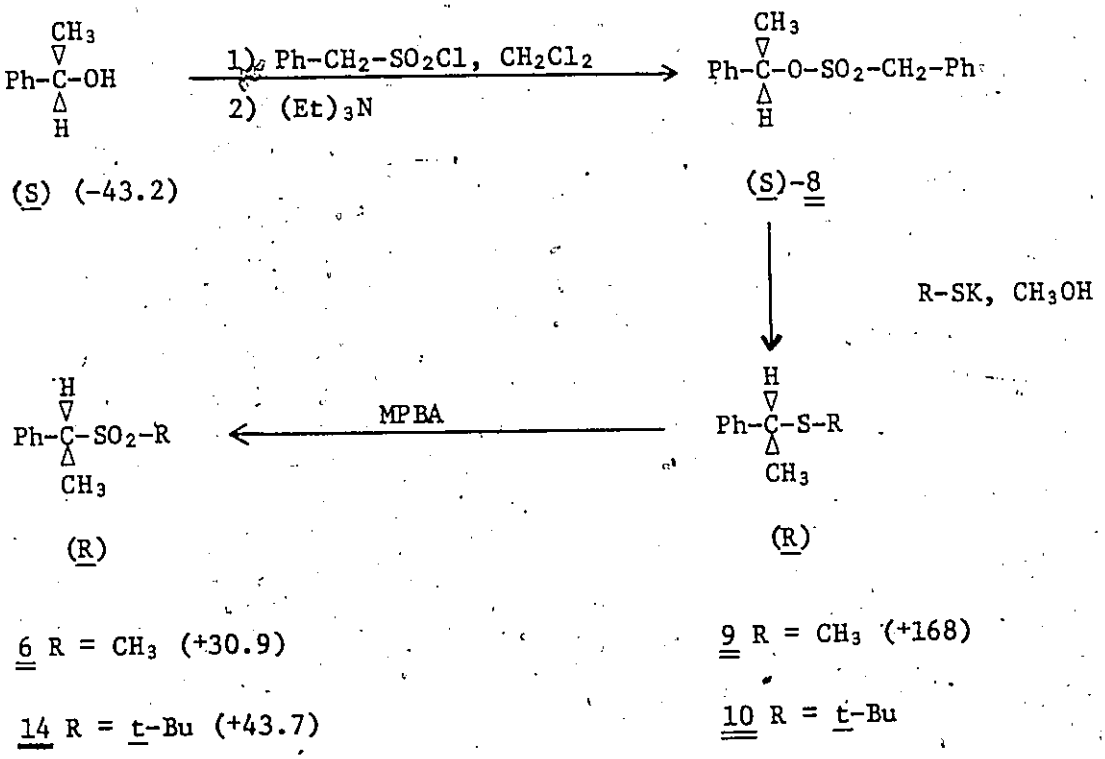
* Intermediate 8 is not stable and decomposed in a few minutes at room temperature. It was therefore not isolated and characterized but was immediately converted to give 9 or 10.

sulfonate ester was reacted with potassium methyl thiolate in CH_3OH to give the (R) sulfide 9 $[\alpha]_D^+$ 168 (C = 0.8, EtOH). It is well known that such displacements (SN2) occur with inversion at carbon (56). Sulfide 9 was then oxidized to (R)- -methylbenzyl methyl sulfone 6', $[\alpha]_D^+$ 31 (C = 0.8, EtOH). The major diastereomer from the methylation reaction therefore had R configuration at carbon. Assuming maximum rotation for sulfone 6' then the optical purity of 6 was 81%, in good agreement with the 85% predicted on the basis of the diastereomer ratio determined in Chapter 3.



6 R = CH_3 (+30.9)

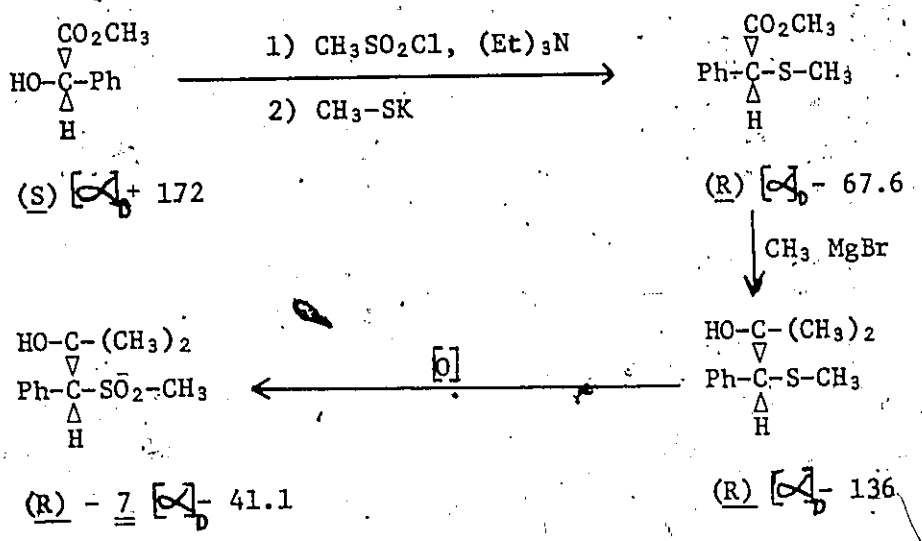
14 R = t-Bu (+43.7)

9 R = CH_3 (+168)

10 R = t-Bu

SCHEME 14

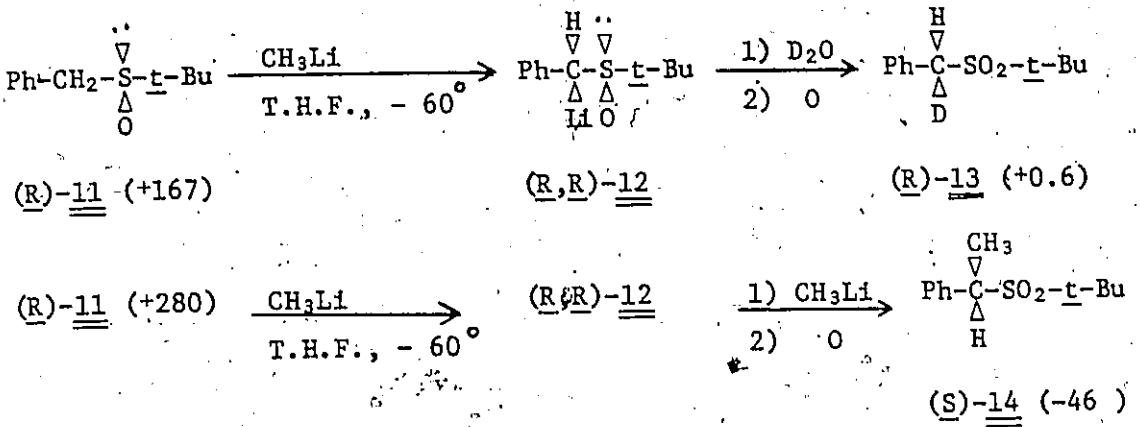
When the lithio sulfoxide 5 was quenched with acetone and the adduct oxidized with MPBA, the sulfone 7, $[\alpha]_D$ - 45.6 (C = 1.9, EtOH), was obtained (Scheme 13). Sulfone 7[1] having R configuration at carbon was obtained from (S) - mandelic acid, $[\alpha]_D$ + 147 (C = 2.5, H_2O), lit. $[\alpha]_D$ + 157 (57) as shown in Scheme (15)*. The hydroxyalkylation of (S) - benzyl methyl sulfoxide thus gave as its major adduct a compound having R configuration at carbon.



SCHEME 15

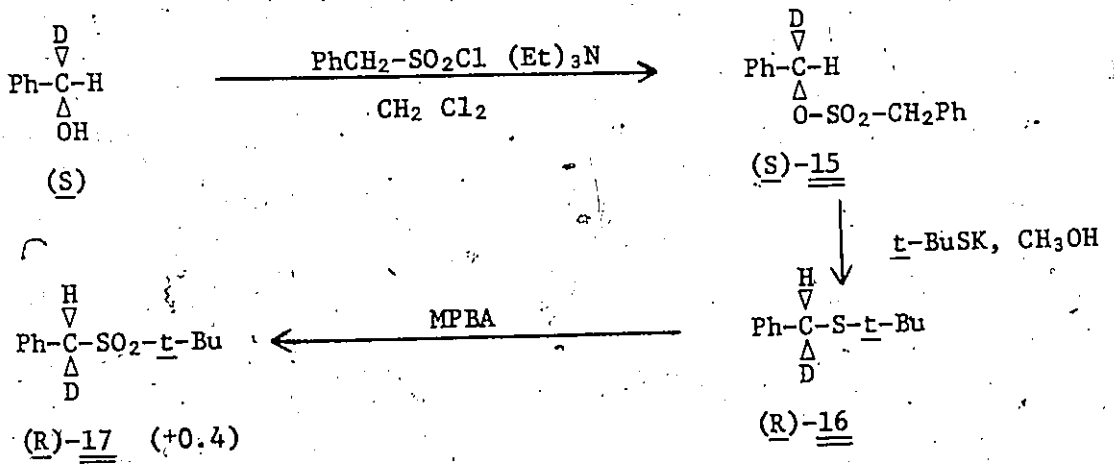
* The retention of optical purity at carbon in this sequence is probably <100% in going from the ester to the sulfide since partial racemization via enolates may have occurred in the thiolate displacement and in the Grignard reaction.

(R) - Benzyl t-butyl sulfoxide 11, $[\alpha]_D^+$ 167 (C = 0.7, EtOH), lit. $[\alpha]_D^+$ 281 (52), was reacted with CH_3Li in T.H.F. at - 60° to give the carbanion 12 which was quenched with either an excess of D_2O or CH_3I (Scheme 16).



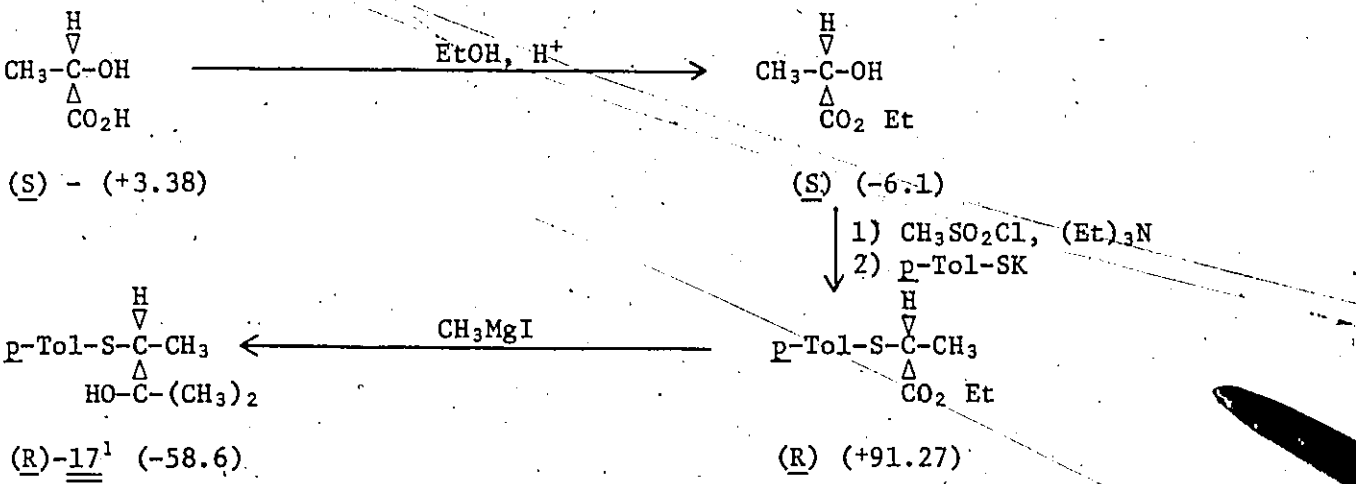
SCHEME 16

The absolute configurations at carbon of the two products thus obtained were shown to be R and S respectively (See Experimental Section and Schemes 14 and 17).



SCHEME 17

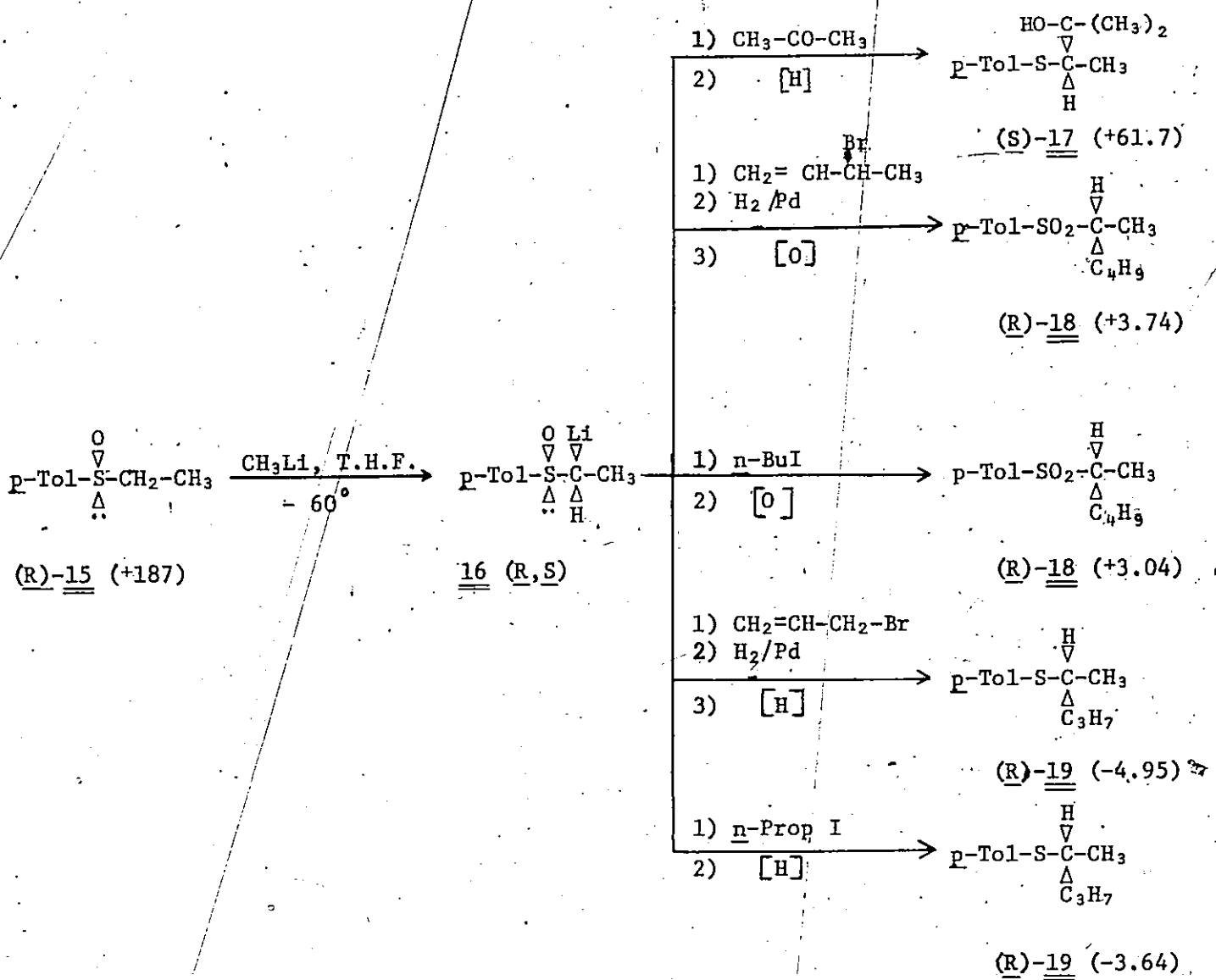
Finally (R)-p-tolyl ethyl sulfoxide 15, $[\alpha]_D^+$ 187 (C = 1.66, $CHCl_3$), reported $[\alpha]_D^+$ 187.5 (6), was reacted with CH_3Li in T.H.F. to give lithio sulfoxide 16 (Scheme 18). When acetone was used to quench 16, and the resulting adduct reduced, sulfide 17, $[\alpha]_D^+$ 61.7 (C = 1.66, $CHCl_3$), of (S) configuration at carbon was obtained. The configuration at carbon was determined by comparison with the (R) sulfide 17[1], $[\alpha]_D^-$ 58.6 (C = 1.33, $CHCl_3$) synthesised from (S) - lactic acid, $[\alpha]_D^+$ 3.38, 65% optically pure (59), via the reactions depicted in Scheme 19.



SCHEME 19

Assuming that no optical activity is lost in the synthesis of (R)-17 (see however footnote p. 73) then the diastereomer product ratio obtained in the hydroxyalkylation reaction is ≤5:1 (Table 2, Chapter 3).

When 16 was reacted with 3-bromo-1-butene (see footnote p.32), the double bond of the adduct hydrogenated and the sulfoxide oxidized, sulfone 18 $[\alpha]_D^+$ 3.74 (C = 2.03, $CHCl_3$) was obtained. When n-butyl iodide was used to quench 16 and the resulting adduct oxidized, sulfone 18



(R)-15 (+187)

16 (R,S)

(S)-17 (+61.7)

(R)-18 (+3.74)

(R)-18 (+3.04)

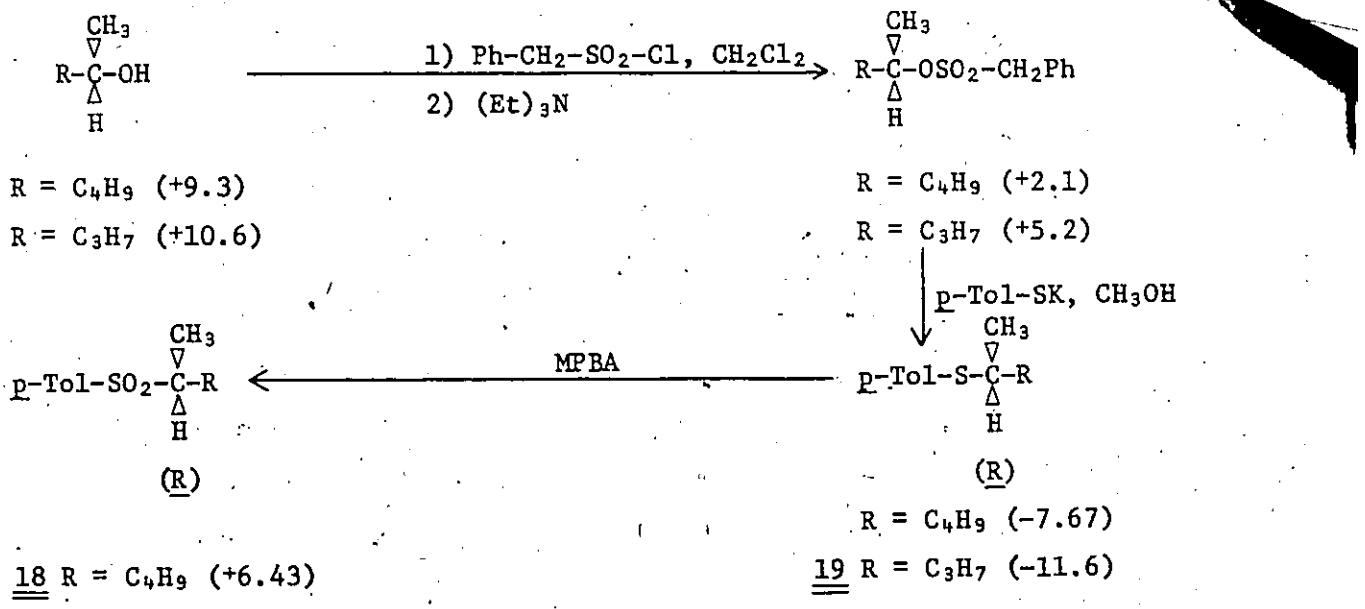
(R)-19 (-4.95)

(R)-19 (-3.64)

SCHEME 18

$[\alpha]_D^+$ 3.04 (C = 6.48, $CHCl_3$) was again obtained. Synthese of (R)-p-tolyl 2-hexyl sulfone 18, $[\alpha]_D^+$ 6.43 (C = 5.5, $CHCl_3$) from (S)-2-hexanol, $[\alpha]_D^+$ 9.3 (neat)* showed that the two above adducts had R configuration at carbon (Scheme 20).

Reaction of 16 with allyl bromide followed by hydrogenation of the adduct's double bond and reduction of the sulfoxide group gave sulfide 19 $[\alpha]_D^-$ 4.95 (C = 0.9, $CHCl_3$). When n-propyl iodide was used to quench 16, sulfide 19, $[\alpha]_D^-$ 3.64 (C = 11.1, $CHCl_3$) was obtained after reduction of the sulfoxide group in the original adduct. The configuration at carbon in 19 was shown to R by synthesis of (R)-p-tolyl 2-pentyl sulfide 19, $[\alpha]_D^-$ 11.6 (C = 13.28, $CHCl_3$) from (S)-2-pentanol, $[\alpha]_D^+$ 10.62 (neat)† (Scheme 20).



SCHEME 20

* The alcohol was 67% optically pure, lit. $[\alpha]_D^+$ 13.9 (neat) (60).

† This alcohol was 91% optically pure, lit. $[\alpha]_D$ = 11.68 (neat) (61).

A summary of the results of our study of the stereochemistry of the reaction of lithio sulfoxides with a number of electrophiles is given in Table 8.

An examination of the results of the deuteration of benzyl methyl and benzyl t-butyl sulfoxides shows that sulfoxides having the same S=O asymmetry give products in which the major diastereomers have the opposite configuration at carbon. This is most clearly illustrated in Fig. 8. Analogous results were obtained in the methylation of these sulfoxides. The alkylation and hydroxyalkylation of benzyl methyl and p-tolyl ethyl sulfoxides having the same S=O asymmetry also gave in each case, products in which the major diastereomers had opposite configuration at carbon.

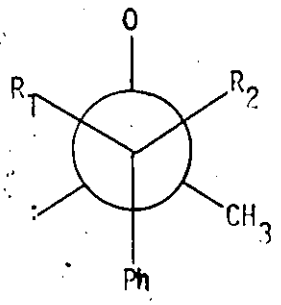
The results shown in Table 8 and Fig. 8 are not those predicted on the basis of McClory's hypothesis regarding the prefered conformations of acyclic α- sulfoxide carbanions discussed in Chapter 3. Benzyl methyl and p-tolyl ethyl sulfoxide carbanions were predicted to produce the same stereochemistry at carbon while the benzyl t-butyl carbanion should produce the opposite stereochemistry at carbon. Only the latter prediction held true, thus the hypothesis must be seriously questioned. Even for the simple series of benzylic

TABLE 8

Stereochemistry of the trapping products from the reactions of various α- lithio sulfoxides in T.H.F. at - 60°.

Parent Sulfoxide	Electrophile	Configuration of Product at Sulfur	Carbon
	D_2O	S	S
$Ph-CH_2-S(O)-CH_3$	CH_3COCH_3	S	R
	CH_3I	S	R
$Ph-CH_2-S(O)-t-Bu$	D_2O	R	R
	CH_3I	R	S
	CH_3COCH_3	R	S
	$CH_2=CH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-Br$ [a]	R	R
$p-Tol-S(O)-CH_2-CH_3$	$CH_2=CH-CH_2-Br$	R	R
	n-PropI	R	R
	n-BuI	R	R

a) This reagent contained 10% of 1-bromo-2-butene, see footnote p. 32.

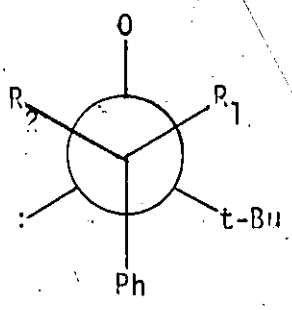


(S,S) R_1=Li, R_2=H

(S,S) R_1=D, R_2=H

(S,R) R_1=H, R_2=CH_3

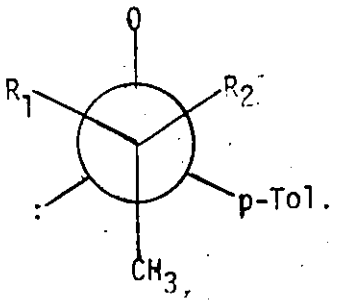
(S,R) R_1=$-C(OH)-(CH_3)_2$, R_2=H



(R,R) R_1=Li, R_2=H

(R,R) R_1=D, R_2=H

(R,S) R_1=H, R_2=CH_3



(R,S) R_1=H, R_2=$-C(OH)-(CH_3)_2$

(R,R) R_1=alkyl, R_2=H

Figure 8

sulfoxides ($Ph-CH_2-S(O)-R$) the application of the hypothesis is questionable, since as the size of the alkyl group (R) is increased from methyl, to ethyl, to i-propyl, to t-butyl, a systematic variation in the product ratios is predicted. An examination of Table 2 in Chapter 3 shows that this is clearly not the case. It therefore appears that a simple treatment for the prediction of the preferred conformations of acyclic sulfoxide carbanions on the basis of only steric and electronic factors is inadequate.

A comparison of the stereochemical course of the reaction of α- lithio benzyl methyl sulfoxide with various electrophiles shows that the deuteration and hydroxyalkylation reactions give products having the same orientation of the substituents at carbon* (Fig. 8, Table 8); the methylation reaction however gives products having opposite configuration at carbon. Similar stereochemical results were also observed for the benzyl t-butyl and p-tolyl ethyl sulfoxide carbanions.

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* The reason for the differences in the R and S designation of the products is due to higher priority of the $(CH_3)_2-C-OH$ group over the phenyl group in this system, thus changing the designation of the hydroxyalkylation product from S to R at carbon.

Evidence has been presented that H - D exchange proceeds with retention of carbanion configuration (7, 11, 27). We will show in the next Chapter that deprotonation and reprotonation of a sulfoxide carbanion proceed via the same stereochemical pathway in both steps, either retention or inversion; therefore the overall process must be occurring with retention at carbon. By anology to the sulfone carbanions we would expect the hydroxyalkylations to proceed with retention of carbanion configuration (62).

Since the deuteration and hydroxyalkylation reactions proceed with retention of carbanion configuration, the alkylation reaction must therefore proceed with inversion of carbanion configuration. The possibility that methylation has proceeded with retention as a result of the less stable carbanion reacting more rapidly is highly unlikely in view of the consistency of the methylation, hydroxyalkylation and deuteration diastereomer ratios reported in Chapter 3.

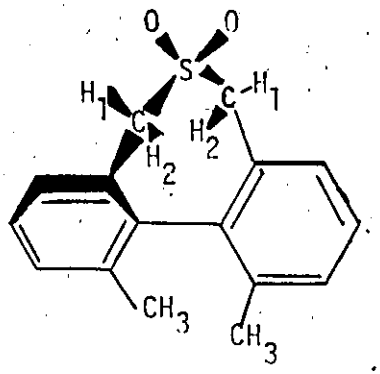
Nishio and co-workers (63) have also recently reported that methylation and deuteration of α- lithiobenzyl methyl sulfoxide occur with opposite stereochemistry. They initially suggested that methylation occurred with retention and deuteration with inversion but have since agreed that the stereochemical course which we have proposed is more likely (50, 78).

Stereochemical Behaviour of Other Sulfur Stabilized Carbanions

A number of electrophilic substitutions at carbon with inversion of configuration have recently been reported (64-67). The most relevant example to our study is the intramolecular alkylation of an α- sulfinyl carbanion to give an episulfoxide (67). When meso-bis (α- dibromobenzyl) sulfoxide and dl - bis (α - dibromobenzyl) sulfoxide were treated with hexamethylphosphorictriamide they gave respectively a cis, anti-episulfoxide and a trans episulfoxide. The only mechanism consist nt with these results is one in which inversion at both reaction sites is occurring (i.e. at the carbanion and alkyl halide carbon). Other examples closely related to our study are the intramolecular alkylations of α- sulfonyl carbanions to give episulfones which are the intermediates in the Ramberg - Backlund rearrangement. The bridgehead carbanion from 1-bromo-9-thiabicyclo (3.3.1) nonene must invert in order to displace bromide ion to give $\Delta^{1,5}$ - bicyclo (3.3.0) octene after loss of SO_2 (65). Bordwell and co-workers (66) have concluded that the formation of cis - α, α^1 - dimethylstilbene from erythro- α-bromo- α-methylbenzyl- α-methylbenzyl sulfone is the result of an inversion at both benzylic carbons. In this example, alkylation with inversion is apparently prefered over rotation and alkylation with retention. In the intermolecular alkylations of α- lithio sulfoxides described in the previous section, both reactions with retention or inversion could have occured directly, the latter seems to be the prefered pathway.

In order to examine the generality of the preference for inversion in the alkylation of sulfur stabilized carbanions we examined the reactions of some conformationally fixed sulfones. The first system examined was 1, 11-dimethyl-5, 7-dihydrodibenz (c, e) thiepin-6, 6-dioxide (20) (Fig. 9).

When the carbanion of 20 was generated and quenched in the usual manner using acetic acid-O-d as the proton source, a 97% yield of pure monodeuterated sulfone was recovered. Integration of the AB quartet of the benzylic protons during deuterium decoupling showed that 79% of the protons exchanges were of the low field half of the AB pattern and 21% of the high field half. Fraser and Schuber (68) have shown that the low field protons in the AB quartet correspond to H_1 in 20 and the high field protons correspond to H_2 in 20. The relationship of H_1 and H_2 to the sulfur asymmetry is best seen in the Newman projection 20a (Fig. 9). Projection 20d shows the major product of the deuteration reaction. This result shows that the carbanion on the bisector of the oxygen-sulfur-oxygen bond is the most stable of the two possible carbanions. This result is qualitatively similar to that reported by Fraser and Schuber for the exchange reaction in t-butanol-sodium phenoxide (69a).



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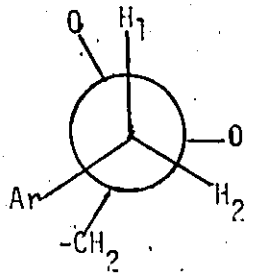
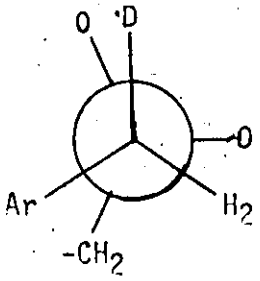


20a



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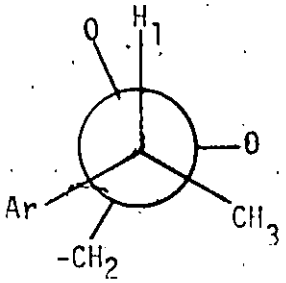

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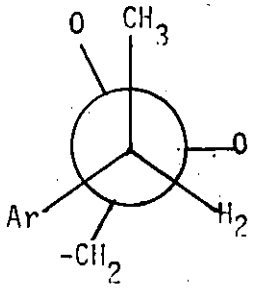

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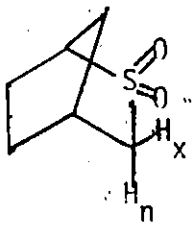

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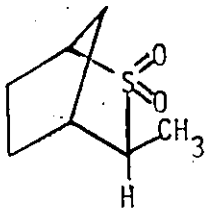

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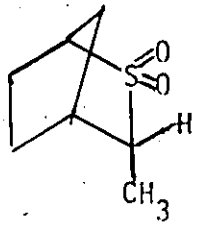

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Figure 9

When the carbanion of 20 was quenched with CH_3I an 88% yield of a 91 to 9 ratio of monomethylated sulfones 21 to 22 was obtained (see Fig. 9 for Newman projections of 21 and 22). The ratio was measured by integration of the methyl doublets which appear at δ = 0.91 for 21 and at δ = 1.68 for 22. The methyl group in 21 lies almost parallel to and above the plane of benzene ring and should experience shielding by this group (74). In 22 the methyl group is parallel and to the side of the benzene ring plane and should thus be deshielded relative to that of 21 (74).

Dreiding models show that the steric interactions in 21 are more severe than in 22. Under equilibrating conditions 21 should therefore isomerise to 22. When the 91 to 9 mixture of 21 to 22 obtained from the carbanion reaction was refluxed for 18 hours in 2M CH_3ONa/CH_3OH, a 91% yield of a 9 to 91 ratio of 21 to 22 was obtained. This confirms the stereochemical assignment made on the basis of the n.m.r. spectra of the two products.

Preliminary results on the carbonation of 20 (i.e. quenching of the carbanion with CO_2) indicate that this reaction also proceeds with the same stereochemical course as the deuteration (35).

The deuteration results show that the carbanion on the bisector of the oxygen-sulfur-oxygen angle is the more stable of the two possible ones; this is in agreement with the order of stability predicted by ab initio calculations (16). However the most striking observation is that the methylation occured with inversion even though this leads to the thermodynamically less stable product.

The second system we decided to examine was d_6-2-thiabicyclo (2.2.1) heptane 2,2-dioxide (23) (Fig. 9). In this compound the stereoelectronic stabilizing factors are the same for both possible carbanions and the effect of steric inhibition on the course of the reaction can be examined exclusive of the stereoelectronic influences. In 23 H_x and H_n appear as an AB quartet, δ = 2.71, δ = 3.0 (J_{AB} = 12 Hz) with the low field doublet corresponding to H_x and high field to H_n. This assignment was made on the basis of long range coupling between H_x and the exo hydrogen on C-5. When the carbanion of 23 was quenched with D_2O the total amount of exchange could be accounted for by exclusive exchange of H_x and some exchange of the bridgehead proton at C_1. This indicates a steric preference for the carbanion to be in the less hindered exo position (see Chapter 4).

When the carbanion of 23 was quenched with CH_3I only one methylated product was obtained in 87% yield. The methine quartet of this product appeared at δ = 2.77, J = 7Hz, and exhibited no long range coupling with the proton on C-5. This compound was therefore assigned structure 24 (Fig. 9), having the methyl group in the exo position. To confirm our assignment a sample of the endo methyl compound 25 was prepared. Treatment of 24 with an equimolar amount of CH_3Li in T.H.F. at - 60°, followed by quenching with H_2O after $\frac{1}{2}$ hour gave a 78% yield of a 1.8:1 mixture of exo 24 and endo 25. The ratio was obtained by integration of the methine quartets of 24 and 25. The quartet for 25 appears at δ = 3.16, (J = 7Hz) and it exhibits long range coupling (~1-2 Hz) with the exo proton on C-5. A spectrum of the total recovered product mixture indicated that 61% of the bridgehead protons on C_1 in both compounds had undergone exchange. This again demonstrates the importance of the orientation of the carbanion relative to sulfur in determining it's stability, and that the carbanion on the bisector of the O-S-O angle (bridgehead carbanion) is more stable than the one eclipsing one of the sulfur oxygens. The ability of bridgehead protons to form sulfone carbanion is well known (65, 70).

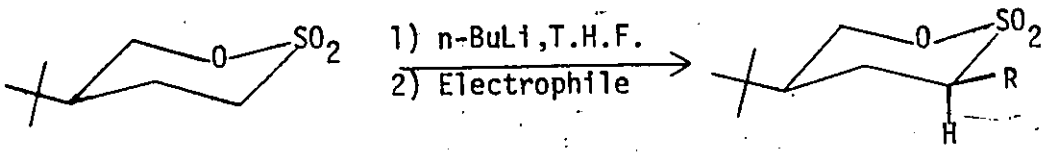
The results in the 2 - thiabicyclo (2.2.1) heptane 2, 2-dioxide system again demonstrate the steric requirement for lithium

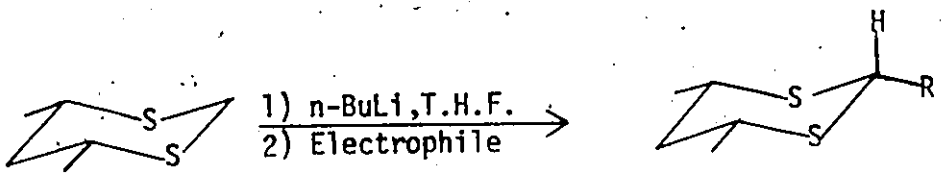
in T.H.F., since only the less hindered exo carbanion appears to form. The methylation and deuteration reactions both give only exo products, both reactions presumably occurring with retention of carbanion configuration. In this system alkylation with inversion (from the endo side) is sterically strongly hindered, and this hindrance may be enough to force the reaction to occur with retention. A similar explanation may be invoked to account for the results obtained when the carbanions of sultone 26 (33) and the 1-3 dithiane 27 (39, 41, 42) (Scheme 21) were reacted with various electrophiles. In both cases alkylation, hydroxyalkylation and deuteration gave exclusively products substituted in the equitorial position.

The generality of the preference for alkylation of sulfur stabilized carbanions with inversion remains to be tested. The above preliminary experiments indicate that the steric course of the alkylation can be either retention or inversion depending on steric factors present in the molecule.

An Explanation for the Stereochemistry of Reaction of Sulfur Stabilized Carbanions

The reason for the difference in the steric course of the reaction of some sulfur stabilized carbanions with alkyl halides as compared to other electrophiles such as D_2O or carbonyl compounds is





R = D,CH_3,$(CH_3)_2$-C-OH

Scheme 21

not clear from the data available. A possible explanation follows:

Recently Allinger et al (71) have carried out quantum mechanical calculations on the stereochemistry of SN2 and SE2 reactions at carbon using the displacement of a hydride by a hydride ion and of a proton by a proton in methane as models. Their calculations revealed that inversion at carbon is favoured over retention for both SN2 and SE2 reactions, for the former by 14.9 and the latter by 5.3 kcal/mole. They suggested that since the energy difference between the retention and inversion pathways in the SE2 reaction was relatively small, exceptions to the inversion rule might occur when other factors (e.g. solvation steric hindrance) intervene to tip the balance in favour of either pathway.

For the reaction of the carbanion with D_2O and ketones one can envisage a 4-centre transition state (Fig. 10)* which would lead to reaction with retention of carbanion configuration. According to

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* By analogy to Grignard reactions one could also envisage 6-centered transition states involving 2 molecules of carbanion per molecule of electrophile (80). At present we have no evidence supporting a 2 to 1 stoichiometry and thus will not discuss this possibility.

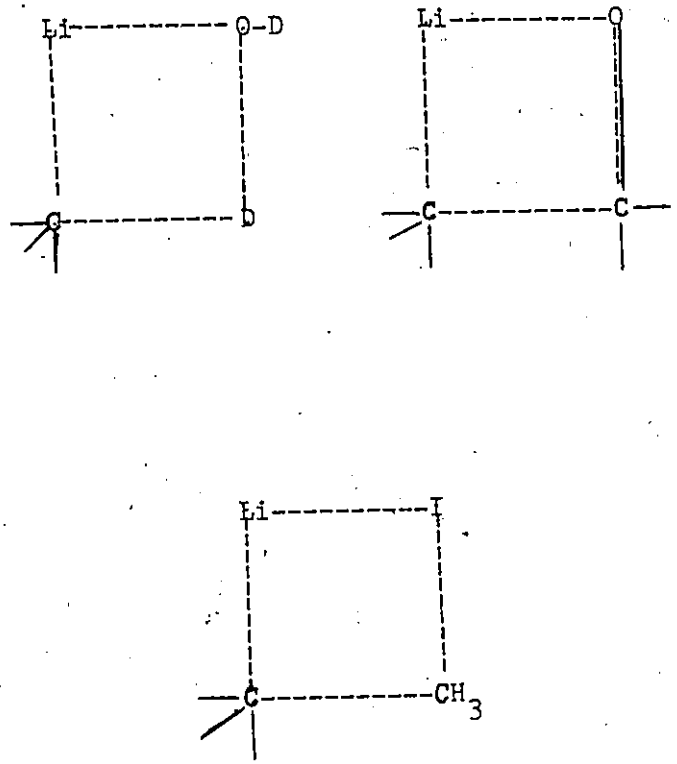
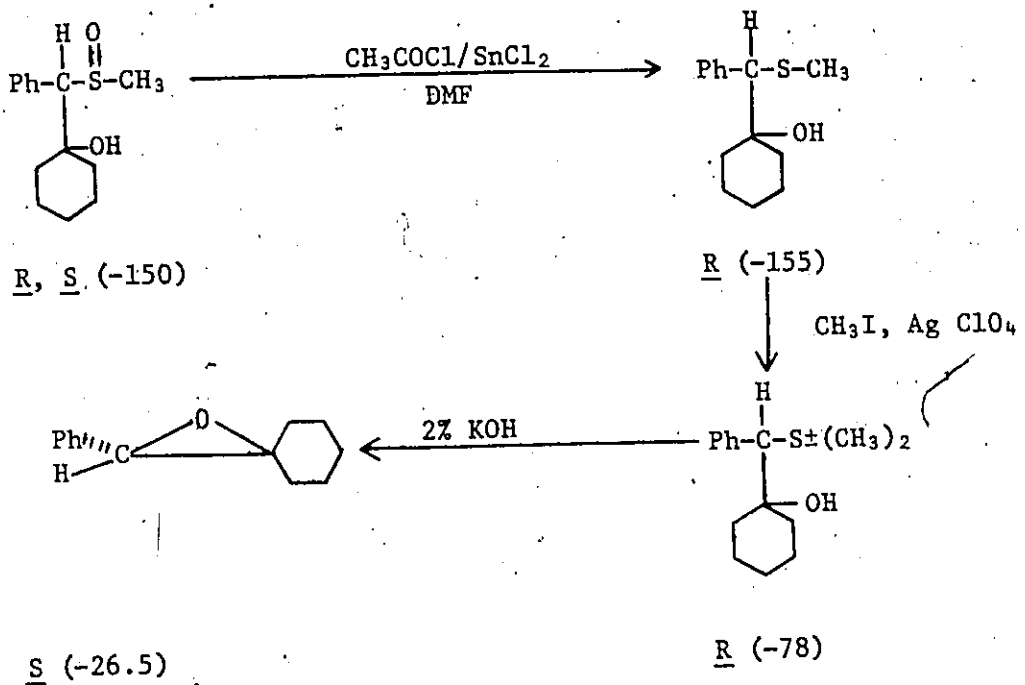


Figure 10

the hard and soft acid-base theory (HSAB) (72) the internal solvation between lithium (hard acid) and oxygen (hard base) should be strong, thus favouring such a transition state. For methyl iodide (Fig. 10) such a transition state is less favoured since iodine is a soft base. More important is that such a transition state also requires the unfavourable retention stereochemistry at the carbon of methyl iodide which is undergoing SN2 attack. The cases were alkylation occured with retention can be explained in terms of strong steric retardation of alkylation with inversion.

Asymmetric Synthesis

One example of the synthesis of an optically active non-sulfur containing compound starting from an optically active sulfoxide has been reported from this laboratory (73). Optically active (S)-epoxide 26, $[\alpha]_D$ -26.5 (C = 2.5, pentane), was obtained in 60% overall yield starting from (S)-benzyl methyl sulfoxide and cyclohexanone. The assignment of (S)-configuration was based on the known stereochemical course of the hydroxyalkylation of benzyl methyl sulfoxide and the subsequent chemistry shown in Scheme 22.



SCHEME 22

We feel that the synthesis of optically active compounds via lithio sulfoxides has significant potential. Some of the advantages are the availability of both enantiomers of optically active sulfoxide (29), the high induction at the alpha carbon by the sulfoxide, the variations in this induction with solvent and possibility of diastereomer purification at an intermediate stage. The major impediment at this time is the lack of methods for the stereospecific cleavage of the C-S bond. Work on this problem is currently underway in this laboratory.

CHAPTER 6

RELATIONSHIP BETWEEN THE KINETIC AND THERMODYNAMIC PREFERENCE FOR THE LITHIATION OF SULFOXIDES

Introduction:

This work was undertaken in order to demonstrate that acyclic lithio sulfoxides equilibrate in T.H.F. at low temperatures (Chapter 3).

During the course of this work Eliel et al (39) reported on the relationship between the kinetic and thermodynamic selectivity in conformationally fixed 1,3-dithianes. They observed that the kinetic selectivity between the equitorial and axial positions, $k_e/k_a = 8.6 \pm 1.3$, was much lower than the thermodynamic selectivity, the latter favouring the equitorial carbanion by a factor of more than 100. In light of this report we felt that an application of this method to the benzyl t-butyl sulfoxide system would also enable us to determine its kinetic selectivity and thence indirectly the thermodynamic selectivity which was unapproachable by direct measurement.

Kinetic Preference Between the Diastereotopic Hydrogens in the Lithiation of Benzyl Methyl Sulfoxide

The kinetic preference for the removal of the diastereotopic hydrogens in benzyl methyl sulfoxide was first investigated. Samples

of α- deuteriobenzyl methyl sulfoxide of known configuration* (Chapters 3 and 5) and isotope content were prepared. The (S,S) - sulfoxide 5† was prepared as described in Chapter 3; the (R,S) - sulfoxide 6† was prepared from α- dideuteriobenzyl methyl sulfoxide in a similar fashion, using H_2O to quench the carbanion. Intermediate mixtures of 5 and 6 were obtained by partial isomerization at sulfur in 5 using $F\text{-}SO_2\text{-}OCH_3$ (29). The ratios of the diastereomeric deuterated sulfoxides were measured as described in Chapter 3 (Table 9).

The total deuterium content of all the sulfoxides was determined by mass spectrometry. Variation of the ionization potential (IP) showed that no $(M-1)^+$ dissociation, corresponding to the loss of a proton from the molecular ion $(M)^+$, occured at low IP (12-15 eV) for all sulfoxides studied. The region from $(M-5)^+$ to $(M-1)^+$ was devoid of peaks in all cases. An average of 15 to 20 measurements of the expanded $(M)^+$ to $(M+5)^+$ region for the nondeuterated parent sulfoxides

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* Although we worked with racemic mixtures, all formulas and discussion in this Chapter will be presented in terms of sulfur chirality as S for ease of discussion.

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† Diastereomerically pure monodeuterated sulfoxides could not be prepared in this fashion, both were contaminated with small amounts of the other diastereomer (Table 9).

were then made in order to determine the natural abundance of isotopes in the sulfoxides. The deuterated sulfoxides were run in a similar fashion and the appropriate corrections for the contribution of the natural abundance isotopes to each peak were made (74). This ensured that machine errors were minimized and permitted the accurate determination of the relative intensities of the $(M)^+$ to $(M+5)^+$ peaks.

A sample calculation for benzyl methyl sulfoxide follows; The isotopic ratios in the parent compound were $(M)^+$: $(M+1)^+$: $(M+2)^+$: $(M+3)^+$: $(M+4)^+$: = 100 : 12.38: 5.52: 0.75: 1.74. The ratios in the deuterated sulfoxides were 7.63$(M)^+$: 100$(M+1)^+$: 18.70 $(M+2)^+$: 6.60 $(M+3)^+$: 1.77 $(M+4)^+$. The correction for the natural isotopic abundance of the parent compound was then applied. The higher isotopes of the $(M)^+$ peak would contribute (7.63 X 12.38)% of the intensity of the $(M+1)^+$ peak. The contribution of the (M^+) peak to the $(M+2)^+$ peak would be (7.63 X 5.52)% and so on for $(M+3)^+$ and $(M+4)^+$ peaks. These values were then subtracted from the intensities of the corresponding peaks. Similar corrections were then made for the contribution of the higher isotopes of the $(M+1)^+$ peaks to the intensities of the $(M+2)^+$, $(M+3)^+$ and $(M+4)^+$ peaks. From the corrected relative intensities, the proportions of undeuterated, monodeuterated and dideuterated sulfoxides could be determined with an accuracy of better than 1%. A good

correspondance (within experimental error) between the percentage of monodeuterated and nondeuterated sulfoxides as measured by mass spectrometry and n.m.r. integration was observed (e.g. benzyl methyl sulfoxide: mass spectrometry 93% d_1, 7% d_0; n.m.r. 96% d_1, 4% d_0; benzyl t-butyl sulfoxide: mass spectrometry 96.4% d_1, 3.5% d_0; n.m.r. 96% d_1, 4% d_0.

Samples of α-deuteriobenzyl methyl sulfoxides of known configuration and isotope content were reacted with CH_3Li under the usual conditions and the reaction quenched with excess CH_3I. The mixtures of α-methylbenzyl methyl sulfoxides 7 and 8 thus obtained (recovered yields were > 90% in all cases) (Scheme 23) were examined for deuterium content by n.m.r. using the benzylic methyl group as the probe.* Appropriate corrections for the presence of nondeuterated and dideuterated sulfoxides in the starting sulfoxides, as determined by mass spectrometry, were made. (Table 9).

---

* The mass spectrum of α-methylbenzyl methyl sulfoxide does not give a molecular ion peak. The amounts of 7 and 8 obtained were measured by integration of the doublet due to the $-CH-CH_3$ methyl peak in 7 vs the singlet for the $-CD-CH_3$ methyl peak in 8 during deuterium decoupling.

The isotope effect† (IE = k_H/k_D) and the selectivity factor ($S = k_{H_S}/k_{H_R}$) were calculated using equations 1) and 2)†* (39) (N_5 and N_6 = mole fractions of 5 and 6 respectively).

TABLE 9

Reaction of ∝- deuteriobenzyl methyl sulfoxide with methyllithium followed by methyl iodide.

Starting Materials:[a]		Products:[b),c),d)]	
% 5	% 6	% 7	% 8
92	8	39	61
53	47	30	70
6	94	20	80

a) Ratios were measured in DMSO-d_6 using a Varian HA-100 Spectrometer equipped with a deuterium decoupler; error ± 5% (Chapter 3).

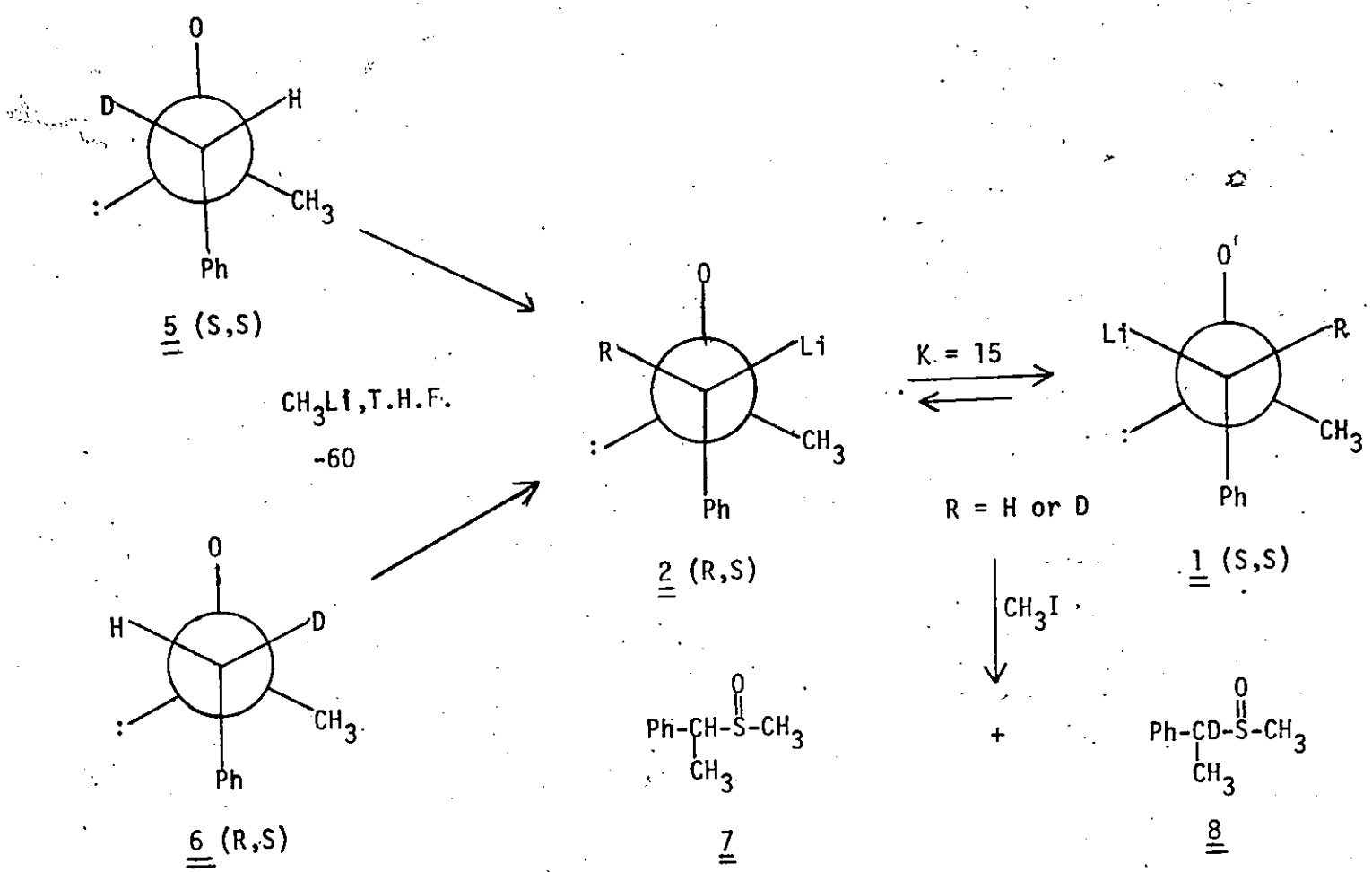
b) See footnote p. 98.

c) These percentages are corrected for the presence of nondeuterated and dideuterated starting materials.

d) These results are averages of at least 2 or more experiments in which the same starting ratio of 5 and 6 were used.

†* These equations are modifications of a set originally derived by D.Y. Curtin and D.B. Kellom (75).

† It is assumed that the isotope effect for the pro S and pro R hydrogen are approximately equal. The same assumption was made by Eliel et al (39).


O
D
H
CH3
Ph
5 (S,S)
CH3Li,T.H.F.
-60
O
H
D
CH3
Ph
6 (R,S)
O
R
Li
CH3
Ph
2 (R,S)
K = 15
R = H or D
O
Li
R
CH3
Ph
1 (S,S)
CH3I
+
Ph-CH-S-CH3
CH3
7
Ph-CD-S-CH3
CH3
8

Scheme 23

$$\frac{\underline{7}}{\underline{8}} = N_5 \left(\frac{S}{IE}\right) + N_6 \left(\frac{1}{S.IE}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 1)$$

$$\frac{\underline{8}}{\underline{7}} = N_5 \left(\frac{IE}{S}\right) + N_6 \left(S.IE\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2)$$

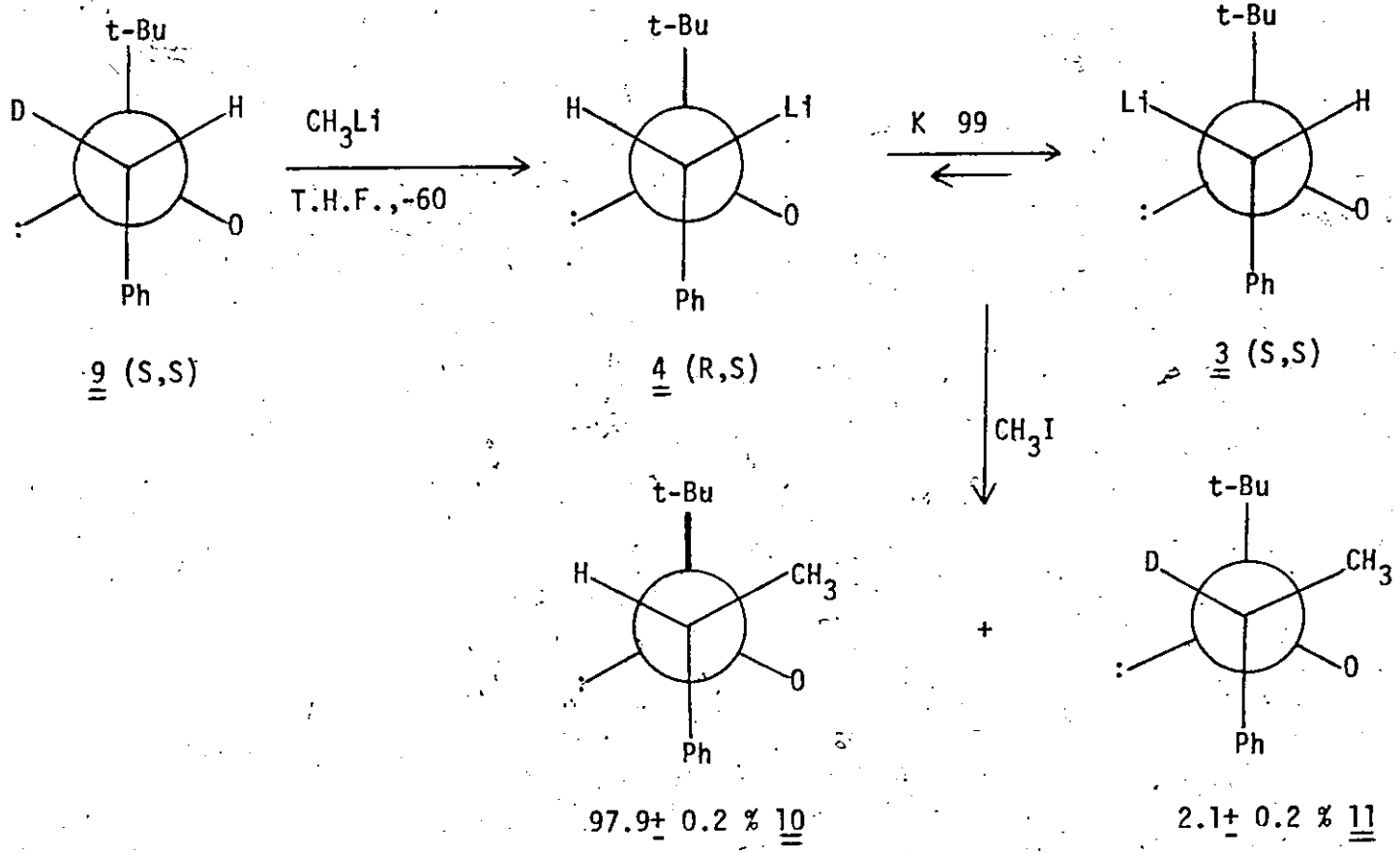
Solution of these equations gave an isotope effect of 2.5 ± 0.4 and a selectivity factor $k_{H_S}/k_{H_R} = 1.7 \pm 0.3$. The magnitude of the isotope effect is reasonable for the rapid reaction of a strong base, CH_3Li, with a relatively acidic carbon acid (77) and is approximately the same as that found by Eliel et al (39) for the reaction of 1,3-dithianes with n-BuLi ($k_H/k_D = 2.5 \pm 0.1$).

Our results differ quite significantly from those obtained by Nishihata and Nishio (78) who reported an isotope effect of 7 and a selectivity factor of 0.66 for the reaction of monodeuterated sulfoxides $\underline{5}$ and $\underline{6}$ with n-BuLi in T.H.F. at - 70°. The reason for these differences are not obvious at present. We have shown in Chapter 2 that in addition to proton abstraction, the displacement reaction $Ph\text{-}CH_2\text{-}S(O)\text{-}CH_3 + \underline{n}\text{-BuLi} \longrightarrow CH_3\text{-}S(O)\underline{n}\text{-Bu} + Ph\text{-}CH_2Li$ occurs to the extent of 40% under the experimental conditions used by these authors. What effect this competing reaction has on the reaction

under study is not clear at present. Our major criticism of this work is that a selectivity factor of less than 1 is highly unlikely since it implies that the less stable carbanion 2 is formed more readily than the more stable carbanion 1. According to Hammond's postulate (45) this means that the less acidic proton is removed preferentially to the more acidic. In light of this we feel that Nishihata and Nishio's results are highly suspect.

Kinetic Preference Between The Diastereotopic Hydrogens in the Lithiation of Benzyl t-Butyl Sulfoxide

When (S,S) α- deuteriobenzyl t-butyl sulfoxide (9), > 99% diastereomerically pure (n.m.r.) and free of dideuterated material (mass spectrometry), was reacted with CH_3Li in the standard fashion and the reaction quenched with excess CH_3I > 90% yields of methylated sulfoxides 10 and 11 were obtained (Scheme 24). Analysis of the products by n.m.r. (see above) indicated < 3% of 11 was present. The product was then analysed by mass spectrometry using an AEI MS-9 High Resolution Mass Spectrometer equiped with a signal averager. A minimum of four hundred measurements were made at 12 eV on samples obtained from duplicate experiments. The proportion of 11 was determined by comparison of the heights of the $C_7\ ^{13}CH_9$ and C_8H_8D peaks. After appropriate corrections for nondeuterated starting


t-Bu
D
H
O
Ph
CH3Li
T.H.F.,-60
H
Li
K 99
Li
CH3I
CH3
9 (S,S)
4 (R,S)
3 (S,S)
97.9± 0.2 % 10
2.1± 0.2 % 11

Scheme 24

material, the proportion of 10 to 11 found was 97.9 ± 0.2% of 10 and 2.1 ± 0.2% of 11.

Assuming that the isotope effect for benzyl t-butyl sulfoxide is the same as for benzyl methyl sulfoxide*, the kinetic selectivity for the removal of the pro S vs the pro R hydrogen is calculated to be (97.9 ± 0.2 / 2.1 ± 0.2) (2.5 ± 0.4) = 117 ± 20. Experimental justification for the assumption concerning the isotope effect was obtained by reacting α- deuteriobenzyl t-butyl sulfone 12 with CH_3Li and trapping the carbanion with CH_3I (Scheme 25).

$$\underset{12}{Ph\text{-}CHD\text{-}SO_2\text{-}t\text{-}Bu} \xrightarrow[2)\ CH_3I]{1)\ CH_3Li,\ T.H.F.,-60} \underset{13}{Ph\text{-}\underset{CH_3}{CH}\text{-}SO_2\text{-}t\text{-}Bu} \pm \underset{14}{Ph\text{-}\underset{CH_3}{CD}\text{-}SO_2\text{-}t\text{-}Bu}$$

SCHEME 25

* It seems highly unlikely that replacement of a methyl group at a position two atoms removed from the reaction site would greatly change the isotope effect.

Greater than 90% yields of mixtures of 13 and 14 were obtained in duplicate experiments. Analysis of the mixture by n.m.r. yielded a value of 2.3 ± 0.2 for the isotope effect, mass spectrometric analysis gave a value of 2.55 ± 0.1.

A kinetic selectivity of > 100 : 1 for the exchange of diastereotopic hydrogens alpha to a sulfoxide is not exceptional in conformationally fixed systems, where selectivities of > 1000 : 1 have been reported by Fraser et al (11). The novelty of the high selectivity observed in 9 is that it occured in an open chain system and more importantly with a base whose pk_a is about 13 pk_a units greater than that of the alpha hydrogens of 9†.

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† The pk_a of methane is 40. Bordwell and co-workers (79) have shown that the change $CH_3-SO_2-CH_3$ to $Ph-CH_2-SO_2-CH_3$ lowers the pk_a from 28.5 to 22. A similar decrease in going from DMSO (pk_a = 33.5) to $Ph-CH_2-S(O)-CH_3$ give the latter a pk_a of about 27.

The high selectivity in 9 can be most readily explained by assuming that benzyl t-butyl sulfoxide exists almost exclusively in the trans conformation (Scheme 24) in which the removal of the pro S hydrogen is strongly favoured over the removal of the pro R hydrogen by a stereoselectronic factor (14), i.e. the carbanion gauche to the lone pair and trans to the oxygen.

The Thermodynamic Preference in α-Lithio-Benzyl t-Butyl Sulfoxide

An estimate of the energy difference between lithio derivatives 3 and 4 can be obtained from the following line of reasoning. The kinetic preference factor of 1.7 to 1 at -60° in favour of the pro S hydrogen in benzyl methyl sulfoxide is equal to a difference in transition state free energies of 0.23 kcal/mole for the removal of the pro S vs the pro S hydrogen. The thermodynamic selectivity of 15.5:1 at - 60° for the (S,S) carbanion 1 vs the (R,S) carbanion 2 is equal to a 1.15 kcal/mole free energy difference. If the removal of the pro S and pro R hydrogens in benzyl methyl sulfoxide leads initially to the lithio derivatives 1 and 2, then the relationship between the transition state energy differences for their formation and their ground state energy differences (Bronsted

coefficient α) is 0.23/1.15 = 0.20*. Finally assuming that the relationship between transition state and ground state energy differences is similar for benzyl methyl and benzyl t-butyl sulfoxides, the energy difference between 3 and 4 can be estimated. The kinetic selectivity of 117:1 at - 60 corresponds to a free energy difference ($\Delta G^{\ddagger\ddagger}$) of 2.17 kcal/mole between the two transition states. The free energy difference ($\Delta G^{\ddagger}$) between 3 and 4 is $\Delta G^{\ddagger} = \Delta G^{\ddagger\ddagger}/\alpha$ or 2.17/0.20 = 10.8 kcal/mole. This free energy difference corresponds to a thermodynamic selectivity of 10^{10} between 3 and 4. The result for the free energy difference between the most stable and least stable carbanion is compatible with that obtained from ab initio calculations (14). We have however shown in Chapter 4 that solvent, which was neglected in the calculations, plays a predominant role in determining the stability of carbanions in different conformations with respect to the sulfur asymmetry. The correspondence between calculations and experimental results is poor in highly polar solvents, but the above results show that in T.H.F. the experimental results parallel the calculated ones.

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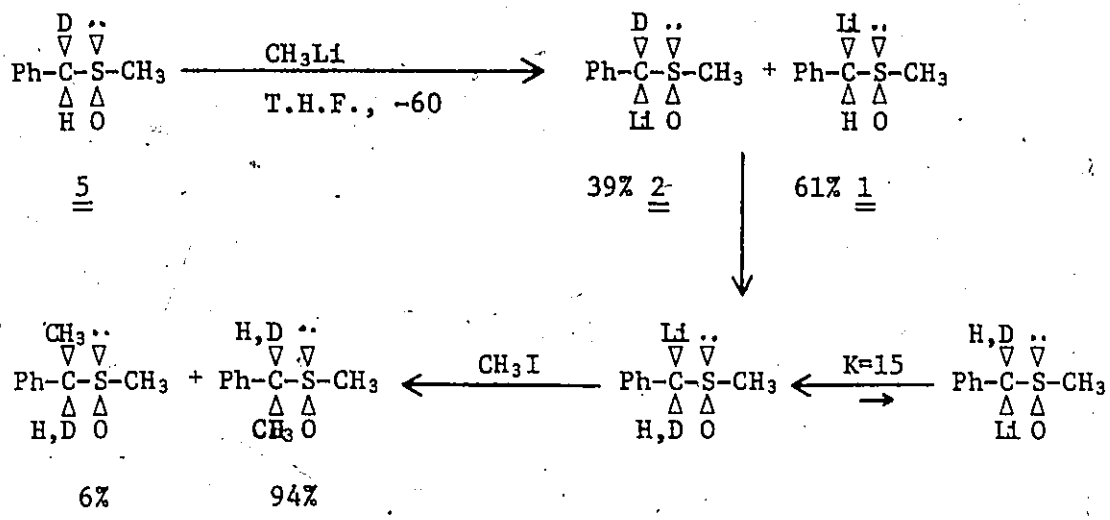
* The Bronsted coefficient α is a measure of the resemblance of the transition state to the product(s) or starting material(s). It is < 0.5 if the reaction in question (as above) is exothermic > 0.5 if endothermic (ref. 77 pp. 156 - 161).

Finally, the result in the t-butyl benzyl system clearly illustrates an important stereochemical consequence: the deprotonation of benzyl t-butyl sulfoxide with CH_3Li and protonation (deuteration) of the α- lithiobenzyl derivative both occur with the same stereochemical course, the more likely one being retention of configuration in each step.

$$\underline{\underline{3}} \xrightleftharpoons{D_2O} \underline{\underline{9}}$$

Equilibration of Sulfoxide Carbanions

The experimental results described for benzyl methyl sulfoxide show conclusively that the benzylic sulfoxide carbanions equilibrate under the reaction conditions employed (T.H.F., - 60°, 1 minute). When essentially pure monodeuterated sulfoxide 5 (containing 8% of 6) was treated with CH_3Li, 61% of the carbanion formation arose by removal of the pro R proton (H) and 39% of the carbanion formation by removal of the pro S proton (D) (see Scheme 29, Table 9). The initially formed proportion of carbanions 1 to 2 was 39 to 61 or 1:1.5. But when the carbanion mixture was trapped with CH_3I after 1 minute, a mixture of methylated products corresponding to a 15:1, (94:6) ratio of 1 to 2 was obtained (Chapter 3). This could only have occured if 2 equilibrated rapidly to 1 under the reaction conditions employed.



SCHEME 26

CHAPTER 7

A COMPARISON OF THE EFFECTS OF SOLVENT AND $Eu(DPM)_3$ ON PROTON SHIELDING IN ACYCLIC SULFOXIDES

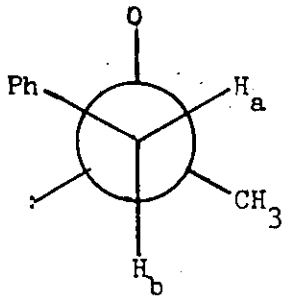
Introduction:

In the last 10 years proton magnetic resonance spectrometry has provided a variety of empirical correlations which have allowed the determination of conformations in cyclic sulfoxides (81, 82, 83). A number of solvent effects have also been successfully correlated with the stereochemistry of the sulfoxide function, e.g. benzene induced shifts have been used to assign configurations in penicillin sulfoxides (84). Trifluoro acetic acid (TFA) has also been claimed to be a useful solvent for sulfoxide configurational assignments (85). A third method involves the spectral changes resulting from the formation of complexes with paramagnetic species, shift reagents. The use of the shift reagent, $Eu(DPM)_3$ (tris- [dipivaloylmethano] europium), for the elucidation of the stereochemistry of cyclic sulfoxides has been described (86), and it's effect on some acyclic sulfoxides has also been reported (87).

We have recently, in cooperation with R.R. Fraser and co-workers, described (88) the effect of added $Eu(DPM)_3$ on both cyclic and acyclic sulfoxides and compared these results with benzene and TFA solvent shifts. In this way the strengths and limitations of these three methods for assigning sulfoxide stereochemistry were examined. The work on the cyclic systems was carried out by Fraser and co-workers; we examined a number of acyclic sulfoxides. Our results and conclusions regarding these sulfoxides will be presented in the following sections.

Effect of Solvents

The sulfoxides examined were benzyl methyl, (1), benzyl phenyl (2), benzyl t-butyl, (3), sulfoxides and the two isomers of α-methylbenzyl phenyl, (4 and 5), and α- methylbenzyl t-butyl sulfoxides, (6 and 7), (Fig. 11). The assignment for each benzylic proton in sulfoxide 1 and 3 was made in an unequivocal fashion by comparison of the spectra of the nondeuterated sulfoxides with those of the monodeuterated sulfoxides of known configuration (Chapters 3, 5) in the various solvents used. The configurations of methylated sulfoxides 6 and 7 are also known (Chapter 5).



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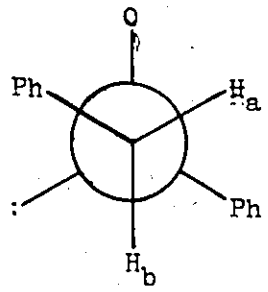

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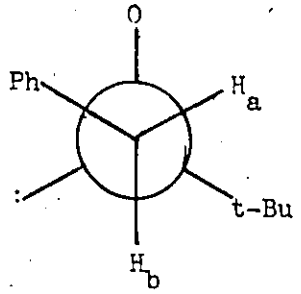

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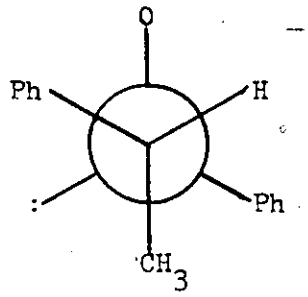

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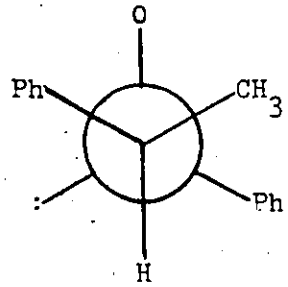

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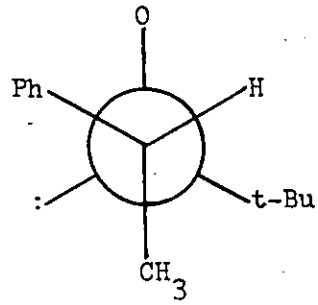

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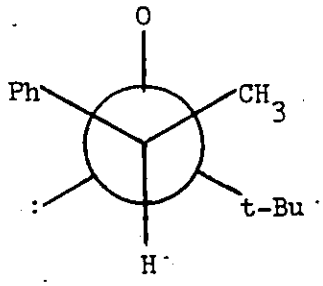

7

Figure 11

The configuration of sulfoxides 4 and 5 were determined by methylation of (R)-benzyl phenyl sulfoxide, α_D^+ 253, (C = 0.58, acetone), in the usual fashion to give a 1.5 to 1 (Chapter 3) mixture of sulfoxides 4 and 5 (n.m.r.). A portion of this mixture was oxidized to α- methylbenzyl phenyl sulfone, α_D^+ 17.35 (C = 4.35, CH_3OH). Corey and Lowrey (90) have previously described the preparation of (R)-α-methylbenzyl phenyl sulfone, $\alpha_D \pm 94$ (C = 1.5, CH_3OH), therefore the major diastereomer from the methylation reaction, 4, has R configuration at carbon, whereas 5 has S configuration at carbon. The diastereomeric sulfoxides 4 and 5 could be separated by chromatography on silica gel. The spectral properties of 4 and 5 are identical with the minor and major products, respectively, obtained from the MPBA oxidation of α- methylbenzyl sulfide (91b). Our assignment of the configuration of 4 and 5 as the minor and major products of this oxydation has been confirmed by Nishio and Nishihata (91).

Strom et al (92) showed that the alpha protons in di-n-butyl-sulfoxide exhibit a greater nonequivalence in benzene than in CCl_4, whereas the benzylic protons of dibenzyl sulfoxide do not. This observation has been verified by Kingsbury (93). Nishio initially assigned the structures 4 and 5 to the major and minor products, respectively, obtained by oxydation of α- methylbenzyl phenyl sulfide

with MPBA on the basis of benzene and TFA solvent shifts for the methine and methyl protons (91b). He reasoned that the major conformers for 4 and 5 ought to be as illustrated in Fig. 11, and thus the methine protons in 4 ought to be less affected by benzene than that of 5, but more affected by TFA. The methyl groups ought to behave in the opposite fashion. Since it is now known that 5 and not 4 is the major product of the oxidation (see above) (91a), both the TFA and benzene solvent shifts led to the wrong assignments. The failure in this case casts doubts upon any assignments of acyclic sulfoxides based on the solvent shift method; e.g. the stereochemistry of the two diastereomers of α- chlorobenzyl phenyl sulfoxide (94) and the designation of diastereotopic protons in substituted benzyl phenyl sulfoxides (85). The weakness of this method is further underscored by our results (Table 10).

As pointed out earlier by Nishio the proton closest to the oxygen atom should experience the largest solvent shift in TFA due to TFA hydrogen bonding to the sulfinyl oxygen. This behaviour was observed for cyclic sulfoxides (88). However, in benzene the opposite ought to be observed since benzene complexes more effectively on the side of the sulfoxide remote from the oxygen thus resulting in consistently greater shielding of the protons more remote from the

oxygen atom. This type of behaviour was again observed for cyclic sulfoxides (88).

As it is generally accepted that CCl_4 is a more inert solvent than $CDCl_3$, it was chosen as our reference solvent. The TFA ($\Delta TFA = \delta TFA - \delta CCl_4$), benzene ($\Delta C_6H_6 = \delta C_6H_6 - \delta CCl_4$) and Eu $(DPM)_3$ ($PS = \delta Eu - \delta CCl_4$) induced shifts are recorded in Table 10.

Examination of Table 10 shows that no significant differentiation exists between the two benzylic protons of benzyl methyl and benzyl phenyl sulfoxides, 1 and 2, in the 3 solvents used. Assuming that the most favoured conformation for benzyl t-butyl sulfoxide (3) is as depicted in Fig. 11, then H_a should be less shielded than H_b by benzene and more deshielded than H_b by TFA relative to CCl_4. In fact the opposite is observed. The remaining sulfoxides must be considered in pairs. If the conformations depicted for 4 and 5 are dominant (Fig. 11), the methyl group of 4 ought to be more strongly shielded than that of 5 in going from CCl_4 to benzene but less deshielded in going to TFA. The magnitudes of the benzene induced shifts are the same while the relative sizes of the TFA shifts are opposite to the above expectations. The relative sizes of the observed shifts for the methine protons in the two diastereomers are also incompatible with this model. For the α-methylbenzyl t-butyl sulfoxides, 6 and 7, the

observed shifts are even more bewildering. Assuming the usual solvent interaction on the sterically most favoured conformers (Fig. 11), the relative magnitudes of the benzene shifts are as expected for the methyl groups but opposite for the methine hydrogens; for the TFA shifts the opposite is observed, the methine hydrogens behave as expected, but the methyl groups do not.

As pointed out above, changes in the n.m.r. spectra of cyclic sulfoxides upon solvent changes from CCl_4 to benzene or TFA occur in a consistent and understandable fashion. In contrast, this method yields inconsistent and uninterpretable results for acyclic sulfoxides, and therefore it seems to be ineffective for the determination of configurations of acyclic sulfoxides. There are perhaps several reasons for this. The most obvious weakness in applying the solvent shift method to acyclic sulfoxides is that it requires the assumption of the most stable conformation. In addition, it is assumed that the same conformation predominates in each solvent used in the comparison. This may not necessarily be true since it is well known that sulfoxides associate with each other in non-polar solvents (95) and hydrogen bond effectively in polar protic solvents (95). Another assumption made in applying this method is that the solvent will affect proton shielding in each conformer to the same extent. It is conceivable that the solvent might exert its greatest shift influence on one of the less stable conformers,

and thus the observed spectrometric changes would not reflect the actual conformer distribution. Finally, when considering pairs of diastereomers, it is necessary to assume that each diastereomer interacts with the solvent in the same manner and to the same extent. That this is not always so is seen by examining the results for 6 and 7 in TFA and benzene. In both solvents opposite conclusions regarding configuration are indicated depending on whether the methine or the methyl group is used as probe.

Effects of $Eu(DPM)_3$

The downfield shifts resulting from the addition of 0.33 equivalents of $Eu(DPM)_3$ are recorded in Table 10. The induced shifts in all likelihood arise from pseudocontact interactions (88).

The use of $Eu(DPM)_3$ - induced shifts to determine the configurations of acyclic sulfoxides suffers from essentially the same limitations as does the solvent shift method. For sulfoxide 1 it fails to distinguish between the benzylic protons, in 2 it gives only a slight differentiation and in 3 (if the conformer in Fig. 11 is the most stable one) it leads to the wrong proton assignment. For the assumed dominant conformer of 4 and 5, the PS values for the methyl groups are opposite to that predicted from a distance dependence. In 6 and 7 the assignment based on the PS values for the methyl groups is correct, but

that based on the methine protons is in error. It is highly likely that 6 and 7 have unequal equilibrium constants for complex formation with $Eu(DPM)_3$, and this is largely responsible for the observed inconsistencies.

Conclusions:

Both solvent shift methods and the shift reagent method are unreliable for the assignment of configurations in acyclic sulfoxides.

TABLE 10

N.m.r. Shifts[a] in Acyclic Sulfoxides

Compound	Proton	CCl_4	C_6H_6	TFA	EU	ΔC_6H_6	ΔTFA	PS
1	H_a	3.86	3.32	4.46	7.17	−0.54	+0.60	+3.31
	H_b	3.86	3.32	4.46	7.17	−0.54	+0.60	+3.31
2	H_a	3.92	3.63	4.46	7.83	−0.29	+0.54[b]	+3.91
	H_b	3.92	3.63	4.46	7.36	..	..	+3.44
3	H_a	3.69	3.34	4.31	6.76	−0.35	+0.62	+3.07
	H_b	3.51	..	4.29	7.66	−0.17	+0.78	+4.25
4	H	3.91	3.66	4.30	7.00	−0.25	+0.39	+3.09
	CH_3	1.52	1.42	1.65	4.49	−0.10	+0.13	+2.97
5	H	3.66	3.52	4.42	c)	−0.14	+0.76	c)
	CH_3	1.55	1.45	1.60	4.02	−0.10	+0.05	+2.47
6	H	3.67	3.32	4.60	5.37	−0.35	+0.93	+1.70
	CH_3	1.67	1.50	1.94	3.23	−0.12	+0.27	+1.56
7	H	3.77	3.56	4.68	6.83	−0.21	+0.91	+3.06
	CH_3	1.55	1.56	1.94	3.96	+0.01	+0.39	+2.35

a) Spectra were measured on either a Varian HA-100 or T-60 spectrometer using 0.2M solution of each sulfoxide. The chemical shifts are reported in δ units and are accurate to ±0.01 ppm; thus the maximum error in Δ or PS values will be ±0.02 ppm.

b) Also noted by Kingsbury and Auerbach (84).

c) Not accurately measurable because of overlap.

EXPERIMENTAL

The chemicals used during the course of this work were supplied by Aldrich Chemical Co., Fisher Scientific and Canlab Ltd. The solvents were supplied by the latter two companies and meet A.C.S. specifications. The 3-bromo-1-butene was obtained from Chemical Samples Co. and contained 10% 1-bromo-2-butene. Optically active 2-pentanol, 91% optically pure, and 2-hexanol, 67% optically pure, were obtained from Norse Laboratories Inc.. Heavy water (99.7% D_2O) was supplied by Atomic Energy of Canada Ltd.. Alkyllithiums were supplied by the Foot Mineral Co., or Ventron Corp., Alfa Products. t-Butylmagnesium chloride (2M in ether) and phenylmagnesium bromide (2M in ether) were obtained from Matheson, Coleman and Bell. All n.m.r. solvents and shift reagents were furnished by Merck, Sharp and Dohme Canada Ltd.. The silica gel used for T.L.C. and preparative T.L.C. was MN-Kieselgel N/UV_{254} supplier Mackeary Nagel & Co.. Silica gel 60, supplied by Brinkman Instruments Canada Ltd. was used for column chromatography.

Melting points were obtained using a Thomas Hoover melting point apparatus and are uncorrected. Similarly all boiling points reported are uncorrected. All n.m.r. spectra were obtained on a Varian HA-100 or T-60 spectrometers using $CDCl_3$ as solvent (unless

otherwise specified). The peak positions are given in ppm downfield from TMS. Infrared spectra were obtained using a Beckman IR-20 or IR-20A spectrophotometer. The spectra of solid compounds were obtained using $CHCl_3$ as solvent; liquids or oils were used neat. Mass spectra were obtained using either a Hatachi RMU-6 spectrometer or an AEI MS-9 spectrometer. Optical rotations were obtained on a Perkin and Elmer 141 polarimeter.

Elemental analysis were carried out by Scandanavian Microanalytical Laboratories, Denmark or the National Research Council of Canada, Ottawa.

Synthesis of Sulfides

General Procedure:

To a solution of the appropriate thiol (1 equivalent) dissolved in methanol (95%) containing 2.5 equivalents of KOH was added in a dropwise fashion a solution of 1 equivalent (1 eq.) of alkyl halide in methanol. The reaction was allowed to stir overnight and the precipitate formed was filtered off. The filtrate was diluted with 200 ml. of H_2O and extracted with 4 X 50 ml. of CH_2Cl_2. The combined organic extracts were washed with 3 X 25 ml. of 10% KOH and 2 X 25 ml. of H_2O, dried over magnesium sulfate and the solvent removed by evaporation on a rotary evaporator. The crude products were

generally purified by distillation under reduced pressure.

Benzyl Methyl Sulfide

Available from Aldrich Chemical Co.

Benzyl t-butyl Sulfide

From 5 gm. of benzyl bromide (0.029 moles) and 2.63 gm. of t-butyl thiol (0.029 moles), 4.4 gm. (84%) of the sulfide, b. p. 63° - 65° / 0.5 mm. (lit. b. p. 114° / 12 mm. (96)), were obtained.

Benzyl Ethyl Sulfide

Available in these laboratories (97).

Benzyl i-propyl Sulfide

From 10 gm. of i-propyl thiol (0.13 moles) and 10.7 gm. of benzyl bromide (0.13 moles) was obtained 17.17 gm. (84%) of the sulfide, b. p. 53° - 55° / 0.5 mm. (lit. b. p. 89° - 90° / 14 mm. (97)).

Synthesis of Sulfoxides

General Procedure:

The appropriate sulfide (1 eq.) was dissolved in 100 ml. of 1:1 methanol / H_2O and the solution cooled in ice. To this was added slowly (over 2 or more hours depending on the scale) with stirring a

0.5M solution of $NaIO_4$ (1 eq.), and the reaction mixture allowed to stir overnight. The precipitate which had formed was filtered off and washed with CH_2Cl_2. The filtrate was extracted with 5 X 75 ml. of CH_2Cl_2 and the combined extracts and washings dried over $MgSO_4$ and the solvent evaporated on a rotary evaporator. The crude sulfoxides were purified by recrystallization and sublimation or both.

Benzyl Methyl Sulfoxide

From 13.7 gm. of benzyl methyl sulfide (0.1 mole) and 21.5 gm. of $NaIO_4$ (0.1 mole), 12.5 gm. (82%) of sulfoxide, m.p. 52 - 53° (lit. m.p. 53 - 54° (96)), were obtained. This sulfoxide sublimed rapidly at 50° / 5 microns.

n.m.r. : 2.44 (s, 3H); 3.98 (AB q : δ_A = 4.05, δ_B = 3.91, J = 13Hz, 2H); 7.43 (s, 5H).

in D_2O : 2.57 (s, 3H); 4.16 (AB q : δ_A = 4.13, δ_B = 4.19, J = 13Hz, 2H); 6.53 (m, 5H).

in DMSO-d_6 : 2.45 (s, 3H); 4.00 (AB q : δ_A = 3.92, δ_B = 4.08, J = 12.6 Hz, 2H); 7.16 (m, 5H).

IR : S = O 1030 cm^{-1}

Benzyl t-butyl Sulfoxide

When 4.42 gm. of benzyl t-butyl sulfide (0.025 moles) were oxidized with 5.27 gm. of $NaIO_4$ (0.025 moles), 3.3 gm. (68%) of

sulfoxide, m.p. 74° - 75° (lit. m.p. 75° - 76° (96)), were obtained after recrystallization from CH_2Cl_2 / Pentane. This sulfoxide sublimed well at 70° / 5 microns.

n.m.r. : 1.28 (s, 9H); 3.70 (AB q : δ_A = 3.60, δ_B = 3.81, J = 12.9 Hz, 2H); 7.32 (s, 5H)

IR : S = O 1025 cm^{-1}

Benzyl Phenyl Sulfoxide

Available in these laboratories, m.p. 40° - 41° (lit. m.p. 40° - 41° (96)).

n.m.r. : 4.02 (s, 2H); 7.20 (m, 10H)

in DMSO-d_6 : 4.15 (AB q : δ_A = 4.08, δ_B = 4.25, J = 12.6 Hz, 2H); 7.27 (m, 10H).

Benzyl Ethyl Sulfoxide

Oxidation of 5 gm. of sulfide (33 moles) with 7.05 gm. of $NaIO_4$ (33 moles) gave 3.62 gm. (64%) of pure sulfoxide, m.p. 53° - 54° (lit. m.p. 54° - 55° (98)), after sublimation at 50° / 5 microns.

n.m.r. : 1.25 (t, 3H); 2.57 (q, 2H); 3.88 (s, 2H); 7.27 (s, 5H)

in DMSO-d_6 : 1.17 (t, 3H); 2.64 (m, 2H); 3.99 (AB q : δ_A = 3.91, δ_B = 4.09, J = 13.1, 2H); 7.33 (s, 5H)

IR : S = O 1025 cm^{-1}

Benzyl i-propyl Sulfoxide

From 8 gm. of sulfoxide (48 moles) and 10.3 gm. of $NaIO_4$ 48 moles), 8.65 gm. (98%) of sulfoxide, m.p. 36° - 38° (lit. m.p. 38° - 39° (94)) were obtained. This sulfoxide sublimed at 60° / 5 microns.

n.m.r. : 1.16 (d, J = 7Hz, 3H); 1.25 (d, J = 7Hz, 3H); 2.65 (m, 1H); 3.85 (s, 2H); 7.30 (s, 5H)

in DMSO-d_6 : 1.18 (d, 6H); 2.78 (m, 1H); 3.93 (AB q : δ_A = 3.82; δ_B = 4.05, J = 12.7 Hz, 2H); 7.32 (s, 5H).

Synthesis of Optically Active Sulfoxides

The synthesis of optically active sulfoxides was carried out in two steps: a) Preparation and purification of menthyl phenylmethane and menthyl p-toluene sulfinates b) Reaction of the menthol esters with appropriate Grignard reagents.

a) i) Preparation of menthyl phenylmethane sulfinate:

Benzenemethane sulfinyl chloride was prepared in 79% yield from benzyl mercaptan according to the method of Douglass et al (102).

In a round bottom 2 neck flask equipped with a nitrogen inlet-outlet system and a self-compensating dropping funnel, a solution of 32.8 gm of the above acid chloride (0.17 moles) in 300 ml. of anhydrous ether was cooled to - 78° in a dry-ice acetone bath. A solution of 23.4 gm of pure l-menthol (0.15 moles) in 60 ml. of 1:1 pyridine/ether

was then added dropwise. After addition the reaction was stirred for 30 minutes at - 78 , then allowed to warm to 0 . The reaction mixture was then washed with successive 100 ml. portions of 5% Na_2CO_3, H_2O, 2% HCl, H_2O. The ethereal layer was dried over $MgSO_4$ and the ether removed on a rotary evaporator. The reddish oil obtained crystallized in the refrigerator overnight and the crystals were filtered off and pressed dry with a "Parafilm" dam. (A polyethylene type film, manufactured by the American Can Co.). The filtrate was put aside and allowed to isomerize at room temperature over a period of six months to yield a second crop of crystals (99). A yield of 32.7 gm (77%) of crude crystalline material was obtained. Two recrystallizations from 60 - 80 petroleum ether (pet. ether) yielded 19 gm of pure white crystals m.p. 73.5 - 74.5 , $[\alpha]_D^+$ 125.4 (c = 0.24, EtOH), lit. m.p. 75.7 - 76.5°, and lit. $[\alpha]_D^+$ 120 (c = 0.25, EtOH) (96).

ii) Preparation of menthyl p-toluene sulfinate

p-Toluene sulfinic acid was obtained in 95% yield from p-toluene sulfonyl chloride by reduction with Na_2SO_3 and subsequent treatment with acid (101). The sulfinic acid (0.38 mmoles) was then refluxed with 40 ml. of $SOCl_2$ (0.56 moles) for 40 minutes, then the excess $SOCl_2$ distilled off. The resulting crude acid chloride was dissolved in 800 ml. of anhydrous ether and cooled to - 78° in a flask equipped as described above. To this solution was added dropwise a mixture of 33 gm of l-menthol

(0.22 moles) in 90 ml of 1:1 ether/pyridine. The reaction mixture was kept for 2 hours at - 78°, then warmed to 0° and worked up as above. The thick orange oil obtained crystallized overnight at room temperature and the crystals filtered off and pressed dry with a "Parafilm" damn. The filtrate isomerized in 8 weeks at room temperature to give a second crop of crystals (99). After 3 recrystallizations from 60-80° pet. ether, 28.3 gm (50%) of pure white crystals, m.p. 105-106°, $[\alpha]_D$ - 192 (c = 2.8, acetone), lit. m.p. 106-107° and lit. $[\alpha]_D$ - 199 (c = 1, acetone) (6), were obtained.

b) Reaction of Menthyl Sulfinate Esters with Grignard Reagents

General Procedure:

The appropriate Grignard reagent (1 - 1.5 equivalents (eq.)) in dilute solution in ether or T.H.F. (<0.5M) was slowly added to a solution of 1 eq. of the menthyl sulfinate ester dissolved in dry ether or T.H.F. After addition, the reaction mixture was stirred for 15 to 30 minutes, then 20 ml of saturated NH_4Cl solution was added to hydrolyse the unreacted Grignard. The total reaction mixture was then poured into 100 ml. of H_2O and the organic layer separated. The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and the solvent removed on the rotary evaporator. The colourless oil thus obtained was washed with pentane to remove the menthol present and the crude sulfoxide was purified

by crystallization, distillation or sublimation.

Benzyl Methyl Sulfoxide:

From 13 mmoles of menthyl phenylmethane sulfinate, $[\alpha]_D^+$ 125.4, and 30 mmoles of CH_3MgBr, 1.38 gm (66%) of pure sulfoxide, $[\alpha]_D^+$ 97.7 (c = 0.7, EtOH), m.p. 52-53°, lit. m.p. 53-54° (96), lit. $[\alpha]_D^+$ 96 (51), were obtained after sublimation.

Benzyl t-butyl Sulfoxide:

When 3 gm. of menthyl phenylmethane sulfinate (10.4 mmoles), $[\alpha]_D^+$ 123 (C = 0.24, EtOH) and 5.4 ml. of 2M t-BuMgCl (11 mmoles) were reacted, 363 mgm (18%) of pure sulfoxide, $[\alpha]_D^+$ 280 (c = 0.26, EtOH), m.p. 74-75°, lit. $[\alpha]_D^+$ 281 (EtOH) (51) and lit. m.p. 75-76° (96), were obtained.

Benzyl Phenyl Sulfoxide:

Menthyl phenylmethane sulfinate (10 mmoles), $[\alpha]_D^+$ 123 (c = 0.24, EtOH), and PhMgBr (27 mmoles) yielded 1.26 gm (54%) of pure sulfoxide, $[\alpha]_D^+$ 253 (c = 0.58, acetone), m.p. 40-41°, lit. $[\alpha]_D^+$ 254 (acetone), and lit. m.p. 40-41° (96)).

p-Tolyl Ethyl Sulfoxide:

From 17 mmoles of menthyl p-toluene sulfinate, $[\alpha]_D^-$ 192 (c = 2.8, acetone) and 32 mmoles of EtMgBr in T.H.F., 890 mgm (53%) of the desired sulfoxide, $[\alpha]_D^+$ 187 (c = 1.66, $CHCl_3$), lit. $[\alpha]_D^+$ 187.5 (acetone) (6), were obtained.

A competing reaction producing diethyl sulfoxide was noted in this case. This latter product could be separated from the desired sulfoxide by distillation under reduced pressure or chromatography on silica gel using ethyl acetate as solvent. The identity of this product was confirmed by comparison of its spectral properties, IR and n.m.r. spectra, with those obtained from an original sample. The amount obtained of this undesired product varied with the time of reaction but not significantly with the concentration of initial reactants. If the reaction was allowed to proceed 20 minutes after the addition of Grignard was completed, 10% of the total sulfoxides recovered was diethyl sulfoxide. After 30 minutes, 20% of recovered sulfoxides and after 45 minutes 58% of recovered sulfoxides were diethyl sulfoxide. The overall yields of products based on starting ester remained constant (i.e. between 60 to 65%). This product presumably arises from a displacement of the p-tolyl group on the originally formed p-tolyl ethyl sulfoxide and is similar to that reported for alkyllithiums (Chapter 2). Further work in this area is in progress in these laboratories.

Sulfoxide Carbanion Reactions:

General Procedure:

One equivalent of sulfoxide* was dissolved in 35 ml. of dry

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* The carbanion reactions were generally carried out on a 1 to 2 millimole scale. The sulfoxides were always freshly distilled or sublimed before use to remove adsorbed water.

T.H.F.† in a 50 ml. 2 neck flask equipped with a nitrogen inlet-outlet system and a rubber sceptum. The solution was then cooled to - 60° in a dry-ice acetone bath and stirred rapidly with a magnetic stirrer. To this cooled solution was added via the sceptum the appropriate alkyllithium (1.1eq.) (e.g. either CH_3Li, 1.6M in ether, or n-BuLi, 1.6M in hexane). The reaction mixture was stirred for 1 minute at - 60°, then an excess of the appropriate electrophile (10 eq. or more) was added with rapid stirring. After 1 minute the entire contents of the reaction vessel were poured into 150 ml. of H_2O saturated with NaCl. The aqueous mixture was extracted with 5 X 40 ml. of CH_2Cl_2, the combined extracts dried over $MgSO_4$, and the solvent removed on a rotary evaporator. The products (generally > 95% pure by n.m.r.) were analysed directly; they could subsequently be purified by recrystallization. chromatography or distillation.

Reactions of α- Lithiobenzyl Methyl Sulfoxide

- With D_2O

A solution of 1.3 mmoles of lithio sulfoxide was quenched with 1 ml. of D_2O (50 mmoles) to give 185 mgm (92%) of α- deuteriobenzyl

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† Dry T.H.F. was obtained by distillation of reagent grade T.H.F. from $LiAlH_4$ under a nitrogen atmosphere immediately prior to its use.

methyl sulfoxide (95% d-incorporation as measured by mass spectrometry was generally achieved). N.m.r. analysis in DMSO-d_6 showed that the high field benzylic proton (pro S, sulfur chirality S) was replaced preferentially to the low field one in a ratio of 15.5:1. Identical ratios were obtained when DCl or acetic acid-O-d were used to quench the reaction.

- With CH_3I or CH_3Br

From 1.95 moles of lithio salt and 2 ml. of methyl iodide (~20 mmoles), 313 mgm (96%) of colourless oil were obtained. Analysis of this oil by n.m.r. showed it was > 95% pure α- methylbenzyl methyl sulfoxide and integration of the sulfur methyl signals gave a diastereomer product ratio of 14.5:1. When CH_3Br was used an 80% yield of product was obtained and the diastereomer ratio was 15:1. n.m.r.: 1.71 (d, J = 7.4 Hz, 3H); 2.16 (s, 3H) (major isomer); 2.27 (s, 3H) (minor isomer); 3.81 (q, J = 7.4 Hz, 1H); 7.32 (m, 5H). IR: S=O 1010cm^{-1}

- With Acetone

When 5.7 mmoles of lithio sulfoxide were reacted with 50 mmoles of acetone, 1.14 gm (94%) of a colourless oil were obtained. This oil > 95% pure methyl 1-phenyl-2-hydroxy-2-methyl-propyl sulfoxide consisted of a 14.9:1 mixture of two diastereomers. This ratio was obtained by integration of the two methine signals of the diastereomers.

n.m.r.: major isomer: 1.07 (s, 3H); 1.64 (s, 3H); 2.37 (s, 3H); 3.94 (s, 1H); 5.22 (s, 1H) (OH); 7.32 (m, 5H).

minor isomer: 1.21 (s, 3H); 1.62 (s, 3H); 2.09 (s, 3H); 3.22 (s, 1H); 3.90 (s, 1H) (OH); 7.40 (m, 5H).

IR: major isomer S=O 1005 cm^{-1}

minor isomer S=O 1015 cm^{-1}

- With 3-bromo 1-butene*

From 1.3 mmoles of carbanion and 15 mmoles of 3-bromo 1-butene, 238 mgm (88%) of methyl 1-phenyl-3-pentenyl sulfoxide were obtained. This product is a colourless oil. Integration of the two sulfur methyl groups indicated that the ratio of diastereomers was 14-15:1.

n.m.r.: 1.64 (m, 3H); 2.11 (d, 3H) (major isomer); 2.26 (d, 3H) (minor isomer); 2.90 (m, 2H); 3.47 (d, J = 6Hz) + 3.57 (d, J = 6Hz)(1H); 5.51 (m, 2H); 7.33 (m, 5H)

IR: S=O 1015 cm^{-1}

- With Allyl Bromide

When 1.3 mmoles of the lithio salt were reacted with 15 mmoles of allyl bromide, 231 mgm (92%) of methyl 1-phenyl-3-butenyl sulfoxide

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* See Footnote page 32.

(> 95% pure by n.m.r.) were obtained. This product was a colourless oil. Using the sulfur methyl group as probe the diastereomer ratio was found to be 14-15:1. This compound was then further purified by chromatography on silica gel using ether as solvent. The spectral properties of the chromatographed product were identical with the crude product. n.m.r.: 2.12 (s, 3H) (major isomer); 2.28 (s, 3H) (minor isomer); 2.93 (m, 2H); 3.52 (d, J = 6.2 Hz) + 3.62 (d, J = 6.2 Hz) (1H); 5.10 (m, 2H); 5.76 (m, 1H); 7.34 (m, 5H). IR: S=O 1015 cm^{-1}

Effect of Temperature on the Reactions of α- Lithiobenzyl Methyl Sulfoxide

- With D_2O at - 20°

When the lithio sulfoxide was generated and quenched as above with D_2O, the only difference being the reaction temperature, - 20°, a 91% yield of a 12.4:1 mixture of diastereomers was obtained.

- With D_2O at 24°

When the carbanion was quenched at 24° an 88% yield of a 7.7:1 mixture of diastereomers was obtained.

Effect of Solvent on the Reactions of α- Lithiobenzyl Methyl Sulfoxide

- With DCl in DMSO at - 24°

When 1.3 mmoles of benzyl methyl sulfoxide were reacted with 1.4 mmoles of CH_3Li in 10 ml. of DMSO (freshly distilled from CaH_2 before use) at 24° and the resulting carbanion quenched with 2 ml. of 6N DCl, 150 mgm (75%) of monodeuterated sulfoxide were obtained. N.m.r. analysis in DMSO-d_6 showed that the low field benzylic proton (pro R, sulfur chirality S) was replaced preferentially by a factor of 1.7:1. When D_2O was used to quench the reaction, variable diastereomer ratios were obtained.

- With Acetic Acid-O-d in Benzene at 24°

When 1.3 mmoles of benzyl methyl sulfoxide were reacted with 1.4 mmoles of CH_3Li in 35 ml. of dry benzene (freshly distilled) at 24° and the lithio salt quenched with acetic acid-O-d, 160 mgm (80%) of monodeuterated sulfoxide were obtained (> 95% pure by n.m.r.). N.m.r. analysis in DMSO-d_6 showed that the pro S (sulfur chirality S) (high field) proton was replaced preferentially by a factor of 9.1:1.

Decomposition Reaction of α- Lithiobenzyl Methyl Sulfoxide

The lithio salt of benzyl methyl sulfoxide was generated in T.H.F. at -60°, then allowed to warm to room temperature, 24°, over one half hour and then quenched with H_2O. N.m.r. analysis of the product indicated the presence of 50% regenerated benzyl methyl sulfoxide and 50% other materials. Chromatography on silica gel using 6:1 Ether/CH_3OH

as solvent yielded pure benzyl methyl sulfoxided (slowest fraction) and a mixture of other products (fastest fractions) whose spectral properties are given in Chapter 2. When the carbanion was generated and kept at -60° for 4 hours before being quenched with H_2O, an identical mixture of starting sulfoxide and decomposition products was obtained as above.

Displacement Reaction at Sulfur in Benzyl Methyl Sulfoxide

When n-BuLi was used to generate the carbanion instead of CH_3Li and the carbanion quenched with H_2O, a mixture of two products was obtained (T.L.C., n.m.r.). One set of peaks comprising of about 60% of the mixture (n.m.r.) corresponded to starting sulfoxide, the other peaks at 0.7-2.0 and 2.2-3.0 ppm were attributed to the presence of 40% methyl n-butyl sulfoxide. This assignment was made by comparison of the spectral properties of this product with those of an original sample. An independent study has since confirmed this assignment (24b).

Reactions of α- Lithiobenzyl t-butyl Sulfoxide

With D_2O

From 5.1 mmoles of lithio sulfoxide and 100 mmoles of D_2O (2 ml.), 944 mgm (94%) of α- deuteriobenzyl t-butyl sulfoxide were obtained (> 95% pure by n.m.r.). The deuterium incorporation was > 95% by mass spectrometry. Analysis of the product by n.m.r. indicated

that the high field benzylic proton (pro R for sulfur chirality R) was exchanged preferentially; no exchange of the low field proton would be detected. The diastereomer ratio was estimated to be > 99:1.

- With CH_3I

When 2.6 mmoles of the lithio salt was reacted with 20 mmoles (2 ml.) of CH_3I, 505 mgm (95%) of ∝- methylbenzyl t-butyl sulfoxide (> 95% pure, n.m.r.) were obtained. N.m.r. analysis revealed the presence of only one diastereomer. After sublimation, the product sulfoxide, a white crystalline material had m.p. 45-47°.

n.m.r.: 1.12 (s, 9H); 1.63 (d, J = 7.2 Hz, 3H); 3.88 (q, J = 7.2 Hz, 1H); 7.30 (m, 5H) IR: S=O 1025 cm^{-1}

Reactions of ∝- Lithiobenzyl Phenyl Sulfoxide

- With D_2O

When 1.4 mmoles of the lithio sulfoxide were reacted with 50 mmoles of D_2O, 1 ml., 273 mgm (91%) of ∝ - deuteriobenzyl phenyl sulfoxide were obtained. N.m.r. analysis in DMSO-d_6 showed that the high field benzylic proton was preferentially replaced by a factor of 1.5:1.

When the lithio salt was quenched with H_2O, an n.m.r. analysis of the total products recovered showed peaks corresponding to those of phenyl methyl sulfoxide. These peaks corresponded to about 2% of the

recovered sulfoxides. An independent study has confirmed this observation (24b).

- With CH_3I

When the carbanion generated from 200 mgm of sulfoxide (0.93 mmoles) was quenched with 1 ml. of CH_3I (10 mmoles) a 94% yield of a mixture of the two diastereomers of α- methylbenzyl phenyl sulfoxide was obtained. The diastereomer product ratio, 1.53:1, was measured by n.m.r. integration of the two methine quartets in CCl_4 (87) and of the methyl doublets in $CDCl_3$. The isomers could be separated by chromatography on silicia gel.

n.m.r.: major isomers: 1.58 (d, J = 7 Hz, 3H); 4.00 (q, J = 7 Hz, 1H); 7.21 (m, 10H). minor isomer: 1.68 (d, J = 7.3 Hz, 3H); 3.85 (q, J = 7.3 Hz, 1H); 7.26 (m, 10H) in CCl_4: (See ref. 91).

Deuteration of Benzyl Ethyl Sulfoxide

When 200 mgm of benzyl ethyl sulfoxide (1.2 mmoles) were treated with CH_3Li (13 mmoles) followed by 1 ml. of D_2O (50 mmoles) as described above, 197 mgm (98%) of monodeuterated sulfoxide were obtained. N.m.r. analysis of the product in DMSO-d_6 showed that the highfield benzylic proton had exchanged preferentially by a factor 9.9:1.

Deuteration of Benzyl i-propyl Sulfoxide

When 200 mgm of benzyl i-propyl sulfoxide (1.1 mmoles) were reacted with CH_3Li (1.2 mmoles), and the resulting carbanion trapped with D_2O, a 90% yield (180 mgm) of monodeuterated sulfoxide was obtained. Analysis by n.m.r. in DMSO-d_6 showed that the high field benzylic proton was preferentially replaced by a factor of 13.1:1.

Proof of Structure of Hydroxyalkylation Adducts of Benzyl Methyl Sulfoxide With Acetone

The gross structures of the two diastereomers obtained from the reaction of ∝- lithiobenzyl methyl sulfoxide with acetone were determined by the sequence of reactions depicted in Scheme 4.

Potassium methyl thiolate (23.5 mmoles) was prepared by bubbling CH_3SH slowly through a solution of 1.35 gm. (23.5 mmoles) of KOH in 150 ml. of CH_3OH for ½ hour. To this solution was added 3.95 gm of ∝- chlorobenzyl methyl ketone (23.5 mmoles) and the mixture stirred for 8 hours in a closed vessel. Unreacted CH_3SH was allowed to evaporate overnight and the reaction mixture poured into 200 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, the extracts dried over $MgSO_4$ and the solvent evaporated on a rotary evaporator to yield a yellow oil. This oil was distilled at reduced pressure, 75°/0.25 mm, to give 3.6 gm (85%) of ∝- mercaptomethylbenzyl methyl ketone.

n.m.r.: 1.99 (s, 3H); 2.12 (s, 3H); 4.56 (s, 1H); 7.30 (s, 5H).

The above keto sulfide, 474 gm (26.2 mmoles), was dissolved in 40 ml. of anhydrous ether and cooled to 0 C in a flask equipped with a nitrogen inlet-outlet system and a selfcompensating dropping funnel. A solution of CH_3MgBr (52.5 mmoles) in ether was slowly added to the above solution. After 2 hours, 25 ml. of H_2O were added, followed by just enough 6N HCl to dissolve the $Mg(OH)_2$ precipitate formed. The organic phase was separated off and the aqueous one extracted with ether. The combined organic fractions were dried over $MgSO_4$ and the ether removed on a rotary evaporator. The crude product was distilled at 88./0.25 mm. to yield 4.90 gm (95%) of methyl 1-phenyl-2-hydroxyl-2-methylpropyl sulfide. n.m.r.: 1.22 (s, 6H); 1.90 (s, 3H); 2.50 (s, 1H) (OH); 3.75 (s, 1H); 7.37 (m, 5H).

The hydroxy sulfide from above, 1 gm (5.1 mmoles), was oxidized to sulfoxide using $NaIO_4$ (5.1 mmoles) as described previously to yield 1 gm (95%) of a mixture of two diastereomeric sulfoxides (~ 50:50 by n.m.r.). The mixture was chromatographed on silica gel using 2:1 Ether/Pentane as solvent; the faster moving fraction corresponded to the major isomer from the carbanion reaction, the slower fraction to the minor product (see above for spectral properties).

Inversion of Configuration at Sulfur in ∝- Methylbenzyl t-butyl Sulfoxide (29).

∝- Methylbenzyl t-butyl sulfoxide, 505 mgm (2.4 mmoles), obtained by alkylation of benzyl t-butyl sulfoxide (see above), was dissolved in 4 ml. of $CHCl_3$ which had been purified by filtration through a silica gel column. To this solution was added 0.41 gm of $CF_3-SO_3-CH_3$ (2.5 mmoles). After 3 minutes, 20 ml. of 2N KOH was added. The aqueous phase was extracted with 4 X 20 ml. of CH_2Cl_2, the extracts dried over $MgSO_4$ and the solvent removed on a rotary evaporator to give 461 mgm (92%) of a mixture of two diastereomeric sulfoxides. The mixture was separated on preparative T.L.C. plates using 3:1 ether/pentane as solvent. The faster moving fraction was a new isomer, the slower moving fraction was identical with starting material (carbanion reaction isomer). n.m.r.: (carbanion reaction isomer): 1.12 (s, 9H); 1.63 (d, J = 7.2 Hz, 3H); 3.88 (q, J = 7.2 Hz, 1H); 7.30 (m, 5H). (new isomer): 1.09 (s, 9H); 1.72 (d, J = 7.2 Hz, 3H); 3.82 (q, J = 7.4 Hz, 1H); 7.33 (m, 5H). IR: S=O 1025 cm^{-1} (both isomers)

Oxidation of Sulfides and Sulfoxides to Sulfones

General Procedure:

The sulfide, 1 eq., was dissolved in 30 ml. of CH_2Cl_2, to which was added MPBA, 3-4 eq. The reaction mixture was then either allowed to stand overnight at room temperature or refluxed for 2 hours.

The reaction mixture was then washed with successive portions of 10% Na_2SO_3, 10% $NaHCO_3$, H_2O and the organic phase dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the sulfones obtained were purified by recrystallization.

The procedure for the oxidation of sulfoxides to sulfones is identical except that only 1.5 – 2.0 equivalents of MPBA per equivalent of sulfoxide were used.

Reduction of Sulfoxides to Sulfide (53)

General Procedure:

The sulfoxide, 1 eq., was dissolved in 14 ml. of 2.5:1 CH_3CN/DMF at 0°. To this solution was added 1.1 eq. of $SnCl_2,2H_2O$ and 3 eq. of acetyl chloride. The reaction mixture was stirred for 1 hour at 0°, 1 hour at room temperature before being poured into 150 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, the extracts washed with successive portion of 3% HCl, 5% $NaHCO_3$, H_2O, and then dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue dissolved in 20–30 ml. of 6:1 pentane/ether. This solution was washed with H_2O to remove residual traces of DMF. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The crude sulfide thus obtained was purified either by chromatography or distillation.

Stereochemistry of Sulfoxide Carbanion Reactions

The stereochemistry of the sulfoxide carbanion reactions was determined by quenching the carbanions of sulfoxides of known configuration at sulfur with various electrophiles. The product sulfoxides were then oxidized or reduced to sulfones or sulfides and the rotations of these compounds compared to those of sulfones or sulfides having known configuration at carbon.

The general procedures for the carbanion, reduction and oxidation reactions have all been given above. The results for each sulfoxide and the details for the synthesis of compounds of known configuration at carbon follows.

Deuteration of (S) - Benzyl Methyl Sulfoxide

(S)-Benzyl methyl sulfoxide, $[\alpha]_D$ + 97.7 (c = 0.7, EtOH), was deuterated as described above to give α- deuteriobenzyl methyl sulfoxide, $[\alpha]_D$ + 92 (c = 0.72, EtOH) in 86% yield.

Oxidation of α- Deuteriobenzyl Methyl Sulfoxide

When a portion of the above α- deuterated sulfoxide was oxidized with MPBA, (S) - α- deuteriobenzyl methyl sulfone, $[\alpha]_D$ - 0.9 (c = 1.15, $CHCl_3$), m.p. 124-125 was obtained in 85% yield (lit. $[\alpha]_D$ - 0.6 (c = 6, $CHCl_3$) (9a), lit. m.p. ($Ph-CH_2-SO_2-CH_3$) 125-126 (104)).

n.m.r.: 2.73 (s, 3H); 4.23 (bs = 1H); 7.40 (s, 5H)

IR: SO_2 1140 cm^{-1} and 1300 cm^{-1}

Reduction of α- Deuteriobenzyl Methyl Sulfoxide

A portion of the α- deuteriobenzyl methyl sulfoxide from above was reduced to (S)- α -deuteriobenzyl methyl sulfide, $[\alpha]_D$ + 0.48 (c = 11.5, $CHCl_3$), lit. $[\alpha]_D$ + 0.73 (c = 12, EtOH) (9a) in 83% yield.

n.m.r.: 1.94 (s, 3H); 3.62 (bs, 1H); 7.27 (s, 5H).

Methylation of (S) - Benzyl Methyl Sulfoxide and Oxidation of Product

(S) - Benzyl methyl sulfoxide, $[\alpha]_D$ + 97.7 (c = 0.7, EtOH), was methylated in 88% yield to give α - methylbenzyl methyl sulfoxide, $[\alpha]_D$ - 6.1 (c = 0.6, EtOH).

Oxidation of this sulfoxide with excess MPBA gave a quantitative yield of white crystalline α - methylbenzyl methyl sulfone, m.p. 108-110°, $[\alpha]_D$ + 24.7 (c = 7, EtOH). The sulfone was recrystallized to constant rotation from ether — CH_2Cl_2/pentane.

n.m.r.: 2.80 (d, J = 7 Hz, 3H); 2.52 (s) (minor isomer) + 2.63 (s) (major isomer) (3H); 4.23 (q, J = 7 Hz, 1H); 7.46 (s, 5H)

IR: SO_2 1135 cm^{-1} and 1305 cm^{-1}

Synthesis of (R) - α - Methylbenzyl Methyl Sulfone

(R) - α - Methylbenzyl methyl sulfone was synthesized from (S)- α - phenethyl alcohol as shown in Scheme 17.

(S)- α -Phenethyl alcohol, $[\alpha]_D$ - 43.2 (neat) (99% pure) (54), 0.5 ml. (4.18 mmoles), and 0.8 gm of α - toluenesulfonyl chloride (4.1 mmoles) were dissolved in 20 ml. of CH_2Cl_2 and the mixture cooled to 0°. To this mixture was added all at once 0.65 ml. of $(Et)_3N$ (4.6 mmoles). The reaction mixture was poured into ice water, the organic layer separated off and the aqueous layer extracted with ether. The combined organic fractions were dried over $MgSO_4$ and the solvent removed under vacuum at 15° (if a much higher temperature was used the product decomposed). The resultant phenylmethanesulfonate, a white crystalline solid, decomposed rapidly if allowed to stand at room temperature for a few minutes. It was therefore not characterized but employed immediately in the next step of the synthesis.

The phenylmethanesulfonate was dissolved in 5 ml. of CH_3OH and added to a solution of CH_3SK (43 mmoles) cooled to - 50°. The CH_3SK solution was prepared by slowly bubbling CH_3SH gas through a solution of KOH (43 moles) in 25 ml. of CH_3OH. The reaction mixture was allowed to warm to room temperature, then it was poured into 150 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, the extracts

washed with 5% KOH and H_2O before being dried over $MgSO_4$. The solvent was removed on a rotary evaporator to give a clear oil which after chromatography on silica gel (pentane as solvent) yielded 150 mgm (24%) of pure colourless α- methylbenzyl methyl sulfide, $[\alpha]_D^+$ 168 (c = 0.8, EtOH). n.m.r.: 1.50 (d, J = 7 Hz, 3H); 2.87 (s, 3H); 3.83 (q, 7 Hz, 1H); 7.27 (s, 3H).

The sulfide (0.98 mmoles) was oxidized using 600 mgm of MPBA (85%, 3 mmoles) to yield 125 mgm (73%) of pure white crystalline (R)-α-methylbenzyl methyl sulfone, m.p. 111-112°, $[\alpha]_D^+$ 30.9 (c = 0.84, EtOH), after 2 recrystallization from ether - CH_2Cl_2/pentane. Its spectral properties were identical to the sulfone obtained via the carbanion route.

Analysis:

Calculated: C = 58.69, H = 6.57

Found: C = 58.89, H = 6.63

Hydroxyalkylation of (S)-Benzyl Methyl Sulfoxide and Oxidation of the Product to Sulfone

When 200 mgm of (S)-benzyl methyl sulfoxide, $[\alpha]_D^+$ 97.7 (c = 0.7, EtOH) (1.3 mmoles), were metallated and quenched with acetone, 230 mgm (85%) of methyl 1-phenyl-2 hydroxy-2-methylpropyl sulfoxide, $[\alpha]_D$- 121 (c = 1.5, $CHCl_3$); were obtained.

The product sulfoxide (1.1 mmoles) was oxidized with MPBA (1.7 mmoles) to give 176 mgm (71%) of pure methyl 1-phenyl-2-hydroxy-2-methylpropyl sulfone, $[\alpha]_D$ - 45.6 (c = 1.95, EtOH), m.p. 120-121°, after 3 recrystallizations from CH_2Cl_2/pentane.

n.m.r.: 1.30 (s, 3H); 1.47 (s, 3H); 2.66 (s, 3H); 3.87 (bs, 1H) (OH); 4.66 (s, 1H); 7.43 (m, 5H).

IR: SO_2 1300 cm^{-1} and 1120 cm^{-1}; OH 3500 cm^{-1}

Analysis:

Calculated: C = 57.88; H = 7.07, S = 14.02

Found: C = 57.91, H = 7.07, S = 14.08

Synthesis of (R) - Methyl 1-Phenyl-2-Hydroxy-2-Methylpropyl Sulfone

An outline of the synthesis is given in Scheme 18.

(S) - Mandelic acid, 20 gm (130 mmoles), $[\alpha]_D$ 147 (c = 2.5, H_2O) (94% pure), was refluxed overnight in 100 ml. of 10:1 CH_3OH/H_2SO_4 (conc). The volume of solvent was halved by evaporation under vacuum and the remaining solution poured into 200 ml. of H_2O. The aqueous mixture was extracted with 6 X 25 ml. of CH_2Cl_2 and the extracts washed with successive 50 ml. portions of K_2CO_3 (saturated solution) and H_2O before being dried over $MgSO_4$. The solvent was evaporated off on a rotary evaporator to give 18.4 gm (84%) of methyl mandelate, m.p. 52-53°, $[\alpha]_D$ + 172 (C = 1.1, $CHCl_3$), lit. m.p. 55-55.4 (99), lit. $[\alpha]_D$ - 167 ($CHCl_3$) for (R) - methyl mandelate.

The methyl mandelate, 15 gm (90 mmoles) and methane sulfonyl chloride, 10.34 gm (99 mmoles) were reacted with $(Et)_3N$ (110 mmoles) in CH_2Cl_2 according to the method of King and Durst (55) to give 21.7 gm (90%) of the mesylate of methyl mandelate. After 2 recrystallizations from CH_2Cl_2/pentane this material had m.p. 112-113° and $[\alpha]_D$ + 109 (c = 1.7, $CHCl_3$). n.m.r.: 3.06 (s, 3H); 3.73 (s, 3H); 5.97 (s, 1H); 7.43 (s, 5H).

IR: C = O 1755^{-1}; O-SO_2 1350 and 1170 cm^{-1}

Analysis:

Calculated: C = 49.18, H = 4.95, S = 13.10

Found: C = 49.35, H = 4.90, S = 13.10

To a solution of CH_3SK (20.5 mmoles) in 150 ml. of CH_3OH, prepared as described above, was added a solution of 5 gm of the mesilate of methyl mandelate (20.5 mmoles) in 15 ml. of CH_3OH. The reaction mixture was allowed to stand overnight, then it was poured into H_2O. The aqueous mixture was extracted with CH_2Cl_2, and the extracts washed with H_2O before being dried over $MgSO_4$. The solvent was removed on a rotary evaporator to yield 3.78 gm (94%) of a clear yellow oil which was chromatographed on silica gel (4:1 petroleum ether /ether as solvent) to give pure sulfide ($Ph-\underset{\underset{S-CH_3}{|}}{CH}-CO_2-CH_3$), $[\alpha]_D$ - 67.6 (c = 1.7, $CHCl_3$).

n.m.r.: 2.03 (s, 3H); 3.70 (s, 3H); 4.50 (s, 1H); 7.33 (m, 5H).

The above sulfide, 1 gm (5 mmoles) was added to an excess of CH_3MgI (21.6 mmoles) in ether and the reaction mixture refluxed for 1 hour. A saturated solution of NH_4Cl, 30 ml. was then added and the precipitate formed was filtered off and washed with ether. The aqueous layer was extracted with ether and the combined ether fractions dried over $MgSO_4$. After evaporation of the ether, 729 mgm (73%) of crude methyl 1-phenyl-2-hydroxy-2-methylpropyl sulfide was obtained. It was purified by chromatography on silica gel to give pure sulfide, $[\alpha]_D$ 136.1 (c = 2.45, $CHCl_3$).

n.m.r.: 1.22 (s, 6H); 1.90 (s, 3H); 2.37 (bs, 1H) (OH); 3.75 (s, 1H); 7.37 (m, 5H).

When 150 mgm of this sulfide (0.77 mmoles) was oxidized with MPBA (2.3 mmoles), 135 mgm of pure sulfone, m.p. 119-121°, $[\alpha]_D$ 41.1 (c = 1.77, EtOH) was obtained after 3 recrystallizations from ether-CH_2Cl_2/pentane. Its spectral properties were identical to those of the sulfone obtained from the carbanion route.

Deuteration of (R) - Benzyl t-Butyl Sulfoxide and Oxidation of The Product To α- Deuteriobenzyl t-Butyl Sulfone

(R) - Benzyl t-butyl sulfoxide (1.35 mmoles), $[\alpha]_D$ + 167

(c = 0.7, EtOH) (60% optically pure), was metallated and quenched with D_2O (50 mmoles) in the usual fashion. The product was oxidized with MPBA (2.8 mmoles) to give 250 mgm (87%) of α - deuteriobenzyl t-butyl sulfone, m.p. 125-126°, lit. m.p. 126-127 (benzyl t-butyl sulfone) (104), $[\alpha]_D$ + 0.6 (C = 14.5, CH, Cl_3) after recrystallization from CH_2Cl_2 - ether /pentane. N.m.r. analysis indicated > 95% deuterium incorporation.

n.m.r.: 1.42 (s, 9H); 4.10 (bs, 1H); 7.33 (bs, 5H).

IR: SO_2 1120 cm^{-1} and 1300 cm^{-1}

Synthesis of (R) -α- Deuteriobenzyl t-Butyl Sulfone

(S)-α-Deuteriobenzyl alcohol (optical purity ~ 30%) was prepared by the method of Wolfe and Rauk (58, 9a) (i.e. reduction of benzaldihyde with diisopinocampheyldeuterioborane prepared from (-) -pinene ($[\alpha]_D$ -48, neat) and deuteriodiborane).

The above alcohol, 1.25 gm (11.5 mmoles) and α- toluenesulfonyl chloride (11.5 mmoles) were reacted with $(Et)_3N$ (11.8 mmoles) according to the method of King and Durst (55) to give 1.75 gm (64%) of white crystalline α- deuteriobenzyl phenylmethanesulfonate after crystallization from CH_2Cl_2/pentane.

n.m.r.: 4.3 (bs, 1H); 4.87 (s, 2H); 7.43 (m, 10H).

IR: $O-SO_2$ 1165 cm^{-1} and 1350 cm^{-1}

To a solution of potassium t-butyl thiolate (6.7 mmoles), prepared from 5 gm of KOH (90 mmoles) and t-BuSH (6.7 mmoles) in 50 ml. of CH_3OH, was added a solution of 910 mgm of ∝ - deuteriobenzyl phenylmethanesulfonate (3.5 mmoles) in 10 ml. of CH_3OH. The reaction mixture was allowed to stand overnight, and then was poured into 200 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, and the extracts washed with 10% KOH and H_2O before being dried over $MgSO_4$. The solvent was evaporated to give crude ∝ -d-benzyl-t-butyl sulfide. The sulfide was chromatographed on silica gel (11:1 pentane/ether as solvent), and then further purified by preparative g.l.c. (a chromosorb 1500 column was used) to give 100 mgm (16%) of pure sulfide.

n.m.r.: 1.35 (s, 9H); 3.77 (bs, 1H); 7.30 (s, 5H).

The above sulfide (0.55 mmoles) was oxidized with MPBA (4 mmoles) to give 104 mgm (88%) of ∝-deuteriobenzyl t-butyl sulfone whose spectral properties were identical to those of the sulfone obtained via the carbanion route. Recrystallization gave material having $[\alpha]_D^{+}$ 0.4 (c = 4.26, $CHCl_3$), m.p. 125-126°, lit. m.p. 126-127 (benzyl t-butyl sulfone) (104).

Methylation of (R) - Benzyl t-Butyl Sulfoxide and Oxidation of The Product To ∝- Methylbenzyl t-butyl Sulfone

When 149 mgm of (R)-benzyl t-butyl sulfoxide (0.76 mmoles), $[\alpha]_D^+$ 280 (C = 0.26, EtOH) were metallated and quenched with excess CH_3I, 155 mgm (97%) of ∝- methylbenzyl t-butyl sulfoxide were obtained.

The crude reaction product (0.74 mmoles) was then oxidized with MPBA (1.5 mmoles) to give 170 mgm (98%) of white crystalline ∝-methyl-benzyl t-butyl sulfone. Recrystallization from ether - CH_2Cl_2/pentane gave material having $[\alpha]_D^-$ 46.3 (c = 0.99, $CHCl_3$) and m.p. 110-110.5°.

n.m.r.: 1.20 (s, 9H); 1.80 (d, J = 7 Hz, 3H); 4.43 (q, J = 7 Hz, 1H); 7.4 (m, 5H).

IR: SO_2 1125 cm^{-1} and 1300 cm^{-1}

Synthesis of (R) -∝- Methylbenzyl t-Butyl Sulfone

An outline of this synthesis is given in Scheme 17.

The phenylmethanesulfonate ester of (S)-∝-phenethyl alcohol, $[\alpha]_D^-$ 43.2 (neat) was prepared as described previously.

The ∝-phenethyl phenylmethanesulfonate (4.18 mmoles) was dissolved in 5 ml. of MeOH and added slowly to a mixture of t-BuSH (4.2 mmoles) and 2.4 gm KOH (43 mmoles) in 25 ml. of CH_3OH at - 50°.

The reaction mixture was allowed to warm to room temperature, stirred for ½ an hour, and poured into 150 ml. of H_2O. The aqueous mixture was extracted with 5 X 40 ml. of CH_2Cl_2; the combined extracts were then washed with 5% KOH and H_2O and then dried over $MgSO_4$. The solvent was evaporated off and the residue chromatagraphed on silica gel (pentane as solvent) to give 139 mgm (18%) of pure ∝- methylbenzyl t-butyl sulfide.

n.m.r.: 1.23 (s, 9H); 1.57 (d, J = 7 Hz, 3H); 4.01 (q, J = 7 Hz, 1H); 7.30 (m, 5H).

The sulfide (0.71 mmoles) was oxidized with MPBA to give 145 mgm (95%) of crude sulfone. Recrystallization from ether - CH_2Cl_2 /pentane gave pure (R)-∝-methylbenzyl t-butyl sulfone, $[\alpha]_D^+$ 43.7 (c= 0.82, $CHCl_3$), m.p. 110-111°. Its spectral properties were identical to those of the sulfone obtained via the carbanion route.

Analysis:

Calculated: C = 63.70, H = 8.02, S = 14.12

Found: C = 63.38, H = 7.92, S = 13.92

Methylation of (R) - Benzyl Phenyl Sulfone

When 487 mgm of (R) - benzyl phenyl sulfoxide, $[\alpha]_D^+$ 253 (c= 0.58, acetone) (2.3 moles), was metallated and quenched with

excess CH_3I in the usual manner, 488 mgm (95%) of a 1.5:1 mixture (by n.m.r.) of the two possible diastereomeric ∝- methylbenzyl phenyl sulfoxides were obtained. These isomers could be separated by chromatography on silica gel.

Oxidation of ∝- Methylbenzyl Phenyl Sulfoxide

A portion of the 1.5:1 mixture of diastereomeric sulfoxides (2.2 mmoles) obtained from the carbanion reaction was oxidized with MPBA (3.9 mmoles) to give 460 mgm (88%) of white crystalline ∝ - methylbenzyl phenyl sulfone. This product was recrystallized once from ether - CH_2Cl_2/pentane to give material having a rotation $[\alpha]_D^+$ 17.4 (c = 4.3, CH_3OH). Comparison of this value with literature values for ∝- methylbenzyl phenyl sulfone (86) indicated that the major carbanion isomer had R configuration at carbon.

n.m.r.: 1.77 (d, J = 7 Hz, 3H); 4.23 (q, J = 7 Hz, 1H); 7.40 (m, 10H).

IR: SO_2 1155 cm^{-1} and 1315 cm^{-1}

Hydroxyalkylation of (R) - p-tolyl Ethyl Sulfoxide and Reduction of the Adduct to Sulfide

(R) - p-tolyl ethyl sulfoxide, $[\alpha]_D^+$ 187 (c = 1.66, $CHCl_3$) was reacted with CH_3Li and quenched with acetone to give a quantitative yield of p-tolyl 3-(-2-hydroxy-2-methyl)-butyl sulfoxide, $[\alpha]_D^+$ 203 (c = 2.23, $CHCl_3$).

n.m.r.: 1.03 (d, J = 7 Hz, 3H); 1.27 (s, 3H); 1.45 (s, 3H); 2.33 (s, 3H); 2.50 (m, 1H); 4.00 (bs, 1H) (OH); 7.36 (q, 4H).

IR: OH 3400 cm^{-1}; S=O 1030 cm^{-1}

The p-tolyl 3-(-2-hydroxy-2-methyl)-butyl sulfoxide obtained above was reduced in the standard way to give a quantitative yield of crude hydroxy sulfide. This sulfide was purified by chromatography on silica gel (6:1 ether/pentane as solvent) to give a clear yellow oil, $[\alpha]_D^+$ 61.7 (c = 1.66, $CHCl_3$).

n.m.r.: 1.30 (bs) + 1.37 (bs) (9H); 2.28 (s, 3H); 2.57 (bs, 1H) (OH); 3.13 (q, J = 7 Hz, 1H); 7.20 (q, 4H).

Analysis:

The analysis was carried by high resolution mass spectrometry using perfluorotributylamine as internal standard. Calculated ratio sulfide to standard = 1.050606. Measured ratio 1.050606.

Synthesis of (R) p-Tolyl 3-(-2-Hydroxy-2-Methyl)-Butyl Sulfide from (S)-Lactic Acid

This synthesis is outlined in Scheme 22.

A 20% solution of lactic acid in H_2O (0.12 mmoles) containing 65% (S)-lactic acid and 35% DL-lactic acid was mixed with 13 ml. of benzene (0.14 moles) and 15 ml. of EtOH (0.23 moles) and a few drops

of conc. H_2SO_4. The solution was distilled over 5 hours till the 63-80° fraction had been collected. The residue was cooled in ice and neutralized with solid K_2CO_3. Chloroform was added, the salts removed by filtration and the filtrate dried over $MgSO_4$. The solvent was removed on a rotary evaporator to give 8.3 gm (50%) of ethyl lactate. n.m.r.: 1.4 (m, 6H); 3.5 (bs, 1H) (OH); 4.26 (m, 3H).

The ester, 8 gm (68 mmoles), and methane sulfonyl chloride, 13.3 gm (74 mmoles), were reacted with $(Et)_3N$ in CH_2Cl_2 using the procedure of King and Durst (55) to give after work up 8.33 gm (62%) of pure white mesylate of ethyl lactate, $[\alpha]_D$ - 52.5 (c = 1.8, $CHCl_3$), m.p. 104-107°. n.m.r.: 1.55 (t, J = 7 Hz, 3H); 1.66 (d, J = 7 Hz, 3H); 3.20 (s, 3H); 4.33 (q, J = 7 Hz, 2H); 5.16 (q, J = 7Hz, 1H). IR: C=O 1750cm^{-1}, O-SO_2 1170cm^{-1} and 1350cm^{-1}

The mesylate, 1.72 gm (8.8 mmoles) was added to a solution of 492 mgm of KOH (8.8 mmoles) and 1.09 gm of thiocresol (8.8 mmoles) in 50 ml. of CH_3OH. The reaction was allowed to proceed overnight, then the reaction mixture was poured into 150 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, and the extracts washed with 10% KOH and H_2O before being dried over $MgSO_4$. The solvent was removed on a rotary evaporator to leave 1.59 gm (85%) of crude sulfide (p-tol-S-$\underset{\underset{CO_2\,Et}{|}}{CH}$-$CH_3$). The sulfide was purified by chromatography on silica

gel (4:1 pentane/ether) to give a pale yellow oil, $[\alpha]_D^+$ 91.25 (c = 3.2, $CHCl_3$). n.m.r.: 1.20 (t, J = 7 Hz, 3H); 1.45 (d, J = 7 Hz, 3H); 2.30 (s, 3H); 3.70 (q, J = 7 Hz, 1H); 4.10 (q, J = 7 Hz, 2H); 7.16 (q, 5H).

The above sulfide (2.4 mmoles) was added to a solution of CH_3MgI (12 mmoles) in ether. The reaction mixture was refluxed for 30 minutes then 30 ml. of saturated NH_4Cl were added. The ether layer was decanted and the aqueous phase extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and the solvent removed on a rotary evaporator. The residue was chromatographed on silica gel (6:1 ether/pentane as solvent) to give 190 mgm (38%) of pure p-tolyl 3-(-2-hydroxy-2-methyl)-butyl sulfide, $[\alpha]_D^-$ 58.6 (C = 1.33, $CHCl_3$). Its spectral properties were identical to those of the sulfide obtained via the carbanion route.

Alkylation of (R) - p-Tolyl Ethyl Sulfoxide With 3-Bromo-1-Butene and Subsequent Conversion of the Product to p-Totyl 2-Hexyl Sulfone

When 500 mgm of (R)-p-tolyl ethyl sulfoxide (3 mmoles), $[\alpha]_D^+$ 215.7 (c = 1.75, $CHCl_3$) was metallated and quenched with excess 3-bromo-1-butene (containing 10% 1-bromo-2-butene), 625 mgm (95%) of p-tolyl 5-hex-2-enyl sulfoxide were obtained. N.m.r. analysis using the non allylic methyl group as probe indicated that the diastereomer

product ratio was 2.7:1 and the cis - trans (or trans - cis) ratio was 2.42:1. n.m.r.: 0.90 (d, J = 6.8 Hz) + 0.92 (d, J = 6.8 Hz) (minor isomer) (3H); 1.05 (d, J = 6.8 Hz) + 1.10 (d, J = 6.8 Hz) (3H) (major isomer); 1.62 (m, 3H); 1.81 - 1.97 (m, 3H); 1.37 + 1.39 (2s, 3H); 6.43 (m, 2H); 7.37 (m, 4H).

The unsaturated sulfoxide, 125 mgm (0.57 mmoles) and 250 mgm of 10% palladium on charcoal were added to 100 ml. of ethyl acetate in a hydrogenating bottle. The bottle was put on a Parr hydrogenator at 25 psi overnight. The catalyst removed by filtration, the solvant dried over $MgSO_4$, and the solvent evaporated off to give 116 mgm (93%) of p-tolyl 2-hexyl sulfoxide.

n.m.r.: (CCl_4) : 0.55 - 1.85 (m, 12H); 2.40 (bs, 4H); 7.30 (q, 4H).

The p-tolyl 2-hexyl sulfoxide (0.52 mmoles) was oxidized in 92% yield to sulfone using excess MPBA (1.1 mmoles). After recrystallization from ether/pentane, p-tolyl 2-hexyl sulfone, $[\alpha]_D^+$ 3.74 (c = 2.03, $CHCl_3$) was obtained.

n.m.r.: 0.60 - 2.20 (m, 12H); 2.43 (s, 3H); 2.93 (m, 1H); 7.50 (q, 4H).

IR: SO_2 1130cm^{-1} and 1290cm^{-1}

Alkylation of (R)-p-Tolyl Ethyl Sulfoxide with n-Butyl Iodide and Oxidation of Product to p-Tolyl 2-Hexyl Sulfone.

When the lithio salt of (R)-p-tolyl ethyl sulfoxide was quenched with an excess of n-BuI an 88% yield of p-tolyl 2-hexyl sulfoxide was obtained (see above for spectral properties).

The above sulfoxide was oxidized with MPBA to give an 80% yield of p-tolyl 2-hexyl sulfone. This sulfone was purified by preparative T.L.C. (silica gel and 1:1 ether/pentane as solvent). The pure sulfone had $[\alpha]_D$ + 3.04 (c = 6.5, $CHCl_3$) and its spectral properties were identical to those reported above.

Synthesis of R p-Tolyl 2-Hexyl Sulfone From (S)-2-Hexanol

(S)-2-hexanol, 1 gm (9.8 mmoles, $[\alpha]_D$ + 9.3 (neat) (67% optical purity) (61), and 1.86 gm of α- toluenesulfonyl chloride (9.8 mmoles) were reacted with $(Et)_3N$ (10.8 mmoles) in CH_2Cl_2 according to the method of King and Durst (55) to give 1.9 gm (75%) of crude 2-hexyl phenylmethanesulfonate. The product after purification by chromatography on silica gel (2:1 pentane/ether) had $[\alpha]_D$ + 2.1 (c = 7.8, $CHCl_3$).

n.m.r.: 0.63 - 1.90 (m, 12H); 4.33 (s, 2H); 4.68 (bq, 1H); 7.37 (s, 5H).

IR: $O-SO_2$ 1165 and 1340cm^{-1}.

A solution of 1 gm of 2-hexyl phenylmethanesulfonate (3.9 mmoles) in 15 ml. of CH_3OH was added dropwise to a solution of 482 mgm of thiocresol (3.9 mmoles) and 0.9 gm of KOH (16 mmoles) in 50 ml. of CH_3OH. The reaction was worked up as previous thiolate reactions to give 627 mgm (77%) of crude p-tolyl 2-hexyl sulfide. This material was chromatographed on silica gel (pentane) then distilled under reduced pressure to give pure sulfide, $[\alpha]_D$ - 7.67 (c = 10.45, $CHCl_3$).

n.m.r.: 0.63 - 1.83 (m, 12H); 2.33 (s, 3H); 3.00 (m, 1H); 7.17 (q, 4H).

Analysis:

Calculated : C = 74.96; H = 9.68, S = 15.36

Found : C = 74.71; H = 9.61, S = 15.70

The sulfide, 127 mgm (0.6 mmoles) was oxidized with MPBA (2.5 mmoles) to give 110 mgm (75%) of pure 2-hexyl p-tolyl sulfone, $[\alpha]_D$ + 6.43 (c = 5.5, $CHCl_3$) after purification by preparative T.L.C. (see above for its spectral properties).

Alkylation of (R) p-Tolyl Sulfoxide with Allyl Bromide and Subsequent Transformation of the Product to p-Tolyl 2-Pentyl Sulfide

Metallation of 500 mgm of (R) p-tolyl ethyl sulfoxide, (3 mmoles), $[\alpha]_D$ + 187 (c = 1.67, $CHCl_3$) followed by excess allyl bromide afforded a quantitative yield of p-tolyl 4-pent-1-enyl sulfoxide.

N.m.r. analysis using the non aromatic methyl group as probe indicated that a 2.40:1 ratio of diastereomers was formed.

n.m.r.: 0.93 (d, J = 6 Hz, 3H) (minor isomer); 1.09 (d, J = 6 Hz, 3H) (major isomer); 1.89 - 2.78 (m, 3H); 2.39 (s, 3H); 5.03 (m, 2H); 5.69 (m, 1H); 7.35 (q, 4H).

I.R.: S=O 1035cm^{-1}

p-Tolyl 4-pent-1-enyl sulfoxide, 625 mgm (3 mmoles), was hydrogenated, on a Parr apparatus using 10% palladium on charcoal as catalyst and ethyl acetate as solvent at 25 psi overnight. A 67% yield of pure p-tolyl-2-pentyl sulfoxide was obtained.

n.m.r.: 0.5 - 2.0 (m, 10H); 2.37 (bs, 4H); 7.30 (q, 4H).

IR: S=O 1035cm^{-1}

The hydrogenated sulfoxide 420 mgm (2 mmoles), was reduced to give 222 mgm (57%) of pure p-tolyl 2-pentyl sulfide, $[\alpha]_D$ - 4.38 (c = 5.36, $CHCl_3$), after chromatography on silica gel (pentane).

n.m.r.: (CCl_4) : 0.66 - 2.0 (m, 10H); 2.33 (s, 3H); 3.00 (m, 1H); 7.37 (q, 4H).

Alkylation of (R) p-Tolyl Ethyl Sulfoxide with n-Propyl Iodide and Reduction of Product to p-Tolyl 2-Pentyl Sulfide

When 3 mmoles of the lithio salt of (R)-p-tolyl ethyl

sulfoxide, $[\alpha]_D^+$ 187 (c= 1.67, $CHCl_3$) were quenched with excess n-propyl iodide, 582 mgm (93%) of p-tolyl 2-pentyl sulfoxide were obtained (see above for its spectral properties).

Reduction of this material (2.4 mmoles) gave 355 mgm (66%) of pure 2-pentyl p-tolyl sulfide, $[\alpha]_D^-$ 3.64 (c = 11.1, $CHCl_3$) after chromatography on silica gel (pentane). Its spectral properties are identical to those reported above.

Synthesis of (R) p-Tolyl 2-Pentyl Sulfide from (S)-2-Pentanol

This synthesis is outlined in Scheme 23. All procedures were identical to those used for the synthesis of p-tolyl 2-hexyl sulfide. The yields and spectral properties of products are given below.

2-Pentyl phenylmethanesulfonate, $[\alpha]_D^+$ 5.2 (c = 2.22, $CHCl_3$) was obtained in 91% yield.

n.m.r.: 0.57 - 1.90 (m, 10H); 4.23 (s, 3H); 4.63 (bq, 1H); 7.30 (s, 5H).

IR: $O-SO_2$ $1165cm^{-1}$ and $1335cm^{-1}$

p-Tolyl 2-pentyl sulfide, $[\alpha]_D^-$ 11.6 (c = 13.28, $CHCl_3$), was obtained in 73% yield after chromatography on silica gel (pentane). (see above for its spectral properties).

Analysis

Calculated : C = 74.19; H = 9.35

Found : C = 73.81; H = 9.20

Experiments Used to Determine the Kinetic Preference Between the Diastereotopic Hydrogen in the Lithiation of Benzyl Methyl and Benzyl t-Butyl Sulfoxides

All experiments were carried out on racemic mixtures of sulfoxides, but they will be described in terms of sulfur chirality as S for convenience.

Preparation of Monodeuterated Sulfoxides and Sulfones:

Monodeuterated (S, S) α - deuteriobenzyl methyl sulfoxide was obtained by deuteration of benzyl methyl sulfoxide as described above. The deuterium content was measured by mass spectrometry (an average of 15 to 20 measurements were taken) and the diastereomer product ratio was obtained by n.m.r. The results are listed in Table 9, Chapter 6.

Intermediate mixtures (~50:50) of (R, S) and (S, S) monodeuterated sulfoxides were obtained by inverting the configuration at sulfur of a portion of pure (S, S) sulfoxide. The reagent used was FSO_3CH_3 and the procedure was identical to that outlined above for the

inversion of configuration at sulfur in ∝- methylbenzyl t-butyl sulfoxide.

(R, S)-∝-Deuteriobenzyl methyl sulfoxide was obtained by first rapidly exchanging both benzylic protons in D_2O - NaOD (8), then metallating this sulfoxide and quenching with H_2O. The deuterium content was measured by mass spectrometry and the ratio of (R, S) to (S, S) by n.m.r. (Table 9).

(S, S) ∝- Deuteriobenzyl t-butyl sulfoxide, >99% diastereomerically pure (n.m.r.) and free of d_2 (mass spectrometry) was obtained by deuteration of benzyl t-butyl sulfoxide in the usual way.

A sample of the above (S, S) ∝-deuteriobenzyl t-butyl sulfoxide of known deuterium content was oxidized to sulfone using MPBA.

Carbanion Reactions of Monodeuterated Sulfoxides and Sulfones:

Duplicate or triplicate samples of the various mixtures of ∝- deuteriobenzyl methyl sulfoxide listed in Table 9 were metallated and quenched with excess CH_3I. Yields of methylated sulfoxides varying between 92% and 94% were obtained. Analyses for the deuterium content in these methylated sulfoxides were carried out as described in Chapter 6 and the results are listed in Table 9. In all cases the

results from duplicate or triplicate experiments agreed within experimental error.

Duplicate samples of (S, S) α- deuteriobenzyl t-butyl sulfoxide were metallated and quenched with excess CH_3I to give >90% yields of alpha methylated sulfoxides. Analysis of these product sulfoxides with a high resolution mass spectrometer equipped with a signal averager showed that the methylated products contained 2.1 ± 0.2% deuterium. (i.e. the values for each run were 2.05% and 2.15% to give the above average value).

Duplicate samples of α- deuteriobenzyl t-butyl sulfone were metallated using CH_3Li in T.H.F. in the same way as the sulfoxides and the carbanions quenched with excess CH_3I. In both experiments 94% yields of a mixture of monodeuterated and non-deuterated α- methylbenzyl t-butyl sulfones were obtained. Analysis of these mixtures by n.m.r., integration of the CH_3 doublet vs the CH_3 singlet during d-decoupling, and by mass spectrometry (Chapter 6) gave respectively average values of 2.30 ± 0.2 and 2.55 ± 0.1 for the kinetic isotope effect in the proton removal reaction. The values from the duplicate runs agreed with each other within experimental error.

Synthesis of Sulfones

Preparation of 3-Phenyl-2-Thia-Trans-Decaline-2, 2-Dioxide

The synthesis of trans-1-chloromethyl-2-benzylmercaptomethyl cyclohexane was carried out as previously described by McClory (20).

The trans sulfide, 8.3 gm (31 mmoles), and MPPA, 19 gm (85% pure, 93 mmoles), were dissolved in 200 ml. of chloroform and refluxed overnight. The reaction mixture was then washed with successive portions of 10% Na_2SO_3, 10% $NaHCO_3$, H_2O and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue recrystallized from ether/pentane to give 5.21 gm (56%) of pure white crystalline sulfone, m.p. 80 - 81°. n.m.r.: 0.8 - 2.46 (m, 10H); 2.63 - 3.14 (m, 2H); 3.45 (bd, J = 3 Hz, 2H); 4.18 (s, 2H); 7.3 (s, 5H).

IR: SO_2 1300cm^{-1} and 1130cm^{-1}

This sulfone, 4.03 gm (13.4 mmoles) was dissolved in 80 ml. of dry T.H.F. in a 2 necked flask equipped with a nitrogen inlet-outlet system and a rubber sceptum and the mixture cooled to - 60°. Methyl lithium (14 mmoles) was added to the mixture via the sceptum and the flask allowed to warm to room temperature and the reaction mixture stirred for 24 hours. It was poured into 150 ml. of H_2O saturated with NaCl and the aqueous mixture extracted with 5 X 40 ml. of CH_2Cl_2. The extracts were

dried over $MgSO_4$, the solvent removed on a rotary evaporator and the residue crystallized from ether/pentane to give 3.38 gm (95%) of pure white crystalline 3-phenyl-2-thia-trans-decaline-2, 2-dioxide, m.p. 47° - 50°. The isomer with the phenyl group in the equitorial position was obtained exclusively.

n.m.r.: 0.85 - 2.59 (m, 12H); 2.64 - 3.16 (m, 8 lines, AB portion of ABC spectrum, by 1st order approximation : Jax-ax = 11.5 Hz, Jex-aq. = 4 Hz, 2H); 4.06 (d of d, Jax-ax = 12.5 Hz, Jax-eq = 3.8 Hz, 1H); 7.36 (m, 5H).

IR: SO_2 1300cm^{-1} and 1130cm^{-1}

Analysis

Calculated : C = 68.16; H = 7.63; S = 12.11

Found : C = 67.76; H = 7.67; S = 12.30

Preparation of 1, 11-Dimethyl-5, 7-Dihydrodibenz (c, e) Thiepin-6, 6-Dioxide

Pure 1, 11-dimethyl-5, 7-dihydrodibenz (c, e) thiepin was supplied by R.R. Fraser and E. Schuber. This material was oxidized to the desired sulfone with MPBA in 95% yield using the method described by Fraser and Schuber (68).

Preparation of Hexadeuterated 2-Thiabicyclo [2.2.1] Heptane-2, 2-Dioxide

Hexadeuterated 3, 3 dichloro-2-thiabicyclo [2.2.1] hept-5-ene -2, 2-dioxide was given to us by R.R. Fraser and Y.Y. Wigfield. This material was converted to hexadeuterio 2-thiabicyclo [2.2.1] heptane-2, 2-dioxide, m.p. 204 - 206°, by the method of Johnson and co-workers (101). (lit. m.p. of undeuterated sulfone 203 - 205°).

n.m.r.: 1.81 (s, 2H); 2.84 (ABq : $\delta A = 2.69$, $\delta B = 3.00$, $J = 12$ Hz, 2H).

IR: SO_2 $1300cm^{-1}$ and $1130cm^{-1}$, lit. (105) $1300cm^{-1}$ and $1130cm^{-1}$

Synthesis of 4-t-Butylchclohexyl Phenyl Sulfone

The synthesis was analogous to that previously described by Eliel and Ro (48).

Equitorial 4 t-butylcyclohexanol, 11 gm (71 mmoles) and 5.9 ml. of methanesulfonyl chloride (78 mmoles) were reacted with $(Et)_3N$ (78 mmoles) in CH_2Cl_2 by the method of King and Durst (55) to give 14.8 gm (89%) of pure 4-t-butylcyclohexyl methansulfonate, m.p. 55 - 56°, after recrystallization from CH_2Cl_2/pentane.

n.m.r.: 0.66 - 2.50 (m, 18H); 3.00 (s, 3H); 4.40 (m, 1H).

IR: $O-SO_2$ $1350cm^{-1}$ and $1175cm^{-1}$

The mesylate, 8.75 gm (37 mmoles), and potassium thiophenolate (37 mmoles), prepared in the usual fashion, were refluxed overnight in 100 ml. of CH_3OH. The reaction was worked up in the usual fashion (see previous thiolate reactions) and the crude sulfide distilled to give 2.70 gm (31%), bp 100-105°/0.15 mm, lit. bp. 184-186/13 mm (48), of pure cis 4-t-butylcyclohexyl phenyl sulfide.

n.m.r.: 0.66 - 2.20 (m, 18H); 3.56 (m, 1H); 7.20 (m, 5H).

The cis sulfide, 2.68 gm (10.8 mmoles) was oxidized with MPBA (30 mmoles) to give pure cis 4-t-butylcyclohexyl phenyl sulfone, m.p. 114 - 115°, lit. m.p. 115 - 116° (48), in 80% yield.

n.m.r.: 0.57 - 2.47 (m, 18H); 3.11 (m, 1H); 7.59 (m, 3H); 7.91 (m, 2H).

IR: SO_2 1300cm^{-1} and 1140cm^{-1}

Cis 4-t-butylcyclohexyl phenyl sulfone, (2.5 mmoles), was refluxed for 16 hours in 2M CH_3ONa-CH_3OH and the reaction mixture poured into 200 ml. of H_2O. The aqueous mixture was extracted with CH_2Cl_2, the extracts dried over $MgSO_4$, and the solvent removed to give a 97% yield of crude sulfone. Recrystallization from ether-CH_2Cl_2/pentane gave pure trans-4-t-butylcyclohexyl phenyl sulfone, m.p. 88 - 89°, lit. m.p. 90 - 91° (48). n.m.r.: 0.56 - 2.30 (m, 18H); 2.86 (t of t, J_{ax-ax} = 12.5 Hz, J_{ax-eq} = 3.5 Hz); 7.58 (m, 3H); 7.84 (m, 2H).

Carbanion Reactions of Sulfones

General Procedure:

The procedure for the generation and trapping of sulfone carbanions is identical to that given above for sulfoxide carbanions. The reaction products, generally >95% pure by n.m.r., were analysed directly before further purification. The products were then purified by recrystallization.

Reactions of 3-Phenyl-2-Thia-Trans-Decalin-2, 2-Dioxide

- Equitorial Phenyl Isomer in T.H.F. at - 60°:

When 200 mgm of the equitorial phenyl isomer (0.76 mmoles) were metallated with CH_3Li in T.H.F. at - 60°, then quenched with excess H_2O, 183 mgm (92%) of a white solid were obtained after work up. N.m.r. analysis of the crude product showed that the AB portion of the ABC pattern of the starting sulfone had dissolved into a multiplet. The benzylic methine proton had also changed from a doublet of doublets to a broad singlet. From this we concluded that the product consisted of >98% of the axial phenyl isomer of the sulfone (Scheme 6). The product after recrystallization from ether/pentane had m.p. 128 - 130°.

N.m.r.: 0.7 - 3.00 (m, 14H); 4.28 (bs, 1H); 7.37 (m, 5H).

IR: SO_2 1295cm^{-1} and 1105cm^{-1}

- Equitorial Phenyl Isomer in DMSO at 24°:

When 100 mgm of the equitorial phenyl isomer (0.38 mmoles) were dissolved in 5 ml. of DMSO (distilled from CaH_2 before use), then treated with CH_3Li (0.5 mmoles) and the resulting carbanion quenched after 1 minute with excess H_2O, an 85% yield of unchanged starting material was recovered on work up.

- Axial Phenyl Isomer in DMSO at 24°:

When 100 mgm of the axial phenyl isomer (0.38 mmoles) were treated in the same manner as the equitorial isomer, 98 mgm (98%) of pure equitorial phenyl sulfone, m.p. 47 - 50°, was recovered (>98% pure by n.m.r.). When DMSO-d_6 was used as solvent, the same result was obtained. Integration of the product showed that no deuterium incorporation occurred during the course of the reaction (i.e.: <5%, n.m.r. experimental error) (see Scheme 11).

Reactions of 4-t-Butylcyclohexyl Phenyl Sulfone

- The cis Isomer in T.H.F. at - 60°:

Pure cis 4-t-butylcyclohexyl phenyl sulfone, 200 mgm (0.72 mmoles), was metallated and quenched with H_2O to give 198 mgm (99%) of crude product. N.m.r. analysis of this product using the sulfur methine proton as probe indicated that a mixture of 77% trans to 23% cis sulfone was obtained. The same result was obtained when 50% excess of CH_3Li

rather than the usual 10% excess was used to generate the carbanion. Triplicate experiments yielded product ratios within 1% of each other.

- The trans Isomer in T.H.F. at - 60°:

Pure trans 4-t-butylcyclohexyl phenyl sulfone, 200 mgm (0.72 mmoles), was metallated and quenched in the same fashion as the cis isomer to give 192 mgm (96%) of a 77% trans to 23% cis mixture of sulfones. Duplicate runs gave values within 1% of each other.

- The cis Isomer in DMSO-d_6 at 24°:

Cis 4-t-butylcyclohexyl phenyl sulfone, 200 mgm (0.73 mmoles), was dissolved in 5 ml. of DMSO-d_6 and treated with CH_3Li (0.80 mmoles). The carbanion was quenched after 1 minute with H_2O to give 186 mgm (93%) of sulfone on work up. N.m.r. analysis showed that the methine proton had completely been exchanged for deuterium during the course of the reaction. Comparison of the high field multiplet of the product with those of the pure cis and pure trans sulfones indicated that the product was mainly trans sulfone.

Reactions of 1, 11-Dimethyl-5, 7-Dihydrodibenz (c, e) Thiepin-6, 6-Dioxide

- With D_2O

The sulfone, 100 mgm (0.37 mmoles) was metallated and quenched with D_2O to yield 97 mgm (97%) of monodeuterated product.

N.m.r. analysis in DMSO-d_6 of the benzylic AB pattern during deuterium decoupling showed that the low field protons were exchanged preferentially to the high field ones by a factor of 79 to 21.

- With CH_3I:

When the lithio sulfone (0.38 mmoles) generated as above was quenched with CH_3I, 93 mgm (88%) of methylated sulfone were obtained. N.m.r. analysis of the methyl doublet showed that a 91 to 9 ratio of isomers was obtained. After recrystallization the pure methylated sulfone had m.p. 210 - 213°.

n.m.r.: 0.91 (d, J = 7.5, 3H) (major isomer); 1.68 (d, J = 7.5, 3H) (minor isomer); 2.12 (s, 6H); 3.97 (m, 3H); 7.30 (s, 3H).

Analysis

Calculated : C = 70.57, H = 5.92, S = 11.75

Found : C = 70.40, H = 6.31, S = 11.38

When 100 mgm of the methylated sulfone (0.35 mmoles) was refluxed for 18 hours in 2M CH_3ONa - CH_3OH a 91% yield of a mixture of sulfones was obtained. Analysis using the methyl doublets as probe showed that this mixture consisted of 9% of the carbanion isomer and 91% of the thermodynamically more stable isomer. After recrystallization, sulfone, m.p. 162 - 164°, was obtained.

Analysis

Calculated : C = 70.57, H = 5.92

Found : C = 71.00, H = 6.30

Reactions of Hexadeuterated 2-Thiabicyclo [2.2.1] Heptane-2, 2-Dioxide

- With D_2O

When 50 mgm of sulfone (0.33 mmoles) were metallated and quenched with D_2O, 43 mgm (86%) of sulfone were recovered on work up. N.m.r. analysis showed that the low field hydrogens of the AB quartet (i.e. exo hydrogens) were the only ones exchanged. When H_2O was used to quench the carbanion, a broad singlet appeared at 3.33 corresponding to about 12% exchange of the bridgehead deuterium at C_1 (88).

- With CH_3I

When 158 mgm of sulfone (1.04 mmoles) were metallated and quenched with excess CH_3I, 150 mgm (87%) of methylated sulfone were obtained. N.m.r. analysis showed that only one methylated sulfone was obtained, that having the methyl group in the exo position.

n.m.r.: 1.27 (d, J = 7 Hz, 3H); 1.83 (bs, 2H); 2.77 (q, J = 7 Hz, 1H).

When 150 mgm of the above exo methylated sulfone (0.9 mmoles) was treated with CH_3Li in T.H.F. at - 60° and the resulting carbanion

quenched after ½ hour with H_2O, 116 mgm (78%) of a mixture of two sulfones were obtained. N.m.r. analysis indicated that this mixture corresponded to 64% exo and 36% endo methyl sulfone. The analysis also indicated that 61% of the bridgehead deuterium at C_1 had exchanged.

n.m.r.: (endo methyl sulfone) 1.31 (d, J = 7 Hz, 3H); 1.75 (bs, 2H); 3.16 (q, J = 7 Hz, J long range ∿ 1-2 Hz, 1H).

REFERENCES

1) a) D.J. Cram, W.D. Neilsen and B. Rickborn
J. Amer. Chem. Soc. 82, 6416 (1960)

b) D.J. Cram, D.A. Scott, W.D. Neilsen
J. Amer. Chem. Soc. 83, 3696 (1961)

c) D.J. Cram, A.S. Wingrove
J. Amer. Chem. Soc. 84, 1496 (1962)

2) E.J. Corey, E.T. Kaiser
J. Amer. Chem. Soc. 83, 490 (1961)

3) H.L. Goering, D.L. Townes, B. Dittmer
J. Org. Chem. 27, 736 (1962)

4) a) For a review see: a) M. Gresser
Mechanism of Reactions of Sulfur Compounds 4, 29 (1969)

b) B.S. Thyagarajan ibid 4, 115 (1969)

5) D.J. Cram, S.H. Pine
J. Amer. Chem. Soc. 85, 1096 (1963)

6) K. Mislow, M.M. Green, L. Laur, J.J. Melillo, T. Simmons,
A.L. Ternay Jr: ibid 87, 1958 (1965)

7) A. Rauk, E. Buncel, R.Y. Moir, S. Wolfe
ibid 87, 5498 (1965)

8) S. Wolfe, A. Rauk Chem. Commun. 778 (1966)

9) a) J.E. Baldwin, R.E. Hackler, R.M. Scott
ibid 1415 (1969)

b) S. Wolfe, A. Rauk, L.M. Tel, I.G. Csizmadia
J. Chem. Soc. B, 136 (1971)

10) a) E.E. Bullock, J.M.W. Scott and P.D. Golding
Chem. Commun. 168 (1967)

b) M. Nishio ibid 562 (1968)

c) M. Cinquini, S. Colonna, U. Folli, F. Montanie
Boll. Sci. Fac. Chim. ind. Bologna 27, 203 (1969)

11) a) R.R. Fraser, F.J. Schuber, Chem. Commun. 397 (1969); Can. J. Chem. 48, 633 (1970)

b) R.R. Fraser, F.J. Schuber, Y.Y. Wigfield J. Amer. Chem. Soc. 94, 8795 (1972)

12) B.J. Hutchinson, K.K. Andersen and A.R. Katritzky J. Amer. Chem. Soc. 91, 3839 (1969)

13) R. Lett, S. Bory, B. Moreau, A. Marquet Tetrahedron Lett. 2851, 2855, 3255 (1971)

14) a) S. Wolfe, A. Rauk, I.G. Czimadia J. Amer. Chem. Soc. 89, 4585 (1967)

b) A. Rauk, S. Wolfe, I.G. Czimadia Can. J. Chem. 47, 113 (1969)

15) D.T. Clark Annual Reports B. J. Chem. Soc. 68, 43 (1971) and ref. therein.

16) S. Wolfe, A. Rauk, I.G. Czimadia J. Amer. Chem. Soc. 91, 1567 (1969)

17) a) E.J. Corey, M. Chaykovsky ibid 87, 1345 (1965)

b) For a review see T. Durst in Advances in Organic Chemistry, E.C. Taylor and H. Wynberg ed., John Wiley and Sons Inc., N.Y. 1969, Vol. 6, p. 289-318

18) J.B. Sidal, A.D. Cross, J.H. Fried J. Amer. Chem. Soc. 88, 862 (1966)

19) T. Durst ibid 91, 1034 (1969)

20) M.R. McClory Msc. Thesis Univ. of Ottawa (1969)

21) D.J. Cram Fundamentals of Carbanion Chemistry, Academic Press Inc., N.Y. 1965, p. 32-45 and references therein

22) V. Franzen "Synopses of Papers Read at an Int. Symposium on Organic Reaction Mechanisms held at Cork, Ireland, July, 1964" Special Publication, no. 19, The Chemical Society, London 172 (1965)

23) J. Jacobus, K. Mislow J. Amer. Chem. Soc. 89, 5228 (1967)

24) a) M. LeBelle Msc. Thesis Univ. of Ottawa (1972)

b) T. Durst, R. Van den Elzen private communication

25) F. Jung private communication

26) K.C. Tin Phd. Thesis Univ. of Ottawa (1972)

27) See ref. 21, Chapter 3

28) R.B. Swingle Phd. Thesis Univ. of Ottawa (1969)

29) C.R. Johnson, and D.M. McCants Jr.
J. Amer. Chem. Soc. 87, 5404 (1965)

30) a) M. Nishio Chem. Commun. 51 (1970)

b) M. Nishio, K. Nishihata ibid 1485 (1970)

31) K.J. Laidler Reaction Kinetics, Pergamon Press, 1963, Vol. 1, p. 10

32) G.W. Castellan Physical Chemistry
Addison-Wesley Co., Reading Mass. U.S.A., 1964, Chap. 29, p. 643

33) T. Durst Tetrahedron Lett. 4171 (1971)

34) M.R. McClory, T. Durst private communication

35) T. Durst private communication

36) a) D.J. Cram, J.L. Mateos, F. Hauch, A. Langeman, K.R. Kopecky, W.D. Neilsen, J. Allinges
J. Amer. Chem. Soc. 81, 5774 (1959) and ref. therein

b) See ref. 21

c) D.J. Cram, B. Rickborne, C.A. Kingsbury, P. Haberfield
J. Amer. Chem. Soc. 83, 3678 (1961)

d) D.J. Cram, C.A. Kingsbury, R. Rickborne
ibid 83, 3688 (1961)

37) D.J. Cram, F. Hauch, K.P. Kopecky and W.D. Nielsen
ibid 81, 5767 (1959)

38) D.J. Cram, D.A. Scott, W.D. Nielsen
ibid 83, 3696 (1961)

39) E.L. Eliel, A. Abatjoglou, A.A. Hartman
ibid 94, 4786 (1972)

40) E.L. Eliel, N.L. Allinger, S.J. Angyal, G.A. Morrison
Conformational Analysis, John Wiley and Sons Inc.,
N.Y. 1965, Chapter 7, p. 436-442

41) E.L. Eliel, A.A. Hartman J. Amer. Chem. Soc. 93, 2572 (1971)

42) E.L. Eliel 23rd Int. Congress of Pure and Applied Chemistry
7, 219 (1971)

43) S. Oae, W. Tagaki, A. Ohno Tetrahedron 20, 427 (1964)

44) K.C. Banks, D.L. Coffen Chem. Commun. 8 (1969)

45) G.S. Hammond J. Amer. Chem. Soc. 77, 334 (1955)

46) W.H. Glaze, C.M. Celman J. Org. Chem. 33, 1987 (1968)

47) F.R. Jensen, K.L. Nakamaye J. Amer. Chem. Soc. 90, 3248 (1968)

48) E.L. Eliel, R.S. Ro ibid 79, 5995 (1957)

49) K.K. Andersen Tetrahedron Lett. 93 (1962)

50) M. Nishio private communication

51) K. Mislow, M.M. Green, M. Raban J. Amer. Chem. Soc. 87, 2761 (1965)

52) J. Jacobus, K. Mislow ibid 89, 5228 (1967)

53) G.V. Kaiser, R.D.J. Cooper, R.E. Kochler, C.F. Murphy,
J.A. Webber, I.G. Wright, E.M. Van Heymingen
J. Org. Chem. 35, 2430 (1970)

54) E.L. Eliel J. Amer. Chem. Soc. 71, 3970 (1949)

55) J.F. King, T. Durst ibid 87, 5684 (1965)

56) A. Streitweiser Jr. Solvolylic Displacement Reactions, McGraw-Hill Inc., N.Y. 1962, Chapter 3

57) Beilstein 1^3, 447

58) S. Wolfe, A. Rauk Can. J. Chem. 44, 2591 (1966)

59) E.L. Eliel Stereochemistry of Carbon Compounds McGraw-Hill Inc., N.Y. 1962, Chapter 3, p. 16

60) Beilstein 1^3, 1616

61) Beilstein 1^3, 1663

62) D.J. Cram, A.S. Wingrove J. Amer. Chem. Soc. 85, 1100 (1963)

63) K. Nishigata, M. Nishio Chem. Commun 958 (1971)

64) a) H.C. Brown, C.F. Lane ibid 521 (1971)

b) D.E. Applequist, G.N. Chmunny J. Amer. Chem. Soc. 89, 875 (1967)

c) W.H. Blaze, C.M. Selman, A.L. Bull Jr. and L.E. Brady J. Org. Chem. 34, 641 (1969)

65) a) L.A. Paquette, R.W. Hauser J. Amer. Chem. Soc. 91, 3870 (1969)

b) E.J. Corey, E. Block J. Org. Chem. 34, 1233 (1969)

66) a) F.G. Brodwell, E. Doomes, P.W.R. Corfield J. Amer. Chem. Soc. 92, 2581 (1970)

b) F.G. Bordwell, B.B. Jarvis, P.W.R. Corfield ibid 90, 5298 (1968)

67) B.B. Jarvis, S.D. Dutkey, H.L. Ammon ibid 94, 2135 (1972)

68) R.R. Fraser, F.J. Schuber Can. J. Chem. 48, 633 (1970)

69) a) R.R. Fraser, F.J. Schuber Chem. Commun. 1474 (1969)

b) R.R. Fraser, F.J. Schuber private communication

70) W. von. E. Doering, L.K. Levy J. Amer. Chem. Soc. 77, 509 (1955)

71) N.L. Allinger, J.C. Tai, F.T. Wee ibid 92, 579 (1970)

72) a) R.G. Pearson ibid 85, 3533 (1963)

b) R.G. Pearson, J. Songstad ibid 89, 1827 (1967)

73) T. Durst, R. Viau, R. Van den Elzen, C.H. Nguyen Chem. Commun. 1334 (1971)

74) F.W. McLafferty Interpretation of Mass Spectra, W.A. Benjamin Inc., 1966, Chapter 2

75) D.Y. Curtin and D.B. Kellom J. Amer. Chem. Soc. 75, 6011 (1953)

76) D.J. Parto, C.R. Johnson Organic Structure Determination, Prentice-Hall Inc., 1969, Chapter 5, p. 171-172

77) J.E. Leffler and E. Grunwald Rates and Equilibria of Organic Reactions, J. Wiley and Sons Inc., N.Y. 1963, p. 167-168

78) K. Nishihata and M. Nishio J. Chem. Soc. Perkin Trans. 2, 1730 (1972)

79) F.G. Bordwell, R.H. Imes, E.C. Steiner J. Amer. Chem. Soc. 89, 3905 (1967)

80) J. March Advanced Organic Chemistry, Reactions, Mechanisms and Structures, McGraw-Hill, 1968, Chapter 16, p. 684-687

81) K.W. Buck, A.B. Foster, W.D. Pardoe, W.H. Qadir, J.M. Webber Chem. Commun. 357 (1966)

82) a) A.B. Foster, J.M. Duxbury, T.D. Inch, J.M. Webber ibid 881 (1967)

b) A.B. Foster, T.D. Inch, M.H. Qadir, J.M. Webber ibid 1086 (1968)

c) E. Johnson and S. Holmquist Ark. Kemi 29, 301 (1968)

d) C.R. Johnson, W.D. Siegl J. Amer. Chem. Soc. 91, 2796 (1970)

e) R.M. Dodson, E.H. Jansis and G. Klose J. Org. Chem. 35, 2520 (1970)

83) J.B. Lambert and R.G. Keske ibid 31, 3429 (1969)

84) a) R.D.G. Cooper, P.V. DeMarco and D.O. Spey
J. Amer. Chem. Soc. 91, 1528 (1969)

b) D.H.R. Barton, F. Comer, P.G. Sommer ibid 91, 1529 (1969)

85) a) M. Nishio Chem. Commun. 51 (1969)

b) M. Nishio Chem. Pharm. Bull. (Tokyo) 17, 262, 274 (1969)

86) R.R. Fraser, Y.Y. Wigfield Chem. Commun. 1471 (1970)

87) K.K. Anderson, J.J. Ubèl Tetrahedron Lett. 5252 (1970)

88) R.R. Fraser, T. Durst, M.R. McClory, R. Viau, Y.Y. Wigfield
Int. J. Sulfur Chem. A, 1, 133 (1971)

89) B.J. Auret, D.R. Boyd, H.B. Henbest, S. Ross J. Chem. Soc.
C, 2371, 2374 (1968)

90) E.J. Corey, T.H. Lowry Tetrahedron Lett. 803 (1965)

91) a) M. Nishio, K. Nishihata Chem. Commun. 1485 (1970)

b) M. Nishio ibid 562 (1968)

92) E.T. Strom, B.S. Snowden Jr., P.A. Toldan
ibid 50 (1969)

93) C.A. Kingsbury, R.A. Auerback J. Org. Chem. 36, 1737 (1969)

94) S. Iriuchijima, T. Tsuchihashi Tetrahedron Lett. 5259 (1969)

95) a) I.M. Kolthoff, M.K. Chantooni Jr., S. Bhowmik
J. Amer. Chem. Soc. 90, 23 (1968)

b) O.L. Chapman, R.W. King ibid 86, 1256 (1964)

96) B.J. Auret, D.R. Boyd, H.B. Henbest, S. Ross
J. Chem. Soc. C, 2371 (1968)

97) G. Modena Gazz. Chim. Ital. 89, 834 (1959); C.A. 54,
22446g

98) A. Carniani, G. Modena, P.E. Todesco
Gazz. Chim. Ital. 90, 3 (1960); C.A. 55, 9322C

99) a) H.F. Herbrandson, R.T. Dickerson, J. Weinstein
J. Amer. Chem. Soc. 78, 2576 (1956)

b) H.F. Herbrandson, R.T. Dickerson ibid 81, 4102 (1959)

100) M. Axebrod, P. Bichait, J. Jacobus, M.M. Green, K. Mislow
ibid 90, 4835 (1968)

101) J.A. Christiansen, W. Drost-Hansen Nature 164, 759 (1949)

102) I.B. Douglass, B.S. Farah, E.G. Thomas
J. Org. Chem. 26 1996 (1961)

103) Dictionary of Organic Compounds, Fyre and Sposttiwode
Publishers Ltd., London, Vol. 4, p. 2054

104) F.G. Bordwell, B.M. Pitt J. Amer. Chem. Soc. 77, 572 (1955)

105) C.R. Johnson, J.E. Keiser, J.C. Sharp J. Org. Chem. 34, 860 (1969).

CLAIMS TO ORIGINAL RESEARCH

1. The effect of solvent on the conformational preference of benzyl methyl sulfoxide was observed.
2. The effect of solvent on the conformational preferene of sulfone carbanions was described.
3. The stereochemistry of the reaction of various acyclic lithio sulfoxides with a number of electrophiles was determined and a reaction mechanism suggested.
4. The stereochemistry of the reactions of some lithio sulfones with D_2O and CH_3I was determined and a reaction mechanism proposed.
5. The relationship between the kinetic and thermodynamic preference between the diastereotopic hydrogens in the lithiation of benzyl methyl and benzyl t-butyl sulfoxide was determined.
6. A comparison of the effects of solvents and $Eu(DPM)_3$ on the proton shielding in acyclic sulfoxides was carried out. It showed that none of the methods produce effects which show any correlation with sulfoxide stereochemistry, contrary to some previous reports.

PUBLICATIONS AND PRESENTED PAPERS

- Kinetic Preference Between Diastereotopic Hydrogen in the Lithiation of Benzyl Methyl and Benzyl t-Butyl Sulfoxides.

  R. Viau, T. Durst J.A.C.S. 95, 1346 (1973)

- α - Sulfinyl Carbanions.

  T. Durst, R. Viau Int. J. Sulfur Chem. (in press).

- A Comparison of the Effects of Solvents and Eu $(DPM)_3$ on Proton Shieldings in Sulfoxides.

  R.R. Fraser, T. Durst, M.R. McClory, R. Viau, Y.Y. Wigfield Int. J. Sulfur Chem. (A), 1, 133 (1971).

- Stereochemical Behaviour of α - Lithio Sulfoxides.

  T. Durst, R. Viau J.A.C.S. 93, 3077 (1971).

- The Stereochemistry of the Reaction of α - Lithio Sulfoxides with Ketones.

  T. Durst, R. Viau, R. Van den Elzen, C.H. Nguyen Chem. Comm. 1334 (1971).

- Solvent Effect on the Conformational Preference of Carbanions derived from Benzyl Methyl Sulfoxide.

  T. Durst, R.R. Fraser, M.R. McClory, R.B. Swingle, R. Viau, Y.Y. Wigfield Can. J. Chem., 48, 2148 (1970).

- On the Equitorial Preference of Lithio Substituents in 6-Membered Ring Sulfoxides, Sulfones and Sultones.

  T. Durst, R. Viau Presented at V Int. Symposium on Organic Sulfur Chemistry, Lund, Sweden, June, 1972.

- Préférence cinétique et thermodynamique dans l'arrachement des protons diastéréotopiques des sulfoxides benzyliques

  R. Viau, T. Durst Presented at 40 Congrès de L'A.C.F.A.S., October, 1972.

- The Preferred Conformations of α - Lithiobenzyl Alkyl Sulfoxides

  T. Durst, R. Viau Presented at C.I.C. Heteroatom Symposium, London, Ontario, September 1970.

GRANTS AND SCHOLARSHIPS

N.R.C. Bursary	1969-1970
Prov. of Ontario Grad. Student Fellowship	1970-1971
N.R.C. Bursary	1971-1973