1990

Stereoelectronic Effects, Mechanism, And Synthesis In Sulfonyl Chemistry

Rajendra Rathore

STEREOELECTRONIC EFFECTS, MECHANISM, AND SYNTHESIS IN SULFONYL CHEMISTRY

by

Rajendra Rathore

Department of Chemistry

Submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Faculty of Graduate Studies

The University of Western Ontario

London, Ontario

July 1990

ISBN 0-315-59095-5

ABSTRACT

This thesis presents four topics in organic sulfur chemistry. The first chapter describes the general synthesis of hydroxyalkanesulfonyl chlorides (see Table 1.1) from mercaptoalkanols. 3-Hydroxy-1-propanesulfonyl and 4-hydroxy-1-butanesulfonyl chlorides (**2b** and **2c**) were obtained for the first time admixed with corresponding sultones **3b** and **3c**) by chlorination of an aqueous solution of corresponding mercaptoalcohols. 3-Hydroxy-1-propanesulfonyl (**2b**) (containing 10% propane sultone **3b**)) and 4-hydroxy-1-butanesulfonyl chlorides (**2c**) (containing 13% butane sultone (**3c**)) were also prepared by chlorination of a dichloromethane suspension of sodium 3-hydroxy-1-propanesulfinate (**8b**) and 4-hydroxy-1-butanesulfinate (**8c**), respectively. Sulfonyl chlorides **2b** and **2c** were characterized by (a) ^{1}H, ^{13}Cmr, and ir spectra, (b) transformation to the corresponding sultones (**3b** and **3c**), and (c) conversion to crystalline derivatives **6b** and **6c**. Compound **2c** was found to form the sultone (**3c**) slowly in nonpolar solvents, much more readily in polar media ($t_{1/2}$ ~20 min in water), and very rapidly in the presence of triethylamine. The cyclizations of **2b** and **2c** in $CDCl_3$ containing 1-butanol followed good first order kinetics. We have also obtained the effective concentration (C_{eff}) of 4.5 x 10^2 and 2.1 x 10^2 M, respectively, for the uncatalyzed cyclization **2b** $\longrightarrow$ **3b** and **2c** $\longrightarrow$ **3c** (in $CDCl_3$-0.9 M butanol at 22°C). Reaction of triethylamine in ethanol-*d* (i) with **2b** gave exclusively the undeuterated sultone **3b**, evidently by a direct cyclization, and (ii) with **2c** produced mainly ethyl 4-hydroxy-1-butanesulfonate largely monodeuterated at the α-position, and presumably formed by way of the sulfene (**25**). The mechanism of the chlorination reaction and the origins of the different products with different substrates and reaction conditions are discussed.

In the second chapter, an easy preparation of simple sultines and hydroxyalkanesulfinate salts is described. In accord with prediction arising from the mechanism

discussed in Chapter 1, a one-pot, two-stage, controlled chlorination-hydrolysis of $HO(CH_2)_nSH$ gave the sultine when n = 3 or 4, and the polymeric sulfinic esters when n = 5 or 6; alkaline hydrolysis of either product yielded the corresponding sodium ω-hydroxy-1-alkanesulfinate.

The third chapter is concerned with the study of stereoelectronic effects in sulfonamides—specifically the variation of delocalization of the electron lone pair on the nitrogen with dihedral angle, which may influence the rates of acid cleavage, pK_a's, $-SO_2-$ stretching bands in infrared spectra, and the conformations of sulfonamides. Previously unknown sultams ***14*** and ***17*** and a number of others were synthesized. The pK_a's of 10 sulfonamides were measured and it was found that pK_a's are sensitive to C-S-N-C dihedral angle and steric factors. Rates of acid-catalyzed hydrochlorinolysis of sulfonamides were measured and it was found that ***14*** and *N*-methylpropane sultam (***12b***) cleave quite readily, respectively, 1100 and 2400 times faster than *N*,*N*-dimethylmethanesulfonamide. The ^{13}Cmr spectra of ***17*** showed the presence of two conformations at low temperature; it is consistent with the picture that a sterically unfavourable conformation ***17c*** was present in which the lone pair of electrons on nitrogen bisects the sulfonyl oxygens along with ***17a***.

The fourth chapter describes results on the hydrogen-deuterium exchange at the α-carbon in a series of 6-membered cyclic sulfones. The rates of the exchange were measured by nmr. In conformationally anchored (or biased) sulfones an equatorial hydrogen exchanges faster than an axial (by about two orders of magnitude). The presence of a β-alkoxyl group accelerates the reaction by different amounts depending on the orientation of the oxygen with respect to the (equatorial) hydrogen: the accelerations due to oxygen (relative to a carbon or hydrogen in the same location) are, respectively for one *syn-clinal* oxygen, 200 to 300, two *syn-clinal*

oxygens, 500–8000 and one *anti–periplanar* oxygen 16000 to 35000, with the difference between the *anti–periplanar vs. syn–clinal* single oxygen being 71 to 95 times. It is proposed that greater effect of the *anti–periplanar* β–oxygen derives from a kinetic anomeric effect (KAE) in which the incipient carbanion is stabilized by electron donation into the carbon–oxygen σ^* orbitals.

To my Guddu

ACKNOWLEDGEMENT

I would like to express my sincere appreciation to my supervisor, Prof. J.F. King, for his guidance, constant encouragement, valuable advice, and his endless patience during this endeavour.

I shall be failing in my duties if I did not acknowledge the contribution of Prof. S. Chandrasekran of The Indian Institute of Technology at present in Indian Institute of Sciences, Bangalore, who introduced me to the real world of chemistry and has been a constant source of encouragement as a friend.

A special thanks goes to Susan Wilson (England) for her continuous encouragement, help, and being a good friend to me. Thanks once again for running millons of proton spectra, kinetics and low temperature nmr spectra for me. Here I would also like to acknowledge Jim and Jessie Wilson and Paul who had filled the gap of my family back in India.

I hereby express my gratitude to Valerie Richardson for running a large number of carbon spectra and of course being a friend. I thank Anita Elworthy for teaching me "Autocad" (a drawing program) and doing numerous drawings for me. A special thanks also goes to Dr. Sujit Roy who had been a good friend and has also helped me a lot in the preparation of this manuscript.

My thanks are also extended to the other members of the faculty, fellow graduate students both past and present, and the staff of the chemistry department for their co-operation and help throughout the years of my studies. To all my friends a most sincere 'Thank you' for making my stay in London enjoyable. I am

also indebted to Prof. N.C. Payne for doing the crystal structures.

Finally, the members of my family in India deserve a special mention in this column for their love, understanding, endless support and constant encouragement. I would like to especially acknowledge my brother Basant Rathore who had been there for me whenever I needed him.

Last but not the least I would like to acknowledge and dedicate this thesis to Guddu who had been my best friend and constant source of inspiration for last 10 years.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

ω-HYDROXY-1-ALKANESULFONYL CHLORIDES FROM CHLORINATION OF MERCAPTOALKANOLS AND ω-HYDROXY-1-ALKANESULFINATE SALTS

1.1 INTRODUCTION

Hydroxyalkanesulfonyl chlorides (*2*) are bifunctional compounds with two related features of interest: (i) reaction of one function with the other leads to coupling, either of separate molecules with ultimate production of polymer, or within the same molecule with formation of a ring, and (ii) the reaction may be expected to occur quite readily. Species with these general properties prompt a number of questions, *e.g.*, (i) can they really be made, or, more precisely, under what conditions (if any) can they be generated, or even isolated, (ii) what factors of structure and conditions control whether they form cyclic or polymeric products, and (iii) are they, in fact, precursors for the synthesis of useful polymers?

A few years ago King and Hillhouse[1,2] noted that chlorination of 2-mercapto-ethanol (*1a*) gave 2-hydroxy-1-ethanesulfonyl chloride (*2a*), thereby providing the first proved example of a hydroxyalkanesulfonyl chloride. A solution of *2a* in $CDCl_3$ (0.1 M) was stable for at least six months at room temperature, whereas the neat compound, though stable at -20°C, was half decomposed after three weeks at room temperature. Compound *2a* could even be distilled under reduced pressure.

More recently[3] King, Skonieczny and Khemani were led from oxygen-labelling studies to conclude that the analogous reaction of 3-mercapto-1-propanol (*1b*) proceeds by way of 3-hydroxy-1-propanesulfonyl chloride (*2b*) which immediately cyclizes to 1,2-oxathiolane 2,2-dioxide (propane 1,3-sultone) (*3b*).

Although 5- and 6-carbon hydroxyalkanesulfonyl chlorides (*2d*, *2e*) were prepared in reasonably pure form (>95% purity) in this laboratory by Webster, Chiba, Parker and Allen, attempts to isolate 4-hydroxy-1-butanesulfonyl chloride, and 3-hydroxy-1-propanesulfonyl chloride were unsuccessful. It seemed likely that the hydroxyalkanesulfonyl chlorides were, in fact, being formed in the chlorination of 3- and 4-carbon mercaptoalkanols, and the former cyclized to produce the correspondin;

sultones. The ultimate proof of any mechanism is to isolate the proposed reaction intermediates, and we have therefore taken up the question of the isolability and oroperties of these intermediate ω-hydroxy-1-alkanesulfonyl chlorides.

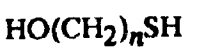
In this chapter, the preparation and some of the properties of these ω-hydroxy-alkanesulfonyl chlorides (2) are described, along with some conclusions on the mechanism of aqueous chlorination of mercaptoalkanols and the general applicability of the aqueous chlorination route to such compounds.

1.2 RESULTS AND DISCUSSION

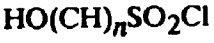
1.2.1 Synthesis and Reactions

4-Hydroxy-1-butylthiouronium chloride (*4c*) was prepared by reaction of the 4-chloro-1-butanol with thiourea.[4] The thiouronium salt (*4c*) was obtained as a syrup showing appropriate peaks in the ^{1}Hmr and ^{13}Cmr spectra, but also containing about 20% of another product which was largely removed by crystallization from the mixture; the crystalline by-product was identified as 1,4-butanebisthiouronium dichloride by (a) the simplicity of its ^{1}Hmr and ^{13}Cmr spectra, and (b) conversion to 1,4-butanedisulfonyl chloride[5,6] on aqueous chlorination. Alternatively, reaction of 4-chloro-1-butyl acetate with thiourea gave mostly *4c*, along with about 15% of 4-acetoxy-1-butylthiouronium chloride. It is noteworthy that the acetoxy group could hydrolyze in such neutral conditions. Alkaline hydrolysis of crude *4c* from either source gave the 4-mercapto-1-butanol (*1c*), which was purified by distillation and converted to the crystalline mono- and bis-carbamates.

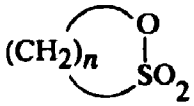
Chlorination of an aqueous solution of *4c* gave, on workup, a roughly 50% yield of a mixture, the ^{1}H and ^{13}Cmr spectra of which showed the presence of about 50% 4-hydroxy-1-butanesulfonyl chloride (*2c*), 25% 4-chloro-1-butanesulfonyl chloride (*5c*), and 25% 1,2-oxathiane 2,2-dioxide (butane 1,4-sultone) (*3c*) (with small amounts of either 1,4-butanedisulfonyl chloride or 4-acetoxy-1-butanesulfonyl chloride, depending on the impurities present in *4c*); the proportions of the major products varied somewhat with reaction conditions. Chlorination of an aqueous solution of the mercaptan (*1c*) gave a similar mixture of *2c*, *3c*, and *5c*. It was found that the cleanest sample of *2c* was obtained by washing the aqueous reaction mixture with a small amount of chloroform to remove some of the sultone (*3c*) and most of the chloro-sulfonyl chloride (*5c*), followed by a thorough extraction with dichloromethane; this gave a product consisting largely (~70%) of the hydroxysulfonyl



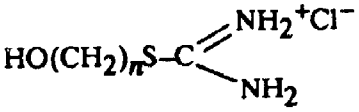
1



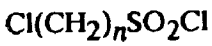
2



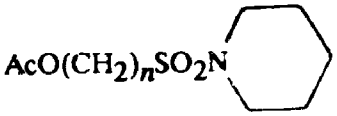
3



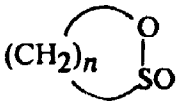
4



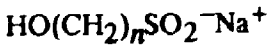
5



6



7



8

a) n = 2; b) n = 3; c) n = 4; d) n = 5; e) n = 6

SCHEME 1.1

chloride (*2c*) along with the sultone (~25%) and a little *5c* (~5%). The structure of *2c* follows from (a) its ir, ^{1}Hmr and ^{13}Cmr spectra, and (b) conversion both to the sultone[7] (*3c*) and to the crystalline piperidide (*6c*) prepared by acylation of *2c* with excess acetyl chloride followed by reaction with piperidine. The identity of 4-acetoxy-1-butanesulfonyl chloride was confirmed by preparing it from 4-acetyl-thio-1-butyl acetate by aqueous chlorination.

Part of the difficulty in obtaining a pure sample of *2c* was due to its conversion to the sultone (*3c*) during workup. This was shown by an experiment in which the crude aqueous reaction mixture (after the chloroform wash) was divided into a number of aliquots; immediate extraction of the first portion gave a product with *2c* and *3c* in a 70:30 ratio, with that extracted after 15 min showing a 40:60 ratio, that after 30 min a 15:85 ratio, and that after 1 h only traces of *2c*. The half life of *2c* in water at room temperature is estimated to be about 20 min; in accord with this a solution containing *2c* in D_2O showed only signals due to *3c* after 1 h. The spontaneous cyclization of *2c* to *3c* is evidently quite a bit slower in nonpolar solvents, with a half life of about 15 h being found in a $CDCl_3$ solution.

These results recall earlier experiments by King, Hillhouse, Skonieczny and Khemani on the chlorination of 3-mercapto-1-propanol,[2,3] in which it was shown that the products were propane 1,3-sultone (*3b*) and 3-chloro-1-propanesulfonyl chloride (*5b*), with the former (*3b*) being formed by very rapid cyclization of the 3-hydroxy-1-propanesulfonyl chloride (*2b*). It appeared at this stage that the only real difference with the four-carbon system was that the cyclization of the sulfonyl chloride (*2c*) to form the 6-membered ring sultone (*3c*) is slower than the analogous formation of the 5-membered homologue (*3b*), thereby allowing *2c* to be (a) observed by nmr spectra as the major component of the reaction mixture, and (b) at least partly separated from the other products and its cyclization observed separately; this, of course, is in accord with the usual pattern of reactivity in 5- and 6-membered

ring formation.[8]

As noted above, the cyclization of 4-hydroxy-1-butanesulfonyl chloride to butane 1,4-sultone (2c → 3c) occurred much faster in water than in chloroform-*d*. This suggested that the likelihood of preparing a purer specimen of 2c and of directly observing 2b, might well be increased by carrying out the reaction in nonpolar media. Accordingly we turned to the cnlorination of the corresponding hydroxy-alkanesulfinate salts (8) in chloroform or dichloromethane,[9] as an appropriate procedure.

Sodium 4-hydroxy-1-butanesulfinate (8c) was obtained as a white solid by alkaline hydrolysis of the corresponding sultine (cyclic sulfinic ester) (7c) which is available by a literature procedure,[10] or, as is described in chapter 2, by a particularly simple method from the hydroxythiol (1c). Peaks at 1011 and 965 cm^{-1} in the ir spectrum[11] taken with a simple four signal ^{13}Cmr spectrum and an appropriate ^{1}Hmr spectrum (see the experimental part in chapter 2) showed the material to be essentially pure 8c. Addition of a solution of chlorine in dichloromethane to 8c, followed by removal of sodium chloride and the solvent, gave a liquid product which showed the characteristic signals in the nmr spectra already assigned to 2c (~87%) along with small peaks indicating the presence of about 13% of the sultone (3c).

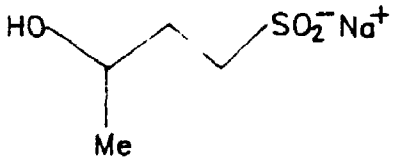
Similar reaction of propane 1,3-sultine (7b) to give 8b followed by chlorination, gave a product showing a ^{13}Cmr spectrum consisting of three major peaks clearly assignable to 3-hydroxy-1-propanesulfonyl chloride (2b) plus three small signals due to about 10% of propane 1,3-sultone (3b). The ^{1}Hmr spectrum was in full accord with the assignment. 3-Hydroxy-1-propanesulfonyl chloride (2b) was further characterized by its conversion both to the sultone (3b) and to the crystalline piperidide (6b) by the general procedure described earlier.

These results encouraged us to see if any 3-hydroxy-1-propanesulfonyl chloride

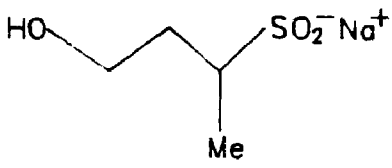
(2b) could be observed directly in the product of the aqueous chlorination of 3-mercapto-1-propanol. Indeed we found that rapid workup after reaction for only 2 min gave a mixture, the ^{1}H ar ^{13}Cmr spectra of which clearly showed the presence of 40% of 2b along with propane 1,3-sultone (3b) (20%) and 3-chloro-1-propanesulfonyl chloride (5b) (40%).

The 5- and 6-carbon hydroxyalkanesulfonyl chlorides (2d, 2e) were also made in good yield from the corresponding sulfinate salts (8d, 8e) (prepared as in chapter 2).

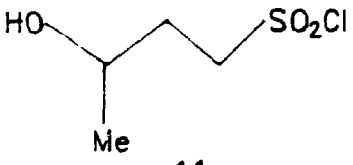
The hydroxyalkanesulfonyl chlorides thus become as easily accessible as the corresponding sultines or hydroxyalkanesulfinate salts and, as is discussed in chapter 2, these can be made in good yield from the mercapto-alcohols.



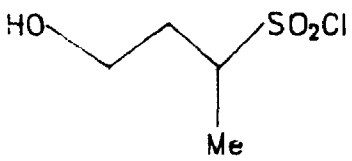
9



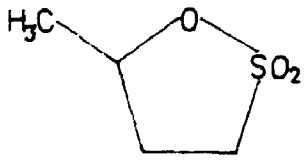
10



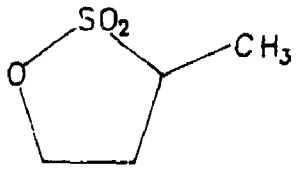
11



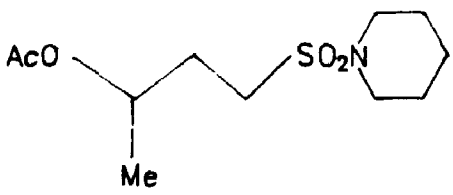
12



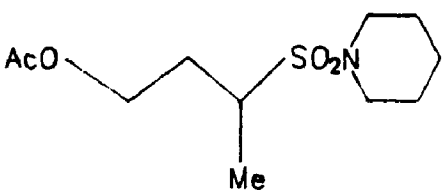
13



14



15

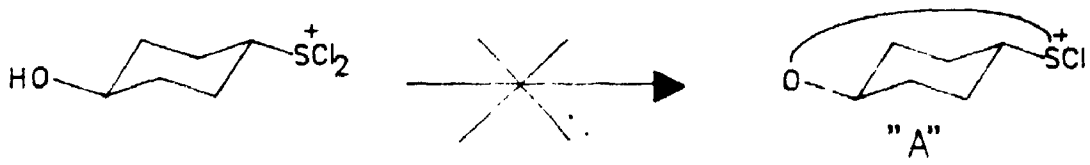


16

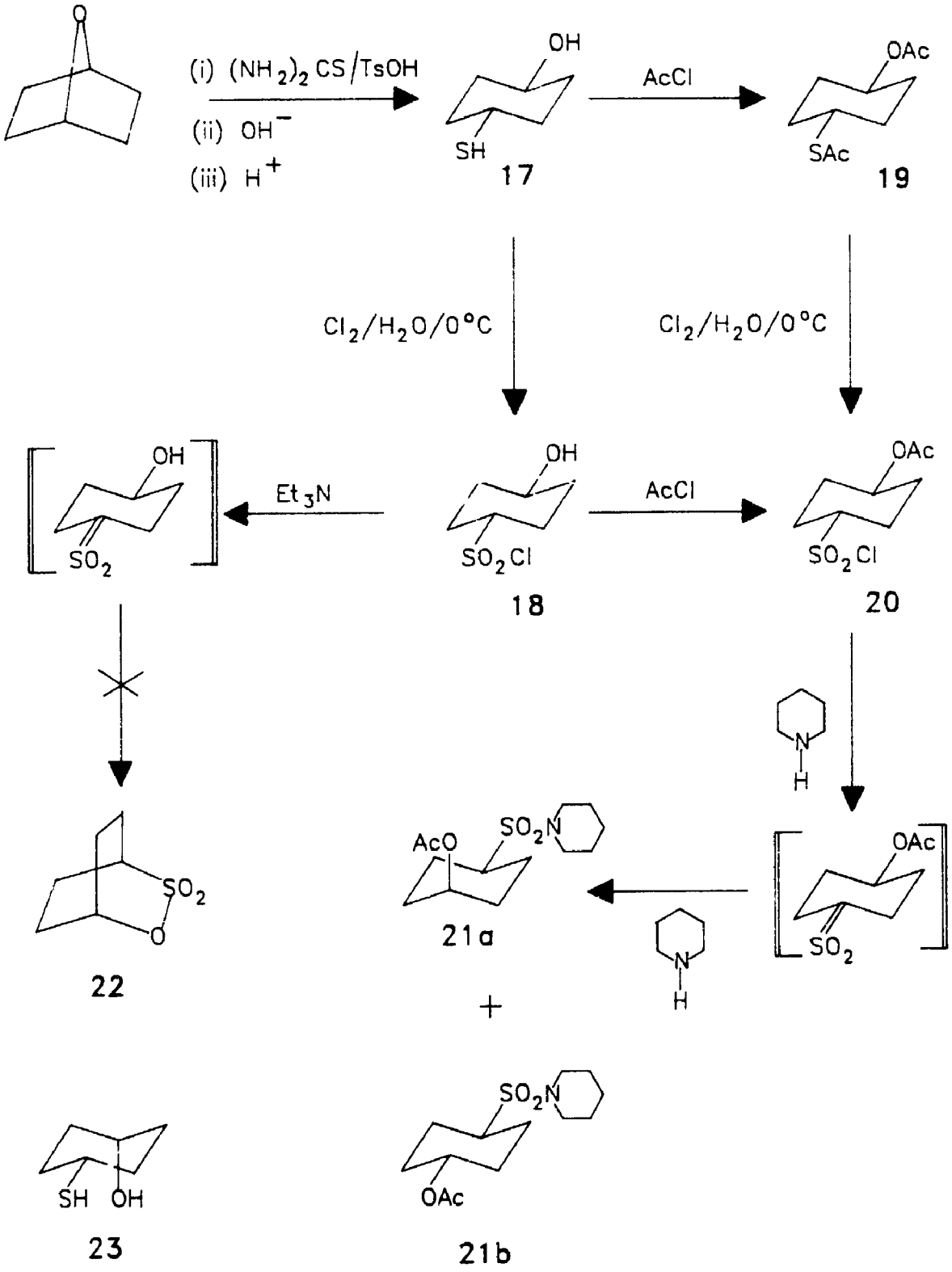
As a further illustration of the generality of the method, 3-hydroxy-1-butanesulfinate (*9*), prepared from corresponding sultine, was similarly treated with chlorine (1 eq.) in dichloromethane to give 3-hydroxy-1-butanesulfonyl chloride (*11*), which (a) cyclized on standing to butane 1,3-sultone (*13*), and (b) was also converted to the acetoxypiperidide (*15*).

Similarly the isomeric 4-hydroxy-2-butanesulfonyl chloride (*12*) was prepared from the hydroxy-sulfinate salt (*10*) by chlorination, and converted to the corresponding sultone (*14*) and the acetoxypiperidide (*16*).

Finally, *trans*-1,4-mercaptocyclohexanol (*17*) was required for the synthesis of a bicyclic sultam sought in connection with the study of stereoelectronic factors as described in chapter 3, and its synthesis prompted us to consider looking into the chlorination of both it and its *cis*-isomer (*23*); compound *23* was not readily prepared and its reaction were not studied. The aqueous chlorination of the 3- and 4-carbon hydroxythiols clearly involves intramolecular participation of hydroxyl group, as is evident from the product composition and oxygen-labelling studies.[3] Hydroxythiol *17* would be expected to behave differently from other hydroxythiols as it can not readily form any cyclic materials, *e.g.* "A", and its chlorination should be like that of a simple alkanethiol.



Indeed on aqueous chlorination, *17* gave pure hydroxysulfonyl chloride *18* in 96% yield, free of any side products (sultone or chlorosulfonyl chloride) resulting from –OH group involvement. It was converted to the acetoxypiperidide *21* as described earlier; this was found to be identical to a sample prepared by the alternative route involving aqueous chlorination of *19* (the diacetate of *17*) followed

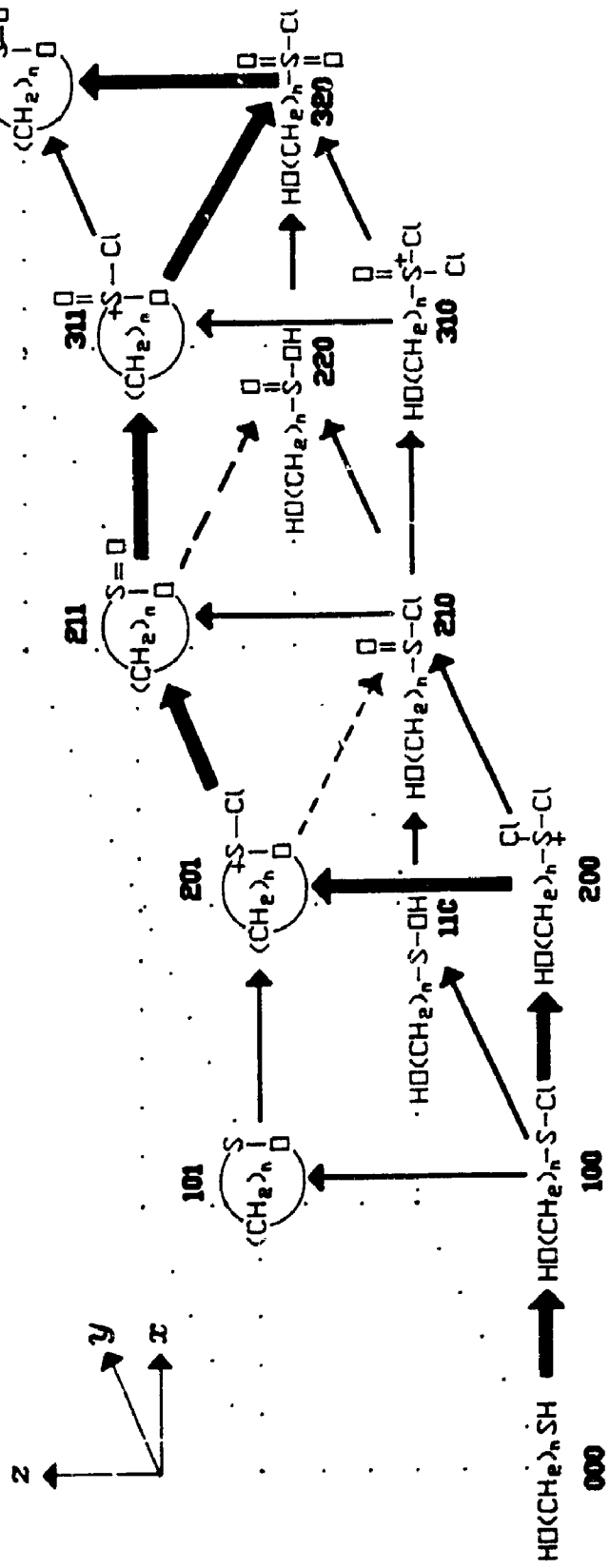

(i) $(NH_2)_2CS/TsOH$
(ii) OH^-
(iii) H^+
AcCl
17
19
$Cl_2/H_2O/0°C$
$Cl_2/H_2O/0°C$
Et_3N
AcCl
18
20
22
21a
21b
23

SCHEME 1.2

by reaction with piperidine in dichloromethane, as described earlier. The important feature of the piperidine reaction is that it gave a mixture of *cis* and *trans* piperidide ***21a*** and ***21b*** (40:60) as is expected when the reaction proceeds via a sulfene mechanism. The bicyclic sultone ***22*** was required to study the stereo-electronic effect, as discussed in chapter 3. Attempts to prepare the bicyclic sultone ***22*** from ***18*** were unsuccessful.

1.2.2 The Mechanism of the Aqueous Chlorination

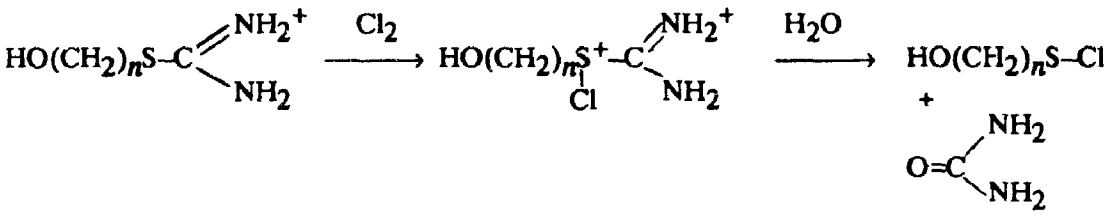
Scheme 1.3 presents in a three-dimensional grid pattern most of the reactions which are regarded as likely contributors to the general conversion of ω-mercapto-1-alkanols (***1***) to the ω-hydroxy-1-alkanesulfonyl chlorides (***2***) by chlorination in an aqueous medium. In this representation we place the starting material at the origin and depict successive reactions with each reagent as progressive movements along a particular axis, *i.e.*, each chlorination leads to the species one position farther along the *x*-axis, each hydrolysis to the position one unit farther on the *y*-axis, and cyclization to the species one unit up the *z*-axis. Starting with the coordinates of the starting material (*0,0,0*), which we write simply as ***000***, and representing each reaction by an integral change in the appropriate coordinate, we obtain designations for each of the various species as shown. Note that for two species connected by a "coordinate step" (*i.e.*, one shown by an arrow parallel to one of the coordinates), two of the coordinates stay the same while that corresponding to the reaction changes by one unit; *e.g.* the cyclization of the hydroxy-sulfonyl chloride, ***320*** → ***321***, alters only the final digit (the *z*-value). A convenient feature of this notation is that the coordinates for any species give the number of "coordinate steps" of the shortest pathway from the starting material to that species. *E.g.*, the hydroxy-sulfonyl chloride (***320***) is obtained from the starting material in three chlorination and two hydrolysis steps; the sum of the coordinates obviously gives the total number of


HO(CH2)nSH
000
HO(CH2)n-S-Cl
100
101
HO(CH2)n-S-OH
110
HO(CH2)n-S-Cl
200
201
HO(CH2)n-S-OH
220
HO(CH2)n-S-Cl
210
211
HO(CH2)n-S-OH
310
HO(CH2)n-S-Cl
320
311
321
z
y
x

SCHEME 1.3

"coordinate steps" in the shortest route.

For reactions starting with a thiouronium salt a slightly modified path to the sulfenyl chloride (*100*) is required:

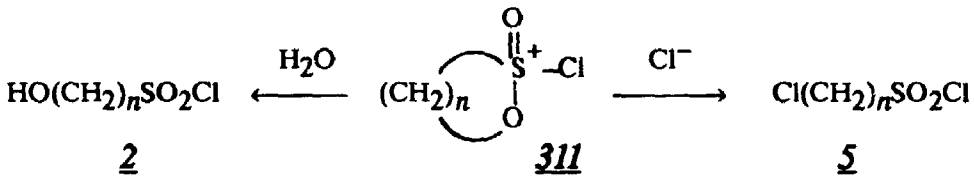


Although, in the above schemes, we represent the product of the chlorination of dicoordinated sulfur as a chlorosulfonium ion (*e.g.* *200*), we are not attempting to draw any distinction between these species and the corresponding sulfurane, $HO(CH_2)_nSCl_3$, or molecular complex structures, $HO-(CH_2)_nS^+-Cl-Cl$, for which there is precedent,[12] and which may well be present as components of the equilibrium or even the important reacting species in these transformations; the same disclaimer holds also for the other cationic species in Scheme 1.3, *i.e.* *201*, *310*, and *311*.

Chlorination of the 5- and 6-carbon thiouronium salts (*4d* and *4e*) in the presence of a large excess of water, as in the present experiments, evidently occurs by a mechanism confined to the *xy*-plane of Scheme 1.3. We have no evidence for distinguishing among the four pathways from *100* to *320*, but since both the chlorination and hydrolysis steps are presumably bimolecular; the relative rates can be altered simply by changing relative concentrations; with a low concentration of chlorine, for example, the sequence *100* → *110* → *210* → *220* → *320* may be the important mechanism, whereas at a higher chlorine concentration the route *100* → *200* → *210* → *310* → *320* may supervene, and at an intermediate concentration ratio all four pathways could perhaps be significant. In this context we point out that the grid pattern picture used in Scheme 1.3 has the advantage of displaying clearly both the number of possible routes and the potential for variation

with reaction conditions, and, though at first glance it may appear rather elaborate, it may well be the least complicated way of representing an intrinsically complex system.

The aqueous chlorination of the 3- and 4-carbon substrates (*1b*, *1c*, and *4c*) clearly involves, in addition to the chlorination and hydrolysis processes, reaction in the *z*-axis to form cyclic species, as might be expected from the high effective concentrations commonly found in 5- and 6-membered cyclization reactions.[8] The available evidence from product composition and oxygen-labelling[5] studies is consistent with formation of both the ω-chloro- and the ω-hydroxy-1-alkanesulfonyl chlorides (*5b* and *5c*, and *2b* and *2c*) by nucleophilic attack on the ω-carbon of the oxochlorosulfoxonium species (*311* in Scheme 1.3) with C–O bond cleavage:



2 *311* *5*

The C–O cleavage mechanism shown here (and in Scheme 1.3 by the solid diagonal arrow, or, less probably,[13] by the dotted diagonal arrow between *201* and *320*) is obviously not the only possible route to the hydroxy-sulfonyl chlorides (*2* ≡ *320*). The oxygen-labelling experiments[3] show, however, that within the experimental uncertainty of the method all of the propane 1,3-sultone (*3b*) is formed by a route involving C–O cleavage of *311* (n = 3). The corresponding labelling studies have not been done with the four carbon system, but the formation of 4-chloro-1-butane-sulfonyl chloride (*5c*) is also most simply accounted for on the basis of similar C–O cleavage pathway. The likely intermediate (*311*, n = 4) might be expected to give much the same ratio of *5* to *2* (or *3*) as that from the three carbon analogue (*311*, n = 3) under similar conditions; that similar product ratios are in fact observed strongly suggests that most, and perhaps all, of the 4-hydroxy-1-butanesulfonyl

chloride arises from the cyclic species (*311*, n = 4).

Scheme 1.3 shows six possible routes to the oxochlorosulfoxonium ion (*311*). In the light of (a) the excess of chlorine used (thereby favouring *100* → *200* over the alternatives), and (b) the high C_{eff} values usually found with 6-membered ring-formation reactions (leading to formation of *201* rather than *210*), it seems likely that the predominant pathway for the formation of *2c* (≡ *320*, n = 4) from *1c* follows the sequence *000* → *100* → *200* → *201* → *211* → *311* → *320*.

1.2.3 Factors Controlling the Synthesis of ω-Hydroxy-1-alkanesulfonyl Chlorides (*2*)

One factor affecting the nature of the products of aqueous chlorination of *1* and (or) *4* is the reaction medium. Goethals and Verzele[4] have reported that chlorination of aqueous suspensions of *1b* to *1e* gave the chlorosulfonyl chlorides (*5b* to *5e*) in yields varying from 31 to 90%; specifically, *1c* gave a 70% yield of *5c* described as containing 5% of the sultone (*3c*). In our hands chlorination of an aqueous solution of either *1c* or *4c* gave a mixture of approximately equal amounts of *2c* and *5c*. This experiment suggests that the key difference between our results and those of the Belgian workers,[4] is not due to the fact that they used the thiols while most of our chlorinations were performed on thiouronium salts, but rather because their reactions were done in an organic phase and ours in water. In the latter medium there is a competition between water and Cl^- for cleavage of the cation *311*, whereas in the organic phase the concentration of water is low and hence the rate of hydrolysis of *311* is slow relative to Cl^- attack. With the 5- and 6-carbon systems the reaction in aqueous solution presumably leads to rapid hydrolysis (*e.g.* *200* → *210*) and thence to the hydroxy-sulfonyl chlorides (*2*). In the organic phase reactions, hydrolysis is slow relative to either cyclization (when C_{eff} is higher than the concentration) or the corresponding intermolecular reaction; the latter process, which was omitted from Scheme 1.3 for simplicity, would yield acyclic

intermediates such as $HO(CH_2)_nSO–O(CH_2)_nSO–Cl$ when C_{eff} is lower than the concentration. Both the cyclic or acyclic species would be expected to lead ultimately to **5** rather than **2**, since under these conditions the chloride concentration would be high relative to that of water, and C–O cleavage of **311** or its acyclic analogue by attack of chloride would be the favoured reaction.

In agreement with this picture it was found that chlorination of **1e** in a mixture of dichloromethane and water gave a mixture in which **5e** predominated over the small amount of **2e**. Though in our view thiols and thiouronium salts react by essentially the same pathway, the latter, by virtue of their ionic character, are much more water-soluble than the thiols and their reaction is much more likely to take place entirely in the aqueous phase. This simple practical consideration favours the use of the thiouronium salts (**4**) over the thiols (**1**) (wherever this is feasible) for the synthesis of hydroxy-sulfonyl chlorides.

Also crucial to determining the course of aqueous chlorination reactions is the structure of the starting material and hence of the possible products. The polymerization of the 5- and 6-carbon hydroxy-sulfonyl chlorides (**2d** and **2e**) is sufficiently slow that, although this reaction evidently limits the storage of these compounds, it does not interfere significantly with their preparation. Experience with the 3- and 4-carbon sulfonyl chlorides (**2b** and **2c**) shows cyclization to the sultone (**3**) to be the key reaction determining if **2** can be isolated. *trans*-4-Mercapto-1-cyclohexanol (**17**) which is unable to form **311** gave an excellent yield (96%) of 4-hydroxy-1-cyclohexanesulfonyl chloride (**18**). We may expect as a general rule that when C_{eff} for **2** $\rightarrow$ **3** is $\leq$100 the hydroxy-sulfonyl chloride (**2**) can be expected to be easily prepared; with increasing C_{eff} values, however, isolation of **2** (instead of **3**) would become more and more difficult and perhaps ultimately impossible.

1.2.4 Spontaneous and Base-induced Reactions of Sulfonyl Chlorides **2b** and **2c**

A sample consisting of 3-hydroxy-1-propanesulfonyl chloride (**2b**) (90%) and propane 1,3-sultone (**3b**) (10%) was dissolved in chloroform-*d* containing 1-butanol (0.9 M) and was found to be smoothly converted entirely to the sultone (**3b**) on standing at room temperature. The reaction was followed by ^{1}Hmr and showed acceptable first order kinetics to >75% reaction with a half-life around 80 to 85 min. corresponding to $k_1 = (1.4 \pm 0.1) \times 10^{-5}$ s^{-1} (see Figure 1.1). Similarly a rate constant of $(6.4 \pm 1.0) \times 10^{-6}$ s^{-1} was found for 4-hydroxy-1-butanesulfonyl chloride (**2c**), prepared by nonaqueous chlorination of sulfinate salt (**8c**). When compared with the second order rate constant (3.1×10^{-7} M^{-1}s^{-1}) for the model reaction of 1-butanesulfonyl chloride and 1-butanol (see Figure 1.2), we obtain effective concentrations[14,8] (C_{eff}) of 4.5×10^2 and 2.1×10^2 M, respectively, for the uncatalyzed cyclizations **2b** → **3b** and **2c** → **3c** (in $CDCl_3$–0.9 M butanol at 22 °C). The C_{eff} for the latter reaction is in good accord with those reported for other 6-*exo*-*tet* processes[8] (*e.g.* 280 M for cyclization of ^-O–$(CH_2)_5Cl$ and 100 M for that of $NH_2(CH_2)_5Br$, but that for the 5-membered ring formation (450 M) seems low in comparison with those of analogous 5-*exo*-*tet* reactions,[8] *e.g.* 6×10^4 M for ^-O–$(CH_2)_4Cl$ ⟶ tetrahydrofuran and ~7×10^3 M for $NH_2(CH_2)_4Br$ ⟶ pyrrolidine. A possible explanation for the slow cyclization of **2b** to **3b** under these conditions is that there is relatively greater ring strain in its transition state; this would be a part of the strain present in 5-membered sultones and cyclic sulfates and which is believed to contribute to their remarkable e[illegible]of ring opening.[15,16]

As was noted in the earlier discussion these cyclizations become slower as the solvent polarity decreases. In chloroform-*d* without any butanol, we have observed a half-life for the reaction **2b** → **3b** of 52 h (see Figure 1.3), and for **2c** → **3c** of about 66 h. Furthermore, we had found previously that for a sample prepared from

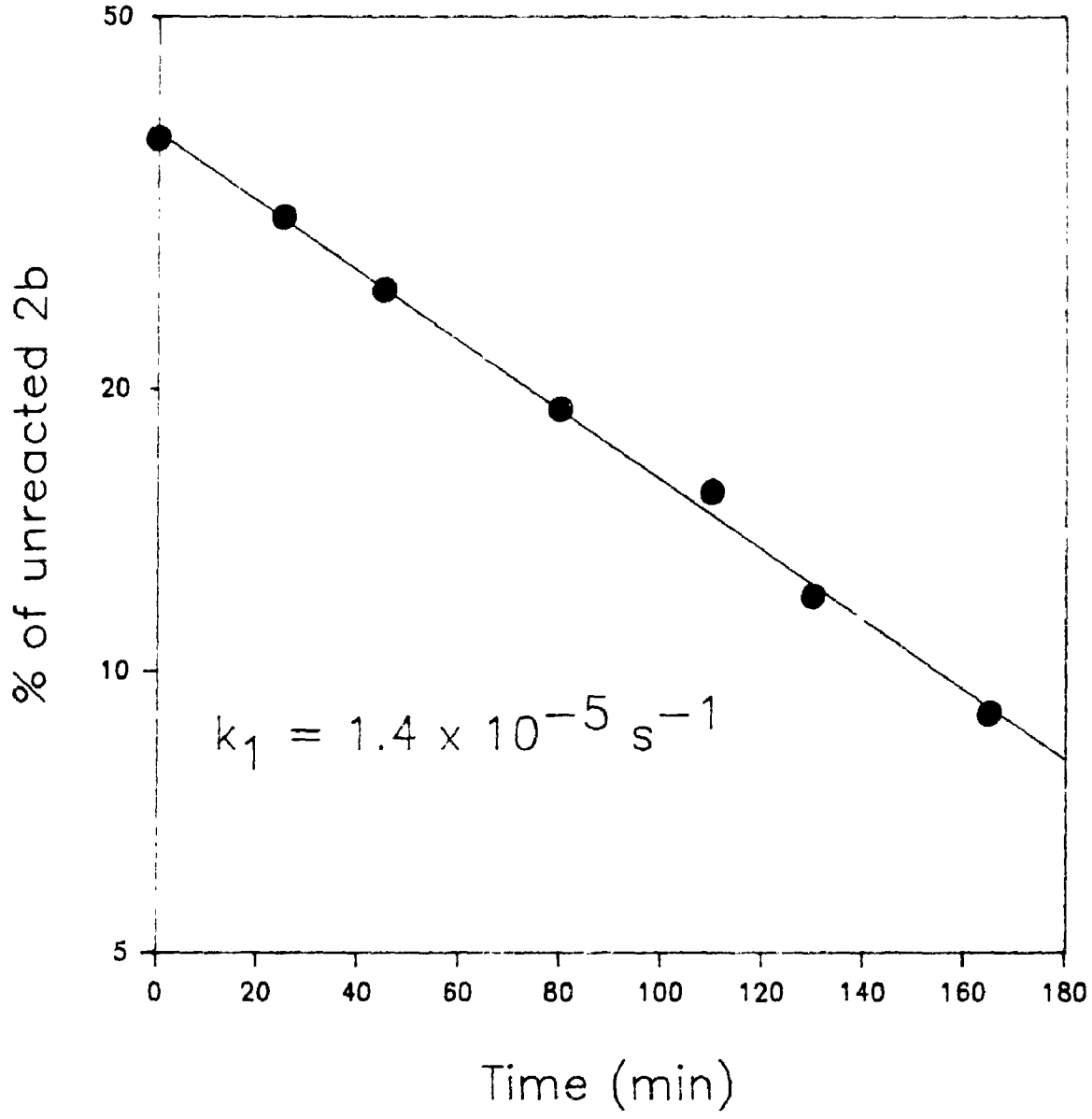


Figure 1.1 Cyclization of 3–hydroxy–1–propanesulfonyl chloride (**2b**) in 0.9 M 1–butanol–$CDCl_3$ at 21° C.

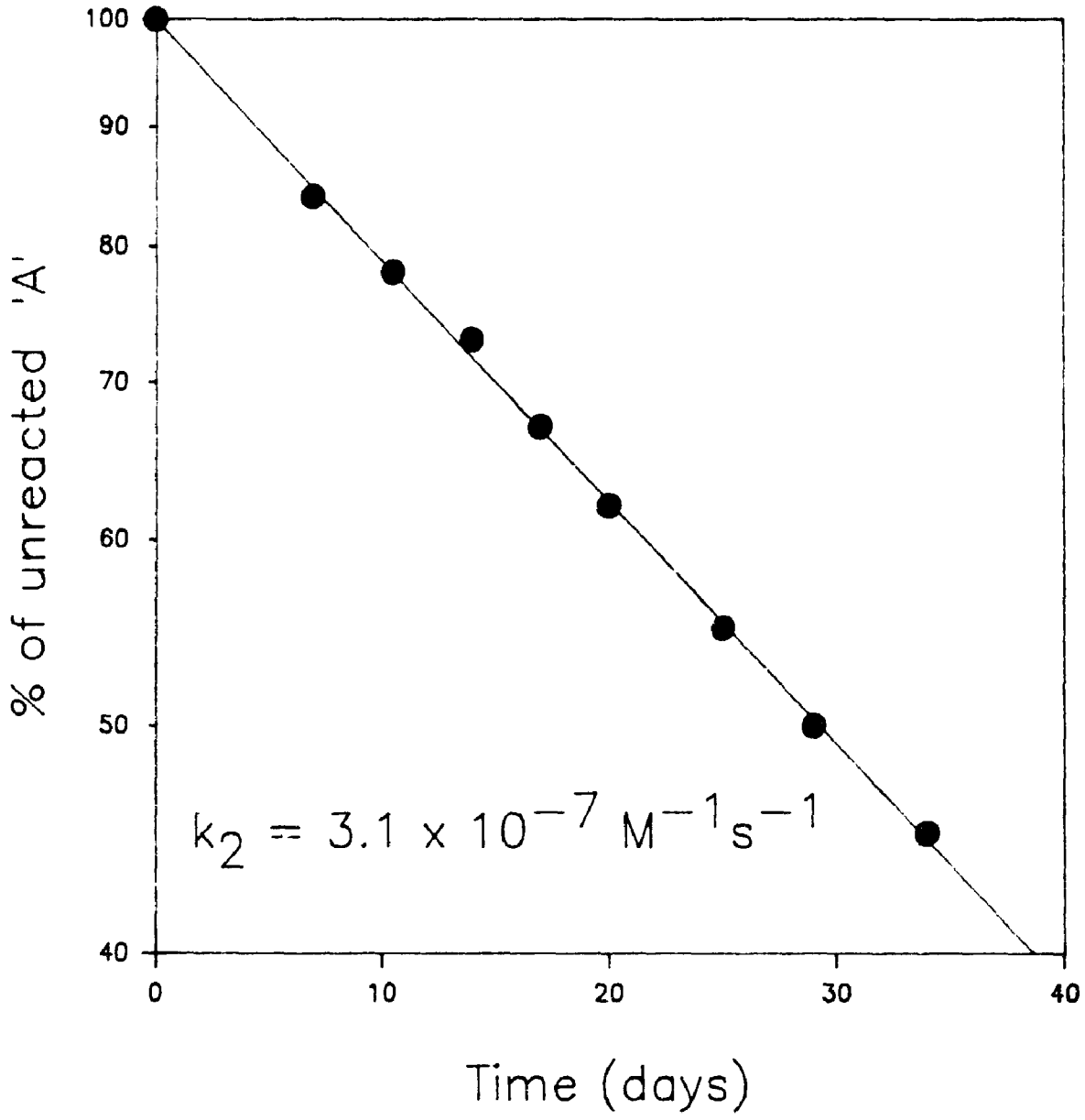


Figure 1.2 Kinetics of the model reaction of 1-butanesulfonyl chloride ('A') and 1-butanol (0.9 M) in $CDCl_3$ at 21° C.

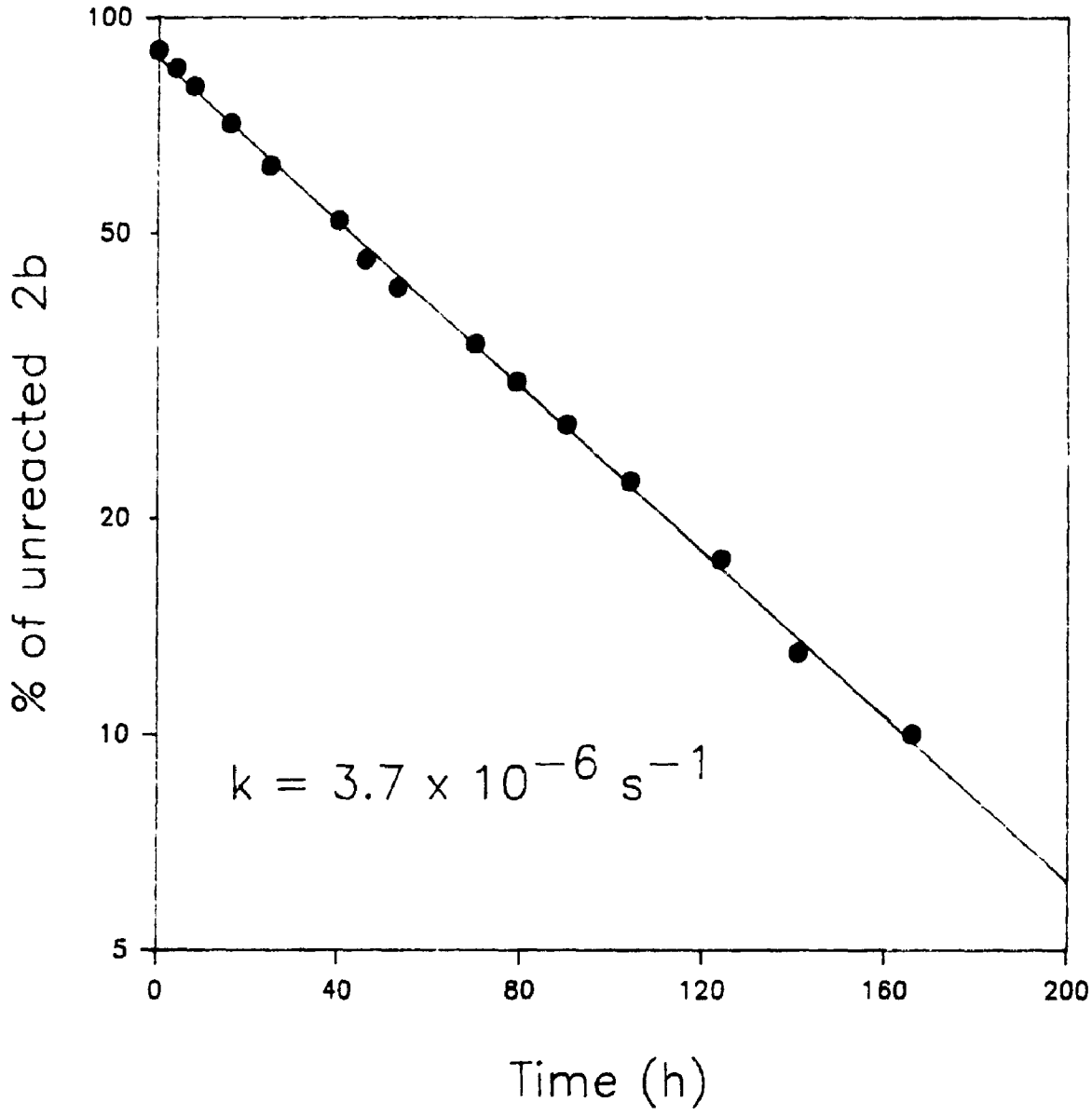


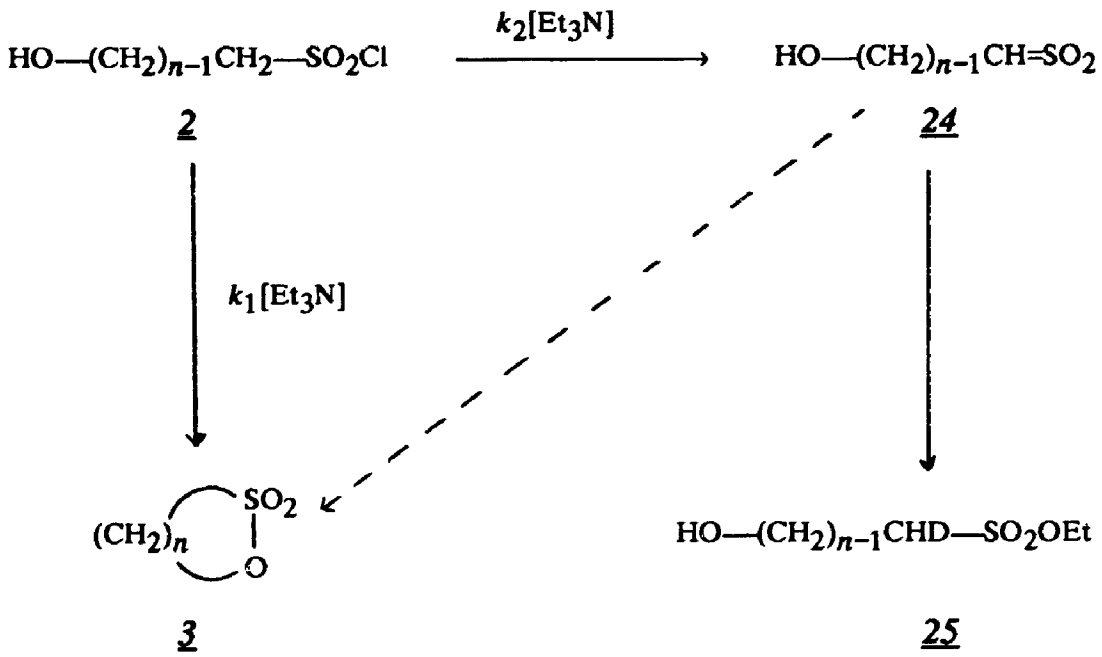
Figure 1.3 Cyclization of 3-hydroxy-1-propanesulfonyl chloride (2b) $CDCl_3$ at 21° C.

aqueous chlorination, $t_{1/2}$ for **2c** → **3c** was 15 h, and on further investigation observed that the rate varied erratically from one sample to another. It seems likely that the variation arises from a sensitivity of the reaction to small amounts of water and perhaps other adventitious materials. The sample prepared in the earlier study, which was obtained by extraction from an aqueous medium, almost certainly contained water which may have accelerated the reaction by acting as a general base catalyst and (or) simply by increasing the solvent polarity. In the cyclizations in chloroform-*d* containing 1-butanol, the rates are evidently reproducible, hence it would appear that the effect of adventitious impurities is swamped by that of the much larger amount of the alcohol.

In chloroform-*d* solution **2b** was instantly converted by addition of triethylamine to propane 1,3-sultone (**3b**) with no sign of any polymer. When the reaction of **2b** with triethylamine was carried out in ethanol-*d* solution, again the only product was the fully-protonated sultone (**3b**) with no evidence of any ethyl 3-hydroxy-1-propanesulfonate or polymer. Reaction of **2c** (containing ~15% **3c**), however, with triethylamine in ethanol-*d* gave the ethyl ester (**25c**) as major product (~90%), along with what appeared to be a small proportion (~10%) of butane sultone (**3c**) in addition to that present in the starting material. The ester was largely (~70 ± 20%) monodeuterated (*i.e.* $HOCH_2CH_2CH_2CHDSO_2OEt$) but the sultone (**3c**) showed no sign of deuterium incorporation. These observations are consistent with the reactions shown in Scheme 1.4. With 3-hydroxy-1-propanesulfonyl chloride (**2b**) k_1 is larger than k_2 (by more than 20 times), and the only observed reaction is the formation of undeuterated propane sultone (**3b**), presumably by general base assisted direct cyclization of **2b**. With 4-hydroxy-1-butanesulfonyl chloride (**2c**), on the other hand, k_2 is apparently ten (or more) times k_1. These reactions may be compared to those reported[2] for 2-hydroxy-1-ethanesulfonyl chloride (**2a**), which reacts with tertiary amines and alcohols (in dichloromethane) to give some of the ester

(corresponding to *25b*) but mainly products derived from further reaction of the sultone (*3a*), *i.e.* k_1 is about twice k_2 (with triethylamine).

Sulfene *24c*, once formed, appears to be trapped largely by the solvent (ethanol) without any sizeable fraction cyclizing to form butane sultone (*3c*). The presence of *3c* in the starting material, however, makes it difficult to see if any of the relatively small amount of sultone (*3c*) that may have been formed in the reaction is terated and hence produced from the sulfene (*24c*). It may be recalled[17] that the sultones *3d* and *3e* are largely monodeuterated when formed in the presence of ethanol-*d* and are therefore formed (largely) by the route *2* → *24* → *3*.



a) n = 2; b) n = 3; c) n = 4; d) n = 5; e) n = 6

SCHEME 1.4

In concluding, we may briefly sum up the present and earlier work[2,17] on the mode of reaction of the known ω-hydroxy-1-alkane-sulfonyl chlorides (*2*) with

triethylamine in the presence of an excess of an alcohol as follows: direct cyclization (*2* → *3*) is the principal reaction with the entropically favoured cases, *2a* and *2b*, whereas the normal sulfene process (*2* → *24* → *3* and (or) *25*) is the chief reaction with the higher homologues (*2c* – *2e*).

1.3 EXPERIMENTAL

Reagent grade chemicals and solvents were used without additional purification unless otherwise noted. Magnetic resonance spectra were obtained using Varian XL200 (^{1}H) and XL300 (^{13}C) instruments; with all chemical shifts were determined relative to tetramethylsilane (TMS) in the organic solutions and sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) with aqueous solutions from spectra obtained with the high field instruments. Infrared (ir) spectra were recorded with an IFS/32 FTIR Bruker spectrometer. Melting points were obtained with a Kofler Hot Stage apparatus and are uncorrected. Mass spectra were run on a Finnigan Mat-311A spectrometer.

Usual workup of reactions refers to partitioning of the reaction mixture between water and an organic solvent, drying of the organic layer with anhydrous magnesium sulfate and evaporating the solvent using a Buchi rotary evaporator connected to a water aspirator. Rate measurements were carried out by integration of ^{1}Hmr signals.

Thiouronium salts

(i) 6-Hydroxy-1-hexylthiouronium chloride (*4e*)

A solution of 6-chloro-1-hexanol[24] (9.17 g, 67.1 mmol) and thiourea (5.59 g, 73.4 mmol) in ethanol (10 mL) and water (40 mL) was refluxed for 22 h; the mixture was then washed with dichloromethane and the aqueous layer evaporated to dryness under reduced pressure to give a white solid (14.5 g, ~100%). Recrystallization from absolute ethanol-ether gave white needles melting at 127-128 °C; ir (KBr) ν_{max}: 3300 (v br), 1638 (vs), 1447 (s), 1288 (m), 1068 (m), 1050 (s), 1033 (s), 982 (m), 686 (m), 610 (m), 490 (m) cm^{-1}; ^{1}Hmr (D_2O) δ: 1.12-1.92 (m, 8H), 3.16 (t, 2H), 3.62 (t, 2H); ^{13}Cmr (D_2O) δ: 31.1, 33.9, 34.3, 37.3, 37.7, 68.3, 178.3.

(ii) 5-Hydroxy-1-pentylthiouronium chloride (*4d*)

5-Chloro-1-pentyl acetate[25] (^{1}Hmr ($CDCl_3$) δ: 1.5-1.9 (m, 6H), 2.05 (s, 3H), 3.5 (t, 2H), 4.07 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 23.3, 27.9, 32.2, 44.7, 64.1, 170.8) (10 g, 61 mmol) was refluxed with a mixture of conc. sulfuric acid (30 mL), water (75 mL), and methanol (100 mL) for 2.5 h; workup followed by distillation gave 5-chloro-1-pentanol (4.17 g, 54%); the chloropentanol (4.17 g, 34 mmol) and thiourea (2.53 g, 33 mmol) in water (40 mL) and ethanol (10 mL) after refluxing for 18 h and workup as above, gave a colourless oil (6.37 g, 94 %) which solidified on standing in the cold; recrystallization from ethanol-ether gave white crystals, mp 91.5-92 °C; ir (KBr) ν_{max}: 3300 (v br), 1660 (vs), 1428 (m), 1400 (br m), 1295 (m), 1235 (m), 1060 (m), 1035 (m), 684 (m) cm^{-1}; ^{1}Hmr (D_2O) δ: 1.22-1.96 (m, 6H), 3.16 (t, 2H), 3.63 (t, 2H); ^{13}Cmr (D_2O) δ: 26.6, 30.2, 33.3 (2C), 64.0, 174.2.

(iii) 4-Hydroxy-1-butylthiouronium chloride (*4c*)

4-Chloro-1-butanol (Aldrich Chemicals Co.) (1.08 g, 10 mmol), thiourea (0.741 g, 9.5 mmol), water (6 mL), and ethanol (2 mL) upon refluxing for 22 h and workup as above gave a colourless viscous liquid (1.64 g) which partly crystallized on standing. The liquid component was dissolved in absolute ethanol and the solid product removed by filtration. This crystalline material (0.295 g, 18%) was shown to be 1,4-butylbisthiouronium chloride; recrystallization from ethanol-water gave white crystals, mp 223-225 °C; ir (KBr) ν_{max}: 3100 (v br), 1625, 1430, 1320, 1210, 700 cm^{-1}; ^{1}Hmr (D_2O) δ: 1.86-1.92 (m, 4H), 3.15-3.22 (m, 4H); ^{13}Cmr (D_2O) δ: 29.3, 32.8, 173.8. Aqueous chlorination of the bis-salt yielded 1,4-butanedisulfonyl chloride, which on recrystallization from light petroleum gave white needles, mp 83-84 °C (reported mp 82.5 °C[5], 83-84 °C[6]); ^{1}Hmr ($CDCl_3$) δ: 2.26-2.33 (m, 4H), 3.73-3.81 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 22.5, 63.9.

Evaporation of the alcohol from the filtrate left *4c* as a viscous liquid (1.35 g,

76%); ^{1}Hmr (D_2O) δ: 1.67–1.88 (m, 2H), 3.16 (t, 2H), 3.62 (t, 2H); signals appropriate to a small amount (5–10%) of the 1,4–bisthiouronium salt were also visible in the nmr spectra; the major peaks in the ^{13}Cmr spectrum were identical to those of the sample from the acetate (below). 4–Chloro–1–butyl acetate[18] (3.65 g, 24.3 mmol) and thiourea (1.89 g, 24.25 mmol), gave a viscous liquid (5.5 g, ~100%), which from its ^{1}Hmr spectrum consisted of ***4c*** with about 15% of its O–acetate derivative (with a singlet at 2.10 and a triplet at 4.12 ppm); ^{13}Cmr (D_2O) δ: 25.6, 31.2, 31.7, 62.0, 172.4.

Mercaptoalkanols (***1***)

(i) 3–Mercapto–1–propanol (***1b***)

3–Mercapto–1–propanol was prepared from thiopropionic acid (19.8 g, 180 mmol) and lithium aluminium hydride (15 g, 393 mmol) in ether (250 mL) according to the method of Djerassi and Gorman;[19] ^{1}Hmr ($CDCl_3$) δ: 1.44 (t, 1H), 1.85 (quintet, 2H), 2.65 (q, 2H), 3.73 (t, 2H), 3.75 (b, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.1, 36.1, 60.5.

Compound ***1b*** was converted to the diacetate[20] by adding 2.2 equivalents of acetyl chloride dropwise and heating the mixture at 50 °C for 0.5 h and distilling the diacetate as a clear oil; ir (neat) ν_{max}: 1742 (vs), 1694 (vs), 1366 (s), 1242 (vs), 1136 (s), 1040 (s), 959 (m), 625 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.91 (quintet, 2H), 2.06 (s, 3H), 2.34 (s, 3H), 2.74 (t, 2H), 4.11 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.8, 25.5, 28.6, 30.5, 62.6, 170.6, 195.0.

(ii) 4–Mercapto–1–butanol (***1c***)

A solution of crude thiouronium salt (***4c***) (5.5 g, 30 mmol) (made from 4–chloro–1–butyl acetate and containing ~15% acetate ester), in aqueous 10% sodium hydroxide was allowed to react for 5 h at room temperature; workup gave

4-mercapto-1-butanol (*1c*) (2.03 g, ~65%), bp 105-106°C (30 torr); ^{1}Hmr ($CDCl_3$) δ: 1.32 (t, 1H), 1.57-1.65 (m, 4H), 2.27 (s, 1H), 2.50 (q, 2H), 3.57 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.5, 30.3, 31.3, 62.0. Heating *1c* with phenyl isocyanate gave a roughly 2:1 mixture of the phenylurethane-thiol ($PhNHCOOCH_2CH_2CH_2CH_2SH$) (mp 124-125°C; ^{1}Hmr ($CDCl_3$) δ: 1.36, (t, 1H), 1.6-1.86 (m, 4H), 2.56 (q, 2H), 4.17 (m, 2H), 6.82 (br s, 1H), 7.0-7.4 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 24.2, 27.7, 30.3, 64.6. 118.7, 123.4, 129.0, 137.9, 153.5), and the bisphenylcarbamate ($PhNHCOOCH_2CH_2CH_2CH_2SCONHPh$) (mp 126-128°C, reported[21] mp 128°C; ^{1}Hmr ($CDCl_3$) δ: 1.74-1.86 (sym m, 4H), 3.04 (t, 2H), 4.19 (t, 2H), 6.56 (br s, 1H), 7.0-7.45 (m, 11H); ^{13}Cmr ($CDCl_3$) δ: 27.0, 27.8, 29.9, 64.7, 118.6, 119.8, 123.4, 124.5, 129.0, 129.1, 137.7, 137.9, 153.5, 180.6) separated by recrystallization from benzene.

4-Mercapto-1-butanol (*1c*) was converted to the diacetate as above; bp 84-86°C (0.3 torr); ir (neat) ν_{max}: 3360 (m), 1740 (vs), 1694 (vs), 1387 (s), 1368 (s), 1239 (vs), 1134 (vs), 1046 (vs), 956 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.75-1.66 (m, 4H), 2.05 (s, 3H), 2.34 (s, 3H), 2.90 (t, 2H), 4.06 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.8, 26.9, 27.6, 28.5, 30.5, 63.6, 170.7, 195.2.

(iii) 5-Mercapto-1-pentanol (*1d*)

A solution of *4d* (10 g, 50 mmol), in aqueous 10% sodium hydroxide (50 mL) was allowed to react under nitrogen, as above; workup gave 5-mercapto-1-pentanol (*1d*) (4.8 g, 80%); ^{1}Hmr ($CDCl_3$) δ: 1.39 (t, 1H), 1.44-1.68 (m, 6H), 2.54 (q, 2H), 3.00 (s, 1H), 3.60 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.5 (2C), 32.0, 33.8, 62.3.

The diacetate of *4d* was prepared as described above in ~100% yield; ir (neat) ν_{max}: 2938 (m), 2863 (w), 1736 (vs), 1690 (vs), 1365 (w), 1240 (s), 1132 (m), 1044 (m), 959 (w), 625 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.35-1.73 (m, 6H), 2.05 (s, 3H), 2.33 (s, 3H), 2.87 (t, 2H), 4.05 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.6, 24.8, 27.8, 28.5,

28.9, 30.3, 63.9, 170.7, 195.3.

(iv) 6-Mercapto-1-hexanol (*1e*)

Crude thiouronium salt (*4e*) (10.7 g, 50 mmol), in aqueous 10% sodium hydroxide (50 mL) was allowed to react under nitrogen, as above; workup followed by distillation gave *1e* (4.4 g, 65%); ^{1}Hmr ($CDCl_3$) δ: 1.34–1.65 (m, 9H), 2.53 (q, 2H), 3.25 (s, 1H), 3.58 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.5, 25.2, 28.1, 32.4, 33.9, 62.4.

Hydroxythiol (*1e*) was converted to diacetate as above in quantitative yield; ir (neat) ν_{max}: 2936 (vs), 2861 (s), 1740 (vs), 1696 (vs), 1458 (m), 1435 (m), 1366 (s), 1240 (vs), 1136 (vs), 1049 (s), 955 (s), 733 (w), 627 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.32–1.75 (m, 8H), 2.04 (s, 3H), 2.32 (s, 3H), 2.86 (t, 2H), 4.04 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.5, 25.1, 28.0, 28.1, 28.5, 29.1, 30.1, 63.9, 170.5, 195.1.

Aqueous chlorination of hydroxyalkanethiouronium salts and (or) hydroxythiols

(i) 4-Hydroxy-1-butanesulfonyl chloride (*2c*)

General procedure: Chlorine was bubbled into water (100 mL) cooled in an ice bath until the solution turned yellow (about 1 min), and an aqueous solution of *4c* (100 mg) in water (5 mL) added quickly. The reaction mixture was extracted immediately with a small portion (3 mL) of chloroform (to remove the *5c* and, where formed, the 1,4-butanedisulfonyl chloride or the acetoxysulfonyl chloride), and then further extracted thoroughly, and as quickly as possible, with dichloromethane (3 × 50 mL); drying of the extract (sodium sulfate) and evaporation of the solvent gave impure (~70%) *2c* as an oil (54 mg, 51%); ir (neat) ν_{max}: 3314 (br s), 2957 (s), 1368 (vs), 1304 (w), 1190 (m), 1167 (vs), 1057 (m), 914 (s), 827 (w), 785 (m), 592 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.70–1.89 (m, 2H), 2.15–2.26 (m, 2H), 3.71–3.82 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 21.6, 30.1, 61.8, 65.4, plus small signals at 23.0, 23.7, 48.4,

74.1 assigned to 3c.

4-Mercapto-1-butanol (1c) (200 mg, 1.89 mmol) on similar chlorination gave (i) in the chloroform wash, a 24:76 mixture (40 mg) of 3c and 5c, and (ii) in the dichloromethane extract, a 65:28:7 mixture of 2c, 3c, and 5c; estimated overall yields: 2c, 89 mg, 27%; 3c, 37 mg, 14%; 5c, 44 mg, 12%. Spectra of authentic specimens: (i) butane 1,4-sultone[7] (3c) ^{1}Hmr ($CDCl_3$) δ: 1.72-1.79 (m, 2H), 2.10-2.17 (m, 2H), 3.06 (t, 2H), 4.45 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 22.8, 22.5, 48.3, 74.1; (ii) 4-chloro-1-butanesulfonyl chloride (5c) (prepared[22] by refluxing a solution of 3c in thionyl chloride containing a little dimethylformamide for 7 days) ^{1}Hmr ($CDCl_3$) δ: 1.93-2.27 (m, 2H), 2.16-2.31 (m, 2H), 3.62 (t, 2H), 3.74 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.9, 30.0, 43.7, 64.5.

The sulfonyl chloride (2c) was characterized by conversion to 4-acetoxy-1-butanesulfonylpiperidide (6c) in two steps as follows: (i) to the sulfonyl chloride in dry dichloromethane was added a seven fold excess of acetyl chloride and the mixture was allowed to stand overnight at room temperature; after washing with aqueous sodium bicarbonate and evaporation of solvent the acetoxysulfonyl chloride was obtained as a clear oil; ^{1}Hmr ($CDCl_3$) δ: 1.83-1.90 (m, 2H), 2.07 (s, 3H), 2.07-2.14 (m, 2H), 3.77 (t, 2H), 4.13 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.6, 21.1, 26.3, 62.8, 64.5, 170.6; (ii) reaction of the acetoxysulfonyl chloride from above with excess piperidine in dichloromethane followed by conventional workup yielded a pale yellow oil which on recrystallization from cold hexane, gave 6c as colourless crystals, mp 44-45 °C; ir (CCl_4) ν_{max}: 2950 (s), 2870 (m), 1745 (vs), 1450 (m), 1365 (s), 1340 (vs), 1240 (vs), 1165 (s), 1145 (s), 1055 (s), 940 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.46-1.69 (m, 10H), 1.90 (s, 3H), 2.77 (t, 2H), 3.05-3.10 (t, 4H), 3.94 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.0, 20.9, 23.8, 25.7, 27.5, 46.6, 48.5, 63.4, 171.0. Calcd. exact mass for $C_{11}H_{21}O_4SN$: 263.1191. Found: 263.1191.

In one chlorination of 4c the aqueous product (after the initial chloroform

wash) was split into five aliquots which were separately extracted with dichloromethane : (i) which was extracted immediately showed the ^{1}Hmr spectrum of a 74:26 ratio of **2c** to **3c**, (ii) extracted after 15 min, 55:45, (iii) 30 min, 23:77, (iv) 45 min, 15:85, (v) 60 min, < 10:90, indicating $t_{1/2}$ around 20 ± 5 min; a solution of **2c** after 1 h at room temperature. In $CDCl_3$ the following ratios of **2c** to **3c** were estimated from the ^{1}Hmr spectrum: start, 76:24; 20 h, 36:64; 27 h, 17:83; 44 h, 9:91; corresponding to $t_{1/2}$ = ~15 ± 3 h at room temperature.

(ii) *trans*-4-Hydroxy-1-cyclohexanesulfonyl chloride (**18**)

trans-4-Mercapto-1-cyclohexanol (**17**) (for preparation see chapter 3) (264 mg, 2 mmol) was added to a cold solution of chlorine in water (50 mL), as described in the general procedure above. Workup gave **18** as a crystalline solid; recrystallized from dichloromethane-cyclohexane (381 mg, 96%); mp 75-78 °C; ir (KBr) ν_{max}: 3262 (br s), 2946 (m), 1372 (vs), 1162 (s), 1066 (vs), 601 (vs) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3-1.5 (m, 2H), 1.76-1.98 (m, 2H), 1.82 (s, 3H), 2.16-2.3 (m, 2H), 2.42-2.56 (m, 2H), 3.51 (tt, J = 11.8, 3.7 Hz, 1H), 3.71 (tt, J = 10.8, 4.3 Hz, 1H); ^{13}Cmr ($CDCl_3$) δ: 25.3, 33.2, 68.4, 73.1.

Compound **18** was converted to the acetoxysulfonyl chloride (**20**), as above; ir (neat) ν_{max}: 2952 (m), 2872 (m), 1732 (vs), 1458 (m), 1369 (vs), 1246 (vs), 1161 (vs), 1046 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.35-1.55 (m, 2H), 1.84-2.06 (m, 2H), 1.98 (s, 3H), 2.15-2.24 (m, 2H), 2.40-2.51 (m, 2H), 3.49 (tt, 1H), 4.69 (tt, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.1, 25.2, 29.6, 70.3, 72.6, 170.3. Reaction of **20** with excess piperidine yielded a mixture of the *cis*- and *trans*-acetoxypiperidide (**21**) (40:60); ir (neat) ν_{max}: 2944 (s), 2861 (m), 1732 (vs), 1323 (s), 1248 (vs), 1146 (s), 1041 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.25-2.30 (m, 14H), 2.04 and 2.08 (two s, 3H), 2.87 (tt, J = 11.9, 3.3 Hz, 1H), 3.3 (t, 4H), 4.68 (tt, J = 11.0, 4.3 Hz, 60% of 1H), 5.02 (m, 40% of 1H); ^{13}Cmr ($CDCl_3$) δ: 21.2, 21.3, 23.9, 24.0, 24.8, 26.2, 28.8, 30.2,

47.1, 47.2, 59.8, 59.9, 67.6, 71.4, 170.4, 170.5.

Chlorination of hydroxyalkanesulfinate salts in dichloromethane

(The preparation of the sultines and hydroxyalkanesulfinate salts is described fully in chapter 2)

(i) 3-Hydroxy-1-propanesulfonyl chloride (*1b*)

A solution of sodium hydroxide (40 mg, 1 mmol) in water (10 mL) was added to propane 1,3-sultine (*7b*) (106 mg, 1 mmol). After the resulting solution was allowed to stand at room temperature for 2 h, the water was removed under reduced pressure to yield *8b* (146 mg, ~100%); ir (KBr) ν_{max}: 3399 (vs), 2953 (vs), 1676 (s), 1466 (s), 1424 (s), 1308 (s), 1009 (s), 963 (s) cm^{-1}; ^{1}Hmr (D_2O) δ: 1.80 (quintet, 2H), 2.39 (t, 2H), 3.66 (t, 2H); ^{13}Cmr (D_2O) δ: 27.1, 59.9, 63.5. Chlorine was bubbled into dichloromethane (10 mL) until the solution turned yellowish-green. The solution was quickly added to *8b* (146 mg). The resulting suspension was immediately dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure to yield a (90:10) mixture of *2b* and *3b* in quantitative yield; ^{1}Hmr ($CDCl_3$) δ: 2.2 (s, 1H), 2.2-2.35 (quintet, 2H), 3.85 (t, 2H), 3.89 (t, 2H) plus small signals at 2.6-2.7 (quintet, 2H), 3.25 (t, 2H), 4.49 (t, 2H) assigned to 10% of *3b*; ^{13}Cmr ($CDCl_3$) δ: 27.2, 59.4, 62.4 (plus small signals at 23.6, 44.1, 68.9 due to *3b*).

A freshly prepared sample of *2b* (containing 10% *3b*) (100 mg) was immediately treated with excess acetyl chloride (2 mL) and the mixture allowed to stand at room temperature for 2 h and work up as before gave 3-acetoxy-1-propanesulfonyl chloride as a colourless oil (115 mg); ir (neat) ν_{max}: 1742 (vs), 1443 (s), 1375 (vs), 1244 (vs), 1165 (vs), 1044 (s), 739 (s), 698 (s), 637 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.09 (s, 3H), 2.31-2.45 (m, 2H), 3.81 (t, 2H), 4.24 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.7, 24.0, 60.9, 62.1, 170.4. The piperidide (*6b*) prepared from the acetoxysulfonyl

chloride mixture as before, followed by chromatography on silica gel, formed white crystals, mp 72-73 °C, from cyclohexane; ir (KBr) ν_{max}: 1738 (vs), 1389 (m), 1360 (m), 1277 (s), 1242 (vs), 1159 (s), 1140 (vs), 1069 (m), 1053 (s), 1037 (s), 939 (vs), 590 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.55-1.65 (m, 6H), 2.03 (s, 3H), 2.03-2.09 (m, 2H), 2.92 (t, 2H), 3.21 (t, 4H), 4.18 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 22.9, 23.8, 25.6, 46.1, 46.6, 62.3, 170.6. Calcd. exact mass for $C_{10}H_{19}O_4SN$: 249.1034. Found: 249.1035.

(ii) 4-Hydroxy-1-butanesulfonyl chloride (*2c*)

Reaction of butane 1,4-sultine (*7c*) (120 mg, 1 mmol), sodium hydroxide (40 mg) and water (5 mL) as above gave *8c* in quantitative yield (160 mg); ir (KBr) ν_{max}: 3382 (vs), 2945 (vs), 1655 (s), 1560 (s), 1456 (s), 1312 (s), 1011 (vs), 965 (vs) cm^{-1}; ^{1}Hmr (D_2O) δ: 1.57-1.65 (m, 4H), 2.37 (t, 2H), 3.61 (t, 2H); ^{13}Cmr (D_2O) δ: 20.8, 33.3, 62.9, 63.8. Chlorination of *8c* (160 mg) as above gave a mixture of *2c* and *3c* (87:13) in quantitative yield; the ^{1}H and ^{13}Cmr spectra are identical to those described earlier.

(iii) 5-Hydroxy-1-pentanesulfonyl chloride (*2d*)

Chlorination of sodium 5-hydroxy-1-pentanesulfinate (*8d*) (174 mg, 1 mmol) in dichloromethane (20 mL) as before, gave *2d* as an oil (186 mg, ~100%); ir (neat) ν_{max}: 3620 (m), 3520-3330 (br m), 2940 (s), 2865 (m), 1456 (m), 1370 (vs), 1264 (s), 1160 (vs), 1065 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.18-2.56 (m, 6H), 2.86 (s, 1H), 3.46-3.88 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 23.9, 24.1, 31.7, 62.1, 65.3.

The acetyl derivative, prepared as above, was a clear, slightly yellow oil; ir ($CHCl_3$) ν_{max}: 2950 (br m), 1730 (s), 1460 (br m), 1370 (s), 1245 (br s), 1160 (br s), 1060 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.48-1.78 (m, 4H), 1.95-2.14 (m, 2H), 2.05 (s, 3H), 3.73 (t, 2H), 4.09 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 24.0, 24.1, 27.9, 63.7,

65.1, 170.1.

The piperidide (*6d*) formed white crystal from cold hexane, mp 30.5–31 °C; ir ($CHCl_3$) ν_{max}: 2896 (m), 1731 (s), 1361 (m), 1336 (s), 1236 (br s), 1156 (s), 1136 (s), 1041 (m), 936 (m), 636 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.45–1.93 (m, 12H), 2.05 (s, 3H), 2.90 (t, 2H), 3.23 (t, 4H), 4.06 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 22.8, 23.8, 25.0, 25.7 (2C), 28.1, 46.6 (2C), 48.7, 63.9, 171.0

(iv) 6-Hydroxy-1-hexanesulfonyl chloride (*2e*)

To sodium 6-hydroxy-1-hexanesulfinate (*8e*) (188 mg, 1 mmol) was added to a solution of chlorine in dichloromethane (20 mL), workup as before gave *2e* (200 mg, ~100%) as a colourless oil; ir (neat) ν_{max}: 3600–3020 (br m), 2936 (s), 2855 (s), 1683 (m), 1453 (m), 1360 (vs), 1156 (vs), 1142 (m), 948 (m), 908 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3–1.8 (m, 6H), 1.8–2.3 (m, 2H), 3.6–3.8 (m, 6H); 5.13 (var s, 1H); ^{13}Cmr ($CDCl_3$) δ: 24.2, 25.1, 27.2, 32.0, 62.3, 65.3.

The acetyl derivative prepared, as described earlier, was a clear pale yellow oil; ir (neat) ν_{max}: 2950 (s), 2870 (m), 1720 (vs), 1360 (vs), 1240 (vs), 1150 (vs), 1040 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.30–1.67 (m, 6H), 1.90–2.05 (m, 2H), 1.98 (s, 3H), 3.63 (t, 2H), 4.00 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 24.1, 25.2, 27.0, 28.0, 64.0, 65.1, 171.2. Reaction of the above acetate with excess piperidine in dichloromethane gave an yellowish oil which, on recrystallization from cold pentane, gave *6e* as white needles, mp 41.5–43.0 °C; ir ($CHCl_3$) ν_{max}: 2940 (m), 2850 (m), 1730 (vs), 1334 (vs), 1320 (s), 1200–1278 (s br), 1159 (s), 1134 (s), 1050 (m), 935 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.35–1.92 (m, 10H), 2.05 (s, 3H), 2.90 (t, 2H), 3.23 (br t, 4H), 4.07 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.0, 23.0, 23.8, 25.5, 25.7, 28.2, 28.3, 46.7, 48.9, 64.2, 171.2.

(v) 3-Hydroxy-1-butanesulfonyl chloride (*11*)

Sodium 3-hydroxy-1-butanesulfinate (*9*) (320 mg, 2 mmol) was chlorinated in dichloromethane (30 mL) as described earlier, to give a (~85:15) mixture of *11* and *13* in quantitative yield; ^{1}Hmr ($CDCl_3$) δ: 1.3 (d, 3H), 1.95-2.40 (m, 2H), 2.45 (s, 1H), 3.75-4.10 (m, 3H) plus small signals at 1.53 (d, 3H), 2.19-2.34 (m, 1H), 2.58-2.75 (m, 1H), 3.20-3.15 (m, 2H), 4.70-4.90 (m, 1H) assigned to 15% of the sultone (*13*); ^{13}Cmr ($CDCl_3$) δ: 23.7, 33.1, 62.5, 65.4 plus small signals at 20.8, 31.2, 46.1, 79.5 due to the sultone (*13*).

A freshly prepared sample of *11* (containing some *13*) was converted to 3-acetoxy-1-butanesulfonyl chloride with excess acetyl chloride; ir (neat) ν_{max}: 2986 (m), 2938 (m), 2880 (w), 1736 (vs), 1449 (m), 1375 (vs), 1242 (vs), 1167 (vs), 1129 (s), 1063 (s), 1030 (s), 957 (m), 897 (w), 839 (w), 760 (s), 702 (w), 633 (w), 594 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.32 (d, 3H), 2.07 (s, 3H), 2.6-2.34 (m, 2H), 3.73 (t, 2H), 5.04 (sextet, 1H); ^{13}Cmr ($CDCl_3$) δ: 19.9, 21.1, 30.5, 61.7, 68.0, 170.3.

The piperidide (*15*) was prepared as described earlier; ir (neat) ν_{max}: 2938 (m), 2857 (m), 1327 (s), 1244 (vs), 1147 (s), 1055 (m), 943 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.17 (d, 3H), 1.5-1.7 (br m, 6H), 1.95-2.15 (m, 2H), 2.05 (s, 3H), 2.92 (m, 2H), 3.24 (t, 4H), 4.98 (sextet, 1H); ^{13}Cmr ($CDCl_3$) δ: 19.9, 21.2, 23.8, 25.7, 29.5, 45.6, 46.6, 69.2, 170.5. Calcd. exact mass for $C_{11}H_{21}O_4SN$: 263.1191. Found: 263.1196.

(vi) 4-Hydroxy-2-butanesulfonyl chloride (*12*)

4-Hydroxy-2-butanesulfinate (*10*) (320 mg, 2 mmol) on similar chlorination in dichloromethane (30 ml) gave a (~85:15) mixture of *12* and *14* in quantitative yield; ^{1}Hmr ($CDCl_3$) δ: 1.65 (t, 3H), 2.1 (br s, 1H), 2.2-2.4 (m, 2H), 3.9-4.0 (m, 1H), 4.3-4.6 (m, 2H) plus small signals at 1.49 (d, 3H), 2.2-2.4 (m, 1H), 2.6-2.8 (m, 1H), 3.39 (sextet, 1H), 4.3-4.5 (m, 2H) assigned to 15% of the sultone (*14*); ^{13}Cmr

($CDCl_3$) δ: 15.2, 33.8, 58.7, 68.7 (plus small signals at 13.7, 31.0, 50.6, 66.8 due to *14*).

The acetyl derivative prepared as above, ir (neat) ν_{max}: 2973 (m), 2907 (m), 1742 (vs), 1458 (m), 1368 (vs), 1239 (vs), 1163 (vs), 1134 (m), 1057 (s), 711 (m), 590 (s), 565 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.65 (d, 3H), 1.67–2.07 (m, 1H), 2.09 (s, 3H), 2.5–2.7 (m, 1H), 3.7–3.9 (m, 1H), 4.15–4.4 (m, 2H); ^{13}Cmr ($CDCl_3$) δ: 15.1, 20.8, 30.4, 60.2, 68.6, 170.7.

The above 4-acetoxy-2-butanesulfonyl chloride was converted to the piperidide (*16*) with excess piperidine in dichloromethane ir (neat) ν_{max}: 2940 (s), 2859 (m), 1740 (vs), 1645 (m), 1323 (vs), 1235 (vs), 1157 (vs), 1051 (s), 737 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.35 (d, 3H), 1.6 (br m, 6H), 1.7–1.9 (m, 1H), 2.06 (s, 3H), 2.2–2.14 (m, 1H), 3.05–3.25 (m, 1H), 3.25–3.4 (br m, 4H), 4.06–4.3 (m, 2H); ^{13}Cmr ($CDCl_3$) δ: 14.1, 20.9, 24.0, 26.2, 29.8, 47.2, 54.5, 61.3, 170.8. Calcd. exact mass for $C_{11}H_{21}O_4SN$: 263.1191. Found: 263.1193.

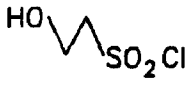
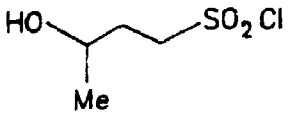
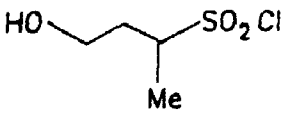
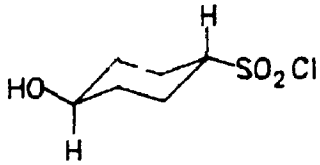
ω-Acetoxy-1-alkanesulfonyl chlorides from the diacetates of ω-mercapto-1-alkanols

Chlorine was bubbled into water (100 mL) cooled in an ice-bath until the solution turned yellow-green. The diacetate (~2 mmol) was added and the mixture stirred vigorously for 5 min and then worked up by thorough extraction with dichloromethane, drying of the extract (magnesium sulfate), and evaporation of the solvent. The acetoxysulfonyl chlorides listed in Table 1.2 were thus obtained in >90% yields. These acetoxysulfonyl chlorides were converted to the piperidide derivatives (*6*) (see Table 1.3).

Chlorination of 6-mercapto-1-hexanol (*1e*) in dichloromethane

Chlorine was bubbled into a vigorously stirred solution of 6-mercapto-1-hexanol (128 mg, 0.94 mmol) in a mixture of dichloromethane (1 mL) and water (0.1 mL)

TABLE 1.1 Chemical shifts[a] for the ω-hydroxy-1-alkanesulfonyl Chlorides from $CDCl_3$ solutions at room temperature.

SN	STRUCTURE	^{1}Hmr(δ)	^{13}Cmr(δ)
2a		2.98(s,1H),3.98(t,2H), 4.28(t,2H)	56.9,67.6
2b		2.2(s,1H),2.2–2.35 (quint,2H),3.85(t,2H), 3.89(t,2H)	27.2,59.4 62.4
2c		1.7–1.9(m,2H),2.15–2.25 (m,2H),3.73(t,2H),3.79 (t,2H),4.3(br s,1H)	21.6,30.1, 61.8,65.4
2d		1.18–2.56(m,6H),2.86 (s,1H),3.65(t,2H), 3.71(t,2H)	23.9,24.1 31.7,62.1, 65.3
2e		1.3–1.8(m,6H),1.8–2.3 (m,2H),3.63,(t,2H), 3.70(t,2H),5.13 (s,1H)	24.2,25.1 27.2,32.0, 62.3,65.3
12		1.3(d,3H),1.95–2.4(m,2H), 2.45(s,1H),3.75–4.1(m,3H)	23.7,33.1, 62.5,65.4
13		1.65(d,3H),2.1(brs,1H) 2.2–2.4(m,2H),3.9–4.0 (m,1H),4.3–4.6(m,2H)	15.2,33.8, 58.7,68.7
18		1.3–1.4(m,2H),1.76–1.98 (m,2H),1.82(s,1H),2.16–2.3 (m,2H),2.42–2.56(m,2H), 3.51(t of t, J=11.8,3.7Hz, 1H),3.7(t of t, J=10.8, 4.3Hz,1H)	25.3,33.2, 68.4,73.1

a) Values for –OH singlets are variable from one sample to other.

TABLE 1.2 Chemical shifts for the ω-acetoxy-1-alkanesulfonyl chlorides from $CDCl_3$ solutions at room temperature.

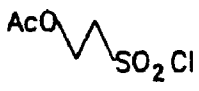
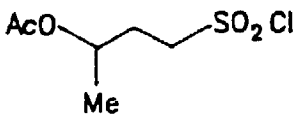
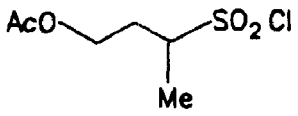
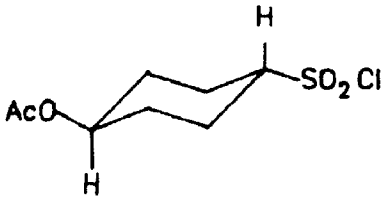
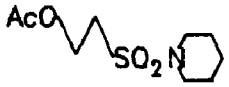
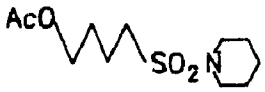
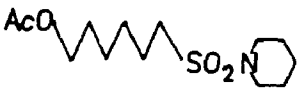
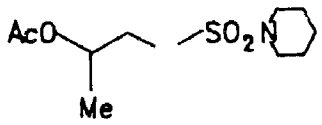
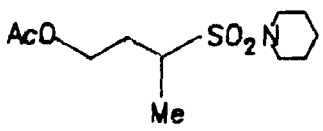
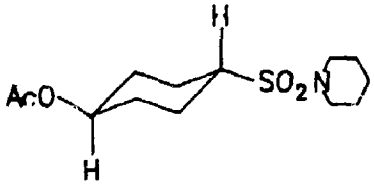
STRUCTURE	^{1} Hmr(δ)	^{13} Cmr(δ)
	2.02(s,3H),3.97(t,2H), 4.54(t,2H)	20.6,57.5, 65.6,170.7
	2.09(s,3H),2.45–2.30 (m,2H),3.81(t,2H),4.24 (t,2H)	20.7,24.0, 60.9,62.1, 170.4
	1.03–1.90(m,2H),2.07 (s,3H),2.07–2.14(m,2H) 3.77(t,2H),4.13(t,2H)	20.6,21.1, 26.3,62.8, 64.5,170.6
	1.48–1.78(m,4H),1.95– 2.14(m,4H),2.05(s,3H), 3.73(t,2H),4.09(t,2H)	20.9,24.0, 24.1,27.9, 63.7,65.1, 170.1
	1.30–1.67(m,6H),1.90– 1.05(m,2H),1.98(s,3H), 3.63(t,2H),4.0(t,2H)	20.9,24.1, 25.2,27.0, 28.0,64.0, 65.1,171.2
	1.32(d,3H),2.07(s,3H), 2.26–2.34(m,2H),3.73 (t,2H),5.04(sextet,1H)	19.9,21.1, 30.5,61.7, 68.0,170.3
	1.65(d,3H),1.67–2.07, (m,1H),2.09(s,3H),2.50– 2.70(m,1H),3.70–3.90 (m,1H),4.15–4.40(m,2H)	15.1,20.8, 30.4,60.2, 68.6,170.7
	1.35–1.55(m,2H),1.84– 2.06(m,2H),1.98(s,3H), 2.15–2.24(m,2H),2.40– 2.51(m,2H),3.49(tt,J=11.8, 3.7Hz,1H),4.69(tt,J=10.8 4.3Hz,1H)	21.1,25.2, 29.6,70.3, 72.6,170.3

TABLE 1.3 Chemical shifts for the ω-acetoxy-1-alkanesulfonylpiperidides from $CDCl_3$ solutions at room temperature.

SN	STRUCTURE	^{1}Hmr(δ)	^{13}Cmr(δ)
6a		1.59–1.73(m,6H),2.10(s,3H), 3.24(t,2H),3.26(t,4H),4.45 (t,2H)	20.9,23.8, 25.7,46.5, 48.4,58.1, 169.9
6b		1.55–165(m,6H),2.03(s,3H), 2.03–2.29(m,2H),2.29(t,2H) 3.21(t,4H),4.18(t,2H)	20.9,22.9, 23.8,25.6, 46.1,46.6, 62.3,170.6
6c		1.46–1.69(m,10H),1.90(s,3H), 2.77(t,2H),3.05–3.10(t,4H), 3.94(t,2H)	20.0,20.9, 23.8,25.7, 27.5,46.6, 48.5,63.4 170.0
6d		1.45–1.93(m,12H),2.05(s,3H), 2.90(t,2H),3.23(t,4H),4.06 (t,2H)	20.9,22.8, 23.8,25.0, 25.7,28.1, 46.6,48.7, 63.9,171.0
6e		1.35–1.92(m,14H),2.05(s,3H), 2.90(t,2H),3.23(t,4H),4.07 (t,2H)	21.0,23.0, 23.8,25.5, 25.7,28.2 28.3,46.7, 48.9,64.2, 171.2
15		1.17(d,3H),1.5–1.7(m,6H), 1.95–2.15(m,2H),2.05(s,3H), 2.92(m,2H),3.24(t,4H),4.98 (sextet,1H)	20.0,21.2, 23.8,25.7, 29.5,45.6, 46.6,69.2, 170.5
16		1.35(d,3H),1.60(m,6H),1.7– 1.9(m,1H),2.06(s,3H),2.2– 2.4(m,1H),3.05–3.25(m,1H), 3.25–3.40(m,4H),4.06– 4.30(m,2H)	14.1,20.9, 24.0,26.2, 29.8,47.2, 54.5,61.3, 170.8
21		1.25–2.30(m,14H),2.04and 2.08(s(2),3H),2.87(tt,J=11.9, 3.3Hz,1H),3.30(t,4H),4.68 (tt,J=11.0,4.3Hz,60%of1H),5.02 (quintet,40%of1H)	21.2,21.3, 23.9,24.0, 24.8,26.2, 28.8,30.2, 47.1,47.2, 59.8,59.9, 67.6,71.4, 170.5

until chlorine absorption ceased. Workup gave a clear oil, which from the following spectra is believed to be mainly 6-chloro-1-hexanesulfonyl chloride plus some 6-hydroxy-1-hexanesulfonyl chloride (*2e*); ir (neat) ν_{max}: 2940 (s), 2930 (s), 2860 (m), 1460 (m), 1370 (vs), 1160 (vs) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.46-2.25 (m, 8H), 3.56 (t, 2H), 3.69 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.2, 26.2, 26.9, 32.0, 44.6, 65.2 (plus small peaks at 24.3, 25.2, 27.4, 32.1, 62.5, 65.3 ascribable to 20% of *3e*), Krebes *et al.*[23] report δ values 65.5 and 44.7 for C-1 and C-6, respectively, of 6-chloro-1-hexanesulfonyl chloride.

Reaction of the hydroxyalkanesulfonyl chlorides (*2b*) and (*2c*) with triethylamine

To a mixture (50 mg) of 4-hydroxy-1-butanesulfonyl chloride (*2c*) (85%) and butane 1,4-sultone (*3c*) (15%) was added a solution of triethylamine (~40 mg) in ethanol-*d* (1 mL). After 5 min the ethanol-*d* and excess amine were removed under reduced pressure; the ^{1}Hmr spectrum of the crude product indicated a mixture of ethyl 4-hydroxy-1-butanesulfonate, butane 1,4-sultone (*3c*), and triethylammonium cation, with the first two in the ratio of 77:23 (from the integrals of the signals at δ 4.30 and 4.56) and with the Et_3NH^+ peaks around δ 3.2 obscuring the signals due to the protons α to the sulfonyl groups. Workup by washing with aqueous HCl and water gave an oil (45 mg), the ^{1}Hmr and ^{13}Cmr spectra ($CDCl_3$) showed signals due to *3c* (at 1.86 (m), 2.26 (m), 3.17 (t), 4.56 (t) and 22.8, 23.6, 48.2, 73.9 ppm, respectively) and peaks at 1.72 (m), 1.96 (m), 3.17 (t, superimposed on that due to *3c*), 3.70 (t), 4.30 (q), and 15.1, 20.2, 30.7, 44.9 (1:1:1, t, J = 23 Hz, plus superimposed singlet at 50.1), 61.8, 65.9 ppm, clearly assignable to the ethyl ester with about 70% $CHDSO_2$ (and 30% CH_2SO_2); the sulfur-bearing carbon in *3c* (at 48.2) showed no sign of splitting due to the presence of deuterium. In an experiment the same except for the use of ordinary ethanol, the nmr peaks were similar except that the CH_2SO_2 signal appeared as a singlet at 50.1 ppm.

3-Hydroxy-1-propanesulfonyl chloride (**2b**) (90%) plus **3b** (10%) (total 50 mg) was treated with EtOD and Et_3N and worked up as above to give an oil (40 mg); the ^{1}Hmr and ^{13}Cmr spectra of which (except for small solvent peaks) were identical to those of authentic **3b**. A similar reaction of **2b** (90%) (50 mg) in $CDCl_3$ instead of EtOD gave only **3b** (35 mg), again as shown by the ^{1}H and ^{13}C nmr spectra.

1.4 REFERENCES AND FOOTNOTES

1. J.F. King and J.H. Hillhouse, *J. Chem. Soc., Chem. Commun.*, 454 (1979).
2. J.F. King and J.H. Hillhouse, *Can. J. Chem.*, ***61***, 1583 (1983).
3. J.F. King, S. Skonieczny, K.C. Khemani, and J.B. Stothers, *J. Am. Chem. Soc.*, ***105***, 6514 (1983).
4. E.J. Goethals and M. Verzele, *Bull. Soc. Chim. Belges*, ***74***, 21 (1965).
5. B. Helferich and H. Grunert, *Ber.*, ***74***, 1531 (1941).
6 J.W. Griffin and D.H. Hey, *J. Chem. Soc.*, 3334 (1952).
7. J.H. Helberger and H. Lantermann, *Liebigs Ann. Chem.*, ***586***, 158 (1954).
8. A.J. Kirby, *Adv. Phys. Org. Chem.*, ***17***, 183 (1980).
9. See, for example, J.F. King and K.C. Khemani, *Can. J. Chem.*, ***63***, 619 (1985).
10. N.K. Sharma, F. de Reinach-Hirtzbach, and T. Durst, *Can. J. Chem.*, ***55***, 44 (1977).
11. Typical frequencies for RSO_2^- are 1020 and 980 cm^{-1}: L.J. Bellamy, "Organic Sulfur Compounds," Vol. *1*, N. Kharasch, Editor, Pergamon Press,Oxford, 1961, pp 47-56.
12. G.E. Wil ı, Jr., *Tetrahedron*, ***38***, 2597 (1982).
13. In principle, the products of the oxygen-labelling experiments starting with 3-mercapto-1-propanol (***1b***) could be accounted for by cleavage of ***201*** to ***210*** (dotted arrow in Scheme 1.3). Labelling experiments starting with propane sultine (***211***, $n = 3$) clearly require the ***311*** $\longrightarrow$ ***320*** route,[3] and hence it is simpler to postulate that this is also the path followed by the thiol (***1***) or the thiouronium salt (***4***). In accord with the higher likelihood of C–O cleavage from ***311*** than from ***201*** is the reactivity pattern observed with the carbon analogues of the chloro-cations: R_2S^+—OCH_3, the analogue of ***201***, normally reacts with nucleophiles (e.g. hydroxide or alkoxides) with S–O cleavage,[26]

though C–O cleavage has been observed.[27] $R_2S^+O—OCH_3$, the analogue of ***311***, however, is a highly reactive species which rapidly *O*-methylates such substrates as water, dimethyl sulfoxide, dimethyl sulfone and cyclopentanone.[28]

14. Also known as "effective molarities" (EM), and defined as $C_{eff} = k_1/k_2$ where k_1 is the first order rate constant for the cyclization and k_2 the second order rate constant for an appropriate model reaction.

15. E.T. Kaiser, *Acc. Chem. Res.*, ***3***, 145 (1970).

16. J.F. King, K.C. Khemani, S. Skonieczny, and N.C. Payne, *Review of Heteroatom Chemistry,* Vol. ***1***, 1988, pp 80.

17. J.F. King, M.R. Webster, N. Chiba, J.K. Allen, K.J.M. Parker, R. Rathore, and S. Skonieczny, *Phosphorus and Sulfur,* ***31***, 161 (1987).

18. J.B. Cloke and F.J. Pilgrim, *J. Am. Chem. Soc.*, ***61***, 2667 (1939).

19. C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, ***75***, 3704 (1953).

20. *Cf.* J F. Dellaria, Jr., C. Nordeen, and L.R. Sweat, *Syn. Comm.*, ***16***, 1043 (1986).

21. J.S. Harding and L.N. Owen, *J. Chem. Soc.*, 1528 (1954).

22. M.J. McGarrity, Ph.D. Thesis, University of Western Ontario, London, Canada, 1984, p 204; for the analogous preparation of (***5b***) see J.F. King, S.M. Loosmore, M. Aslam, J.D. Lock, and M.J. McGarrity, *J. Am. Chem. Soc.*, ***104***, 7108 (1982).

23. S. Krebes, W. Pritzkow, W. Schmidt-Renner,and K. Schmitz, *J. Prakt. Chem.*, ***322***, 291 (1980).

24. K.N. Campbell and A.H. Sommers, *Org. Syn., Coll. Vol.* ***3***, 446 (1965).

25. M.E. Synerholm, *J. Am. Chem. Soc.*, ***69***, 2581 (1947).

26. For a review see J.P. Marino, *Topics Sulfur Chem.*, ***1***, 1 (1976), esp. pp 73–75.

27. C.R. Johnson and W.G. Phillips, *J. Org. Chem.*, ***32***, 1926 (1967).

28. M.M. Abdel-Malik, P.A.W. Dean and J.F. King, *Can. J. Chem.*, ***62***, 69 (1984).

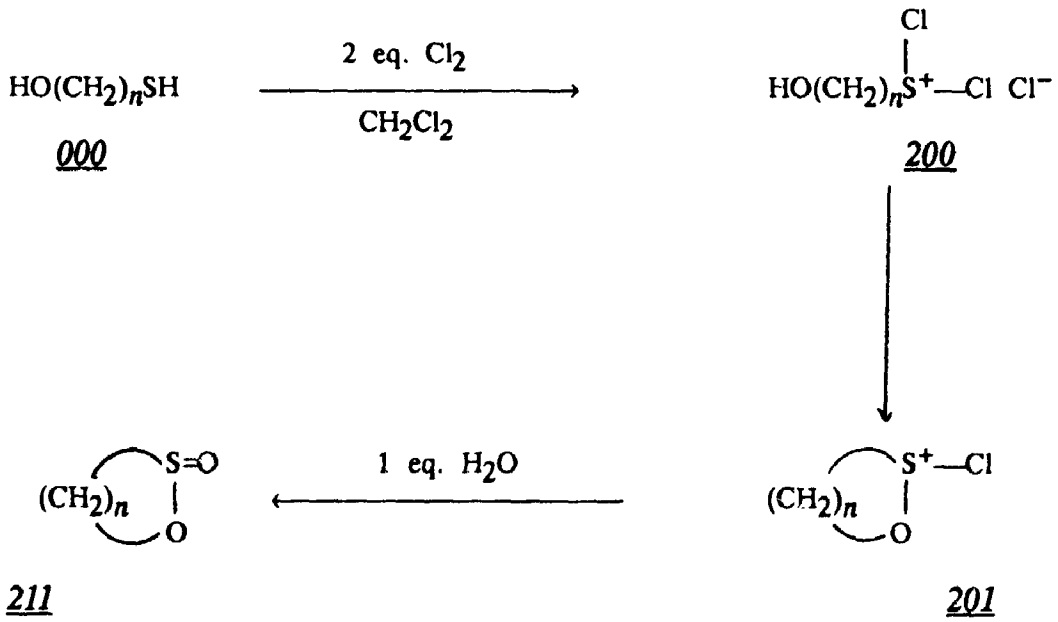
CHAPTER 2

PREPARATION OF SIMPLE SULTINES AND HYDROXYALKANESULFINATE SALTS

2.1 INTRODUCTION

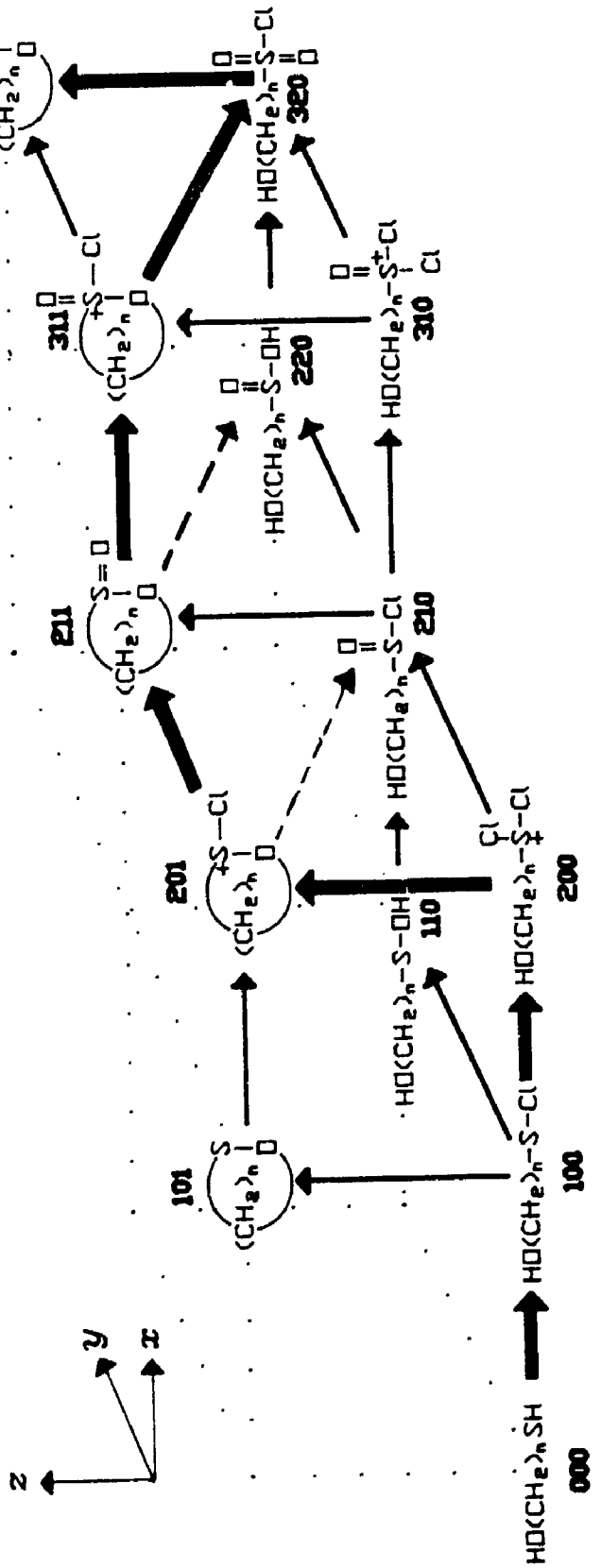
Chlorination of α,ω-hydroxythiols (***000***) in water, as discussed in chapter 1, was shown to give ω-hydroxy-1-alkanesulfonyl chlorides (***320***), or, when n = 3 or 4, also the ω-chloro-1-alkanesulfonyl chloride, $Cl(CH_2)_nSO_2Cl$, and the corresponding sultone (***321***). The path shown by the heavy arrows in the three dimensional grid pattern in Scheme 2.1 (see chapter 1 for details) has been proposed as a likely route for the latter reaction.

A prediction of this mechanism is that, if the chlorination proceeds readily and in the same way in a non-polar medium, the addition of two equivalents of chlorine should give the acyclic chlorosulfonium ion (***200***). In those cases with a relatively high effective concentration for the cyclization ***200*** → ***201***, the reaction with 2 mol of Cl_2 would give the cyclic chlorosulfoxonium ion (***201***), and this product in turn with an equivalent of water should yield the cyclic sulfinate ester (sultine) (***211***).



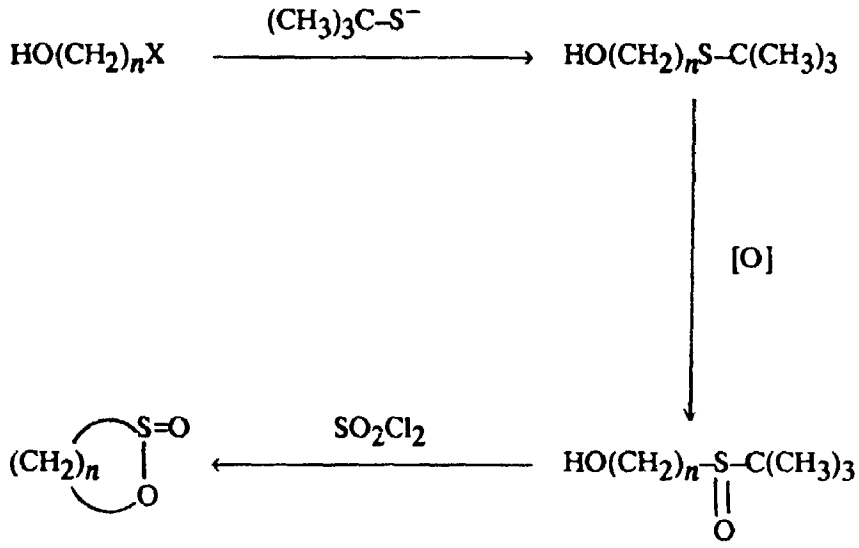
SCHEME 2.2

Verification of the above prediction would supply evidence for the proposed


HO(CH2)nSH
000
HO(CH2)n-S-Cl
100
HO(CH2)n-S-OH
110
HO(CH2)n-S-Cl
200
HO(CH2)n-S-OH
220
HO(CH2)n-S-Cl
210
HO(CH2)n-S-Cl
310
HO(CH2)n-S-Cl
320
101
201
211
311
321
z
y
x

SCHEME 2.1

mechanism of chlorination of α,ω-hydroxythiols and also provide a simple preparation of sultines (Scheme 2.2).

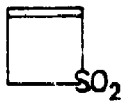
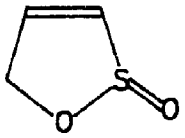
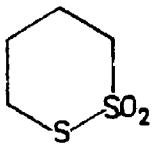
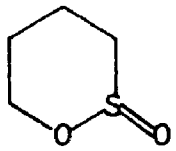
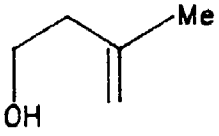
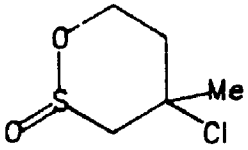
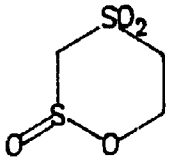
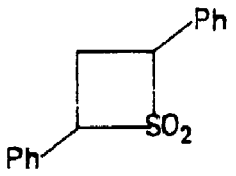
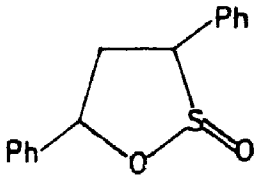
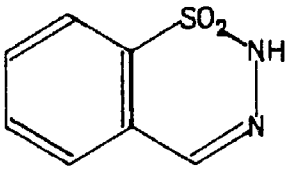
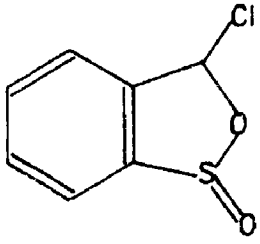
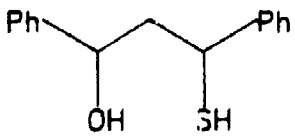
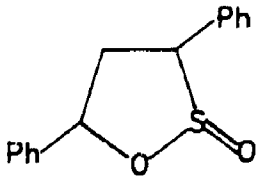


SCHEME 2.3

Sharma, de Reinach-Hirtzbach and Durst have reported[1] a method for synthesizing a variety of sultines; this procedure involves a number of steps including controlled oxidation of sulfide to sulfoxide (see Scheme 2.3). These authors list the other routes that have been used to prepare specific sultines (shown in Table 2.1). Most of these procedures are not suitable as general methods for preparing sultines, either because they involve expensive reagents or drastic conditions, or else suffer from low yields or are not adequately general.

The chlorination of α,ω-hydroxythiols in nonaqueous medium has now been explored and is described in this chapter. This method provides a very simple way of preparing the 5- and 6-membered ring sultines and hydroxyalkanesulfinate salts, making these, in effect, as available as the hydroxythiols. Sultines are, of course, analogues of lactones and sultones, though much less well known. Their importance as chemical intermediates has not been fully established, but ready availability is often a prerequisite of finding whether species are useful or not.

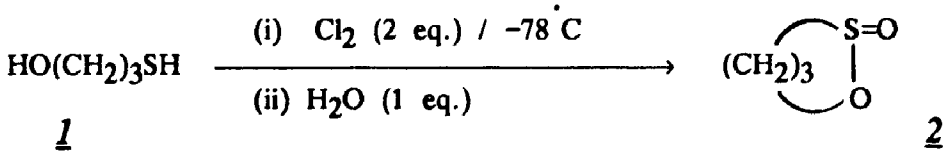
TABLE 2.1[1,2]

HYDROXYTHIOL	REACTION CONDITIONS	SULTINE
	Δ /600°C	
	$P(NEt_2)_3$	
	$SOCl_2$	
	(i) $Ba(OH)_2/H_2O$ (ii) H_2SO_4	
	t-BuOMgBr	
	Cl_2 /CH_2Cl_2	
	SO_2Cl_2 /HOAc	

2.2 RESULTS AND DISCUSSION

The precursors, 3-mercapto-1-propanol (*1*), 4-mercapto-1-butanol (*3*), 5-mercapto-1-pentanol (*5a*), and 6-mercapto-1-hexanol (*5b*) required for the synthesis of unsubstituted 5- to 8-membered ring sultines are readily available, (see the experimental part of chapter 1). A solution of Cl_2 (2 mol for each mol of thiol) in dichloromethane was added to a stirred solution of thiol *1* in dichloromethane at -78°C. The reaction mixture was stirred for 5 min and then water (1 mol for each mol of thiol) was added. The flask was removed from the cooling bath; the mixture was stirred as it came to room temperature, and then dried with magnesium sulfate. Evaporation of the solvent and distillation of the crude product gave the sultine *2* in 90% yield.

The above process can be summarized as follows:



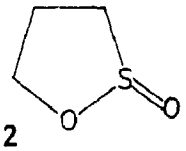
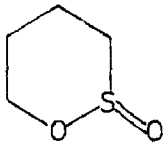
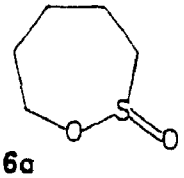
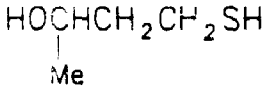
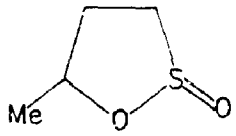
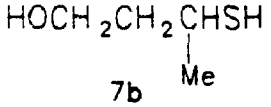
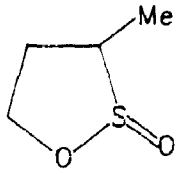
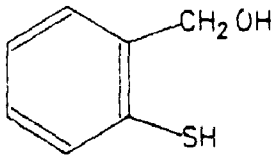
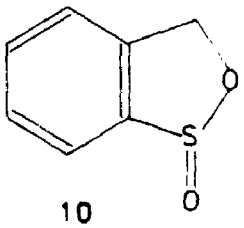
1 *2*

When carried out as a one-pot, two-step process the reaction gave good yields of 5- and 6-membered sultines shown in Table 2.2.

The 5-carbon thiol, $HO(CH_2)_5SH$, (*5a*) gave a low yield of the sultine *6a* (Table 2.2) on distillation; the crude product (mostly apparent polymer plus some sultine) on reaction with aqueous sodium hydroxide gave sodium 5-hydroxy-1-pentane sulfinate (> 85%), which in turn with lorine in dichloromethane yielded 5-hydroxy-1-pentanesulfonyl chloride, which was characterized by comparing its ^{1}Hmr, ^{13}Cmr anc ir spectra with those of an authentic specimen.[3]

TABLE 2.2

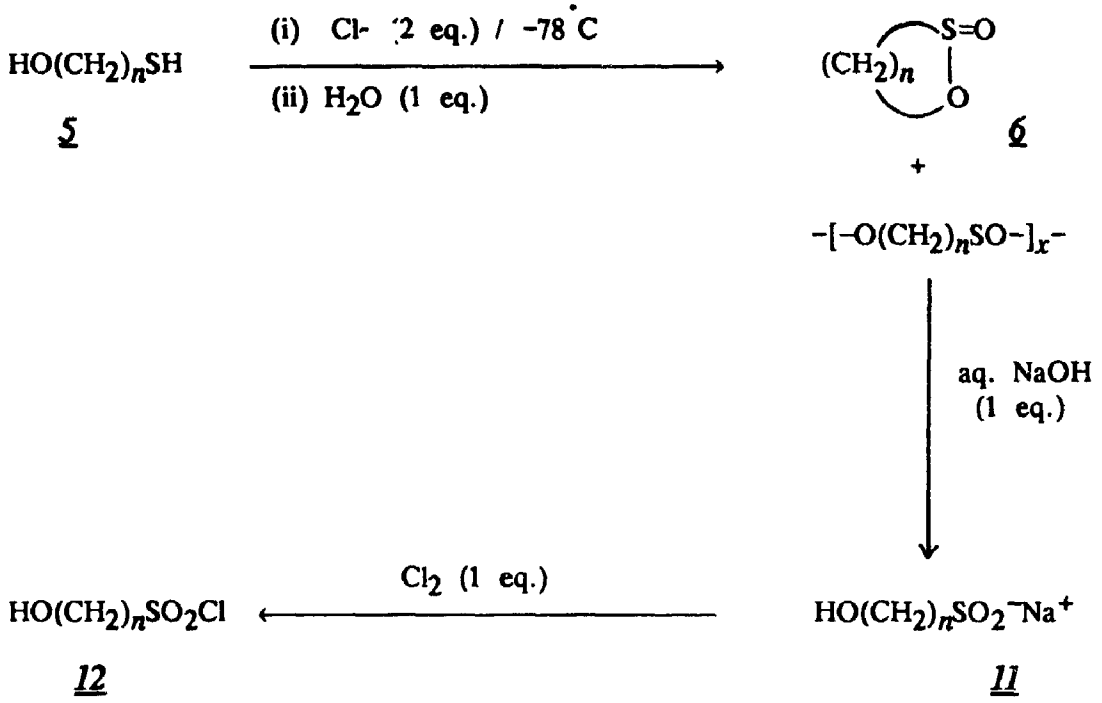
One–pot, two–stage chlorination of hydroxythiols.

SN	HYDROXYTHIOL	SULTINE	YIELD (%)[a]
1	$HO(CH_2)_3SH$ **1**	 **2**	90
2	$HO(CH_2)_4SH$ **3**	 **4**	85
3	$HO(CH_2)_5SH$ **5a**	 **6a**	10[b]
4	 **7a**	 **8a**	70[c]
5	 **7b**	 **8b**	70[c]
6	 **9**	 **10**	80

a) of distilled product

b) The major product was undistillable, presumably $-[O(CH_2)_5SO]_x-$

c) mixture of diastereomers



(a) n = 5; (b) n = 6

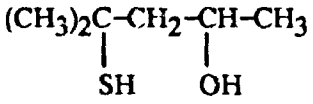
SCHEME 2.4

Similarly, the 6-carbon thiol, $HO(CH_2)_6SH$ (*5b*), gave a product which showed only weak signals in the δ 3.8-4.2 range expected for the sultine, but displayed strong approximate triplets at δ 3.7 and 2.7 appropriate to an acyclic sulfinic ester.[4] Alkaline hydrolysis of the crude product gave sodium 6-hydroxy-1-hexanesulfinate, $HO(CH_2)_6SO_2^-Na^+$ (*11b*) (> 85%), as shown by: (a) the presence of only six strong peaks in the ^{13}Cmr spectrum, (b) an appropriate ^1Hmr spectrum, (c) formation of 6-hydroxy-1-hexanesulfonyl chloride, $HO(CH_2)_6SO_2Cl$ (*12b*) on brief treatment with Cl_2.

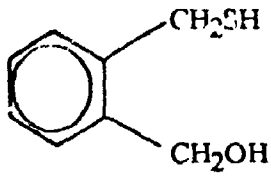
A polymeric ester structure for the chlorination hydrolysis product, $-[O-(CH_2)_nSO]_x-$ (where n = 5 or 6), is consistent with these observations, and, in fact, is to be expected when the effective concentration of the cyclization *200* → *201* is less than the actual concentration of RS^+Cl_2 and ROH groups, and hence coupling is favoured over cyclization.

To illustrate the versatility of the sultine synthesis, three substituted sultines (*8a*, *8b* and *10*) were prepared in good yields (see Table 2.2) from corresponding mercapto alcohols (*7a*, *7b* and *9*). The mercapto alcohols *7a* and *7b* were prepared from the addition of thioacetic acid to α,β-unsaturated carbonyl compound[5] (*e.g.* methyl vinyl ketone for *7a* and crotonaldehyde for *7b*) followed by sodium borohydride reduction and subsequent treatment with aqueous sodium hydroxide as shown in Scheme 2.5.

Sultines *8a* and *8b* were characterized, as described in chapter 1, by conversion to the hydroxysulfinate salts (*14*) which on treatment with Cl_2 gave a mixture of short lived hydroxysulfonyl chlorides (*15*) and sultones (*16*). Hydroxysulfonyl chloride *15* was converted to acetoxypiperidide *19* which was compared with authentic sample (prepared by chlorination of *17* to give *18* followed by reaction with piperidine to afford *19*). Sultines *8a* and *8b* were also oxidized to the sultones (*16a* and *16b*) using *m*-chloroperbenzoic acid (see Scheme 2.5).

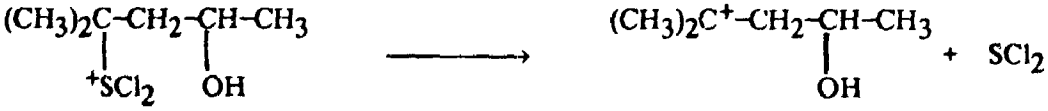


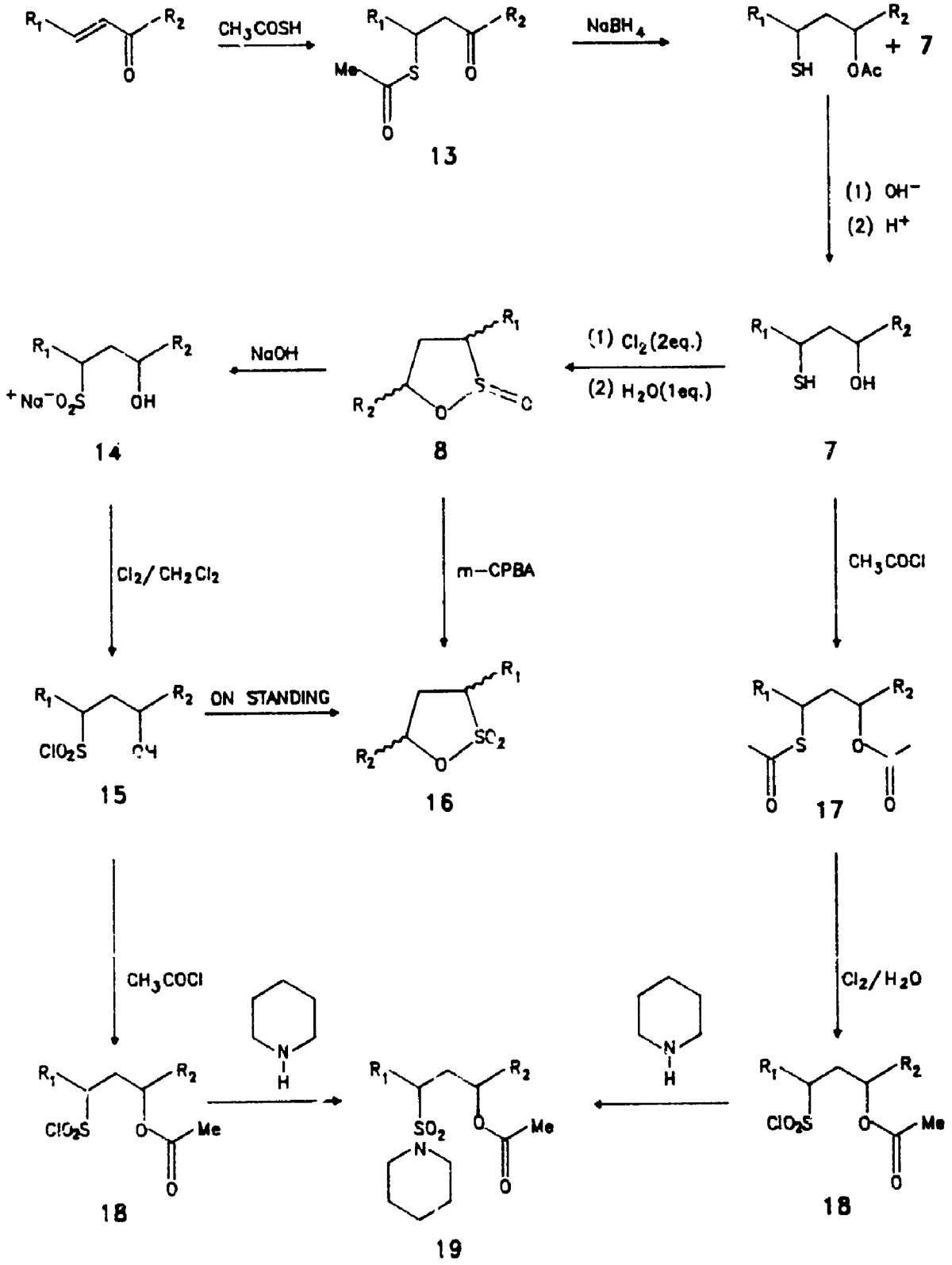
20



21

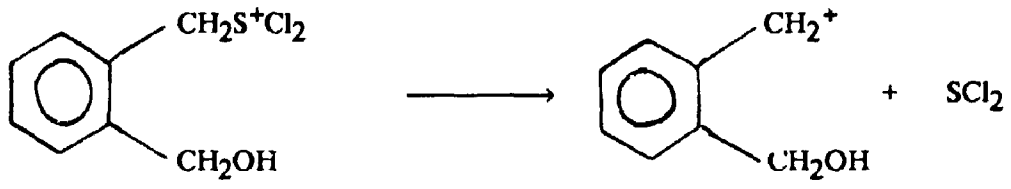
Hydroxythiols *20* and *21*, however, gave intractable material with no sign of any cyclic or polymeric sulfinic ester. We infer that the normal reaction is precluded when *200* is constituted so that the loss of SCl_2 may lead to a relatively stable (tertiary or benzylic) cation.





a) R_1 = H, R_2 = Me
b) R_1 = Me, R_2 = H

SCHEME 2.5



Although this synthesis has limitations, it provides not only strong support for the mechanism shown in Scheme 2.1, but also an especially convenient route to hydroxyalkanesulfinate salts and the simplest sultines.

A comment on the spectra of sultines

In the case of the sultines described above, one helpful spectroscopic method for determining sultine structures has been infrared spectroscopy. Sultines characteristically show a strong absorption band between 1120 and 1149 cm^{-1} due to stretching vibrations of the sulfur–oxygen "double" bond.[6]

A second diagnostically useful feature of sultine chemistry is the complexity of their ^{1}Hmr spectra (see Figure 2.4–2.6). This arises because of the magnetic anisotropy associated with chiral sulfinyl sulfur which deshields the proton *cis* to sulfinyl oxygen.[7,8] The result of this effect for the examples given has been to shift the *cis*–proton down field 0.40–0.70 ppm from the *trans* proton. Deshielding seems to be greatest for methylene group β to the sulfinyl group. The complexity of the sultine ^{1}Hmr spectra coupled with simplicity of the ^{13}Cmr spectra can be used as a visual test for this reaction because, in contrast, the starting materials and other products of the chlorination have relatively simple spectra (for example, see Figure 2.1, 2.2, and 2.3)

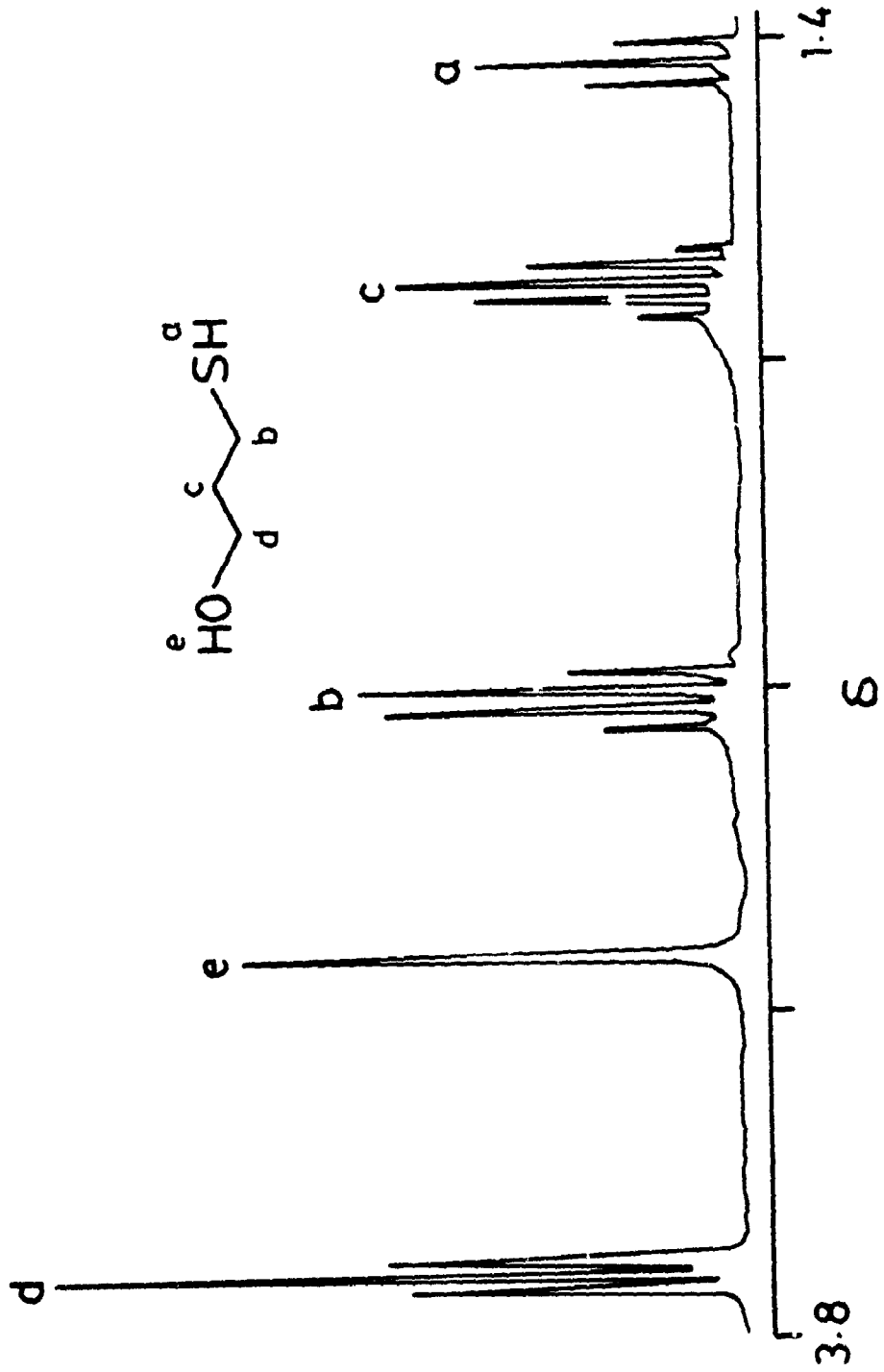


Figure 2.1: The ^{1}Hmr spectrum of 3-mercapto-1-propanol (1) in $CDCl_3$ at 20°C.

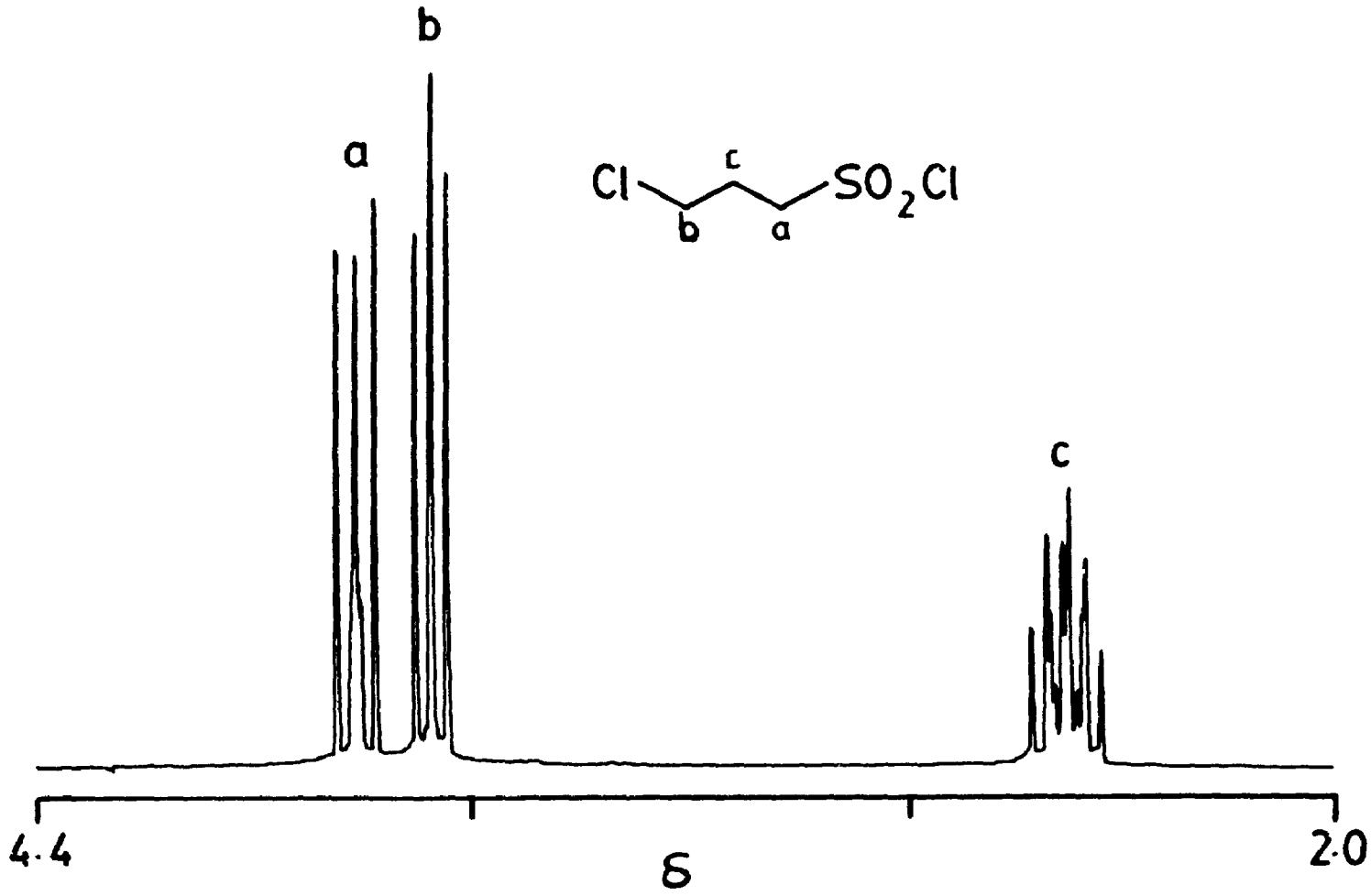


Figure 2.2: The ^{1}Hmr spectrum of 3-chloro-1-propanesulfonyl chloride in $CDCl_3$ at 20°C.

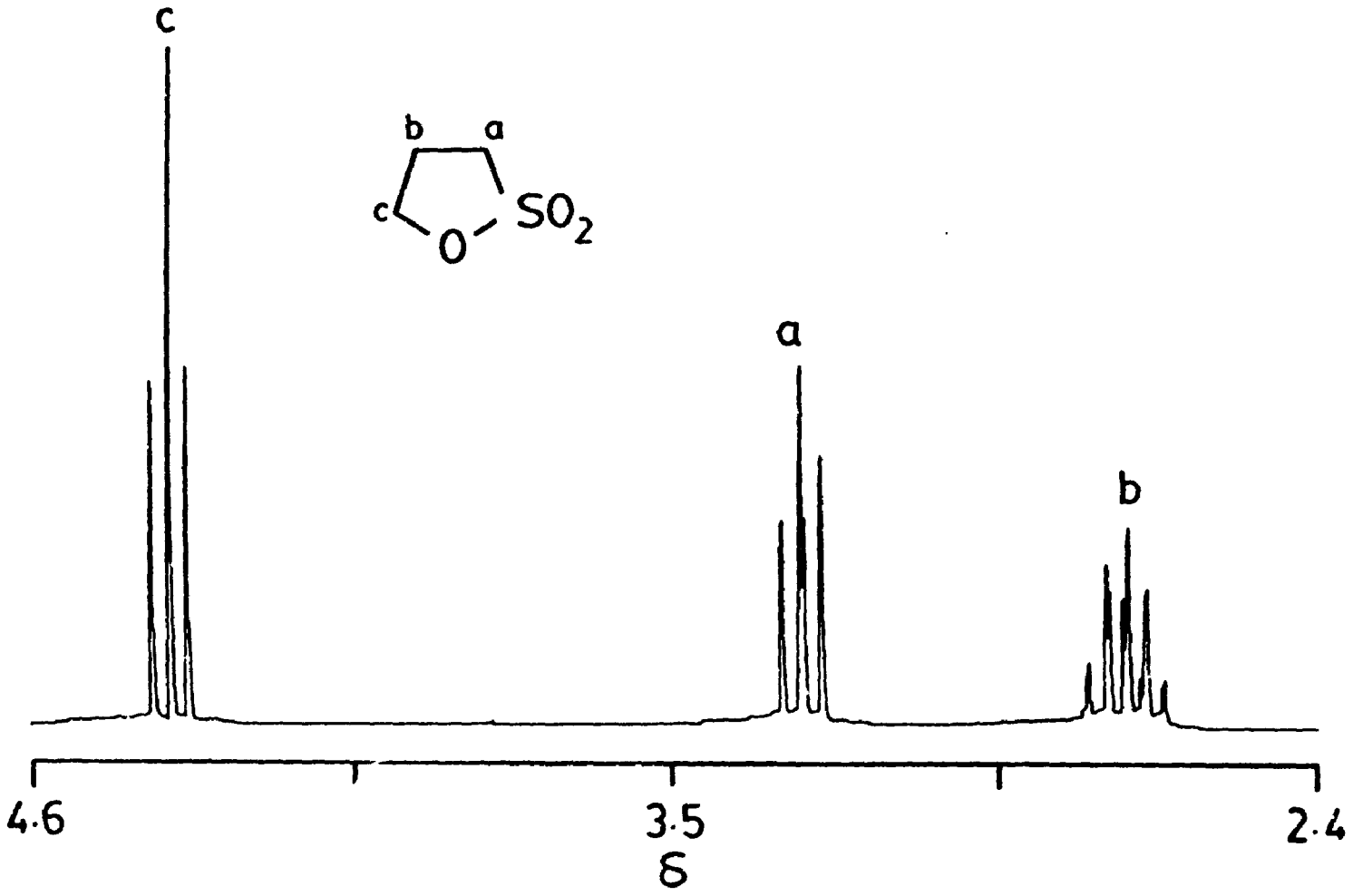


Figure 2.3: The ^{1}Hmr spectrum of 1,2-oxathiolane 2,2-dioxide (propane 1,3-sultone) in $CDCl_3$ at 20°C.

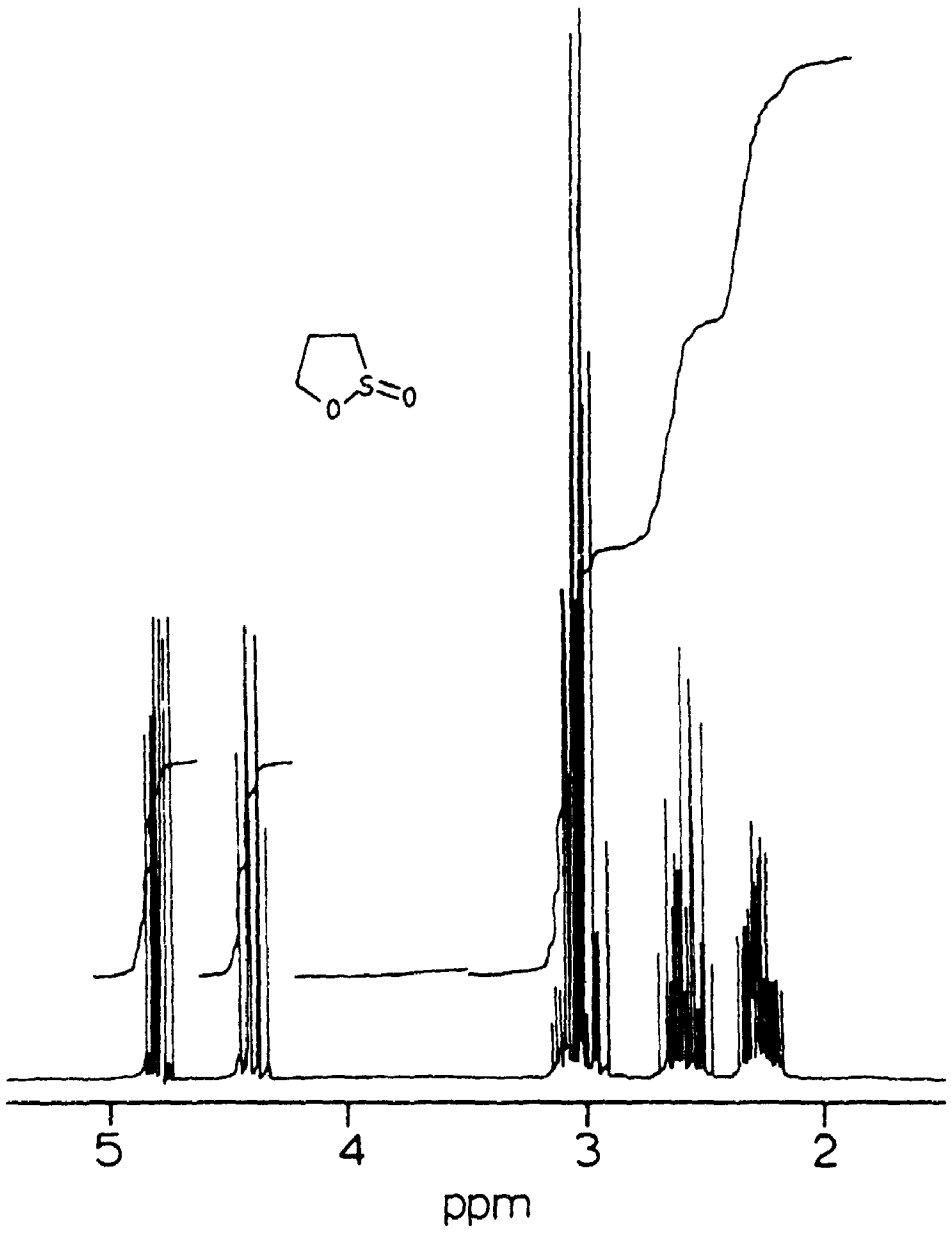


Figure 2.4: The ^{1}Hmr spectrum of 1,2-oxathiolane 2-oxide (2) in $CDCl_3$ at 20°C.

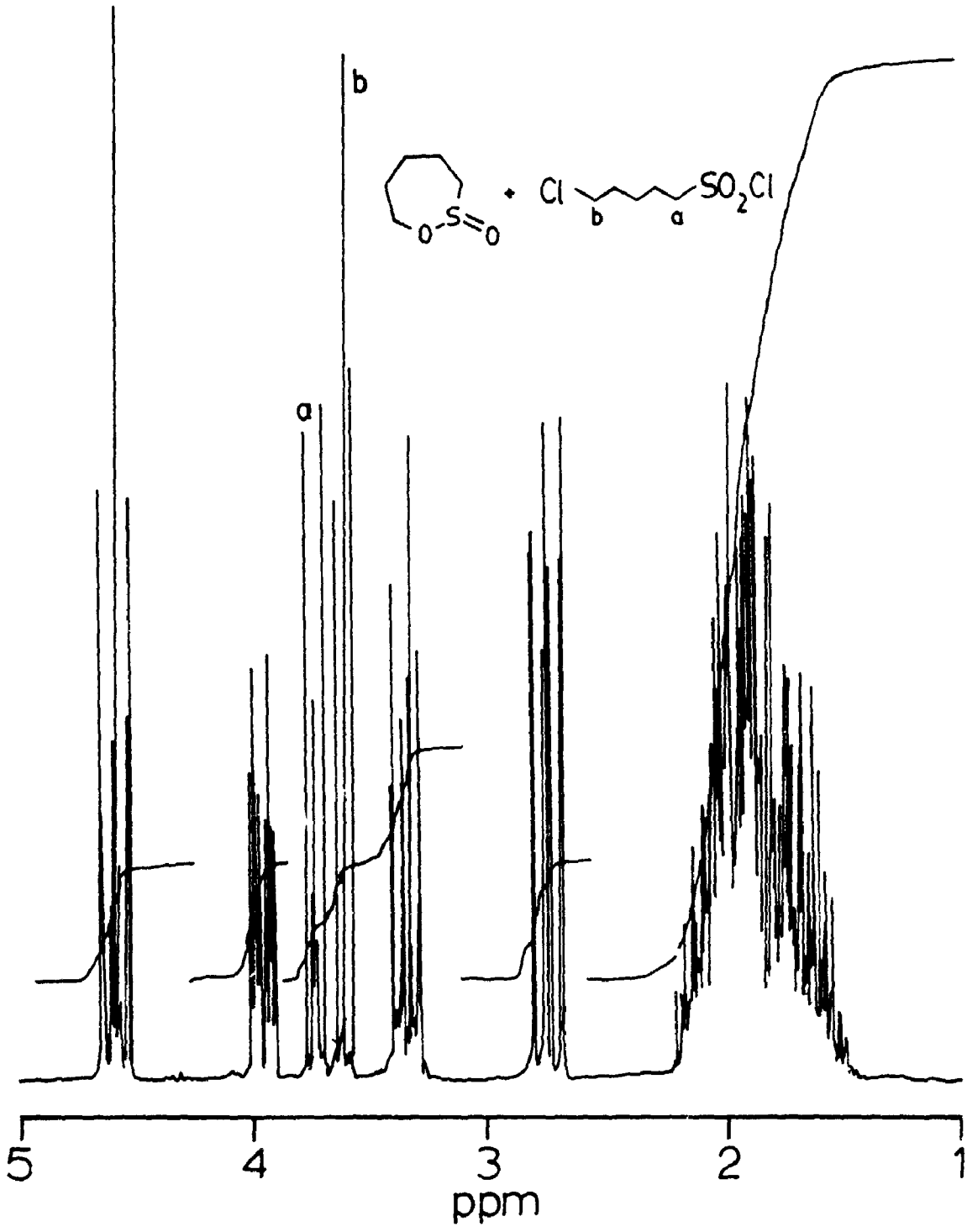


Figure 2.5: The ^{1}Hmr spectrum of 1,2-oxathiepane 2-oxide (*6a*) (contaminated with small amount of 5-chloro-1-pentanesulfonyl chloride) in $CDCl_3$ at 20°C.

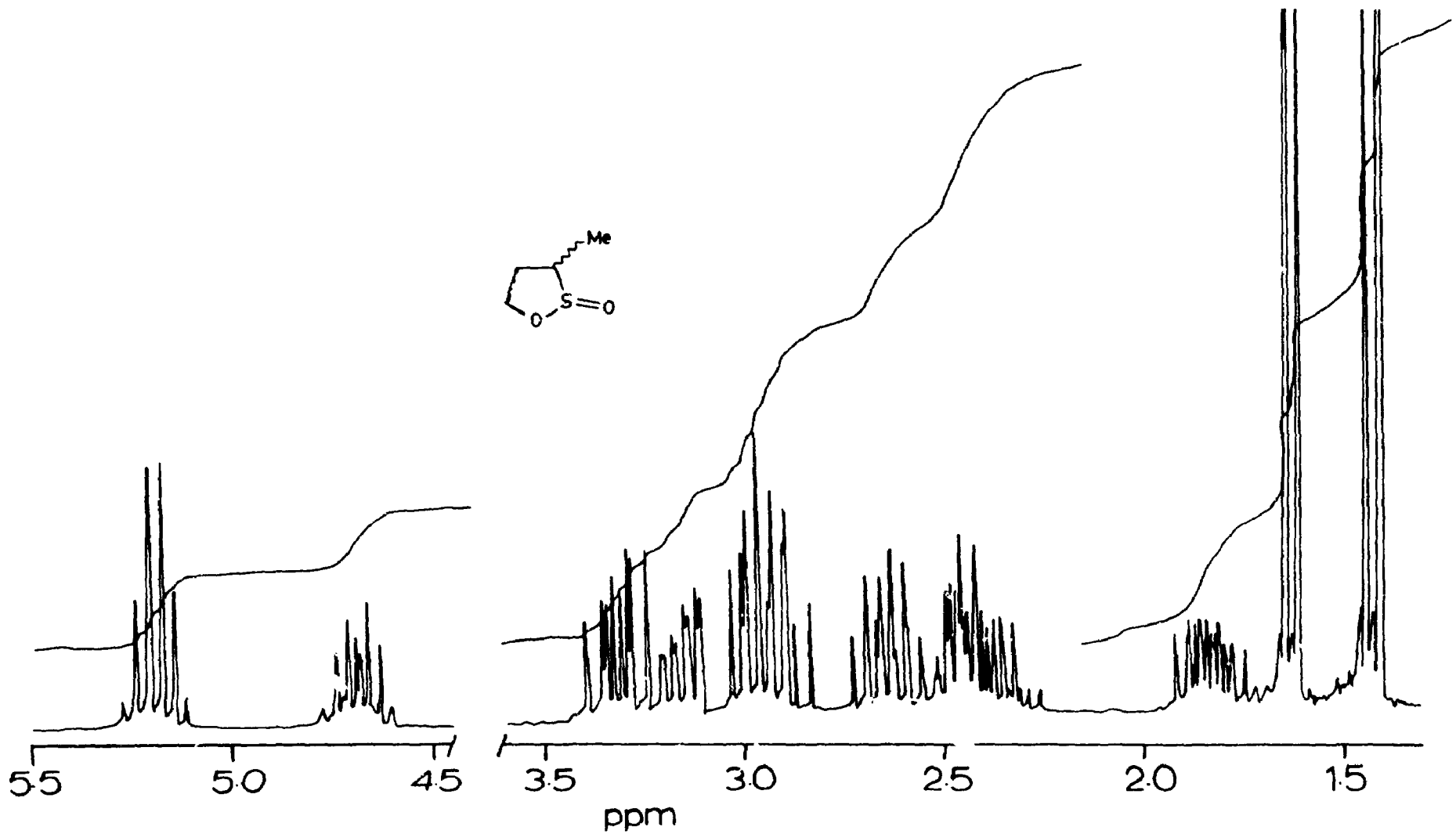


Figure 2.6: The ^{1}Hmr spectrum of 5-methyl-1,2-oxathiolane 2-oxide (*8a*) in $CDCl_3$ at 20°C.

2.3 EXPERIMENTAL

The general procedure and instrumentation are as described in the experimental part of chapter 1, except for the following points.

Methylene chloride was dried by distillation over phosphorus pentoxide. Thiosalicylic acid, methyl vinyl ketone (MVK), crotonaldehyde and mesityl oxide were purchased from Aldrich chemical company; sulfuryl chloride was purchased from J.T. Baker Chemical Company, and used immediately after distillation. Chlorine gas (HP grade) was purchased from Union Carbide Company.

Mercaptoalkanols

The synthesis of following mercaptoalkanols is described in chapter 1: (i) 3-Mercapto-1-propanol (*1*) (see Figure 2.1 for ^{1}Hmr spectrum), (ii) 4-Mercapto-1-butanol (*3*), (iii) 5-Mercapto-1-pentanol (*5a*), and, (iv) 6-Mercapto-1-hexanol (*5b*).

(v) 4-Mercapto-2-butanol (*7a*)

A solution of methyl vinyl ketone (MVK) (13.3 g, 190 mmol) and thioacetic acid (14.5 g, 190 mmol) in benzene (50 mL) and petroleum ether (50 mL) was refluxed overnight,[5] evaporation of the solvent and distillation gave 4-thioacetoxy-2-butanone (*13a*) (22 g, 80%; ir (neat) ν_{max}: 2926 (m), 1717 (vs), 1690 (vs), 1418 (s), 1358 (s), 1136 (m), 1109 (s), 1071 (m), 955 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.16 (s, 3H), 2.32 (s, 3H), 2.79 (t, 2H), 3.09 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 22.9, 29.8, 30.4, 43.2, 170.4, 195.7). This product on reaction with sodium borohydride (5.7 g, 150 mmol) in methanol (100 mL) at 0 °C for 12 h afforded a product, which from its ^{1}H and ^{13}Cmr spectra was evidently a mixture (1:1) of 4-mercapto-2-butyl

acetate and 4-mercapto-2-butanol (*7a*); ^{1}Hmr ($CDCl_3$) δ: 0 1.20 (d, 3H), 2.24 (d, 3H), 1.47 (q, 2H, two SH), 1.65-2.0 (m, 4H), 2.03 (s, 3H), 2.46-2.7 (m, 4H), 3.2 (br s, 1H, OH), 3.85-4.0 (m, 1H), 4.94-5.10 (m, 1H); ^{13}Cmr ($CDCl_3$) δ: 19.8, 20.5, 21.1, 23.5, 40.2, 43.0, 65.9, 69.3, 170.6. This on treatment with 10% aqueous sodium hydroxide (100 mL) under nitrogen for 4 h at 100°C gave *7a* as colourless oil (11.1 g, 70%); ir (neat) ν_{max}: 3360 (s), 2969 (s), 2930 (s), 2554 (w), 1422 (m), 1375 (m), 1279 (m), 1124 (m), 970 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.21 (d, 3H), 1.43 (t, 1H, SH), 1.68-1.80 (m, 2H), 2.65 (q, 2H), 2.72 (br s, 1H, OH), 3.95 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.2, 23.5, 42.8, 66.4.

The mercaptobutanol (*7a*) was converted to the diacetate by adding 2.2 equivalents of acetyl chloride dropwise and with stirring, then heating the mixture at 50°C for 0.5 h; distillation gave the diacetate *17a* as a colourless oil; ir (neat) ν_{max}: 2980 (m), 2940 (m), 1736 (vs), 1694 (vs), 1443 (s), 1370 (s), 1244 (vs), 1132 (s), 1057 (s), 954 (m), 632 (vs) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.24 (d, 3H), 1.78-1.90 (m, 2H), 2.06 (s, 3H), 2.33 (s, 3H), 2.89 (t, 2H), 4.88-5.05 (m, 1H); ^{13}Cmr ($CDCl_3$) δ: 19.9, 21.3, 25.1, 30.6, 35.7, 69.5, 170.7, 195.6. Calcd. exact mass for $C_8H_{14}O_3S$: 190.0663. Found 190.0663.

(vi) 3-Mercapto-1-butanol (*7b*)

3-Mercapto-1-butanol (*7b*) was prepared from crotonaldehyde (5 g, 71 mmol) and thioacetic acid (5.4 g, 71 mmol) as described above. The following were thus obtained. 3-Acetylthio-1-butanal (*13b*) colourless oil; ir (neat) ν_{max}: 2973 (m), 2930 (m), 2832 (m), 2734 (m), 1690 (vs), 1725 (vs), 1456 (s), 1419 (s), 1354 (s), 1115 (vs), 1053 (s), 953 (s), 633 (vs), 596 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.38 (d, 3H), 2.74 (t of d, 2H), 3.99 (sextet, 1H), 9.70 (t, 1H); ^{13}Cmr ($CDCl_3$) δ: 20.6, 30.2, 33.1, 49.5, 194.5, 199.4. 3-Mercapto-1-butanol (*7b*), colourless oil; ir (neat) ν_{max}: 3347 (vs), 2959 (vs), 2552 (w), 1449 (m), 1377 (m), 1049 (s), 992 (m), 878

(m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.39 (d, 3H), 1.57 (d, 1H, SH), 1.63- 1.90 (m, 2H), 2.98 (br s, 1H, OH), 2.99-3.13 (m, 1H), 3.76 (sym m, 2H); ^{13}Cmr ($CDCl_3$) δ: 26.1, 32.4, 43.1, 60.4. 3-Acetylthio-1-butyl acetate (*17b*), colourless oil; ir (neat) ν_{max}: 2965 (m), 2928 (m), 1742 (vs), 1692 (vs), 1455 (m), 1366 (s), 1239 (vs), 1115 (s), 1046 (vs), 955 (s), 631 (vs), 606 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.34 (d, 3H), 1.85-1.95 (m, 2H), 2.05 (s, 3H), 2.31 (s, 3H), 3.65 (sextet, 1H), 4.12 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.4, 20.9, 30.2, 34.7, 35.7, 61.3, 170.3, 194.5. Calcd. exact mass for $C_8H_{14}O_3S$: 190.0663. Found: 190.0662.

(vii) 4-Mercapto-4-methyl-2-pentanol (*20*)

Compound *20* was synthesized from mesityl oxide (9.8 g, 100 mmol) and thioacetic acid (7.6 g, 100 mmol) as described above. The following were thus obtained. 4-Acetylthio-4-methylpentane-2-one, a pale yellow oil; ir (neat) ν_{max}: 2967 (m), 2928 (m), 1717 (s), 1684 (s), 1358 (m), 1111 (s), 949 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.52 (s, 6H), 2.13 (s, 3H), 2.24 (s, 3H), 3.10 (s, 2H); ^{13}Cmr ($CDCl_3$) δ: 17.2, 31.0, 31.4, 48.3, 51.1, 196.6, 206.0.

4-Mercapto-4-methyl-2-pentanol, a colourless oil; ir (neat) ν_{max}: 3409 (br s), 2967 (vs) 2926 (s), 2552 (w), 2363 (w), 1458 (m), 1370 (s), 1142 (vs), 1049 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.21 (d, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.62-1.76 (m, 2H), 1.92 (s, 1H, SH), 3.25 (s, 1H, OH), 4.04-4.19 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 24.8, 31.9, 34.7, 43.7, 54.1, 65.4. Calcd. exact mass for $C_6H_{14}OS$: 134.0765. Found: 134.0767.

(viii) 2-(Mercaptomethyl)phenylmethanol (*21*)

Thiophthalic anhydride was prepared in 55% yield from phthalic anhydride and sodium sulfide by the method of Reissert and Holle,[9] the malodorous compound was obtained as yellow needles, mp 113-114 °C (lit[9] 114 °C); ir (CH_2Cl_2) ν_{max}: 3056 (w),

2984 (w), 1791 (w) 1738 (w), 1701 (s), 1659 (w), 1594 (w), 1417 (w), 955 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 7.8–8.1 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 123.6, 134.9, 138.4, 189.4. This compound (3.28 g, 20 mmol), under nitrogen, in anhydrous tetrahydrofuran (20 mL) was added dropwise over 10 min to a stirred refluxing suspension of lithium aluminium hydride (2.28 g, 60 mmol) in anhydrous tetrahydrofuran (100 mL). The mixture was refluxed for an additional 4 h, cooled in an ice-bath and treated dropwise with water (5 mL). The gray paste was poured into ice-cold 4 N sulfuric acid (100 mL), then extracted with ether (4 x 50 mL). The ether extract was dried with magnesium sulfate and the solvent evaporated to dryness. Further azeotropic drying with benzene (2 x 20 mL) gave a clear, foul-smelling oil (2.6 g). T.l.c. with 1:2 ethyl acetate-petroleum ether (bp 30–60 °C) on silica gel (E. Merck, silica gel 60-F-254, 0.25 mm thickness) showed two spots (R_f = 0.35 and 0.05). Using the flash chromatography technique,[10] the crude product was purified with 1:2 ethyl acetate-petroleum ether (bp 30–60 °C). The compound giving the T.l.c. spot of R_f = 0.05 was shown, by comparison with authentic sample,[11] to be 2-(hydroxymethyl)phenylmethanol. The second compound (R_f = 0.35) was the required 2-(mercaptomethyl)phenylmethanol (*21*), bp 80–82 °C (0.0005 Torr); ir ($CHCl_3$) ν_{max}: 3600 (s), 3445 (br m), 3069 (w), 3007 (s), 2948 (w), 2887 (w), 2579 (w), 1490 (w), 1452 (m), 1385 (w), 1240 (w), 1099 (w), 1003 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.81 (t, 1H), 3.20 (br t, 1H), 3.72 (d, 2H), 4.62 (d, 2H), 7.19–7.29 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 25.7, 62.3, 127.3, 128.1, 128.7, 129.0, 137.8, 138.9

(ix) 2-Mercaptophenylmethanol (*9*)

Under nitrogen, thiosalicylic acid (3.08 g, 20 mmol) in tetrahydrofuran (20 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (2 g) in anhydrous tetrahydrofuran (100 mL). The mixture was then refluxed for an additional 6 h. The workup as before afforded a yellow liquid which on distillation gave

pure 2 (1.6 g, 60%); ^{1}Hmr ($CDCl_3$) δ: 2.5 (s, 1H), 3.6 (s, 1H), 4.6 (d, 2H), 7.0-7.5 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 63.7, 126.0, 128.1, 128.4, 129.9, 131.0, 138.4.

One pot, two-stage, controlled chlorination of mercaptoalkanols

(i) Chlorination of 3-mercapto-1-propanol (1):

1,2-Oxathiolane 2-oxide (2)

General Procedure: A solution of chlorine (1.42 g, 20 mmol, as determined by iodimetric titration) in dichloromethane was added dropwise to a stirred solution of 3-mercapto-1-propanol (1) (920 mg, 10 mmol) in dry dichloromethane (200 mL) at -78°C (acetone-dry-ice bath). The reaction mixture was stirred for 5 min and then water (180 μL, 10 mmol) added from a micro-syringe. The flask was removed from cooling bath; the mixture was stirred as it came to room temperature (~10 min), and then dried with magnesium sulfate. Evaporation of the solvent and distillation of the crude product gave the sultine (2) in 90% yield (954 mg), ir (neat) ν_{max}: 2980 (m), 2905 (m), 1449 (w), 1416 (w), 1269 (m), 1125 (vs), 1032 (s), 938 (s), 897 (m), 849 (vs), 843 (s), 733 (s); ^{1}Hmr ($CDCl_3$) δ: 2.18-2.36 (m, 1H), 2.51-2.70 (m, 1H), 2.92-3.14 (m, 2H), 4.35-4.47 (m, 1H), 4.76-4.87 (m, 1H) (see Figure 2.4); ^{13}Cmr ($CDCl_3$) δ: 22.9, 58.3, 74.8.

As an alternative procedure, addition of two equivalents of sulfuryl chloride (2.9 g, 20 mmol) in dichloromethane (25 mL), instead of chlorine, to a cooled (-78°C) solution of 1 (920 mg, 10 mmol) in dry dichloromethane (200 mL) and workup as above, gave, in our hands, similar or slightly poorer yields of the 2.

The hydrolysis was carried out by stirring the sultine (106 mg, 1 mmol) with sodium hydroxide (40 mg, 1 mmol) in water (10 mL) for 1 h. The aqueous phase was washed with dichloromethane; evaporation of the solvent under reduced pressure gave the sodium 3-hydroxy-1-propanesulfinate in quantitative yield (146 mg), for spectra see the experimental part in chapter 1.

The salt was chlorinated by addition of chlorine (1 eq.) in dichloromethane with stirring at room temperature. Immediate filtration to remove the sodium chloride, and evaporation of the solvent under reduced pressure to yield a (90:10) mixture of 3-hydroxy-1-propanesulfonyl chloride and propane 1,3-sultone in quantitative yield (158 mg). The 3-hydroxy-1-propanesulfonyl chloride cyclized on standing, to propane 1,3-sultone (see Figure 2.3 for ^{1}Hmr spectrum), for other spectra see the experimental part on chapter 1.

A small portion of the sultine (2) (100 mg) was oxidized to propane 1,3-sultone with *m*-chloroperbenzoic acid (*m*-CPBA) in ether.[5] The ir, ^{1}H and ^{13}Cmr spectra were identical to those obtained from the above sample.

(ii) Chlorination of 4-mercapto-1-butanol (3):

1,2-Oxathiane 2-oxide (4)

4-Mercapto-1-butanol (3) (1.06 g, 10 mmol) was chlorinated in dichloromethane (200 mL) with chlorine (1.42 g, 20 mmol) as above to give the sultine (4) in 85% yield (1.02 g); ir (CCl_4) ν_{max}: 3040 (w), 2940 (vs), 2850 (s), 1433 (m), 1255 (s), 1160 (w), 1120 (vs), 1035 (m), 990 (s), 940 (m), 900 (vs), 880 (vs), 820 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.64-2.10 (m, 3H), 2.39-2.64 (m, 2H), 2.78-2.92 (m, 1H), 3.74-3.84 (m, 1H), 4.50-4.64 (m, 1H); ^{13}Cmr ($CDCl_3$) δ: 13.4, 24.4, 49.3, 58.5.

Treatment of 4 (120 mg, 1 mmol) with aqueous sodium hydroxide yielded sodium 4-hydroxy-1-butanesulfinate (160 mg, ~100%),[3] which on reaction with chlorine in dichloromethane gave a mixture (87:13) of the short-lived 4-hydroxy-1-butanesulfonyl chloride and butane 1,4-sultone. The hydroxy-sulfonyl chloride cyclized to butane 1,4-sultone on standing, for spectra see the experimental part in chapter 1. Sultine 4 (100 mg) was also oxidized to butane 1,4-sultone with *m*-CPBA in ether.

(iii) Chlorination of 5-mercapto-1-pentanol (*5a*):

1,2-Oxathiepane 2-oxide (*6a*)

As above, 5-mercapto-1-pentanol (*5a*) (240 mg, 2 mmol) and chlorine (284 mg, 4 mmol) in dichloromethane (250 mL) gave, on distillation, a low yield of sultine (*6a*) (27 mg, 10 %), (contaminated with ~20% of 5-chloro-1-pentanesulfonyl chloride); ^{1}Hmr ($CDCl_3$) δ: 1.50-2.17 (m, 6H), 2.64-2.78 (m, 1H), 3.25-3.37 (m, 1H), 3.86-4.0 (m, 1H), 4.49-4.62 (m, 1H) (plus small signals at 1.5-2.2 (m, 6H), 3.58 (t, 2H), 3.7 (t, 2H) due to 5-chloro-1-pentanesulfonyl chloride) (see Figure 2.5); ^{13}Cmr ($CDCl_3$) δ: 20.8, 28.7, 29.0, 59.7, 62.9 (plus small signals at 23.7, 24.9, 31.7, 44.1, 65.0 due to 5-chloro-1-pentanesulfonyl chloride).

The undistilled crude product from another run (mostly apparent polymer plus some sultine) with aqueous NaOH gave sodium 5-hydroxy-1-pentanesulfinate (*11a*) (228 mg, 85%) as a white solid; ir (KBr) ν_{max}: 3231 (br s), 2930 (s), 1665 (m), 1453 (s), 1308 (w), 1217 (m), 1019 (vs) cm^{-1}; ^{1}Hmr (D_2O) δ: 1.4-1.9 (m, 6H), 2.35 (t, 2H), 3.60 (t, 2H); ^{13}Cmr (D_2O) δ: 24.2, 27.2, 33.7, 63.3, 64.1.

The salt (*11a*) (100 mg) was chlorinated with chlorine in dichloromethane (20 mL) to give 5-hydroxy-1-pentanesulfonyl chloride (*12a*), which was characterized by comparison with the authentic sample[3] and converted to 5-acetoxy-1-pentanesulfonyl piperidide (for spectra, see the experimental part in chapter 1).

(iv) Chlorination of 6-mercapto-1-hexanol (*5b*)

6-Mercapto-1-hexanol (*5b*) (200 mg, 1.49 mg) and chlorine (212 mg, 2.98 mmol) in dichloromethane (200 mL) was reacted, as above, to afford a viscous liquid, which on distillation gave no sultine (*6b*). The crude product from another run (apparently polymer) was treated with aqueous sodium hydroxide for 1 h. The aqueous phase was washed with dichloromethane and the water stripped under reduced pressure to give the sodium 6-hydroxy-1-hexanesulfinate (*11b*) (240 mg, ~85%);

^{1}Hmr (D_2O) δ: 1.3-1.8 (m, 8H), 2.32 (t, 2H), 3.56 (t, 2H); ^{13}Cmr (D_2O) δ: 24.3, 27.4, 30.5, 33.7, 63.3, 64.3.

The salt (*11b*) was chlorinated by addition of chlorine in dichloromethane (25 mL) at room temperature. The sodium chloride was filtered, and evaporation of the solvent gave 6-hydroxy-1-hexanesulfonyl chloride (*12b*), which was characterized by comparison with the authentic specimen and converted to the crystalline derivative 6-acetoxy-1-hexane-sulfonyl piperidide, and compared with the authentic sample[3] (for spectra, see experimental in chapter 1).

(v) Chlorination of 4-mercapto-2-butanol (*7a*):

5-Methyl-1,2-oxathiolane 2-oxide (*8a*)

4-Mercapto-2-butanol (*7a*) (212 mg, 2 mmol) and chlorine (284 mg, 4 mmol) in dichloromethane (100 mL), as above, gave the 5-methyl-1,2-oxathiolane 2-oxide (*8a*) as a mixture of diastereomers in 70% yield (158 mg); ir (neat) ν_{max}: 2980 (w), 2936 (s), 1223 (m), 1125 (vs), 1037 (m), 897 (s), 828 (vs), 721 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.42 (d, 3H), 1.62 (d, 3H), 1.74-1.91 (m, 1H), 2.25-2.72 (m, 3H), 2.83-3.02 (m, 2H), 3.10-3.20 (m, 1H), 3.24-3.39 (m, 1H), 4.58-4.76 (m, 1H), 5.10-5.26 (sym m, 1H) (also see Figure 2.6); ^{13}Cmr ($CDCl_3$) δ: 21.1, 23.1, 30.0, 30.3, 58.4, 58.9, 83.7, 87.6. Calcd. exact mass for $C_4H_8O_2S$: 120.0245. Found: 120.0244.

The hydrolysis was carried out by stirring the sultine (*8a*) (120 mg, 1 mmol) with sodium hydroxide (40 mg) in water (10 mL), as above, to give sodium 3-hydroxy-1-butanesulfinate (*14a*) as a crystalline white solid (160 mg, ~100%); ^{1}Hmr (D_2O) δ: 1.18 (d, 3H), 1.70 (q, 2H), 2.38 (t, 2H), 3.88 (sextet, 1H); ^{13}Cmr (D_2O) δ: 21.6, 30.0, 56.6, 66.7.

The salt (*14a*) was chlorinated in dichloromethane (20 mL), as above, to give a mixture of the short-lived 3-hydroxy-1-butanesulfonyl chloride (*15a*) and sultone

(*16a*). The hydroxy-sulfonyl chloride cyclized, on standing, to the sultone *16a*. A freshly prepared sample of *15a* was converted to 3-acetoxy-1-butanesulfonyl piperidide (*19a*) and was compared with the authentic sample, for spectra, see the experimental in chapter 1.

Oxidation of the sultine (*8a*) (100 mg) with *m*-chloroperbenzoic acid in ether gave the 5-methyl-1,2-oxathiolane 2,2-dioxide (*16a*). ^{1}Hmr and ^{13}Cmr spectra were identical to those obtained earlier.

(vi) Chlorination of 3-mercapto-1-butanol (*7b*):

3-Methyl-1,2-oxathiolane 2-oxide (*8b*)

3-Mercapto-1-butanol (*7b*) (212 mg, 2 mmol) and chlorine (284 mg, 4 mmol) in dichloromethane (100 mL), as above, gave 3-methyl-1,2-oxathiolane 2-oxide (*8b*) (168 mg, 70%) as a mixture of diastereomers; ir (neat) ν_{max}: 2977 (m), 2936 (m), 2907 (w), 1455 (m), 1175 (m), 1127 (vs), 1021 (m), 928 (s), 866 (s), 716 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.10 (d, 3H), 1.28 (d, 3H), 1.72-2.88 (m, 3H), 2.53-2.71 (sym m, 1H), 2.87-3.05 (m, 1H), 3.14-3.30 (sym m, 1H), 4.15-4.28 (sym m, 1H), 4.33-4.45 (sym m, 1H), 4.59-4.74 (sym m, 2H); ^{13}Cmr ($CDCl_3$) δ: 10.9, 12.8, 29.5, 29.8, 62.4, 66.4, 74.6, 75.2. Calcd. exact mass for $C_4H_8O_2S$: 120.0245. Found: 120.0244.

A portion of sultine (*8b*) (100 mg) was oxidised to the sultone (*16b*) using *m*-chloroperbenzoic acid.

The sultine (*8b*) (120 mg) was hydrolysed, as above, to give sodium 4-hydroxy-2-butanesulfinate (*14b*) in quantitative yield (160 mg) as a white solid; ^{1}Hmr (D_2O) δ: 1.32 (d, 3H), 1.82 (q, 2H), 2.65 (m, 1H), 3.82 (t, 2H); ^{13}Cmr (D_2O) δ: 12.7, 33.5, 60.3, 62.0.

The salt (*14b*) was chlorinated in dichloromethane, as above, to give a mixture of the short-lived 4-hydroxy-2-butanesulfonyl chloride (*15b*) and 2-methyl-1,2-oxa-

thiolane 2,2-dioxide (*16b*). The hydroxy-sulfonyl chloride cyclized on standing to the sultone *16b*. A freshly prepared sample of *15b* was converted to 4-acetoxy-2-butanesulfonyl piperidide (*19b*), and was compared with authentic sample, for spectra see the experimental in chapter 1.

(vii) Chlorination of 2-mercaptophenylmethanol (*9*)

3H-2,1-Benzoxathiole 1-oxide (*10*)

2-Mercaptophenylmethanol (*9*) (140 mg, 1 mmol) and chlorine (142 mg, 2 mmol) in dichloromethane (50 mL), as above, gave the 3H-2,1-benzoxathiole 1-oxide (*10*) (124 mg, 80%), mp 41-42°C (lit[12] mp 40-41°C); ir (CCl_4) ν_{max}: 3070 (w), 2930 (w), 2870 (w), 1580 (w), 1468 (m), 1450 (m), 1210 (m), 1185 (w), 1130 (vs), 1060 (m), 950 (s), 710 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 5.42 and 5.78 (AB quartet, J = 13.7 Hz, 2H), 7.3-7.75 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 78.4, 121.9, 123.4, 129.2, 132.2, 138.1, 149.6.

A small portion of sultine (*10*) was oxidized to the 3H-2,1-benzoxathiole 1,1-dioxide, with hydrogen peroxide,[12] to give a crystalline solid, mp 113-114°C (lit.[13] 113-114°C); ir (KBr) ν_{max}: 2970 (w), 1474 (w), 1464 (s), 1331 (vs), 1217 (s), 1190 (vs), 1138 (m), 955 (vs), 835 (m), 787 (s), 719 (m), 648 (m), 571 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 5.53 (s, 2H), 7.42-7.84 (m, 4H); ^{13}Cmr ($CDCl_3$) δ: 71.2, 121.8, 123.4, 130.2, 131.6, 133.8, 135.2.

(viii) Chlorination of 4-mercapto-4-methyl-2-pentanol (*20*)

Similarly the chlorination of *20* (120 mg, 1 mmol) with chlorine (142 mg, 2 mmol) in dichloromethane (50 mL), gave a complex mixture with no identifiable product.

(ix) Chlorination of 2-(mercaptomethyl)phenyl methanol (*21*)

Compound *21* (154 mg, 1 mmol) and chlorine (142mg, 2 mmol) in dichloromethane (50 mL) was reacted at -78°C, as above. ^{1}Hmr and ^{13}Cmr spectra of the product showed it to be a complex mixture with no readily identifiable constituents.

2.4 REFERENCES AND FOOTNOTES

1. (a) Previous work on the synthesis of sultines has been well-summarized: N.K. Sharma, F. de Reinach-Hirtzbach, and T. Durst, *Can. J. Chem.*, **54**, 3012 (1976); (b) G.W. Buchanan, N.K. Sharma, F. de Reinach-Hirtzbach, and T. Durst, *Can. J. Chem.*, **55**, 44 (1977); (c) R.M.J. Liskamp, H.J.M. Zeegers, and H.C.J. Ottenheijm, *J. Org. Chem.*, **46**, 5408 (1981)
2. R.S. Henion, *Eastman Organic Chemical Bulletin*, **41**, No. 3 (1969).
3. (a) J.F. King, M.R. Webster, N. Chiba, J.K. Allen, K.J.M. Parker, R. Rathore, and S. Skonieczny, *Phosphorus and Sulfur*, **31**, 161 (1987); (b) J.F. King and R. Rathore, *Phosphorus and Sulfur*, **33**, 165 (1987).
4. R.V. Norton and I.B. Douglass, *Org. Mag. Res.*, **6**, 89 (1974).
5. M.W. Bullock, J.A. Brockman, Jr., E.L. Patterson, J.V. Pearce, M.H. von Saltza, F. Sanders, and E.L.R. Stokstad, *J. Am. Chem. Soc.*, **76**, 1828 (1954).
6. For an analysis of the infrared spectra of acyclic sulfinates, see: S. Detoni, and D. Hadzi, *J. Chem. Soc.*, 3163 (1955), and also L.J. Bellamy, "Organic Sulfur Compounds," Vol. **1**, N. Kharasch, Editor, Pergamon Press, Oxford, 1961.
7. J.G. Pritchard, and P.C. Lauterbur, J. Am. Chem. Soc. **83**, 2105 (1961).
8. R.M. Dodson, P.D. Hammen, and R.A. David, *J. Chem. Soc., Chem. Commun.*, 9, (1968).
9. F. Reissert and H. Holle, *Chem. Ber.*, **44**, 3027 (1911).
10. W.C. Still, M. Kuhn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
11. L. Nystrom and H.C. Brown, *J. Am. Chem. Soc.*, **69**, 1198, (1947).
12. J.F. King, B.L. Huston, A. Hawson, J. Komery, D.M. Deaken, and D.R.K. Harding, *Can. J. Chem.*, **49**, 936 (1971).

CHAPTER 3

STEREOELECTRONIC EFFECTS IN SULFONAMIDES

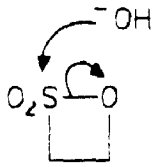
3.1 INTRODUCTION

Delocalization of an electron pair from an attached atom into a sulfonyl group has long been postulated:[1]

$$-SO_2X- \longleftrightarrow -^{-}SO_2=X^{+}-$$

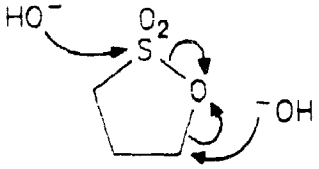
X = N, O, F, C^{-}, C=C, etc.

When one recalls the evidence showing that α-sulfonyl carbanions have a strong stereoelectronic preference for the conformation depicted in structure *1* (Figure 3.1),[2] it is natural to suggest that the analogous conformations (*3* to *5*) are favoured by sulfonamides, sulfonic esters and arylsulfones respectively. Lipscomb and coworkers[3] and also Jennings and Spratt[4] have suggested that conformation *4* is favoured by sulfonamides, and a similar suggestion with respect to sulfonic esters has, in fact, been put forward by Smith and Wolinsky[5] to account for ^{13}Cmr chemical shifts in 5- and 6-ring sultones. In none of these cases was the idea applied to problems of chemical reactivity.



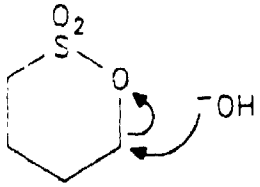
6

S–O Cleavage



7

both

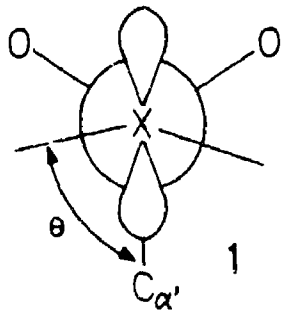


8

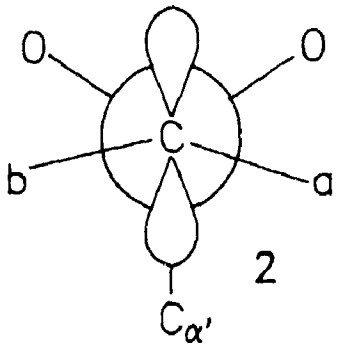
C–O Cleavage

King and coworkers[6] have recently suggested that this stereoelectronic effect may account for ...ered reactivity patterns in the smaller ring sultones. They showed by ^{18}O-labelling studies that cleavage of β-sultone (*6*) with hydroxide gives

Apparently generally preferred conformation:

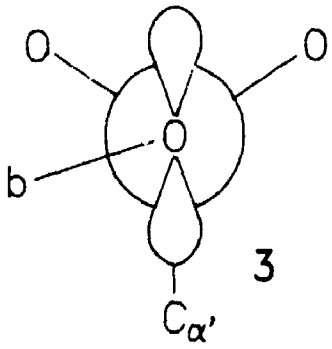


1



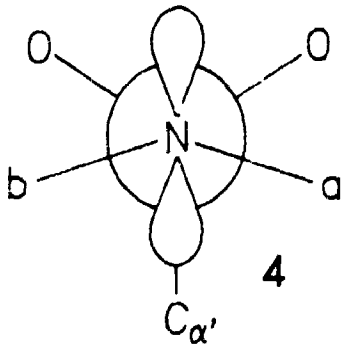
2

Sulfonyl Carbanions



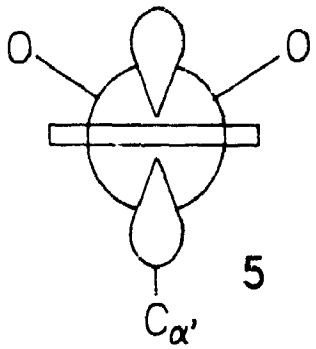
3

Sulfonic Esters



4

Sulfonamides



5

Aryl Sulfones

Figure 3.1 The most preferred conformations of sulfonyl compounds.

2-hydroxyethanesulfonate by way of S–O cleavage rather than C–O cleavage. Reaction of hydroxide with propane 1,3-sultone (7) took place with 55% S–O cleavage and 45% C–O cleavage, but with butane 1,4-sultone (8) went entirely with C–O cleavage.

The explanation, at least for the attack of hydroxide at sulfur rather than carbon in "smaller ring sultones," is as follows. In 4- and 5-ring sultones, the oxygen lone pair of electrons does not bisect the sulfonyl oxygen effectively ($\theta = 0^{\circ}$), and one might expect lessened O→S electron donation which would lead to (a) lowering of the S–O bond order, (b) decrease of δ^+ on the oxygen-bearing carbon, and (c) increase of the magnitude of δ^+ on sulfur (relative to unconstrained sulfonic esters). The combined effect of these three factors would tend to favour S–O cleavage in these sultones, rather than the usual C–O cleavage.

Some S–O cleavage of ethylene sulfate and propane 1,3-sultone[7,8] (7), and rate accelerations of up to 10^7-fold in certain related 5-membered sultones,[7] had been reported and attributed largely to relief of ring strain in the transition state. A comparable relief of ring strain and hence acceleration in rate is, however, not observed in the corresponding C–O cleavage observed with 7 with nucleophiles other than OH^-. For instance, it has been reported by Osterman-Golkar, *et al.*[9] that the C–O cleavage of 7 with various nucleophiles was only 5 to 31 times faster than that of the simple acyclic model ethyl methanesulfonate. Similar results were reported by Mori, *et al.*[8], who found that the relative rates of hydrolysis of the 5-membered sultone 7, the 6-membered sultone 8, and ethyl ethanesulfonate, in water were 37:1:7. The transition states for both C–O and S–O cleavage are believed to be close to trigonal-bipyramidal, and examination of molecular models shows no clear basis for very much greater relief of simple ring strain in one case over the other.

The proposed dihedral angle dependent delocalization would be expected to show itself in other ways, such as in a clear preference for the conformation shown in 1

(Figure 3.1). A search of the Cambridge Crystallographic Data Centre files by King and coworkers[10] have provided relevant information about the geometry of sulfonyl compounds. The C–S–X–C dihedral angles (where X = O, N, or Ar) in sulfonic esters, aryl sulfones and sulfonamides were distributed as shown in Figures 3.2, 3.3 and 3.4 respectively.

In sulfonic esters, the following two points may be noted, (a) most of the dihedral angles (80 out of 121) are in the range 60–90°, (b) except for three 5–ring sultones, in which a small value of θ is enforced, there are no sulfonic esters with θ less than 50°. The fact that there is no similar avoidance of C–O eclipsing (that is, conformations in which θ = 115°) suggests strongly that this dihedral angle preference (θ = 70°) is not primarily due to a simple C–C eclipsing effect. From these crystallographic data, it was concluded that alteration of θ to values less than 50° would lead to (a) an increase in energy and hence possibly to higher reactivity, and (b) to diminished electron delocalization onto the sulfur atom and hence to the altered reactivity patterns (for example, S–O cleavage rather than the C–O cleavage) as pointed out above.

Examination of the C–S–$C_{ipso}C_{ortho}$ dihedral angle in aryl sulfones also displays the same geometric preference, with 197 out of 208 angles in the 60–120° range and none less than 50° (see Figure 3.3).

As has been implied above, the basic idea of a conformational preference in the $-SO_2-X$ system began with α–sulfonyl carbanions, for which, among other supporting evidence (also see chapter 4), recent X–ray structure determinations of a number of α–sulfonyl carbanions are particularly convincing.[2c] The effect of dihedral angle dependence was shown in this laboratory by observing the pattern of chemical reactivity and X–ray structural evidence for sulfonic esters as discussed earlier. It was therefore decided to look at the conformations of sulfonamides, which, except for the pioneering paper by Lipscomb and coworkers[3] and the nmr study by Jennings

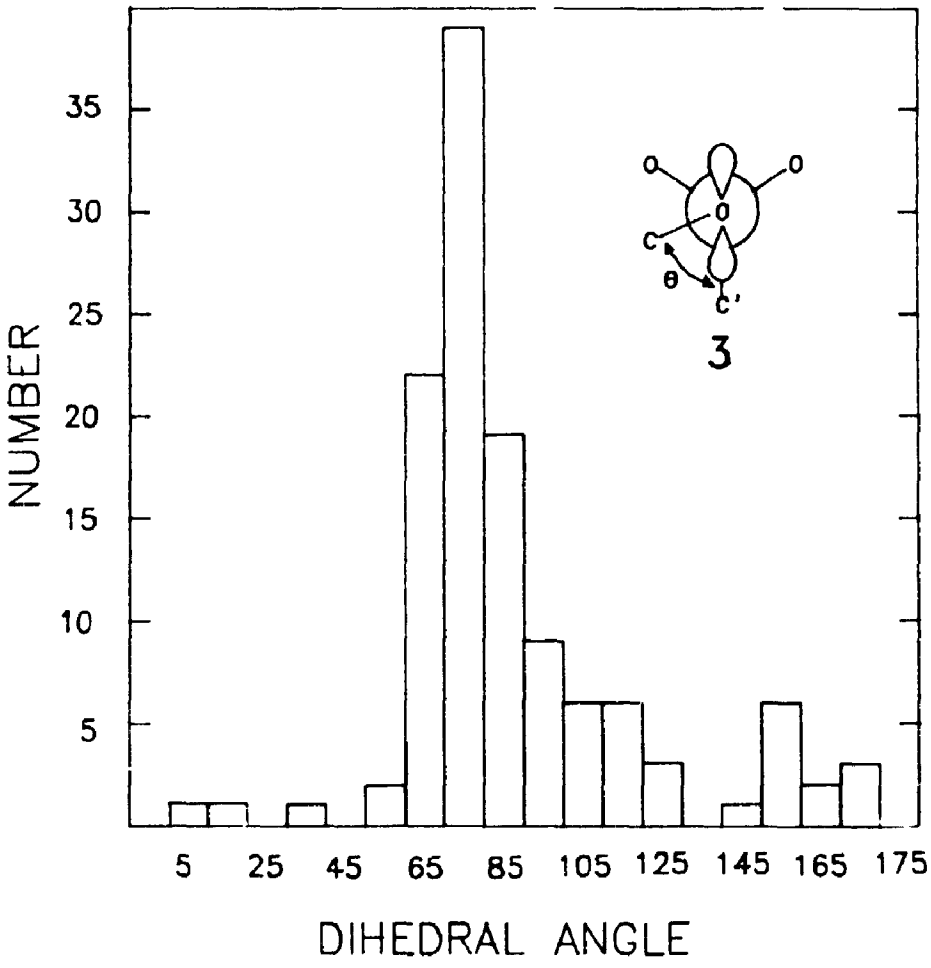


Figure 3.2 Sulfonic Esters: population distribution with the C–S–O–C dihedral angle. The number specified as the 'dihedral angle' refers to the range encompassed by that number ± 5°, specifically, 85° for example includes the range from 80.00 to 89.99°.

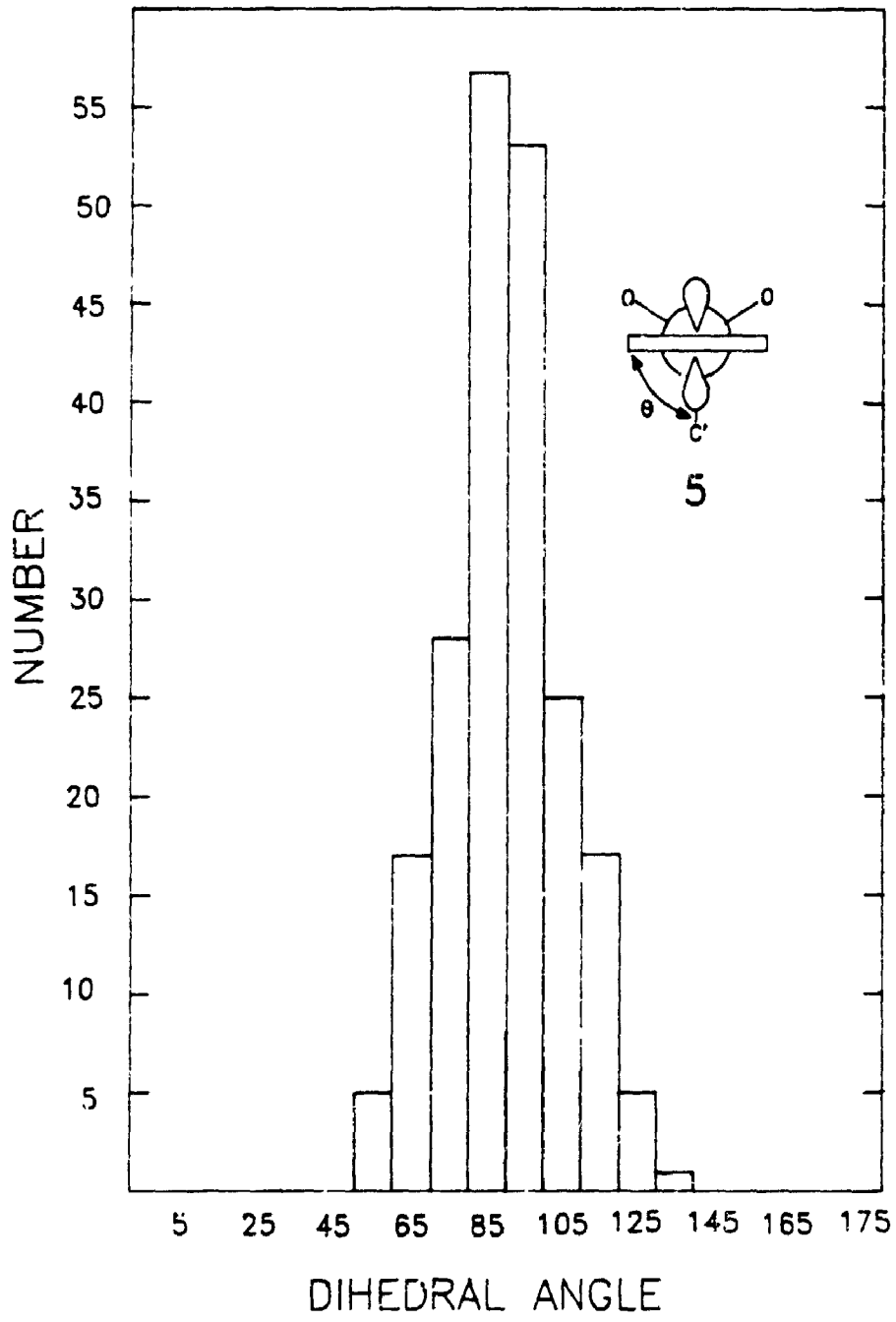


Figure 3.3 Aryl Sulfones: population distribution with the C–S–C_{ipso}–C_{ortho} dihedral angle.

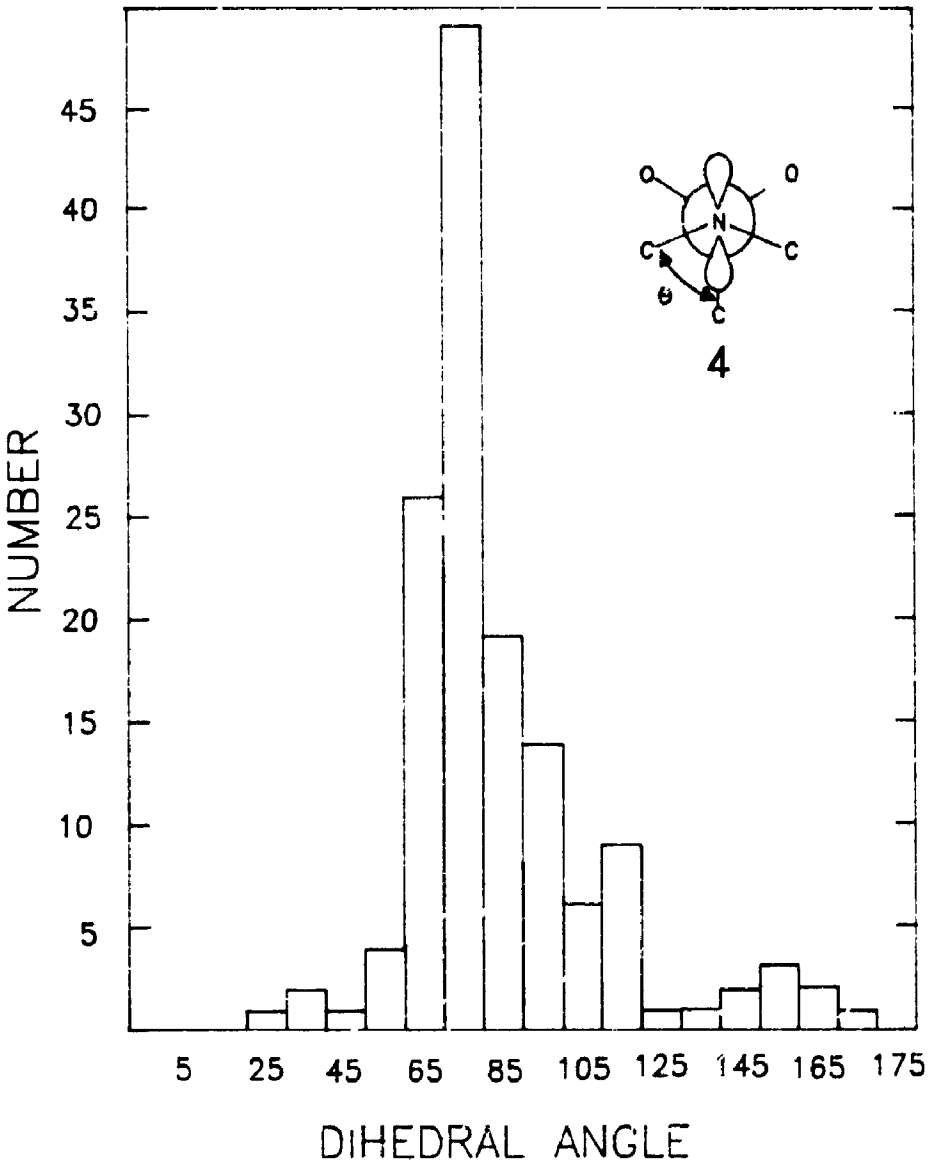
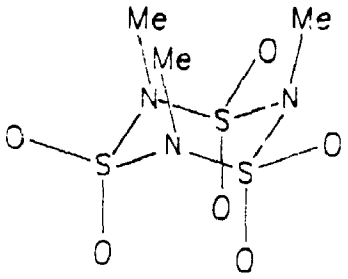
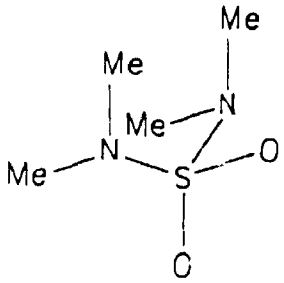


Figure 3.4 N,N–Dialkylsulfonamides: population distribution with the C–S–N–C dihedral angle.

and Spratt,[4] would appear to have been little studied.

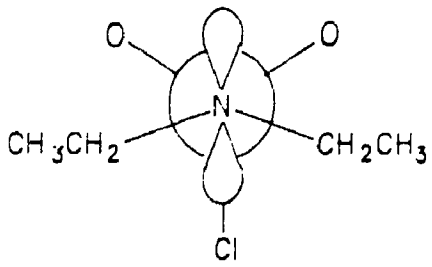


9



10

The X-ray structures of compound *9* determined by Hazell[11] and of compound *10* by Lipscomb and coworkers,[3] are shown above. In compound *9* all the methyl groups take (more or less) axial position so that the lone pair of electrons on nitrogen can bisect the sulfonyl oxygens.



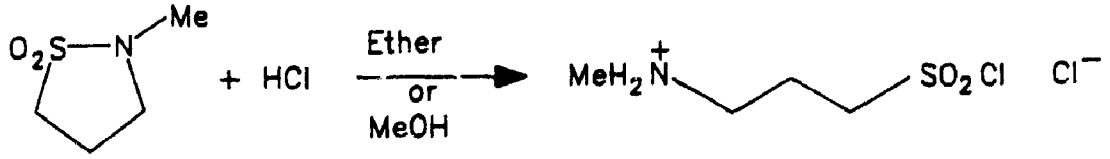
11

Low temperature ^{1}Hmr spectra of *N,N*-diethylsulphamoyl chloride (*11*) in $CHCl_2F$ solution at −70°C resolved into a ABM_3 system which was a normal quartet at ambient temperature.[4] The observed chemical shift nonequivalence of the geminal methylene protons at low temperature indicated a molecular dissymmetry on the nmr time scale, which may be interpreted in terms of either slow nitrogen inversion or slow rotation around N–S bond. It was suggested by Jennings and Spratt[4] that the measured barrier (11.5 $kcal^{-1}$ mol^{-1}) in *11* is due to torsion around the N–S bond rather than the nitrogen inversion as the latter is considered to be a much lower

energy process for the following reasons: (1) the barrier to nitrogen inversion is typically only ~6.5 Kcal mole^{-1}, (2) bonding between the nitrogen lone pair and vacant sulfur orbitals should decrease the inversion barrier below that in a simple amine; this latter effect has been observed in *N*-sulfonyl aziridines.[12] An electron diffraction study[13] of Me_2NSO_2Cl has indicated flattening of the nitrogen pyramid, and that the molecule has the conformation shown in ***11***.

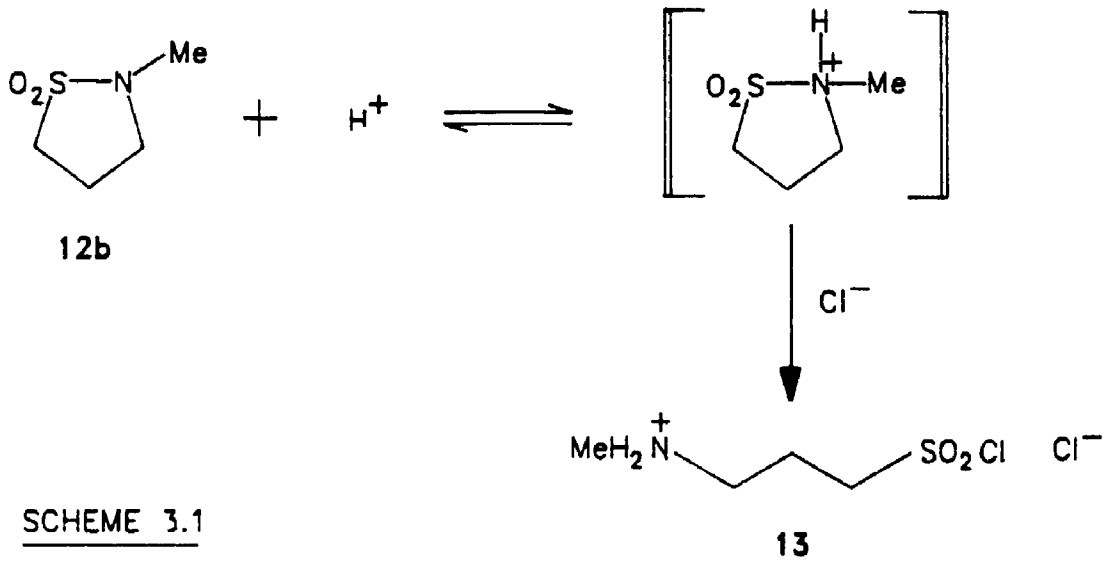
The C-S-N-C dihedral angles of *N,N*-dialkylsulfonamides from the Cambridge Data Base Files are summarized by Figure 3.4.[10] Again the same pattern appeared, with 124 out of the 140 angles being in the range 60-120° (*i.e.*, more or less as shown in ***4***) and no C-S-N-C angles less than 50° except for two sulfonylaziridines in which the small angle is required by the three membered ring. The X-ray structure data, along with Jennings and Spratt's results[4] and MO studies[3,14] clearly indicate that the general conformation shown in ***4*** represents the principal conformational minimum for dialkylsulfonamides.

Erman and Kretschmar[15] showed that 5-membered ring sulfonamides (propane 1,3-sultams) (*e.g.* ***12***) could be rapidly cleaved at room temperature by methanolic or ethereal hydrogen chloride solution, to give the corresponding *N*-alkyl 3-chlorosulfonylpropanaminium chloride ($RN^+H_2CH_2CH_2CH_2SO_2Cl\ Cl^-$) (***13***). In contrast, a series of acyclic sulfonamides were unaffected under the same acidic conditions.



12b **13**

The postulated mechanism of the above reactions is shown in Scheme 3.1.



12b

13

SCHEME 3.1

A mechanism akin to this was put forward by Klamann and Hofbauer;[16] they appear to favour unimolecular ring opening of protonated sulfonamide followed by the reaction of chloride, although they also suggested bimolecular ring opening of protonated sulfonamide. Mr. Li from this laboratory has recently shown by kinetic studies that the rate of the reaction is dependent on chloride concentration, thereby confirming the bimolecular process.

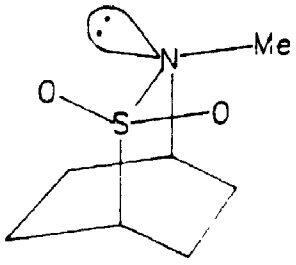
The objective of this chapter is to inquire about the effect of the stereoelectronic factor in sulfonamides and to find how the chemical and spectral properties of these compounds vary with change in the C–S–N–C dihedral angle. A second feature of this project is to find the relative importance of ring strain and the stereoelectronic effect in the rate acceleration of cleavage of 5–membered cyclic sulfonyl compounds.

Sulfonamides are isoelectronic with α–sulfonyl carbanions and would serve as a useful model system to study the effect of dihedral angle (θ) dependence on chemical reactivity. In principle, it should be possible to separate the stereoelectronic and strain factors in reactions which involve coordination of the free electron pair in a preliminary step, *e.g.*, acid–catalysed cleavage of sulfonamides.

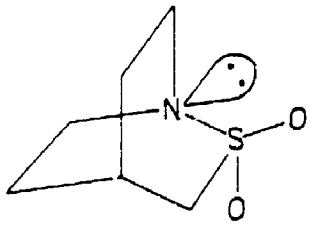
$$RSO_2NR'_2 + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} RSO_2\overset{+}{N}HR'_2 \xrightarrow{k_2} \text{Product}$$

In the simplest approximation, K_1 can be expected to be sensitive to variation in the C-S-N-C dihedral angle (*i.e.* a stereoelectronic effect), while k_2 would show the effect(s) of angle strain. This separation of the stereoelectronic and steric effects, especially in 5-membered ring sultams should generate more information about the higher reactivity of 5-membered ring sultones as well as sultams.

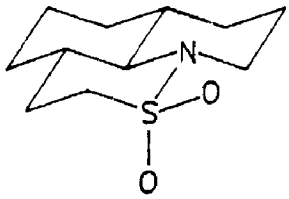
To pinpoint this stereoelectronic effect, it was necessary to synthesize cyclic compounds in which the sulfonamide functionality is locked in such a way that neither the rotation around the N-S bond nor nitrogen inversion would result a conformation in which the nitrogen lone pair of electrons can bisect the sulfonyl oxygens (*i.e.*, $\theta \leqslant 80^{\circ}$), and to compare the chemical behaviour of these sulfonamides with those in which the lone pair of electrons is at the bisector of sulfonyl oxygen. Some possible examples (*i.e.*, *14*, *16*, and *18*) are shown below.



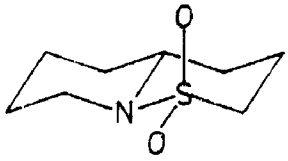
14



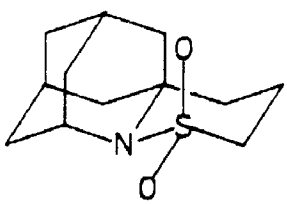
15



16

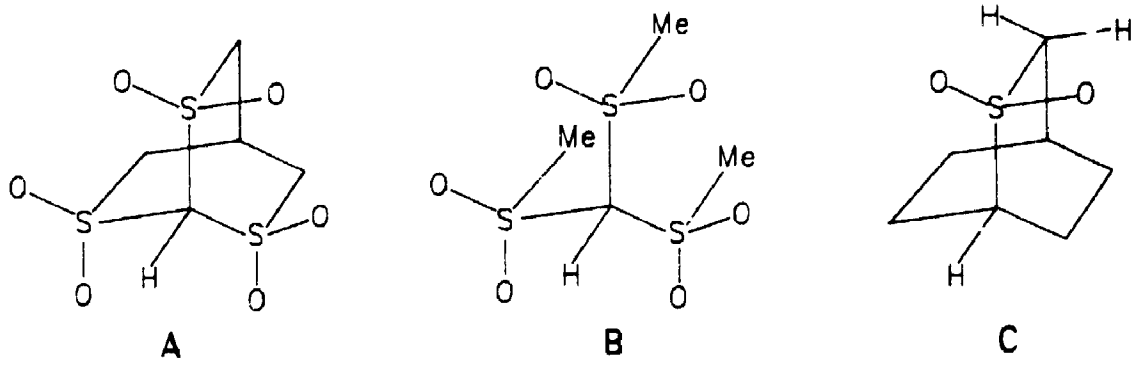


17



18

The compounds *14*, and *17* have been synthesized and are described in this chapter; quinuclidine sultam *15* has recently been made by Mr. D. Klassen in this laboratory. The sultam *15* is of interest as the lone pair of electrons at the bridgehead nitrogen is at the bisector of the sultonyl oxygens in the [2.2.2]bicyclic system. It should provide some insight as to what effect, if any, is produced on the base strength by placing the nitrogen atom at the bridgehead of a [2.2.2]bicyclic system. It should be noted that the bridgehead hydrogen in [2.2.2]bicyclic trisulfone (*A*) is quite acidic (pK_a = 3.3) but apparently appreciably less so than the corresponding hydrogen in tris(methylsulfonyl)methane (*B*).[17] Recently we have shown that the bridgehead hydrogen in 2–thiabicyclo[2.2.2]octane 2,2–dioxide (*C*) exchanges ~50 times more slowly than the methylene hydrogens.[18]



Studies of the rate of acid hydrolyses, pK_a determinations, low temperature nmr studies, and infrared spectra on these compounds and various other sulfonamides, provide evidence that the variation of delocalization of the electron pair on the nitrogen with dihedral angle, can substantially influence the properties of sulfonamides. This work constitutes the content of this chapter.

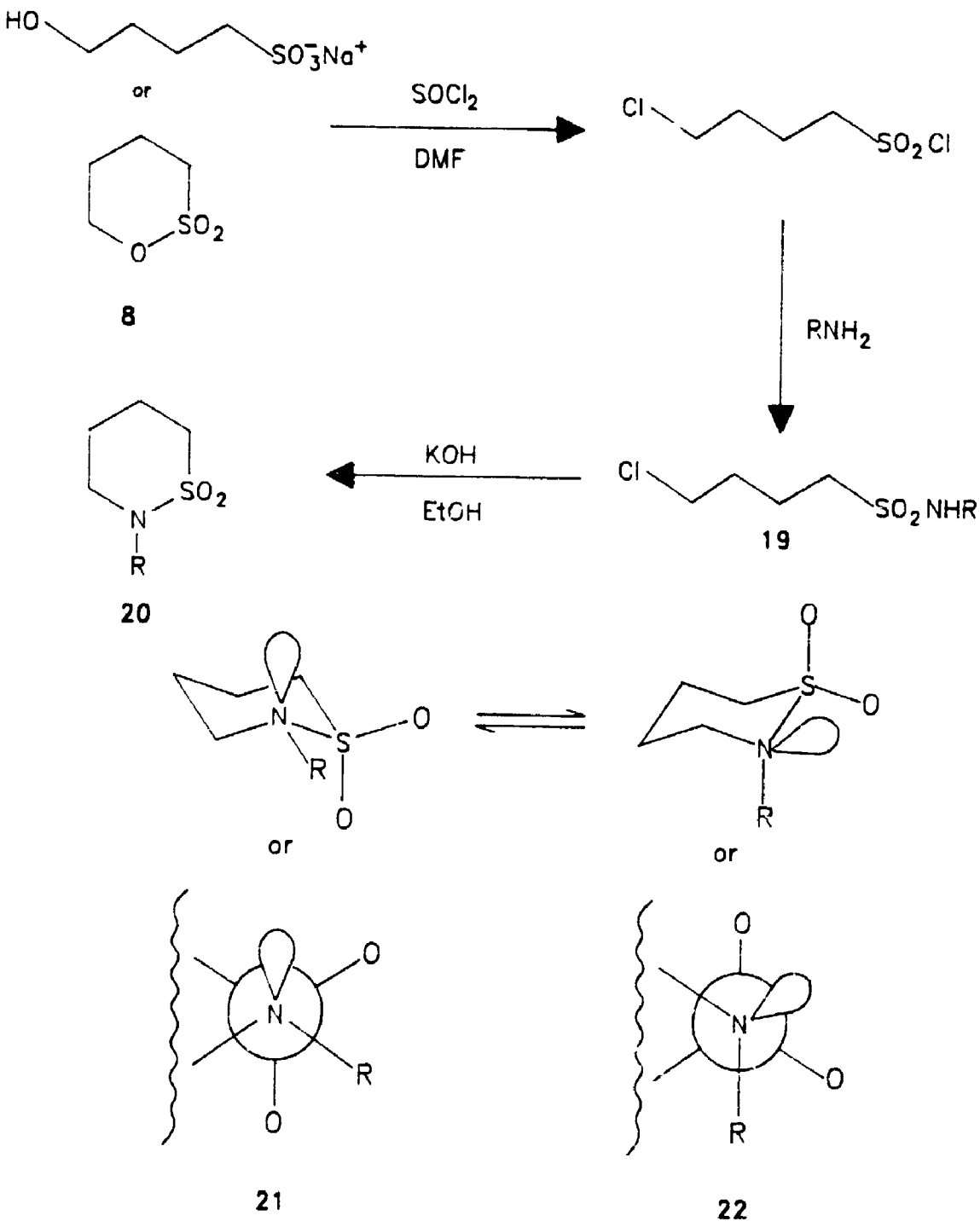
3.2 RESULTS AND DISCUSSION

3.2.1 Preparation of Sultams (Cyclic Sulfonamides) and Acyclic Sulfonamides

There are a number of methods for preparing sultams; these are summarized by Erman and Kretschmar.[15] A general procedure is outlined in Scheme 3.2 for the synthesis of 6-ring sultams (butane 1,4-sultams) with various substitutents on nitrogen. A bulky group on cyclohexane derivatives is known to result in an anchored conformation with the substituent oriented equatorially. By analogy, it might be expected that *N*-*t*-butylbutane 1,4-sultam (*20c*), *N*-isopropylbutane 1,4-sultam (*20e*), and *N*-phenylbutane 1,4-sultam (*20d*) should have the conformation as shown in *21*, *e.g.* $\theta \leqslant 50^{\circ}$ or in other words with the lone pair of electrons on nitrogen not at the bisector of the sulfonyl oxygens (see Scheme 3.2). Compounds *20a* to *20e* were obtained as crystalline solids except for *N*-methylbutane sultam (*20b*) and *N*-isopropylbutane sultam (*20e*) which were clear liquids. These compounds solidified in the freezer, but repeated attempts to recrystallize *20b* and *20e* were unsuccessful.

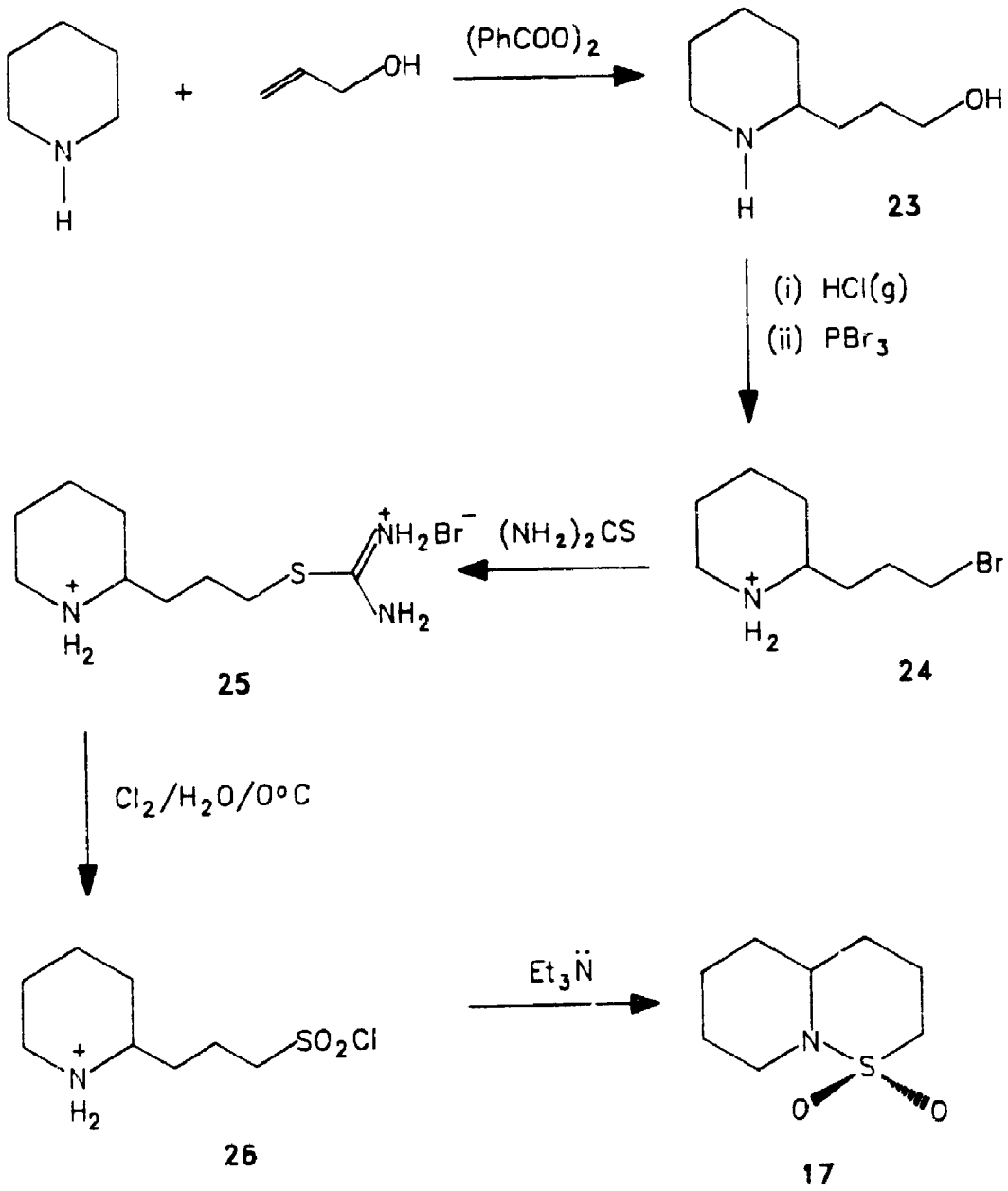
These butane 1,4-sultam derivatives (*20*) were characterized with the help of ^{1}Hmr, ^{13}Cmr, ir and mass spectroscopy; a comment about the infrared spectra of the sultams will be made in a later section of this chapter.

1,9-Thiazadecalin 1,1-dioxide ("decalin sultam") (*17*), with a bridgehead nitrogen, was synthesized as outlined in Scheme 3.3. Free radical addition[20] of allyl alcohol to piperidine gave 2-[3-hydroxypropyl]piperidine (*23*) which on reaction with phosphorus tribromide[21] gave the bromo-ammonium salt *24* which upon successive nucleophilic substitution with thiourea[22] (*24* → *25*), chlorination[23] in water (*25* → *26*), and cyclization of the ammoniosulfonyl chloride *26* with triethylamine gave the decalin sultam (*17*). Compound *17* was characterized by ^{1}Hmr, ^{13}Cmr, ir, and mass spectroscopy including exact mass determination.



a) R = H; b) R = Methyl; c) R = t-Butyl;
d) R = Phenyl; e) R = Isopropyl

SCHEME 3.2


(PhCOO)2
OH
23
(i) HCl(g)
(ii) PBr3
Br
24
(NH2)2CS
NH2Br−
S
NH2
25
Cl2/H2O/0°C
SO2Cl
26
Et3N
N
S
O
O
17

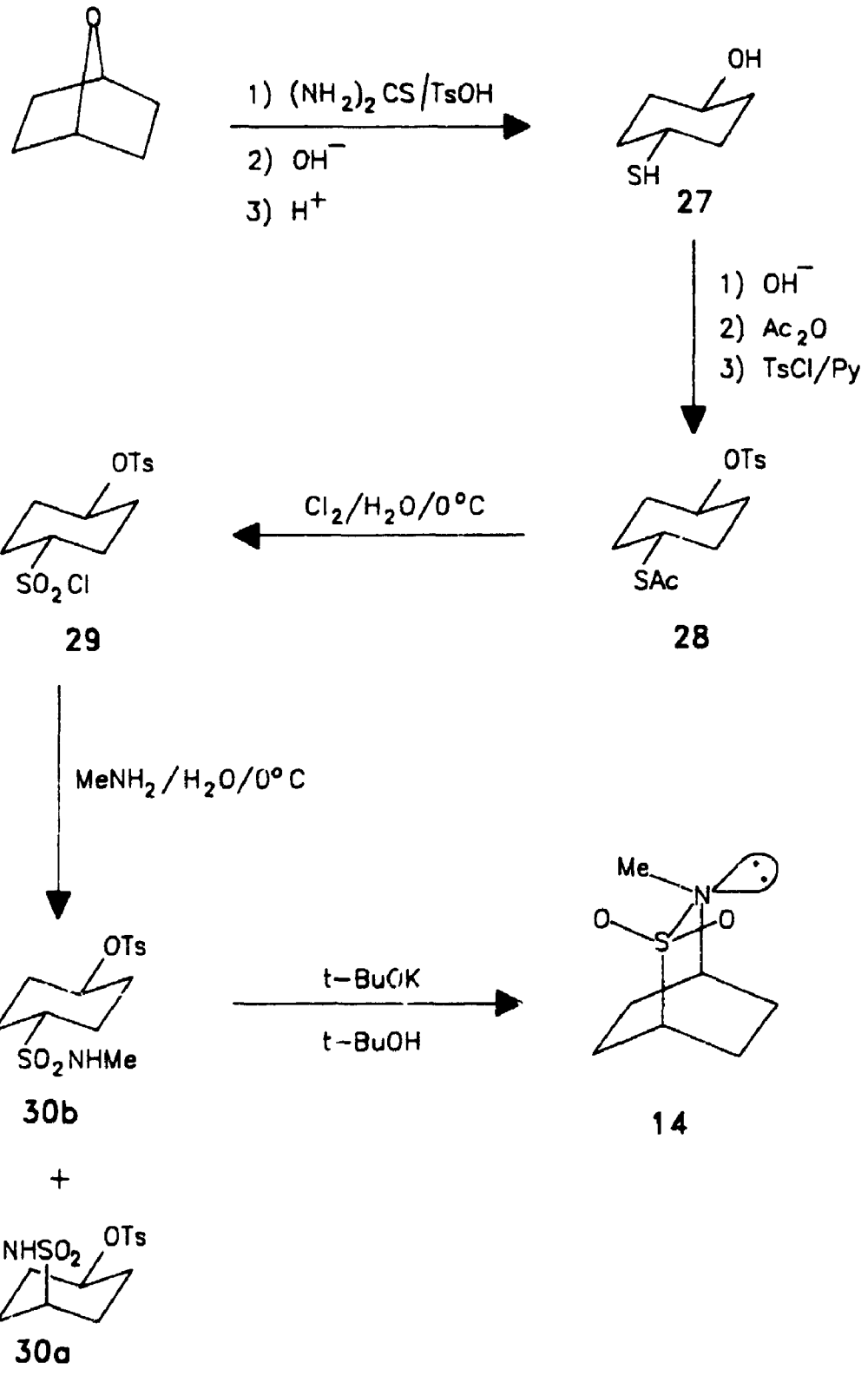
SCHEME 3.3

N-Methyl-2,3-thiazabicyclo[2,2,2]octane 2,2-dioxide (*14*) was synthesized as outlined in Scheme 3.4. *trans*-4-Mercaptocyclohexanol *27* was synthesized by the procedure developed by Corey and Block[24] and was converted to *trans*-4-acetylthio-cyclohexyl tosylate (*28*) which on chlorination gave *trans*-4-tosyloxycyclohexanesulfonyl chloride (*29*). Compound *29* on treatment with methylamine gave a mixture (1:1) of *cis*- and *trans*- isomers of *N*-methyl-4-tosyloxycyclohexanesulfonamide (*30a* and *30b*) as a result of the formation of the sulfene in the first step of the elimination-addition reaction of the amine and the alkanesulfonyl chloride (see Chapter 1 for details). The *trans*-sulfonamide *30b* was separated by flash chromatography;[25] this was followed by cyclization with potassium *t*-butoxide in *t*-butyl alcohol to give the bicyclic sulfonamide *14*; which was characterized by nmr, ir and mass spectroscopy. Interestingly, the ^{13}Cmr of *14* showed 5 signals (21.9 and 22.4 (methylenes, double intensity), 31.9 and 58.6 (methines), 50.6 (*N*-Me)) instead of 7 signals, suggesting that nitrogen inversion is very fast in this molecule resulting in equivalent methylene signals[26] (or there is only one symmetrical conformation present).

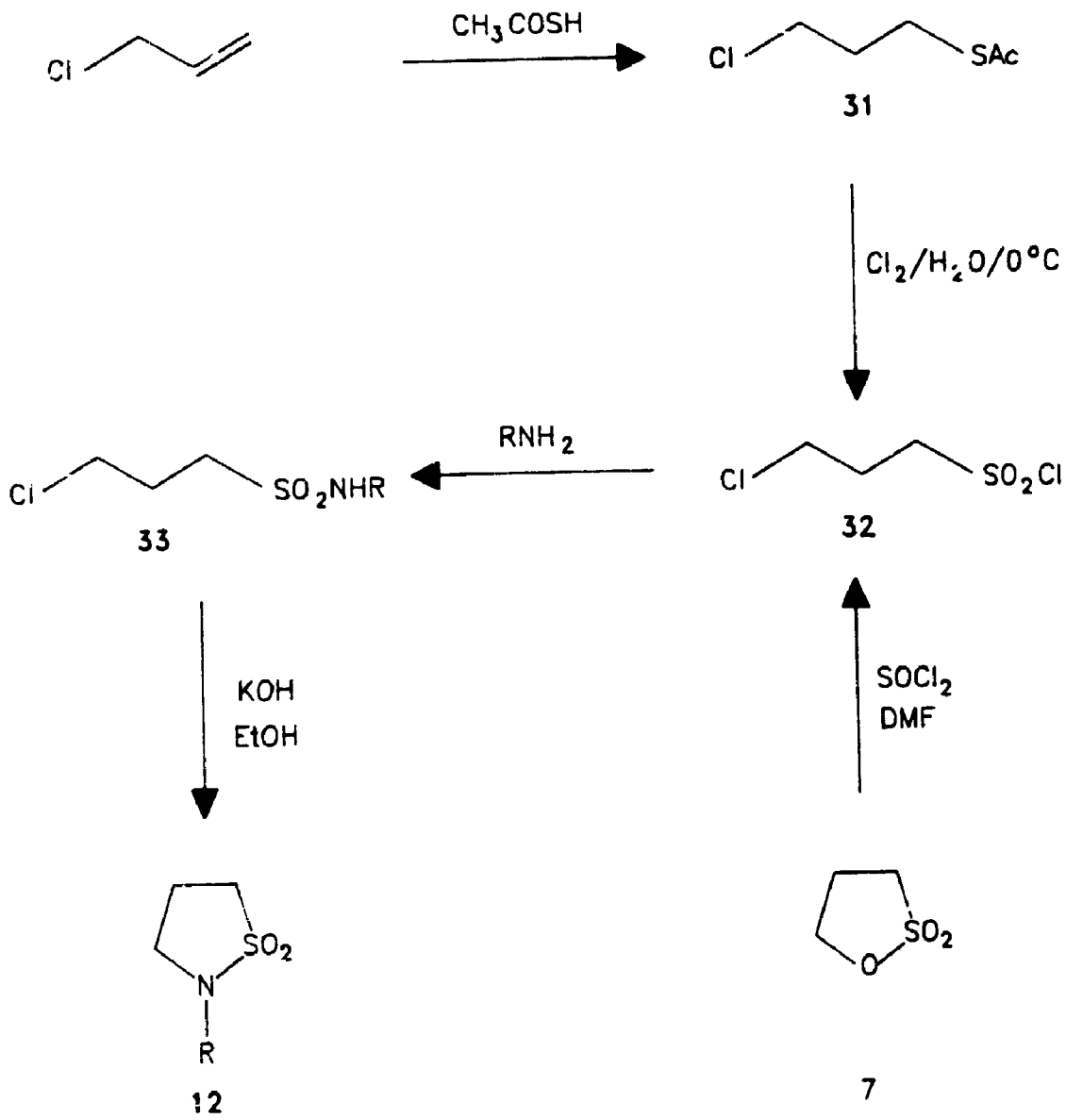
Various 5-membered ring sultams ("propane 1,3-sultams") (*12a* to *12d*) were prepared using 3-chloro-1-propanesulfonyl chloride (*32*) and the corresponding amines, followed by base catalysed cyclization (see Scheme 3.5). These sultams were characterized as before.

The camphor sultam (*38*) was synthesized according to the procedure of Vandewealle and Eycken[27] and was converted to *N*-methylcamphor sultam (*39*) using KOH and MeI (see Scheme 3.6).

Acyclic sulfonamides *40*, *41*, *42*, and *43* were synthesized by reaction of methanesulfonyl chloride with the corresponding amines.

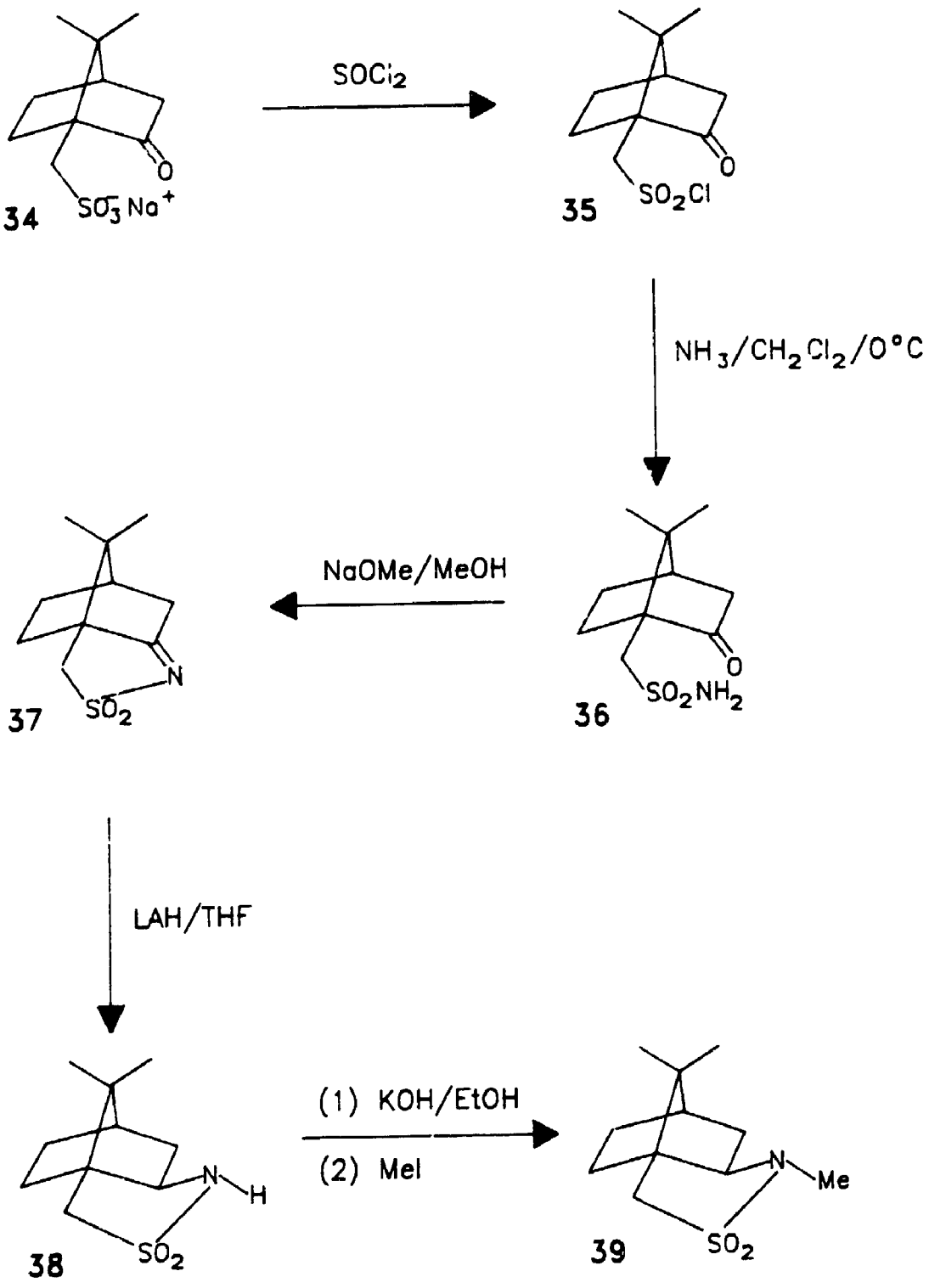

1) $(NH_2)_2CS/TsOH$
2) OH^-
3) H^+
OH
SH
27
1) OH^-
2) Ac_2O
3) TsCl/Py
OTs
SAc
28
$Cl_2/H_2O/0°C$
OTs
SO_2Cl
29
$MeNH_2/H_2O/0°C$
OTs
SO_2NHMe
30b
+
$MeNHSO_2$
OTs
30a
t-BuOK
t-BuOH
Me
N
O
S
O
14

SCHEME 3.4



a) R = H; b) R = Methyl; c) R = t-Butyl; d) R = Phenyl;

SCHEME 3.5

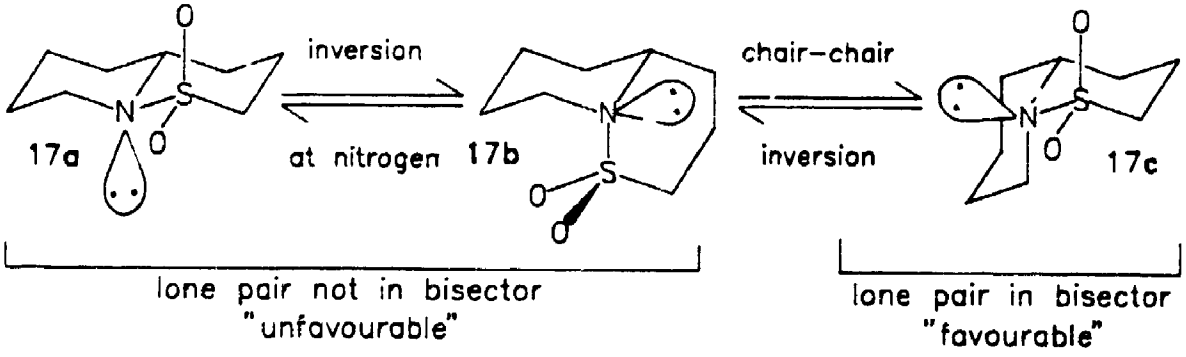

SOCl2
34
35
NH3/CH2Cl2/0°C
NaOMe/MeOH
36
37
LAH/THF
(1) KOH/EtOH
(2) MeI
38
39
Me

SCHEME 3.6

3.2.2 Low Temperature Nmr Studies of Sultams

The low temperature nmr. spectra in CD_2Cl_2–$CFCl_3$ at -110°, for **20b** to **20e** did not show any sign of signal broadening.

There are three relatively stable conformations possible for decalin sultam (**17**), as shown below:



Normally the conformation of **17** expected to be most favourable on steric grounds would be the one in which the rings are *trans*-fused (**17a**). But in conformation **17a**, unlike the conformation **17c** in which the rings are *cis* fused, the lone pair of electrons on nitrogen does not lie at the bisector of the sulfonyl oxygens. However, *cis*-**17** has two interconvertible chair conformations (**17b** and **17c**), one of which has the sulfonyl group equatorially oriented with respect to the nitrogen containing ring (**17c**) and other one has the axially oriented sulfonyl group (**17b**). In **17c**, o t in **17b** (or **17a**) the lone pair is located at the O–S–O bisector. On steric grounds conformation **17a** can be assumed to be favoured, but **17c** may well have much the same or lower free energy because of the stereoelectronic factor which may compensate for the greater steric energy in the *cis* form. The aim of synthesizing **17** was to see if it would be possible to determine the position of equilibrium due to nitrogen inversion in **17a** ⇆ **17b** ⇆ **17c**. Unfortunately **17** was not readily recrystallizable for X-ray studies. A series of ^{13}Cmr spectra were run from room temperature to -112°C in $CFCl_3$–CD_2Cl_2 (see Figure 3.5). The ^{13}Cmr spectrum of

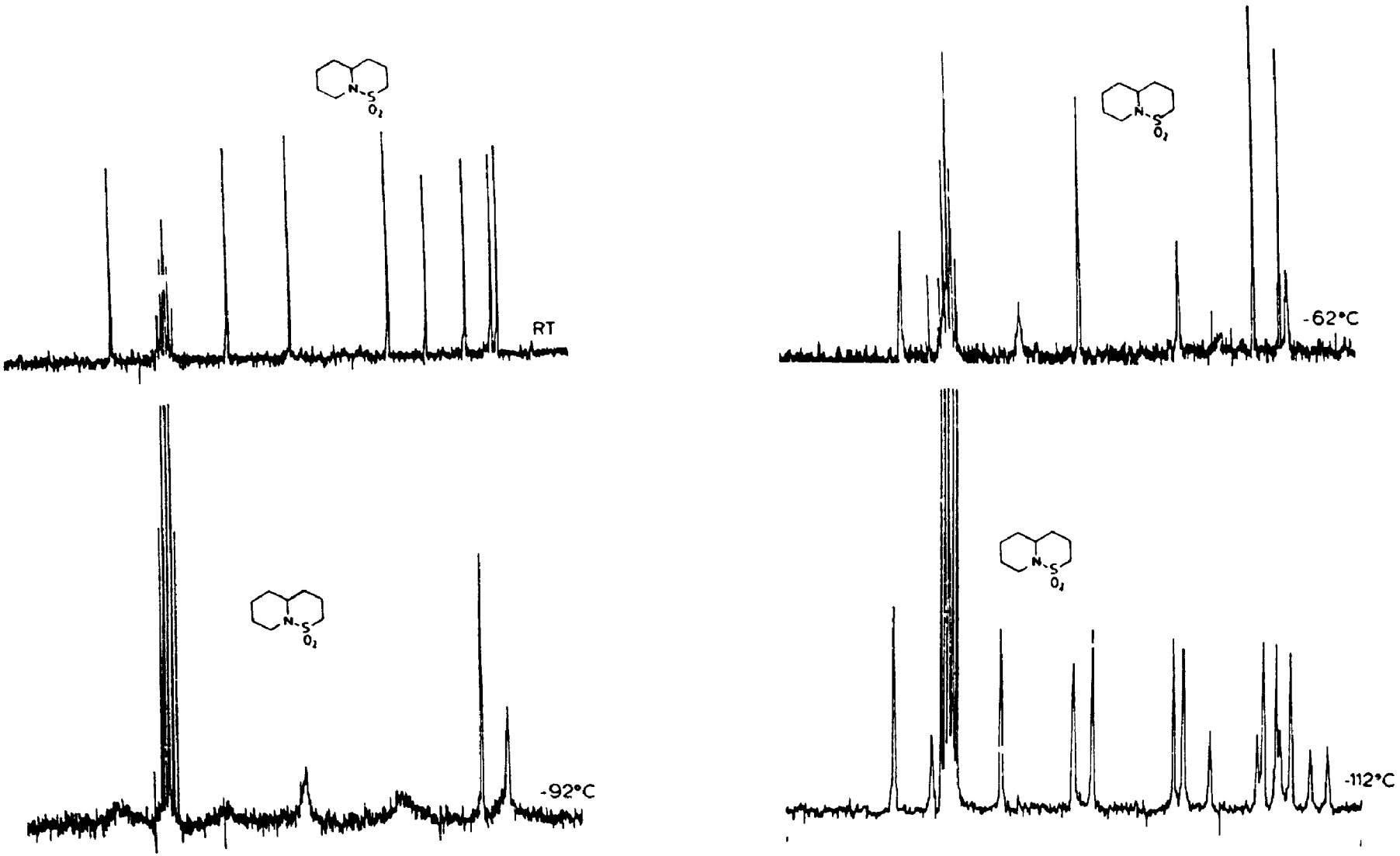
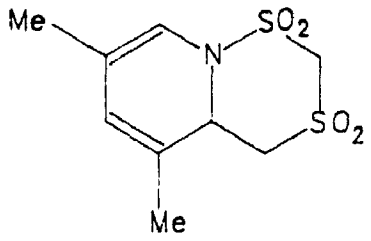


Figure 3.5 The ^{13}Cmr spectra of 1,9–thiazadecalin 1,1–dioxide (17) in CD_2Cl_2–$CFCl_3$ (1:1) at temperatures 20°C to –112°C.

17 at room temperature showed the normal eight peaks for the eight carbons in the molecule. These peaks broadened at -80 °C and two sets of eight peaks appeared at -112 °C. Our conclusions regarding the preferred conformations of **17** rest primarily on its ^{13}Cmr spectra and ^{1}Hmr spectra. The observed two sets of peaks at low temperature indicates the presence of two conformations on the nmr time scale. It is not certain which two conformation are present but from the above discussion it would seem that they must be **17a** and **17c**, and hence that the stereoelectronic effect is large enough to counter the steric factors favouring **17a**. It should be noted that a crystal structure performed on a bicyclic sultam (**44**) by Grossert *et al.*[28] showed that the rings are *cis* fused.



44

3.2.3 pK_a (or H_o Value at 50% Protonation)[29] Determination of Sulfonamides and Sultams

The basicity (or pK_a of the conjugate acids) of a number of sulfonamides and sultams were determined by the method of Laughlin.[30] This method is based on the determination of ^{1}Hmr chemical shifts as a function of acidity in aqueous sulfuric acid using the H_o scale of Jorgenson and Hartter.[31] The success of this method depends upon the observation of significant difference(s) in chemical shifts between protonated and unprotonated forms, and that the influence of medium on chemical shifts be minimal or at least regular. One major drawback with this method is that compounds with large number of carbons (especially those with aromatic substituents)

do not dissolve in sulfuric acid solutions.

It has been shown by Birchall and Gillespie[32] from the multiplicity of ^{1}Hmr signals in fluorosulfuric acid (FSO_3H) that *N*-methyl- and *N*,*N*-dimethyl-*p*-toluene-sulfonamides were protonated on the nitrogen and not the oxygen atoms of the sulfonamide functionality. Laughlin[30] carried out similar experiments with *N*-methyl-, *N*-ethyl-, and *N*,*N*-dimethylmethanesulfonamides and found the splitting appropriate to *N*-protonations. Menger and Mandell[26] and also Laughlin[30] have suggested that their results did not exclude the presence of a small amount of the *O*-protonated tautomer. Laughlin[30] further went on to suggest that the difference in acidity between $R'SO_2NH^+R_2$ and R_3NH^+ (~16 p*K* units) was too large to be accounted for on the basis of an inductive effect, and argued that these results indicate that N→S delocalization of electrons is important in sulfonamides.

In this present study the shapes of the curves, for the determination of H_o's at 50% protonation of sulfonamides, were calculated by assuming that δ is linearly related to $(BH^+)/(B)$[33] and also by correcting for medium effect (see experimental section).

Figure 3.6–3.14 show the dependence of chemical shifts on $-H_o$ (where H_o is the acidity function in aqueous sulfuric acid) for *N*,*N*-dimethylmethanesulfonamide (***40***), *N*-isopropylbutane sultam (***20e***), *N*-methylbutane sultam (***20b***), *N*-methyl-2,3-thiazabicyclo[2,2,2] 2,2-dioxide (***14***), *N*-methylpropane sultam (***12b***), methanesulfonyl-piperidide (***41***), methanesulfonylpyrrolidide (***42***), *N*,*N*-diethylmethanesulfonamide (***43***), and *N*-methylcamphor sultam (***39***); the values of $-H_o$ at 50% protonation (or pK_a values) of their conjugate acids are listed in Table 3.1. Treatment of the data by 'excess acidity method' of Cox and Yates[34] gave the same pK_a's for the various sulfonamides (see Figure 3.15 for a representative plot). The bicyclic sultam ***14*** in which $\theta = 0^\circ$ (and $\theta' = \sim 170^\circ$) was found to be distinctly more basic than its acyclic counterpart, *N*,*N*-dimethylmethanesulfonamide (***40***) by a factor approaching two

Me_2NSO_2Me

40

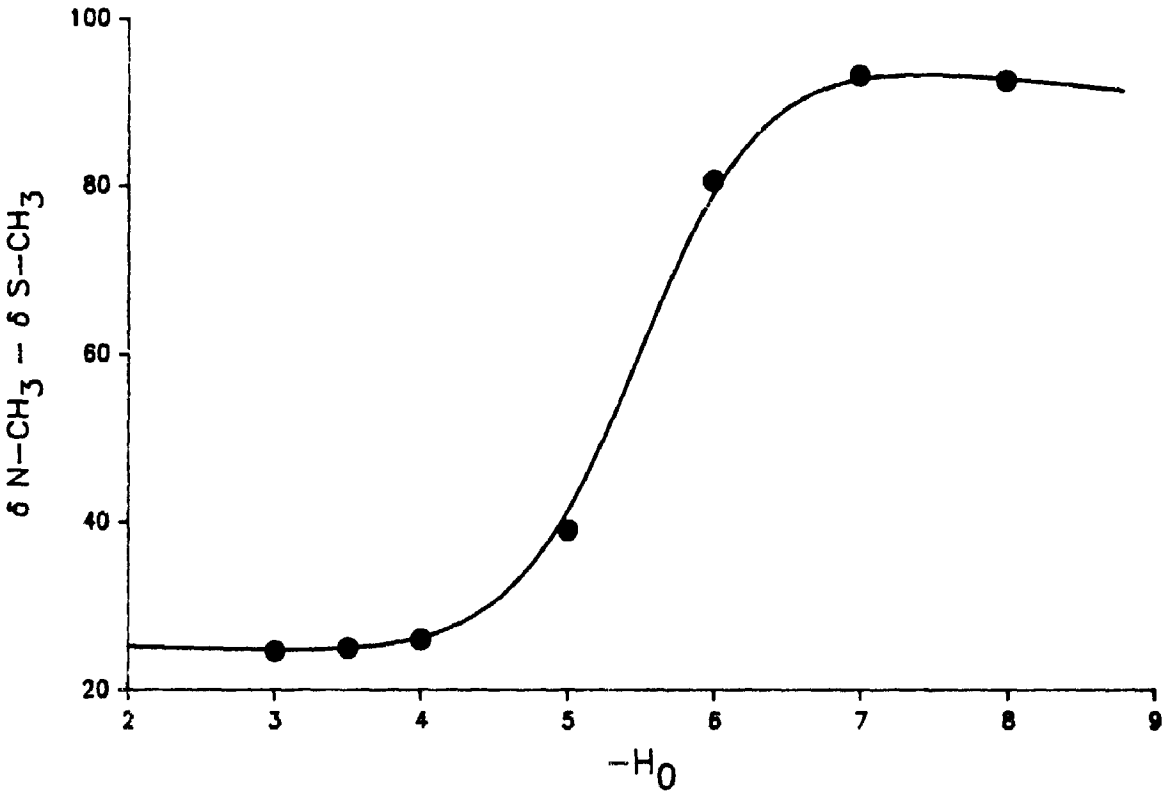
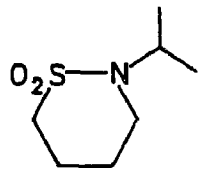


Figure 3.6 A plot of chemical shifts *vs.* $-H_0$ for *N*,*N*-dimethylmethanesulfonamide (*40*). Points are experimental; the curve is obtained using equation (5), where m = 0.6, n = 2.0, and pK_a = -5.51.



20e

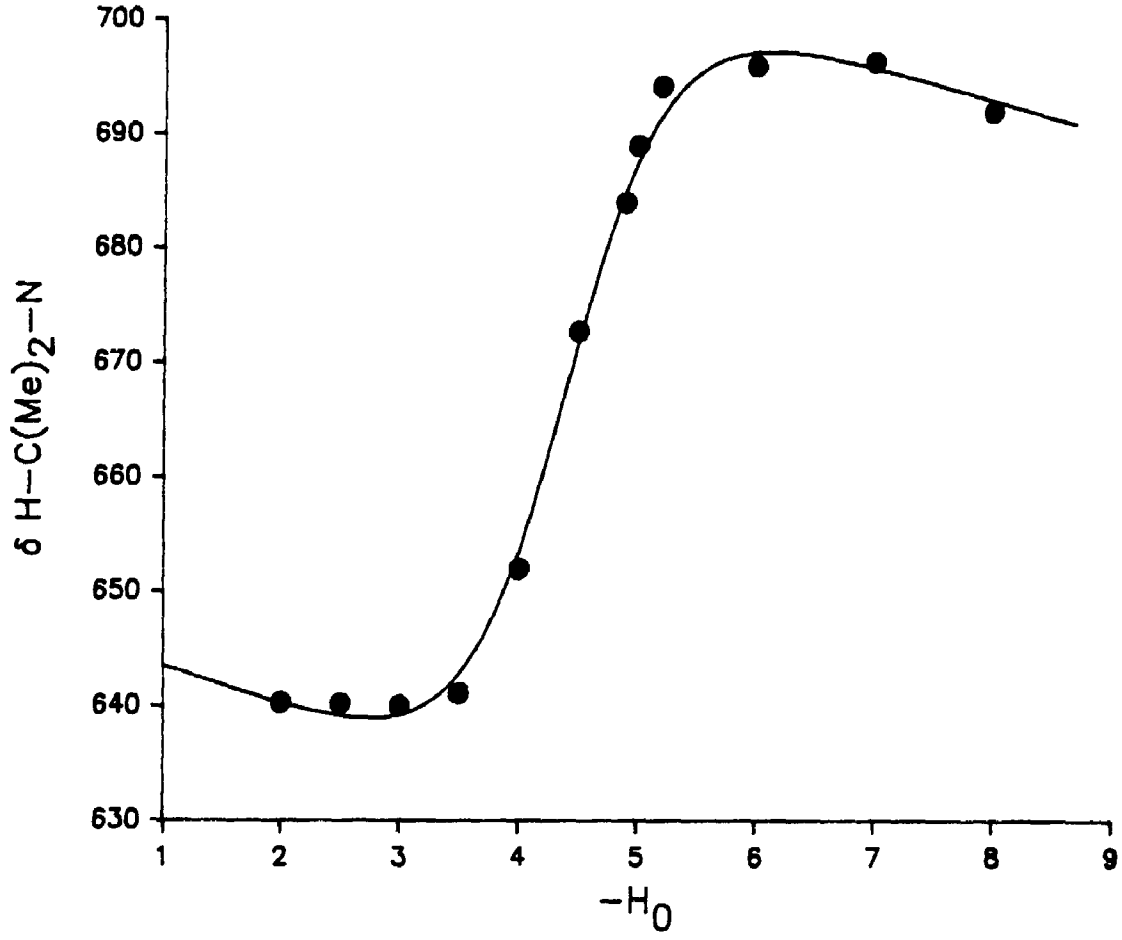


Figure 3.7 A plot of chemical shifts *vs.* $-H_0$ for *N*-isopropylbutane sultam (*20e*). Points are experimental; the curve is obtained using equation (5), where m = 3.5, n = 3.0, and pK_a = -4.40.

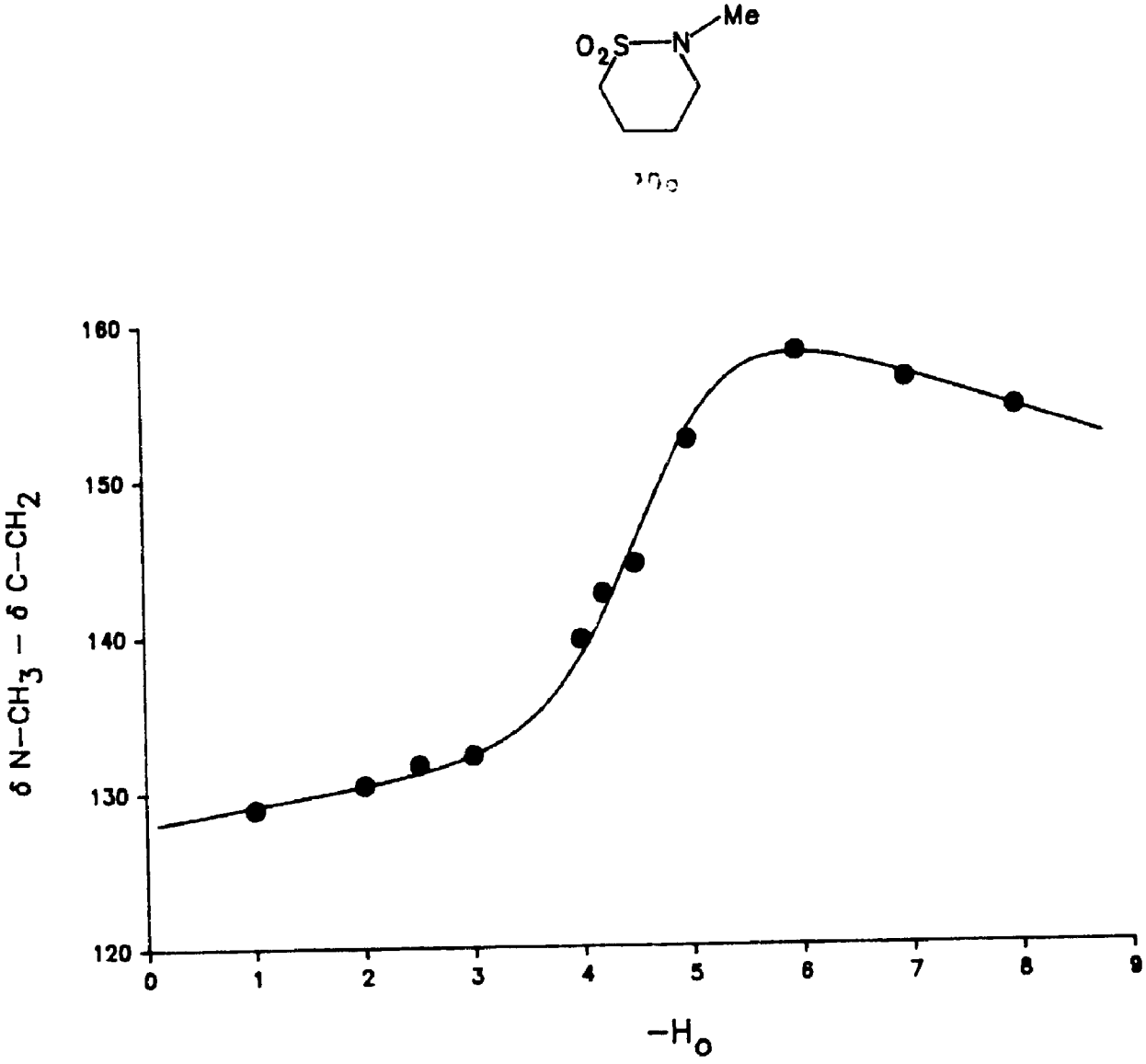
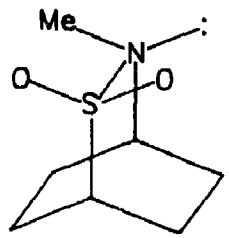


Figure 3.8 A plot of chemical shifts *vs.* $-H_o$ for *N*-methylbutane sultam (*20b*). Points are experimental; the curve is obtained using equation (5), where m = −1.2, n = 2.28, and pK_a = −4.62.



14

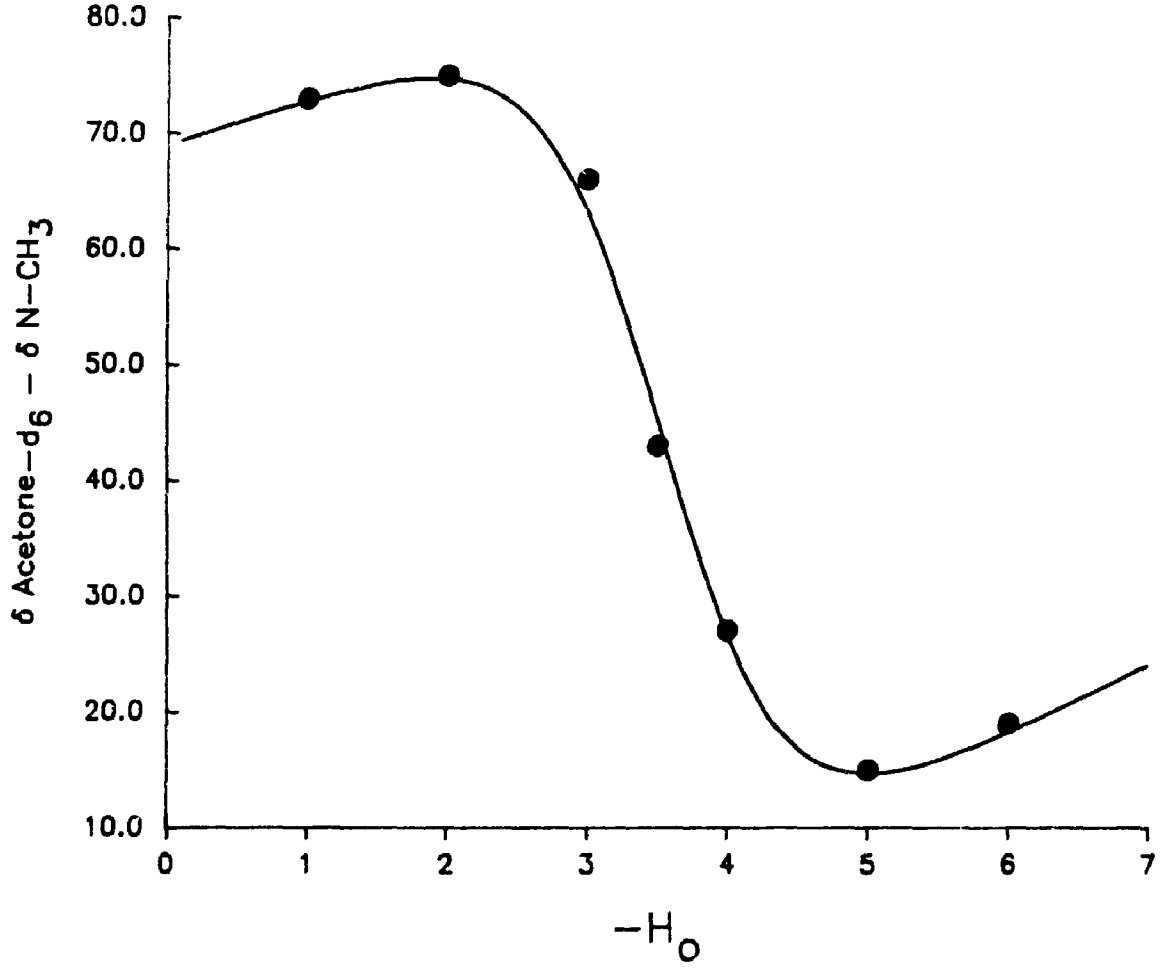
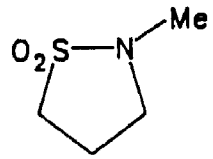


Figure 3.9 A plot of chemical shifts *vs.* $-H_o$ for *N*-methyl-2,3-thiazabicyclo[2.2.2] 2,2-dioxide (*14*). Points are experimental; the curve is obtained using equation (5), where m = -4.0, n = -6.0, and pK_a = -3.55.



12b

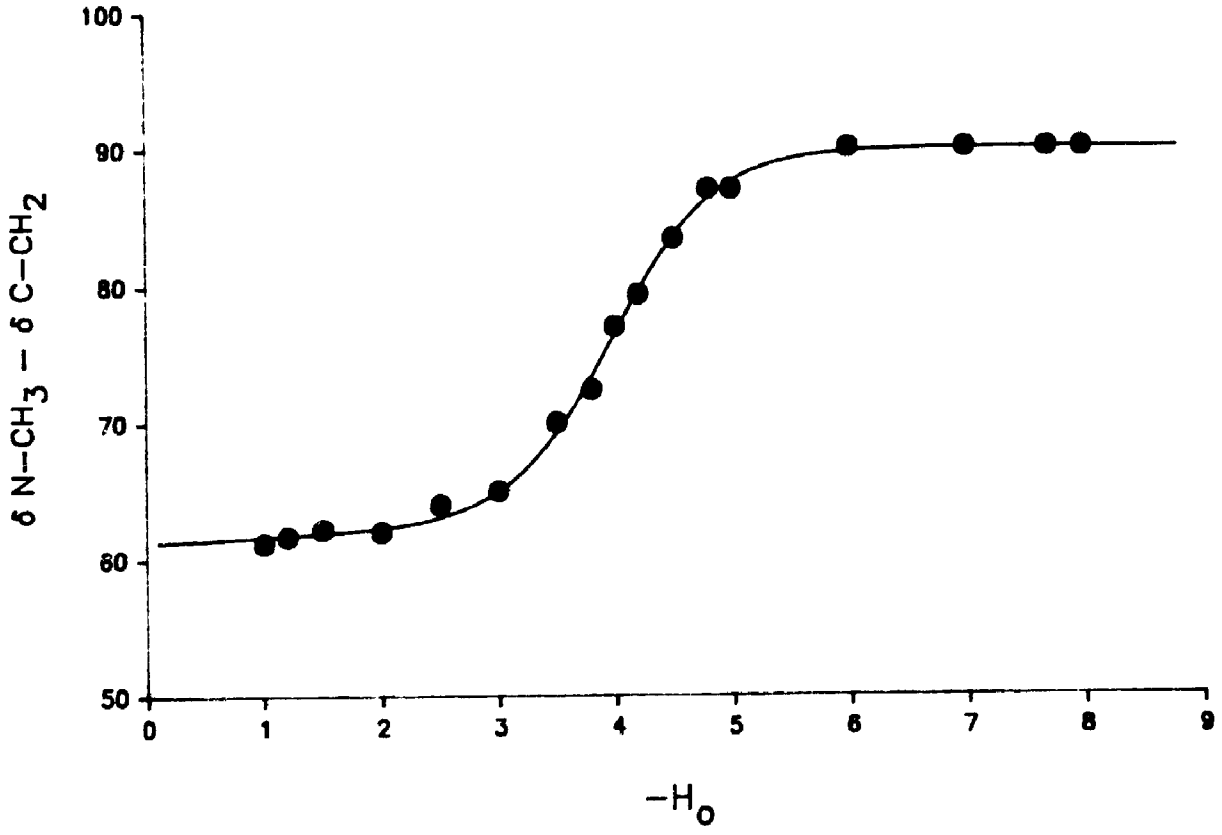


Figure 3.10 A plot of chemical shifts *vs.* $-H_0$ for *N*-methylpropane sultam (*12b*). Points are experimental; the curve is obtained using equation (5), where m = -0.4, n = 0.0, pK_a = 4.00.

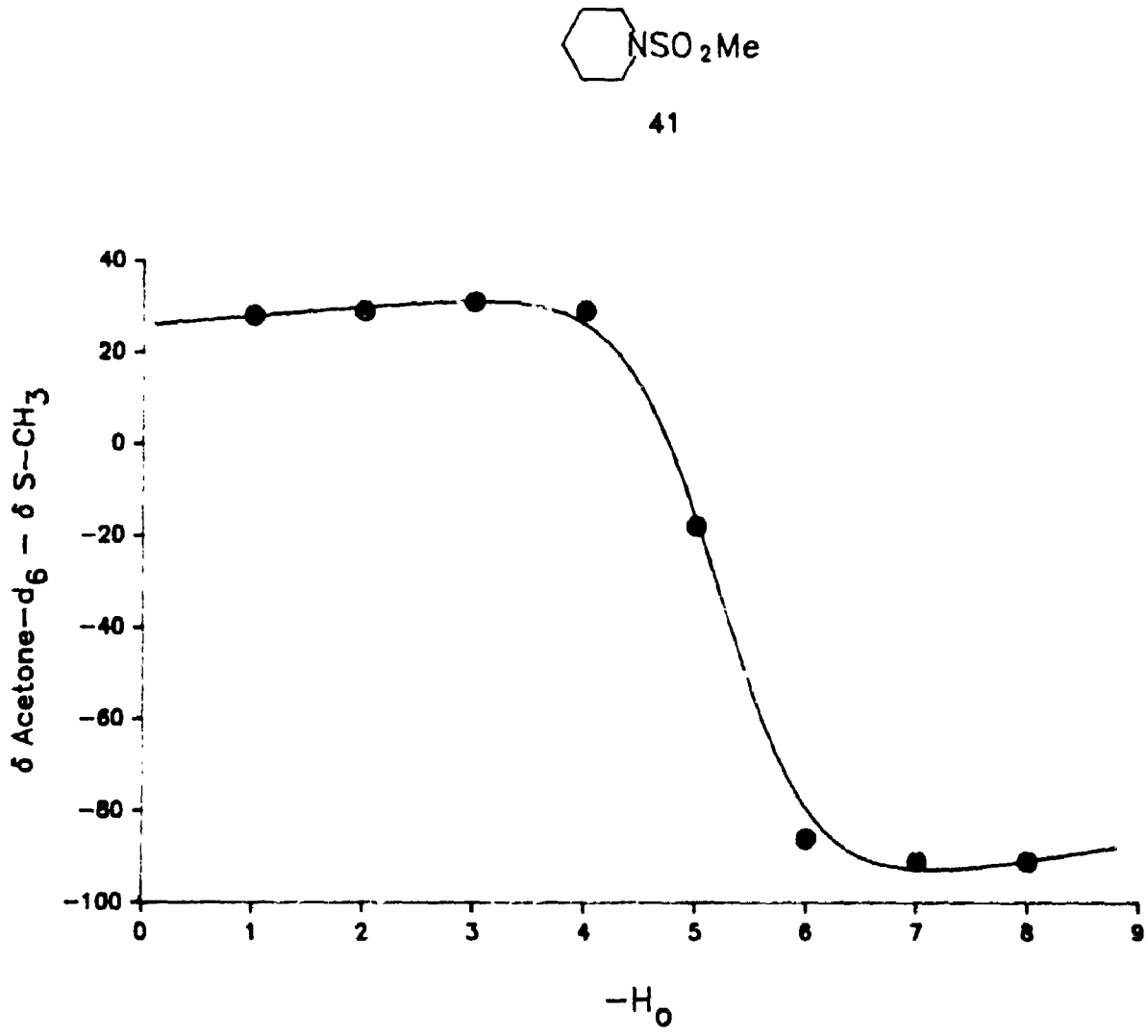


Figure 3.11 A plot of chemical shifts *vs.* $-H_o$ for methanesulfonylpiperidide (*41*). Points are experimental; the curve is obtained using equation (5), where m = -2.0, n = -1.0, and pK_a = -5.22.

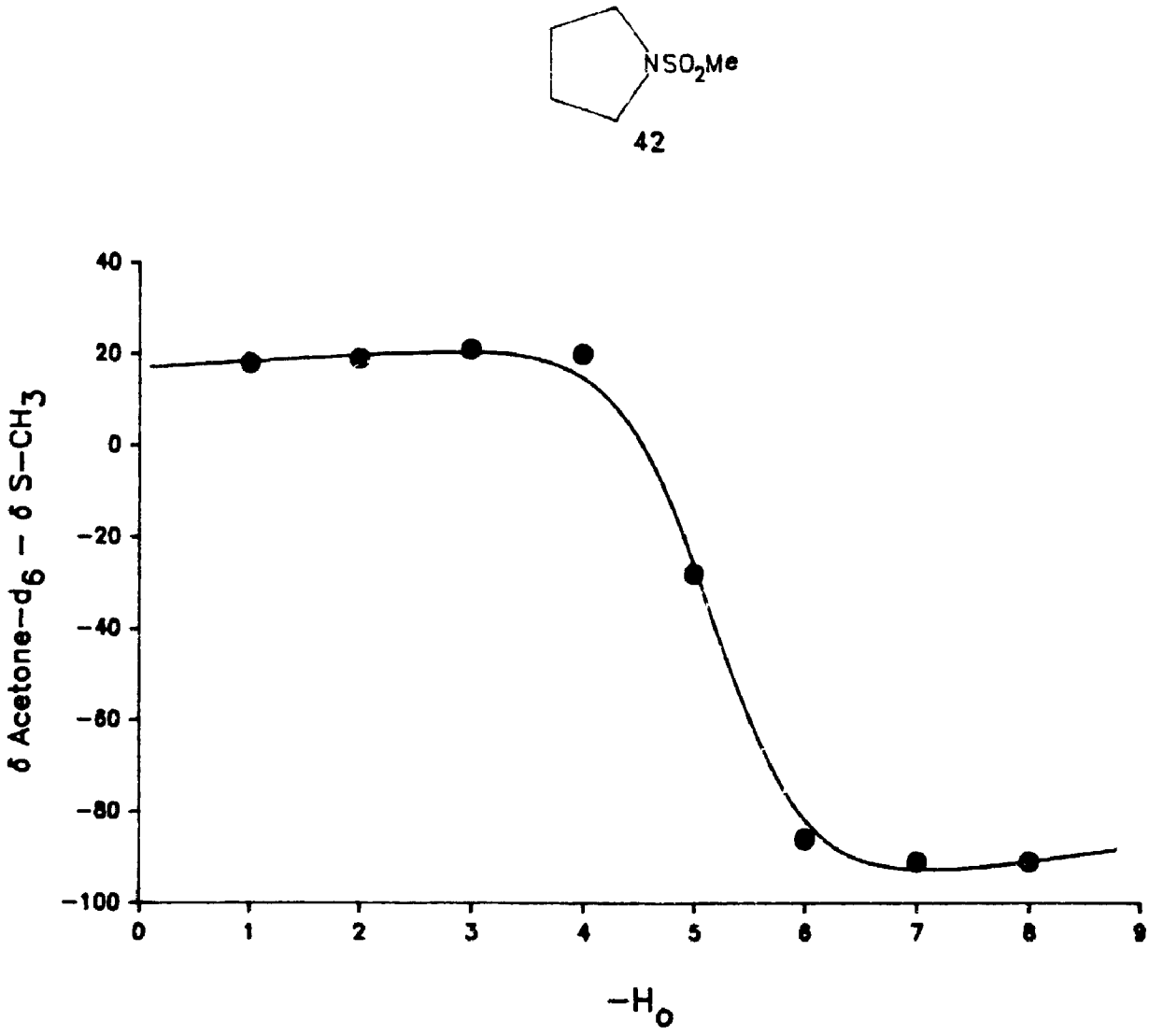


Figure 3.12 A plot of chemical shifts *vs.* $-H_0$ for methanesulfonylpiperidide (**42**). Points are experimental; the curve is obtained using equation (5), where m = -1.4, n = -3.5, and pK_a = -5.18.

Et_2NSO_2Me

43

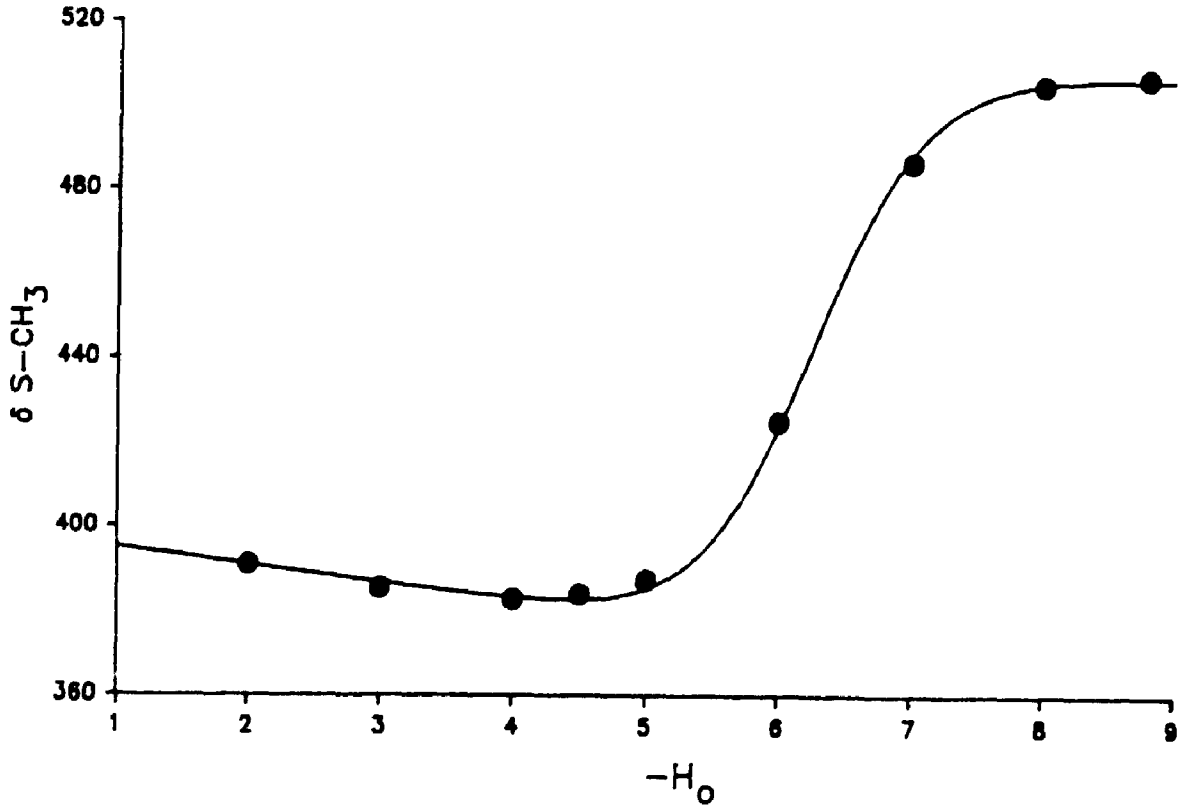
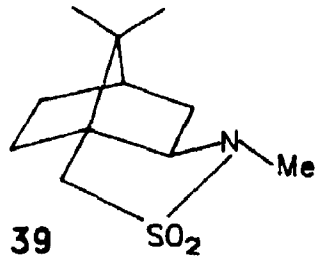


Figure 3.13 A plot of chemical shifts *vs.* $-H_0$ for *N*,*N*–diethylmethanesulfonamide (43). Points are experimental; the curve is obtained using equation (5), where m = 4.0, n = 1.28, and pK_a = –6.25.



39

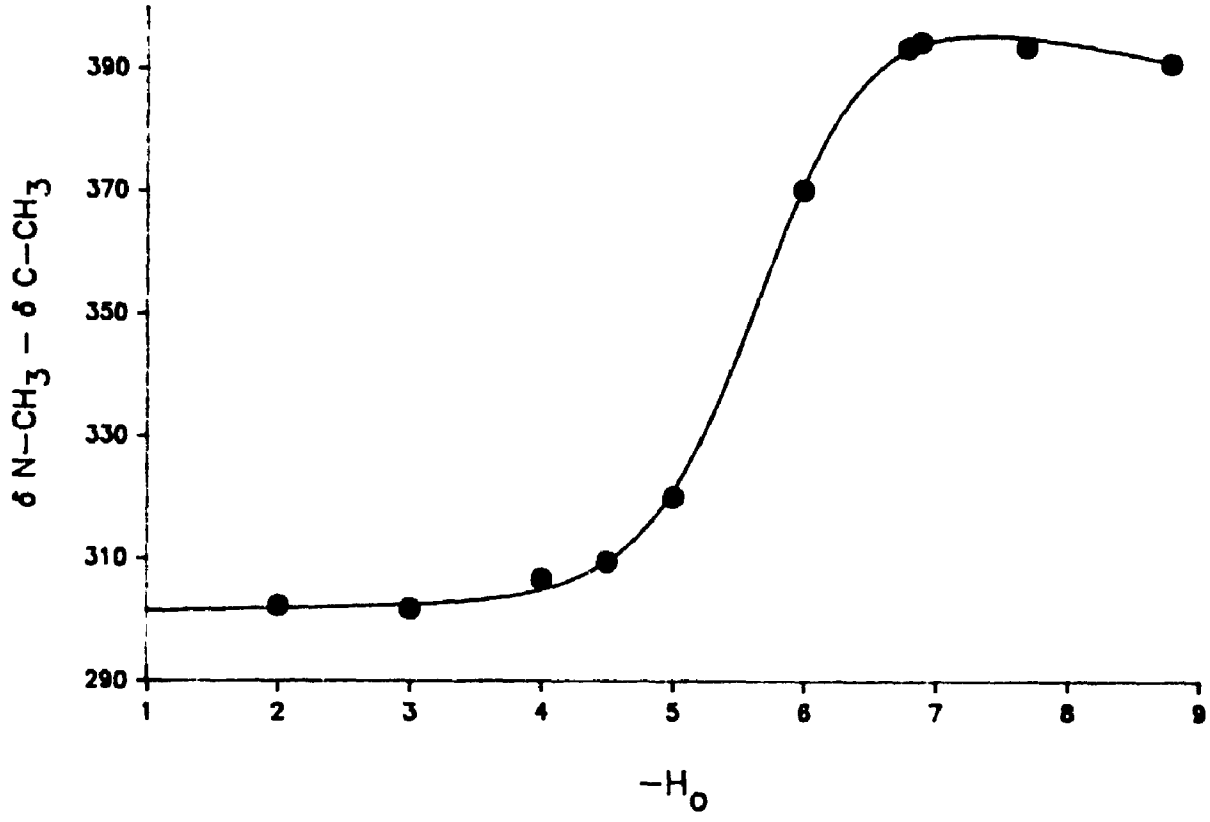
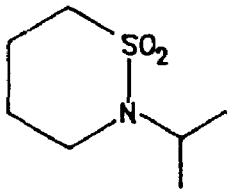
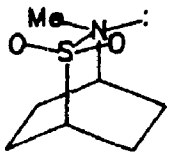
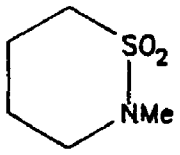
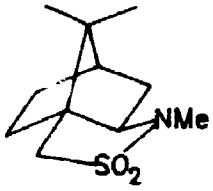
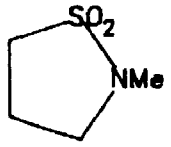
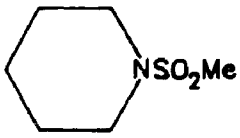
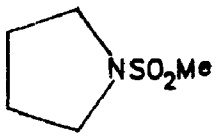
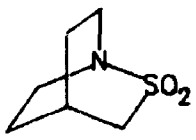
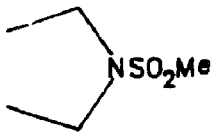


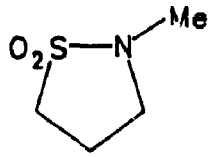
Figure 3.14 A plot of chemical shifts *vs.* $-H_0$ for *N*-methylcamphor sultam (39). Points are experimental; the curve is obtained using equation (5), where m = –0.4, n = 4.4, and pK_a = –5.69.

TABLE 3.1 Acidities of protonated sulfonamides.[a]

SN	Compound	$-pK_a$[b]	SN	Compound	$-pK_a$[b]
40	$MeSO_2NMe_2$	5.51	20e		4.40
14		3.55	20b		4.62
39		5.69	12b		4.00
41		5.22	42		5.18
15		3.97	43		6.25

a) At 20°C in aqueous sulfuric acid, determined from ^{1}Hmr spectra, using the H_0 scale of Jorgenson and Hartter.[31]

b) H_2SO_4 concentration (expressed as $-H_0$) at 50% protonation.



12b

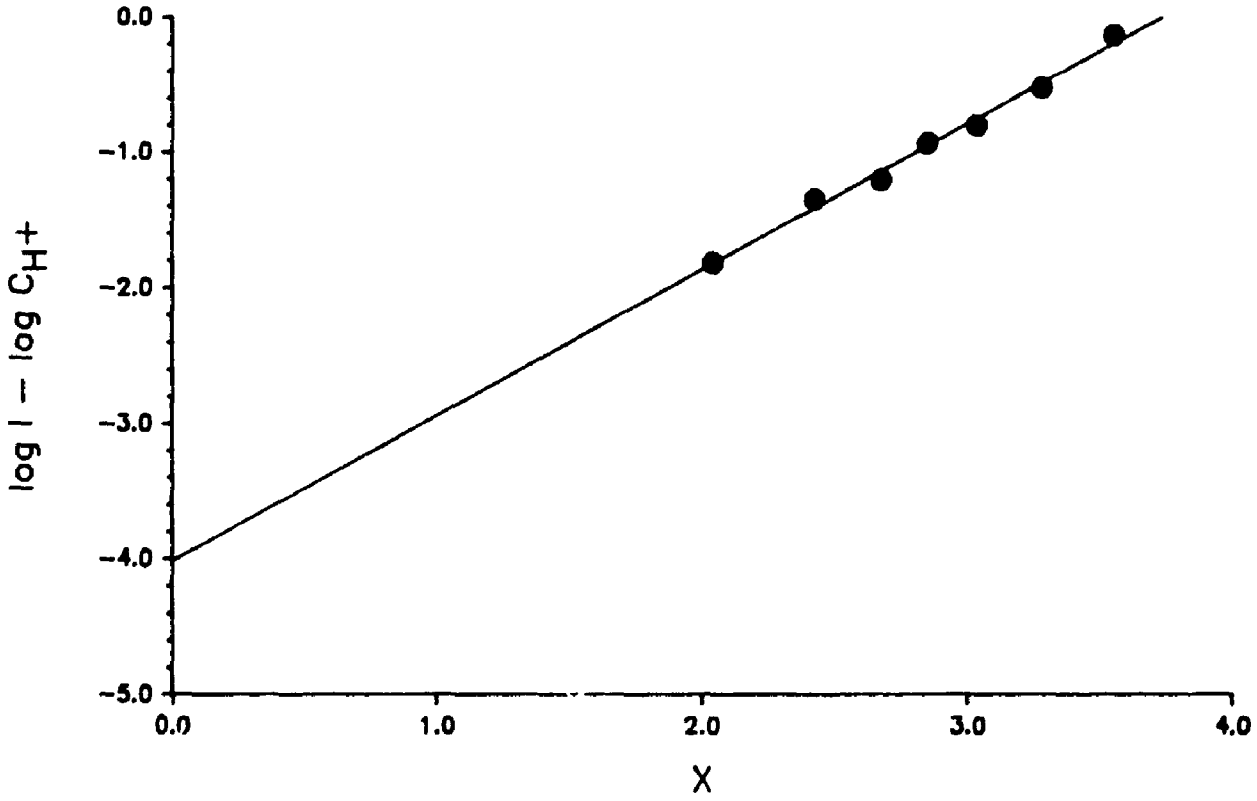


Figure 3.15 Plot of (log I − log C_{H^+}) *vs.* X for *N*-methylpropane sultam (*12b*) in aqueous sulfuric acid.[34]

orders of magnitude (ΔpK_a = 1.96). This is not surprising, because as was pointed earlier, in ***14*** the lone pair of electrons on nitrogen is not at the bisector of the sulfonyl oxygens (*i.e.*, $\theta \neq \sim 80^\circ$) in contrast to ***40*** in which $\theta = \sim 80^\circ$; it then is more readily available for protonation in ***14*** (less N⟶S delocalization) than in ***40***. The difference of pK_a's between 5-membered sultam ***12b*** and ***40*** was somewhat smaller (~1.51). As can be seen by examination of molecular models and a rough crystal structure of *N*-methylpropanesultam (***12b***) (determined by Professor N.C. Payne in this department), that the lone pair of electrons on nitrogen can not get to at the bisector of the sulfonyl oxygens without introducing considerable ring strain in the molecule, as will be discussed in a later section. The pK_a difference between 5- and 6-membered sultams (***12b*** and ***20b***) and between ***20b*** and *N*,*N*-dimethyl-methanesulfonamide (***40***) was 0.62 and 0.89 respectively. To ascertain that the pK_a difference of 0.62 between the 5- and 6-membered sultams is not simply due to the presence of the nitrogen in 5- and 6-membered rings, the pK_a's of methanesulfonyl-piperidide (***41***) and methanesulfonylpyrolidide (***42***) were determined and were found to be almost identical (~5.2).

The *N*-methylcamphor sultam (***39***) (a 5-membered sultam) gave an unexpectedly high pK_a (-5.69) (see Figure 3.14). The X-ray crystal structure of ***39*** was determined by professor N.C. Payne (see figure 3.16) and it is evident that the nitrogen lone pair of electrons is not at the bisector of sulfonyl oxygens (an "unfavourable" conformation for N⟶S delocalization). Inspection of molecular models indicates that if the N^+–H bond is in the same position as the nitrogen lone pair of electrons the solvation of the cation would not be efficient owing to the steric hindrance posed by C-10 methyl group; this would decrease the pK_a of the sulfonamide.[35,36] In the case of ***39*** two effects, lessened N⟶S delocalization and steric shielding of solvation act in opposite directions, with the stereoelectronic effect increasing the basicity and steric shielding of solvation decreasing it, with the net result very close to that of

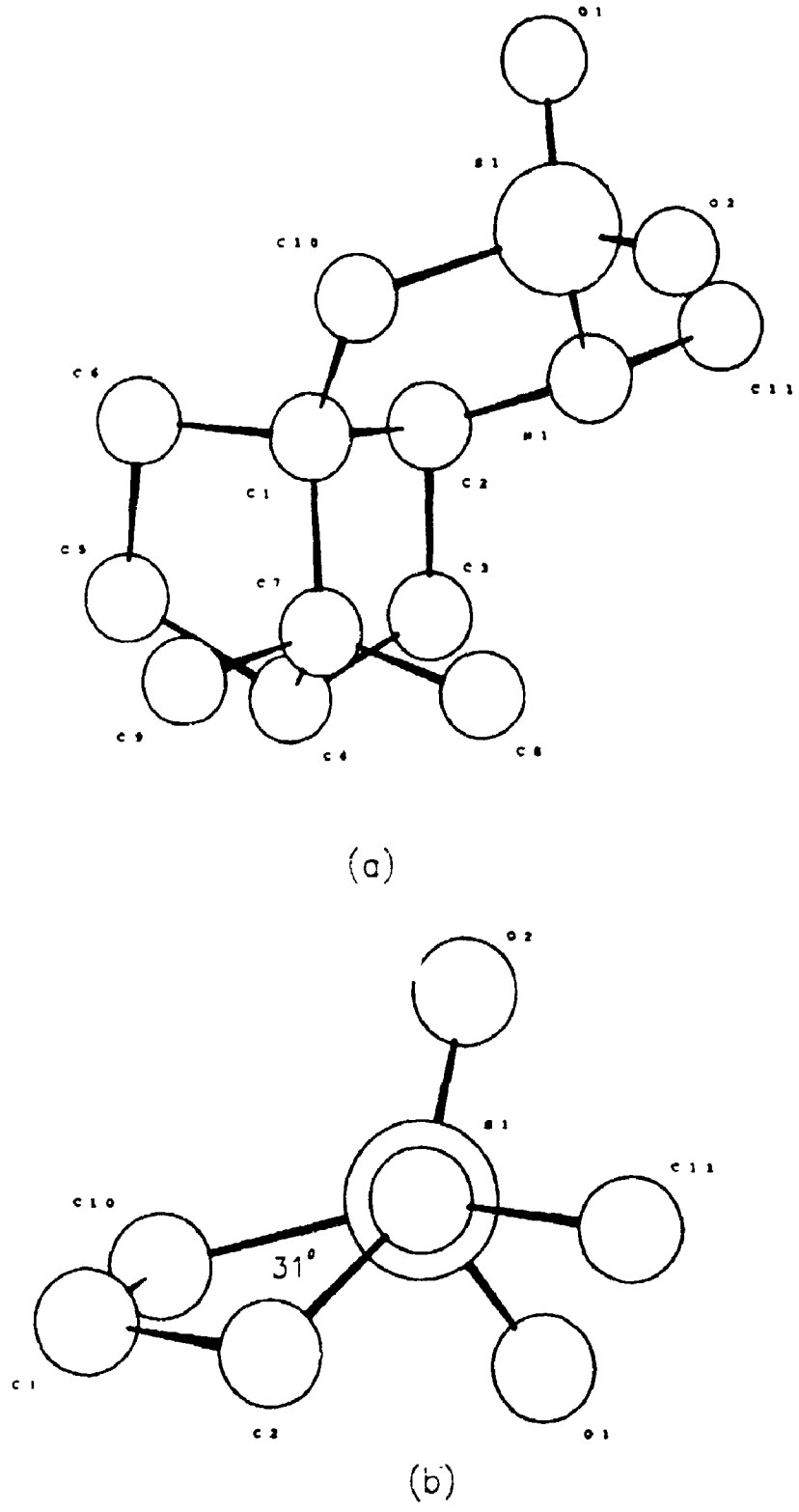


Figure 3.16 ORTEP Drawings of the N-methylcamphor sultam (**39**) (a) the full view, (b) the view of hetrocyclic ring looking through N-S bond.

40. The lower pK_a of *N,N*-diethylmethanesulfonamide (*43*) (-6.25) than of *N,N*-dimethylmethanesulfonamide (*40*) (-5.51) is probably an example of the decrease in pK_a due to steric shielding of solvation;[36] note that change of methyl group to ethyl in a less congested molecule, as in $CH_3SO_2NHCH_3$ to $CH_3SO_2NHC_2H_5$ has no effect on the pK_a.[30]

Attempts to measure the pK_a values of *N*-*t*-butyl sultams were unsuccessful as the *t*-butyl compound were found to be fragile in strongly acidic media. It was expected that bulky *t*-butyl group will occupy the equatorial position in *N*-*t*-butyl-butane sultam (*20c*) thus making the lone pair on nitrogen more accessible for protonation; but protonation was followed by rapid cleavage of the *t*-butyl group (presumably *via* the *t*-butyl carbocation) to give butane 1,4-sultam. *N*-Isopropyl-butane sultam (*20e*) gave a pK_a value of -4.40 (see Figure 3.7) which is slightly higher (0.22) than corresponding *N*-methyl sultam (*20b*). This is in reasonable agreement as isopropyl group (*A* value[37] = 2.15) is slightly bigger than the methyl group (*A* value[37] = 1.70), therefore in an equilibrium involving equatorial and axial alkyl groups, the isopropyl group has a higher probability of being in the equatorial position than the methyl group.

It is evident that change from the normal C-S-N-C dihedral angle (~80°), or in other words, when the lone pair of electrons on nitrogen can not bisect the sulfonyl oxygens, the N→S delocalization is diminished and, the base strength of the sulfonamides increased. This change in dihedral angle is believed to be responsible for the observed relatively high pK_a's of the conjugate acids of *14*, *12b*, *20b*, and *20e*.

3.2.4 Kinetics of Hydrochloric Acid promoted Cleavage (or Hydrochlorinolysis) of Sulfonamides

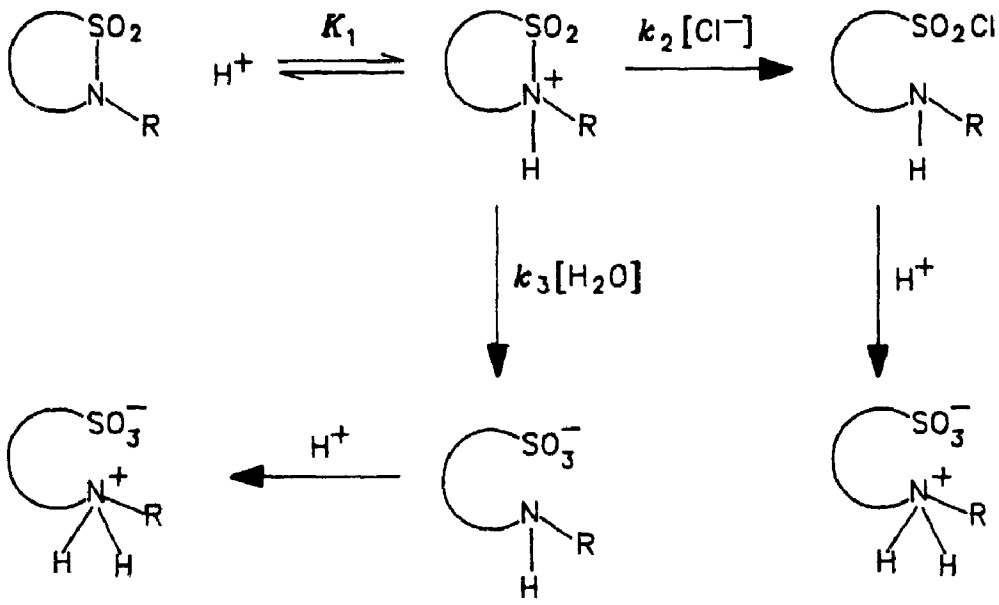
The rate constants of the hydrochlorinolysis (cleavage by hydrogen chloride) of sulfonamides and sultams were measured by ^{1}Hmr spectrosocopy in concentrated DCl–D_2O and HCl–H_2O at 21 °C. Under these reaction conditions, plots of the concentrations of unreacted starting material *vs.* tim. gave good first order rate plots for the hydrochlorinolysis reactions; from these plots values of k_{obs}, the pseudo first order rate constant, were obtained (see Experimental).

The products of the hydrochlorinolysis reactions were *N*–alkyl 3–chlorosulfonyl–alkanaminium chlorides (S–N cleavage by Cl^-) and the ammoniosulfonic acids (S–N cleavage by H_2O) with the former reaction predominating strongly.[38]

As mentioned earlier, the major product in each of the above reactions was the *N*–alkyl chlorosulfonylalkanaminium chloride. In case of ***12a***, ***12b***, ***14***, and ***39*** it was shown by making authentic samples of the *N*–alkyl chlorosulfonylalkanaminium chlorides (***13***, ***45***, ***46***, and ***47***) by the reaction of the sultams (***12b***, ***12a***, ***14***, and ***39*** respectively) with HCl in ether or methanol. These sulfonyl chlorides were characterized by ir, ^{1}H and ^{13}Cmr spectra. Their identity with the products of the reaction of sultam in concentrated HCl was shown by comparing the ^{1}H and ^{13}Cmr spectra of sulfonyl chlorides in D_2O–DCl with those of the reaction products. These chlorosulfonylalkanaminium chlorides were further characterized by their conversion to the corresponding sultams by reaction with triethylamine in ≥ 95% yield. In the cases of ***40*** and ***20b***, where the hydrochlorinolysis reaction was quite slow, the presence of methanesulfonyl chloride and *N*–methyl 4–chlorosulfonylbutaneaminium chloride was also detected by ^{1}H and ^{13}Cmr.

It has been found that the hydrochlorinolysis of the *N*–methylpropane sultam (***12b***) is much faster than that of either the corresponding 6–membered sultam ***20b***, or the acyclic counterpart *N*,*N*–dimethylmethanesulfonamide (***40***) (8652 times). The

pseudo first order rate constants were obtained for compounds ***40***, ***39***, ***20b***, ***12b***, ***14***, and ***15*** are included in Table 3.2.

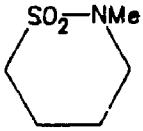
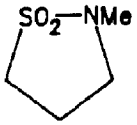
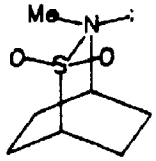
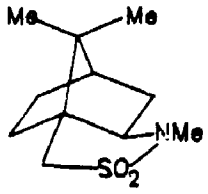
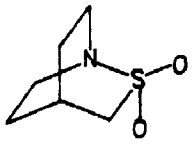


SCHEME 3.7

It was pointed out earlier that the sultams can be expected to exhibit the stereoelectronic effect in the initial step (protonation step) and the strain effect in the second step (S–N bond cleavage); *e.g.* the sultams would require the initial protonation on nitrogen as the initial step, and the *N*–protonated sultam would be attacked by nucleophile Cl^- or H_2O/D_2O. The proposed mechanism of the hydrochlorinolysis of sultams in D_2O–DCl or H_2O–HCl is shown in Scheme 3.7. From the above Scheme 3.7, the following equation for the observed rate constants (k_{obs}) can be obtained.

$$k_{obs} = \frac{k_2[Cl^-] + k_3}{1 + K_a/a_{H^+}} \qquad \text{.....(1)}$$

TABLE 3.2 Rate constants of the hydrochlorinolysis of the sulfonamides in D_2O/DCl and/or H_2O/HCl at 21° C.

Compound	$k_{obs}(s^{-1})^a$ (DCl/D_2O, 21°C) (rel. rates)	$-pK_a$	$k_{obs}(s^{-1})^b$ (HCl/H_2O, 21°C) (rel. rates)	$k_2'(s^{-1})$ (rel. rates)
40 $MeSO_2NMe_2$	3.7×10^{-8}	5.51	2.30×10^{-8} (1)	5.62×10^{-7} (1)
20b 	3.8×10^{-8}	4.62	6.27×10^{-8} (2.7)	2.70×10^{-7} (0.5)
12b 	3.3×10^{-4}	4.00	1.99×10^{-4} (8652)	3.43×10^{-4} (610)
14 	6.1×10^{-6}	3.55	3.44×10^{-6} (150)	4.33×10^{-6} (7.7)
39 	1.5×10^{-5}	5.69	9.63×10^{-6} (419)	3.38×10^{-4} (601)
15 	--	3.97[c]	5.77×10^{-7}[c] (25)	9.67×10^{-7} (1.7)

a) Determined by ^{1}Hmr.

b) Measured by Mr. J.H. Li.

c) Measured by Mr. D. Klassen.

As pointed out earlier, in support of this (and contrary to the mechanism of Klamann and Hofbauer[16]) J.H. Li in this laboratory found k_{obs} to depend linearly on $[Cl^-]$. For the slower reaction, where accurate determination of $k_2[Cl^-]$ and k_3 terms was not feasible (owing to conversion of the sulfonyl chloride to the sulfonic acid under the reaction conditions); the equation (1) may be simplified as:

$$k_{obs} = \frac{k_2'}{1 + K_a/a_{H^+}} \qquad \text{.....(2)}$$

where

$$k_2' = k_2[Cl^-] + k_3 \qquad \text{.....(3)}$$

The term K_a/a_{H^+} (protonation term, *i.e.*, ratio of unprotonated and protonated sulfonamide) would be expected to show primarily the stereoelectronic effect in the reaction in which the coordination of free electron pair involves, as mentioned earlier; and the term k_2' should show the effect of strain in the reaction in which the cleavage of S–N bond takes place. The values of k_2', were calculated using equation (2) and are listed in Table 3.2.

Sulfonamides ***20b***, ***12b***, ***14***, and ***40*** were chosen to investigate the relation between the calculated k_2''s and the observed rate constants (k_{obs}) of hydrochlorinolysis of *N*–methylated sulfonylammonium salts. The reaction of the sulfonylammonium salts with D_2O–DCl or H_2O–HCl is believed to be the same as the second step of the cleavage of sulfonamides, and the rate constants of the hydrochlorinolysis of sulfonylammonium salts should follow a pattern analogous to the k_2' term of the corresponding *N*–protonated sulfonylammonium salts. The *N*–methylated sulfonylammonium salts (or sulfonylammonium salts) were prepared by reacting the sultams with methyl trifluoromethanesulfonate ($CF_3SO_2OCH_3$), a known procedure,[41] and

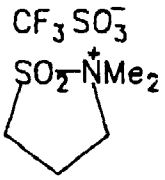
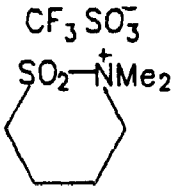
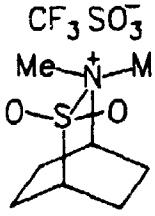
their rates of hydrochlorinolysis were measured in D_2O–DCl (37%) and/or H_2O–HCl at 20°C. The observed rate constants (k_{obs}) for the hydrochlorinolysis of sulfonylammonium salts and the estimated values of k_2' for the corresponding sulfonamides are listed in Table 3.3. These rate data indicate that the rates of hydrochlorinolysis of sulfonylammonium salts are much faster than those of the corresponding sulfonamides; and a plot of log k_{obs} of the sulfonylammonium salts *vs.* log k_2' shows that the rate constants of the sulfonylammonium salts follow a roughly linear relationship with the estimated k_2' values for the corresponding sulfonamides (slope = ~1) (see Figure 3.17) in accord with the postulated mechanism.

Comparison of the rate of hydrochlorinolysis in ***40*** vs. ***12b*** showed that the presence of ring strain associated with the 5-membered ring system[7,8] is responsible for more (by a factor of ~610 out of 8652 times) with a smaller rate acceleration of the reaction (by a factor of ~14) ascribed to the stereoelectronic effect (protonation factor) (see Table 3.4). Similarily, comparison of the rates of ***40*** *vs.* ***14*** showed that rate acceleration of 150 is largely due to the stereoelectronic effect (~20-fold), but that there is a further factor of 7.7 ascribable to strain, most probably torsional strain. The stereoelectronic effect in sulfonamides which do not have the lone pair of electrons on the nitrogen at the bisector of the sulfonyl oxygens, is evidently responsible for a rate acceleration of at least 15–20–fold. Tne rate differences due to the stereoelectronic effect in sulfonamides ***12b*** and ***14*** are relatively small because these rates of hydrochlorinolysis are measured in very acidic media (H_0 = –4.14) in which these sulfonamides are mostly protonated. Observed rate constants (k'_{obs}) of the sulfonamides may be estimated, using equation (5), for a higher H_0 value, where they would not be completely protonated; these values indicate a higher protonation factor. At H_0 = –2, for example, the stereoelectronic effect (or protonation factor) would probably lead to rate difference, of about 88– and 33–fold.

The amount of ring strain factors in 6–membered sultams ***20b*** and ***15*** are of

TABLE 3.3

Rate constants of the hydrochlorinolysis of the sulfonylammonium salts in D_2O–DCl and/or H_2O–HCl at 21°C.

Compound	k_{obs} (s^{-1})[a] (DCl/D_2O, 21°C) (rel. rates)	k_2'(s^{-1}) (DCl/D_2O, 21°C) (rel. rates)	k_{obs} (s^{-1})[a,b] (HCl/H_2O, 21°C) (rel. rates)	k_2'(s^{-1}) (HCl/H_2O, 21°C) (rel. rates)
$MeSO_2\overset{+}{N}Me_3$ $CF_3SO_3^-$ **50**	2×10^{-5}	4.9×10^{-7}	1.5×10^{-5}	5.62×10^{-7}
 **51**	1×10^{-2}	4.6×10^{-4}	3.0×10^{-3}	3.43×10^{-4}
 **52**	9×10^{-7}	1.0×10^{-7}	9.6×10^{-7}	2.70×10^{-7}
 **53**	3×10^{-5}	7.0×10^{-6}	--	4.33×10^{-6}

a) Determined by ^{1}Hmr.

b) Measured by Mr. J.H. Li.

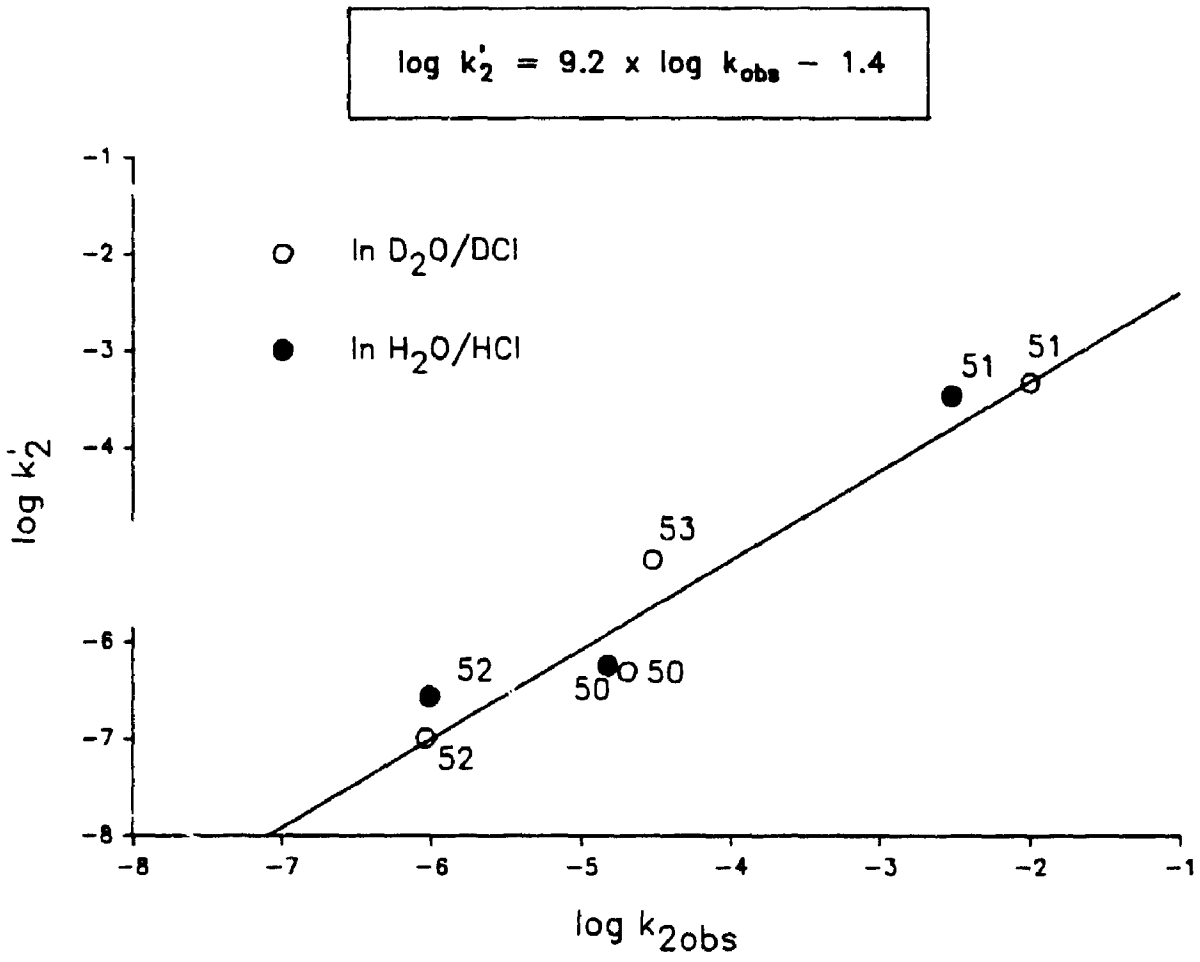
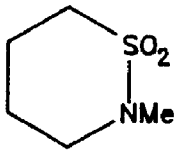
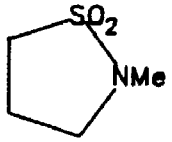
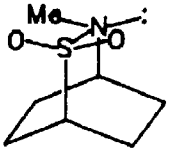
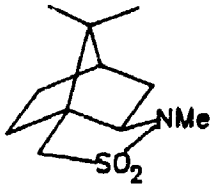
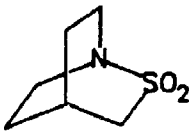


Figure 3.17 A plot of log k_{obs} (observed rate constant of hydrochlorinolysis of sulfonylammonium salts) *vs.* log k_2' (the second step in the hydrochlorinolysis of the sulfonamides). The slope (r) of the line is ~0.9.

TABLE 3.4 Total relative rate constants of the sulfonamides in concentrated hydrochloric acid at 21° C and their analysis.

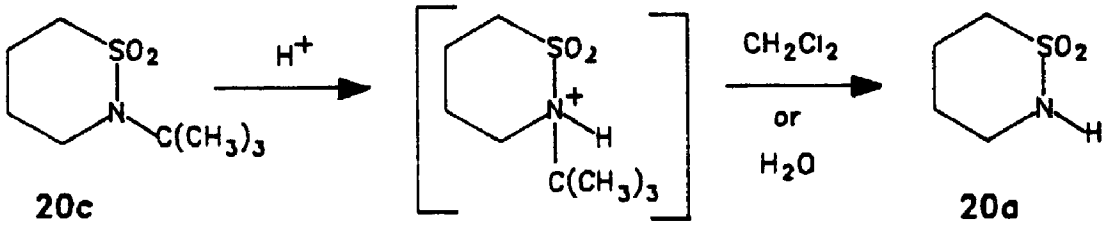
SN	Compound	Total Relative Rates	Ring–opening Factor	Protonation Factor
40	$MeSO_2NMe_2$	(1)	(1)	(1)
20b		2.7	0.5	5.4
12b		8652	610 (angle strain)	14.2
14		150	7.7	20
39		419	601 (angle strain)	0.7
15		25	1.7	14.7

similar order but the protonation factor is about 5.4 and 15 respectively. In the case of *15* it is in clear accord with the earlier experiments[18] that, although the nitrogen lone pair is at the bisector of sulfonyl oxygens, it is probably unable to donate the electrons fully into the sulfonyl sulfur because shortening of the N–S bond and flattening of nitrogen pyramid would introduce ring strain into the molecule.[42] As was pointed out earlier, the six membered sultams can exist in two conformations in which one of them has the substituent equatorial, sterically the favoured arrangement, and other one has the substituent axial, stereoelectronically the favoured arrangement. The *N*–methyl substituted sultam *20b* is a liquid and shows two sets of SO_2 stretching bands in infrared spectrum (see section 3.2.6) suggesting that this compound has both conformations present. The increase in rate of hydrochlorinolysis by a factor of 5.4 when compared with *40* may be due to the presence of the equatorially substituted sultam, which does not have the nitrogen lone pair at the bisector of sulfonyl oxygens. The 5–membered sultam *39* does not show a substantial increase in rate due to the protonation factor, but has similar ring strain (rate increase by a factor of 601) when compared with *N*–methylpropane sultam (*12b*) (a factor of 610). It has already been pointed that in the protonation step the *N*–protonated sulfonamide *39* is inhibited owing to poor solvation arising because of steric hindrance.

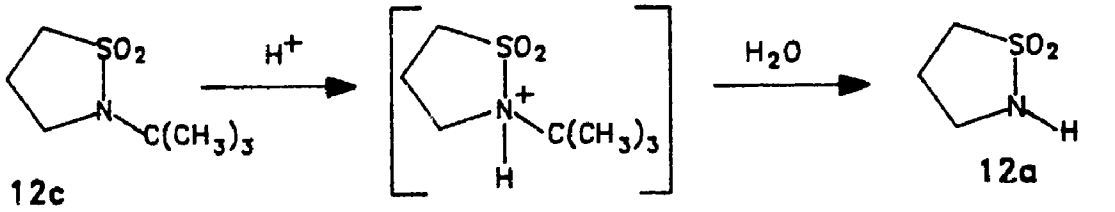
It is evident that the protonation factor in which the stereoelectronic effect is of importance in sulfonamides, and this can be demonstrated in the variation of reactivity with variation in the C–S–N–C dihedral angle, which can be related to variation in the delocalization of the electron lone pair on the nitrogen.

3.2.5 The Hydrochlorinolysis of *N*-*t*-Butyl Substituted Sultams

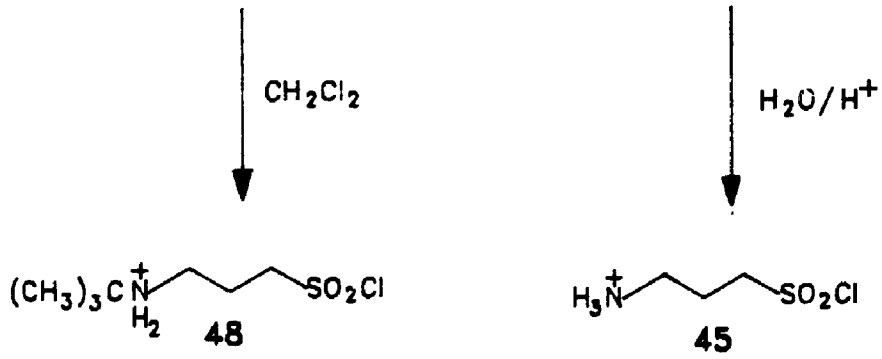
Usually sulfonamides are cleaved at the sulfur nitrogen bond by acid hydrolysis, but when the nitrogen atom is substituted by an alkyl group that forms a stable carbocation, the cleavage is also capable of taking place at the carbon-nitrogen bond, and dealkylated sulfonamides are formed (see Scheme 3.8). Briscoe and coworkers,[39] for example, found that *N*-*t*-butyl-*p*-toluenesulfonamide with hydrochloric acid gave *t*-butyl chloride and *p*-toluenesulfonamide. *N*-*t*-Butylbutane sultam (***20c***) and *N*-*t*-butylpropane sultam (***12c***) on treatment with D_2O-DCl in an nmr tube resulted in corresponding dealkylated compounds ***20a*** and ***12a*** within two minutes, as shown by ^{1}Hmr spectroscopy. In the case of ***12a*** it further reacted to give 3-chlorosulfonyl- propanaminium chloride (***45***) ($t_{1/2}$ = 45 min) whereas ***20a*** remain unchanged even after 1 week. Reaction of ***20c*** with HCl gas in dichloromethane also resulted dealkylated product (***20a***), whereas ***12c*** in similar reaction conditions gave *N*-*t*-butyl 3-chlorosulfonylpropanaminium chloride (***48***). It is well known[40] that S_N1 reactions are slower in nonpolar media (CH_2Cl_2) than in polar media (D_2O). It has been pointed out earlier that a 5-membered sultam is much more reactive than its 6-membered analogue and it is therefore not surprising that in dichloromethane solution the bimolecular attack of chloride ion at sulfonyl sulfur to give ***48*** is faster than S_N1 cleavage of *t*-butyl group.



20c 20a



12c 12a



SCHEME 3.8

3.2.6 The Infrared Spectra of Some Cyclic and Acyclic Sulfonamides

Although detailed studies have been made of the infrared spectra of the carboxyamides,[43] only a few papers on infrared spectra of the sulfonamides have appeared.[44] Baxter, Cymerman-Craig, and Willis,[45] who have examined the infrared spectra of twenty-five unsubstituted, *N*-monosubstituted, and *N*,*N*-disubstituted sulfonamides both in the solid state and in solution, found that all the sulfonamides show two strong bands at frequencies near 1160 and 1350 cm^{-1}. These bands had been assigned to the symmetric (ν_s) and asymmetric (ν_{as}) vibrations of the S–O bonds. Both frequencies, and particularly the higher one, are greater than the frequencies for sulfones (1124–1150 and 1299–1313 cm^{-1} in the solid state). The frequencies for sulfonamides and sulfones are, however, lower than the corresponding frequencies for sulfonyl chlorides (1168–1183 and 1361–1384 cm^{-1}), sulfonyl fluorides (1167–1197 and 1401–1412 cm^{-1}), and sulfonic esters (1420–1330 and 1200–1145 cm^{-1}).[46]

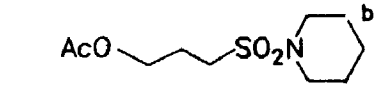
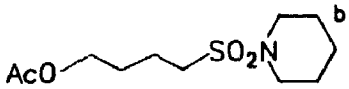
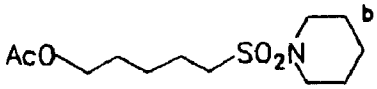
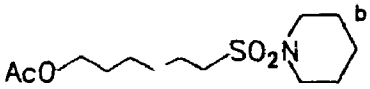
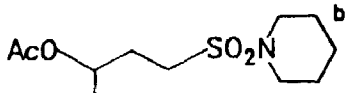
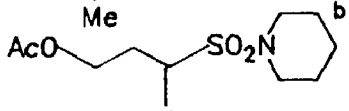
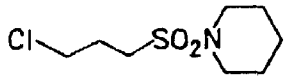
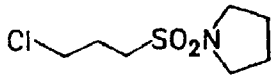
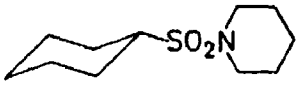
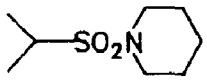
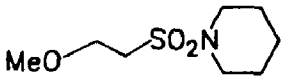
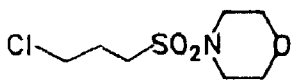
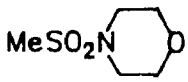
It was pointed by Baxter *et al.*[45] that the lower frequency (symmetric stretching), 1155–1170 cm^{-1}, is little affected by the change from solid to solution, but the higher frequency (asymmetric stretching) is 10–20 cm^{-1} greater in carbon tetrachloride solution than in the solid state. These authors have also pointed out that both frequencies show slight increase on changing the sulfonamide from the unsubstituted through the mono- to the disubstituted compounds.

In the course of this work, we have measured the infrared spectra of a number of mono- and disubstituted sulfonamides as well as cyclic sulfonamides (sultams), mainly in the solid state (KBr pellets), with also a few in solution; the frequencies are listed in Table 3.5.

It has been pointed earlier that the most favourable conformation of sulfonamides is evidently the one in which the lone pair of electrons on nitrogen bisects the sulfonyl oxygens (*i.e.* $\theta = \sim 80^{\circ}$) (see Figure 3.4). Most acyclic compounds can attain this conformation without much difficulty, whereas, in some cyclic compounds either

TABLE 3.5

Symmetric and asymmetric vibration frequencies[a] of the $-SO_2-$ group.

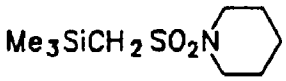
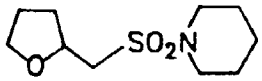
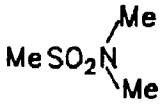
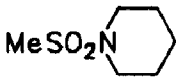
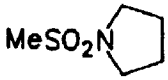
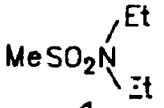
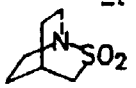
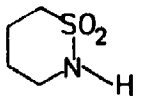
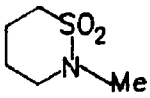
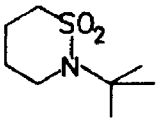
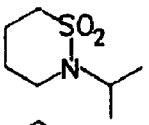
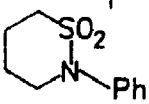
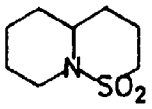
SN	Sulfonamide	ν_{as}	ν_s	Mean wave number
54	 [b]	1333	1140	1236.5
55	 [b]	1340	1145 (1165)	1242.5 (1252.5)
56	 [b]	1336	1136 (1145)	1236 (1240.5)
57	 [b]	1334 (1320)	1134 (1159)	1234 (1239.5)
58	 [b]	1327	1148	1237.5
59	 [b]	1323	1157	1240
60	 [b]	1323	1148	1235.5
61		1333 (1291)	1140 (1157)	1236.5 (1224)
62		1329 (1291)	1138 (1197)	1233.5 (1244)
63		1318 (1281)	1138 (1163,1117)	1228 (1222,1199)
64		1323 (1273)	1136 (1163)	1229.5 (1218)
65		1335	1163 (1140,1117)	1249 (1237.5,1226)
66		1341 (1262)	1154 (1113)	1247.5 (1187.5)
67		1325 (1344)	1154 (1111)	1239.5 (1227.5)

[a] Values in parenthesis indicate the minor band.

[b] See chapter 1 for the synthesis and spectra of compounds 54–60.

TABLE 3.5 continued....

Symmetric and asymmetric vibration frequencies of the $-SO_2-$ group.

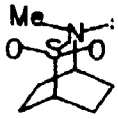
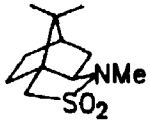
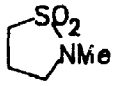
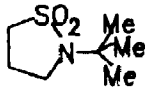
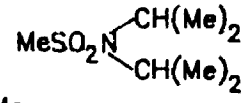
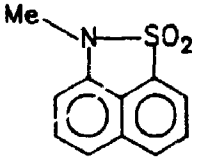
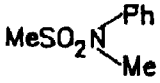
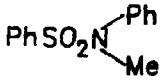
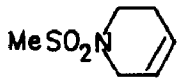
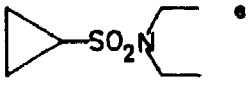
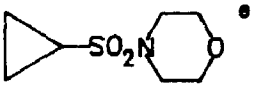
SN	Sulfonamide	ν_{as}	ν_s	Mean wave number
68		1320 (1331)	1140 (1151,1166)	1230 (1241,1248.5)
69		1333 (1359)	1163 (1142)	1248 (1250.5)
40		1325	1152	1238.5
41		1325	1156	1240.5
42		1321	1146	1233.5
43		1327	1146	1236.5
15	 [d]	1327	1138	1232.5
20a		1314 (1291)	1129 (1177)	1221.5 (1234)
20b		1331 (1293)	1144 (1157)	1237.5 (1225)
20c		1325 (1294)	1134 (1194)	1229.5 (1244)
20e		1325 (1296)	1138 (1184)	1231.5 (1240)
20d		1298 (1325)	1134 (1192)	1216 (1258.5)
17	 [c]	1321 (1294)	1138 (1175)	1229.5 (1234.5)

[c] Low temperature ^{13}Cmr indicated the presence of two conformations.

[d] Synthesized by Mr. D. Klassen.

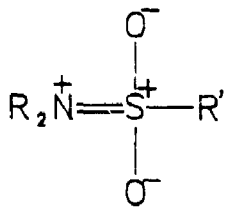
TABLE 3.5 continued....

Symmetric and asymmetric vibration frequencies of the $-SO_2-$ group.

SN	Sulfonamide	ν_{as}	ν_s	Mean wave number
14		1287	1132	1209.5
39		1310	1132	1221
12a		1296	1136	1216
12b		1293	1125	1209
12c		1291	1129	1210
12d		1289 (1308)	1136	1212.5 (1222)
70		1308	1138 (1192)	1223 (1250
73		1306	1134 (1165)	1220 (1235.5)
71		1331	1144 (1179)	1237.5 (1255)
72		1347	1179 (1156)	1263 (1235.5)
74		1341	1159	1250
75		1329	1142	1235.5
76		1345	1156	1250.5

[e] Synthesized by Mr. J. Lam

this conformation results in a sterically crowded molecule or the geometry of molecule is such that the favourable conformation can not be achieved. The fact that the sulfonamides with 'favourable conformation' (i) have lower pK_a's and (ii) are relatively slow to hydrolyse, compared to the sulfonamides which do not have this 'favourable conformation,' suggests that the lone pair of electrons is less available for the protonation in these compounds. As was pointed out earlier, the adjacent nonbonding electrons from nitrogen are withdrawn by resonance into the sulfonyl sulfur as indicated by the canonical form shown below:



Sulfonyl compounds are generally considered analogues of carbonyl compounds, but an interesting distinction between them is that sulfonyl compounds are much less subject to mesomeric conjugative effects through the π_p orbitals. Nitrogen substituents, for example, result in a marked upward shift in SO_2 stretching frequencies in sulfonyl compounds, when compared with carbonyl compounds. Bellamy[43] has suggested that as the electronegativity of the substituent increases the S–O bond becomes more covalent.

Bellamy and Williams[50] have also pointed to an interesting correlation of $-SO_2-$ symmetric and asymmetric stretching frequencies. On the basis that both symmetric and asymmetric frequencies are essentially free from mass and coupling effects, both of these frequencies would be expected to be dependent on any common factors (*e.g.*, electronic effect of the substituents), and they should therefore be directly related to each other. They have demonstrated that a plot of asymmetric frequency *vs.* symmetric frequency of acyclic sulfonamides showed a good linear relationship (see

Figure 3.18), and a provisional identification of one of these bands can be confirmed by reference to the precise position of the other.[50] The asymmetric stretching frequencies were plotted against symmetric frequencies for a number of cyclic and acyclic sulfonamides prepared in this laboratory, as shown in Figure 3.19. The acyclic compounds followed the Bellamy and Williams' prediction quite satisfactorily. The sultams with fixed conformation, namely ***14***, ***39***, ***12a***, ***12b***, ***12c***, and others which do not have the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens, fell together as if they were member of electronically different species (*e.g.* in the zone of sulfones). The 6-membered sultams (***20a*** to ***20e*** and ***17***) are believed to have two most probable conformations, (i) one which does not have the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens, but is sterically less crowded (see structure ***21*** in Scheme 3.2 and ***17a***), (ii) one which has the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens is, sterically more crowded (see structure ***22*** in Scheme 3.2 and ***17c***). Compound ***17*** showed the presence of two conformations at low temperature, which leads one to suggest that the two sets of $-SO_2-$ stretching bands in infrared may arise from two different conformations. It is speculated that analogous splitting observed in the infrared spectra of other 6-membered sultams may very well arise due to presence of two conformations, though it is not certain at present if this splitting of the $-SO_2-$ bands could be due to another reason, for example Fermi resonance.[47] One of the two sets of $-SO_2-$ stretching bands following the Bellamy-William pattern, and the other set of bands showed deviation from this general prediction. It was suggested that bands which do not fall on Bellamy-Williams line (see Figure 3.19) are arising from the conformation which does not have the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens (structures ***21*** and ***17a***). Interestingly, the $-SO_2-$ stretching bands of simple sulfene[48] ($CH_2=SO_2$) do not follow the Bellamy-Williams pattern.

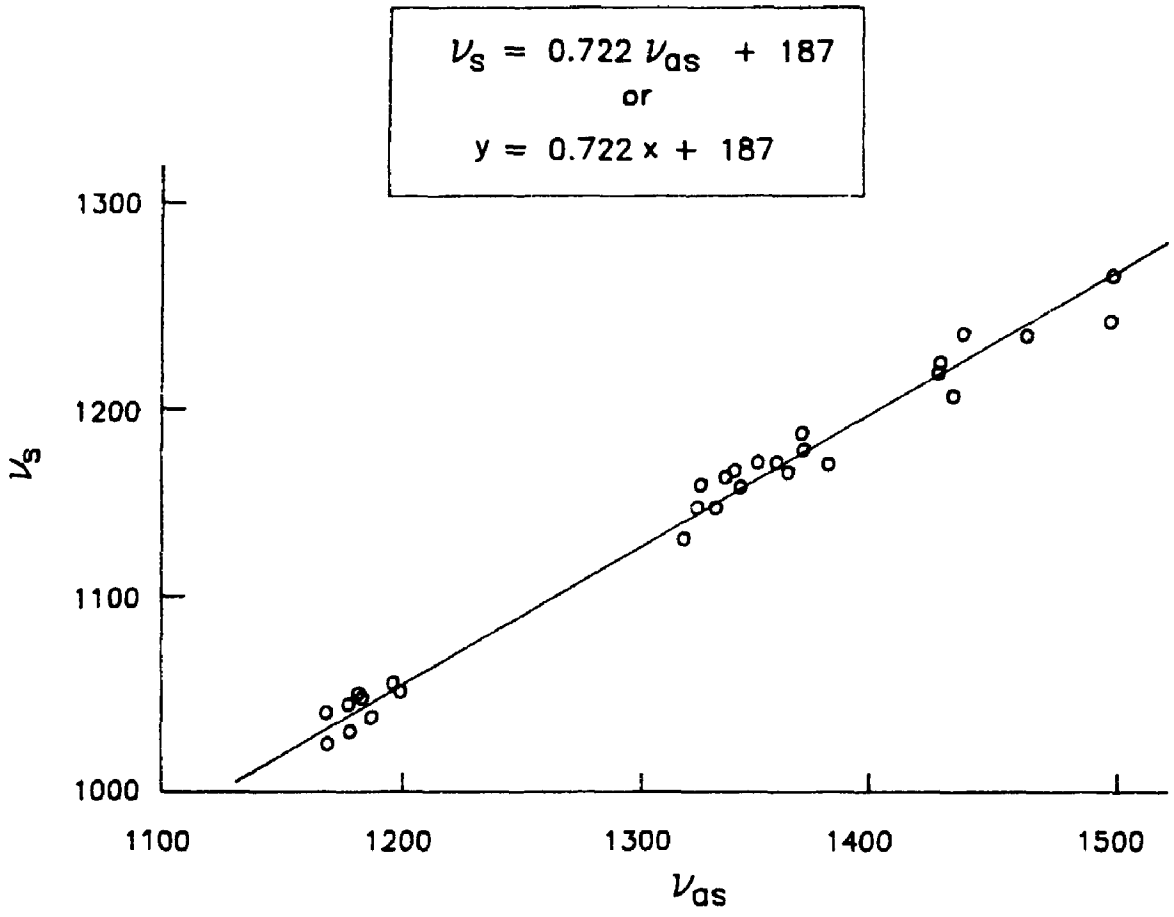


Figure 3.18 Correlation of symmetric and asymmetric S–O stretching frequencies of sulfonyl compounds.[48]

$$\nu_s = 0.722\,\nu_{as} + 187$$

or

$$y = 0.722\,x + 187$$

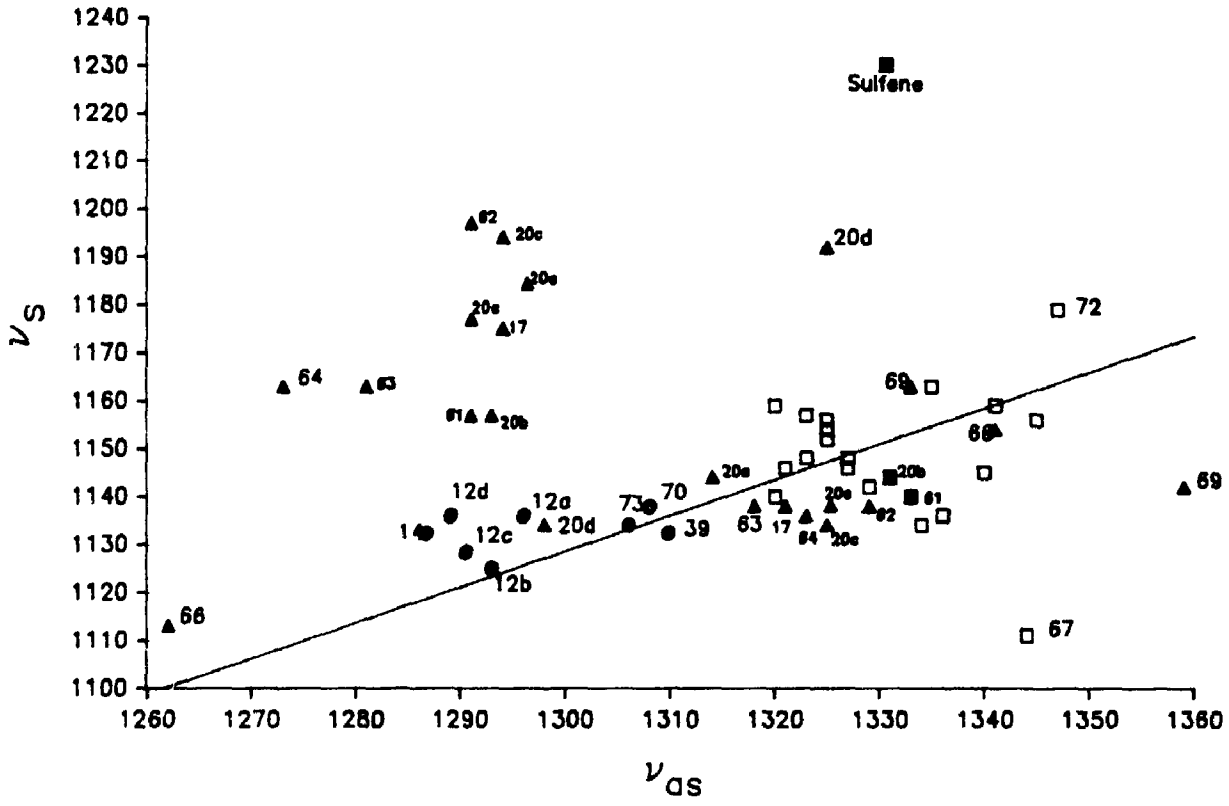


Figure 3.19 Correlation of symmetric and asymmetric S–O stretching frequencies of sulfonamides. The line is same as in the Bellamy–Williams' plot (see Figure 3.18).

Momose *et al.*,[49] have pointed out that the sulfonyl frequencies in arylsulfonamides are sensitive to the inductive effect of substituents on nitrogen as well as on sulfur. They have shown that the magnitude of these shifts in *p*-substituted benzenesulfonamides is linear to Hammett's σ-values. In this connection, compound ***66***, ***72***, ***74***, and ***76*** are of importance as the $-SO_2-$ stretching frequencies are on the higher side and can be accounted on the basis of inductive effect.

The $-SO_2-$ stretching frequencies of sulfonamides qualitatively fall into three groups, (1) sulfonamides which can have the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens (range 1135-1155 and 1320-1335) and named as "normal frequencies," for example most of the acyclic sulfonamide, (2) sultams which have the sulfonamide functionality locked in such a way that the nitrogen lone pair of electrons can not get at the bisector of sulfonyl oxygens (range 1125-1137 and 1289-1310) and named as "abnormal frequencies," for example ***14***, ***39***, ***12a***, ***12b***, ***12c***, ***12d***, ***73***, and ***70***, (3) and sulfonamides which have mobile conformations in which one conformation has the nitrogen lone pair at the bisector of sulfonyl oxygens (the frequencies fall in the normal range), whereas the other conformation, though sterically less crowded, does not have the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens (range 1145-1205 and 1285-1295), exemplified by ***20a*** to ***20e***, and ***17***.

Variation of dihedral angle would appear to influence the $-SO_2-$ stretching frequencies and would suggest that these frequencies may be used as an indicator of diminished N→S electron delocalization. Further work to find the relationship between $-SO_2-$ stretching frequencies and C-S-N-C dihedral angle is in progress in this laboratory.

3.3 CONCLUSIONS

The pK_a's of a number of sulfonamides were measured in sulfuric acid solutions and it was found that steric crowding decreases the pK_a due to steric shielding of solvation. The pK_a's of ***12b***, ***14***, ***20b***, and ***20e*** solutions were found to have higher values than that of the acyclic sulfonamide ***40***. This was interpreted as evidence that change from normal C–S–N–C dihedral angle (~80°) diminishes the N⟶S delocalization of nitrogen lone pair of electrons. The pK_a of ***39*** compared to ***12b*** and of ***43*** compared to ***40*** is believed to reflect combination of steric shielding of solvation and low N⟶S delocalization. This was supported by examination of the X-ray crystal structure and molecular models of ***39***, which showed that although the lone pair of electrons on nitrogen is not at the bisector of the sulfonyl oxygens (which presumably increases the pK_a of ***39***) the adverse effect of shielding of solvation may be expected to decrease the pK_a. Decalin sultam ***17*** was found to show the presence of two conformations at low temperature (by ^{13}Cmr spectra). This was accounted for by the presence of (i) a sterically crowded *cis* conformation (***17c***), with the nitrogen lone pair of electrons at the bisector of sulfonyl oxygens, along with (ii) the *trans* conformation (***17a***). It was also found that 6-membered sulfonamides which can either have equatorially disposed substituent (stereoelectronically unfavourable conformation) or axial substituents (stereoelectronically a favourable conformation) showed two sets of $-SO_2-$ stretching bands in their infrared spectra. It was suggested that compounds which do not have the nitrogen lone pair of electrons at the bisector of the sulfonyl oxygens (***12a***, ***12b***, ***39***, ***14***, and ***22***) have lower $-SO_2-$ stretching frequencies than the compounds with the nitrogen lone pair bisecting the sulfonyl oxygens.

Evidence for the mechanism of the hydrochlorinolysis of the sultams has been presented and the rates of the reactions analyzed in terms of the contributing steric and stereoelectronic effects. The rates of hydrochlorinolysis of various sulfonamides

suggested that the rapid rate of the reaction of the five membered sultam *12b* was partly due to the stereoelectronic effect (~15-fold), but mainly due to release of steric strain. With the bicyclic sultam *14* a rate acceleration of 20-fold was assigned to the stereoelectronic effect, and a factor of 8-fold to steric strain.

The pK_a's, conformational studies, X-ray structure data, rates of hydrochlorinolysis, and also $-SO_2-$ stretching frequencies indicate that variation of delocalization of the electron lone pair on the nitrogen with dihedral angle contributes in a qualitatively predictable manner to the reactivity and the physical properties of sulfonamides.

3.4 EXPERIMENTAL

The general procedure and the instrumentation are as described in chapter 1, except for the following points.

Many reactions were carried out using anhydrous hydrogen chloride (HCl) gas. The HCl gas was prepared by adding conc. sulfuric acid dropwise to a mixture of sodium chloride and concentrated hydrochloric acid and was dried by passing through concentrated sulfuric acid before bubbling into the reaction mixture.

Triethylamine (Aldrich) was distilled from calcium hydride prior to use. Methyl trifluoromethanesulfonate (Aldrich) was also distilled prior to use. All other reagents were commercially available, and unless otherwise specified, used without further purification.

All kinetic runs were followed by ^{1}Hmr using Varian XL-200 nmr spectrometer. The concentration of unreacted starting material, as determined from the integral of one of its peaks relative to that of an inert peak, was monitored with respect to time.

The pK_a's were also measured by ^{1}Hmr using the same Varian XL-200 nmr spectrometer. Aqueous sulfuric acid solutions were standardized by titrating a measured volume with standard 2 M sodium hydroxide.

Preparation of butane 1,4-sultam derivatives

(i) 4-Chloro-1-butanesulfonyl Chloride

Method a: Butane 1,4-sultone[51] (8) (10g, 72 mmol) was refluxed for 72 h with dimethylformamide (DMF) (1 mL) in thionyl chloride (30 mL). After the excess thionyl chloride was removed by distillation, the residual oil was poured onto ice (200 g) then extracted with methylene chloride (50 mL × 3). The extract was dried over magnesium sulfate and solvent evaporation gave a clear colourless oil (10.3 g, 75%).

Fractional distillation through a short Vigreux column, after a short forerun of DMF, gave 4-chloro-1-butanesulfonyl chloride as a clear colourless oil (9.8 g, 70%), bp 123-126°C at 2 mm (lit[52] 96-100°C at 0.3 mm); ir (neat) ν_{max}: 2959 (s), 2872 (m), 1458 (m), 1374 (vs), 1165 (vs), 911 (m), 733 (s), 592 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.93-2.27 (m, 2H), 2.16-2.31 (m, 2H), 3.62 (t, 2H), 3.74 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.9, 30.0, 43.7, 64.5.

Method b: Sodium 4-hydroxy-1-butanesulfonate[53] was refluxed (10 g, 57 mmol) as above for 24 h with a catalytic amount of DMF (1 mL) in thionyl chloride (30 mL). After the excess thionyl chloride was removed by distillation the residual oil was worked up as described in Method a. Distillation afforded 4-chloro-1-butanesulfonyl chloride as a colourless oil (9.3 g, 82%), with ^{1}H, ^{13}C, and ir spectra identical to those obtained earlier.

(ii) 4-Chloro-1-butanesulfonamide[54] (*19a*)

Anhydrous ammonia was slowly bubbled through a cooled solution (in ice and acetone bath) of 4-chloro-1-butanesulfonyl chloride (3.82 g, 20 mmol) in dichloromethane (50 mL) until no further formation of precipitate was observed (10 min). After the mixture was stirred overnight at room temperature, the solvent was removed by evaporation and the residue was extracted with hot anhydrous ether (4 x 100 mL). The extract was dried over magnesium sulfate and then evaporated to dryness to give *19a* as a brown viscous oil (3.2 g, 94%). This material was not further purified; ir (neat) ν_{max}: 3264 (vs), 2965 (s), 2876 (s), 1553 (m), 1453 (m), 1323 (vs), 1190 (w), 1150 (vs), 1042 (w), 1019 (w), 997 (w), 912 (s), 828 (m), 785 (m), 737 (m), 650 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.97 (m, 4H), 3.16 (s, 2H), 3.20 (t, 2H), 3.61 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.2, 30.6, 44.2, 54.0.

(iii) *N*-Methyl-4-chloro-1-butanesulfonamide (*19b*)

40% Aqueous methylamine (10 mL, large excess) was added dropwise with stirring over 10 min to a cooled solution of 4-chloro-1-butanesulfonyl chloride (3.82 g, 20 mmol) in methylene chloride (50 mL). After stirring for 1 h, the organic layer was separated and the aqueous phase extracted with dichloromethane (25 mL x 3). The combined organic extract was washed with saturated aqueous sodium carbonate (50 mL) and brine (50 mL), and dried over magnesium sulfate. Removal of the solvent by evaporation followed by azeotropic drying with benzene (25 mL x 2) left the title compound as a clear brown viscous oil (3.3 g, 90%) which was not further purified; ^{1}Hmr ($CDCl_3$) δ: 1.95 (m, 4H), 2.80 (d, 3H), 3.07 (t, 2H), 3.59 (t, 2H), 4.79 (q, 1H, -NH); ^{13}Cmr ($CDCl_3$) δ: 21.1, 29.3, 30.8, 44.1, 50.2.

(iv) *N*-*t*-Butyl-4-chloro-1-butanesulfonamide (*19c*)

A mixture of *t*-butylamine (1.9 g, 26 mmol) and triethylamine (2.63 g, 26 mmol) was added dropwise with stirring to a cooled solution of 4-chloro-1-butane-sulfonyl chloride (4.8 g, 25 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for 0.5 h and then washed with dilute hydrochloric acid solution (5%) (20 mL x 2) followed by water and then dried over magnesium sulfate. Evaporation of solvent gave *19c* as a pale yellow viscous oil (5.0 g, 88%), ir (neat) ν_{max}: 3278 (m), 2973 (s), 2876 (w), 1393 (w), 1368 (m), 1318 (vs), 1171 (w), 1138 (vs), 999 (s), 739 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.37 (s, 9H), 1.8-2.2 (m, 4H), 3.07 (t, 2H), 3.58 (t, 2H), 4.83 (br s, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.6, 30.3, 30.8, 44.1, 54.5, 55.1.

(v) *N*-Phenyl-4-chloro-1-butanesulfonamide (*19d*)

A mixture of aniline (1.86 g, 0.02 mol) and triethylamine (2.1 g, 0.02 mol) was similarly added to a solution of 4-chloro-1-butanesulfonyl chloride (3.82 g, 20 mmol)

in methylene chloride (100 mL), as above and the reaction mixture stirred for 0.5 h and worked up as above to give ***19d*** as a viscous oil (4.5 g, 90%); ir (neat) ν_{max}: 3266 (vs), 2961 (w), 1412 (m), 1497 (m), 1345 (m), 1302 (s), 1152 (vs), 922 (s), 737 (s), 696 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.80–2.05 (m, 4H), 3.14 (t, 2H), 3.45 (t, 2H), 7.17–7.39 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 20.9, 30.6, 43.9, 50.5, 120.4, 125.1, 129.5, 136.5.

(vi) *N*-Isopropyl-4-chloro-1-butanesulfonamide (***19e***)

As described above, a mixture of isopropylamire (1.2 g, 20 mmol) and triethylamine (2.0 g, ~20 mmol) was added to a solution of 4-chloro-1-butanesulfonyl chloride (3.82 g, 20 mmol) in dichloromethane (100 mL). Workup as before gave ***19e*** as a light brown viscous oil (3.6 g, 85 %); ^{1}Hmr ($CDCl_3$) δ: 1.24 (d, 6H), 1.95 (sym m, 4H), 3.06 (t, 2H), 3.59 (m, 3H), 5.05 (br d, 1H): ^{13}Cmr ($CDCl_3$) δ: 21.3, 24.2, 30.8, 44.3, 46.2, 52.6.

(vii) Tetrahydro-2H-1,2-thiazine 1,1-dioxide (butane sultam) (***20a***)

General procedure[54]

4-Chloro-1-butanesulfonamide (***19a***) (2.57 g, 15 mmol) in absolute alcohol (5 mL) was added dropwise to a stirred refluxing solution of sodium hydroxide (0.6 g, 15 mmol) in absolute alcohol (25 mL). The reaction mixture was refluxed for additional 2 h then neutralized with hydrochloric acid (1 M), filtered and then evaporated to dryness. The residue was extracted with methylene chloride (3 x 50 mL) which was then removed by evaporation to give a light brown solid. Recrystallization from dichloromethane–petroleum ether (bp 30–60°C) gave ***20a*** as off-white crystalline solid (1.42 g, 70%); mp 116–118°C; ir (KBr) ν_{max}: 3235 (vs), 2992 (w), 2965 (s), 2932 (w), 2978 (w), 1878 (w), 2822 (w), 1455 (m), 1439 (m), 1424 (s), 1410 (m), 1360 (m), 1314 (vs), 1291 (vs), 1256 (m), 1239 (m), 1177 (vs), 1129 (vs),

1067 (s), 1032 (s), 955 (s), 912 (w), 874 (m), 797 (m), 766 (vs), 679 (s), 577 (m), 513 (s), 500 (s), 444 (m); ^{1}Hmr ($CDCl_3$) δ: 1.64 (sym m, 2H), 2.22 (sym m, 2H), 3.11 (t, 2H), 3.41 (q, 2H), 4.72 (br t, 1H); ^{13}Cmr ($CDCl_3$) δ: 23.6, 24.1, 45.4, 50.1.

(viii) 2-Methyltetrahydro-2H-1,2-thiazine 1,1-dioxide (*N*-methylbutane sultam)[55] (***20b***)

N-Methyl-4-chloro-1-butanesulfonamide (***19b***) (3.5 g, 19 mmol) in absolute alcohol (10 mL) was reacted with refluxing NaOH (0.76 g, 19 mmol) in absolute alcohol (mL) for 2 h. Workup as described in the general procedure followed distillation gave ***20b*** as a colourless oil (3.0 g, 77%), bp 108-110°C / 0.7 torr), ir (neat) ν_{max}: 2947 (m), 2884 (w), 1495 (w), 1453 (w), 1356 (m), 1331 (vs), 1293 (s), 1215 (m), 1157 (s), 1144 (vs), 920 (s), 750 (s), 569 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.71 (m, 2H), 2.19 (m, 2H), 2.81 (s, 3H), 3.03 (t, 2H), 3.33 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 20.8, 24.3, 35.0, 47.1, 52.8.

(ix) 2-*t*-Butyltetrahydro-2H-1,2-thiazine 1,1-dioxide (*N*-*t*-butylbutane sultam) (***20c***)

Similarly, *N*-*t*-butyl-4-chloro-1-butanesulfonamide (***19c***) (3.4 g, 15 mmol) in absolute alcohol (10 mL) was added to refluxing solution of NaOH (0.6 g, 15 mmol) in absolute alcohol (25 mL). The reaction mixture was refluxed for an additional 3 h Workup as before, followed by recrystallization from ether-petroleum ether (bp 40-60°C) gave ***20c*** as white plates (2.65 g, 92%), mp 46-48°C; ir (KBr) ν_{max}: 2975 (s), 1325 (vs), 1294 (s), 1194 (s), 1134 (vs), 914 (w), 891 (s), 733 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.42 (s, 9H), 1.61 (sym m, 2H), 2.13 (sym m, 2H), 2.97 (t, 2H), 3.43 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.0, 24.7, 30.4, 46.4, 52.0, 59.9. Calcd. exact mass for $C_8H_{17}SO_2N$: 191.0980. Found: 191.0981.

(x) 2-Phenyltetrahydro-2H-1,2-thiazine 1,1-dioxide (*N*-phenylbutane sultam)[55] (**20d**)

As above, *N*-phenyl-4-chloro-1-butanesulfonamide (**19d**) (2.48 g, 10 mmol) in absolute alcohol (10 mL) was added to a refluxing solution of NaOH (0.4 g, 10 mmol) in absolute alcohol (25 mL) and then the mixture was stirred for 3 h. Workup as before, followed by recrystallization from ether–petroleum ether (bp 40–60°C) gave white crystals (2.0 g, 95%); mp 112–113°C; ir (KBr) ν_{max}: 2949 (m), 2936 (m), 2976 (m), 2885 (m), 1493 (s), 1325 (s), 1298 (vs), 1210 (s), 1192 (s), 1 134 (vs), 1041 (w), 880 (vs), 776 (m), 741 (s), 698 (m), 550 (s), 515 (m). 482 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.87 (sym m, 2H), 2.30 (sym m, 2H), 3.18 (t, 2H), 3.71 (t, 2H), 7.20–7.39 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 24.2, 24.5, 50.6, 53.5, 126.9, 127.3, 129.1, 140.5. Calcd. exact mass for $C_{10}H_{13}SO_2N$: 211.0667. Found: 211.0664.

(xi) 2-Isopropyltetrahydro-2H-1,2-thiazine 1,1-dioxide (*N*-isopropylbutane sultam) (**20e**)

N-Isopropyl-4-chloro-1-butanesulfonamide (**19e**) (3.34 g, 15 mmol) in absolute alcohol (10 mL) was added dropwise to a refluxing solution of NaOH (0.6 g, 15 mmol) in absolute alcohol (25 mL) and the reaction mixture was refluxed for additional 3 h. Workup, followed by removal of solvent gave a colourless liquid which solidified on standing (2.5 g, 88%); ir (neat) ν_{max}: 2978 (s), 2944 (s), 2869 (m), 1468 (m), 1443 (m), 1414 (m), 1391 (m), 1372 (m), 1320 (s), 1289 (s), 1200 (s), 1167 (s), 1134 (vs), 1071 (m), 1032 (s), 951 (w), 922 (s), 868 (m), 847 (w), 814 (w), 743 (s), 658 (m), 569 (m), 538 (m), 504 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.16 (d, 6H), 1.71 (sym m, 2H), 2.20 (sym m, 2H), 3.00 (t, 2H), 3.23 (t, 2H), 4.33 (septet, 1H); ^{13}Cmr ($CDCl_3$) δ: 20.4, 23.8, 24.5, 42.0, 45.7, 50.8. Calcd. exact mass for $C_7H_{15}SO_2N$: 177.0824. Found: 177.0824.

Synthesis of *N*-Methyl-2-thia-3-azabicyclo[2.2.2]octane 2,2-dioxide (*14*)

(i) *trans*-4-Mercaptocyclohexanol[24] (*27*)

A solution of 7-oxabicycloheptane (9.8 g, 100 mmol), *p*-toluenesulfonic acid (25.8 g, 150 mmol) and thiourea (11.4 g, 150 mmol) in absolute ethanol (300 mL) was refluxed for 21 h. The solvent was removed under reduced pressure to afford the thiouronium salt as a white solid which was recrystallized from ethanol-ether (28.4 g, 82%); mp 182-185°C; ir (KBr) ν_{max}: 3494 (vs), 3131 (vs), 3088 (vs), 2859 (m), 2772 (m), 1919 (w), 1811 (w), 1661 (vs), 1495 (m), 1410 (s), 1246 (s), 1194 (s), 1123 (vs), 1065 (vs), 1032 (s), 1007 (vs), 899 (m), 970 (m), 816 (s), 6830 (s), 565 (vs) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.2-1.6 (m, 4H), 1.9-2.2 (m, 4H), 2.36 (s, 3H), 3.43 (sym m, 1H), 3.64 (sym m, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}Cmr ($CDCl_3$) δ: 23.9, 32.6, 35.9, 45.7, 71.1, 128.0, 132.1, 142.1, 145.1, 172.9.

The thiouronium salt (20.7 g, 60 mmol) was dissolved in ethanol (50 mL) and 15% aqueous NaOH solution (65 mL) was added rapidly, under nitrogen, with vigorous stirring. The mixture was gently refluxed for 2 h and then the ethanol was removed by distillation. Ice-cold sulfuric acid (~10%) was added slowly while the contents of the flask were stirred and cooled in an ice-bath. Workup gave a slightly yellow oil which on distillation gave pure *trans*-4-mercaptocyclohexanol (*27*) as a colourless, foul-smelling viscous oil which solidified on standing (4.75 g, 60%); ir (neat) ν_{max}: 3455 (vs), 2952 (s), 2863 (m), 2550 (w), 1453 (s), 1366 (m), 1300 (w), 1200 (m), 1142 (w), 1071 (s), 968 (m), 895 (m), 820 (w), 735 (m), 554 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.1-1.5 (m, 4H), 1.47 (d, 1H, SH), 1.8-2.1 (m, 4H), 2.1 (s, 1H, OH), 2.71 (sym m, 1H), 3.52 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 35.3, 35.7, 37.1, 69.3. *trans*-4-Mercaptocyclohexanol (*27*) (1.0 g, 7.6 mmol) was converted to the diacetate by addition of 2.2 equivalents of acetyl chloride (1.35 g, ~17 mmol) and heating the reaction mixture for 0.5 h at 50°C. Usual workup afforded the diacetate as a crystalline solid (1.64 g, ~100%); mp 66-68°C (lit[24] mp 66.6-68°C); ir (neat)

ν_{max}: 2950 (s), 2865 (m), 1728 (vs), 1684 (vs), 1431 (m), 1383 (m), 1358 (m), 1246 (vs), 1152 (m), 1121 (s), 1040 (s), 953 (m), 903 (w), 830 (w), 760 (w), 654 (m), 639 (s), 610 (w), 550 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3–1.7 (m, 4H), 1.90–2.15 (m, 4H), 2.03 (s, 3H), 2.31 (s, 3H), 3.42 (sym m, 1H), 4.71 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.3, 30.1, 30.7, 30.9, 40.8, 71.3, 170.5, 195.5.

(ii) *trans*-4-Acetylthiocyclohexyl tosylate[24] (28)

Compound 28 was prepared by dissolving mercaptocyclohexanol (27) (4.0 g, 30 mmol) in distilled water (25 mL) containing NaOH (1.2 g, 30 mmol). Then at 0°C, purified acetic anhydride (3.06 g, 30 mmol) was added dropwise during 5 min. The solution was saturated with NaCl and extracted with dichloromethane (4 x 50 mL). The organic layer was dried with magnesium sulphate and filtered through a layer of filter papers (5 filter papers) (filter paper is extremely efficient in absorbing small amounts of water) (ir (neat) ν_{max}: 3366 (vs), 2938 (vs), 2861 (s), 1686 (vs), 1447 (m), 1360 (m), 1119 (s), 1065 (s), 959 (m), 637 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.42 (sym m, 4H), 2.01 (sym m, 4H), 2.30 (s, 3H), 2.93 (br s, 1H), 3.36 (sym m, 1H), 3.61 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ:30.5, 30.7, 34.8, 41.1, 69.0, 195.8). This solution was cooled to −20°C (acetone–ice bath) and a solution of *p*-toluenesulfonyl chloride (5.72 g, 30 mmol), pyridine (10.4 mL, 100 mmol), and dichloromethane (25 mL) was added dropwise, stirring was continued for 34 h at 0°C. Usual workup gave a colourless, practically odourless solid which was recrystallized from ethyl acetate–hexanes (8.4 g, 85%), mp 108–110°C (lit[24] mp 109–110°C); ir (KBr) ν_{max}: 2944 (s), 2865 (m), 2925 (w), 1692 (vs), 1597 (m), 1352 (vs), 1309 (m), 1291 (m), 1175 (vs), 1109 (s), 1007 (m), 941 (s), 855 (s), 756 (w), 710 (w), 666 (m), 633 (m), 565 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3–2.1 (m, 8H), 2.29 (s, 3H), 2.45 (s, 3H), 3.41 (tt, 1H), 4.47 (tt, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.5, 29.3, 30.6, 31.1, 40.0, 79.6, 127.4, 129.7, 134.3, 144.5,

194.9. Calcd. exact mass for $C_{15}H_{20}O_4S_2$: 328.0804. Found: 328.0805.

(iii) *trans*-4-Tosyloxycyclohexanesulfonyl chloride (*29*)

Chlorine was bubbled into ice cold (200 mL) water for 5 min and then a solution of *28* (8.2 g, 25 mmol) in dichloromethane (15 mL) was added rapidly with vigorous stirring. After 10 min the aqueous layer was extracted with dichloromethane (4 x 50 mL) dried with magnesium sulfate and solvent evaporated to give *29* as a colourless crystalline solid, which was recrystallized from ether–*n*–hexane (7.4 g, 84%); mp 145–147°C; ir (KBr)ν_{max}: 2967 (m), 2932 (m), 2867 (m), 1599 (m), 1495 (w), 1451 (m), 1391 (w), 1356 (vs), 1333 (s), 1190 (vs), 1175 (vs), 1159 (vs), 1138 (m), 1076 (m), 1003 (s), 953 (vs), 855 (vs), 808 (m), 669 (m), 602 (s), 567 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.45–2.48 (m, 8H), 2.46 (s, 3H), 3.53 (sym m, 1H), 4.43 (sym m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.7, 24.7, 30.1, 71.9, 77.9, 127.7, 130.0, 134.0, 145.0.

(iv) *trans*-4-Tosyloxy-*N*-methyl-cyclohexanesulfonamide (*30b*)

Aqueous methylamine (40%) (10 mL, large excess) was added dropwise to a solution of *29* (7.05 g, 20 mmol) in dichloromethane (100 mL) at 0°C. The mixture was stirred for an additional 5 min; workup gave a mixture (1:1) of *cis* and *trans* sulfonamides (*30a* and *30b*) in 80% yield (5.6 g). The mixture of *30a* and *30b* was separated by flash chromatography, using ether–pentane (60:40) as the eluting solvent. The *cis* compound (*30a*) was obtained as a crystalline solid (2.52 g), mp 122–124°C; ir (KBr) ν_{max}: 3360 (vs), 2961 (m), 1442 (m), 1401 (s), 1337 (vs), 1320 (vs), 1291 (m), 1177 (vs), 1146 (vs), 1103 (m), 1092 (m), 1071 (m), 905 (vs), 887 (vs), 847 (s), 810 (s), 677 (vs), 592 (s), 561 (m), 554 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.40–2.08 (m, 8H), 2.45 (s, 3H), 2.81 (d, 3H), 2.78–2.98 (m, 1H), 4.39 (q, 1H, –NH), 4.76 (m, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H);

^{13}Cmr ($CDCl_3$) δ: 20.6, 21.7, 29.6, 29.8, 59.2, 76.5, 127.6, 129.9, 134.2, 144.8. Calcd. exact mass for $C_{14}H_{21}NO_5S_2$: 347.0861. Found: 347.0861. The required *trans*-isomer (*30b*) was obtained as a crystalline solid (2.75 g), mp 155-156°C; ir (KBr) ν_{max}: 3314 (vs), 2983 (m), 1447 (m), 1348 (vs), 1318 (vs), 1183 (m), 1173 (vs), 1150 (s), 1130 (m), 1076 (w), 939 (s), 866 (m), 850 (m), 814 (m), 669 (s), 571 (m), 554 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.42-1.76 (m,4H), 2.20-2.32 (m, 4H), 2.46 (s, 3H), 2.79 (d, 3H), 2.74-2.92 (m, 1H), 4.14 (q, 1H, -NH), 4.38 (sym m, 1H), 7.36 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.7, 24.4, 29.7, 30.7, 58.1, 79.5, 127.6, 130.0, 134.0, 144.9. Calcd. exact mass for $C_{14}H_{21}NO_5S_2$: 347.0861. Found: 347.0861.

(v) *N*-Methyl-2-thia-3-azabicyclo[2.2.2]octane 2,2-dioxide (*14*)

trans-4-Tosyloxy-*N*-methylcyclohexanesulfonamide (*30b*) (600 mg, 1.73 mmol) was dissolved in *t*-butanol (20 mL) and potassium *t*-butoxide (224 mg, 2.0 mmol) was added in several portions. The mixture was refluxed for 24 h and solvent removed under reduced pressure. The residue was dissolved in ether and passed through a short column of silica gel; evaporation of the solvent gave a crystalline solid which on recrystallization from ether-cyclohexane gave white needles (257 mg, 85%), mp 155-156°C; ir (KBr) ν_{max}: 2942 (s), 2957 (m), 1464 (m), 1359 (w), 1321 (w), 1287 (vs), 1213 (s), 1204 (m), 1132 (vs), 1105 (m), 970 (m), 909 (s), 749 (m), 644 (m), 594 (m), 504 (w), 480 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$): 1.50-1.68 (m, 2H), 1.90-2.25 (m, 4H), 2.29-2.48 (m, 2H), 2.75 (s, 3H), 3.20 (sym m, 1H), 3.33 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 21.9, 22.4, 31.9, 50.6, 58.6. Calcd. exact mass for $C_7H_{13}NO_2S$: 175.0667. Found: 175.0667.

Synthesis of 1,9-thiazadecalin 1,1-dioxide (*17*)

(i) 2-(3-Hydroxypropyl)piperidine[20] (*23*)

A reaction mixture containing piperidine (385 g, 4.53 mmol), allyl alcohol (19 g, 0.33 mol) and *t*-butyl peroxide (4.5 g, 0.031 mol) was heated in 6 thick-walled sealed glass tubes at 120-130 °C for 2 days. Distillation gave *23* as a pale yellow oil (8 g, 17%), bp 93-96 °C at 1 mm; ^{1}Hmr ($CDCl_3$) δ: 1.01-2.02 (m, 10H), 2.40-2.25 (m, 2H), 3.0-3.15 (m, 1H), 3.45-3.70 (m, 3H), 3.90 (br s, 1H); ^{13}Cmr ($CDCl_3$) δ: 24.3, 26.0, 29.5, 32.5,34.7, 46.2, 56.3, 61.7.

(ii) 1,9-Thiazadecalin 1,1-dioxide (*17*)

Hydrogen chloride gas was bubbled through a cooled solution of *23* (2.0 g, 14 mmol) in dichloromethane (25 mL) for 5 min. On removal of the solvent a syrup was obtained; to this syrup PBr_3 (1.9 g, 7 mmol) was added directly and within a few minutes an exothermic reaction commenced with evolution of dense hydrogen bromide fumes. After the gas evolution had ceased, the volatile materials were removed *in vacuo*, the syrupy residue was washed with ether and the bromide *24* was directly treated with absolute alcohol (25 mL) and thiourea (1.06 g, 14 mmol). This mixture was refluxed for 24 h and the solvent was removed to afford thiouronium salt *25* as semi-solid syrup. Compound *25* was used in the next step without further purification.

Chlorine was bubbled into a cooled mixture of water (50 mL), ethanol (5 mL), and chloroform (20 mL), and a solution of *25* in water was added with vigorous stirring, after 5 min the reaction mixture was extracted with dichloromethane (5 x 25 mL) and dried over magnesium sulfate. Excess triethylamine (3 mL) was added to the above solution at 0 °C and the mixture was stirred for 0.5 h, then washed with dil. HCl and water, dried over magnesium sulfate. The solvent was evaporated to give a viscous liquid (450 mg) which was chromatographed over silica gel using

ether–petroleum ether (bp 30–60°C) to give pure *17* as a viscous oil (375 mg, 14%); ir (KBr) ν_{max}: 3060 (w), 2938 (vs), 2857 (s), 1664 (w), 1447 (m), 1410 (m), 1321 (vs), 1294 (vs), 1248 (m), 1229 (m), 1175 (s), 1138 (vs), 1047 (m), 912 (s), 885 (m), 561 (vs), 546 (vs) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.3–1.9 (m, 8H), 2.0–2.33 (m, 2H), 2.80–3.14 (m, 3H), 3.27–3.52 (m, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.9, 22.3, 24.8, 28.7, 32.0, 41.2, 47.2, 57.9. Calcd. exact mass for $C_8H_{15}NO_2S$: 189.0824. Found: 189.0823.

Preparation of propane 1,3–sultam derivatives

(i) 3–Chloro–1–propanesulfonyl chloride[56] (*32*)

Method a: A mixture of propane 1,3–sultone (*7*) (10 g, 82 mmol) and thionyl chloride (20 g, 168 mmol) with catalytic amount of DMF (~0.05 mL) was refluxed overnight. The excess thionyl chloride was removed by distillation and the product (13.1 g, 90%) obtained as a pale yellow oil by distillation, bp 115–117°C at 12 mm (lit[56] bp 102–104°C at 0.55 mm), ir (neat) ν_{max}: 2975 (m), 2924 (m), 1443 (m), 1377 (vs), 1314 (s), 1269 (m), 1167 (vs), 747 (m), 706 (m), 594 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.51 (m, 2H), 3.74 (t, 2H), 3.89 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 27.2, 41.5, 62.3.

Method b: A mixture of thiolacetic acid (9 mL, 127 mmol) and allyl chloride (10.3 mL, 127 mmol) was refluxed overnight. Distillation using the water aspirator gave 3–chloro–1–propanethioacetate[57] (*31*) as an oil (15.5 g, 80%).

Chlorine was bubbled into water (100 mL) at 0°C and then *31* (10 g, 65 mmol) added rapidly and the reaction mixture stirred for 10 min. Workup as before gave 3–chloro–1–propanesulfonyl chloride (*32* (9g, 78%). Infrared, ^{1}H and ^{13}Cmr spectra were identical to those obtained from the above sample.

(ii) 3-Chloropropanesulfonamide[57] (*33a*)

Ammonia was bubbled to a cooled solution (0°C) of 3-chloro-1-propanesulfonyl chloride (*32*) (5.0 g, 28 mmol) in dichloromethane 50 mL until no further formation of precipitate was observed (~20 min). After the reaction mixture was stirred overnight at room temperature, the solvent was removed and the residue was extracted with hot ether (3 x 50 mL). The organic layer was dried over magnesium sulfate; solvent evaporation gave a brown viscous oil which solidified on standing (4.0 g, 90%), mp 63-65°C; ^{1}Hmr ($CDCl_3$) δ: 2.34 (quintet, 2H), 3.33 (t, 2H), 3.71 (t, 2H), 4.86 (br s, 2H); ^{13}Cmr ($CDCl_3$) δ: 27.1, 42.7, 52.6.

(iii) *N*-Methyl-3-chloropropanesulfonamide[56] (*33b*)

To a solution of 3-chloropropanesulfonyl chloride (*32*) (5.0 g, 28 mmol) in dichlormethane (50 mL) at 0°C was added dropwise an aqueous solution of methyl amine (40%, 10 mL) with vigorous stirring. The organic layer was washed with sodium bicarbonate, dried over magnesium sulfate and the solvent was removed under reduced pressure to give *33b* as an oil (4.5 g, 93%). This material was used without further purification. ^{1}Hmr ($CDCl_3$) δ: 2.25 (quintet, 2H), 2.76 (s, 3H), 3.16 (t, 2H), 3.65 (t, 2H), 4.30 (br s, 1H); ^{13}Cmr ($CDCl_3$) δ: 26.8, 29.3, 42.9, 48.3.

(iv) *N*-*t*-Butyl-3-chloropropanesulfonamide (*33c*)

To a cooled solution of 3-chloro-1-propanesulfonyl chloride (*32*) (5.0 g, 28 mmol) in dichloromethane (50 mL) was added dropwise a mixture of triethylamine (3.03 g, 30 mmol) and *t*-butylamine (2.04 g, 28 mmol). The reaction mixture was stirred for 10 min, then washed with dilute hydrochloric acid solution followed by water, dried over magnesium sulfate, and the evaporation of solvent gave *33c* (5.1 g, 85%) as a brown viscous liquid. This material was used in the next step without further purification. ^{1}Hmr ($CDCl_3$) δ: 1.29 (s, 9H), 2.22 (quintet, 2H), 3.13 (t,

2H), 3.60 (t, 2H), 4.75 (s, 1H); ^{13}Cmr ($CDCl_3$) δ: 27.1, 30.1, 42.8, 53.0, 54.5.

(v) *N*-Phenyl-3-chloropropanesulfonamide (*33d*)

As above, a mixture of triethylamine (3.03 g, 30 mmol) and aniline (2.6 g, 28 mmol) was added to a cooled solution of 3-chloro-1-propanesulfonyl chloride (*32*) (5.0 g, 28 mmol) in dichloromethane (50 mL). Workup as before gave *33d* as a brown solid (5.75 g, 88%) which was used without furtner purification. ^{1}Hmr ($CDCl_3$) δ: 2.26 (quintet, 2H), 2.42 (s, 1H), 3.27 (t, 2H), 3.61 (t, 2H), 7.13-7.38 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 26.5, 42.5, 48.7, 120.6, 125.1, 129.6, 136.7.

(vi) *N*-Methylpropane sultam (*12b*)

General procedure[56]

N-Methyl-3-chloropropanesulfonamide (*33b*) (4.0 g, 23.3 mmol) was dissolved in absolute ethanol (25 mL) and added dropwise to a refluxing solution of potassium hydroxide (1.4 g, 25 mmol) in absolute ethanol (10 mL) over 20 min. The reaction mixture was refluxed for a further 1 h. The solvent was removed under reduced pressure and the resulting syrup was partitioned between water and dichloromethane, and the aqueous layer extracted with dichloromethane (2 x 50 mL); the combined organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a pale brown oil which was recrystallized from ether-petroleum ether (bp 30-60°C) with charcoal to give white crystals (2.22 g, 70%); mp 47-49°C (lit[41] mp 46-49°C); ir (KBr) ν_{max}: 2990 (w), 2882 (w), 2826 (w), 1454 (w), 1293 (vs), 1227 (w), 1192 (m), 1163 (s), 1125 (vs), 999 (m), 677 (m), 588 (w), 505 (m), 465 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.35 (quintet, 2H), 2.70 (s, 3H), 3.19 (t, 3H), 3.23 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 18.2, 30.3, 45.7, 48.7.

(vii) Propane sultam (*12a*)

3–Chloropropanesulfonamide (*33a*) (3.15 g, 20 mmol) in absolute ethanol was added to a refluxing solution of potassium hydroxide (1.18 g, 21 mmol) in absolute ethanol (25 mL) as above and the reaction further refluxed for additional 1 h; workup as before afforded the propane sultam as a crystalline solid (2.0 g, 83%), recrystallized from ether–petroleum ether, mp 23–24°C (lit[56] mp 23.8–24.2°C); ir (KBr) ν_{max}: 3565 (s), 3268 (vs), 2965 (s), 1394 (m), 1296 (vs), 1136 (vs), 1044 (m), 999 (m), 928 (w), 735 (m), 600 (w), 484 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.52 (quintet, 2H), 3.10 (t, 2H), 3.42 (t, 2H), 4.60 (br s, 1H); ^{13}Cmr ($CDCl_3$) δ: 23.9, 42.2, 46.6.

(viii) *N–t*–Butylpropane sultam (*12c*)

N–t–Butyl–1–chloropropanesulfonamide (*33c*) (4.0 g, 18.7 mmol) in absolute ethanol (25 mL) was added to refluxing solution of potassium hydroxide (1.18 g, 25 mmol) in ethanol (10 mL) as above, and the reaction mixture was heated for 2 h; workup as before affording *12c* as a solid (2.8 g, 85%) which was recrystallized from ether–petroleum ether (bp 30–60°C), mp 57–58°C; ir (KBr) ν_{max}: 2986 (s), 2874 (m), 2494 (w), 2361 (w), 1487 (w), 1466 (w), 1401 (w), 1377 (m), 1291 (vs), 1219 (s), 1129 (vs), 1096 (w), 1040 (s), 999 (s), 878 (w), 801 (w), 729 (m), 654 (m), 585 (w), 529 (m), 498 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.41 (s, 9H), 2.28 (quintet, 2H), 3.18 (t, 2H), 3.37 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 18.8, 27.9, 43.9, 49.6, 56.2. Calcd. exact mass for $C_7H_{15}SO_2N$: 177.0823. Found: 177.0826.

(ix) *N*–Phenylpropane sultam (*12d*)

A solution of *N*–phenyl–1–chloropropanesulfonamide (*33d*) (3.5 g, 14 mmol) in ethanol (20 mL) was added dropwise to a refluxing solution of potassium hydroxide (842 mg, 15 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 2 h,

workup as above afforded a solid (2.43 g, 88%) which was recrystallized from methanol; mp 123–124°C; ir (KBr) ν_{max}: 3071 (w), 2994 (w), 2944 (w), 1597 (s), 1497 (vs), 1478 (m), 1368 (m), 1287 (vs), 1136 (vs), 1096 (s), 1073 (m), 1036 (m), 947 (s), 766 (vs), 737 (s), 695 (s), 681 (m), 507 (vs), 455 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.46 (quintet, 2H), 3.33 (t, 2H), 3.76 (t, 2H), 7.10–7.39 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 18.7, 46.7, 48.3, 119.3, 124.4, 129.3, 137.7. Calcd. exact mass for $C_9H_{11}SO_2N$: 197.0510. Found: 197.0509.

Synthesis of *N*-methylcamphor sultam (39)

(i) 7,7-Dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-methanesulfonyl chloride (camphorsulfonyl chloride) (35)

A mixture of camphor-10-sulfonic acid (34) (23.2 g, 0.1 mol) and thionyl chloride (50 mL) was refluxed for 2 h at steam-bath. Excess thionyl chloride was removed by distillation and a mixture of ice and water was added to the reaction mixture. The sulfonyl chloride was extracted from the aqueous layer with dichloromethane (3 x 100 mL). Drying of the organic layer with magnesium sulfate and evaporation of the solvent gave a crystalline solid, which was recrystallized from ether–cyclohexane yielding pure camphorsulfonyl chloride (35) (21.3 g, 85%); mp 82–84°C (lit[58] mp 83–85°C); ^{1}Hmr ($CDCl_3$) δ: 0.93 (s, 3H), 1.14 (s, 3H), 1.50 (sym m, 1H), 1.78 (sym m, 1H), 2.00 (d, J = 18.7 Hz, 1H), 2.05–2.20 (m, 2H), 2.38–2.53 (m, 2H), 3.75 (d, J = 14.67 Hz, 1H), 4.31 (d, J = 14.67 Hz, 1H); ^{13}Cmr ($CDCl_3$) δ: 19.6, 19.7, 25.2, 26.8, 42.3, 42.7, 48.2, 59.7, 64.3, 212.7.

(ii) 7,7-Dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-methanesulfonamide (Camphorsulfonamide) (36)

A stirred solution of camphorsulfonyl chloride (35) (21 g, 84 mmol) in toluene (200 mL) was saturated with gaseous ammonia under cooling with ice. Filtration and

washing of the insoluble residue with toluene, drying with magnesium sulfate and removal of the solvent under reduced pressure gave a crystalline solid, which was recrystallized from dichloromethane–cyclohexane to give the pure sulfonamide **36** (14.4 g, 75%); ^{1}Hmr ($CDCl_3$) δ: 093 (s, 3H), 1.01 (s, 3H), 1.7–2.6 (m, 7H), 3.13 (d, J = 15.0 Hz, 1H), 3.52 (d, J = 15.0 Hz, 1H), 5.5 (br s, 2H); ^{13}Cmr ($CDCl_3$) δ: 19.4, 20.0, 26.7, 27.0, 42.8, 43.1, 49.1, 53.9, 59.3, 217.6.

(iii) 10,10–Dimethyl–5–thia–4–azatricyclo[5.2.1.$0^{3,7}$]dec–3–ene 5,5–dioxide (**37**)

A 1% solution of NaOMe in dry MeOH (1.5 mL) was added to a solution of camphorsulfonamide (**36**) (14.2 g, 61.4 mmol) in MeOH (400 mL). After stirring the reaction mixture at room temperature for 4 h, another portion of NaOMe in MeOH (0.6 mL) was added and the reaction mixture was left stirring for 60 h. The solvent was removed under reduced pressure, the residue treated with water–chloroform (1:1, 150 mL), and the aqueous layer extracted with chloroform (2 x 100 mL). The chloroform layer was dried over magnesium sulfate and evaporation of the solvent gave a white solid, which was recrystallized from ether–cyclohexane to afford pure **37** (12 g, 92%); ^{1}Hmr ($CDCl_3$) δ: 0.87 (s, 3H), 1.09 (s, 3H), 1.48 (t, 1H), 1.77 (t, 1H), 2.01–2.13 (m, 2H), 2.27 (sym m, 1H), 2.39 (d, J = 19.4, 1H), 2.78 (m, 1H), 2.98 (d, J = 13.33 Hz, 1H), 3.20 (d, J = 13.33 Hz, 1H); ^{13}Cmr ($CDCl_3$) δ: 18.9, 19.4, 26.6, 28.4, 35.9, 44.6, 48.9, 49.4, 64.5, 195.6.

(iv) 10,10- Dimethyl–5–thia–4–azatricyclo[5.2.1.$0^{3,7}$]decane 5,5–dioxide (camphor sultam) (**38**)

$LiAlH_4$ (1.25 g, 33 mmol) was added at 0 °C to a stirred solution of imide **37** (7 g, 33 mmol) in THF (300 mL) and after stirring for 2 h, the mixture was quenched by the addition of 1 M aq. HCl. Filtration, and washing the solid residue with dichloromethane, extraction of aqueous layer with dichloromethane, drying with

magnesium sulfate, and evaporation of solvent gave a crystalline solid, which was recrystallized from absolute alcohol to give pure sultam **38**, (6 g, 85%), ir (KBr) ν_{max}: 3279 (s), 2993 (w), 2955 (s), 2880 (m), 1287 (vs), 1273 (vs), 1229 (w), 1173 (m), 1173 (vs), 1069 (w), 1040 (w), 961 (w), 911 (w), 870 (w), 789 (w), 747 (w), 669 (w), 577 (m), 540 (w), 513 (s), 473 (w), 448 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.94 (s, 3H), 1.13 (s, 3H), 1.3-2.1 (m, 7H), 3.12 (d, J = 1.13 Hz, 2H), 4.22 (br s, 1H); ^{13}Cmr ($CDCl_3$) δ: 20.45, 20.5, 26.8, 31.9, 36.1, 44.7, 47.5, 50.4, 55.0, 62.8.

(v) 10,10,4-Trimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane 5,5-dioxide (*N*-Methyl-camphor sultam) (**39**)

Camphor sultam **38** (2.15 g, 10 mmol) was added to a solution of KOH (600 mg) in ethanol (25 mL) and the reaction mixture was stirred for 15 min, then methyl iodide (5 g, large excess) was added. This reaction mixture was refluxed for 8 h and then workup as before to give a solid product which was recrystallized from methanol (2.1 g, 90%), mp 88-89°C; ir (KBr) ν_{max}: 2995 (m), 2950 (m), 2882 (m), 1453 (m), 1410 (w), 1310 (vs), 1258 (m), 1206 (m), 1165 (m), 1132 (vs), 1099 (w), 814 (m), 787 (w), 737 (w), 544 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.92 (s, 3H), 1.10 (s, 3H), 1.20-2.00 (m, 7H), 2.53 (s, 3H), 2.93 (q, 1H), 3.12 (s, 2H); ^{13}Cmr ($CDCl_3$) δ:20.0, 20.3, 27.0, 31.9, 34.6, 44.3, 47.6, 48.9, 49.9, 68.1. Calcd. exact mass for $C_{11}H_{19}O_2SN$: 229.1136. Found: 229.1136.

Synthesis of acyclic sulfonamides

All the acyclic sulfonamides were synthesized by adding the excess amine to a cooled solution of sulfonyl chloride in dichloromethane and stirring the reaction mixture for 5 to 30 min. Usual workup followed by recrystallization or distillation gave the pure sulfonamides. The ir, ^{1}H and ^{13}Cmr spectra are recorded below.

(i) *N,N*-Dimethylmethanesulfonamide (*40*)

Recrystallized from ether and hexane, mp 47–48°C; ir (KBr) ν_{max}: 3019 (w), 2979 (w), 2936 (w), 2899 (w), 2816(w), 1483 (m), 1460 (m), 1410 (w), 1325 (vs), 1256 (m), 1184 (m), 1152 (vs), 1049 (w), 963 (s), 945 (m), 783 (s), 669 (m), 525 (m), 488 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.79 (s, 3H), 2.86 (s, 6H); ^{13}Cmr ($CDCl_3$) δ: 33.3, 37.8.

(ii) *N,N*-Diethylmethanesulfonamide (*43*)

A clear liquid at room temperature; ir (KBr) ν_{max}: 2979 (s), 2940 (m), 2880 (w), 1468 (m), 1416 (m), 1350 (m), 1327 (vs), 1202 (s), 1146 (vs) 1099 (w), 1021 (s), 965 (s), 965 (s), 932 (m), 770 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.21 (t, 6H), 2.84 (s, 3H), 3.30 (q, 4H); ^{13}Cmr ($CDCl_3$) δ: 14.2, 38.8, 41.7.

(iii) Methanesulfonylpiperidide (*41*)

Recrystallized from ether and pentane, mp 44–45°C; ir (KBr) ν_{max}: 3015 (m), 2996 (w), 2936 (vs), 2867 (m), 2851 (m), 1443 (m), 1389 (w), 1325 (vs), 1283 (m), 1211 (m), 1258 (w), 1150 (vs), 1161 (vs), 1105 (m), 1055 (m), 1028 (m), 930 (s), 857 (w), 835 (w), 781 (s), 691 (w), 551 (s), 523 (s), 488 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.48–1.70 (m, 6H), 2.70 (s, 3H), 3.13 (t, 4H); ^{13}Cmr ($CDCl_3$) δ: 23.6, 25.3, 34.3, 46.7.

(iv) Methanesulfonylpyrolidide (*42*)

Recrystallized from ether and hexane, mp 70–71°C; ir (KBr) ν_{max}: 3019 (w), 2982 (m), 2894 (w), 1321 (vs), 1250 (w), 1198 (m), 1146 (vs), 1107 (m), 1059 (m), 1009 (m), 972 (w), 912 (w), 781 (m), 558 (s), 521 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.88 (t, 4H), 2.76 (s, 3H), 3.26 (t, 4H); ^{13}Cmr ($CDCl_3$) δ: 25.7, 34.4, 47.8.

(v) Cyclohexanesulfonylpiperidide (63)

Recrystallized from methanol, mp 56–57°C, ir (KBr) ν_{max}: 2936 (vs), 2857 (s), 1451 (m), 1318 (vs), 1281 (m), 1219 (w), 1163 (m), 1138 (vs), 1117 (w), 1057 (m), 1026 (m), 941 (s), 897 (w), 855 (w), 833 (w), 768 (w), 708 (m), 594 (m), 561 (m), 492 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.04–2.10 (m, 16H), 2.84 (t of t, J = 3.4, 11.8 Hz, 1H), 3.25 (br t, 4H); ^{13}Cmr ($CDCl_3$) δ: 24.0, 25.2, 25.3, 26.2, 26.6, 47.1, 61.1.

(vi) Isopropylsulfonylpiperidide (64)

Colourless liquid, ir (neat) ν_{max}: 2979 (m), 2938 (vs), 3855 (s), 1456 (m), 1356 (w), 1323 (vs), 1273 (m), 1221 (w), 1163 (s), 1136 (vs), 1049 (s), 1026 (w), 943 (s), 882 (w), 855 (w), 833 (w), 731 (s), 664 (w), 577 (w), 542 (w), 494 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.27 (d, J = 6.9 Hz, 6H), 1.54 (m, 6H), 3.11 (septet, J = 6.9 Hz, 1H), 3.24 (t, 4H); ^{13}Cmr ($CDCl_3$) δ: 16.7, 23.9, 26.1, 47.1, 52.9.

(vii) *N,N*-Diisopropylmethanesulfonamide (70)

Recrystallized from ether and pentane, mp 67–68°C; ir (KBr) ν_{max}: 2986 (s), 2963 (m), 2938 (m), 3021 (w), 1476 (w), 1460 (w), 1404 (m), 1383 (w), 1308 (vs), 1192 (s), 1169 (m), 1138 (vs), 1030 (w), 984 (s), 881 (w), 861 (w), 768 (s), 637 (m), 563 (s), 536 (s), 513 (m), 477 (w), 446 (w); ^{1}Hmr ($CDCl_3$) δ: 1.27 (d, J = 6.9 Hz, 12 H), 2.82 (s, 3H), 3.72 (septet, J = 6.9 Hz, 2H); ^{13}Cmr ($CDCl_3$) δ: 22.1, 42.5, 48.4.

(viii) Methanesulfonylmorpholide (67)

Recrystallized from ether and hexane, mp 91–92°C; ir (KBr) ν_{max}: 3015 (w), 2971 (m), 2936 (w), 2897 (w), 2859 (s), 1460 (w), 1364 (w), 1344 (m), 1325 (vs), 1298 (m), 1264 (m), 1221 (w), 1154 (vs), 1111 (s), 1080 (m), 1021 (w), 968 (s), 941 (s), 849 (w), 785 (m), 700 (w), 594 (w), 523 (s), 504 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ:

2.80 (s, 3H), 3.22 (t, 2H), 3.79 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 34.0, 45.9, 66.3.

(ix) 2-Methoxyethanesulfonylpiperidide (65)

A colourless liquid, ir (neat) ν_{max}: 2940 (s), 2857 (m), 2201 (w), 1456 (m), 1387 (w), 1335 (vs), 1279 (w), 1217 (w), 1163 (vs), 1140 (s), 1117 (s), 1055 (m), 1028)w), 938 (m), 857 (w), 837 (w), 745 (m), 585 (w), 548 (w), 507 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.48-1.72 (m, 6H), 3.18 (t, 2H), 3.23 (t, 4H), 3.38 (s, 3H), 3.76 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 23.7, 25.6, 46.2, 49.3, 58.7, 66.0.

(x) (Trimethylsilyl)methanesulfonylpiperidide (68)

(Trimethylsilyl)methanesulfonyl chloride was prepared by a one-pot synthesis from (trimethylsilyl)methane magnesium chloride. SO_2 was bubbled into the commercial Grignard reagent (1 M solution of (Trimethylsilyl)methane magnesium chloride in hexane) (20 ml) for 5 min at 0°C; evaporation of the solvent followed by addition of 1 eq. of chlorine in dichloromethane (25 mL) gave the pure (trimethylsilyl)methane-sulfonyl chloride in 90% yield (3.1 g). ^{1}Hmr ($CDCl_3$) δ: 0.29 (s, 9H), 3.60 (s, 2H); ^{13}Cmr ($CDCl_3$) δ: -1.0, 60.2.

The titled piperidide was obtained as a crystailine solid in quantitative yield and was recrystallized from ether-hexane mixture, mp 93-94°C; ir (KBr) ν_{max}: 2952 (s), 2936 (s), 2855 (m), 1360 (w), 1331 (vs), 1320 (vs), 1279 (w), 1250 (m), 1166 (s), 1151 (s), 1140 (vs), 1098 (m), 1053 (m), 1030 (m), 962 (w), 932 (s), 851 (vs), 787 (s), 766 (m), 716 (w), 673 (w), 575 (m), 527 (w), 486 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.18 (s, 9H), 1.5-1.7 (m, 6H), 2.32 (s, 2H), 3.01 (t, 4H); ^{13}Cmr ($CDCl_3$) δ: -1.0, 23.6, 25.2, 35.8, 46.8.

(xi) Tetrahydrofurfurylsulfonylpiperidide (69)

Tetrahydrofurfurylthiol was prepared by addition of thiourea on tetrahydrofurfuryl

chloride which on reaction with aqueous NaOH gave tetrahydrofurfurylthiol (see chapter 1 for general procedures) (the thiol was required for the study of another project). This thiol on chlorination in water (general procedure described in chapter 1) gave tetrahydrofurfurylsulfonyl chloride. This compound on treatment with excess piperidine in dichloromethane, followed by workup afforded the title compound as a syrup. Tetrahydrofurfurylthiol: ^{1}Hmr ($CDCl_3$) δ: 1.50 (t, 1H, -SH), 1.68 (sym m, 1H), 1.84-2.15 (m, 3H), 2.64 (sym m, 2H), 3.72-4.02 (m, 3H); ^{13}Cmr ($CDCl_3$) δ: 26.0, 29.5, 30.2, 68.4, 80.0. Tetrahydrofurfurylsulfonyl chloride: colourless liquid; ir (neat) ν_{max}: 2984 (s), 2884 (s), 2255 (w), 2218 (w), 1462 (w), 1372 (vs), 1293 (w), 1246 (m), 1163 (vs), 1107 (m), 1057 (s(, 951 (m), 812 (w), 756 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.68-1.85 (m, 1H), 1.99 (quintet, 2H), 2.27 (sym m, 1H), 3.79-4.04 (m, 4H), 4.52 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 25.3, 31.4, 68.7, 70.0, 73.3. Tetrahydrofurfurylsulfonylpiperidide: a clear colourless liquid; ir (neat) ν_{max}: 2940 (s), 2859 (s), 1452 (w), 1359 (w), 1333 (vs), 1279 (w), 1253 (w), 1214 (w), 1163 (vs), 1142 (s), 1107 (m), 1053 (s), 1028 (w), 938 (s), 858 (w), 837 (w), 781 (m), 712 (w) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.50-2.78 (m, 7H), 1.86-2.00 (m, 2H), 2.11-2.26 (m, 1H), 2.98 (part of doublet of AB quartet, 1H), 3.16 (other part of doublet of AB quartet, but partially superimposed by δ 3.25 peak, 1H), 3.25 (t, 4H), 3.73-3.95 (m, 2H), 4.28 (apparent quintet, a superimposed doublet of triplet); ^{13}Cmr (CDl_3) δ: 23.8, 25.4, 25.7, 31.7, 46.4, 54.1, 687.2. Calcd. exact mass for $C_{10}H_{19}O_3SN$: 233.1086. Found: 233.1085.

(xii) 3-Chloropropanesulfonylpiperidide (*61*)

Recrystallized from ether-hexane, mp 52-53°C; ir (KBr) ν_{max}: 2948 (s), 3857 (m), 1447 (m), 1406 (m), 1362 (w), 1333 (vs), 1291 (s), 1254 (w), 1213 9w), 1157 (s), 1140 (vs), 1103 (w), 1057 (m), 1030 (w), 934 (s), 799 (m), 743 (m), 698 (m), 538 (s), 534 (s), 494 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.5-1.7 (m, 6H), 2.24 (quintet,

2H), 3.02 (t, 2H), 3.21 (br t, 4H), 3.65 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 25.6, 26.4, 43.1, 46.1, 46.6.

(xiii) 3-Chloropropanesulfonylpyrrolidide (62)

Recrystallized from ether-hexane, mp 72-73°C, ir (KBr) ν_{max}: 2980 (s), 2934 (m), 2892 (m), 1445 (w), 1408 (w), 1329 (vs), 1291 (s), 1252 (m), 1225 (w), 1198 (s), 1138 (vs), 1082 (m), 1051 (w), 1017 (m), 911(w), 868 (w), 799 (s), 747 (m), 714 (m), 619 (s), 523(s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.96 (sym m, 4H), 2.31 (quintet, 2H), 3.14 (t, 2H), 3,37 (sym m, 4H), 3.70(t, 2H); ^{13}Cmr ($CDCl_3$) δ: 25.9, 26.5, 43.1, 46.4, 47.7.

(xiv) 3-Chloropropanesulfonylmorpholide (66)

A colourless liquid, ir (neat) ν_{max}: 2969 (m), 2923 (m), 2861 (m), 1456 (m), 1341 (vs), 1262 (m), 1154 (vs), 1113 (s), 1076 (m), 1019 (w), 951 (s), 866 (w), 848 (w), 747 (m), 554 (m), 544 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.30 (quintet, 2H), 3.10 (t, 2H), 3.28 (t, 4H), 3.75 (m, 6H); ^{13}Cmr ($CDCl_3$) δ: 26.11, 42.86, 45.66, 45.69.

(xv) *N*-Methylsulfonyl-1,2,4,5-tetrahydropyridine (74)

Reaction of 4-hydroxypiperidine (Aldrich) (3.35 g, 33 mmol) with methanesulfonyl chloride (8 g, 70 mmol) and triethylamine (8 g, 80 mmol) in dichloromethane (50 mL) at 0°C gave *N*-methylsulfonyl-4-methanesulfonyloxypiperidine (7.8 g, 92%) as a solid which was recrystallized from dichloromethane and ethanol, mp 132-133°C; ^{1}Hmr ($CDCl_3$) δ: 2.07 (sym m, 4H), 2.82(s, 3H), 3.06 (s, 3H), 3.55 (t, 4H), 4.93 (quintet, 1H); ^{13}Cmr ($CDCl_3$) δ: 31.2, 35.2, 38.8, 42.1, 75.6.

N-Methylsulfonyl-4-methanesulfonyloxypiperidine (1.03 g, 4 mmol) was dissolved in a solution of 2% KOH in ethanol (25 mL) and the reaction mixture was refluxed for 5 h. The usual workup afforded the titled compound as a syrup (386 mg, 60%),

ir (neat) ν_{max}: 3040 (m), 2930 (vs), 2863 (s), 1464 (s), 1341 (vs), 1242 (m), 1206 (m), 1159 (vs), 1113 (m), 1089 (m), 1049 (m), 1010 (m), 961 (s), 928 (m), 878 (w), 789 (s), 764 (s), 658 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.27 (sym m, 2H), 2.82 (s, 3H), 3.37 (t, 2H), 3.77 (sym m, 2H), 5.72 (sym m, 1H), 5.83 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 24.9, 35.0, 42.2, 44.4, 122.8, 125.2.

(xvi) *N,N*-Phenylmethylmethanesulfonamide (*71*)

Recrystallized from ether–pentane, mp 69–70°C; ir (KBr) ν_{max}: 3065 (w), 3009 (m), 2932 (m), 2891 (w), 2818 (w), 2463 (w), 2293 (w), 1966 (w), 1898 (w), 1767 (w), 1595 (m), 1493 (s), 1456 (m), 1422 (m), 1331 (vs), 1266 (m), 1179 (vs), 1144 (vs), 1079 (s), 1026 (m), 967 (s), 920 (m), 876 (s), 770 (s), 698 (s), 544 (s), 522 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.84 (s, 3H), 3.33 (s, 3H), 7.27–7.47 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 35.1, 38.1, 126.2, 127.4, 129.3, 141.0.

(xvii) *N,N*-Phenylmethylbenzenesulfonamide (*72*)

Recrystallized from methanol, mp 76–77°C; ir (KBr) ν_{max}: 3069 (w), 3021 (w), 1595 (w), 1495 (m), 1449 (m), 1347 (vs), 1179 (vs), 1156 (s), 1139 (m), 1090 (m), 1065 (m), 1026 (w), 688 (m), 774 (m), 758 (w), 731 (m), 689 (s), 596 (m), 565 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.17 (s, 3H), 7.04–7.60 (m, 10H); ^{13}Cmr ($CDCl_3$) δ: 38.1, 126.6, 127.3, 127.8, 128.7, 128.8, 132.8, 136.3, 141.4.

(xviii) *N*-Methylnapthosultam (*73*)

Commercial 1,8-napthosultam (Aldrich) (2.5 g, 12.2 mmol) was added to a solution of KOH (0.7 g, 13 mmol) in ethanol (25 mL) with stirring, then methyl iodide (3.1 g, 24 mmol) was added and the reaction mixture was refluxed for 6 h. Workup followed by recrystallization gave the titled sultam in 80% yield (2.0 g); ir

(KBr) ν_{max}: 1630 (w), 1591 (m), 1495 (m), 1464 (m), 1379 (m), 1306 (vs), 1223 (m), 1190 (m), 1165 (s), 1134 (vs), 924 (m), 808 (s), 797 (m), 762 (s), 750 (m), 739 (m), 609 (s), 584 (m), 531 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.36 (s, 3H), 6.70 (dd, J = 0.82, 7.01 Hz), 7.49 (sym m, 2H), 7.73 (dd, J = 8.21, 8.31 Hz, 1H), 7.96 (d, J = 6.67 Hz, 1H), 8.05 (d, J = 8.17, 1H); ^{13}Cmr ($CDCl_3$) δ: 26.8, 102.9, 118.3, 119.4, 119.8, 128.0, 129.4, 130.3, 130.5, 131.1, 137.1.

Preparation of authentic samples of the chlorosulfonylalkanaminium chlorides

(i) *N*-Methyl 3-chlorosulfonylpropanaminium chloride[15] (*13*)

A solution of *N*-methylpropane sultam (*12b*) (200 mg, 1.5 mmol) in anhydrous ether (10 mL) was added to a ether solution (25 mL) which was saturated with dry hydrogen chloride (HCl) gas. A precipitate began tc form almost immediately upon addition of the sultam. The reaction mixture was stirred for 0.5 h and the crystalline product was collected by filtration under nitrogen atmosphere. The colourless crystals were washed well with anhydrous ether and were dried *in vacuo* to afford 215 mg (85%) of *13*; ir (KBr) ν_{max}: 2932 (vs), 2791 (vs), 2710 (vs), 2411 (m), 1469 (m), 1366 (vs), 1159 (vs), 1015 (m), 870 (m), 770 (m), 733 (m), 542 (s), 515 (s), 484 (s) cm^{-1}; ^{1}Hmr (CD_3OD) δ: 2.43 (quintet, 2H), 2.74 (s, 3H), 3.23 (t, 2H), 4.16 (t, 2H); ^{13}Cmr (CD_3OD) δ: 22.5, 33.7, 47.6, 62.7.

(ii) 3-Chlorosulfonylpropanaminium chloride (*45*)

A solution of propane sultam (121 mg, 1.0 mmol) in anhydrous ether (5 mL) was added to a ether solution (15 mL) which was saturated with dry hydrogen chloride (HCl) gas. The reaction mixture was stirred for 0.5 h and workup as above afforded the crystalline product (125 mg, ~80%); ir (KBr) ν_{max}: 3029 (vs), 2645 (m), 1576 (s), 1524 (m), 1451 (w), 1375 (vs), 1219 (w), 1169 (vs), 1049 (w), 1007 (m), 974 (m), 901 (w), 845 (w), 756 (s), 596 (w), 548 (m), 521 (s) cm^{-1}; ^{1}Hmr

(CD_3OD) δ: 2.45 (quintet, 2H), 3.20 (t, 2H), 4.05 (t, 2H), 4.65 (s, 3H); ^{13}Cmr (CD_3OD) δ: 22.9, 37.7, 52.2.

(iii) *N*-Methyl 4-chlorosulfonylcyclohexanaminium chloride (*46*)

A solution of bicyclic sultam *14* (50 mg, 0.28 mmol) in dichloromethane (2 mL) was added to dichloromethane (10 mL) saturated with hydrogen chloride. The reaction mixture was left under nitrogen overnight and the workup as above afforded the crystalline solid in quantitative yield (60 mg); ir (KBr) ν_{max}: 2946 (s), 2897 s), 2726 (s), 2473 (m), 2371 (w), 1538 (w), 1456 (m), 1360 (vs), 1341 (w), 1157 (vs), 1082 (w), 644 (m), 583 (s), 557 (w), 540 (m) cm^{-1}; ^{1}Hmr (CD_3OD) δ: 1.9-2.5 (m, 8H), 2.78 (t, 3H), 3.42 (sym m, 1H), 4.18 (sym m, 1H), 4.85 (br s, 2H); ^{13}Cmr (CD_3OD) δ: 24.5, 26.2, 33.4, 57.7, 73.7.

(iv) 7,7-Dimethyl-2-(*N*-methylamine hydrochloride)-bicyclo[2.2.1]heptane-1-methanesulfonyl chloride (*47*)

N-Methylcamphor sultam (*39*) (100 mg, 0.33 mmol) was dissolved in anhydrous ether (10 mL) and was added to ether (20 mL) saturated with hydrogen chloride. The reaction mixture was left for 10 days and the workup as before gave a solid which was a 40:60 mixture of unreacted *N*-methylcamphor sultam and the sulfonyl chloride *47*; ^{1}Hmr ($CDCl_3$) δ: 0.97 (s, 3H), 1.24 (s, 3H), 2.25-2.13 (m, 7H), 2.75 (t, 3H), 3.26 (m, 1H), 3.86 (d, J = 14.5 Hz, 1H), 5.40 (d, J = 14.5 Hz, 1H); ^{13}Cmr (CD_2Cl_2) δ: 20.6, 20.9, 27.9, 34.3, 35.6, 36.2, 51.1, 52.6, 66.7, 67.9.

(v) *N*-*t*-Butyl 3-chlorosulfonylpropanaminium chloride (*48*)

A solution of *N*-*t*-butylpropane sultam (*12c*) (100 mg, 0.57 mmol) in dichloromethane (5 mL) was added to the dichloromethane (20 mL) saturated with hydrogen chloride. The reaction mixture was left overnight; workup as before yielded

the crystalline solid (120 mg, ~100%); ir (KBr) ν_{max}: 3431 (m), 2982 (vs), 2799 (vs), 2489 (w), 2419 (w), 1592 (m), 1483 (w), 1408 (w), 1368 (vs), 1333 (m), 1264 (w), 1232 (w), 1192 (m), 1167 (vs), 1003 (m), 773 (m), 598 (m), 548 (s), 527 (s) cm^{-1}; ^{1}Hmr (CD_3OD) δ: 1.40 (s, 9H), 2.41 (quintet, 2H), 3.21 (t, 2H), 4.15 (t, 2H), 4.91 (s, 2H); ^{13}Cmr (CD_3OD) δ: 23.3, 25.8, 40.1, 58.6, 62.6.

N-Methyl 4-chlorosulfonylbutanaminium chloride (*49*)

N-Methylbutane sultam (20 mg) was dissolved in dichloromethane-d_2 in an nmr tube and the HCl gas was bubbled in the tube for two min and the tube was sealed. After a week in ^{13}Cmr spectra two sets of peaks were observed, where smaller peaks (~25%) can easily be assigned to *49*. ^{13}Cmr (CD_2Cl_2) δ: 14.0, 21.9, 33.5, 48.6, 64.7. ^{1}Hmr (CD_2Cl_2) δ: 3.90 (t, 2H, *S*-CH_2), 2.75 (t, 3H, *N*-CH_3), rest of the peaks were overlapping with the starting material.

Preparation of trialkylsulfonylammonium salts

(i) Trimethyl(methylsulfonyl)ammonium trifluoromethanesulfonate[41] (*50*) from *N,N*-dimethylmethanesulfonamide (*40*)

A solution of methyl trifluoromethanesulfonate (2 mL, in large excess) in anhydrous dichloromethane (10 mL) was added dropwise to a solution of *40* (800 mg, 6.5 mmol) in anhydrous dichloromethane with stirring at 0°C under a nitrogen atmosphere. The mixture was stirred overnight and the crystals were collected by filtration and washed with dichloromethane to give the title compound (1.5 g, 80%). ^{1}Hmr (CD_3CN) δ: 3.34 (s, 9H), 3.83 (s, 3H); ^{13}Cmr (CD_3CN) δ: 36.1, 49.5.

(ii) 2,2-Dimethylisothiazolidinium 1,1-dioxide trifluoromethanesulfonate[41] (*51*) from *N*-methylpropane sultam (*12b*)

Similarly the addition of methyl trifluoromethanesulfonate (2.5 g, 15 mmol) in dichloromethane (25 mL) to a solution of *12b* (650 mg, ~5 mmol) in dichloromethane (25 mL) at 0°C. The reaction mixture was kept under nitrogen for 1 h and then the product was collected by filtration under nitrogen. The crystalline product was washed with anhydrous dichloromethane to give the product as white solid (1.3 g, 90%). ^{1}Hmr (CD_3CN) δ: 2.52 (m, 2H), 2.82 (s, 6H), 3.84 (t, 2H), 3.98 (t, 2H); ^{13}Cmr (CD_3CN) δ: 20.6, 44.1, 49.2, 57.7.

(iii) 2,2-Dimethyltetrahydro-1,2-thiazinium 1,1-dioxide trifluoromethanesulfonate[41] (*52*) from *N*-methylbutane sultam (*20b*)

Methyl trifluoromethanesulfonate (3 g, 18 mmol) in dichloromethane (25 mL) was added to a solution of *20b* (1 g, 6.6 mmol) in dichloromethane (25 mL). The reaction mixture was kept at room temperature for three days under nitrogen atmosphere and then workup as above afforded the crystalline solid (2 g, 95%). ^{1}Hmr (CD_3CN) δ: 1.98-2.13 (m, 2H), 2.21-2.33 (m 2H), 3.29 (s, 6H), 3.81 (t, 2H), 4.09 (t, 2H); ^{13}Cmr (CD_3CN) δ: 19.6, 23.5, 46.6, 49.3, 66.1.

(iv) *N,N*-Dimethyl-2,3-thiaziniumbicyclo[2.2.2]octane 2,2-dioxide trifluoromethanesulfonate (*53*) from *N*-methyl-2-thia-3-azabicyclo[2.2.2]octane 2,2-dioxide (*14*)

Similarly, treatment of methyl trifluoromethanesulfonate (164 mg, 1 mmol) in dichloromethane (5 mL) with *14* (50 mg, 0.3 mmol) in dichloromethane (5 mL) and stirring the reaction mixture for 4 h gave the titled compound as a solid in quantitative yield. ^{1}Hmr (CD_3CN) δ: 1.82-2.48 (m, 8H), 3.00 (s, 6H), 3.96 (m, 1H), 4.10 (m, 1H); ^{13}Cmr (CD_3CN) δ: 19.4, 21.4, 34.5, 56.4, 65.5.

Determination of pK_a's of the protonated sulfonamides

Aqueous sulfuric acid solutions were standardized by titrating a measured volume with standard 2 N sodium hydroxide; H_0 values were determined from a plot of Jorgenson and Hartter's data.[31] Nmr spectra were determined on solutions prepared within 5-10 min of measurement, using an acetone-d_6 or a mixture of acetone-d_6 and TMS capillary reference. No evidence of hydrolysis appeared from the spectra. In case of *N*-methylpropane sultam (*12b*) this was shown by isolating the sultam from sulfuric acid solution (H_0 = -4) as in the following experiment. The sultam *12b* (25mg) was dissolved in 5 ml of sulfuric acid solution, after running the spectrum the sulfuric acid solution was added to a mixture of ice and water. The product was isolated by extraction with dichloromethane in greater than 85% yield and was shown to be *12b* by ^1H and ^{13}Cmr spectra. All ^1Hmr spectra were measured with a Varian XL-200 nmr spectrometer. The nmr data were obtained on 0.5% solutions (by weight) for all the sulfonamides.

The shapes of the curves, for the determination of H_0's at 50% protonation of sulfonamides, can be calculated[59] from the equation (1) shown below if there is not a significant difference in chemical shifts of unprotonated and protonated forms (B and BH^+ respectively) from medium effect, and also assuming that δ is linearly related to $(BH^+)/(B)$:[33]

$$pK_a = H_0 + \log \frac{\delta - \delta_B}{\delta_{BH} - \delta} \qquad \text{.....(4)}$$

The above equation (4) can be modified as shown:

$$\delta = \frac{\delta_B + \delta_{BH}\, e^{2.303(pK_a - H_0)}}{1 + e^{2.303(pK_a - H_0)}} \qquad \text{.....(5)}$$

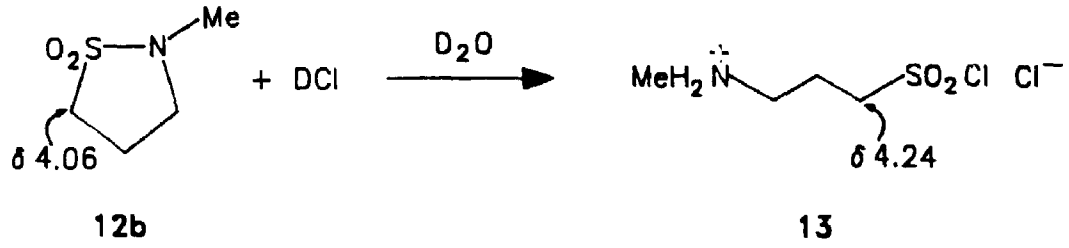
In practice, in most cases there is substantial medium effect on the chemical shifts of B and BH^+. For the calculation of the $(BH^+)/(B)$ ratio the assumption was made that the medium effect on δ_B and δ_{BH^+} remains linear with the acidity function;[56] the equation (5) may be modified to equation (6) shown below:

$$\delta = \frac{m(H_o-(H_o)_a) + (\delta_B)_a + [n(H_o-(H_o)_b) + (\delta_{BH})_b]\, e^{2.303(pK_a-H_o)}}{1 + e^{2.303(pK_a-H_o)}} \qquad \text{.....(6)}$$

Where $(\delta_B)_a$ is the value of δ_B at a particular value of H_o (*i.e.* $(H_o)_a$ and $(\delta_{BH})_b$ is the value of δ_{BH} at another particular value of H_o (*i.e.* $(H_o)_b$), and where m and n are the respective slopes of the dependence of δ_B and δ_{BH^+} on H_o; when $m = n = 0$, this equation reduces to equation (5).

Kinetics of Hydrochlorinolysis of Sulfonamides

General procedure: A 10 mg sample of the sulfonamide was dissolved in D_2O–DCl and placed in an nmr tube. The progress of the reaction was followed using XL–200 nmr spectrometer at a probe temperature of 21 °C by measuring the integration of a *N*–Me peak of the starting material and the *N*–Me peak of the products produced by the hydrochlorinolysis and reaction with H_2O. The percentage of the remaining starting material at any time during the reaction was then calculated by taking the ratio of the integration of *N*–Me peak of starting material to the sum of the *N*–Me of starting material and the product. The natural log of the percentage starting material remaining *vs.* time was plotted to give a straight line as shown in Figure 3.20 for the hydrochlorinolysis of *N*–methylpropane sultam (*12b*). The value of the pseudo first order rate constant in reciprocal seconds was obtained from the slope of the line. The observed rate constants (k_{obs}) of hydrochlorinolysis for various sulfonamides are listed in Table 3.2.



12b **13**

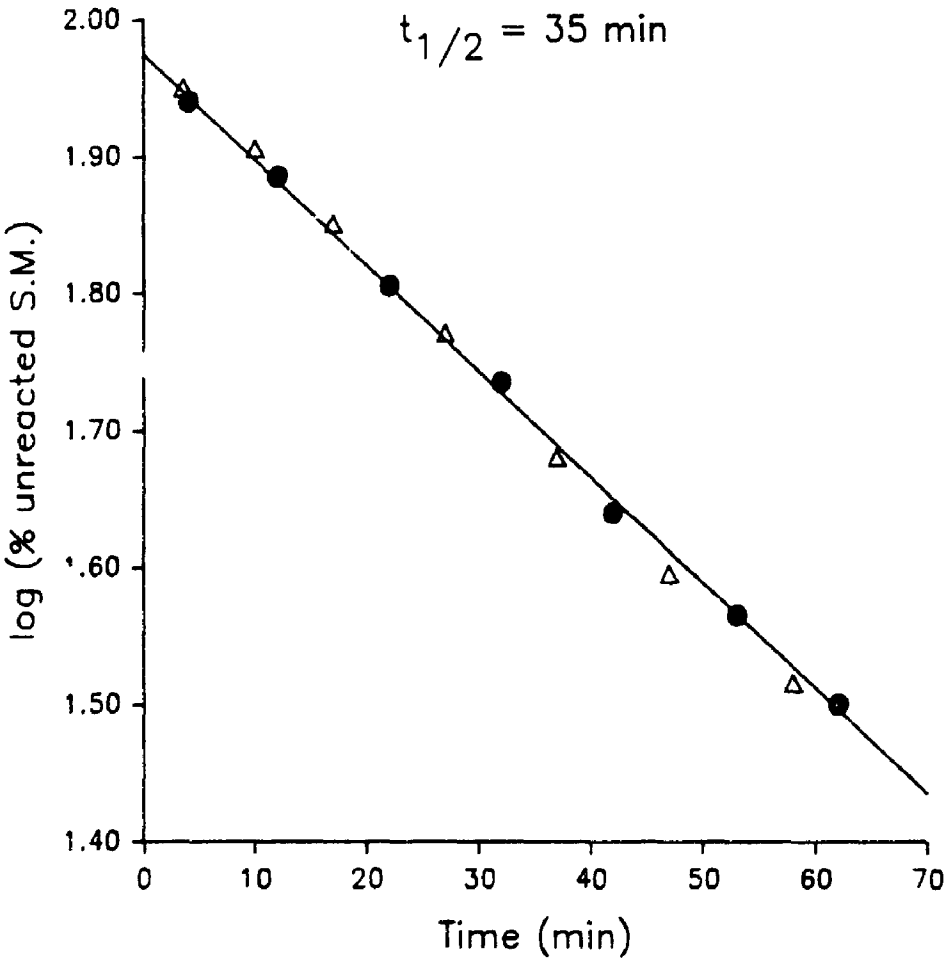


Figure 3.20 A typical first order plot for the hydrochlorinolysis reaction of **12b** in D_2O–DCl at 21°C. The % unreacted S.M. was calculated from the following equation: (∫ δ 4.06/ ∫ δ 4.06 + ∫ δ 4.24).

The products of the hydrochlorinolysis of sulfonamides were characterized by comparing the ^{1}Hmr and ^{13}Cmr spectra with those of the authentic samples prepared from hydrochlorinolysis of sultams in organic solvents and were found to be identical. The nmr spectra of authentic samples in D_2O–DCl are recorded below:

N-Methyl 3-chlorosulfonylpropanaminum chloride (*13*)

^{1}Hmr (D_2O–DCl) δ: 2.51 (quintet, 2H), 2.83 (t, 2H, *N*–Me), 3.35 (quintet, 2H, *N*–CH_2), 4.19 (t, 2H, *S*–CH_2); ^{13}Cmr (D_2O–DCl) δ: 23.0, 35.7, 48.8, 63.7.

N-Methyl 4-chlorosulfonylcyclohexanaminium chloride (*46*)

^{1}Hmr (D_2O–DCl) δ: 1.92–2.54 (m, 8H), 2.78 (t, 3H, *N*–Me), 3.42 (m, 1H), 4.18 (m, 1H), 7.85 (br s, 2H); ^{13}Cmr (D_2O–DCl) δ: 24.5, 26.2, 33.4, 57.7, 73.5.

N-Methyl 10-chlorosulfonylcamphor-3-aminium chloride (*47*)

^{1}Hmr (D_2O–DCl) δ: 0.99 (s, 3H), 1.11 (s, 3H), 1.2–2.15 (m, 7H), 2.82 (t, 3H, *N*–Me), 3.50 (m, 1H, *N*–CH), 4.36 (d, *J* = 14.8 Hz, 1H), 4.68 (d, *J* = 14.8 Hz, 1H); ^{13}Cmr (D_2O–DCl) δ: 21.5, 22.0, 28.4, 33.6, 36.1, 46.1, 49.6, 52.0, 70.7.

N-Methyl 4-chlorosulfonylbutanaminium chloride (*49*)

^{13}Cmr (D_2O) δ: 14.8, 22.6, 34.8, 49.4, 65.8; ^{1}Hmr (D_2O) δ: 4.06 (t, 2H, *S*–CH_2), 2.79 (s, 3H, *N*–CH_3), rest of the peaks were overlapping with the starting material.

The rates of hydrochlorinolysis of sulfonylammonium salts were measured similarly as described in the general procedure and are listed in Table 3.4.

3.5 REFERENCES AND FOOTNOTES

1. D.W.J. Cruickshank, *J. Chem. Soc.*, 5486 (1961).
2. (a) D.A. Bors and A. Streitwieser, *J. Am. Chem. Soc.*, **108**, 1397 (1986); (b) J.S. Grossert, J. Hoyle, T.S. Cameron, S.P. Roe, and B.R. Vincent, *Can. J. Chem.*, **65**, 1407 (1987); (c) G. Boche, *Angew. Chem. Int. Ed. Engl.*, **28**, 277 (1989) and references cited therein.
3. T. Jordan, H.W. Smith, L.L. Lohr, Jr., and W.N. Lipscomb, *J. Am. Chem. Soc.*, **85**, 846 (1963).
4. W.B. Jennings and R. Spratt, *J. Chem. Soc., Chem. Commun.*, 1418 (1970).
5. M.B. Smith and J. Wolinsky, *Org. Magn. Res.*, **19**, 129 (1982).
6. J.F. King, K.C. Khemani, S. Skonieczny, and N.C. Payne, *J. Chem. Soc., Chem. Commun.*, 416 (1988).
7. E.T. Kaiser, M. Panar, and F.H. Westheimer, *J. Am. Chem. Soc.*, **85**, 602 (1965); E.T. Kaiser, *Acc. Chem. Res.*, **3**, 145 (1970).
8. A. Mori, M. Nagayama, and H. Mandai, *Bull. Chem. Soc.*, **44**, 1669 (1971).
9. S. Osterman-Golkar and C.A. Wachtmeister, *Chem.-Biol. Interactions*, 1425 (1976); S. Osterman-Golkar, L. Ehrenberg, and C.A. Wachtmeister, *Radiation Botany*, **10**, 303 (1970).
10. J.F. King, K.C. Khemani, S. Skonieczny, and N.C. Payne, in Reviews on Heteroatom Chemistry, Vol. *1*, editor S. Oae, N.Y.U. Tokyo, 1988, pp 80-93
11. A.C. Hazell, *Acta. Cryst.*, **B30**, 2724 (1974).
12. F.A.L. Anet, R.D. Trepka, and D.J. Cram, *J. Am. Chem. Soc.*, **89**, 357 (1967).
13. L.V. Vilkov, and I.Y. Khargittai, *Dolkady Akad. Nauk., S.S.S.R.*, **168**, 1065 (1965).
14. S. Wolfe, A. Rauk, and I.G. Csizmadia, *J. Am. Chem. Soc.*, **91**, 1567 (1969).

15. W.F. Erman and M.C. Kretschmer, *J. Org. Chem.*, **26**, 4841 (1961).

16. D. Klamann and G. Hofbauer, *Ann.*, **581**, 182 (1953); and also see D. Klamann and H. Bertsch, *Ber.*, **92**, 2610 (1959); S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959) and references cited therein.

17. W.v.E. Doering and L.K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955).

18. J.F. King, R. Rathore, and D. Klassen, unpublished results. The 2-thia-bicyclo[2.2.2]octane 2,2-dioxide (**A**) was synthesized by Reich and Trend's procedure.[19] Cycloaddition of thiophosgene (3.1 ml, 40 mmol) with cyclohexa-diene (3.2 g, 40 mmol) in pentane (25 mL) and reduction with lithium aluminium hydride gave 2-thiabicyclo[2.2.2]oct-5-ene in 35% yield (^{1}Hmr ($CDCl_3$) δ: 1.26–2.20 (m, 5H), 2.51 (m, 1H), 2.97 (m, 1H), 3.39 (m, 1H), 6.21 (t, 2H), 6,55 (t, 1H); ^{13}Cmr ($CDCl_3$) δ: 23.0, 23.9, 30.1, 32.4, 33.1, 131.2, 134.2), and followed by reduction with diimide gave 2-thiabicyclo-[2.2.2]octane (^{1}Hmr ($CDCl_3$) δ: 1.54–2.15 (m, 9H), 2.52 (quintet, 1H), 2.77 (d, 2H); ^{13}Cmr ($CDCl_3$) δ: 23.2, 24.5, 29.3, 30.38, 30.44) which was oxidized using hydrogenperoxide (30%) in acetic acid to afford 2-thiabicyclo[2.2.2]-octane 2,2-dioxide in 90% yieid (^{1}Hmr ($CDCl_3$) δ: 1.52–2.05 (m, 6H), 2.25–2.45 (m, 3H), 2.85 (quintet, 1H), 3.13 (d, 2H); ^{13}Cmr ($CDCl_3$) δ:21.4, 21.8, 28.7, 50.8, 60.7). The rate of H–D exchange was measured in solution of NaOD in dimethylsulfoxide-d_6 and CD_3OD (1.1) and found that the methylene hydrogens exchanges 50 times faster than the methine hydrogen. Recently Mr. D. Klassen has measured the rates in NaOD solution in CD_3OD–D_2O (1:1) and found that the difference in rate of exchange of methylene and methine hydrogens is ~25.

19. H.J. Reich and J.E. Trend, *J. Org. Chem.*, **38**, 2673, 1973)

20. W.H. Urry and O.O. Juveland, *J. Am. Chem. Soc.*, **80**, 3322 (1959); D.C. Curran, *Synthesis*, 489 (1988).

21. O. Vogl and M. Pohm, *Monatsh. Chem.*, **83**, 541 (1952).

22. S. Searles Jr., G.E. Roelofs, M. Tamres, and R.N. McDonald, *J. Org. Chem.*, **30**, 3443 (1965).

23. H.H. Otto and P. Schwenkkraus, *Tetrahedron Lett.*, **23**, 5389 91982).

24. E.J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

25. W.C. Still, M. Kuhn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1979).

26. F.M. Menger and L. Mandell, *J. Am. Chem. Soc.*, **89**, 4424 (1967).

27. M. Vandewalle and J.V.D. Eycken, *Tetrahedron*, **42**, 4035 (1986); W. Oppolzer, C. Chapuis, and G. Bernardinelli, *Helv. Chim. Acta*, **67**, 1397 (1984).

28. J.S. Grossert, M.M. Bharadwaj, R.F. Langler, T.S. Cameron, and R.E. Cordes, *Can. J. Chem.*, **56**, 1183 (1978).

29 The values of dissociation constants of protonated sulfonamides in concentrated sulfuric acid solutions are expressed as '$-pK_a$' for the sake of convenience although they are measured in the solvents which are much different from water. Thus these values are, in fact, $-H_0$ at 50% protonation of sulfonamides. See, R. Stewart, Academic Press, New York, The Proton: Application To Organic Chemistry, Vol. **46**, pp 14-18 (1985).

30. R.G. Laughlin, *J. Am. Chem. Soc.*, **89**, 4268 (1967).

31. M.J. Jorgenson and D.R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963); and also see M.A. Paul and F.A. Long, *Chem. Rev.*, **57**, 1 (1957); R.A. Cox and K. Yates, *Can. J. Chem.*, **61**, 2225 (1983)..

32. T. Birchall and R.J. Gillespie, *Can J. Chem.*, **41**, 2642 (1963).

33. E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, **27**, 641 (1957).

34. R.A. Cox and K. Yates, *J. Am. Chem. Soc.*, **100**, 3861 (1978).

35. Applications of Dissociation Constants, Optical Activity, and Other Physical Measurements by J.F. King in "Technique of Organic Chemistry," Editor A. Weissberger, pp 311-412 (1963), Interscience Publishers, John Wiley, NY, New

York.

36. K.M. Dyumaev and B.A. Korolev, *Russ. Chem. Rev.*, **49**, 1021 (1980) and referces cited therein.

37. J.A. Hirsch, *Top. in Stereochem.*, **1**, 199 (1967).

38. It is evident from J.H. Li's studies of rates of hydrochlorinolysis of sultams in H_2O-HCl that more than 20% of sulfonic acid was formed in case of **12b**, whereas in D_2O-DCl only about 5% of the sulfonic acid was produced along with sulfonyl chloride (95%). A small part of the sulfonic acid may have been produced by hydrolysis of sulfonyl chloride, but the major portion of it was a result of attack of H_2O or D_2O on the protonated sulfonamide. The greater $k_2[H_2O]$ term compared to $k_2[D_2O]$ may reflect a solvent isotope effect.

39. P.A. Briscoe, F. Challenger, and P.S. Duckworth, *J. Chem. Soc.*, 1757 (1956).

40. C.K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York (1953).

41. J.F. King, S.M. Loosmore, M. Aslam, J.D. Lock, and M.J. McGarrity, *J. Am. Chem. Soc.*, **104**, 7108 (1982).

42. K.J. Shea, *Tetrahedron*, **36**, 1683 (1980).

43. L.J. Bellamy, "The Infrared Spectra of Complex Organic Molecules," Richard and Clay Company, Ltd., Methuen, London, pp 203-230 (1958).

44. K.C. Schreiber, *Analyt. Chem.*, **21**, 1168 (1949); R. Adams and J.J. Tjepkema, *J. Am. Chem. Soc.*, **70**, 4204 (1948) and references therein.

45. J.N. Baxter, J. Cymerman-Craig, and J.B. Willis, *J. Chem. Soc.*, 669 (1955).

46. The infrared spectra of organo-sulfur compounds, by L.J. Bellamy in "Organic Sulfur Compounds," Edited by N. Kharasch, pp 47-56 (1961).

47. See for example K. Nakanishi, "Infrared Absorption Spectroscopy -Practical," Holden-Day, Inc., San Francisco, 1962.

48. J.F. King, R.A. Marty, P. de Mayo, and D.L. Verdun, *J. Am. Chem. Soc.*,

93, 6304 (1971) and R. Langendries, F.C. de Schryver, P. de Mayo, R.A. Marty, and J. Schuyster, *J. Am. Chem. Soc.*, *96*, 2964 (1974).

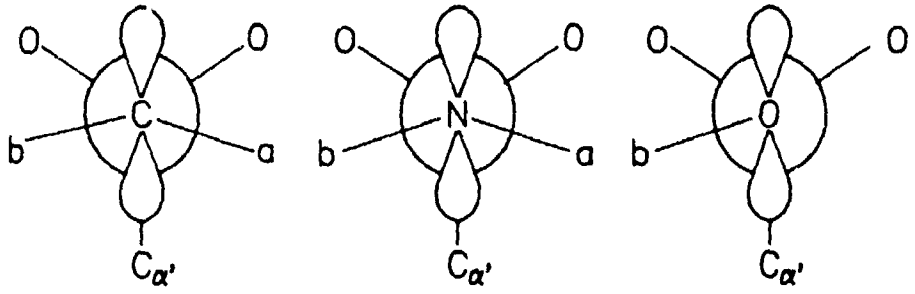
49. T. Momose, Y. Ueda, T. Shoji, and H. Yano, *Chim. Pharm. Bull.*, *6*, 669 (1958).
50. L.J. Bellamy and R.L. Williams, *J. Chem. Soc.*, 863 (1957), and also see E.R. Robinson, *Can. J. Chem.*, *39*, 247 (1961).
51. J.H. Helberger and H. Lantermann, *Liebigs Ann. Chem.*, *586*, 158 (1954).
52. E.J. Goethals and M. Verzele, *Bull. Soc. Chim. Belges*, *74*, 21 (1965).
53. B. Helferich and K.G. Kleb, *Ann. Chem.*, *635*, 93 (1960).
54. M.J. McGarrity, Ph.D. Thesis, University of Western Ontario, London, Canada (1984).
55. E.M. Kaiser and P.L. Knutson, *J. Org. Chem.*, *40*, 1342 (1975).
56. J.D. Lock, Ph.D. Thesis, University of Western Ontario, London. Canada (1984).
57. A.D. Bliss, W.K. Cline, C.E. Hamilton, and O.J. Sweeting, *J. Org. Chem.*, *28*, 3537 (1968).
58. S. Smiles and T.P. Hilditch, *J. Chem. Soc.*, *91*, 519 (1907).
59. A. Koeberg-Telder and H. Cerfontain, *J. Chem. Soc. Perkin II*, 226 (1975).

CHAPTER 4

A STEREOELECTRONIC EFFECT ON THE RATE OF H-D EXCHANGE ALPHA TO A SU-2HLFONYL GROUP

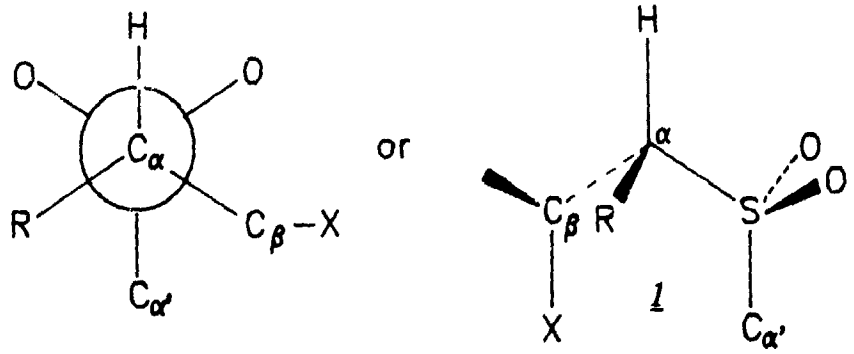
4.1 INTRODUCTION

It has already been pointed out in chapter 3 that there is evidence that the most stable conformations of sulfonyl carbanions, sulfonamides and sulfonic esters are those shown below:



Sulfonyl Carbanions | Sulfonamides | Sulfonic Esters

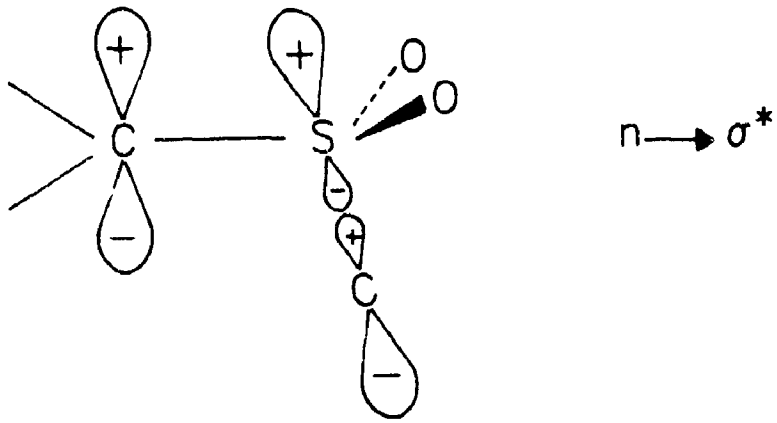
α-Sulfonyl carbanions, $\rangle\bar{C}\text{-}SO_2\text{-}$, have received intensive experimental[1] and theoretical attention[2] ever since the observation that α-chiral sulfones undergo base catalysed H-D exchange with retention of chirality.[3] The readiest deprotonations, for example, are observed when the C-H bond is as shown in *1*, *i.e.* arranged so that it is aligned with the internal bisector of the O-S-O angle, or, alternatively, *anti-periplanar* to the S-$C_{\alpha'}$ bond.



A number of recent X-ray crystal structures on α-sulfonyl carbanions also indicate

that *1* is the lowest energy conformation.[4]

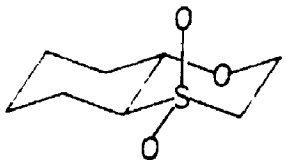
Wolfe, Stolow and LaJohn[5] have suggested that this conformational preference in α–sulfonyl carbanions is due to the donation of the lone pair electrons from the anionic carbon–atom to the antibonding orbital (σ^*) of S–C_α bond, *i.e.* a version of the anomeric effect.



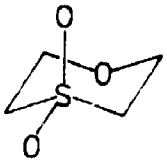
Results reported by Stirling and Thomas[6] for the detritiation of β–substituted acyclic phenyl sulfones, $PhSO_2CHTCH_2X$, in ethanolic sodium ethoxide, showed that the reaction depended strongly on X, with a rate increase of about 5 x 10^4 on changing X from a methyl to a phenoxyl group. A Taft plot was obtained by plotting log *k* *vs* the σ^*–value of the $-CH_2X$ groups and the Taft parameter (ρ^*) was found to be 4.89, indicating[6] that the ionization of sulfone is very sensitive to polar effects of β–substituents (X). Conventionally, the term polar effect, is used to characterize the observed influence of unconjugated, sterically remote substituents on equilibrium or kinetic processes.[7] This designation permits the use of terms, inductive and field effect, for the description of the transmission mechanism. The purpose of this study is to find whether there is a geometry–dependent component (*i.e.* a stereoelectronic factor) present in the "polar" effect.

The firm stereoelectronic control exerted by the sulfonyl group should enable one to find out if any related geometry–dependent factors operate at adjacent carbon

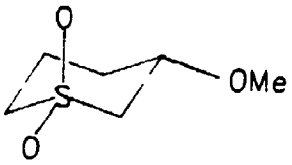
centres, the specific case examined in the present study being the effect of the orientation of an alkoxyl group beta to the sulfonyl function, as in *1* (X = OR).



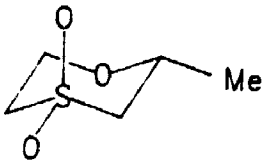
2



3



4



5

It was decided to compare the base-catalysed rate of H–D exchange of hydrogens alpha to sulfonyl in compounds *2*, *3*, *4*, and *5*. If the effect of a β-substituent on the rates of H–D exchange of the above compounds is entirely due to the inductive effect (after correcting for any steric effect), then *3* and *4* should have the same rates for H–D exchange (the question of field effect will be discussed later). In reality, the rate of H–D exchange in *3* was distinctly faster than that in *4*.

A systematic study of rate of exchange on various β-alkoxysulfones has now been completed and it is clear that the ease of formation of α-sulfonyl carbanion depends on the spatial arrangement of the alkoxy oxygen. These results are described in the present chapter.

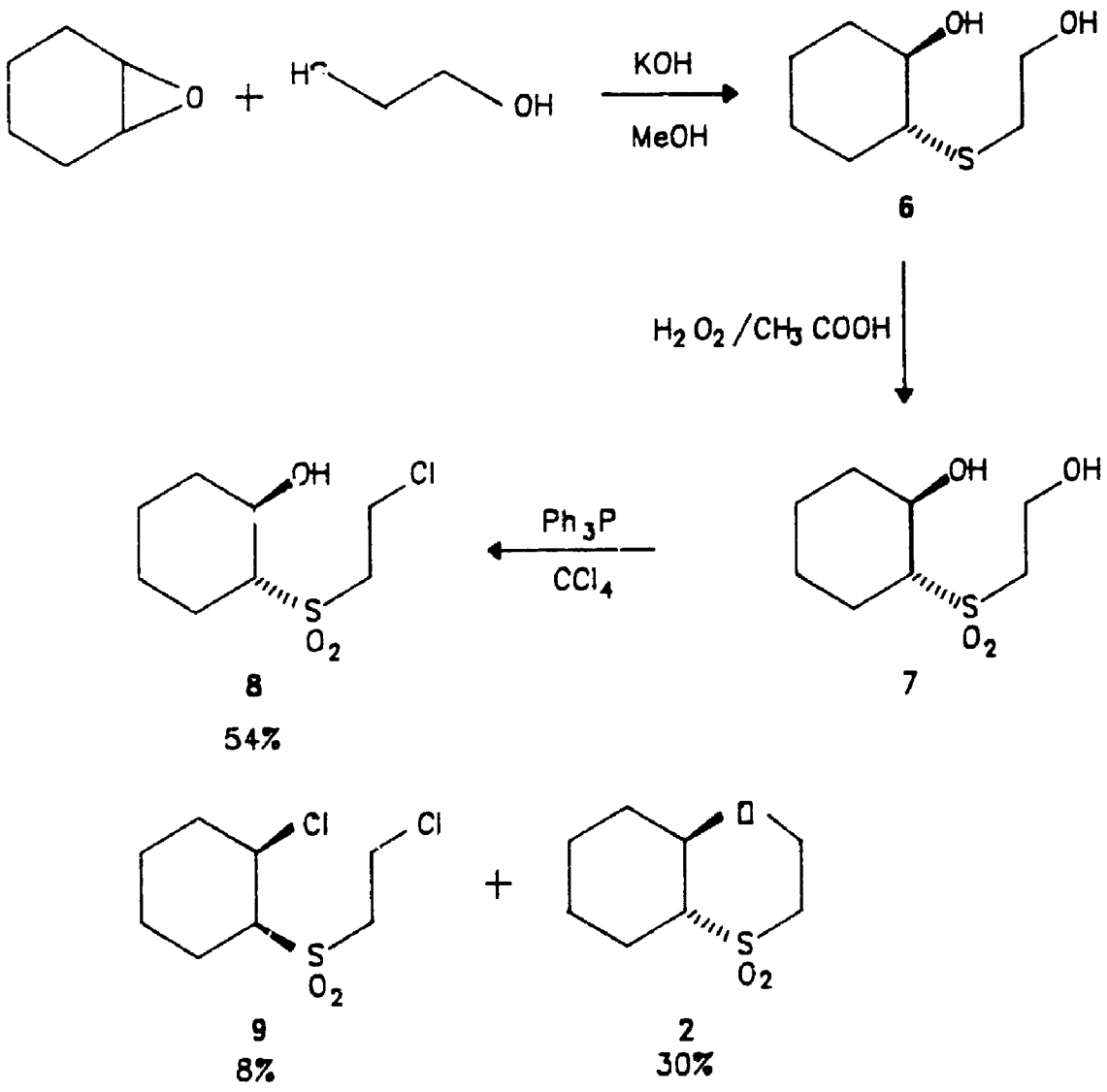
4.2 RESULT AND DISCUSSION

4.2.1 Synthesis and Nmr Assignments

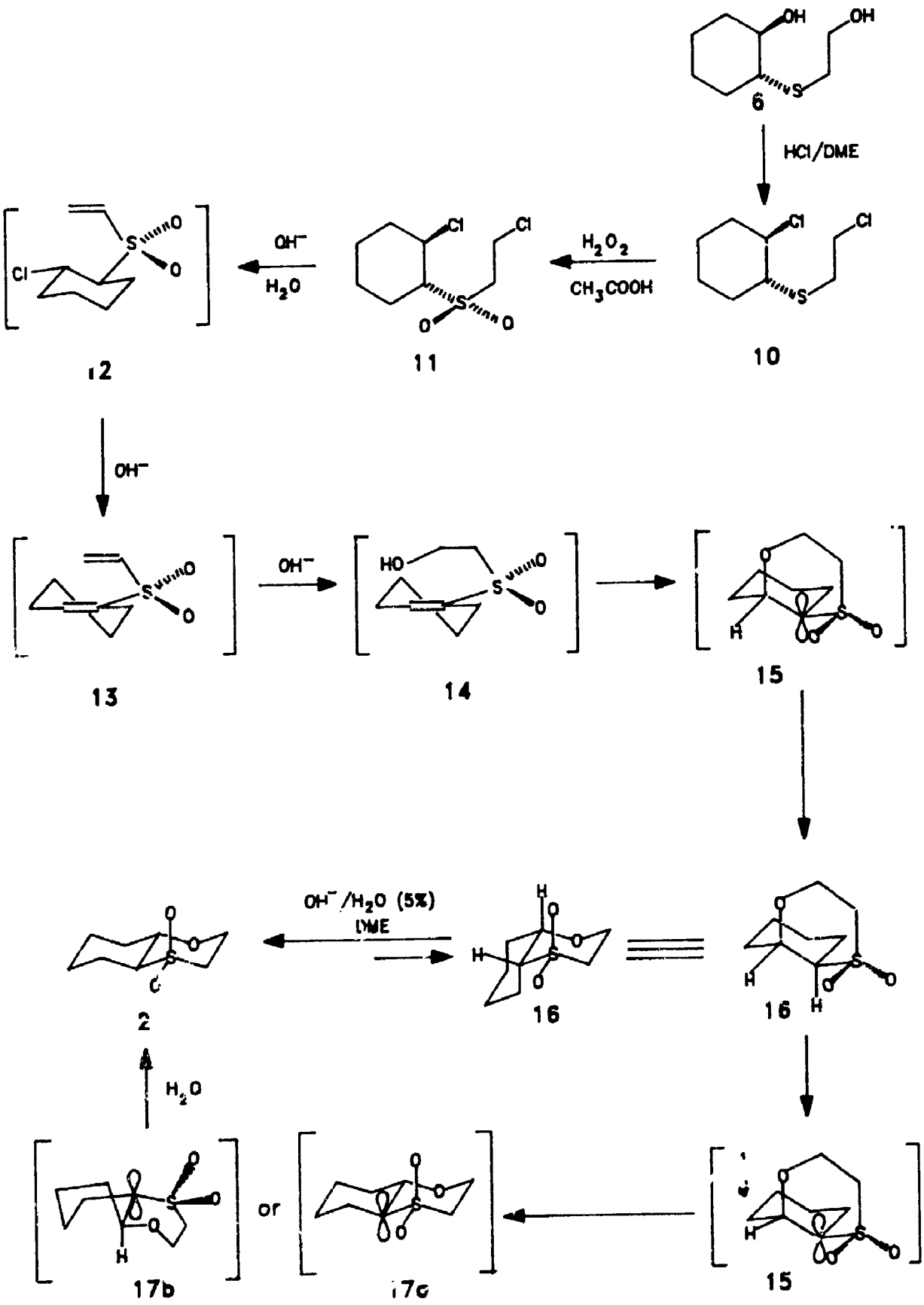
trans-Octahydro-1,4-benzoxathiane 4,4-dioxide (or *trans*-oxathiadecalin dioxide) (**2**), was synthesized according to the procedure of Evans and coworkers[8] as shown in Scheme 4.1. This method involved the treatment of *trans*-2-[(2-hydroxyethyl)-sulfonyl]-cyclohexanol (**7**) with 1.1 equivalents of triphenylphosphine (TPP) in CCl_4, which gave a mixture of 54% of *trans*-2-[(2-chloroethyl)sulfonyl]-cyclohexanol (**8**), 30% of desired **2** and 8% of *cis*-2-[(2-chloroethyl)sulfonyl]-chlorocyclohexane (**9**).

The low yield and a tedious chromatographic separation of the products of the above synthesis prompted the design of an alternative synthesis of **2** starting from the dihydroxy sulfide **6** (see Scheme 4.2). Treatment of **6** with HCl at room temperature afforded the dichloro sulfide **10**, which on oxidation gave the dichlorosulfone **11**. The latter on treatment with hydroxide afforded a crystalline solid (**16**) in excellent yield along with traces of **2**. Spectroscopic data (^1H, ^{13}Cnmr, ir, and MS) revealed that **16** is the *cis*-isomer of **2**. Treatment of **16** in 10% KOH for 100 h gave an equilibrium mixture of **16** and **2** (1:9), which was easily separated by recrystallization. This method offers an easy access to both the isomers of 1,4-oxathiadecalin dioxide (*i.e.* **2** and **16**).

A likely mechanism for the base catalyzed cyclization of **11** to the *cis*-oxathiadecalin dioxide (**16**) is shown in Scheme 4.2. It is interesting to note that unlike the dihydroxysulfone (**7**), the dichlorosulfone (**11**) cyclizes to the thermodynamically less favourable *cis*-oxathiadecalin dioxide (**16**). Though at first glance surprising, this result may be understood when one recognizes that the final step of cyclization, *i.e.* **14** $\rightarrow$ **16** (see Scheme 4.2), results in a carbanion intermediate (**15**) in which the lone pair of electrons bisects the sulfonyl oxygens and is *anti-periplanar* to the C-O bond (**15**) (a preferred arrangement for an α-sulfonyl



SCHEME 4.1


OH
OH
6
HCl/DME
Cl
Cl
10
H_2O_2
CH_3COOH
Cl
Cl
11
OH^-
H_2O
12
OH^-
HO
13
14
15
OH^-/H_2O (5%)
DME
2
16
16
H_2O
or
17b
17c
15

SCHEME 4.2

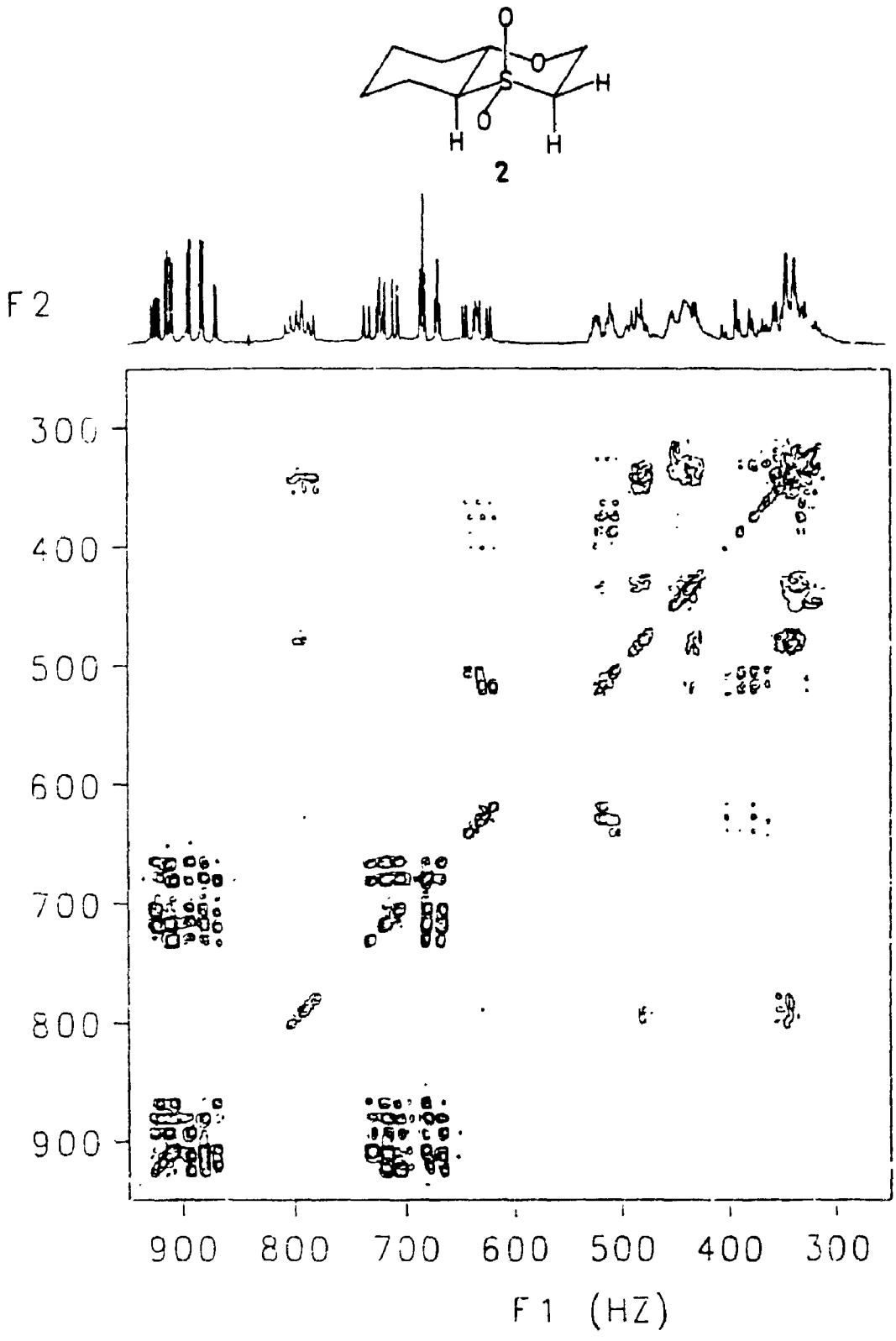


Figure 4.1 Contour plot of $^{1}H-^{1}H$ homonuclear correlated nmr ("COSY") spectrum of 1,4-dithiadecalin 4,4-dioxide (2) in $CDCl_3$ at 20°C (arbitrary scale).

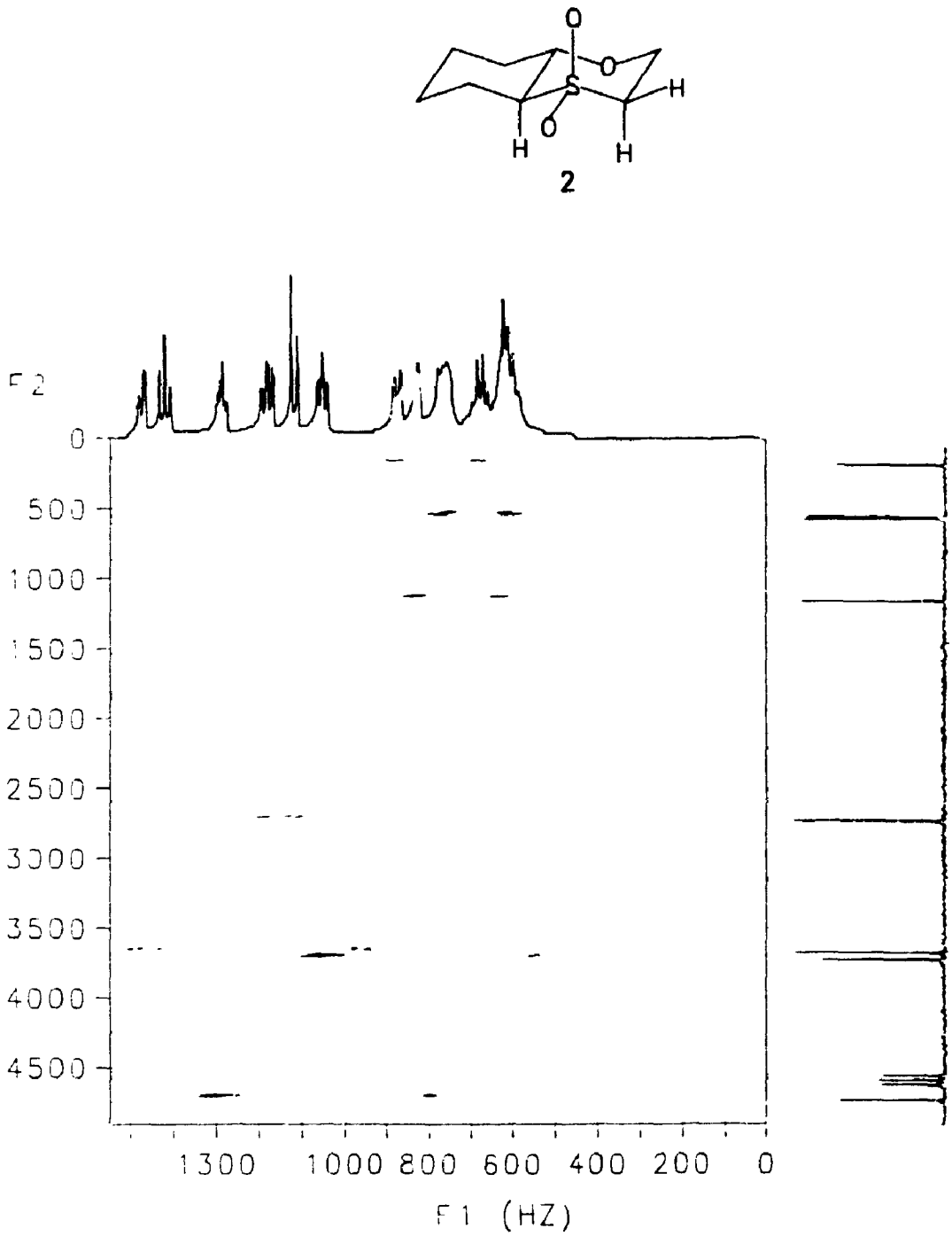
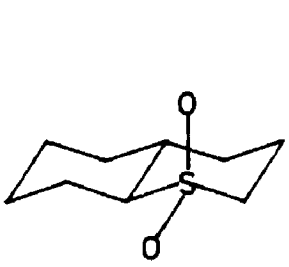


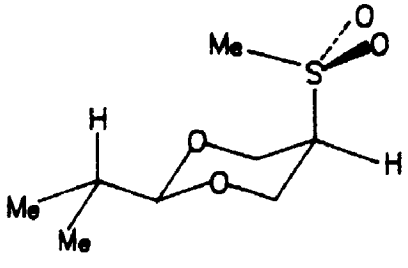
Figure 4.2 Contour plot of $^{1}H-^{13}C$ hetronuclear correlated nmr ("HETCOR") spectrum of 1,4-oxathiadecalin 4,4-dioxide (**2**) in $CDCl_3$ at 20 °C (arbitrary scale).

carbanion), hence making the *cis*-sulfone the kinetically favoured product. The carbanion (*17*) which lead to the *trans*-compound (*2*) is not well arranged for stabilization either by bisecting the sulfonyl oxygens or by the β-oxygen (anomeric stabilization, as discussed later). As may be seen by examination of the molecular models of *17*, bisection of the sulfonyl oxygens by the lone pair of electrons in *17*, may be approached only when both the rings have the twist boat conformation, a sterically unfavourable arrangement (see Scheme 4.2).

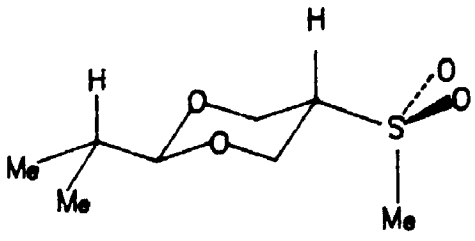
The ^{1}H and ^{13}Cmr signals of *2* were assigned[9] with the help of HOMCOR ("COSY") (Figure 4.1) and HETCOR (Figure 4.2). As a general rule[10] the equatorial hydrogen is more deshielded than the axial hydrogen in cyclohexane ring systems in ^{1}Hmr ($+\Delta\delta$), although in *2*, for C-3 the axial hydrogen ($C\text{-}3H_a$) was more deshielded than the equatorial hydrogen ($C\text{-}3H_e$) ($-\Delta\delta$). The anomalous chemical shifts for the hydrogens alpha to sulfonyl in *2* are not well understood but it has been suggested by Evans and coworkers[11] that the bond anisotropies of the C-S and $C\text{-}SO_2$ bonds are opposite in sign to those of C-C, C-O, and C-SO. This argument, however, fails to account for the normal sign of anisotropy for $C\text{-}SO_2$ bond (and $+\Delta\delta$), in thiadecalin dioxide (*18*). Khan and *et al.*[12] designed an arbitrary convention to express the chemical shift difference between the axial and equatorial hydrogens in 6-membered ring system, where $+\Delta\delta$ indicates that the equatorial hydrogen is more deshielded than the axial and $-\Delta\delta$ indicates that axial hydrogen is more deshielded than the equatorial hydrogen.



18

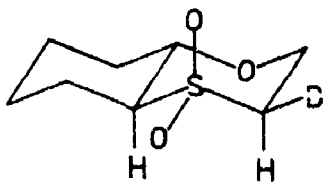


19

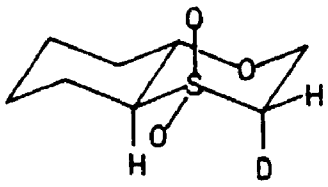


20

In *cis*- and *trans*-2-isopropyl-5-methylsulfonyl-1,3-dioxane (**19** and **20**) the C-5 equatorial hydrogen in **19** is 0.84 ppm higher field than the C-5 axial hydrogen in **20** (*i.e.*, $-\Delta\delta = 0.84$). It seems reasonable to assume that the reversal of the sign of $\Delta\delta$ in **2**, **19** and **20**, and other β-alkoxy sulfones may be due to the presence of β-oxygens.



26

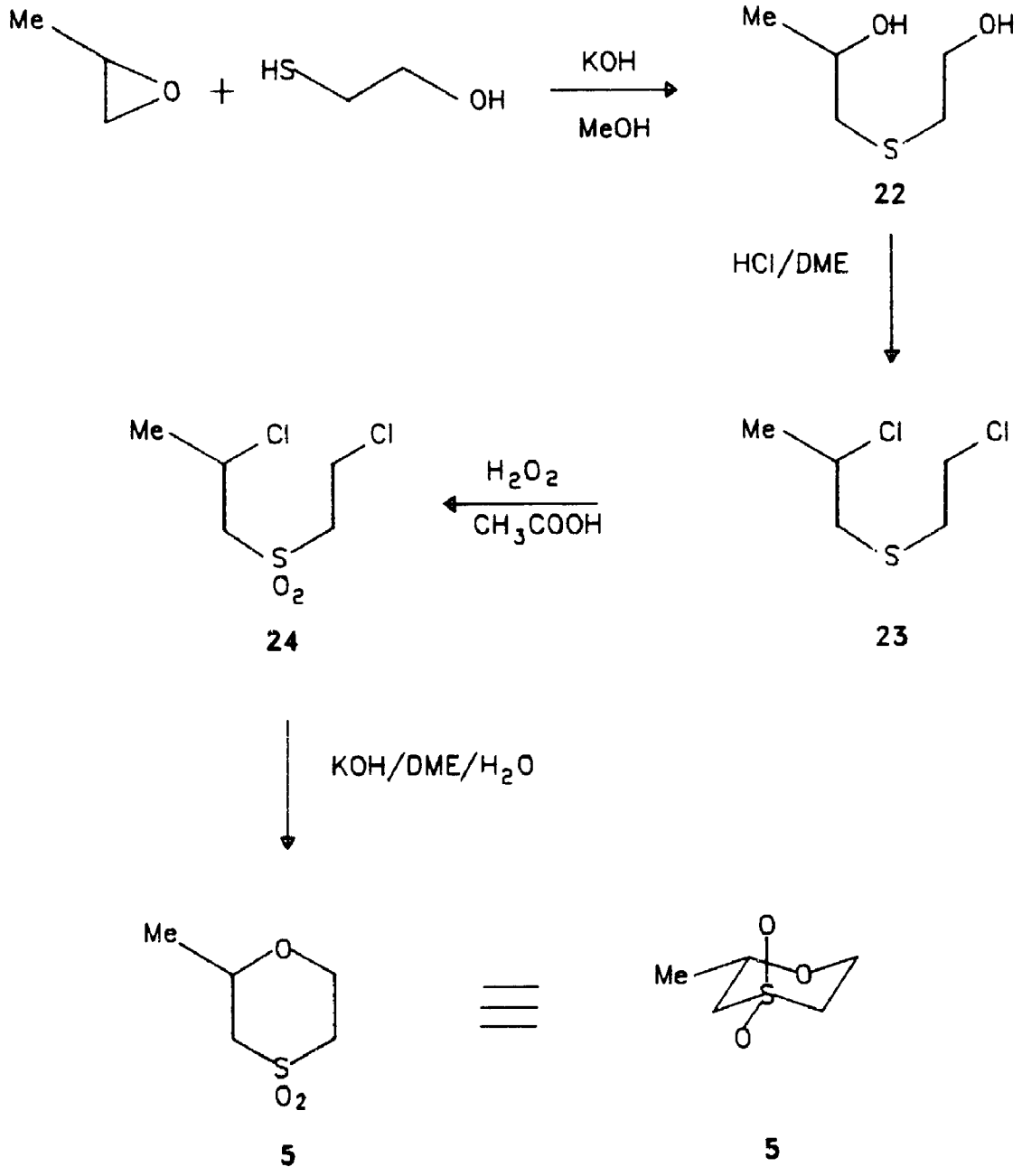


28

For the purpose of the present study, it was necessary to establish the previous assignment of equatorial and axial hydrogens in compound **2** beyond any doubt. It is known that in infrared spectra the equatorial carbon-deuterium vibration is almost always found at a higher frequency than is the axial.[13] The C-D stretching frequencies in the infrared spectra of the compounds **26** and **28** were 2245 and 2205 cm^{-1}, respectively for equatorial ($C\text{-}3D_e$) and axial ($C\text{-}3D_a$) deuterium, in good agreement with known equatorial and axial C-D stretching frequencies in 6-membered ring systems; this observation confirms the earlier assignment of equatorial and axial hydrogens by nmr spectroscopy.

^{1}Hmr Spectrum of 1,4-oxathiane 4,4-dioxide (**3**) showed two simple triplets which were easily assigned, the low-field peak to the C-3 hydrogens and higher-field peak to the C-2 hydrogens. 3-Methoxy-tetrahydrothiapyron 1,1-dioxide (**4**) and tetrahydro-1-thiapyran-3-one-ethyleneketal 1,1-dioxide (**21**) were synthesized from the known precursor tetrahydrothiapyron-3-one,[14] (see experimental) and were characterized by ir, ^{1}H and ^{13}Cmr spectra and exact mass determination.

3-Methyl-1,4-oxathiane 4,4-dioxide (**5**) was prepared from propylene oxide and mercaptoethanol, as shown in Scheme 4.3. The ^{1}Hmr and ^{13}Cmr signals for **5** were


Me
O
HS
OH
KOH
MeOH
Me
OH
OH
S
22
HCl/DME
Me
Cl
Cl
S
23
H_2O_2
CH_3COOH
Me
Cl
Cl
S
O_2
24
KOH/DME/H_2O
Me
O
S
O_2
5
O
Me
O
S
O
5

SCHEME 4.3

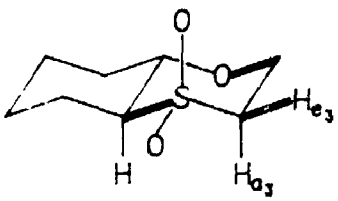
assigned with the help of HOMCOR and HETCOR.

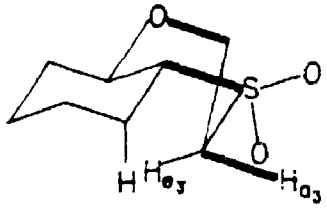
Thiane 1,1-dioxide (25) was obtained by oxidation of commercial pentamethylene sulfide. 1-Thiadecalin 1,1-dioxide (18) was synthesized according to the procedure of Dronov and coworkers[15] and its ^1H and ^{13}Cmr signals assigned with the help of HOMCOR and HETCOR.

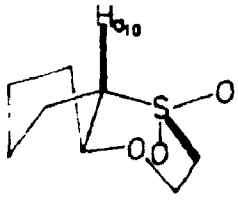
The *cis*-sulfone 19 was prepared by base-catalyzed isomerization of *trans*-sulfone 20, which was synthesized by the procedure of Eliel and coworkers[16] (see experimental part for details).

4.2.2 Kinetics of H-D Exchange

The H-D exchange rates of sulfones were measured by ^1Hmr in D_2O-NaOD at 20°C (as detailed in the experimental part). Under different [OD^-] concentration the plots of unreacted starting material *vs.* time gave good first order rate plots for the H-D exchange of 1,4-oxathiane 4,4-dioxide (3). A plot of the observed rate constants (k_{obs}) *vs.* [OD^-] for the sulfone 3 gave a straight line (see Figure 4.3); this clearly demonstrated that the second order rate constants for H-D exchange of β-alkoxy sulfones were depended on [OD^-] concentration with first order kinetics.

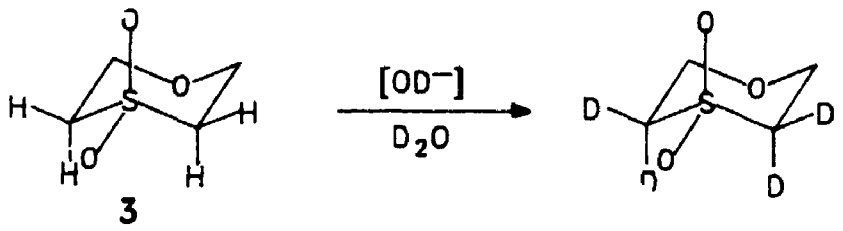






2 chair-chair chair-twist twist-twist

The 1,4-oxathiadecalin 4,4-dioxide structure (2) has three important features of interest (i) the C-3H_e bond is *anti-periplanar* to the S-$C_{\alpha'}$ bond (or bisects the O-S-O angle), as well as being *anti-periplanar* to the C-O bond; (ii) C-3H_a can



3

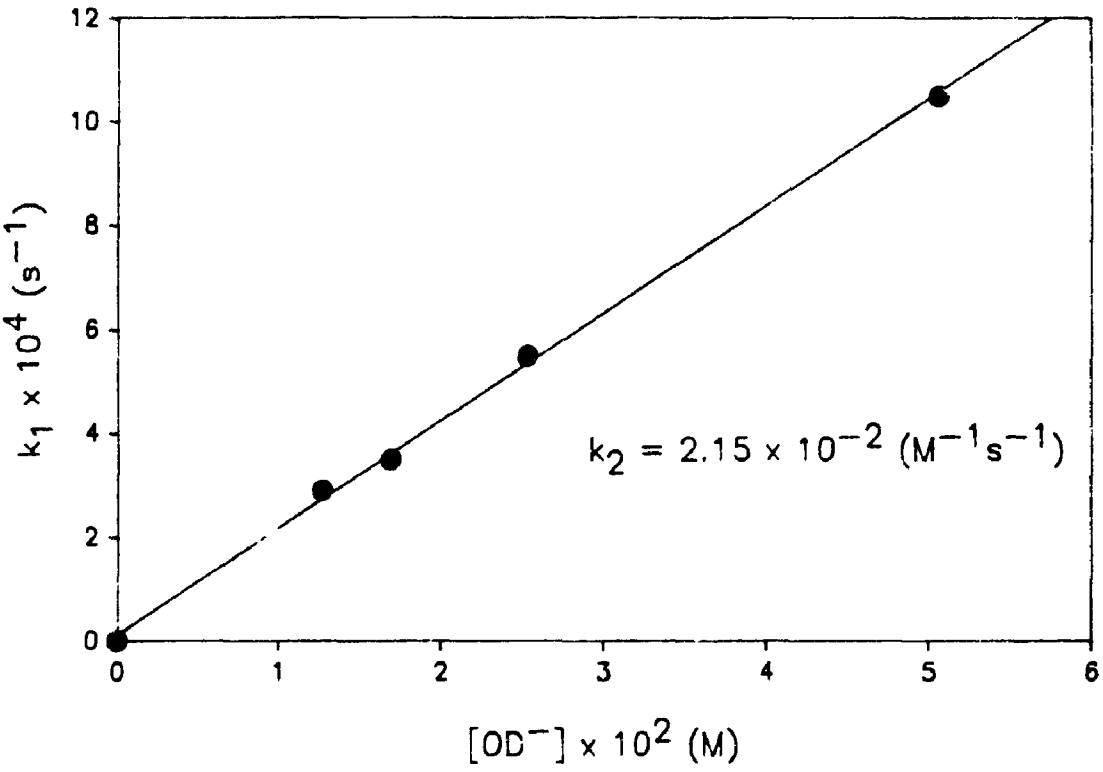


Figure 4.3 Determination of kinetic order with respect to [OD^-] of H–D exchange in 1,4–oxathiane 4,4–dioxide (3).

neither bisect the O–S–O angle nor be *anti–periplanar* to the C–O bond unless the oxathiane ring flips into a twist form; (iii) C–10H_a can only bisect O–S–O angle if both the rings change into twist conformations (an unfavourable process) and can not be *anti–periplanar* to the C–O bond in any accessible conformation.

In 2% potassium carbonate in D_2O–CD_3OD+60H(9:1) at room temperature (20°C), the equatorial hydrogen on C–3 in oxathiadecalin dioxide (2) was found to exchange readily, with a half–life of approximately 1.5 h. After 10 half–lives, a clear 1:1:1 triplet (due to coupling with the single deuterium) was observed for C–3 in the ^{13}Cmr spectrum and in the ^{1}Hmr spectrum the small coupling (for C–3H_e) disappeared from the signals of C–2 hydrogens (see Figure 4.4). The amounts of C–3H_a and C–10H_a were unchanged as determined by careful integration of the ^{1}Hmr signals.

The H–D exchange rates for oxathiadecalin dioxide (2) in NaOD–D_2O at 20°C were found to be the following:

C–3H_e	3.2×10^{-2} $M^{-1}s^{-1}$
C–3H_a	1.6×10^{-4} $M^{-1}s^{-1}$
C–10H_a	$<10^{-8}$ $M^{-1}s^{-1}$ (no sign of exchange in 6 months)

These rate differences for the H–D exchanges alpha to sulfonyl in 2 are large enough that all of the possible mono or doubly α–deuterated compounds can be prepared selectively in one or two steps by altering the reaction conditions (see Figure 4.4. Scheme 4.4, and also the experimental section).

From the above second order rate constants for the exchange of the α–hydrogen in 2, it is evident that the α–hydrogen with the favoured *anti–periplanar* orientation with respect to the S–$C_{\alpha'}$ bond and the C–O bond, *i.e.* the equatorial hydrogen (C–3H_e), exchanges distinctly faster than the axial hydrogen (C–3H_a), the difference

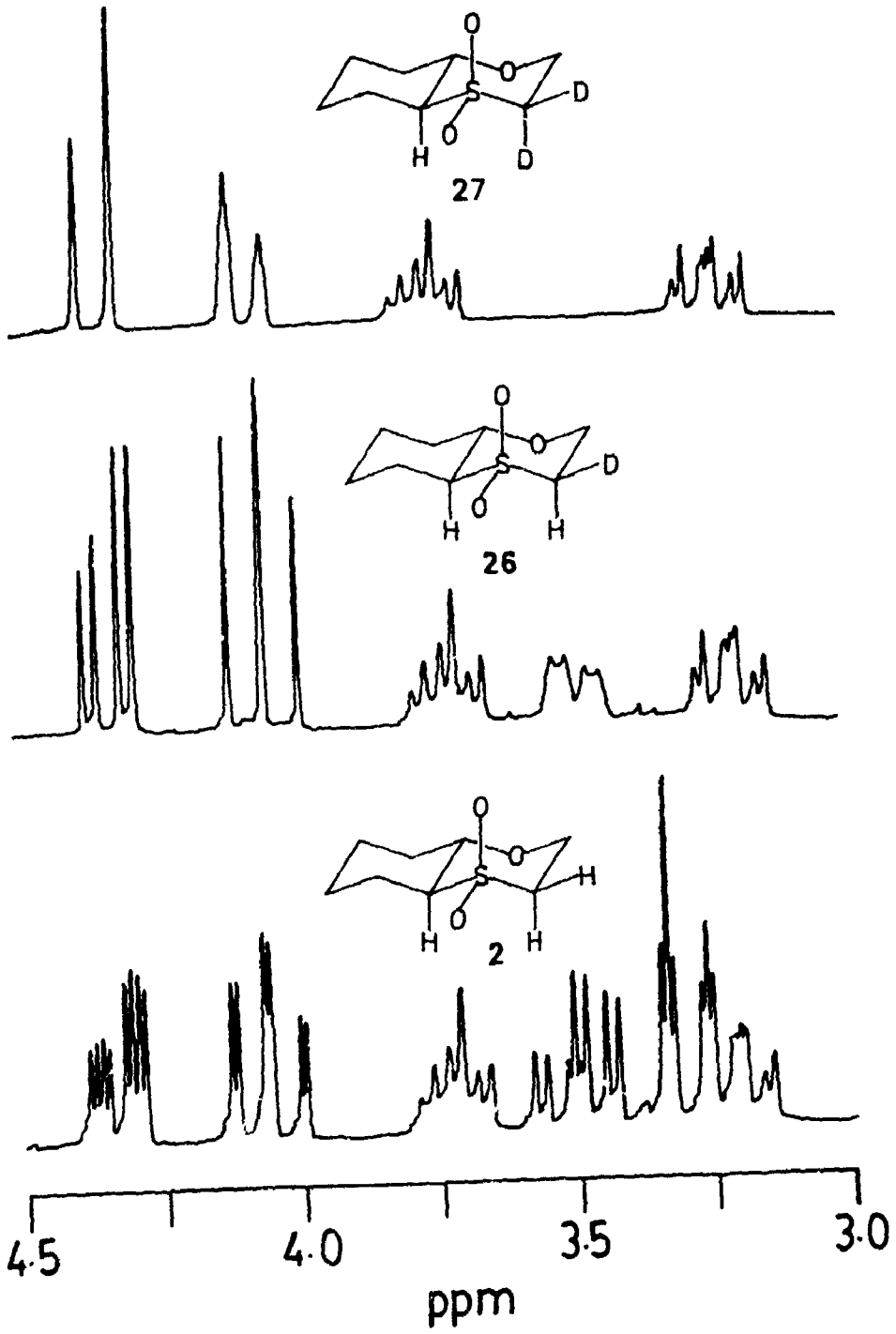
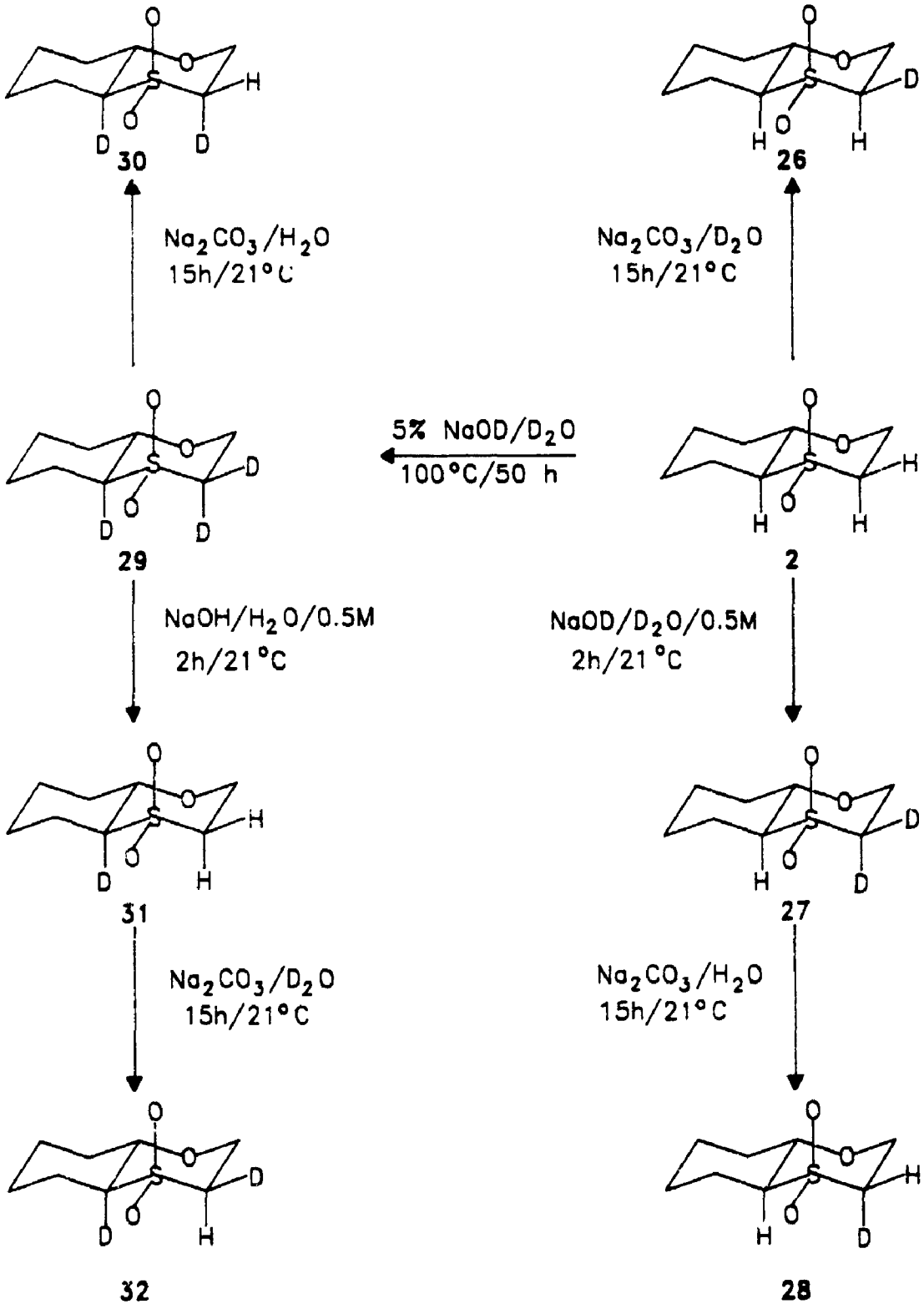


Figure 4.4 H–D Exchange rate measurement by ^{1}Hmr spectroscopy of **2** in NaOD–D_2O (0.025 M) at 20° C.



SCHEME 4.4 Selective H–D Exchange in *trans*–1,4–Oxathiadecalin 4,4–dioxide (2).

in **2** being 200-fold. The axial hydrogen at bridgehead (C-10H_a) did not show any sign of exchange in 6 months under the above conditions, pointing to a rate constant of $<10^{-8}$ $M^{-1}s^{-1}$.

In *cis*-1,4-oxathiadecalin 4,4-dioxide (**16**), the rate constants for H-D exchange of the hydrogens alpha to the sulfonyl were as follows:

C-3H_e	4.8×10^{-2} $M^{-1}s^{-1}$
C-3H_a	1.6×10^{-4} $M^{-1}s^{-1}$
C-10H_e	3.3×10^{-5} $M^{-1}s^{-1}$

In *cis*-1,4-oxathiadecalin 4,4-dioxide (**16**) the C-3H_e and C-3H_a e change with rates similar to those of corresponding *trans*-compound (**2**) (the ^{1}Hmr spectra as shown in Figure 4.5). The α-equatorial hydrogen (C-3H_e) with the favoured *anti-periplanar* orientation with respect to S-$C_{\alpha'}$ bond and the C-O bond exchanges 300 times faster than the α-axial hydrogen. The bridgehead hydrogen in **16**, is equatorial with respect to the oxathiane ring and axial to the cyclohexane ring; it will be referred to here as an equatorial hydrogen (C-10H_e) because it is at the bisector of the sulfonyl oxygens, like the e orial hydrogens in other 6-membered ring sulfones. The bridgehead hydrogen (C-10H_e) in **16**, however, exchanges faster (3.3×10^{-5} $M^{-1}s^{-1}$) than the bridgehead hydrogen (C-10H_a) in *trans* (**2**) ($k = <10^{-8}$ $M^{-1}s^{-1}$). It is not surprising because, as pointed out above, C-10H_e (in **16**) is at the bisector of the sulfonyl oxygens as well as *anti-periplanar* to the C-O bond.

The rate difference between the equatorial hydrogen (C-2H_e) and the axial hydrogen (C-2H_a) in thiadecalin dioxide (**18**) was found to be ~90 when subjected for H-D exchange in NaOD in D_2O-CD_3OD. In another experiment, **18** was heated at 80°C in 5% NaOD in D_2O-CD_3OD for 12 h. The C-2H_e and C-2H_a were exchanged completely, whereas the bridgehead hydrogen (C-9H_a) remained

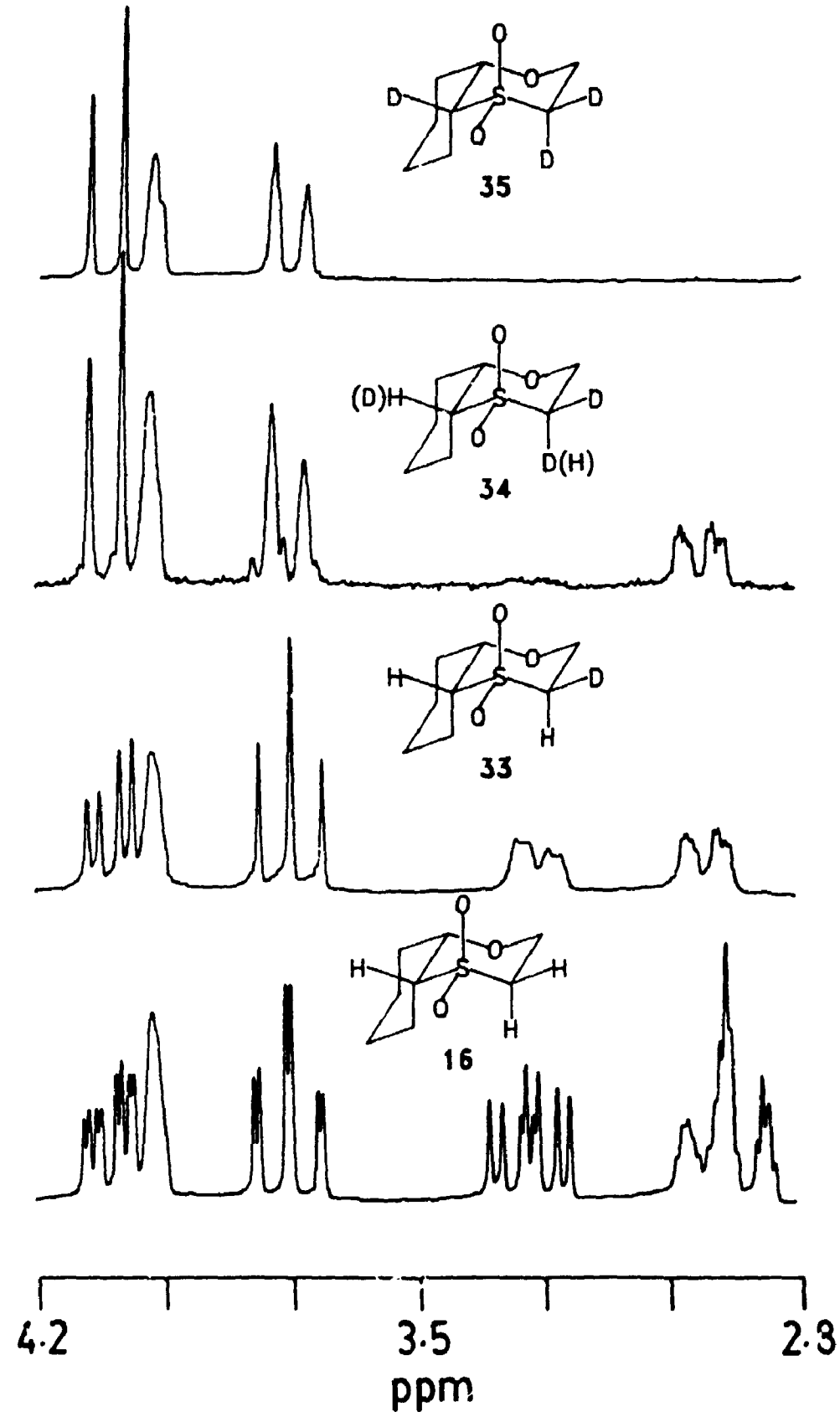


Figure 4.5 H–D Exchange rate measurement by ^{1}Hmr spectroscopy of **16** in NaOD–D_2O (0.032 M) at 20°C.

unexchanged, as determined by ^1H, ^{13}C and ^2Hmr spectra; this suggests that C-9H_a exchanges at least 100 times more slowly than C-2H_a. The mechanism of generating a carbanion from the axial hydrogens alpha to a sulfonyl in 6-membered cyclic sulfones will be discussed in section 4.2.4.

The rate of H-D exchange in the other compounds was measured similarly and individually described in the experimental part; the second-order rate constants are listed in Table 4.1. These rate constants reflect that α-equatorial hydrogens exchange 25-300 times faster than the corresponding α-axial hydrogen in anchored 6-membered cyclic sulfones; the rate constant ratios among H-D exchange reactions of equatorial *vs.* axial α-hydrogens are listed in Table 4.2. An observation reported by Fuji and coworkers[17] is consistent with the above results; in the exchange of the equatorial and axial hydrogens in 6-methyl-1,3-oxathiane 3,3-dioxide (*36*), it was found that k_e/k_a = 15 to 25 (where k_e is rate of H-D exchange of an equatorial hydrogen and k_a for axial hydrogen on the same carbon). It is reasonable to conclude that in the exchange reactions for the compounds which lack anchoring groups listed in Table 4.1 (*i.e.* *3*, *25*, and *21*); the rate constants reflect primarily the ease of exchange of α-equatorial hydrogens in the different structures, in other words the half of the exchanging hydrogens are axial in compounds *3*, *25*, and *21* at any particular instant.

4.2.3 The Effect of the β-Substituent on the Rate of H-D Exchange Alpha to a Sulfonyl Group

Comparison of these rates of exchange in *4* vs *25* and *18* shows that the presence of a *β-syn-clinal* oxygen atom accelerates the reaction by a factor of about 200. Introduction of another *syn-clinal* oxygen to the same carbon, as in *21*, leads to a further 20-fold rate increase. An *anti-periplanar* oxygen, however, as in *2*, *3*, and *16* increases the rate 3000 to 4000 times relative to *25* and *18*; alternatively, it

Table 4.1 Rate Constants for H–D Exchange of Alpha Hydrogens in Six-Membered Cyclic Sulfones.[a]

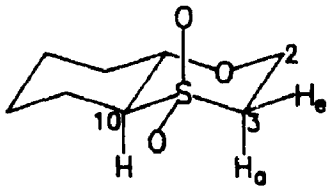
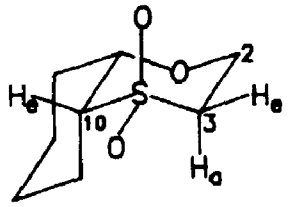
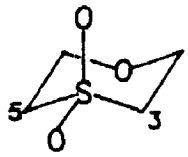
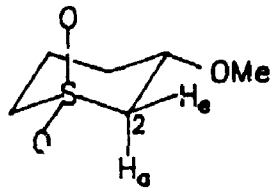
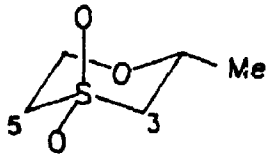
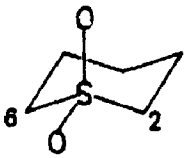
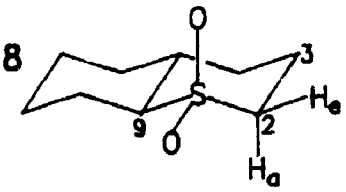
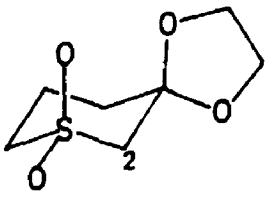
compound[b]	reaction	k^{exch} ($M^{-1}s^{-1}$)[b]
2 	C–3H$_e$ ⟶ C–3D$_e$ C–3H$_a$ ⟶ C–3D$_a$ C–10H$_a$ ⟶ C–10D$_a$	3.2×10^{-2} 1.6×10^{-4} $<10^{-8}$
16 	C–3H$_e$ ⟶ C–3D$_e$ C–3H$_a$ ⟶ C–3D$_a$ C–10H$_e$ ⟶ C–10D$_e$	4.8×10^{-2} 1.6×10^{-4} 3.3×10^{-5}
3 	(C–3H$_2$, C–5H$_2$) ⟶(C–3D$_2$, C–5D$_2$)	2.15×10^{-2} (4.30×10^{-2})[b]
4 	C–2H$_e$ ⟶ C–2D$_e$ C–2H$_a$ ⟶ C–2D$_a$	4.5×10^{-4} c
5 	C–3H$_e$ ⟶ C–3D$_e$ C–5H$_e$ ⟶ C–5D$_e$ (C–3H$_a$, C–5H$_a$) ⟶(C–3D$_a$, C–5D$_a$)	1.6×10^{-2} 2.3×10^{-2} $\sim 10^{-4}$
25 	(C–2H$_2$, C–6H$_2$) ⟶(C–2D$_2$, C–6D$_2$)	$\sim 10^{-6}$ $(\sim 2 \times 10^{-6})$[b]
18 	C–2H$_e$ ⟶ C–2D$_e$ C–2H$_a$ ⟶ C–2D$_a$ C–9H$_a$ ⟶ C–9D$_a$	1.2×10^{-6} est. $\sim 10^{-8}$ est. $\geqslant 10^{-10}$
21 	C–2H$_2$ ⟶ C–2D$_2$	4.8×10^{-3} (9.6×10^{-3})[b]

Table 4.1 (continued).....

a) With NaOD (0.017 to 0.05 M) in D_2O at 20°C; determined by ^{1}Hmr (and ^{13}Cmr) spectroscopy.

b) The values shown in parentheses are second order rate constants for H–D exchange on a *per–hydrogen* basis, and were obtained by multiplying the experimental value (k_{exch}) by the statistical factor of two. This factor has its origin in the circumstance that at any particular instant half of the exchanging hydrogens (*i.e.* those that are axial at that time) are not in a conformation favourable for exchange. The values in parentheses are used in calculating the relative rates discussed in the text.

c) Not determined, but nmr spectra show the axial exchange in **4** to be at least 25 times slower than the equatorial.

Table 4.2 Rate constant ratios among H–D exchange reaction of equatorial and axial alpha hydrogens in six–membered cyclic sulfones.[a]

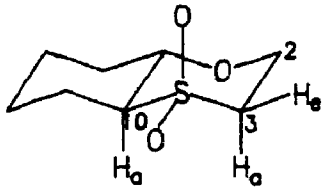
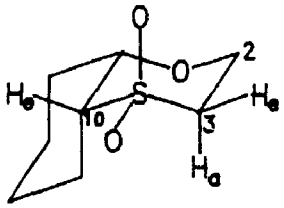
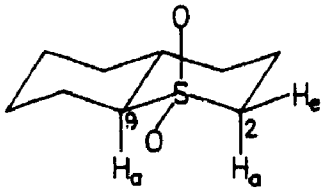
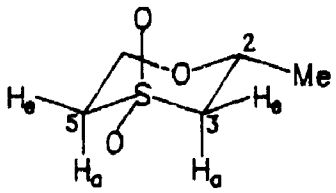
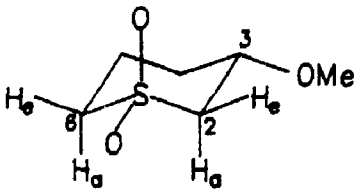
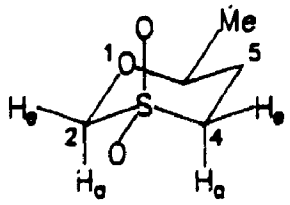
S.N	Compound	Exchange Process[b]	Relative Rates
2		C–3H$_e$/C–3H C–3H$_e$/C–10H$_a$ C–3H$_a$/C–10H$_a$	200 >3.2 x 10^6 >1.6 x 10^4
16		C–3H$_e$/C–3H$_a$ C–3H$_e$/C–10H$_e$ C–3H$_a$/C–10H$_e$	300 1455 ~4.9
18		C–2H$_e$/C–2H$_a$ C–2H$_a$/C–9H$_a$ C–2H$_e$/C–9H$_a$	>90 >100 >10000
5		C–3H$_e$/C–3H$_a$ C–5H$_e$/C–5H$_a$	90 90
4		C–2H$_e$/C–2H$_a$ C–6H$_e$/C–6H$_a$	>25 >25
36		C–2H$_e$/C–2H$_a$ C–4H$_e$/C–4H$_a$	15[c] 25[c]

Table 4.2 (continued).....

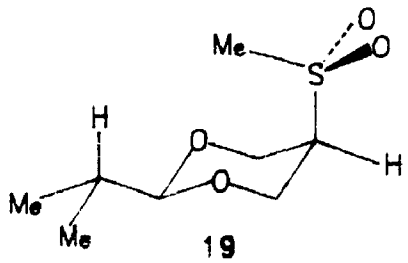
a) In $NaOD-D_2O$ at 20°C.

b) *E.g.* $C-3H_e$ / $C-3H_a$ refers to the ratio of the rate constants for the exchange of the equatorial hydrogen divided by that for the C-3 axial hydrogen; the rate constants are listed in Table 4.1.

c) These values are taken from the work by Fuji and coworkers.[17]

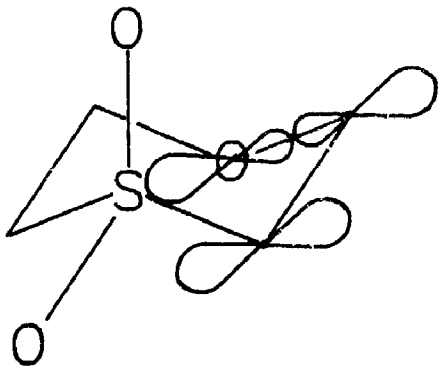
we compare **2**, **3**, and **16** with **4**, changing the oxygen from the *syn-clinal* to the *anti-periplanar* orientation increases the rate by 71- and 95-fold respectively. That this substantial rate difference is not primarily due to simple steric effects or the presence of an extra β-carbon, is shown by examining the rates of exchange in the methyl substituted oxathiane dioxide (**5**); comparing the rate of exchange at C-3 with either (a) that at C-5 or (b) those of the corresponding reactions in **2**, **3**, and **16**, none of which differ by a factor of > 3, shows clearly that neither the steric nor the electronic effect of the methyl group is of any significance in this case. We conclude that the factor which is most important in the rapid exchange of the α-equatorial hydrogens in **2**, **3**, and **16** relative to **4** (and **21**) is the orientation of the hydrogen with respect to the oxygen – specifically, in this case, the *anti-periplanar* geometry in **2**, **3**, and **16**.

This conclusion suggested that the sulfone **19** (which has been shown[16] to have the conformation as drawn) would be expected to be well-arranged for exchange of



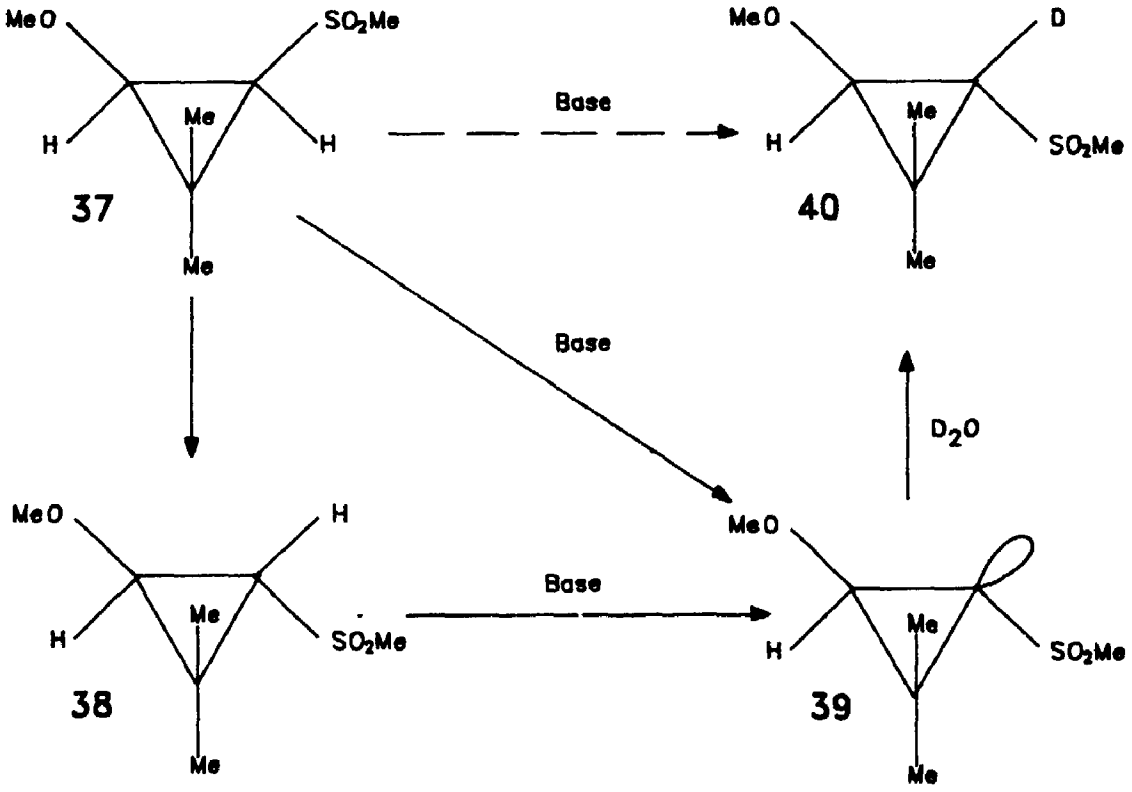
19

the α-sulfonyl methine hydrogen; we find that exchange in **19** is indeed rapid, occurring almost 200 times faster than that of **2** (on a per-hydrogen basis).[18]



n ⟶ σ* of C–O

A particularly attractive explanation for our observations is that the incipient carbanion in the transition state is stabilized by electron donation into the carbon–oxygen $n \rightarrow \sigma^*$ orbital, i.e. that it is a "kinetic anomeric effect".[19]



SCHEME 4.5

A related anomeric stabilization of a sulfonyl carbanion has been proposed by Padwa and Wannamaker to account for a strong preference for a *syn–periplanar* arrangement in a methoxy–substituted cyclopropyl carbanion.[20] They have demonstrated by a series of experiment that when α–sulfonyl carbanions were quenched with a variety of electrophiles (*e.g.*, D_2O, MeI, allyl bromide, and $ClCO_2CH_3$) gave stereoselectively only the one stereoisomer **40** in which the incoming electrophile was *cis* to the methoxy group (see, for example, Scheme 4.5 where H–D exchange always gave only one product (**40**) starting either from *cis* (**37**)

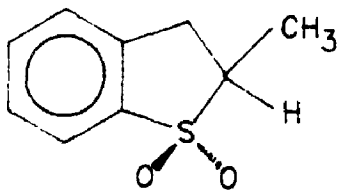
or *trans* (38) isomer).

There is another interesting feature of the work by Fuji and coworkers,[17] in the light of the present study. 6-Methyl-1,3-oxathiane 3,3-dioxide (36) was lithiated not at C-2 but at C-4 preferentially, which revealed that an α-alkoxy group destabilizes the slfonyl carbanion in this ring system. In addition, exchange studies carried out in CD_3O^-/CD_3OD showed that equatorial hydrogen at C-2 exchanged about 1.7 times slower than that on C-4. Although the rate difference is not very large, it does suggest that oxygen at the α-position destabilizes the carbanion, in remarkable contrast to what we find for β-oxygen (see Table 1).

Two points of interest emerge from these results. First, it has been suggested in a recent review[21] that effects ascribed to a kinetic anomeric effect can be more consistently explained on the basis of the principle of least nuclear motion (PLNM).[22] The present results present a good case for a kinetic anomeric effect which can not be satisfactorily accounted for by PLNM. Second, and more significantly, our observations and those of Padwa and Wannamaker combine to show the existence of a geometry-dependent substituent effect such that an electron pair (incipient or fully formed) is stabilized by either an *anti-periplanar* or *syn-periplanar* oxygen much more than by a *clinal* oxygen. These observations are not adequately rationalized in terms of the conventional components of the "polar effect", i.e. the "inductive" and "field" effects,[7] and we conclude that the polar effect of the oxygen atom in these reactions has a stereoelectronic component as well. Any detailed general analysis of the "polar effect" that is offered in future, must therefore, contain an explicit consideration of possible stereoelectronic contributions or simply be dismissed as incomplete.

4.2.4 The Mechanism of the Exchange of the Axial Hydrogens

It is well established[3] that α-sulfonyl carbanions undergo H-D exchange with retention of configuration. The rate of H-D exchange, k_e, *vs.* that of racemization, k_α, reached as high as 2000 when the exchange of 1-methylheptyl phenyl sulfone was carried out in *t*-BuOD containing *t*-BuOK. In solvents of high dielectric constant such as DMSO, k_e/k_α dropped to about 10. This variation can be explained in terms of the lifetime of the carbanion; since its lifetime would be expected to be greater in DMSO than in *t*-BuOD, the carbanion had a greater opportunity for racemization.[23]



41

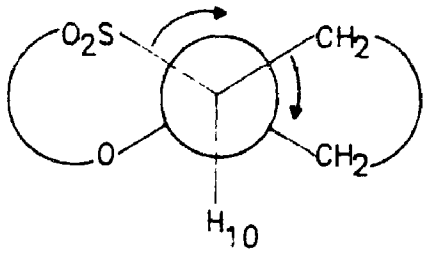
In a case where the carbanion is not at the bisector of sulfonyl oxygens one observes 100% racemization, *e.g.*, the base catalyzed H-D exchange of sulfone *41* gave k_e/k_α values in the range 0.64-0.73; the rate of racemization is faster than that of exchange.[24]

As described earlier (see Table 4.2) the α-equatorial hydrogens exchange 15-300 times faster than the α-axial hydrogens in 6-membered cyclic sulfones. These rate differences between α-equatorial and α-axial hydrogens, though surprising in the light of an earlier report[25] (which is discussed latter) that indicated only a small preference, is precisely what is expected on the basis of (a) the *anti-periplanar* orientation of the α-equatorial hydrogens with respect to S-$C_{\alpha'}$ bond, and (b) the comparative difficulty for the (normally) α-axial hydrogens to achieve this

arrangement. As has been pointed out earlier, such an orientation in compound **2**, **16**, and **18** can be achieved *via* the twist boat form, or *via* the alternative (higher energy) chair conformations in case of **4**, **5**, **36**, and possibly **16**.

The bridgehead α–hydrogens in **2** and **18** are not at the bisector of the sulfonyl oxygens and can not easily acheive such a conformation in which they can be *anti–periplanar* to S–$C_{\alpha'}$ bond, whereas in **16**, on the other hand, the bridgehead α–hydrogen is at the bisector of the sulfonyl oxygens. Furthermore, the exchange of the bridgehead α–axial hydrogen in **2** and **18** is much slower than the α–axial hydrogen at methylene (~10^4 times), whereas in **16** this difference between the α–axial of methylene *vs.* α–equatorial of bridgehead is small (~5 times) (see Table 4.2).

Inspection of molecular models of compound **2**, **16**, and **18** suggests the following points: (i) the bridgehead α–axial hydrogen in **2** and **18** can not bisect the sulfonyl oxygen unless both the rings attain the twist boat conformation, (ii) as pointed out earlier, there are no accessible conformations, in which the bridgehead



2

hydrogen in **2** is *anti–periplanar* to C–O bond. In contrast, the bridgehead α–hydrogen in what is believed to be the most stable conformation of **16** bisects the sulfonyl oxygens and is *anti–periplanar* to C–O bond.

There are a few questions to be addressed before any conclusions can be drawn about the reactivity of bridgehead α–axial hydrogens: (i) how much difference in

reactivity is caused by changing from methylene to methine, (ii) how much ring strain is introduced in the molecule in generating a carbanion at the bridgehead, (iii) what are the structures of bridgehead carbanions generated from **2**, **16**, and **18**.

To estimate the difference in reactivity between methine and methylene hydrogens, the H–D exchange rate was measured on isopropyl ethyl sulfone ($(CH_3)_2CHSO_2CH_2CH_3$) in $NaOD-D_2O$ at 21 °C. It was found that the methine hydrogen exchanges about 10 times more slowly than the methylene.

Compounds **2** and **16** are the *trans* and *cis* isomers of 1,4–oxathiadecalin 4,4–dioxide. As described earlier both of these compounds are readily made by hydroxide catalyzed cyclization to the *cis*–isomer (**16**), followed by equilibration in strong base to the 1:9 mixture of the *cis* and *trans* compounds. The carbanions generated from **2** and **16** do not have the same structure, as the bridgehead hydrogen in **16** can be exchanged completely without any sign of the formation of **2**; also bridgehead C–H in **2** can be exchanged without forming *cis*–isomer (**16**). As indicated in Figure 4.6, carbanion **15** is at least 3 kcal/mol more stable than the carbanion **17**. (This value was deduced on the assumption that the protonation of **15** and **17** have similar free energies of activation.) The free energies of actvation for generating **15** and **17** were calculated[26] from H–D exchange rate constants for the exchange of bridgehead hydrogens in **2** and **16** (see Figure 4.6).

This result is in accord with the assumption that if the lone pair of electrons on carbanion **17b** bisects the sulfonyl oxygens it increases the steric and angular strain or if it does not bisect (**17a**) then it loses at least some of the stabilization by the sulfonyl group; both of the carbanions (**17a** and **17b**) also lack anomeric stabilization associated with *anti–periplanar* oxygen.

Fraser and Schuber[27] determined the rate constants, k_A and k_B, for the base–catalysed H–D exchange of H_A and H_B protons of sulfone **42** and estimated the k_A/k_B value 3 ± 0.5. Examination of molecular models suggests that the two

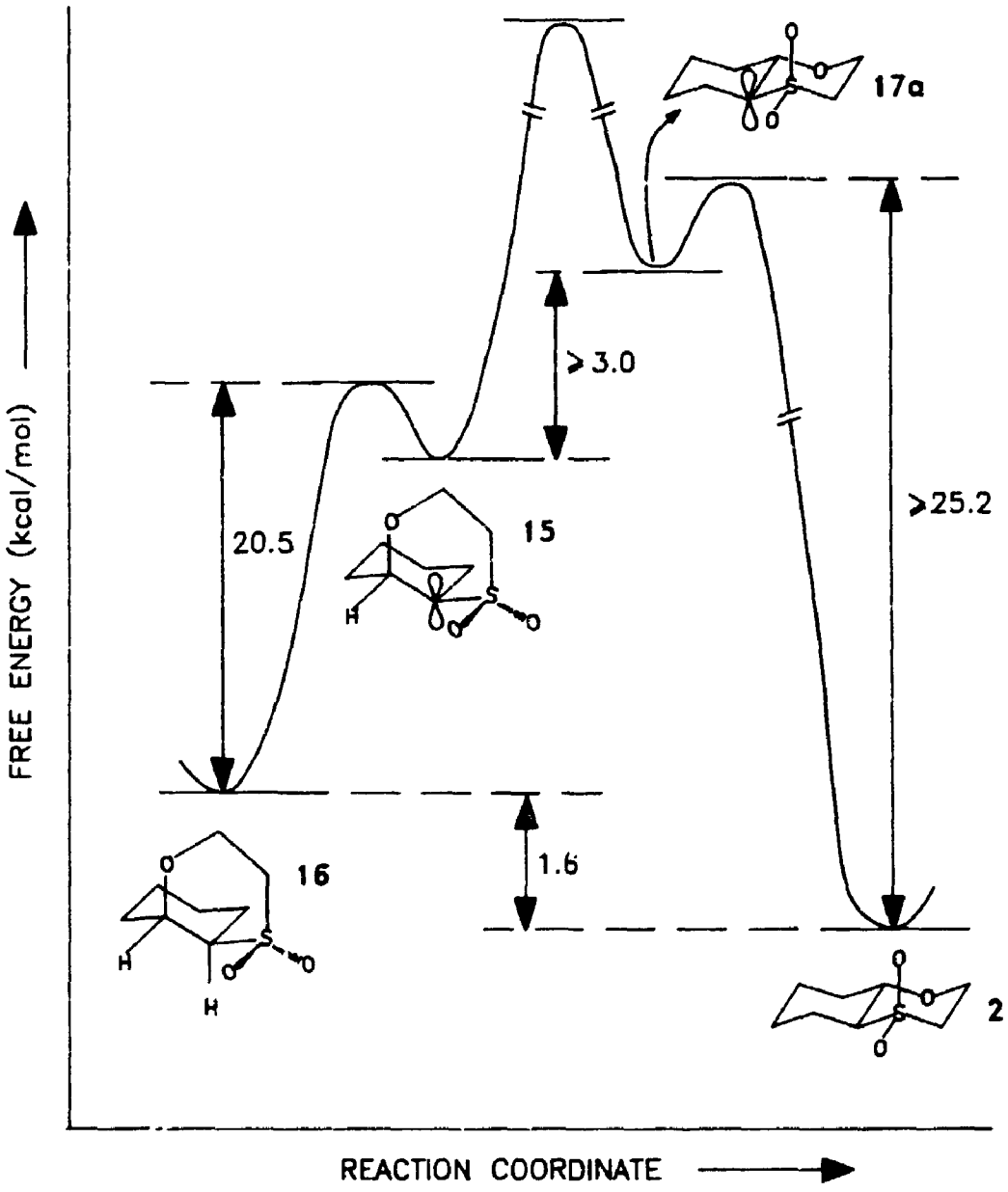
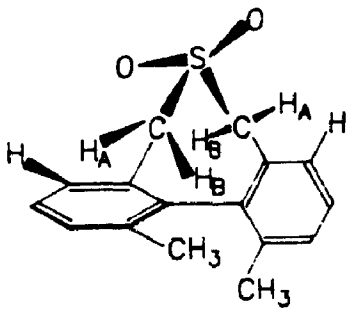
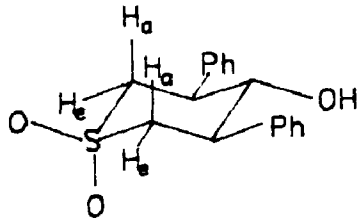


Figure 4.6 Free energy vs. reaction coordinate diagram for the reaction of bridgehead hydrogen in **2** and **16** with base.

conformations from which H_A and H_B exchange may have a very small energy barrier.



42



43

As mentioned earlier, Brown *et al.*,[25] found a small rate difference between the axial and equatorial hydrogen in *cis*-3,5-diphenyl-*trans*-4-hydroxythian 1,1-dioxide **43**. The base catalyzed H-D exchange of **43** gave results corresponding to k_e/k_a = 1.6. This rate difference in sulfone **43** does not agree with our observations on a number of 6-membered ring sulfones (see Table 4.2). The small rate difference in this case may be due to the solvent, as their exchange reactions are carried out in DMSO whereas ours were in D_2O-NaOD, or could arise from a number of factors and perhaps in combination. Compound **43** may not be the ideal molecule for determination of the rate difference between axial and equatorial hydrogens because the bulky phenyl substituents may interfere, and also because the hydroxyl group could complicate the reaction by participating in intramolecular hydrogen-bonding.

The results listed in Table 4.2 suggest that the hydrogens which bisect the sulfonyl oxygens in the most stable conformation (*i.e.* the equatorial hydrogens) exchange at least 15-300 times faster than axial hydrogens in 6-membered ring sulfones (which can not bisect the sulfonyl oxygens in the most stable chair conformation, but can easily do so in a twist boat form or the alternative chair conformation).

4.3 CONCLUSIONS

In this study the rates of H–D exchange at the α–carbon in a series of 6–membered cyclic sulfones has been measured by nmr (in NaOD–D_2O at 20 °C). These rate data allow us to draw the following conclusions: (i) The presence of a β–alkoxyl group accelerates the reaction by different amounts depending on the orientation of the oxygen with respect to the exchanging (equatorial) hydrogen: the accelerations due to oxygen (relative to a carbon or hydrogen in the same location) are, respectively, for one *syn–clinal* oxygen, 200 to 300, two *syn–clinal* oxygens, 5000 to 8000 and one *anti–periplanar* oxygen 16000 to 35000, with the difference between the *anti–periplanar vs syn–clinal* single oxygen being 71 to 95 times. It is proposed that the greater effect of the *anti–periplanar* β–oxygen derives from a kinetic anomeric effect (KAE) in which the incipient carbanion is stabilized by electron donation into the carbon–oxygen σ^* orbital. These results taken with those of an earlier report by Padwa and Wannamaker,[20] lead to the suggestion that the inductive and field effects do not suffice to account for the observed polar effect of an alkoxyl group in these reactions and must be supplemented by a geometry–dependent, *i.e.* stereoelectronic, component (such as KAE), and that this effect may be expected to be general. (ii) In conformationally anchored (or biased) sulfones (*e.g.* **2**, **4**, **5**, **16**, and **18**) an equatorial hydrogen exchanges faster than an axial (by about two order of magnitude). It is suggested that this rate difference, though much higher than an earlier report[25] that indicated only a small preference for equatorial exchange (~1.6 times), is due to the comparative difficulty for the α–axial hydrogens to achieve favoured arrangement of the hydrogen with respect to the S–$C_{\alpha'}$ bond (*e.g. via* the twist boat form or alternative chair conformation).

44.4 EXPERIMENTAL

The general procedures and instrumentation are as described in the experimental part of chapter 1, except for the following points.

Methanol-d_4 (CD_3OD) and dimethyl sulfoxide-d_6 were supplied by MSD Isotopes. Cyclohexene oxide, mercaptoethanol, propylene oxide, ethyl γ-chlorobutyrate, ethyl thioglycolate, and *m*-chloroperbenzoic acid (*m*-CPBA) were purchased from Aldrich Chemical Company and were used without further purification.

1,4-Oxathiane 4,4-dioxide (5)

Purchased from Aldrich, mp 131-133°C; ^{1}Hmr ($CDCl_3$) δ: 3.13 (t, 4H, C-3H_2 and C-5H_2), 4.14 (t, 4H, C-2H_2 and C-6H_2); ^{13}Cmr ($CDCl_3$) δ: 52.8 (C-3 and C-5), 66.1 (C-2 and C-4).

Pentamethylene sulfone (25)

m-Chloroperbenzoic acid (3.46 g, 20 mmol) was added in portions to a solution of pentamethylene sulfide (Aldrich) (1.02 g, 10 mmol) in dichloromethane (50 mL). The reaction mixture was stirred overnight, washed with sodium bicarbonate, and the solvent removed on the rotary evaporator to afford pentamethylene sulfone (25) (1.2 g, 90%), recrystallized from ethanol, mp 98-99°C (lit[28] mp 98.5-99°C); ir (KBr) ν_{max}: 2940 (s), 2956 (m), 1446 (w), 1319 (m), 1281 (vs), 1196 (m), 1130 (vs), 1067 (w), 963 (w), 849 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.58 (sym m, 2H), 2.03 (m, 4H), 2.97 (t, 4H, C-2H_2 and C-6H_2); ^{13}Cmr ($CDCl_3$) δ: 23.8, 24.2, 52.1 (C-2 and C-6).

2-Methyl-1,4-oxathiane 4,4-dioxide (5)

Mercaptoethanol (9.0 g, 115 mmol) was added to a solution of KOH (6.46 g, 115 mmol) in water (5 mL) and ethanol (50 mL) and the mixture stirred for 20 min; propylene oxide (6.7 g, 115 mmol) was then added dropwise, and the mixture stirred for 12 h. The ethanol was removed under reduced pressure, and the resulting syrup suspended in water and extracted with dichloromethane (3 x 50 mL); the organic layer was dried over magnesium sulfate and the solvent evaporated to give **22** as a clear liquid (15 g, 96%); ^{1}Hmr[29] ($CDCl_3$) δ: 1.25 (d, 3H), 2.5-2.8 (m, 4H), 3.75 (t, 2H), 3.9 (sym m, 1H), 4.1 (br s, 2H); ^{13}Cmr ($CDCl_3$) δ: 21.9, 35.1. 41.0, 61.0, 66.4.

Concentrated hydrochloric acid (25 mL) was added slowly to a solution of 2-hydroxyethyl 2-hydroxypropyl sulfide (**22**) (5 g, 37 mmol) in DME (10 mL). The mixture was left at room temperature overnight, extracted with dichloromethane (2 x 50 mL) and the extract dried over magnesium sulfate; evaporation of the solvent gave **23** as a clear oil (6.2 g, ~100%); ^{1}Hmr ($CDCl_3$) δ: 1.56 (d, 3H), 2.74-3.00 (m, 4H), 4.09 (sextet, 1H), 3.62 (t, 2H); ^{13}Cmr ($CDCl_3$) δ: 23.8, 35.0, 41.9, 42.9, 56.7.

2-chloroethyl 2-chloropropyl sulfide (**23**) (2 g, 11.8 mmol) was oxidized with *m*-chloroperbenzoic acid (4 g, 24 mmol) as above to afford **24** as a viscous liquid (2.68 g, 90%), ir (neat) ν_{max}: 2984 (s), 2934 (m), 1451 (m), 1395 (s), 1318 (vs), 1125 (vs), 1034 (s), 868 (s), 735 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.71 (d, 3H), 3.34-3.79 (m, 4H), 3.93 (t, 2H), 4.56 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 25.2, 35.6, 49.7, 56.5, 62.9.

The above sulfone **24** was dissolved in DME (5 mL) and refluxed for 5 h with 10% KOH (15 mL); workup afforded **5** as a crystalline solid, which was recrystallized from ether and petroleum ether, mp 110-111 °C; ir (KBr) ν_{max}: 2974 (m), 2936 (m), 1375 (s), 1314 (s), 1287 (vs), 1256 (s), 1196 (s), 1127 (vs), 1082 (vs), 509 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.34 (d, 3H, C-2Me), 2.83-3.23 (m, 4H, C-3H$_2$ and C-5H$_2$),

3.95–4.13 (m, 2H, C–6H_2), 4.30 (ddq, J = 12.7, 2.3, 4.7 Hz, 1H, C–2H); ^{13}Cmr ($CDCl_3$) δ: 21.2 (–Me), 51.5 (C–5), 58.4 (C–3), 65.0 (C–6), 72.7 (C–2). Calcd. exact mass for $C_5H_{10}O_3S$: 150.0351. Found: 150.0352.

Preparation of tetrahydro–1–thiapyran–3–one ethylene ketal 1,1–dioxide (*21*)

Ethyl γ–chlorobutyrate (38 g, 250 mmol) was condensed in ethanol (100 mL) with the sodium salt of ethyl thioglycolate (30 g, 250 mmol) to give ethyl γ–(carbethoxymethylmercapto)–butyrate following the procedure of Fehnal[14] (bp 139–142°C/4 mm; ir (neat) ν_{max}: 2982 (s), 2938 (s), 1734 (vs), 1418 (m), 1447 (m), 1273 (s), 1190 (s), 1097 (s), 1032 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.26 (t, 3H), 1.29 (t, 3H), 1.93 (quintet, 2H), 2.43 (t, 2H), 2.69 (t, 2H), 3.22 (s, 2H), 4.08–4.24 (two q, 4H); ^{13}Cmr ($CDCl_3$) δ: 14.2, 14.3, 24.2, 31.9, 32.9, 33.4, 60.4, 61.3, 170.4, 172.8; yield: 53.0 g, 90%).

Dieckmann cyclisation[14] of the above diester (40 g, 171 mmol) gave 2–carbethoxytetrahydrothiapyran–3–one (yield: 26 g, 80%), which was decarboxylated without further purification with 10% sulfuric acid to give tetrahydrothiapyran–3–one (8 g, 50%); ir (neat) ν_{max}: 2921 (m), 1707 (vs), 1653 (m), 1410 (m), 1231 (m), 1161 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 2.44 (m, 4H), 2.80 (t, 2H), 3.21 (s, 2H); ^{13}Cmr ($CDCl_3$) δ: 28.1, 33.2, 38.2, 41.4, 203.6.

A solution of tetrahydrothiapyran–3–one (2 g, ~17 mmol), ethylene glycol (2.13 g, ~34 mmol) and *p*–toluenesulfonic acid (50 mg) in benzene was refluxed using a Dean–Stark trap for 4 h. Workup gave a clear oil (2.5 g, ~90%); ir (neat) ν_{max}: 2950 (vs), 1437 (m), 1414 (m), 1356 (m), 1285 (s), 1204 (m), 1107 (vs), 1057 (s), 1036 (s), 1011 (m), 961 (s), 949 (m), 928 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.69 (t, 2H), 2.06 (m, 2H), 2.51 (t, 2H), 2.61 (s, 2H), 4.00 (s, 4H); ^{13}Cmr ($CDCl_3$) δ: 26.8, 27.1, 34.8, 35.1, 64.3 (double intensity), 104.9.

The thiapyran ketal (1.5 g, 9.4 mmol) was oxidized using *m*–chloroperbenzoic

acid (3.24 g, 18.8 mmol) in ether (50 mL) at room temperature for 12 h to give tetrahydrothiapyran-3-one ethylene ketal 1,1-dioxide (*21*) (1.44 g, 80%) as a crystalline compound, which after recrystallization from ether-petroleum ether gave white crystals melting at 139-141°C; ir (KBr) ν_{max}: 2992 (m), 2951 (m), 2894 (m), 1352 (m), 1294 (vs), 1146 (s), 1090 (vs), 1059 (m), 957 (s), 925 (m), 868 (s), 657 (m), 446 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.83 (t, 2H, C-4H_2), 2.16 (m, 2H, C-5H_2), 3.02 (t, 2H, C-6H_2), 3.20 (s, 2H, C-2H_2), 4.04 (s, 4H, -O-CH_2-CH_2-O-); ^{13}Cmr ($CDCl_3$) δ: 18.7 (C-5), 34.1 (C-4), 51.1 (C-6), 58.6 (C-2), 65.1 (double intensity, -O-CH_2-CH_2-O-), 106.3 (C-3). Calcd. exact mass for $C_7H_{12}O_4S$: 190.0456. Found: 190.0455.

3-Methoxytetrahydrothiapyran 1,1-dioxide (*4*)

Sodium borohydride (1.7 g, 45 mmol) was added to a solution of tetrahydrothiapyran-3-one (5 g, 43.1 mmol) in methanol (100 mL) at -10°C; the reaction mixture was stirred overnight and the methanol removed under reduced pressure. The residue was suspended in water, extracted with ether (4 x 50 mL) and the extract dried over magnesium sulfate. The solvent was evaporated to give pure tetrahydrothiapyran-3-ol (4.6 g, 90%; ^{1}Hmr ($CDCl_3$) δ: 1.4-2.15 (m, 4H), 2.4-2.58 (m, 3H), 2.77 (d of d, J = 12.8, 3.3 Hz, 1H), 3.85 (t of t, J = 8.4, 3.3 Hz, 1H); ^{13}Cmr ($CDCl_3$) δ: 25.9, 28.0, 34.3, 35.7, 67.0).

Tetrahydrothiapyran-3-ol (1.1 g, 9 mmol) was converted to 3-bromotetrahydrothiapyran[14] with freshly distilled PBr_3 (1.0 g, 3.54 mmol) (^{13}Cmr ($CDCl_3$) δ: 27.7, 30.4, 37.2, 38.0, 50.5) and without further purification, was oxidized with excess *m*-chloroperbenzoic acid (3.1 g, 19 mmol) to 3-bromotetrahydrothiapyran 1,1-dioxide (^{13}Cmr ($CDCl_3$) δ: 23.0, 35.3, 40.8, 50.4, 60.2). The above crude compound was refluxed with 1 M methanolic sodium methoxide (20 mL) to give 3-methoxytetrahydrothiapyran 1,1-dioxide (900 mg) according to the procedure of Fehnal,[14] and

recrystallized from benzene–petroleum ether, mp 66–68 °C: ^{1}Hmr ($CDCl_3$) δ: 1.27–1.48 (m, 1H), 1.8–2.3 (m, 3H), 2.76–2.93 (m, 2H, C–2H$_a$ and C–6H$_a$), 2.96–3.09 (m, 1H, C–6H$_e$), 3.39 (s, 3H, –OMe), 3.42 (sym m, 1H, C–2H$_e$), 3.69 (t of t, J = 10.7 and 3.8 Hz, 1H, C–3H); ^{13}Cmr ($CDCl_3$) δ: 19.4, 30.4, 50.9 (C–6), 56.0 (C–2), 56.6 (–OMe), 75.7 (C–3).

trans–1,4–Oxathiadecalin 4,4–dioxide (2)

trans–1,4–Oxathiadecalin 4,4–dioxide (2) was prepared by the method of Evans and coworkers[8] as follows. Cyclohexene oxide (12.5 g, 128 mmol) was added dropwise to a solution of sodium salt of mercaptoethanol prepared by addition of mercaptoethanol (10 g, 128 mmol) to a solution of KOH (7.18 g, 128 mmol) in methanol (100 mL), and the reaction mixture stirred at room temperature for 12 h. Workup as usual gave *trans*–2–(2–hydroxyethylthio)cyclohexanol (6) in 95% yield (21.4 g) as a clear viscous liquid; bp 120–133 °C/0.5 torr; ^{1}Hmr ($CDCl_3$) δ: 1.2–1.5 (m, 4H), 1.6–1.9 (m, 2H), 2.0–2.2 (m, 2H), 2.43 (sym m, 1H), 2.79 (sym m, 2H), 3.34 (sym m, 1H), 3.75 (t, J = 6 Hz, 2H), 4.01 (br s, 2H); ^{13}Cmr ($CDCl_3$) δ: 24.4, 26.3, 33.5, 33.9, 34.3, 53.2, 61.7, 73.4.

A solution containing 30% hydrogen peroxide (14 g, 120 mmol) and 40 mL of glacial acetic acid was added to a solution of 6 (8.8 g, 50 mmol) in glacial acetic acid (40 mL). The resulting solution was stirred overnight (~12 h) at room temperature and then heated on a steam bath for an additional 24 h and finally concentrated to a syrup under reduced pressure (rotary evaporator). The crude sulfone 7 was recrystallized from hexane–ethyl acetate (7.8 g, 75% yield), mp 57–59 °C; ir (KBr) ν_{max}: 3459 (br vs), 2936 (vs), 2863 (s), 1453 (m), 1437 (m), 1293 (vs), 1123 (vs), 1065 (vs), 1013 (m), 951 (m), 708 (m) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.2–2.35 (m, 8H), 3.1 (sym m, 1H), 3.48 (sym m, 2H), 3.9–4.2 (m, 5H); ^{13}Cmr ($CDCl_3$) δ: 23.2, 23.9, 24.4, 35.1, 56.1, 56.9, 67.5, 69.4.

The dihydroxysulfone 7 (1.5 g, 7.2 mmol) and triphenylphosphine (1.88 g, 7.2 mmol) in carbon tetrachloride (25 mL) were heated at 70°C for 24 h. Workup gave a mixture of *trans*-1,4-thioxadecalin 1,1-dioxide (2), of *trans*-2-(2-chloroethylsulfoxyl)cyclohexanol (8) and of 2-chloroethyl *cis*-2-chlorocyclohexyl sulfone (9) as shown by ^{1}H and ^{13}Cmr spectra.[8] The compound 2 was isolated from the above mixture by flash chromatography using ether-petroleum ether to give 2 as a crystalline solid (340 mg, ~25%); mp 120-121°C; ir (KBr) ν_{max}: 2942 (s), 2870 (s), 1456 (m), 1308 (vs), 1269 (vs), 1227 (w), 1183 (m), 1130 (vs), 1024 (m), 939 (w), 853 (w), 729 (m), 538 (s) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.97-2.45 (m, 8H), 2.86 (dddd, 1H, C-10H$_a$), 3.07 (d of t, J_{gem} = 13.6, J_{ea} = 2.83, J_{ee} = 2.6, 1H, C-3H$_e$), 3.28 (d of q, J_{gem} = 13.6, J_{aa} = 10.9, J_{ae} = 5.3 Hz, 1H, C-3H$_a$), 3.67 (quintet, 1H, C-9H$_a$), 4.12 (d of t, J_{gem} = 12.8, J_{aa} = 10.9, J_{ae} = 2.83 Hz, 1H, C-2H$_a$), 4.28 (d of q, J_{gem} = 12.8, J_{ee} = 2.6, J_{ea} = 5.3 Hz, 1H, C-2H$_e$) (the chemical shifts of 2 were dependent on the solvent); ^{13}Cmr ($CDCl_3$) δ: 18.9, 23.8, 24.0, 31.8, 52.6, 65.1, 65.8, 79.0. Calcd. exact mass for $C_8H_{14}O_3S$: 190.0664. Found: 190.0663.

cis-1,4-Oxathiadecalin 4,4-dioxide (16)

Dihydroxysulfide 6 (5 g, 28.4 mmol) in DME (10 mL) was added to conc. HCl (25 mL) and the reaction mixture left overnight. The usual workup gave dichlorosulfide 10 in almost quantitative yield (6 g); ^{1}Hmr ($CDCl_3$) δ: 1.22-1.85 (m, 6H), 2.16-2.35 (m, 2H), 2.86 (ddd, 1H), 2.99 (ddd, 2H), 3.65 (t, 2H), 3.98 (ddd, 1H); ^{13}Cmr ($CDCl_3$) δ: 23.5, 24.0, 31.6, 34.4 (2C), 43.2, 51.3, 64.0.

The sulfide 10 (6 g) was oxidized with 30% H_2O_2 (10 mL) in acetic acid (30 mL) and acetic anhydride (10 mL) to afford dichlorosulfone 11 in 90 % yield (6.3 g); ^{1}Hmr ($CDCl_3$) δ: 1.3-2.05 (m, 6H), 2.3-2.5 (sym m, 2H), 3.28 (sym m, 1H), 3.66-4.0 (m, 4H), 4.25 (sym m, 1H); ^{13}Cmr ($CDCl_3$) δ: 23.9, 24.1, 24.7, 35.8, 36.6, 57.2, 57.7, 67.9.

The above sulfone *11* was mixed with 5% KOH (50 mL) and DME (10 mL), and was heated on the steam bath for 3 h. Workup as usual gave a crystalline solid, which on recrystallization from ether and cyclohexane gave *16* as white crystals (4.5 g, 85% yield); mp 130–131°C; ir (KBr) ν_{max}: 2944 (s), 2869 (m), 1449 (w), 1393 (m), 1291 (vs), 1240 (s), 1136 (s), 1121 (s), 1094 (vs), 1021 (m), 959 (w), 855 (w), 527 (m); ^{1}Hmr ($CDCl_3$) δ: 1.16–2.20 (m, 8H), 2.79 (sym m, 2H, C–3H$_e$ and C–10H$_e$), 3.25 (d of q, J_{gem} = 12.2, J_{aa} = 11.1, and J_{ae} = 4.9 Hz, 1H, C–3H$_a$), 4.00 (d of t, J_{gem} = 12.4, J_{aa} = 11.1, and J_{ae} = 2.2 Hz, 1H, C–2H$_a$), 4.20 (br m, 1H, C–9H$_a$), 4.25 (d of q, J_{gem} = 12.5, J_{ee} = 4.9, J_{ea} = 2.5 Hz, 1H, C–2H$_a$) (the chemical shifts were dependent on solvent); ^{13}Cmr ($CDCl_3$) δ: 19.1, 22.5, 24.7, 31.7, 47.5, 62.4, 65.2, 74.0. Calcd. exact mass for $C_8H_{14}O_3S$: 190.0664. Found: 190.0660.

Equilibration of *cis*– and *trans*–1,4–oxathiadecalin 4,4–dioxide (*2* and *16*)

trans–Oxathiadecalin dioxide (*2*) (500 mg) was heated at 100°C in 25 mL 10% KOH in H_2O–EtOH (3:1) for ~100 h. The cooled reaction mixture was acidified with 5% HCl solution and extracted with dichloromethane. Evaporation of the solvent gave in quantitative yield 1:9 mixture of *cis*– and *trans*–oxathiadecalin dioxide (*16* and *2* respectively) as determined by ^{1}H and ^{13}Cmr spectra. Similar treatment of *16* gave a reaction mixture with the same ^{1}H and ^{13}Cmr spectra as those from *2*.

1–Thiadecalin 1,1–dioxide (*18*)

To allylmagnesium bromide (prepared from allyl bromide (14.5 g, 119 mmol) and excess magnesium powder (11.5 g, 474 *g*–atom)) in ether (125 mL) at –10°C was slowly added cyclohexene sulfide (8 g, 70 mmol) (prepared by the method of Tamelen;[30] ^{1}Hmr ($CDCl_3$) δ: 1.2–1.4 (m, 2H), 1.5–1.7 (m, 2H), 1.72 (sym m, 4H), 3.21 (sym m, 2H); ^{13}Cmr ($CDCl_3$) δ: 19.4, 25.8, 36.9). The cooling bath was

removed the mixture stirred at room temperature for 1 h, and then refluxed for 8 h and left overnight. With cooling in a current of nitrogen the mixture was decomposed with 10% HCl, the organic layer was separated and the aqueous layer extracted with ether (3 x 50 mL). The combined organic extract dried over magnesium sulfate. Evaporation of the solvent gave 2-allylcyclohexane-1-thiol (8.75 g, 80%); ^{1}Hmr ($CDCl_3$) δ: 0.95-2.18 (m, 9H), 1.3 (d, 1H, SH), 2.40-2.65 (m, 2H), 2.70 (qd, 1H), 4.98-5.08 (m, 2H), 5.60-5.85 (m, 1H); ^{13}Cmr ($CDCl_3$) δ: 25.9, 27.0, 31.7, 38.7, 39.0, 43.8, 45.6, 116.5, 136.1.

The 2-allylcyclohexane-1-thiol (neat) (2 g) was left open in a flask for two weeks. After two weeks the cyclization[15] had occurred to give a 70% yield of a mixture of 1-thiadecalin and 2-methoxy-1-thiahydrindan (1.5 g). The mixture was oxidized with *m*-CPBA in dichloromethane and purified by flash chromatography using ether-petroleum ether, mp 114-115 °C (lit[15] mp 114-114.9 °C); ^{1}Hmr ($CDCl_3$) δ: 1.0-2.25 (m, 13H), 2.59 (ddd, J = 12.5, 10.0, 3.5 Hz, 1H, C-9H_a), 2.91 (m, 1H, C-2H_a), 3.10 (dddd, J = 13.5, 4.0, 3.5, 1.4 Hz, 1H, C-2H_e); ^{13}Cmr ($CDCl_3$) δ: 20.1, 22.9, 24.6, 24.9, 32.0, 32.7, 39.6 (C-10), 51.5 (C-2), 65.3 (C-9).

trans-2-Isopropyl-5-methylsulfonyl-1,3-dioxane (*20*)

Potassium hydroxide (5.6 g, 100 mmol) was dissolved in 40 mL of absolute ethanol, and mixed with a solution of methanethiol (4.8 g, 5.6 mL, 100 mmol) in 20 mL of ethanol. The mercaptide solution was poured into a cold solution (20 mL) of diethyl chloromalonate (22.3 g, 100 mmol) (prepared by mixing equimolar quantities of SO_2Cl_2 and diethyl malonate; ^{1}Hmr ($CDCl_3$) δ: 1.18 (t, 6H), 4.17 (q, 4H), 4.74 (s, 1H); ^{13}Cmr ($CDCl_3$) δ: 14.0, 55.6, 63.2, 164.6) in ethanol). The reaction mixture was stirred at room temperature for 2 h, diluted with water and extracted with ether (3 x 100 mL). Drying of the extract with magnesium sulfate and evaporation of solvent afforded diethyl (methylthio)malonate as a yellow oil which was

further distilled, bp 68–71°C (0.25 torr) (15 g, ~75%). ^{1}Hmr ($CDCl_3$) δ: 1.32 (t, 6H), 2.26 (s, 3H), 4.23 (q, 4H), 3.94 (s, 1H); ^{13}Cmr ($CDCl_3$) δ: 13.3, 50.8, 54.9, 62.5, 163.9.

Following the procedure of Eliel *et al.*,[16] diethyl (methylthio)malonate was converted to ***20*** (contaminated by ~5% of ***19***) and the ^{1}H and ^{13}Cmr spectra were found to be identical to those reported earlier.[16] ^{1}Hmr ($CDCl_3$) δ: 0.91 (d, J = 6.8 Hz, 6H, $-C(CH_3)_2$), 1.82 (sym m, 1H, CH), 2.89 (s, 3H, $S-CH_3$), 3.47 (t of t, J = 11.7 and 4.1 Hz), 1H, C–3H), 3.98 (t of d, J = 11.7 and 1.0 Hz, 2H, C–4H_a and C–6H_a), 4.23 (d, J = 4.88, 1H, C–2H), 4.45 (d of d, J = 8.1 and 4.42 Hz, 2H, C–4H_e and C–6H_e) (plus small signals at 0.93 (d, J = 6.7 Hz, 6H, $-C(CH_3)_2$), 1.51–2.07 (m, 1H, –CH), 2.64 (m, 1H, C–5H_e), 3.10 (d, J = 1.12 Hz, 3H, $S-CH_3$), 4.16 (sym m, 2H, C–4H and C–6H), 4.32 (d, J = 4.6 Hz, 1H, C–2H), 4.69 (br d, J = 13 Hz, 2H, C–4H and C–6H) due to *cis* isomer ***19***); ^{13}Cmr ($CDCl_3$) δ: 16.8, 32.3, 40.1, 56.1, 64.6, 105.9 (plus small signals at 16.7, 32.6, 42.9, 50.7, 59.0, 106.4 for *cis*–isomer ***19***).

The above mixture of *cis*– and *trans*–sulfones (***19*** and ***20***) was isomerized to *cis*–sulfone ***19*** by stirring in 0.1 M NaOH in H_2O and DME for 12 h. Workup and recrystallization from *n*–hexane afforded pure *cis*–isomer (***19***); mp 90–92°C (lit.[16] mp 90–92°C).

Selective H–D exchange in 1,4–oxathiadecalin 4,4–dioxide (***2***)

(i) 3(e)–^{2}H–*trans*–1,4–Oxathiadecalin 4,4–dioxide (***26***)

Oxathiadecalin dioxide (***2***) (100 mg) was dissolved in DME (5 mL) and added to 2% K_2CO_3 solution in D_2O (20 mL). After 15 h the mixture was extracted with several portions of ether and the extracts dried over $MgSO_4$; evaporation of the solvent followed by recrystallization from ether–cyclohexane gave the monodeuterated

oxathiadecalin dioxide (*26*) in quantitative yield. (For ^{1}H and ^{13}Cmr spectra see Figure 4.7 and 4.8).

(ii) 3(e)-^{2}H-3(a)-^{2}H-*trans*-1,4-Oxathiadecalin 4,4-dioxide (*27*)

Similarly compound *2* (100 mg) was dissoved in DME (5 mL) and added to 0.5 M NaOD-D_2O (20 mL) solution. The reaction mixture was left at room temperature for 3 h; workup as above gave *27* (95% yield). (For ^{1}H and ^{13}Cmr spectra see Figure 4.7 and 4.8).

(iii) 3(a)-^{2}H-*trans*-1,4-Oxathiadecalin 4,4-dioxide (*28*)

The above dideuterated compound (*27*) (50 mg) in DME (5 mL) was treated with 2% K_2CO_3 solution in H_2O (10 mL) for 15 h. Workup as above gave *28* as a crystalline solid (48 mg, 95% yield). (For ^{1}H and ^{13}Cmr spectra see Figure 4.9 and 4.10).

(iv) 3,3-$^{2}H_2$-10-^{2}H-*trans*-1,4-Oxathiadecalin 4,4-dioxide (*29*)

A mixture of *26*, *27*, and *28* or *2* (200 mg) was refluxed in 0.5 M NaOD solution in D_2O-CD_3OD (3:1) (25 mL) for 50 h. The reaction mixture was cooled and worked up as usual to give *29* as a white solid (180 mg, 90% yield), contaminated by small quantity of the *cis*-isomer (*16*) (~5%). (For ^{1}H and ^{13}Cmr spectra see Figure 4.9 and 4.10).

(v) 3(a)-^{2}H-10-^{2}H-*trans*-1,4-Oxathiadeclin 4,4-dioxide (*30*)

The above trideuterated compound (*29*) (50 mg) in DME (3 mL) was added to 2% K_2CO_3 solution in H_2O (10 mL). After 15 h the reaction mixture was worked up as described previously to give *30* (44 mg, 88%). (For ^{1}H and ^{13}Cmr spectra see Figure 4.9 and 4.10).

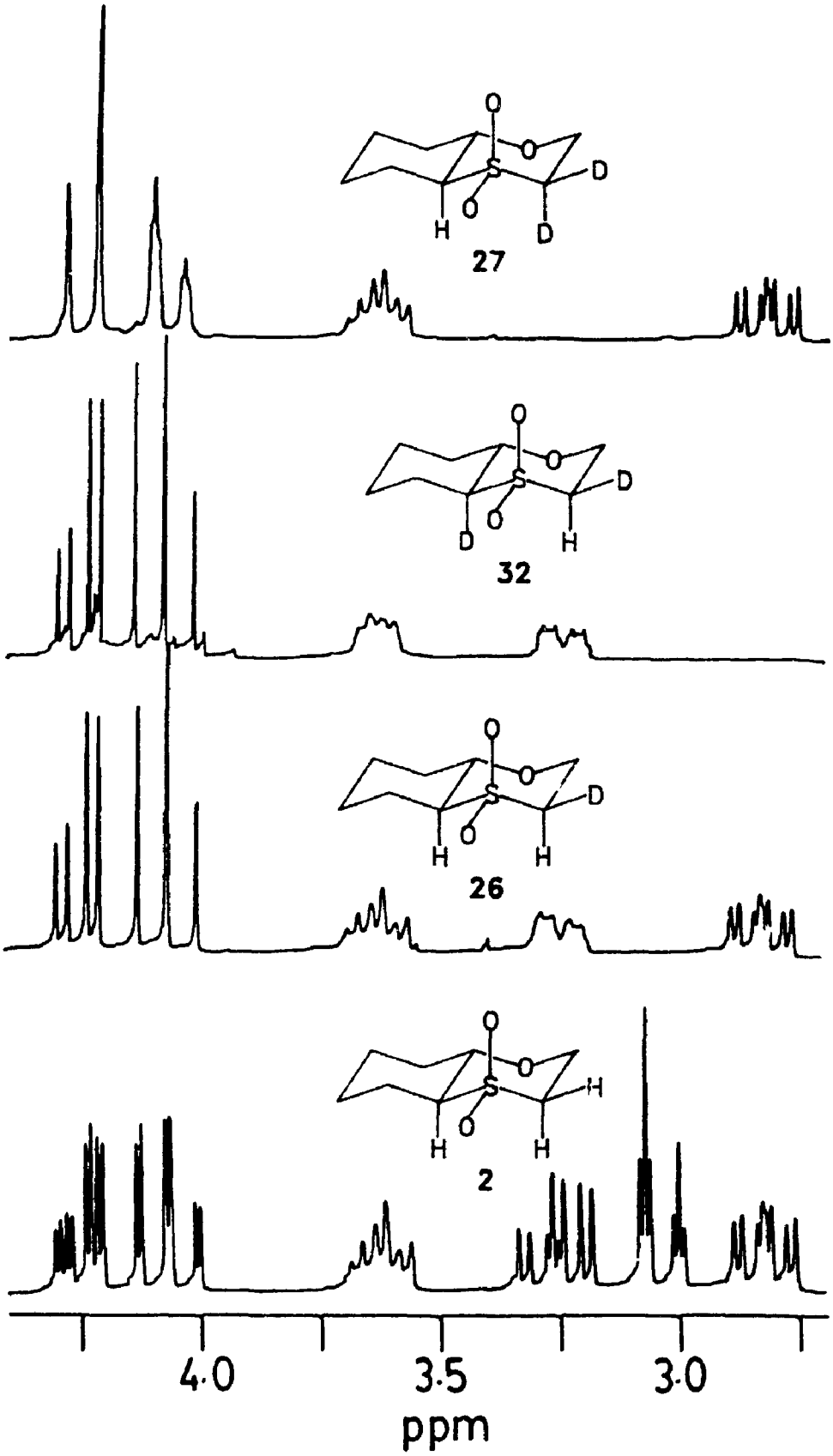


Figure 4.7 ^{1}Hmr Spectra of various deuterated 1,4–oxathiadecalin 4,4–dioxides (**2**, **26**, **27**, and **32**) in $CDCl_3$.

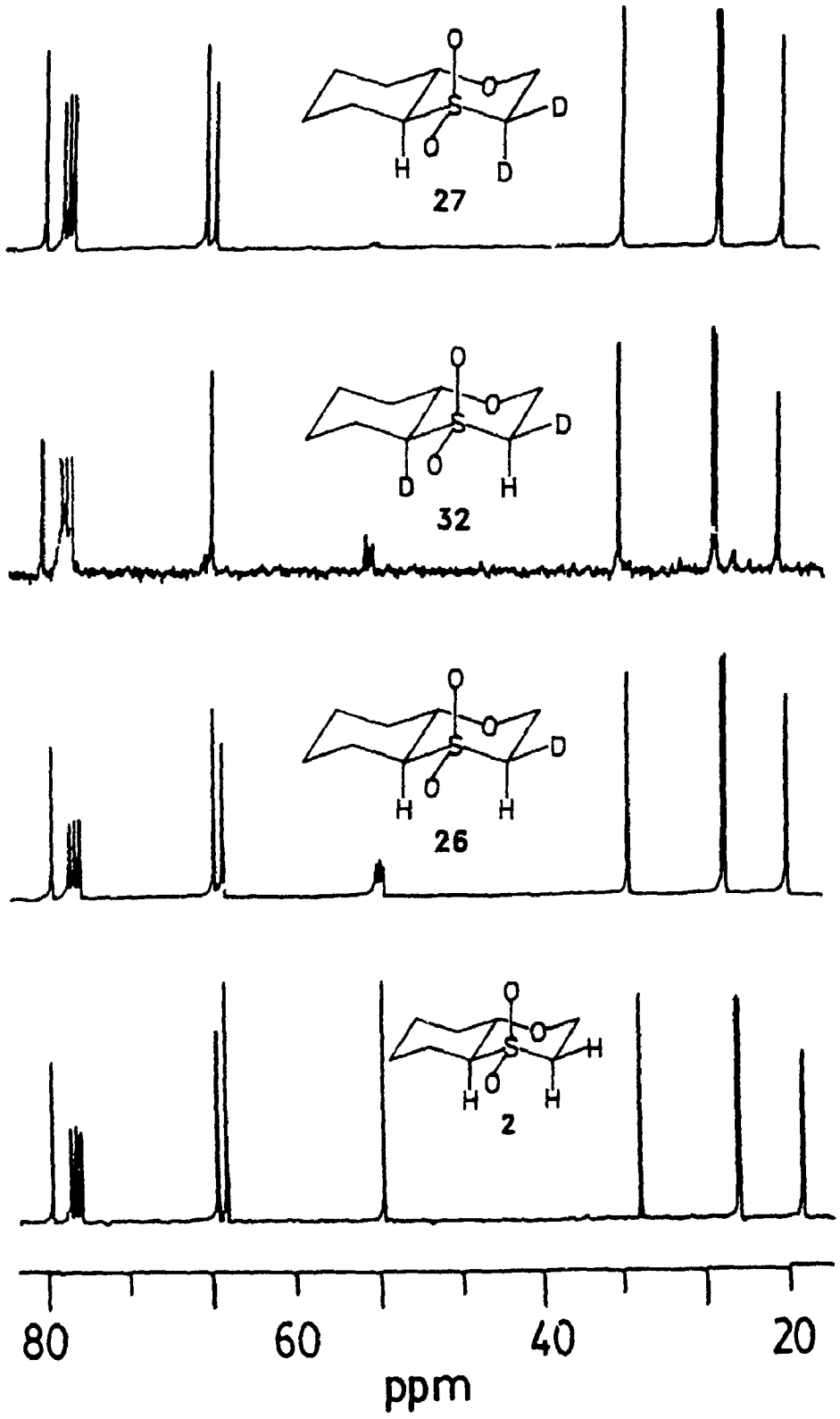


Figure 4.8 ^{13}C Spectra of various deuterated 1,4-oxathiadecalin 4,4-dioxides (**2**, **26**, **27**, and **32**) in $CDCl_3$.

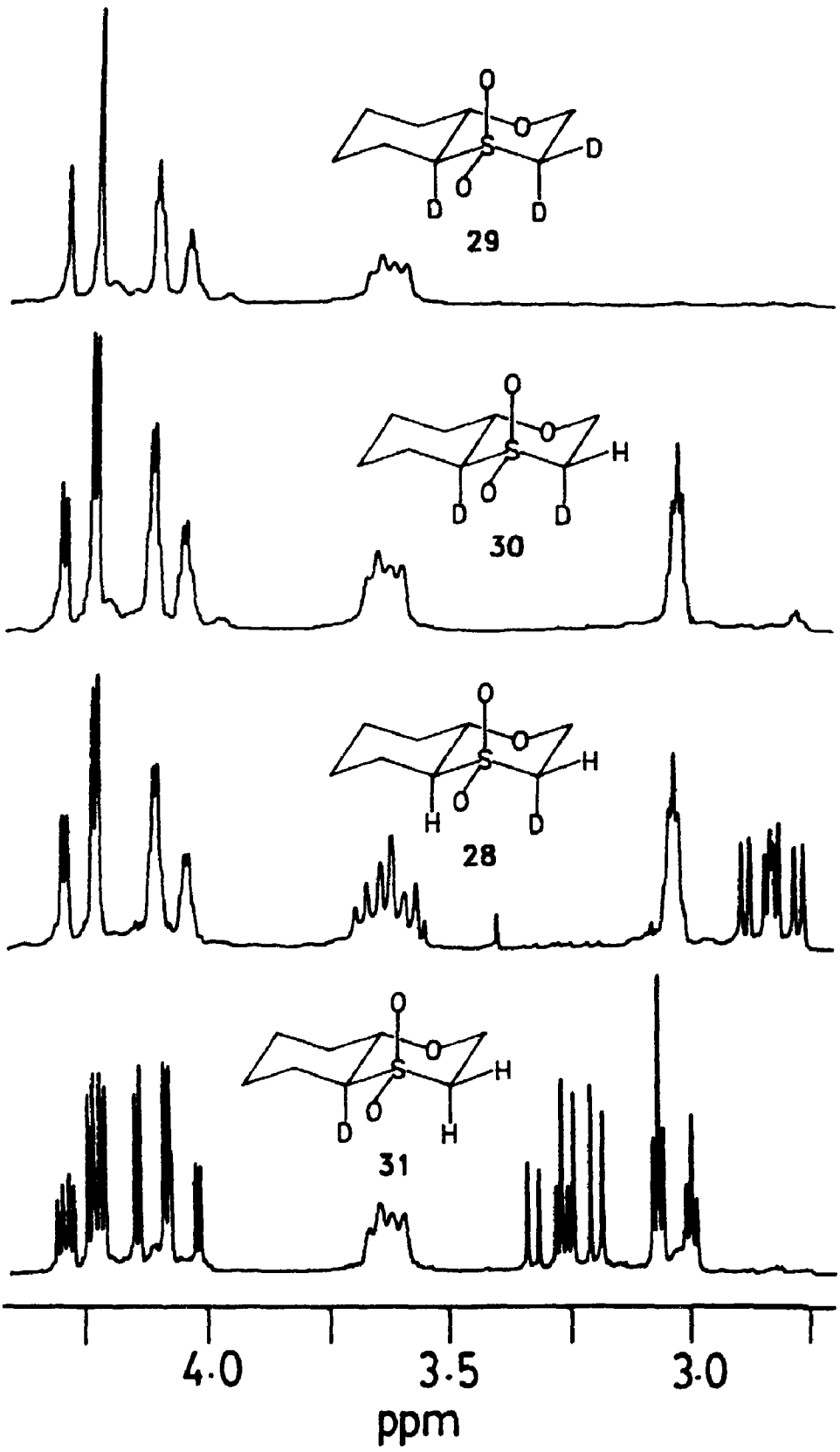


Figure 4.9 ^{1}Hmr Spectra of various deuterated 1,4–oxathiadecalin 4,4–dioxides (**28**, **29**, **30**, and **31**) in $CDCl_3$.

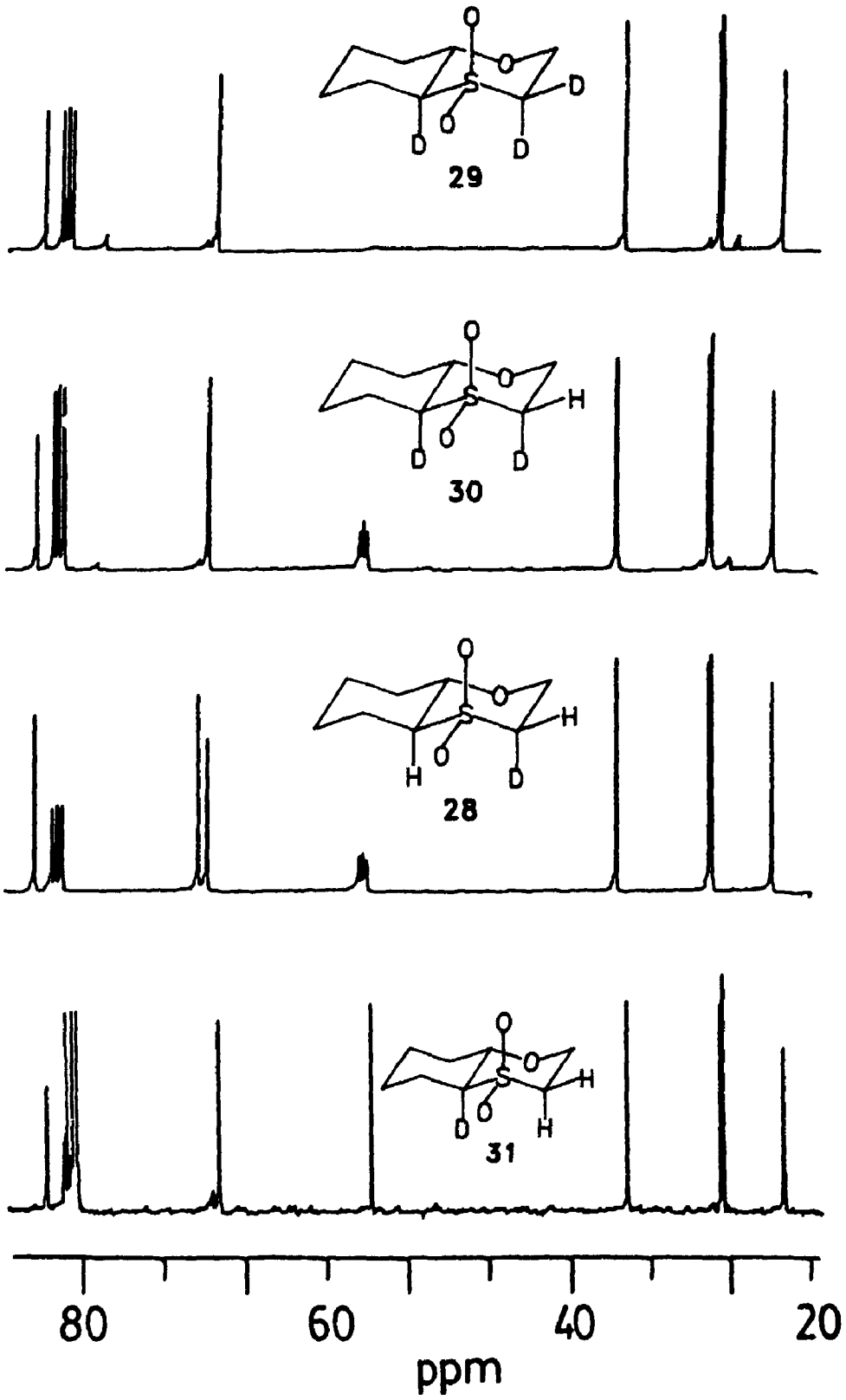


Figure 4.10 ^{13}C Spectra of various deuterated 1,4–oxathiadecalin 4,4–dioxides (**28**, **29**, **30**, and **31**) in $CDCl_3$.

(vi) 10-^{2}H-*trans*-1,4-Oxathiadecalin 4,4-dioxide (*31*)

The trideuterated compound (*29*) and/or dideuterated compound (*30*) (100 mg) in DME (5 mL) was added to NaOH in H_2O (0.5 M, 20 mL). After 3 h, work up as above gave *31* (9 .., 92%). (For ^{1}H and ^{13}Cmr spectra see Figure 4.9 and 4.10).

(vii) 3(e)-^{2}H-10-^{2}H-*trans*-1,4-Oxathiadecalin 4,4-dioxide (*32*)

The monodeuterated compound (*31*) (50 mg) in DME (3 mL) was treated with 2% K_2CO_3 in D_2O (10 mL) for 15 h. The work up as above gave *32* as a crystalline solid (45 mg, 90%). (For ^{1}H and ^{13}Cmr spectra see Figure 4.7 and 4.8).

Kinetic measurements

General procedure:

A typical run involved the preparation of 0.01 to 0.0 5M solutions of NaOD in D_2O by dissolving Na-metal in D_2O under nitrogen and titrating the solution using 0.01 M HCl solution. A 0.05 mL of above solution (of known [OD^-]) was transferred with a syringe into an nmr tube, 10 mg of the compound quickly added, and the tube was shaken for approximately 5 seconds to dissolve the compound. The time was noted as zero when shaking was started. For those reactions which proceeded fast enough to be followed in the spectrometer, the nmr tube was then quickly placed into the XL-200 instrument which had been set at the required temperature. For the slower reactions the nmr tube was flame sealed and then placed in a previously equilibrated water bath. The amount of unexchanged starting material (>75% exchange, unless otherwise noted) was determined by comparing the integral of the disappearing signal alpha to the sulfonyl divided by the integral of a signal alpha to the oxygen (which can not participate in exchange reaction), for

example, in 1,4-oxathiane 4,4-dioxide (3), the integral for the C_3 hydrogen (δ = 3.2 ppm) divided by the integral for the C_2 hydrogens (δ = 4.0 ppm) and multiplied by 100 gave the amount of unexchanged starting material.

% Unreacted starting material = (∫C-3 Hydrogens/∫C-2 Hydrogens) x 100

The time for each point was taken as an average of the start of data collection and the stop of data collection. The values of k_{obs}, *i.e.*, the log (% unreacted starting material) *vs.* time was obtained from the slope of a plot of (100 - % reaction) *vs.* time on a semilog paper (plots were obtained for ≥75% reaction, unless otherwise noted). The second order rate constants (k_2) were obtained by dividing k_{obs} by $[OD^-]$, *i.e.*

$$k_2 = k_{obs} / [OD^-]$$

(i) Kinetics of H-D exchange of the 1,4-oxathiane 4,4-dioxide (3)

The kinetic order with respect to deuteroxide was determined by measuring the rates of H-D exchange (as described above) of 3 (10 mg) at four different concentrations of deuteroxide at 20°C. The following rate constants were obtained:

$[OD^-]$ (M)	k_{obs} (s^{-1})
1.27×10^{-2}	2.9×10^{-4}
1.69×10^{-2}	3.5×10^{-4}
2.53×10^{-2}	5.5×10^{-4}
5.06×10^{-2}	10.5×10^{-4}

A plot of k_{obs} *vs.* $[OD^-]$ gave a straight line (see Figure 4.3). The second

order rate constant for H–D exchange of **3** was calculated from the slope of above plot was found to be, $k_2 = 2.15 \times 10^{-2}$ $M^{-1}s^{-1}$.

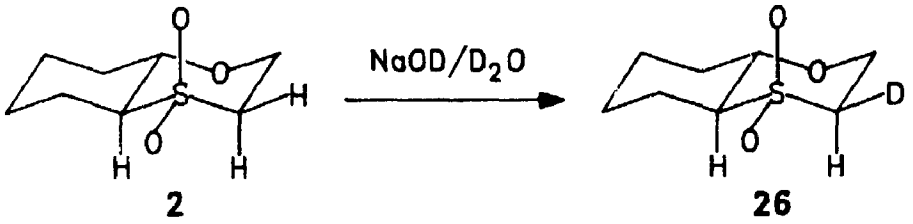
(ii) Rate of H–D exchange of the *trans*–1,4–oxathiadecalin 1,1–dioxide (**2**)

As described in the general procedure, the reaction of **2** (10 mg) with NaOD in D_2O (0.5 mL, 0.025M) was monitored by nmr spectroscopy at 20°C, the signals due to C–$3H_e$ (see Fig. 4.3) disappeared as the reaction proceeded, are seen clearly in C–$2H_e$ and C–$2H_a$ signals due to disappearence of the smaller coupling constants in the ^{1}Hmr. A ^{13}Cmr spectrum was run (after ~10 h) which showed a 1:1:1 triplet for C–3 carbon, indicating the incorporation of only one deuterium. The % of unexchanged starting material was calculated by dividing the integral of C–$3H_e$ by average of integrals of C–$2H_e$, C–$2H_a$ and C–$9H_a$ and were plotted against time on semilog–paper (see Figure 4.11). The observed rate constant was calculated from the slope ($k_{obs} = 7.9 \times 10^{-4}$ s^{-1}) and was converted to k_2 by dividing by [OD^-] ($k_2 = 3.2 \times 10^{-2}$ $M^{-1}s^{-1}$).

The above sample was carefully sealed and the ^{1}Hmr spectra were run every other day. The amount of unexchanged starting material was calculated by dividing the integral of C–$3H_a$ by the average integral of hydrogens alpha to oxygen (*e.g.* C–$2H_e$, C–$2H_a$, and C–$9H_a$) and rate was calculated as described above ($k_{obs} = 4 \times 10^{-6}$ s^{-1} and $k_2 = 1.6 \times 10^{-4}$ $M^{-1}s^{-1}$).

(iii) Rate of H–D exchange of the *cis*–1,4–oxathiadecalin 4,4–dioxide (**16**)

The rate constant for C–$3H_e$ in *cis*–oxathiadecalin dioxide (**16**) was measured in (0.032 M) NaOD–D_2O solution; and for C–$3H_a$ and C–$10H_e$ in 0.38 M solution as described above. The k_{obs} and k_2 for α–hydrogens in **16** were obtained as following



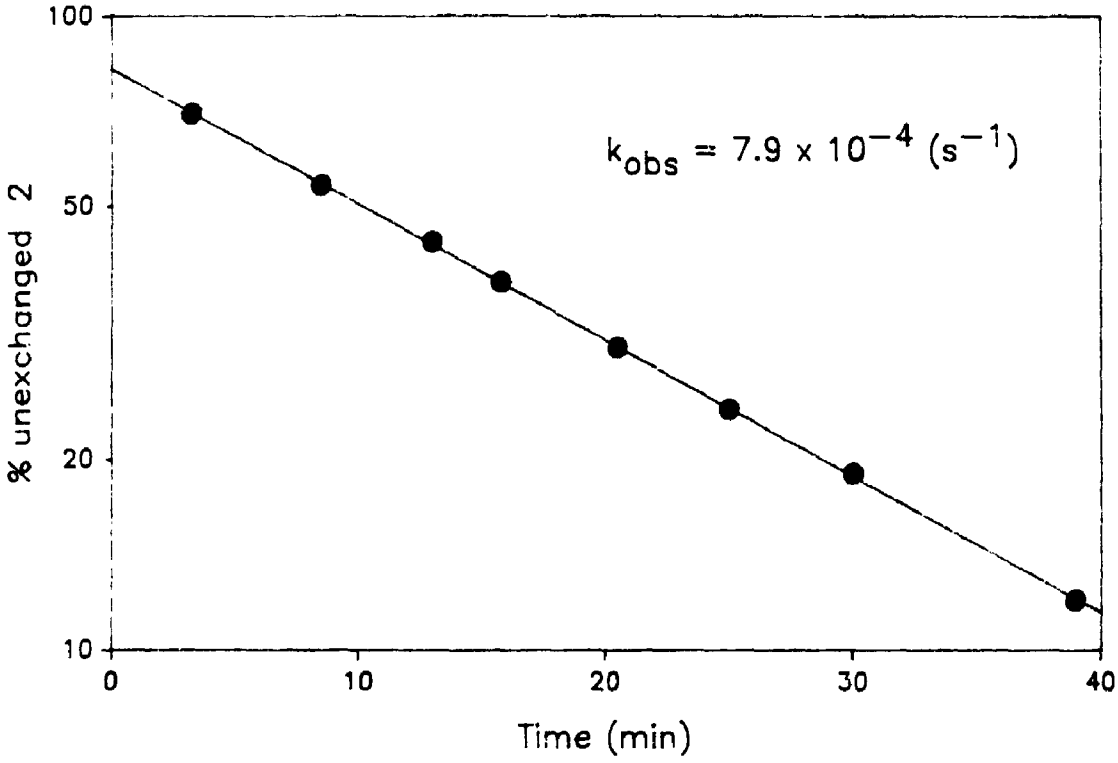


Figure 4.11 A typical pseudo–first order rate plot for the exchange of 1,4–oxathiadecalin 4,4–dioxide (**2**) in NaOD–D_2O (0.025 M) at 20° C.

	k_{obs} (s^{-1})	k_2 ($M^{-1}s^{-1}$)
C–3H_e	1.5×10^{-3}	4.8×10^{-2}
C–3H_a	6.1×10^{-5}	1.6×10^{-4}
C–10H_e	1.3×10^{-5}	3.4×10^{-5}

(iv) Rate of H–D exchange of the 3–methoxytetrahydrothiopyran 1,1–dioxide (*4*)

Similarly, the reaction of *4* (10 mg) in NaOD–D_2O (0.5 mL, 0.051 M) was monitored by nmr spectroscopy. The disappearance of the α–equatorial hydrogen (C–2H_e) signal was calculated by dividing the integration of C–2H_e by C–3H_a (alpha to oxygen) and was plotted on semilog paper against time. It gave a straight line and the observed rate constant (k_{obs} = 2.3×10^{-5} s^{-1}) was calculated from the slope. The second order rate constant $k_2 = 2.3 \times 10^{-5} \div 0.051 = 4.5 \times 10^{-4}$ $M^{-1}s^{-1}$. After >95% exchange of C–2H_e a ^{13}Cmr spectrum was run on the same sample (data were collected for ~1 h), which showed a clear triplet at same position as C–2. The rate for axial hydrogen (C–2H_a) was estimated to be at least >25 times slower than the equatorial hydrogen (C–2H_e).

(v) Rate of H–D exchange of the 2–methyl–1,4–oxathiane 4,4–dioxide (*5*)

The reaction of *5* (10 mg) with D_2O–NaOD (0.5 mL, 0.012 M) was monitored with the help of ^{1}H and ^{13}Cmr spectroscopy. The disappearance of the α–equatorial hydrogens C–3H_e and C–5H_e (calculated by dividing the integrals of C–3H_e and C–5H_e by the average integrals of C–2H_a and C–6H_2. The observed rate constant was calculated from the slope (k_{obs} = 2×10^{-4} s^{-1}) and was converted to second order rate constants by dividing with [OD^-] (k_2 = 1.6×10^{-2} (for C–3H_e ⟶ C–3D_e) and 2.3×10^{-2} (for C–5H_e ⟶ C–5D_e) $M^{-1}s^{-1}$). A similar kinetic run was

carried out using ^{13}Cmr spectroscopy (see Figure 4.12). The integral of the 1:1:1 triplet for C–2 was divided by the integral of 1:1:1 triplet for C–5, which indicated that C–5H_e exchanges about 1.4 times faster than C–2H_e (for rate constants see Table 4.1). The rate constant for the exchange of α–axial hydrogens (*i.e.* C–2H_a and C–5H_a) were obtained as above (k_2 = ~2 x 10^{-4} $M^{-1}s^{-1}$).

(vi) Rate of H–D exchange of tetrahydro–1–thiapyran–3–one ethylene ketal 1,1–dioxide (*21*)

Compound *21* (10 mg) was dissolved in D_2O–NaOD (0.25 M, 0.5 mL) and the disappearance of C–2 α–hydrogens was monitored with the help of ^{1}Hmr spectroscopy. The % exchange was calculated by dividing the integral of the C–2 signal by the integral of ethylene signal and multiplying by 2 (because the ethylene signal has 4 hydrogens). The plot of % reaction vs. time on semilog paper gave a straight line. The observed rate constant was calculated from the slope, k_{obs} = 1.2 x 10^{-4} sec^{-1} (k_2 = 4.8 x 10^{-3} $M^{-1}sec^{-1}$ on a per hydrogen basis).

(vii) Rate of H–D exchange of pentamethylene sulfone (*25*)

Rate of H–D exchange of *25* was measured following general procedure. Pentamethylene sulfone (*25*) (10 mg) was dissolved in 0.8 M NaOD–D_2O solution (0.5 mL). The % of unexchanged starting material was calculated by dividing the integral of C–2H_2 and C–6H_2 signal (alpha to sulfonyl) by the integral of C–3H_2 and C–5H_2 signal. (k_{obs} = 8 x 10^{-7} s^{-1}; k_2 = ~10^{-6} $M^{-1}s^{-1}$).

(viii) Rate of H–D exchange of thiadecalin 1,1–dioxide (*18*)

Thiadecalin 1,1–dioxide (*16*) (10 mg) was exchanged in 0.20 M NaOD in D_2O–DMSO (80:20). The k_{obs} for α–equatorial hydrogen (C–2H_e) was found to be 2.4 x 10^{-7} s^{-1} (k_2 = 1.2 x 10^{-6} $M^{-1}s^{-1}$). The relative rate of the equatorial and

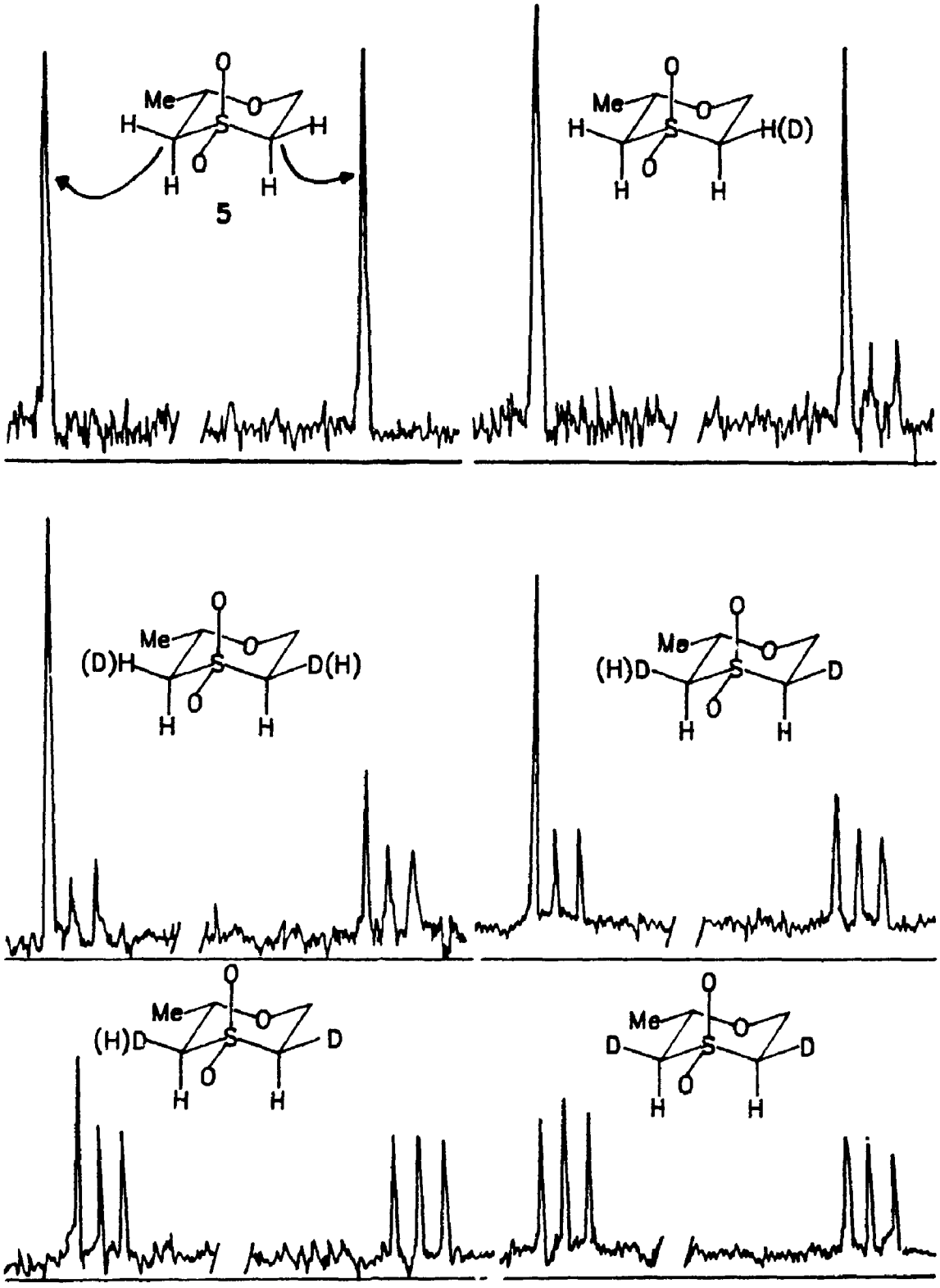


Figure 4.12 A series of ^{13}Cmr spectra of 2-methyl-1,4-oxathiane 4,4-dioxide (5) in NaOD-D_2O (0.012 M) at 20° C.

axial hydrogens were determined in ~1.0 M NaOD in D_2O–CD_3OD (75:25). The ^1H and ^{13}Cmr spectra showed that only equatorial (C–$2H_e$) hydrogen was exchanged after 24 h at room temperature as determined by careful integrations of C–$2H_a$ and C–$9H_a$ signals and also a 1:1:1 triplet for C–2 in ^{13}Cmr spectrum was observed (indicating the presence of only one deuterium). The rate constant for axial hydrogen was estimated to be ~10^{-8} $M^{-1}s^{-1}$. Heating of the same mixture for a further 24 h at 80°C gave total exchange of the C–2 hydrogens and no sign of any exchange at C–9.

4.5 REFERENCES AND FOOTNOTES

1. For a recent review of α–sulfonyl carbanions see G. Boche, *Angew. Chem. Int. Ed. Engl.*, **28**, 277 (1989).
2. S. Wolfe, A. Rauk, I.G. Csizmadia, *J. Am. Chem. Soc.*, **91**, 1567 (1969); S. Wolfe, A. Rauk, L.M. Tel, I.G. Csizmadia, *J. Chem. Soc., Chem. Commun.*, **96** (1970); S. Wolfe, *Stud. Org. Chem. (Amsterdam)*, **19**, 133 (1985) and earlier work cited therein; D.A. Bors, A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **108**, 1397 (1986).
3. E.J. Corey, E.T. Kaiser, *J. Am. Chem. Soc.*, **83**, 490 (1961); J.N. Roitman, D.J. Cram, *J. Am. Chem. Soc.*, **93**, 2225 (1971).
4. H. Gais, J. Volhardt, G. Hellmann, H. Paulus, H.J. Lindner, *Tetrahedron Lett.*, **29**, 1259 (1988); see also reference 1.
5. S. Wolfe, A. Stolow, L.A. LaJohn, *Tetrahedron Lett.*, **24**, 4071 (1983).
6. C.J.M. Stirling, P.J. Thomas, *J. Chem. Soc. Perkin Trans 2*, 1909 (1977).
7. L.M. Stock, *J. Chem. Ed.*, **49**, 400 (1972).
8. C.N. Barry, S.J. Baumrucker, R.C. Andrews, S.A. Evans, Jr., *J. Org. Chem.*, **47**, 3980 (1982).
9. R. Benn, H. Gunther, *Angew. Chem. Int. Ed. Engl.*, **22**, 350 (1983); and also see, H. Kessler, M. Gehrke, C. Griesinger, *Angew. Chem. Int. Ed. Engi.*, **27**, 490 (1988).
10. A.E. Derome, Modern nmr Techniques for Chemistry Research, Pergamon Press Canada, (1987).
11. D.M. Frieze, P.F. Hughes, R.L. Merrill, S.A. Evans Jr., *J. Org. Chem.*, **42**, 2206 (1977).
12. S.A. Khan, J.B. Lambert, O. Hernandez, F.A. Carey, *J. Am. Chem. Soc.*, **97**, 1468 (1975).

13. E.L. Eliel, N.L. Allinger, S.J. Angyal, G.A. Morrison, Conformational Analysis, Interscience Publishers, 1965, pp. 142–145.

14. E.A. Fehnal, *J. Am. Chem. Soc.*, **74**, 1569 (1952); and also see E.A. Fehnal and P.A. Lackey, *J. Am. Chem. Soc.*, **73**, 2473 (1951).

15. V.I. Dronov, V.P. Krivonogov, V.S. Nikitina, *Khim. Geterosikl. Soedin.*, **6**, 335 (1970) (Chem. Abs. **73**, 66363J (1970)); see also P.C. Claus, F.W. Vierhapper, R.L. Willer, *J. Org. Chem.*, **42**, 4016 (1977).

16. M.K. Kaloustian, N. Dennis, S. Mager, S.A. Evans, F. Alcudia, E.L. Eliel, *J. Am. Chem. Soc.*, **98**, 956 (1976). In 8.0 x 10^{-4} M NaOD in CD_3OD–D_2O (40.60 v/v), k_{obs} for **19** is 3.9 x 10^{-4} and for **3**, 1 x 10^{-6} s^{-1}.

17. K. Fuji, Y. Usami, K. Sumi, K. Ueda, K. Kajiwara, *Chem. Lett.*, 1655 (1986).

18. Corrected for comparision on a per–hydrogen basis by multiplying $k_{exch.}$ by the statistical factor of two. To see the origin of this factor note that at any particular instant half of the exchanging hydrogens in **3** (those that are axial at that time) are not in a favourable conformation, *i.e.* the axial hydrogen are not at the bisector of the sulfonyl oxygens.

19. A.J. Kirby. The Anomeric Effect and Related Stereoelectronic Effects at Oxygen, Springer Verlag, Berlin, pp. 78 ff. (1983).

20. A. Padwa, M.W. Wannamaker, *Tetrahedron Lett.*, **27**, 2555 (1986).

21. M.L. Sinnott, *Adv. Phys, Org. Chem.*, **24**, 113–204.

22. PLNM enshrines the idea that those reactions are favoured in which nuclear motions are minimized.[21]

23. F.G. Bordwell, E. Doomes, *J. Org. Chem.*, **39**, 2298 (1974)

24. E.J. Corey, H. Konig, T.H. Lowry, *Tetrahedron Lett.*, 515 (1962).

25. M.D. Brown, M.J. Cook, B.J. Hutchinson, A.J. Katritsky, *Tetrahedron*, **27**, 593 (1971).

26. See for example, T.H. Lowry and S.K. Richardson, Mechanism and Theory in

Organic Chemistry, Harper and Row, New York, 3rd Edition, 1987, pp 209.

27. R.R. Fraser, F.J. Schuber, *J. Chem. Soc., Chem. Commun.*, 1474 (1969).

28. E. Grischkewitsch-Trochimowski, *Chem. Zentr.*, *1*, 1503, (1923).

29. W.T. Murray, J.W. Kelly, S.A. Evans, Jr., *J. Org. Chem.*, *52*, 525 (1987).

30. E.E. van Tamelen, *Org. Synthesis Coll. Vol. IV*, 232, (1963).