Nucleophilic Substitution at Tricoordinate Sulfur

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Contents

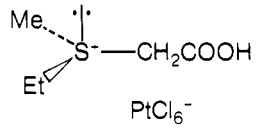
I. Introduction and Scope

This review discusses nucleophilic displacement reactions in organosulfur compounds which have three groups or ligands (excluding the lone pair of electrons) bonded to a sulfur atom of valency four. Some of the more important compounds which fall into this category are the sulfoxides, R_2SO; sulfinyl derivatives, RSOX, e.g., sulfinate esters (X = OR), sulfinamides (X = NH_2), sulfinyl halides (X = halogen), sulfinyl sulfones (X = SO_2R); sulfite esters, $(RO)_2SO$; sulfimides (also termed sulfilimines or iminosulfuranes), R_2S = NX; and sulfonium salts, $R_3S^+X^-$.

The chiral properties associated with the molecular symmetry of such compounds when three different groups are attached to the central sulfur atom have made possible a detailed study of the stereochemical course of nucleophilic substitution at tricoordinate sulfur. One of the most important questions about the mechanisms of such reactions concerns the timing of bond breaking and bond formation in the rate-determining step. Is bond formation complete before bond breaking starts to occur or do both processes occur simultaneously? The former situation would imply the existence of an actual intermediate along the reaction pathway. Tetracoordinate sulfur species have been proposed as intermediates in many nucleophilic displacement reactions at tricoordinate sulfur. Although sulfuranes have not so far been isolated from these reactions, a number of such compounds have been synthesized independently and their structures determined. The present manuscript covers the literature through May 1975.

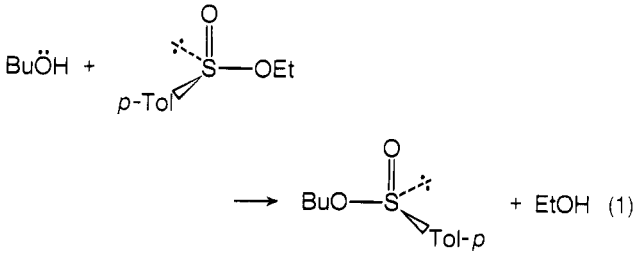
II. Stereochemistry of Substitution

The first resolution of optically active sulfur compounds was reported in 1900 by Pope and Peachey[1] and by Smiles[2] who isolated sulfonium salts as their D-camphorsulfonates or hexachloroplatinates **1**. The earliest evidence of the stereochemical

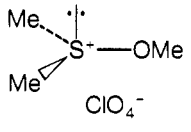


1

course of substitution comes from Phillips' resolution of sulfinates into enantiomers.[3] He showed that transesterification of (−)-ethyl *p*-toluenesulfinate with 1-butanol gives (+)-*n*-butyl *p*-toluenesulfinate of opposite configuration. Although no kinetic evidence was obtained, this observation suggests that nucleophilic substitution in these compounds involves a Walden-type inversion (eq 1).



Many of the stereochemical transformations of sulfoxides and related compounds involve conversion to a sulfonium salt. Dimethyl sulfoxide is known to form both O-alkyl and S-alkyl derivatives, e.g., dimethylmethoxysulfonium perchlorate (**2**) and trimethyloxosulfonium iodide (**3**). Smith and Winstein showed



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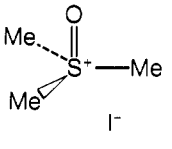
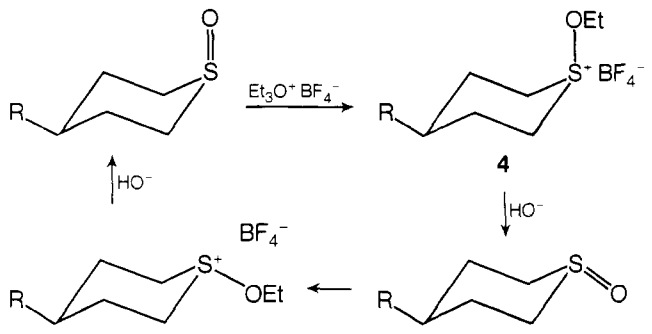


3

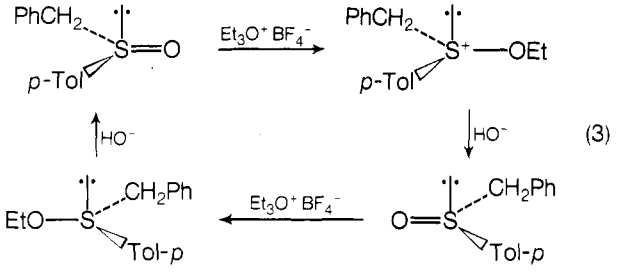
that O-alkyl derivatives were rapidly hydrolyzed by alkaline solution whereas the S-alkyl salts are inert to such treatment.[4]

Johnson and his co-workers were the first to show that the alkalie hydrolysis of an alkoxysulfonium salt is accompanied by inversion.[5,6] Alkylation of *cis*-4-*p*-chlorophenylthiane 1-oxide with triethyloxonium tetrafluoroborate gave the ethoxysulfonium ion **4** which on alkaline hydrolysis gave the trans sulfoxide.



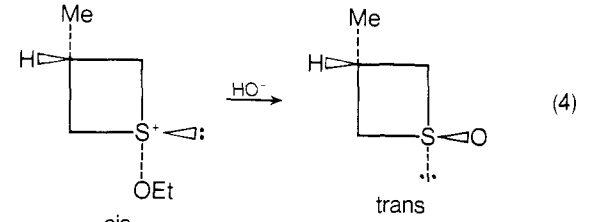
(2)

Repetition of alkylation and hydrolysis gave back the starting material to complete this totally achiral Walden cycle (eq 2). Similar behavior was obtained with optically active benzyl *p*-tolyl sulfoxide (eq 3). The base-catalyzed hydrolyses of both *cis*- and



(3)

trans-1-ethoxy-3-methylthietanium ions also proceed with complete inversion[7] (eq 4 and 5). This observation is of con-



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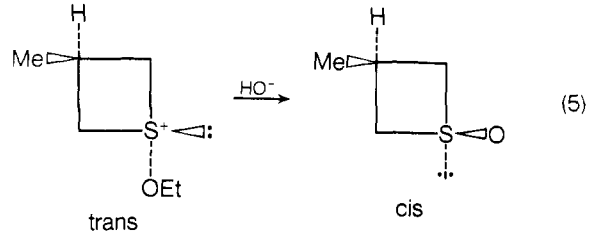
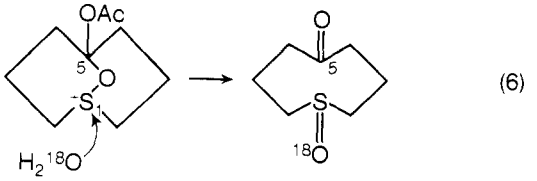


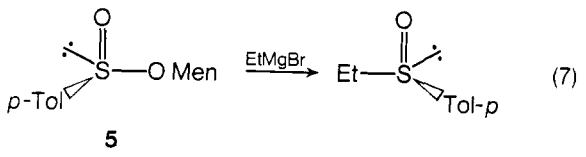
(5)

siderable mechanistic importance and is discussed further in section X. Another striking example of inversion in an alkoxysulfonium ion has been observed in the solvolysis of 5-acetoxy-9-oxa-1-thioniabicyclo[3.3.1]nonane perchlorate.[8] After hydrolysis in oxygen-18 labeled water, the oxygen in position 1 had completely exchanged with the solvent whereas the oxygen in position 5 was not enriched at all. This suggests backside attack at S-1, frontside attack being prevented by the oxygen bridge (eq 6).



(6)

The first stereospecific synthesis of sulfoxides was reported by Andersen[9] who showed that the reaction of sulfinic esters with Grignard reagents occurs with inversion on configuration (eq 7). Andersen and his co-workers[10] synthesized a number of



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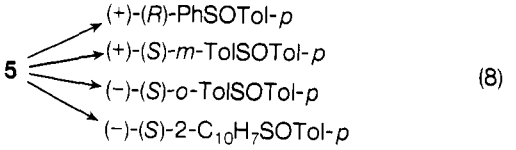
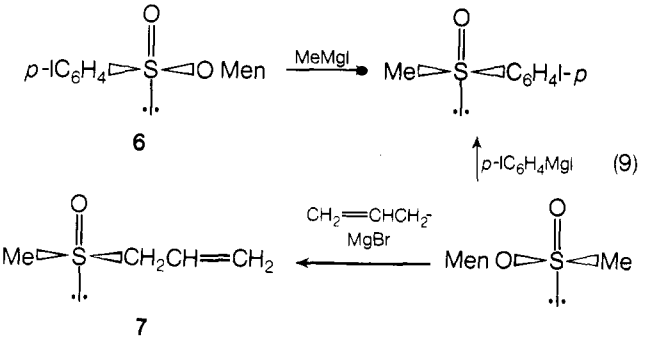
sulfoxides from (−)-methyl *p*-toluenesulfinate (**5**) by this method, the reaction always proceeding with inversion (eq 8) although



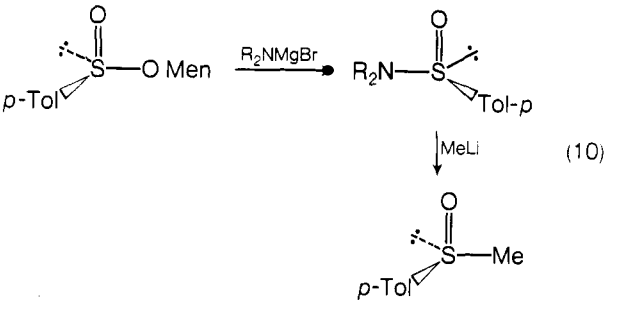
(8)

the configurational symbol may be *R* or *S* depending on the order of priority of the aryl groups. Originally the configurations of reactants and products were deduced from ORD and cd curves, and from tentative structural assignments which had been made to sulfinates and sulfoxides. The absolute configurations of sulfoxides and sulfinates were subsequently linked by Mislow and his co-workers[11] using stereochemical cycles involving an odd number of Grignard reactions and related to those of sulfoxides whose structures had been determined crystallographically. Thus **6** and **7** of known absolute and opposite configura-



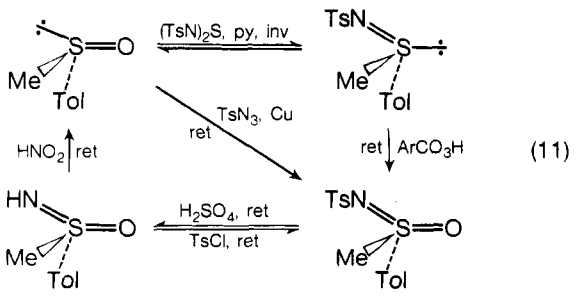
(9)

tions were related by the series of reactions shown in eq 9. The conversion of optically active methyl *p*-toluenesulfinate into the corresponding sulfinamide and the subsequent conversion of the sulfinamide into sulfoxide both proceed with inversion at sulfur[12,13] (eq 10).



(10)

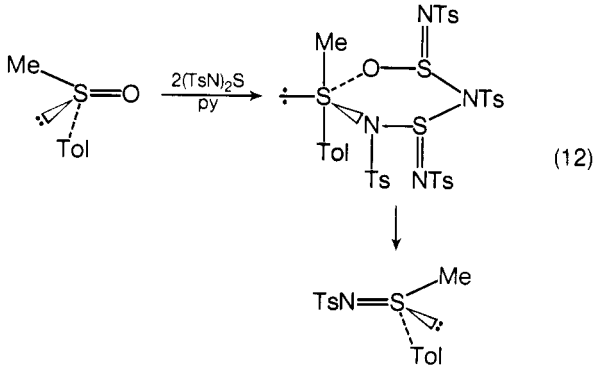
Several different groups of investigators[14-21] have shown that the conversion of sulfoxides to sulfimides proceeds with inversion at sulfur. Cram and his co-workers[14-18] established the stereochemical relationships of the complete sulfoxide–sulfimide–sulfoximide cycle (eq 11) for open-chain sulfoxides. A new



(11)

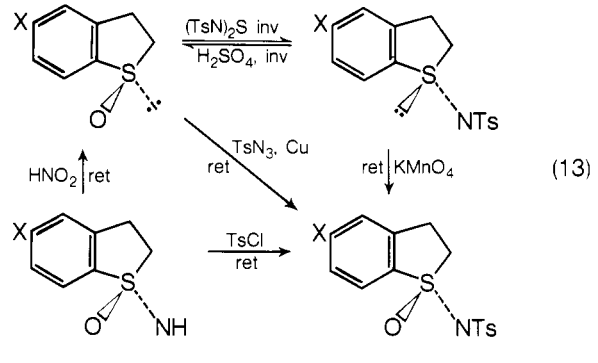
terminology was introduced[21,22] to describe stereochemical cycles; that shown in eq 11 would be termed a diligostatic cycle since two ligands (the tolyl and methyl groups) are common to all members of the cycle.

Both Cram and his co-workers[16] and Milow[23] have discussed in detail the possible geometries of the transition states or intermediates which might arise from nucleophilic substitution at tricoordinate (tetrahedral) sulfur. It has been generally assumed that such intermediates would resemble a trigonal bipyramid (rather than a square pyramid) since all tetracoordinate sulfur species of known structure have approximately this shape. The inversion of configuration observed in the sulfoxide–sulfimide conversion (eq 11) could arise from a trigonal-bipyramidal intermediate with an axial–axial (a,a) or equatorial–equatorial (e,e) arrangement of entering and leaving groups. The conversion in pyridine was found to be second order in bis(*N*-tosylsulfurdiimine). Cram and his co-workers[16] therefore proposed a trigonal-bipyramidal intermediate or transition state in which the



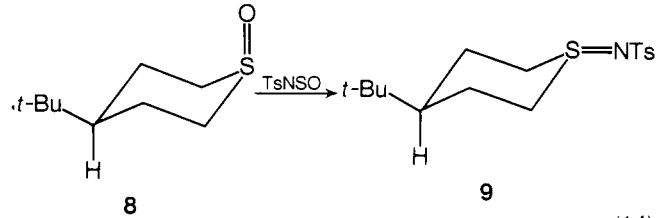
(12)

entering and leaving groups occupy equatorial positions (eq 12). The ring structure connecting the entering and leaving groups would have difficulty in accommodating the alternative a,a mechanism. Inversion was also observed in the conversion of a cyclic sulfoxide into a cyclic sulfimide[18] (eq 13).



(13)

Similar stereochemical results have been reported by Johnson and Rigau[20] for the conversion of 4-*tert*-butylthiane (**8**) into the *N*-*p*-toluenesulfonylsulfimide (**9**) which was assigned the trans structure (eq 14). In yet another stereochemical cycle (eq 15)



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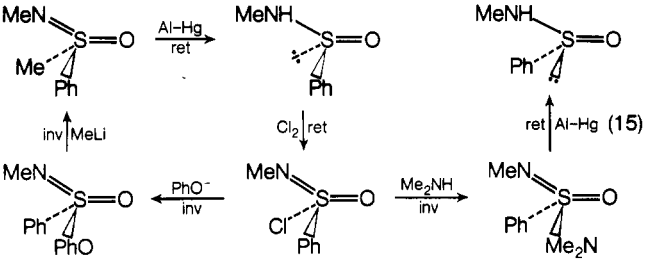
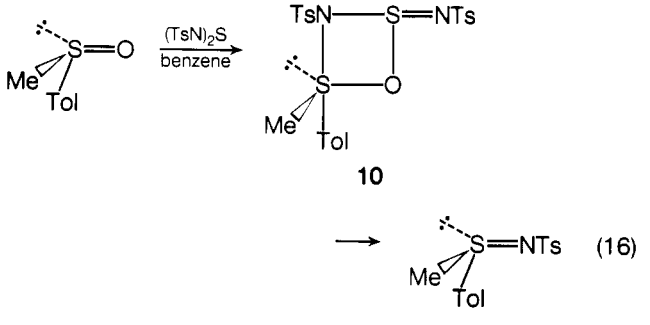
(14)

Johnson and Jonsson[24] confirmed that substitution at sulfur occurs generally with inversion while chlorination and reduction occur with retention.



While all the examples discussed so far have involved inversion of configuration accompanying nucleophilic substitution at sulfur, several examples of substitution with retention have been reported. Oae and his co-workers[25] found that chiral aryl benzyl sulfoxides labeled with oxygen-18 exchanged oxygen with dimethyl sulfoxide while racemization was only just detectable (see section III). Christensen and Kjaer[26] also reported that the conversion of *N*-phthaloylmethionine sulfoxide to the corresponding sulfimide with *N*-sulfinyl-*p*-toluenesulfonamide in benzene occurred with retention of configuration. In a more general study Christensen[27] subsequently showed that the reactions of both methyl tolyl and methyl butyl sulfoxide with $(TsN)_2S$ in benzene proceed with retention of configuration. On the other hand, in pyridine the latter sulfoxide forms a sulfimide with inversion in accordance with Cram and Day's observations[15] for that solvent. Christensen proposed that the reaction in benzene proceeds via a four-center transition state **10** analogous



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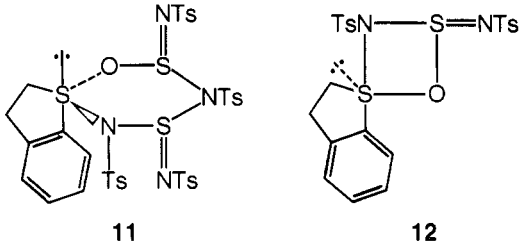
(16)

to that proposed for the Wittig reaction[28] in which incoming and outgoing groups occupy e,a positions (eq 16).

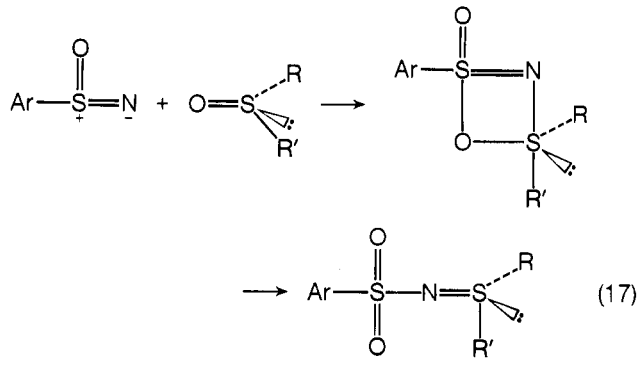
Consistent with this mechanism, the sulfoxide ⇌ sulfimide conversion in benzene was found to be first order in TsNSO in contrast to the second-order dependence observed in pyridine (loc. cit.). The proposed trigonal-bipyramidal intermediates for the conversion of cyclic sulfoxides into cyclic sulfimides in pyridine (e,e inversion mechanism) and benzene (e,a retention mechanism) are shown in **11** and **12**. It is interesting to note that



11 12

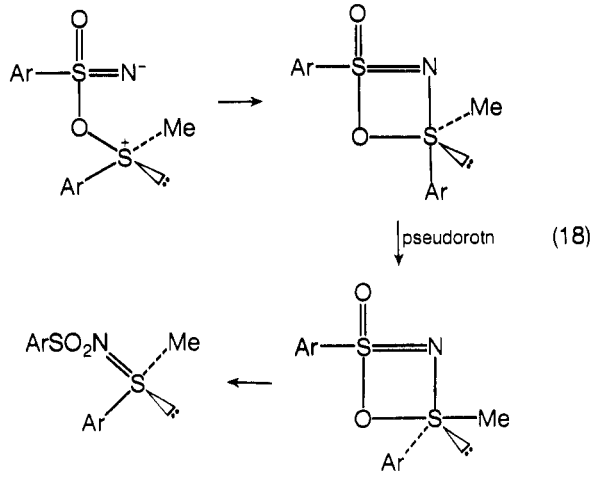
in both solvents, the cyclic systems reacted 50–100 times faster than the acyclic analogues.[18] Similar kinetic acceleration has been observed for phosphorus heterocycles.[29] Strain associated with the five-membered ring will be relieved by the decrease in the C–S–C bond angle in passing from a tetrahedral to a trigonal-bipyramidal arrangement.

A four-membered cyclic intermediate has also been proposed to explain the retention of configuration observed in the conversion of a sulfoxide into a sulfimide using *p*-toluenesulfinylnitrene (eq 17) in acetonitrile as solvent.[30] This mechanism is



(17)

clearly analogous to that proposed by Christensen[27] and by Cram et al.[16] for the sulfoxide → sulfimide interconversion in benzene. Maricich and Hoffman[30,31] have suggested that an alternative to this a,e mechanism is one in which both axial attack and expulsion occur via pseudorotation (eq 18), although Tang and

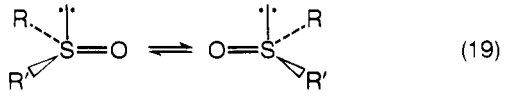


(18)

Mislow[7] have concluded from experiments with thietanium salts that pseudorotation in cyclic sulfurane intermediates is probably much slower than in the corresponding phosphorus analogues (see section X).

III. Sulfoxides

The reactions which establish that nucleophilic substitution at the sulfinyl sulfur of sulfoxides generally occurs with inversion of configuration have been discussed in the previous section. The detailed mechanisms of the interconversion of stereoisomeric sulfoxides by a variety of chemical methods form the major part of this section. Racemization may also be brought about by both thermal[32-34] and photochemical methods.[35] Thermal stereomutation may occur either by a simple pyramidal inversion (eq 19), a homolytic dissociation mechanism,[33] or a



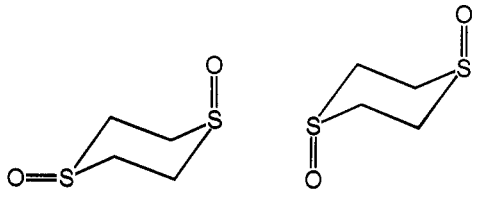
(19)

cyclic rearrangement.[36] Photochemical racemization probably takes place predominantly by pyramidal inversion although other concurrent mechanisms have been proposed.[37]

A. Racemization and Related Reactions

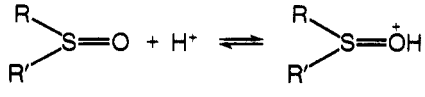
1. Acid and Halide Ion Catalysis

Mislow has shown that the racemization of many simple sulfoxides, e.g., methyl *p*-tolyl sulfoxide, takes place quite rapidly at room temperature in concentrated hydrochloric acid.[38] No racemization, however, could be detected after 11 days using hydrofluoric acid. With other mineral acids such as hydrobromic and hydriodic acid, reduction of the sulfoxide to sulfide accompanies racemization. Some sulfoxides are even decomposed by hydrochloric acid. Thus Bell and Bennett[39] attempted to convert *cis*-1,4-dithiane to the trans isomer and obtained only 1,3-dithiane. This interconversion, now known[40] to involve interconversion of the axial–equatorial isomer **13** to the diaxial structure **14**, can, however, be effected at room temperature using hydrofluoric acid.[41]



13 **14**

The concurrent reduction, racemization and oxygen-exchange rections of sulfoxides have been studied by several groups of workers.[38,42-44] All these reactions are considered to involve a common preequilibrium protonation of the sulfoxide (eq 20)



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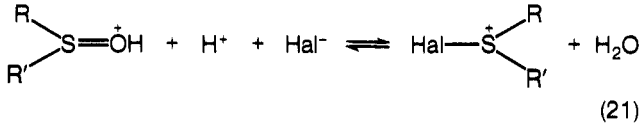
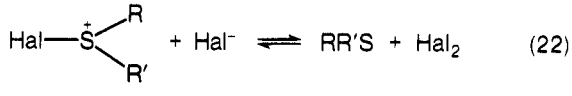


(21)

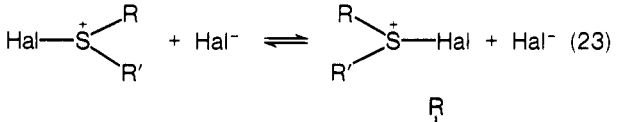
followed by the formation of a halosulfonium ion intermediate (eq 21). The halosulfonium ion may be reduced to sulfide by a second halide ion (eq 22). The position of equilibrium of eq 22



(22)

determines whether reduction or racemization will predominate. For the reaction of sulfoxides with iodide ion, this equilibrium is shifted to the right and reduction is observed. On the other hand, for reaction with chloride and bromide ions, equilibrium 22 is usually shifted to the left, leading to predominant racemization and oxygen exchange.

Racemization can occur not only by reversal of eq 22 but by various other processes such as rapid halogen exchange (eq 23) or through the formation of a dihalide intermediate (eq 24)



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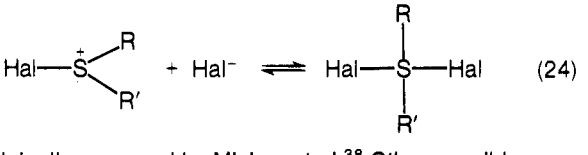
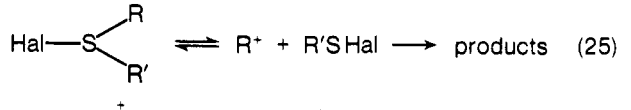


(24)

as originally proposed by Mislow et al.[38] Other possible competing reactions include carbon–sulfur bond cleavage (eq 25 and



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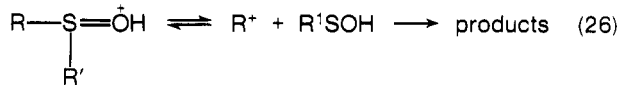

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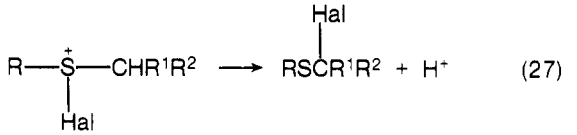


(27)

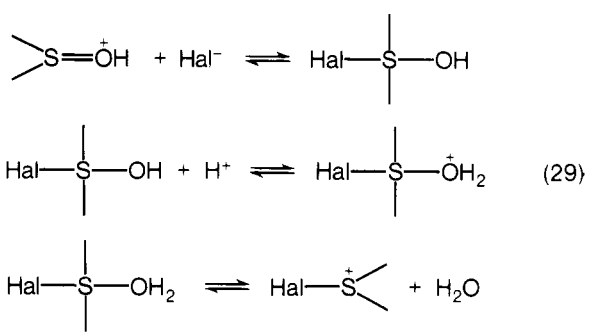
26) or a Pummerer rearrangement (eq 27).

Elucidation of the various reaction pathways requires a knowledge of the acid–base equilibria of sulfoxides. Landini et al.[45] showed that the protonation of sulfoxides follows the H_A acidity function rather than H_0. On the basis of NMR spectroscopy in "superacids" Olah and his co-workers[46] proposed that the protonation of sulfoxides occurs on sulfur. It is still generally considered, however, that under normal racemization conditions, protonation of sulfoxides occurs on oxygen.[47]

The rates of both the reduction and racemization of sulfoxides are first order in both halide ion and sulfoxide concentration[43,44,48] except for the special case of certain sulfinyl carboxylic acids.[42] The stoichiometric equation for reduction is

$$RR^1SO + 2H^+ + 2I^- \rightarrow RR^1S + H_2O + I_2 \qquad (28)$$

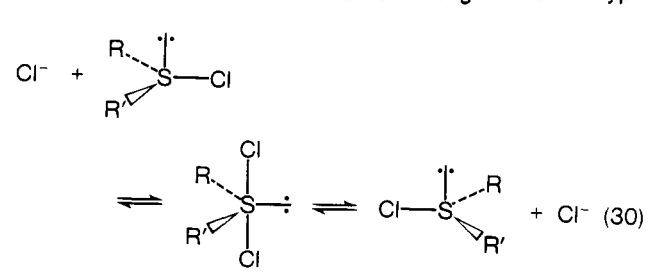
The dependence of reaction rate on acid concentration has been the cause of some confusion. Sulfoxides are moderately basic substrates (e.g., for *p*-nitrophenyl methyl sulfoxide, $pK_a = -2.9$[43]) and will be protonated to a considerable extent in 5.0 M acid. Modena and his co-workers[43] found that log k_p (where k_p is the first-order rate coefficient for reaction of the protonated substrate) for the reduction of several sulfoxides varied in a linear fashion with H_A (slope ~1.5). The high slopes observed were attributed to the involvement of two protons. Support for this view is provided by the high values of ϕ (Bunnett–Olsen) and by Kruger's observation of a second-order dependence on hydrogen ion concentration for the reduction of dimethyl sulfoxide by iodide ion in aqueous DMSO solvent.[49] These observations are consistent with a mechanism (eq 29) involving rate-determining



(29)

formation of a halosulfonium ion and where the second halide ion implicated by eq 28 intervenes after the rate-determining step. Landini et al.[50] have suggeted that in some cases general acid rather than specific hydrogen ion catalysis may occur. The way in which both the racemization and reduction reactions of sulfoxides have a common rate-determining step and only differ subsequently at the product-determining stage is illustrated by the similarity in the order of reactivity of halide ions toward sulfoxides (I > Br > Cl) with that for attack at other sulfinyl centers, e.g. for sulfinyl sulfones.[51]

Mislow and his co-workers[38] originally proposed that the hydrochloric acid catalyzed racemization of sulfoxides occurs through the reversible formation of a sulfur dichloride intermediate (eq 24). This can be formulated as a trigonal-bipyramidal intermediate, **15**, in the interconversion of one enantiomeric chlorosulfonium ion to its enantiomer through a Walden-type

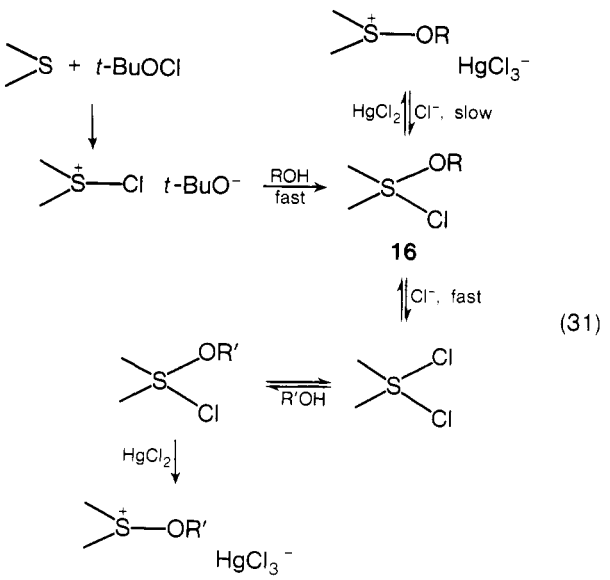


(30)

15

inversion (eq 30). Alternatively chloride ion exchange among ion pair intermediates could also lead to racemization.

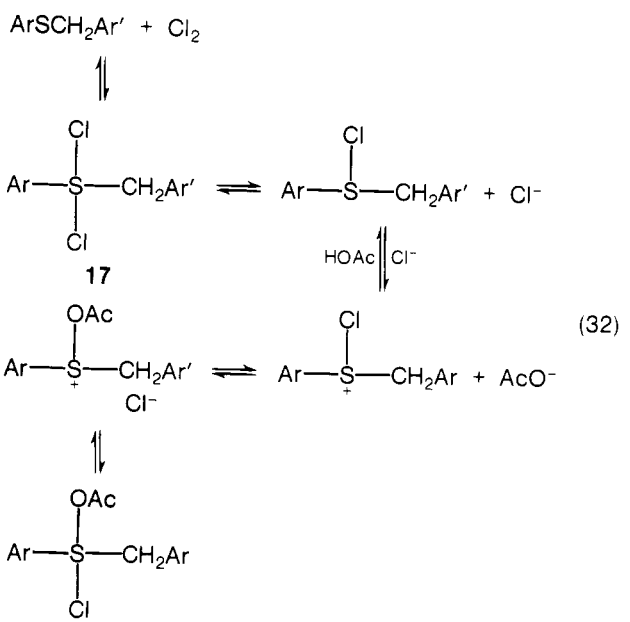
There is now a considerable body of evidence which supports the existence of tetracoordinate sulfur intermediates proposed in eq 29. On the basis of an NMR study, Johnson and Rigau[52] proposed a tetracoordinate structure for the alkoxysulfonium chloride intermediate **16** formed in the oxidation of sulfoxides by *tert*-butyl hypochlorite (eq 31). In a related study, Kwart et



(31)

16

al.[53,54] proposed that the chlorinolysis of sulfides in acetic acid proceeds through a tetracoordinate intermediate **17** which is in equilibrium with several sulfonium ion pairs (eq 32).



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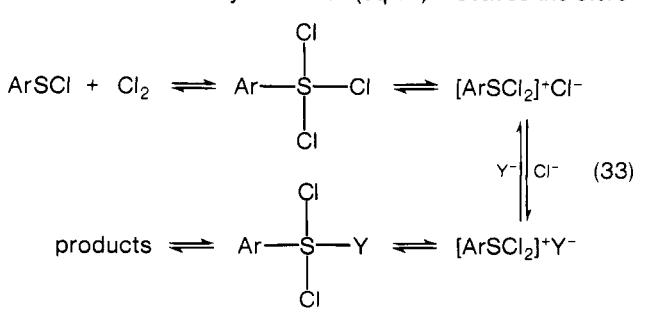
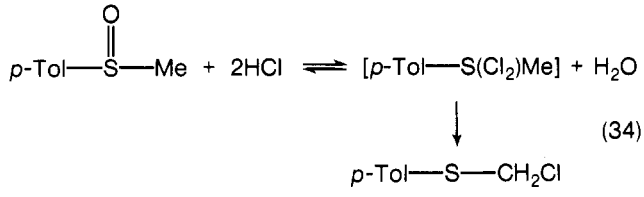
17

Kwart and Givens[55] also proposed multiple equilibria between sulfonium ions and tetracoordinate sulfur species for the chlorination of arenesulfenyl chlorides (eq 33). Because the stere-



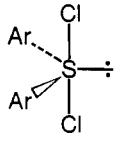
(33)

omutation of sulfoxides and the chlorinolysis of sulfides differ markedly in their dependence of the water content of the solvent, Kwart and Omura[56] suggested that the hydrochloric acid-catalyzed stereomutation of sulfoxides could occur through a 1,1-dihydroxy sulfide intermediate without formation of a chlorosulfonium ion. Further support for the idea of a dichloride intermediate in the racemization of sulfoxides, however, comes from the observation that the products of chlorination of sulfides can be obtained by treatment of sulfoxides with hydrochloric acid in the presence of molecular sieve to force the equilibrium in a favorable direction[57] (eq 34).



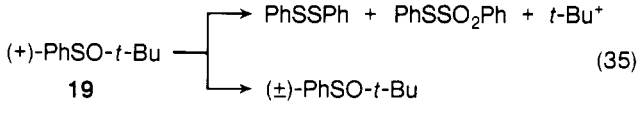
(34)

It is interesting to note that Maner et al.[58] have shown by X-ray analysis that the chlorine complex of bis(p-chlorophenyl) sulfide has the trigonal-bipyramidal structure **18**, analogous to that proposed by Mislow and his co-workers[38] for the dichloride **15**.



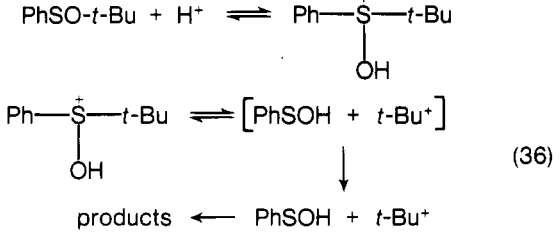
18

Anomalous behavior is shown by *tert*-butyl phenyl sulfoxide (**19**). This undergoes both racemization and cleavage (cf. eq 26) in aqueous perchloric acid[59] (eq 35).



(35)

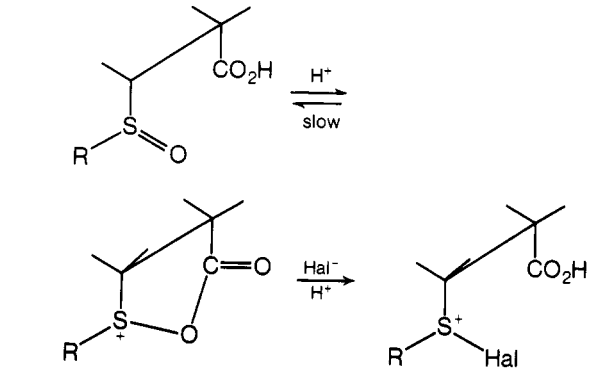
Experiments with oxygen-18 labeled **19** and (R_S,R_C)-phenylethyl phenyl sulfoxide showed that racemization at sulfur does not occur via oxygen exchange and is accompanied by partial racemization o the carbon chiral center. Modena and his coworkers preferred a sulfenic acid–ion pair mechanism (eq 36) rather than the alternative alkyl group migration mechanism.



(36)

2. Neighboring Group Effects

Several examples of neighboring carboxyl group effects on the reduction and racemization of sulfoxides have been reported.[60-65] Allenmark and his co-workers showed that while the racemization of (+)-methyl *p*-tolyl sulfoxide is first order in halide ion concentration, (+)-3-benzylsulfinylbutyric acid behaves quite differently, and its racemization becomes independent of the nature or concentration of the nucleophile at quite low halide ion concentrations. This was attributed to the formation of a cyclic acyloxy sulfonium ion intermediate which can subsequently undergo either reduction or racemization (eq 37). Two different mechanisms have been proposed to explain this anchimeric assistance[62,66] (eq 38).



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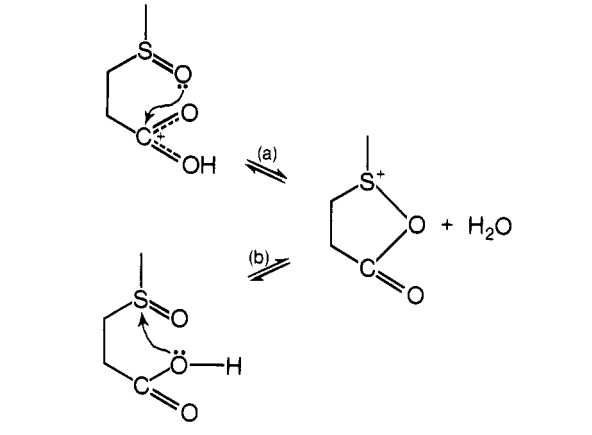


(38)

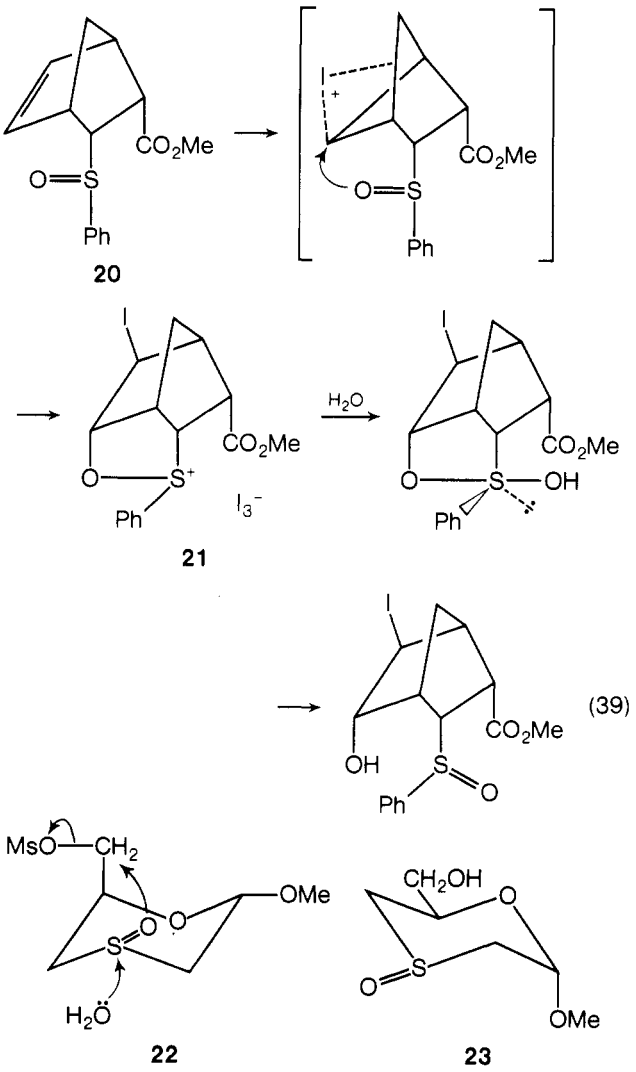
As well as a difference in dependence on halide ion concentration, Landini et al.[66] showed that *o*-methylsulfinylbenzoic acid is reduced (I^-) or racemized (Br^- or Cl^-) about 10^3–10^4 times faster than the corresponding methyl ester. Moreover, oxygen exchange of the sulfinyl atom is faster than racemization in the presence of halide ions, and no exchange occurs at the carboxy group.[67] This is consistent with a mechanism of intramolecular catalysis involving nucleophilic attack at sulfinyl sulfur by the carboxyl group eq 38, path b.

Exo-electrophilic attack of I^+ on the double bond of sulfoxide **20** is followed by intramolecular attack of the sulfinyl oxygen at the 5-endo position to form the sulfoxonium salt **21** which can be isolated[68] (eq 39). Hogeveen et al.[68] suggested that nucleophilic substitution at the sulfur atom of **21** proceeds via a trigonal-bipyramidal intermediate in which entering and leaving groups occupy axial positions leading to inversion of configuration at sulfur. Similar inversion was obtained with esters in the exo series.[69]

Another example of neighboring group participation by a sulfinyl group leading to inversion is found in derivatives of 1,4-oxathiane 5-oxide.[70] Intramolecular displacement by the sulfinyl oxygen of **22** followed by attack of water on the resulting sulfoxonium salt gives the sulfoxide **23** of inverted configuration.

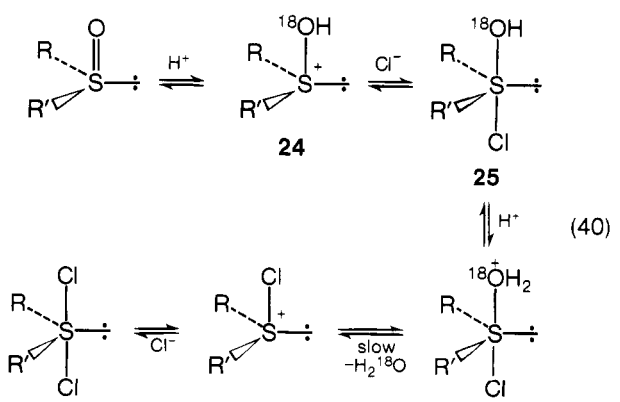
3. Oxygen Exchange

Mislow and his co-workers[38] were the first to show that the rate of oxygen-18 exchange (k_{ex}) was identical with the rate of racemization (k_{rac}) of phenyl *p*-tolyl sulfoxide in aqueous hy-



(39)

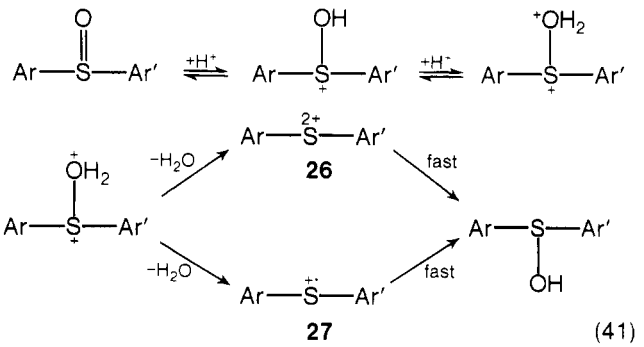
drochloric acid. A similar ratio was found for the hydrochloric acid catalyzed racemization of oxygen-18 labeled phenyl *p*-tolyl sulfoxide.[71] The hydrochloric acid catalyzed oxygen exchange of sulfoxides proceeds at least ten times faster than that catalyzed by other mineral acids and is itself accelerated by added chloride ion.[72] Several groups of workers have reported a linear dependence of k_{rac} on h_0 for various sulfoxides in hydrochloric acid[43,71,72] suggesting a mechanism (eq 40) in which the rate-



(40)

determining step involves unimolecular sulfur–oxygen bond cleavage. Reversal of all the steps (and combination with H_2O) leads to both racemization and oxygen exchange.

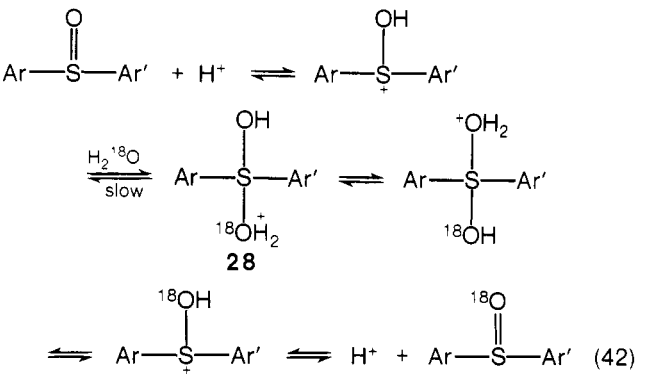
The oxygen exchange and racemization of sulfoxides proceeds by two different mechanisms in sulfuric acid. In 96% sulfuric acid, $k_{ex}/k_{rac} \simeq 1$, k_{rac} correlates well with h_A, and the entropies of activation are positive or very small negative values.[73-75] These observations are consistent with an A-1 mechanism involving S–O bond fission, where each oxygen exchange causes racemization. Two possible routes involving either a dication **26** or a radical cation intermediate **27** have been



(41)

considered. Although no ESR signals could be detected from solutions of diphenyl sulfoxide in concentrated sulfuric acid,[74,76] they have been observed for solutions of para-substituted diphenyl sulfoxides with good electron-releasing groups; this fact tends to lead support to the radical-chain mechanism.

In less concentrated sulfuric acid concurrent oxygen exchange and racemization still take place, but k_{rac} no longer correlates with H_A and the ratio k_{ex}/k_{rac} becomes approximately 0.5.[75,77] An A-2 type of mechanism was proposed (eq 42) in which the



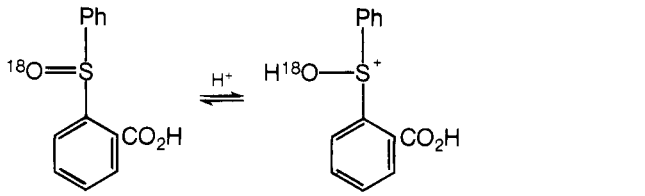
(42)

rate-determining step involves nucleophilic attack on the conjugate acid by a water molecule and every exchange would result in inversion at sulfur. In the presence of chloride ion, the conjugate acid **24** will react primarily to form **25** rather than **28**. A gradual changeover in mechanism from A-1 to A-2 occurs with decreasing sulfuric acid concentration. Associated with this change, values of $\Delta S^{\ddagger}$ become more negative and the value of k_{ex}/k_{rac} falls from 1.0 to 0.5.[75]

An interesting exception to the above generalization is provided by the oxygen-exchange reaction of optically active *o*-carboxyphenyl phenyl sulfoxide (**29**), which proceeds in 65.7% sulfuric acid about 10^4 times faster than that of racemization which is the same order of magnitude as that of both the oxygen exchange and racemization of the corresponding meta- and para-substituted diphenyl sulfoxides.[78,79] The high rate of exchange of **29** is attributed to neighboring group participation by the *o*-carboxy group forming a cyclic acyloxysulfonium ion **30** which on subsequent attack by water forms the original sulfoxide. Thus the whole process leads to net retention of configuration by a double inversion (eq 43).

The racemization of the *o*-carboxylphenyl phenyl sulfoxide is not assisted by the neighboring carboxyl group, and Oae and his co-workers[79] suggest that the rate-determining step for this process involves slow heterolysis of the cyclic ion **30**. The oxygen exchange and racemization of sulfoxides are also catalyzed by carboxylic aids such as chloro-substituted acetic acids,[80] trifluoroacetic acid[81] and phosphoric acid.[82]

Oae and his co-workers have carried out extensive studies of the reactions of sulfoxides with acetic anhydride.[83-86] De-



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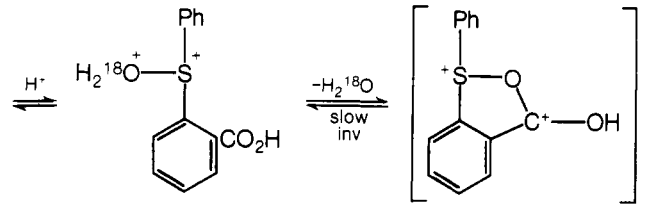

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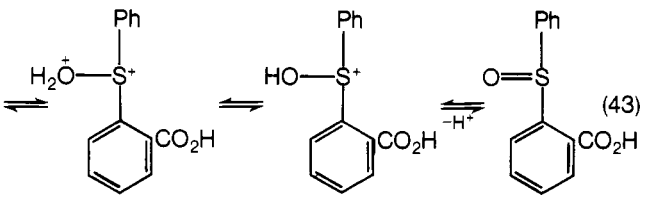
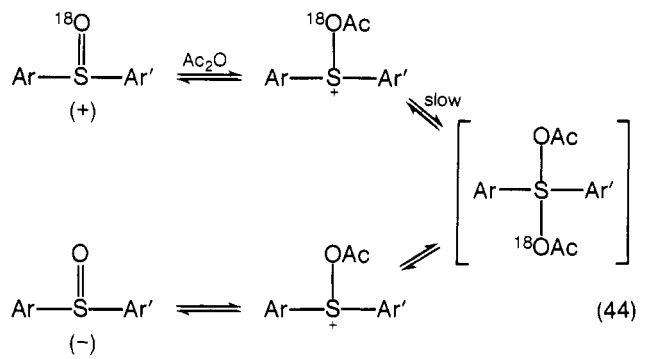


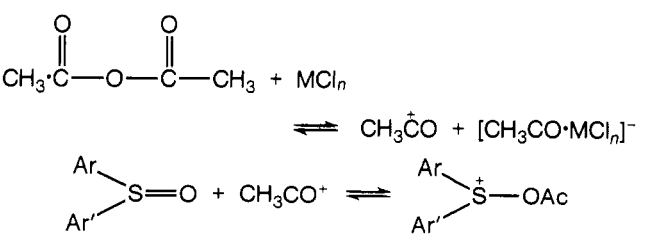
(43)

pending on the conditions used, three different reactions may occur: (a) oxygen exchange, (b) racemization, and (c) Pummerer rearrangement. In acetic acid–dioxane solvent the rate of racemization of sulfoxides is first order in both acetic anhydride and sulfoxide concentration, and $k_{rac}/k_{ex} \sim 0.5$ suggesting a rate-determining Walden inversion at sulfur (eq 44).

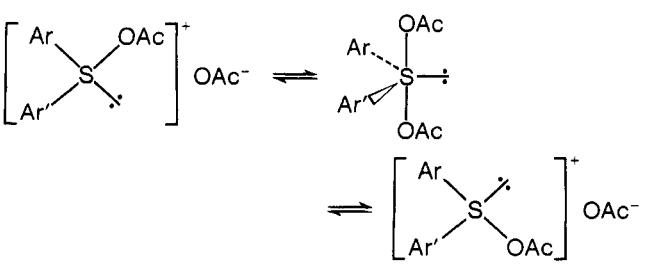


(44)

The racemization of sulfoxides in acetic anhydride is also catalyzed by Lewis acids[87,88] such as $AlCl_3$ which facilitates the formation of an incipient acetylium ion:

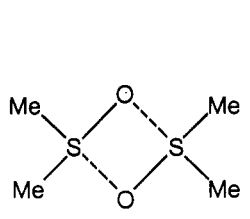


Racemization then occurs as in acetic acid by exchange of acetate groups through a symmetrical intermediate:



When racemization is carried out in the presence of small amounts of both acetic acid and a Lewis acid, k_{ex}/k_{rac} becomes unity[86] as it does in very concentrated sulfuric acid[74] suggesting an A-1 type mechanism. The oxygen-exchange and racemization of sulfoxides in phosphoric acid[82] and dinitrogen tetroxide[86] are also thought to follow such a mechanism.

Sulfoxides are known to be associated, e.g., dimethyl sulfoxide as in **31**, and the oxygen exchange of aryl benzyl sulfoxides with dimethyl sulfoxide was attributed to bimolecular attack within the associated structure. A trigonal-bipyramidal intermediate **32** in which entering and leaving groups occupy a,e positions was suggested to explain the observed retention of configuration.[25]



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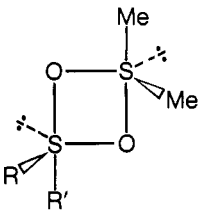
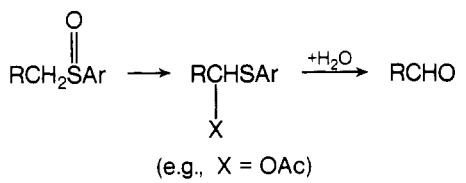


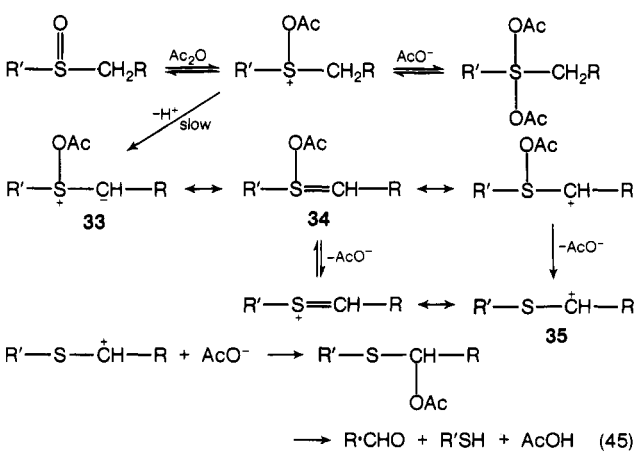
32

4. Pummerer Reaction

Sulfoxides containing α-hydrogen atoms are converted by acids, anhydrides, and acyl halides[89,90] to α-substituted sulfides which give aldehydes on hydrolysis.



Various α-hydroxy acid derivatives can be synthesized by this reaction. In acetic acid the rapidly formed acyloxysulfonium ion undergoes a rate-determining proton removal to form the sulfonium ylide **33**. This in turn collapses to the ylene **34** from which the carbonium ion **35** is generated (eq 45).[91-97]



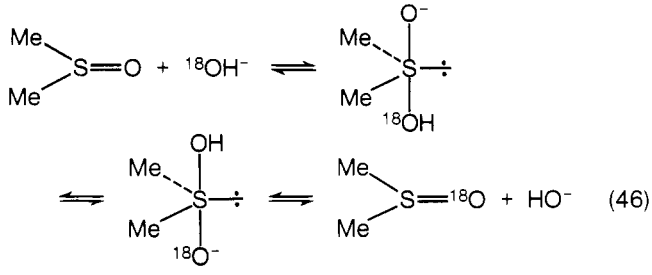
(45)

5. Base Catalysis

Dimethyl sulfoxide readily exchanges oxygen completely with potassium *tert*-butoxide-^{18}O after 10 min under reflux.[98] Exchange was also observed for di(*n*-butyl), *p*-tolyl methyl, and diphenyl sulfoxides. Exchange occurs, however, less readily for this latter group of sulfoxides, suggesting a dependence on the steric bulk of groups attached to the central sulfur atom which is consistent with a mechanism involving nucleophilic displacement at that center.

Dimethyl sulfoxide will also undergo oxygen exchange in aqueous alkaline solution although much more vigorous conditions are needed, e.g., 4–5 h at 150° with excess potassium

hydroxide.[98] A simple nucleophilic displacement mechanism has been suggested (eq 46). *p*-Methoxyphenyl methyl sulfoxide-^{18}O also undergoes slow oxygen exchange although di(*n*-butyl), *p*-tolyl methyl, and diphenyl sulfoxides will not do so under such conditions. Many other optically active sulfoxides will not racemize even under strongly basic conditions with potassium *tert*-butoxide in *tert*-butyl alcohol or dimethyl sulfoxide at 60–135 °C.[99–101]

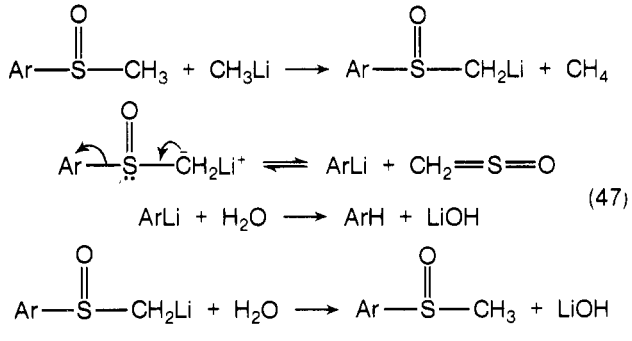


(46)

B. Other Reactions

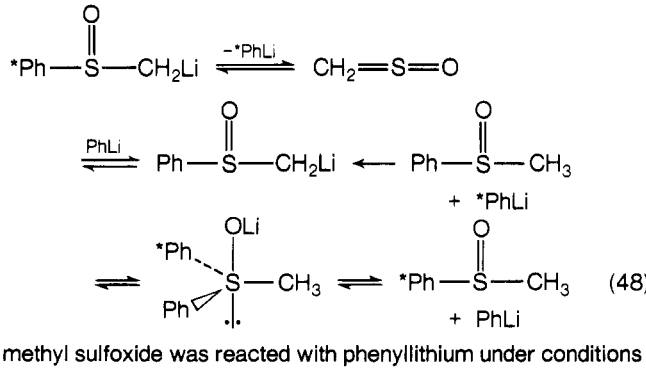
1. With Lithium Alkyls and Aryls

Although many sulfoxides cannot be racemized under strongly basic conditions, Mislow and Jacobus[102] showed that the reaction of chiral sulfoxides containing labile α-hydrogens, e.g., aryl methyl sulfoxides, with methyllithium in dimethoxyethane at room temperature followed by hydrolysis leads to the formation of partially racemic sulfoxide and an arene. The first step in the reaction is thought to be proton abstraction to form an arenesulfinylmethide ion from which methylenesulfine is subsequently eliminated (eq 47). Mislow attributed the lack of any



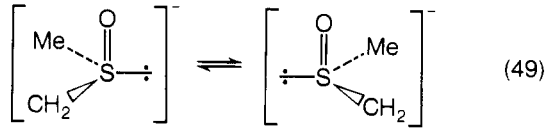
(47)

direct evidence of a sulfine intermediate in this reaction to its exceptional reactivity with methyllithium.[103] An addition–elimination mechanism was ruled out for the above reaction because methyl phenyl sulfoxide can be recovered undiluted in carbon-13 from the reaction of $^{13}CH_3SOPh$ with $^{12}CH_3Li$. This mechanism, however, does provide a minor route for the reaction of phenyllithium with aryl methyl sulfoxides (eq 48). When phenyl-^{14}C methyl sulfoxide was reacted with phenyllithium under conditions which led to 50% racemization, the recovered sulfoxide had lost 11% of its enrichment.



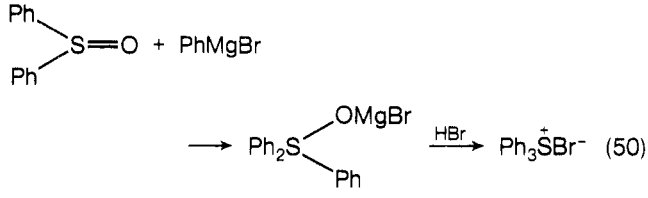
(48)

As an alternative to the sulfine mechanism, arenesulfinylmethide ions might undergo relatively rapid pyramidal inversion and could therefore racemize much more easily than the corresponding sulfoxides (eq 49). Mislow has suggested that for those sulfoxides for which racemization cannot be observed under basic conditions,[99–101] the concentration of sulfinylmethide ions in protic solvents is too low to permit racemization at sulfur but sufficiently high to allow deuterium exchange on the α carbon.



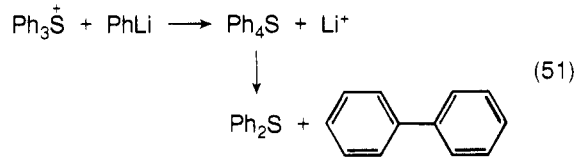
(49)

When an ethereal solution of phenyl sulfoxide was heated with phenyllithium, phenyl sulfide (87% yield) and biphenyl (65%) were the main products.[104] The corresponding reaction with *p*-tolyl sulfoxide produced *p*-tolyl sulfide (66%), *p,p'*-bitolyl (31%), and *m,p'*-bitolyl (26%). Originally it was suggested that an arylsulfonium ion might be an intermediate in this reaction since such species are formed in the reaction between diphenyl sulfoxide and phenylmagnesium bromide (eq 50).



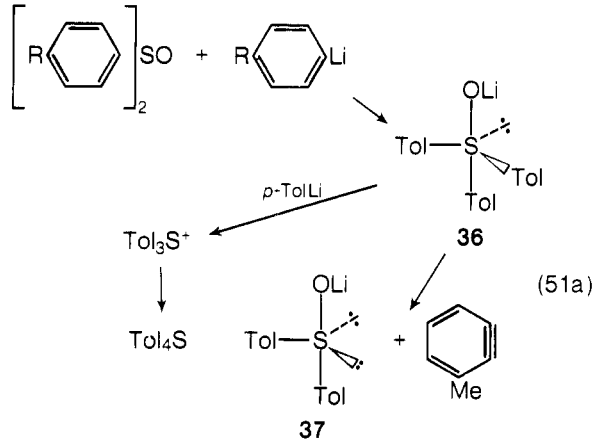
(50)

The reaction of triarylsulfonium salts with aryllithiums has been the subject of some controversy (see section X). It is now generally accepted[105,106] that the major pathway for this reaction involves breakdown of a tetraarylsulfurane (eq 51). Andersen



(51)

and his co-workers[106] have reached the same conclusion for the reaction of diaryl sulfoxides with an aryllithium. The initially formed intermediate **36** can react with *p*-tolyllithium to form the triarylsulfonium ion and subsequently the tetraarylsulfurane which can decompose as in eq 51. Alternatively **36** could form



(51a)

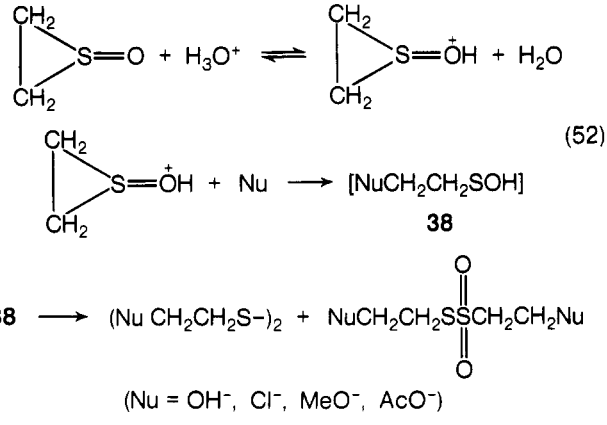
37

the unusual species **37** and 4-toluyne. In a reinvestigation of this problem Andersen and his co-workers[106] could detect only a small amount of *m,p'*-biolyl (~5%), indicating that the latter mechanism provides only a minor route to the product.

2. Cyclic Sulfoxides

The fragmentation reactions of acyclic sulfoxides have their counterpart in cyclic sulfoxides like ethylene episulfoxide which undergoes acid catalyzed ring-opening in aqueous hydrochloric acid.[107] Because of the instability of the sulfenic acid **38** initially

formed, the products are a disulfide and a thiolsulfonate (eq 52).



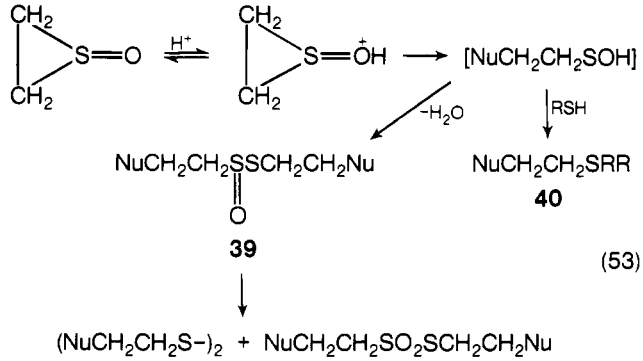
(52)

(Nu = OH^-, Cl^-, MeO^-, AcO^-)

A kinetic study[108] of the hydrolysis of ethylene episulfoxide in aqueous perchloric acid supported the A-2 mechanism proposed by Haskell and Paige[107] (eq 52). The value of $\Delta S^{\ddagger}$ (−8.2 eu) is similar to that for the acid-catalyzed hydrolyses of other three-membered heterocycles such as ethylene oxide (−6.1 eu)[109] and ethylenimine (−9.4 eu),[110] which after some controversy are also considered to hydrolyze by an A-2 mechanism.[111]

The facile ring-opening of ethylene episulfoxide in the presence of acids is in marked contrast to the behavior of five- and six-membered cyclic sulfoxides which racemize quite readily. Several studies of the relative basicities of cyclic sulfoxides using indirect methods have led to inconsistent results.[112,113] A recent NMR shift study[114] in aqueous sulfuric acid has shown that there is no appreciable influence of ring size on basicity except in the case of the four-membered thietane 1-oxide, which is less basic than the corresponding acyclic sulfoxides. Using a hydrogen-bonding method Tillett and his co-workers[108] found that ethylene episulfoxide and thiethane 1-oxide were of comparable basicity. The enormous difference in reactivity between the three-membered and other cyclic sulfoxides cannot therefore be attributed to changes in basicity but probably arises from severe enthalpy strain.

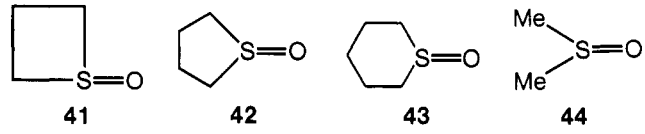
Kondo and his co-workers have shown that the main product in the acid-catalyzed hydrolysis of ethylene episulfoxide in methanol is the thiolsulfinate **39**. In the presence of ethyl mercaptan the disulfide **40** is formed. When the solvent was changed from alcohol to acetic acid, or if the episulfoxide were treated with dry hydrogen chloride in ether, no **40** could be detected. Instead a mixture of disulfide and thiolsulfonate was obtained (eq 53).



(53)

On the basis of the products obtained in the acid-catalyzed methanolysis of a number of episulfoxides, Kondo and his co-workers[115,116] suggested that ring-opening in methanol proceeds via an A-1 mechanism. This is in marked contrast to the mechanism proposed for aqueous perchloric acid (eq 52), and clearly further work is needed to determine the dependence of mechanism on solvent.

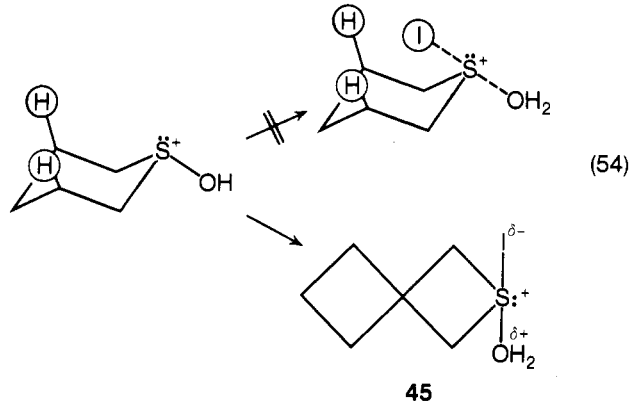
Five-membered cyclic sulfoxides undergo hydrochloric acid catalyzed stereomutation some 300 times faster than their six-membered analogues.[117] Similar relative reactivities (35:717:1.00:33) have been reported by Oae and his co-workers[113] for the acid-catalyzed iodide ion reduction of sulfoxides **41–44**.



41 **42** **43** **44**

Quite recently, however, Scorrano and his co-workers[118] have shown that while the dependence on acidity of the rate of reduction of **41** and **42** is quite similar to that of dimethyl sulfoxide, the acid dependence for thiane 1-oxide (**43**) is quite different. These authors have therefore pointed out that considerable care has to be used in interpreting reactivity data determined at a single acid concentration and throws some doubt on the relative rates of stereomutation[117] and reduction[113] of **42** and **43**. Scorrano and his co-workers[118] showed that the relative rates of reduction of **41:42:44** vary in the order of 4:19:1, with the six-membered **43** being less reactive than **42** by a factor depending on the acidity. In the reduction of sulfoxides by sodium hydrogen sulfite, thiolane 1-oxide was found to be more reactive than **41** or **42**.[119]

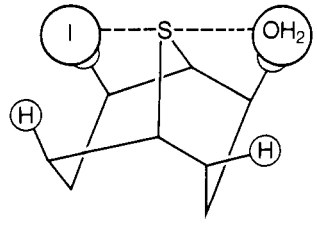
Oae and his co-workers[113] attributed the high reactivity of **42** to its much more favorable entropy of activation (−15 eu) compared to −22.2 for **44**. They suggested furthermore that in the reduction of **43** attack of sulfur by iodide ion is hindered by the steric effects of β-axial hydrogens and that such interactions can be minimized by twisting of the ring into a half-chair form **45** (eq 54). Some support for this view comes from the extremely



(54)

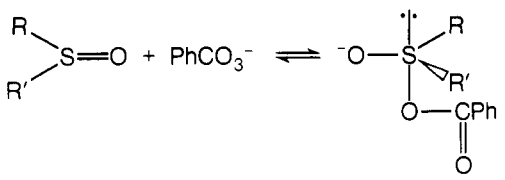
45

low reactivity toward reduction of the bicyclic [3.3.1] 9-sulfoxide **46**, which is so rigid that it cannot bend to minimize steric effects.



46

The oxidation of sulfoxides by peroxy acids in alkaline media (unlike that in acidic media) has been proposed[120] to occur via a two-step mechanism involving formation of an intermediate adduct, **47**, formed by nucleophilic attack at sulfur (eq 55). The ring size effects on the relative rates of alkaline oxidation of cyclic sulfoxides by this method are very small,[118] with the five-membered ring being the least reactive. This is in marked contrast to the alkaline hydrolyses of cyclic sulfites (see section



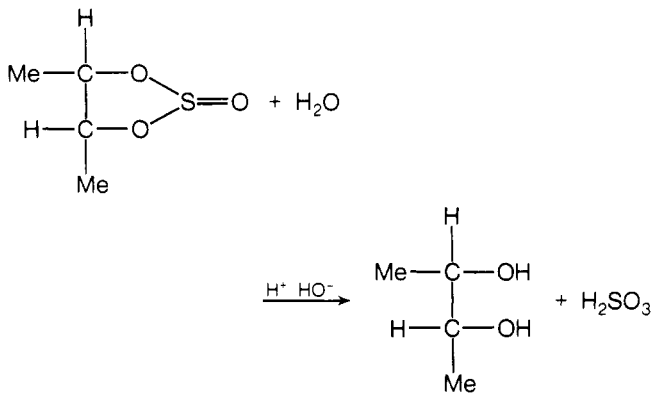
47

$$\longrightarrow PhCO_2^- + RR'SO_2 \quad (55)$$

IV) where the five-membered ring reacts about 250 times faster than the six-membered analogue.

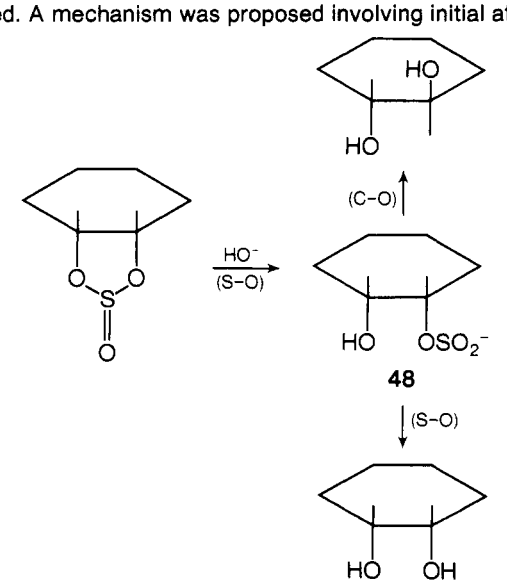
IV. Sulfites

One of the simplest nucleophilic displacement reactions of organic sulfites which has been studied in detail is the hydrolysis reaction. Garner and Lucas[121] showed that the acid- and base-catalyzed hydrolysis of (−)-2,3-butanediol sulfite occurs with complete retention of configuration at carbon, suggesting that nucleophilic attack occurs at sulfur with S–O bond fission:



Bunton and de la Mare and their co-workers[122-126] using oxygen-18 tracer techniques showed that the hydrolyses of a large number of cyclic and open-chain sulfites proceed with S–O bond fission. This has been confirmed by the more accurate experimental data of Kerr and Lauder[127] who showed that the hydrolysis of diethyl sulfite under acidic or basic conditions proceeds with at least 99.8% S–O bond fission.

The hydrolysis of the two isomeric cyclohexanediol sulfites provides an apparent exception to exclusive S–O bond fission.[128] While the trans sulfite was found to hydrolyze with S–O bond fission to give the trans diol under both acidic and basic conditions, the cis sulfite gave the cis diol under acidic conditions, but in the presence of base the product consisted mainly of the trans diol with only a small amount of the cis diol being formed. A mechanism was proposed involving initial attack at sulfur to form the intermediate **48** which can then undergo either C–O or S–O bond fission (eq 56).

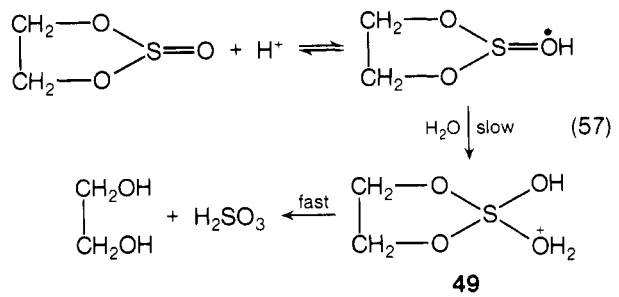


(56)

48

A. Acid Hydrolysis

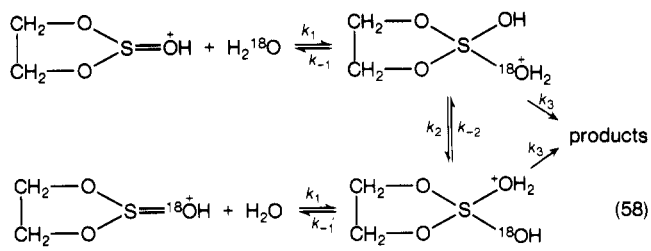
Bunton and de la Mare and their co-workers[124,125] showed that the perchloric acid catalyzed hydrolyses of cyclic and open-chain sulfites proceed via an A-2 mechanism (eq 57) in



(57)

49

which the proton has been sited on the exocyclic oxygen atom although it could equally well be on one of the ring oxygens. The rate-determining step is formulated as the formation of the tetracoordinate intermediate **49**. Attempts to obtain evidence for the formation of such an intermediate by search for a "Bender effect" [129] proved unsuccessful. Unreacted sulfite recovered after partial hydrolysis in $H_2{}^{18}O$ failed to show the enrichment expected if **49** were an intermediate (eq 58). The absence of



(58)

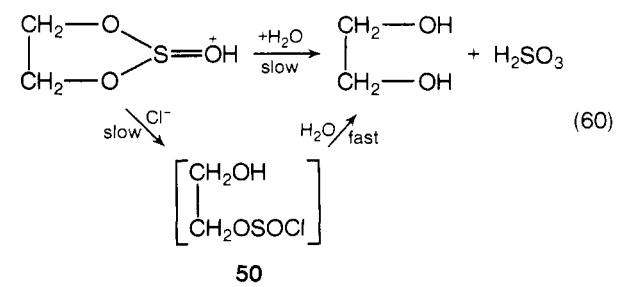
such exchange, however, does not preclude the formation of such an intermediate (see discussion on alkaline hydrolysis—section B) but indicates that if it is formed it decomposes to products faster than reverting to reactants, i.e., $k_2 \ll k_{-1}$ or k_3.

For the acid-catalyzed hydrolysis of sulfite esters in mineral acids the order of effectiveness of added acids reflects the decreasing nucleophilicity of the acid anion toward sulfur in sulfite esters, viz. $Br^- > Cl^- > HSO_4^- > ClO_4^-$. The general rate equation for catalysis by an acid HNu is

$$k_{obsd} = \underset{(a)}{k_0} + \underset{(b)}{k_0'[Nu]} + \underset{(c)}{k_{H^+}[H^+]} + \underset{(d)}{k_{Nu}[H^+][Nu]} \quad (59)$$

where the terms represent (a) a spontaneous reaction, (b) nucleophilic catalysis, (c) the acid-catalyzed (A-2) reaction, and (d) a hydrogen ion dependent nucleophilic catalysis pathway. The first two terms are negligible for the hydrolysis of aliphatic cyclic and open-chain sulfites in aqueous perchloric acid.

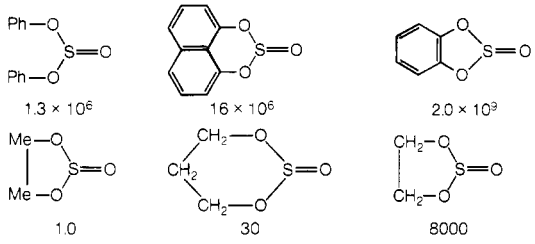
With hydrochloric acid as catalyst, nucleophilic catalysis is considered to occur via slow formation of a chlorosulfite intermediate **50** (eq 60). A large number of five-membered cyclic



(60)

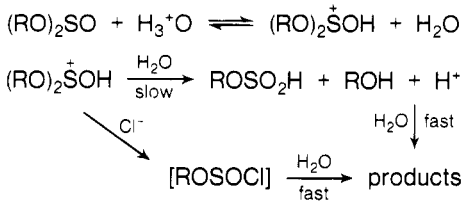
50

TABLE I. Relative Rates of Alkaline Hydrolysis of Organic Sulfites[a,138,139]



[a] In aqueous (1%) dioxane at 25 °C.

sulfites[130] and their six- and seven-membered ring analogues[131] have been found to hydrolyze by the same mechanism. Dialkyl sulfites including dimethyl,[125] diethyl,[125] and dicyclohexyl sulfite[131] also hydrolyze by concurrent A-2 and nucleophilic catalysis pathways (eq 61). Attempts to identify an A-1 mode of

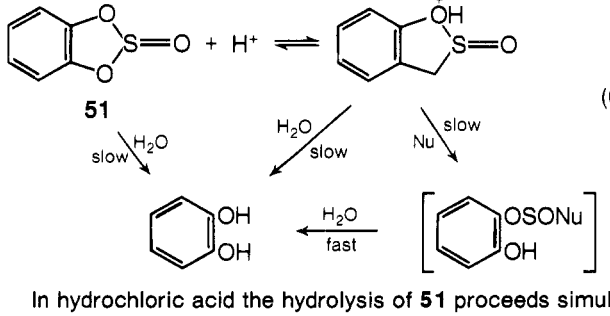


(61)

hydrolysis in dialkyl sulfites in which the group R has incipient carbonium ion properties have proved unsuccessful. Cholesteryl methyl, menthyl methyl, dibornyl and bis-*endo*- and *exo*-2-norbornyl sulfites all hydrolyze in aqueous perchloric acid by the general A-2 mechanism.[132]

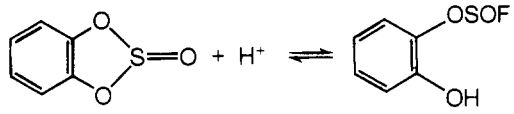
Structural effects on the rates of acid-catalyzed hydrolysis of organic sulfites are small, and it is not known whether these arise from differences in basicity or in the relative reactivities of the conjugate acids.

The kinetic behavior of *o*-phenylene sulfite (**51**) in aqueous acidic dioxane is quite different from that of aliphatic sulfites. The pH–rate profile is dominated by a high spontaneous rate (term (a) in eq 59) which is comparable in magnitude to the acid-catalyzed rate. Tillett also showed[133] that while the observed rate of hydrolysis increases steadily with increasing hydrochloric acid concentration, in perchloric acid, k_{obsd} passes through a maximum. This rate maximum arises not from extensive protonation but from the superposition of a large negative salt effect by perchlorate ion on the spontaneous reaction. At higher acidity this predominates over the relatively weak acid catalysis.



(62)

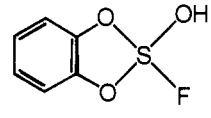
In hydrochloric acid the hydrolysis of **51** proceeds simultaneously (eq 62) by three of the four possible pathways suggested by eq 59. Bunton and Schwerin[134] showed that the kinetic behavior for the hydrolysis of **51** in aqueous solution differed slightly from that observed in aqueous dioxane owing mainly to the reduced reactivity of nucleophiles arising from increased solvation. In addition, whereas most univalent salts were found to decrease the spontaneous rate, quite small amounts of fluoride ion catalyze the spontaneous hydrolysis in water quite markedly. Bunton and Schwerin[134] attributed this unusual reactivity to nucleophilic catalysis which is independent of hydrogen ion concentration (term (b) in eq 59) and suggested that this could occur either by formation of the fluorosulfite **52** (eq 63) or to the facile formation



(63)

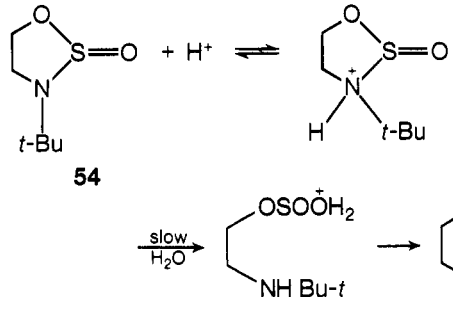
52

of a tetracoordinate intermediate **53**. Fluoride ion was also found to catalyze the hydrolysis of diphenyl sulfite. The absence of such a nucleophilic catalysis term in the hydrolyses of aliphatic sulfite esters like diethyl sulfite was attributed to the poor leaving group ability of EtO^- from sulfur.



53

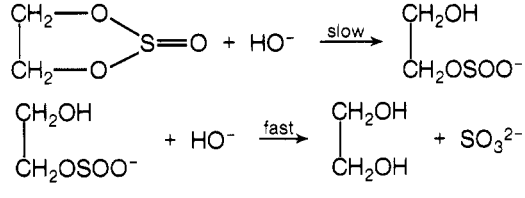
In contrast to the behavior of cyclic sulfites, the acid-catalyzed hydrolysis of the cyclic amidosulfite **54** is unaffected by added nucleophiles.[135] The rate maximum which is observed at about 3.0 M acid is attributed to extensive protonation of the substrate. This view is substantiated by the values of the kinetic solvent isotope effect, $k_1^{D_2O}/k_1^{H_2O}$, which fall steadily with increasing acidity. The value of $\Delta S^{\ddagger}$ (−19 eu) is also consistent with the proposed A-2 mechanism (eq 64).



(64)

B. Base Hydrolysis

The alkaline hydrolyses of sulfite esters proceed with S–O bond fission.[122-125] The mechanism of hydrolysis was formulated[123] as a two-stage process involving rate-determining attack by hydroxide ion on sulfur, e.g., for ethylene sulfite:

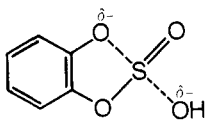


(65)

Computer analysis of the rate data confirms that the second step is at least 100 times faster than the first step.[136] Davis reached a similar conclusion from a study of the alkaline hydrolysis of ethylene and dimethyl sulfites.[137]

de la Mare, Tillett, and van Woerden carried out an extensive study of substituent effects on the alkaline hydrolysis of sulfites[138,139] (Table I). In both the aliphatic and aromatic series of sulfites, the relative order of reactivity is the same: the five-membered cyclic sulfites react much faster than the corresponding six-membered or open-chain analogues. The origin of kinetic acceleration in cyclic esters has been the subject of much speculation[140] and was originally thought to arise from some kind of ring strain.[141] That this is not the case for sulfite esters is shown by the close simularity in the heats of hydrolysis of cyclic and open-chain sulfites in both the aliphatic and aro-

matic series.[137,142] The main cause of this observed kinetic acceleration has been attributed to entropy strain.[143,144] In both series the five-membered cyclic ester has a much more favorable entropy of activation of hydrolysis than the corresponding six-membered or alicyclic esters. The transition state **55** for the



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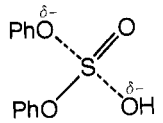
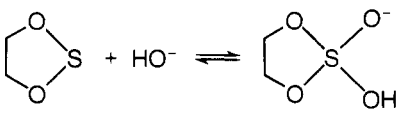


56

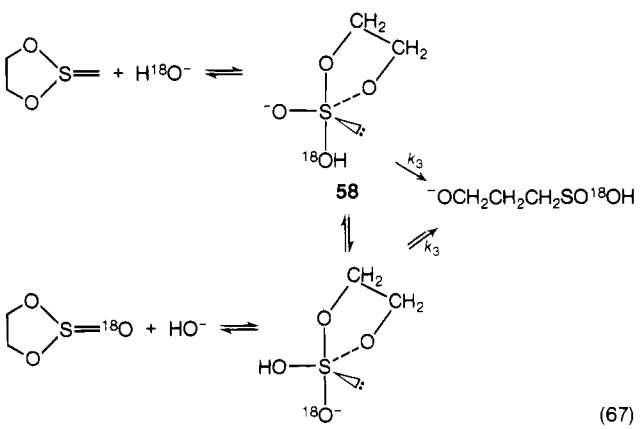
hydrolysis of *o*-phenylene sulfite is therefore energetically more stable than that for diphenyl sulfite (**56**). If the hydrolytic ring opening of ethylene sulfite proceeds through a tetracoordinate sulfur intermediate **57** (eq 66), then oxygen exchange of the ester



57

$$\longrightarrow \bar{O}CH_2CH_2OSO_2H \quad (66)$$

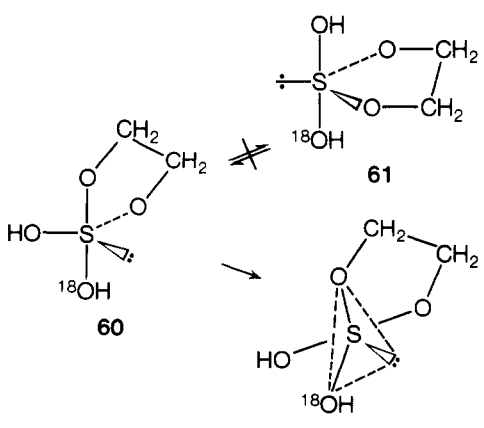
with the solvent might be anticipated. Bunton and de la Mare and their co-workers,[123] however, were unable to detect any trace of such back-exchange for hydrolysis under either acidic or basic conditions. The simplest pathway for oxygen exchange of a trigonal-bipyramidal intermediate, in which the ring is allowed to span a,e positions, is by a simple proton transfer **58** → **59** (eq 67).



58 **59**

(67)

Kice and Walters have pointed out,[145] however, that **59** with an O^- group in an axial position would be a high-energy intermediate, and so proton transfer by this mechanism would be slow compared to the breakdown of **57** in either a forward or reverse direction. They suggested, however, that oxygen exchange could occur if prior protonation occurred (eq 68). The



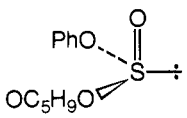
60 **61** **62**

(68)

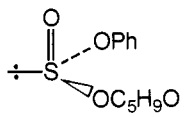
trigonal-bipyramidal intermediate **60**, derived from **58**, by protonation, cannot readily undergo pseudorotation about the ring carbon atom as pivot (**60** → **61**) because this would expand the ring angle to an unfavorable 120°. Pseudorotation could occur about the lone pair of electrons (**60** → **62**) without any special energy constraints although as shown by Tang and Mislow[7] pseudorotation in such a system is likely to be much slower than in the analogous phosphoranes and slower than the cleavage reactions of **57** in either the forward or reverse directions. Thus the absence of oxygen exchange in the alkaline hydrolyses of sulfite esters is not inconsistent with the formation of a tetracoordinate intermediate.

C. Enzyme Catalysis

It is interesting that the pepsin-catalyzed hydrolysis of sulfite esters is stereospecific. This specificity has been used to achieve the first resolution of an asymmetric sulfite into its enanthiomeric forms **63** and **64**. Reid and his co-workers[146]

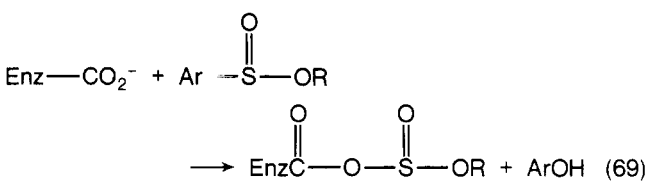


63



64

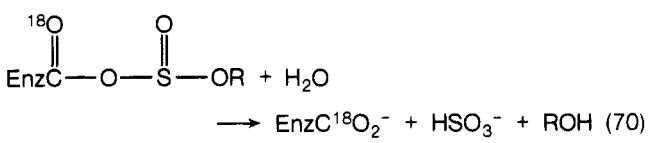
showed that pepsin preferentially catalyzes the hydrolysis of one of the enantiomers of phenyl tetrahydrofurfuryl sulfite. A mechanism was suggested involving nucleophilic displacement at sulfur by a carboxyl group at the active site of pepsin to form a mixed carboxylic–sulfurous anhydride intermediate **65** which is subsequently rapidly decomposed by water (eq 69). Experi-



65

(69)

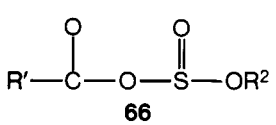
ments with oxygen-18 labeled pepsin[147] showed that oxygen-18 from the enzyme carboxyl group becomes incorporated into the bisulfite ion, indicating that decomposition of **65** occurs by attack of water at the acyl carbon atom rather than at sulfur (eq 70). Mixed anhydrides of the type of **66** (R′ = R^2 = Me or Et) have



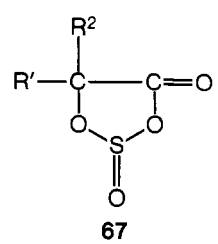
(70)

been isolated and can be stored at 0 °C for several days without decomposing, but in water they appear to decompose instantly.[148]

The preparation of a range of alkyl- and phenyl-substituted anhydro sulfites, which can be regarded as cyclic mixed carboxylic–sulfurous anhydrides, **67**, has also been reported.[149-152]

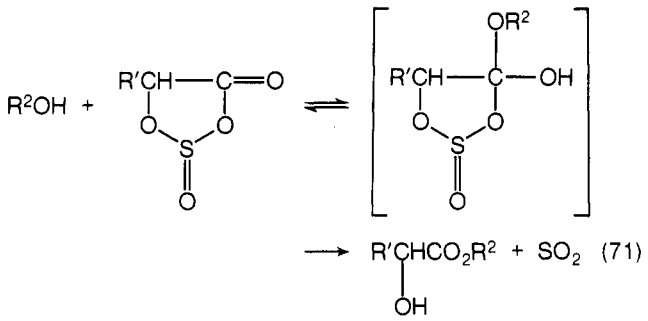


66

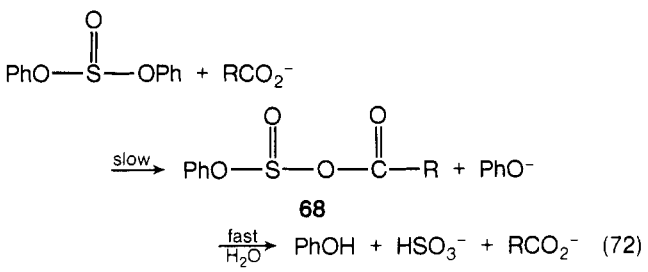


67

Such compounds decompose rapidly in the presence of water and mineral acids to form the corresponding hydroxy acid. The detailed mechanism of hydrolysis is not known. Nucleophilic attack on anhydro sulfites by alcohols occurs at the acyl carbon atom as in open-chain anhydrides and results in ring opening (eq



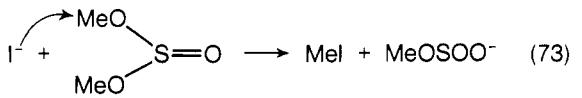
71). Further evidence for the involvement of a mixed anhydride intermediate in the pepsin-catalyzed hydrolysis of diaryl sulfites has been obtained from kinetic and inhibition studies by Kaiser and his co-workers.[153-156] They also showed that the hydrolyses of diphenyl and bis(*p*-nitrophenyl) sulfite in aqueous solution were catalyzed by carboxylic acid buffers. The high Bronsted β value (0.85) and the kinetic solvent isotope effect, $k_{OAc}^{H_2O}/k_{OAc}^{D_2O}$ = 1.32, are consistent with a nucleophilic catalysis mechanism (eq 72).



The detection of acetohydroxamic acid in trapping experiments when diphenyl and bis(*p*-nitrophenyl) sulfites were hydrolyzed in acetate buffers, in the presence of hydroxylamine, provides further support for the intervention of a mixed anhydride intermediate **68** (R = Me).

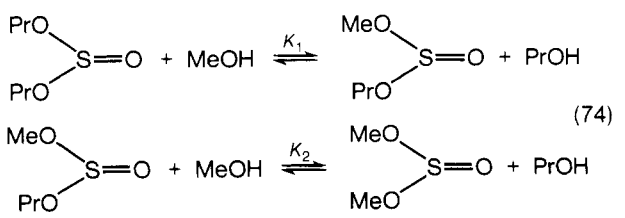
D. Other Reactions

The characteristic reactions of organic sulfites have been reviewed by van Woerden.[157] They are particularly powerful alkylating agents,[158] and, in such reactions which involve C–O bond fission, sulfites are converted into alkyl sulfite ions; e.g., for the reaction of dimethyl sulfite with iodide ions:[159]

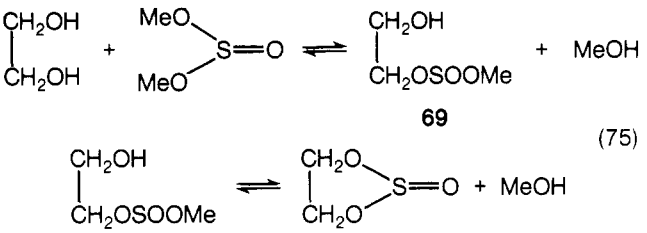


Similarly when cyclic sulfites of 1,3-diols are refluxed in acetone with sodium iodide, sodium iodoalkyl sulfites are formed.[160] Dimethylaniline is obtained in 96% yield from the reaction of dimethyl sulfite and aniline.[161] In a number of other reactions, organic sulfites can undergo attack a both carbon and sulfur.

The reaction of sulfite esters with alkoxide ions is complicated by concurrent nucleophilic substitution and transesterification.[162] Alkoxy exchange is subject to both acid and base catalysis and is accelerated by heating. An NMR study of diisopropyl sulfite–methanol exchange gave values of the equilibrium constants K_1 and K_2 (eq 74) of approximately unity.

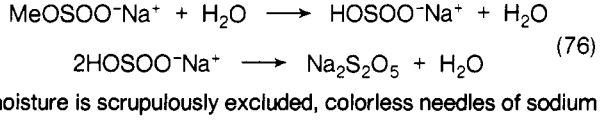


The exchange reaction of ethylene sulfite and methanol has also been investigated (eq 75). The existence of the intermediate

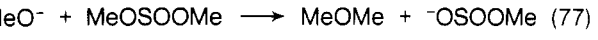


69, which was identified by its NMR spectrum, and its facile cyclization, provides additional evidence that the five-membered cyclic sulfite ring is not strained. A similar open-chain transesterification intermediate has been observed in the ethylene carbonate–methanol system.[163]

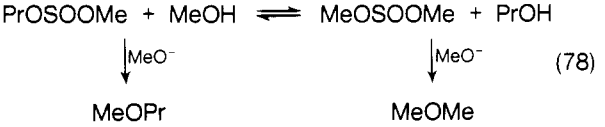
Dimethyl sulfite reacts with sodium methoxide to form sodium metabisulfite which is thought to arise[159,162] from the rapid hydrolysis of sodium methyl sulfite by traces of water:



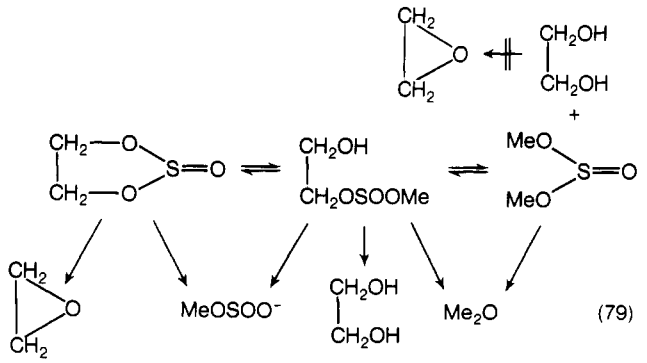
If moisture is scrupulously excluded, colorless needles of sodium methyl sulfite separate out. Dimethyl ether is formed by nucleophilic displacement at carbon:



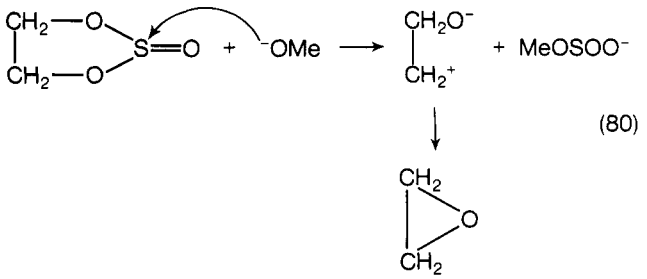
Similarly diethyl sulfite reacts rapidly with sodium ethoxide in refluxing ethanol to form diethyl ether. Isopropyl methyl ether is formed almost quantitatively from dimethyl sulfite and sodium isopropoxide. In addition some dimethyl ether can be detected. This is formed by nucleophilic substitution occurring after alkoxy exchange (eq 78).



Ethylene sulfite reacts with sodium methoxide to form ethylene oxide, dimethyl ether, ethanediol, and sodium methyl sulfite[162] (or metabisulfite depending on the conditions). These products can arise in a number of different ways as shown in eq 79. The surprising absence of ethanediol mono- or dimethyl ether



among the products suggests that initial alkoxide ion attack occurs exclusively at sulfur possibly via a zwitterionic intermediate (eq 80). These observations are consistent with those

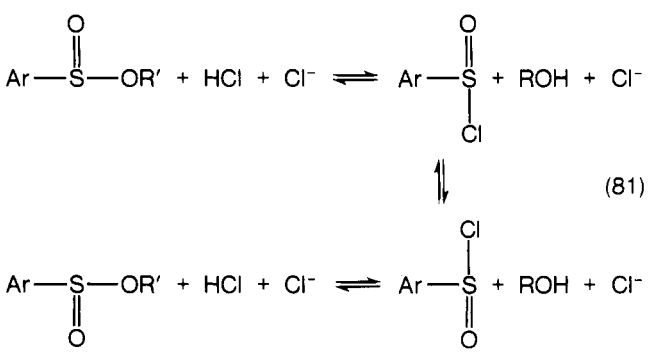


of Gillis[164] who obtained tetrahydrofuran from tetramethylene sulfite by using a tertiary nitrogen base as catalyst under more vigorous conditions. No cyclic ether formation could, however, be detected from five- or six-membered cyclic sulfites.

V. Sulfinates

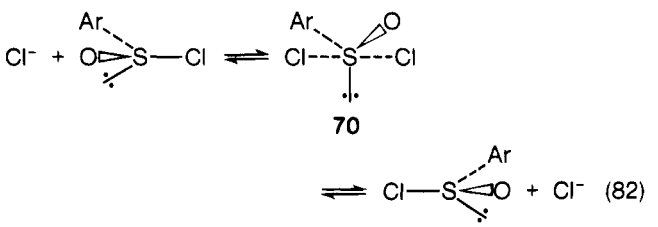
Transesterification of an optically active sulfinate with an alcohol proceeds with inversion of configuration at sulfur (eq 1) and was the basis of the method used by Phillips[3] to separate enantiomers of sulfinates. Andersen's demonstration[10] that the reaction of chiral sulfinates with Grignard reagents occurs with inversion of configuration has been discussed in section II. A study of the reaction of methyl *p*-toluenesulfinate-*sulfinyl*-^{18}O with phenylmagnesium bromide has confirmed that S–O bond fission occurs.[165]

The racemization of sulfinate esters is catalyzed by hydrochloric acid in organic solvents. Herbrandson and Dickerson found[166] that methyl arenesulfinates in nitrobenzene epimerize in the presence of hydrogen chlorid and chloride ions. A mechanism involving reversible formation of a sulfinyl chloride was proposed (eq 81). The epimerization was accounted for by



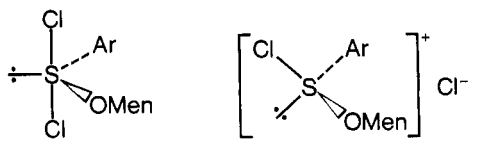
(81)

rapid chloride ion exchange accompanied by racemization at sulfur via the symmetric transition state **70** (eq 82).

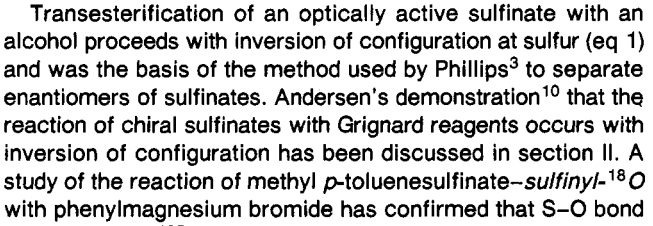


(82)

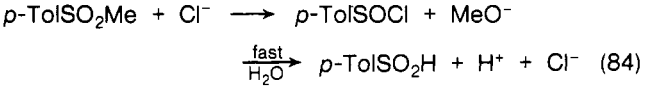
Mislow and his co-workers[38] on the basis of their experiments with sulfoxides suggested that epimerization of menthyl arenesulfinates occurs via either a tetracoordinate sulfur intermediate **71** or a sulfonium ion **72**.



The hydrolysis of methyl *p*-toluenesulfinate in acidic $H_2{}^{18}O$–dioxane proceeds with S–O bond fission.[167] Bunton and Hendry also showed[167,168] that the hydrolysis of methyl *p*-toluenesulfinate with halogen acids proceeds concurrently via an A-2 and a hydrogen ion dependent nucleophilic catalysis mechanism (eq 83). The *p*-toluenesulfinyl chloride intermediate can be synthesized independently and is found to hydrolyze too rapidly to be followed by conventional methods. The kinetic behavior of methyl *p*-toluenesulfinate under acidic conditions is similar to that observed for sulfite esters (section IV.A). A slow spontaneous reaction was found to be catalyzed by added sodium chloride (eq 84). Such hydrogen ion-independent nucleophilic



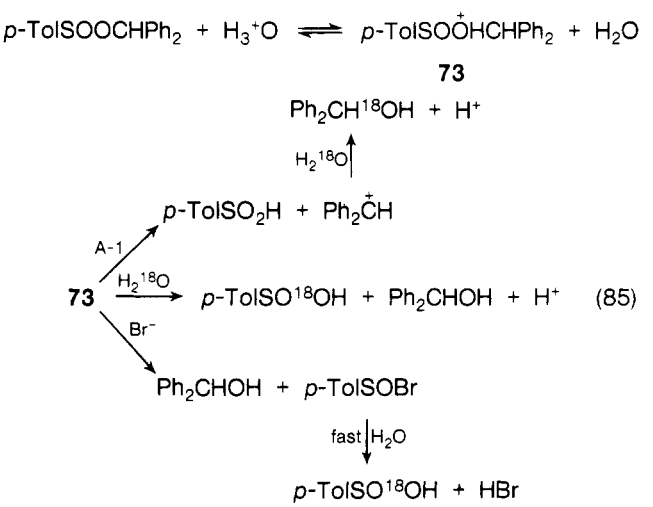
(83)



(84)

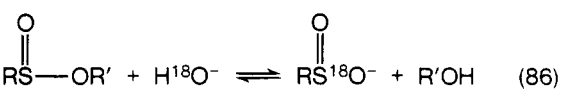
catalysis was observed by Bunton and Schwerin[134] for the fluoride ion catalyzed hydrolysis of *o*-phenylene sulfite but not for other halides or dialkyl sulfites.

The acid-catalyzed hydrolysis of diphenylmethyl *p*-toluenesulfinate shows quite complex kinetic behavior[169] and is accompanied by slow spontaneous hydrolysis in neutral aqueous dioxane. Perchloric acid is a particularly effective catalyst, and the values of $\Delta S^{\ddagger}$ (+2 eu) and the solvent isotope effect ($k_2{}^{D_2O}/k_2{}^{H_2O} = 2.0$) suggest an A-1 mechanism. Tracer experiments with $H_2{}^{18}O$, however, show that hydrolysis proceeds with 80% C–O and 20% S–O bond fission indicating concurrent displacement at both carbon and sulfur. Nucleophilic catalysis by Br^- (but not by Cl^-) was accounted for by the general reaction scheme (eq 85):



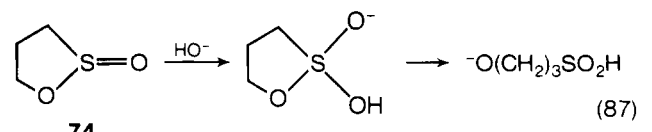
(85)

Bunton and Hendry showed[169] that the alkaline hydrolysis of simple sulfinate esters follows second-order kinetics, and the rate-determining step involves nucleophilic attack at sulfur (eq 86).



(86)

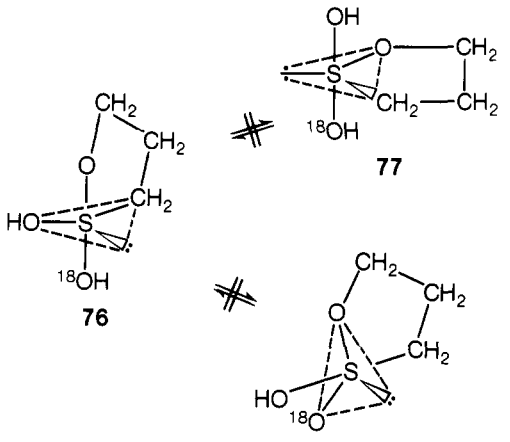
Najam and Tillett[170] were unable to detect any oxygen exchange in the alkaline hydrolysis of the five-membered cyclic sulfinate **74** (ethylene sultine) which might be expected if a tetracoordinate intermediate **75** were formed in this reaction (eq 87). As in the hydrolysis of the structurally related ethylene sulfite



(87)

for which exchange could not be detected,[123] oxygen equilibration of **75** via simple proton transfer can probably be ruled out. Neither of the two pseudorotation mechanisms considered by Kice and Walters[145] for ethylene sulfite are available for **75**. The trigonal-bipyramidal intermediate **76** derived from **75** by protonation cannot readily undergo pseudorotation either about the ring carbon as pivot (**76** → **77**) which would expand the ring

angle to 120°, or about the lone pair of electrons (**76** → **78**) which would place the methylene group in an unfavorable axial position. The conjugate acid of **75** is therefore "frozen" in the trigonal-bipyramidal **76**, preventing oxygen exchange from occurring.



76 **77** **78**

The relative reactivities toward hydroxide ion of five- and six-membered cyclic sulfinates and methylmethane sulfinate were found to show only small differences[170] in contrast to the behavior of cyclic sulfites (section IV.B). The main cause of difference in reactivity between five- and six-membered sultines was found to arise from entropy strain rather than from enthalpy differences.

The alcoholysis of sulfinates can proceed with either S–O or C–O bond fission. The former involves transesterification and leads to the formation of another sulfinate (eq 88) while the main products of C–O bond fission are a sulfinic acid and an ether (and/or a sulfone) (eq 89).

$$ArSOOR + R'OH \rightleftharpoons ArSOOR' + ROH \quad (88)$$

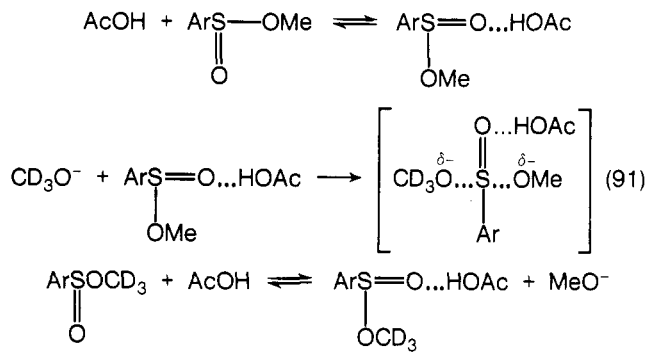
$$ArSOOR + R'OH \rightleftharpoons ArSO_2H + ROR' \quad (89)$$

Sulfur–oxygen bond fission has been observed in the alcoholysis of *n*-butyl[3] and α-phenylethyl *p*-toluenesulfinates.[171,172] The ethoxide ion catalyzed ethanolysis of diastereoisomeric (−)-menthyl (+)-*p*-iodobenzenesulfinate and (−)-menthyl *p*-iodobenzenesulfinate also involves S–O bond fission. The formation of sulfones and substitution products in the solvolysis of several arenesulfinates, however, indicates that under certain conditions C–O bond fission can occur.[173–175]

Darwish and Noreyko[176] showed that the base-catalyzed solvolysis of *p*-methoxyneophyl benzenesulfinate proceeds exclusively with S–O fission. The small steric effect observed with two methyl groups ortho to sulfur is consistent with a mechanism involving nucleophilic attack at that site. The rate of reaction was found to vary enormously with the nature of the added base, the order of reactivity being consistent with either nucleophilic or general base catalysis. Kice and Walters[145] attempted to distinguish between these possibilities by studying the exchange of methoxy groups between methanol-d_3 and methyl *p*-toluenesulfinate (eq 90).

$$CD_3OH + p\text{-TolSOOMe} \rightleftharpoons p\text{-TolSOOCD}_3 + MeOH \quad (90)$$

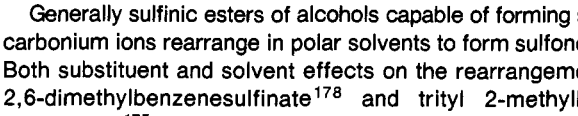
While a nucleophilic catalysis mechanism seems unlikely, the solvent isotope effect ($k_{OAc}^{MeOH}/k_{OAc}^{MeOD}$ = 1.4–1.5) was found to be somewhat smaller than that normally associated with base catalysis. Kice and Walters suggested that in this system general base catalysis arises from a combination of specific methoxide ion catalysis and general acid catalysis by acetic acid and that the rate-determining step is the reaction of CD_3O^- with a hydrogen-bonded complex of the sulfinate and acetic acid (eq 91).



The effect of basicity of the nucleophile and the leaving group on the reaction of oxygen nucleophiles with aryl esters of methanesulfinic acid has been studied.[177] A good Bronsted correlation was obtained for the leaving group (β_L = −0.71), but the Bronsted plot for nucleophilic reactivity was curved. Ciuffarin and Fava and their co-workers have concluded that the value of β cannot be related simply to the extent of bond-breaking or bond-forming in the transition state.

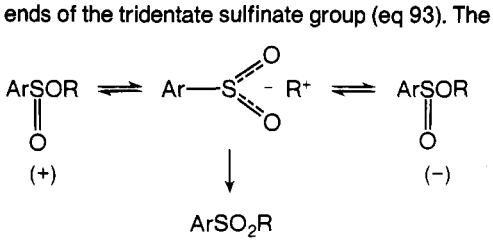
Darwish and Noreyko's work[176] has drawn attention to the fact that it is possible to considerably reduce the rate of attack at sulfur by using very weak bases. In systems where C–O bond fission can also occur, it is possible to vary the type of bond fission by varying the base. Thus the ethanolysis of allyl 2,6-dimethylbenzenesulfinate (in anhydrous ethanol with AcO^- as base) forms only ethyl 2,6-dimethylbenzenesulfinate with a trace of allyl 2,6-dimethylphenyl sulfone. However, with 2,6-lutidine the reaction was slower and allyl 2,6-dimethylphenyl sulfone was the only detectable product.

Generally sulfinic esters of alcohols capable of forming stable carbonium ions rearrange in polar solvents to form sulfones.[174] Both substituent and solvent effects on the rearrangement of 2,6-dimethylbenzenesulfinate[178] and trityl 2-methylbenzenesulfinate[175] point to an ionic mechanism which could involve either recombination of dissociated ions or an ion pair mechanism (eq 92). The trityl carbonium ion formed in the rearrangement of trityl 2-methylbenzenesulfinate can be diverted to trityl azide if the rearrangement is carried out in the presence of tetra-*n*-butylammonium azide.[175] Cope and his co-workers showed[179] that the same mixture of α-methylallyl and crotyl phenyl sulfones was obtained from either α-methylallyl or crotyl benzenesulfinate.



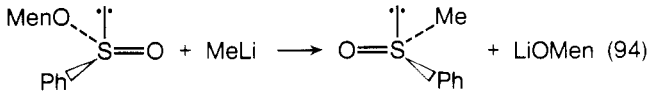
(92)

Fava and his co-workers[180] suggested that both the racemization and ionization of benzhydryl *p*-toluenesulfinate occurs via a common step leading to the formation of carbonium and sulfinate ions which can undergo return with either the oxygen or sulfur ends of the tridentate sulfinate group (eq 93). The small amount of solvolysis product suggested that this reaction occurs mainly through an ion-pair intermediate rather than through free ions.

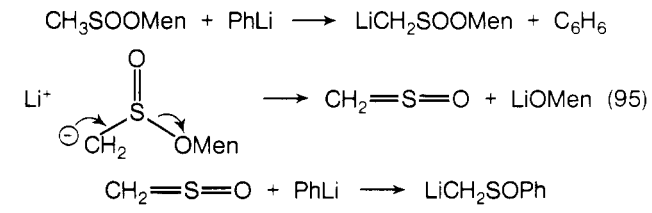


(93)

Sulfinate esters react with lithium alkyls and aryls in a similar way to sulfoxides. Thus methyl benzenesulfinate[180] reacts with methyllithium by a direct displacement mechanism to form methyl phenyl sulfoxide of inverted configuration (eq 94). For



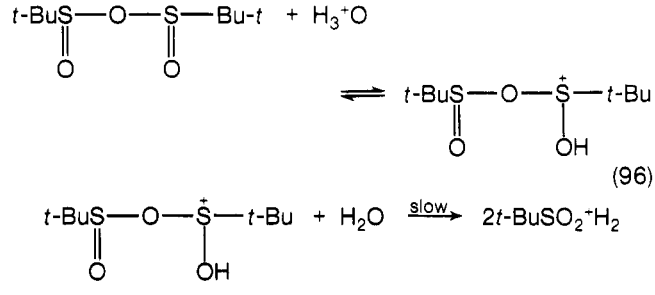
the reaction of organolithium reagents with sulfinate esters containing labile α-hydrogens, sulfine intermediates have been proposed. The reaction of (−)-menthyl methanesulfinate with phenyllithium gives predominantly racemic methyl phenyl sulfoxide (eq 95). Andersen and his co-workers[106] found that both



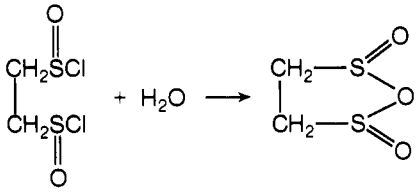
methyl *p*-toluenesulfinate and methyl *p*-tolyl sulfoxide reacted with *p*-tolyllithium to form roughly the same proportions of *m,p'* and *p,p'*-bitolyls and proposed a similar mechanism for both reactions (section III.B).

VI. Sulfinic Anhydrides and Sulfinyl Chlorides

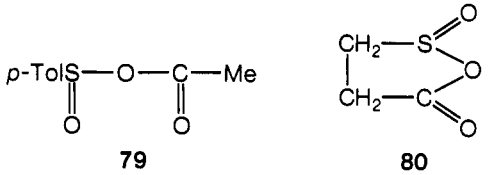
Di-*tert*-butylsulfinic anhydride which has been recently synthesized[181] readily hydrolyzes in aqueous dioxane to the corresponding sulfinic acid by both a spontaneous and an acid-catalyzed pathway. An A-2 mechanism was proposed for the latter process (eq 96). Such behavior is in marked contrast to the hydrolysis of sulfinyl sulfones (see next section) which is not catalyzed by added acids.



The simplest cyclic anhydride, that of ethanedisulfinic acid, has been obtained by controlled hydrolysis of ethane bis(disulfinyl) chloride.[182] This anhydride hydrolyzes back to the parent

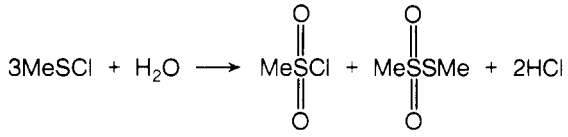


acid almost quantitatively after boiling for 1 min in water. A mixed carboxylic–sulfinic anhydride, **79**, has been postulated[183] as an intermediate in the reaction of sodium *p*-toluenesulfinate with acetyl chloride. The cyclic anhydride of β-carboxyethanedisulfinic acid (**80**) has been reported[184] to be exceptionally stable.

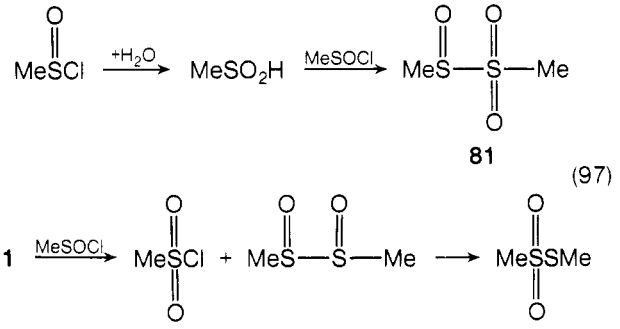


79 **80**

Cram and his co-workers[185] showed that methanesulfinic acid can be obtained by careful hydrolysis of methanesulfinyl chloride at −30 °C. Douglas and his group, however,[186] showed that at room temperature a sulfonyl chloride and a thiolsulfonate are formed:

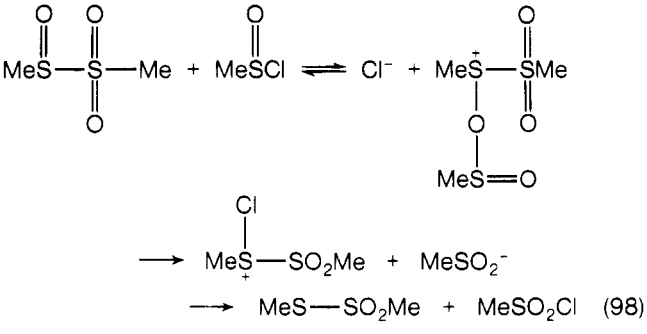


The products were explained by the following mechanism (eq 97). NMR evidence was found for the existence of the sulfinyl



(97)

sulfone **81**. An alternative mechanism (eq 98) has been proposed by Kice.[187]



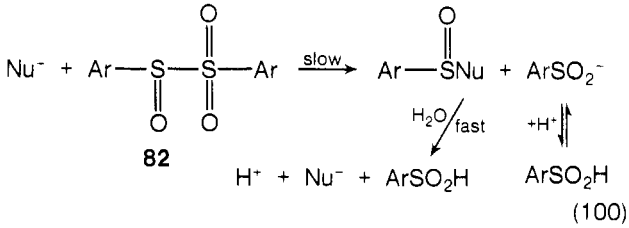
(98)

VII. Sulfinyl Sulfones

In acidic aqueous dioxane the hydrolysis of aryl sulfinyl sulfones occurs almost exclusively by a spontaneous pathway even in quite acidic media.[192] In the presence of added nucleophiles the rate of hydrolysis, k_{obsd}, is given by

$$k_{obs} = k_{spont} + k_{Nu}[Nu] + k'_{Nu}[H^+][Nu] \qquad (99)$$

Thus the spontaneous hydrolysis of *p*-toluenesulfinyl *p*-tolyl sulfone (**82**) is not catalyzed by acids, but both a nucleophilic catalysis and a hydrogen ion-dependent nucleophilic catalysis mechanism can be discerned. The mechanism proposed for nucleophilic catalysis which is dominant at low acidity (<0.1 M acid) is shown in eq 100. The absence of nucleophilic catalysis

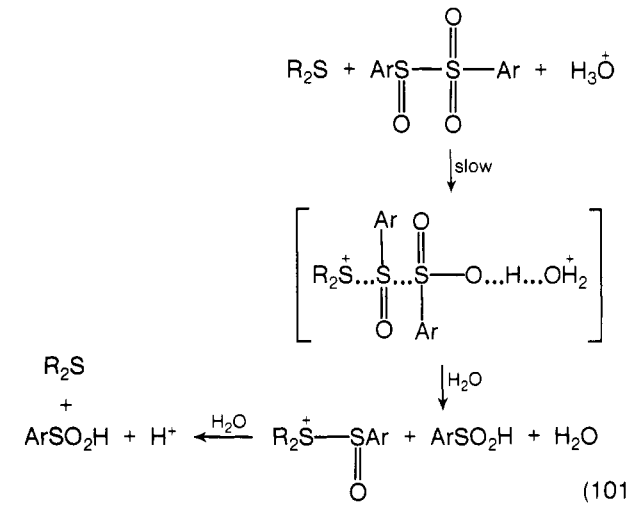


(100)

in the hydrolysis of dialkyl sulfites in contrast to its predominance in the hydrolysis of sulfinyl sulfones has been attributed by Kice and Guaraldi[192] to the easier displacement of $ArSO_2^-$ from **82** compared to RO^- from $(RO)_2SO$.

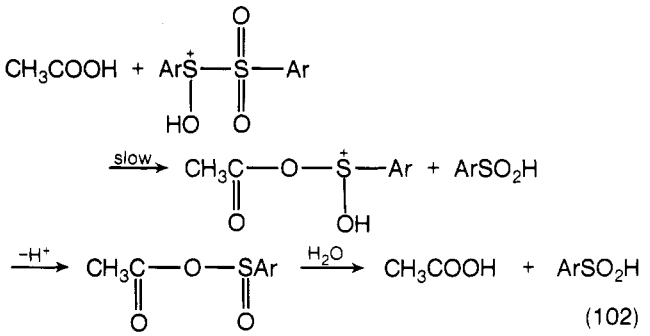
The relative rate of nucleophilic attack at the sulfinyl sulfur of **82** ($I^- > SCN^- > Br^- > Cl^- \simeq AcO^- > F^-$)[189] falls in between that expected for the relatively "soft" sulfenyl center, on the one hand, and the relatively "hard" sulfonyl center, on the other. The order is consistent with that observed for attack at sp^3 carbon which has been classed as "medium soft."[190,191]

The acid-catalyzed hydrolysis of **82** is also catalyzed by the addition of alkyl sulfides.[192] The solvent isotope effect (k_{H_2O}/k_{D_2O} = 1.4) suggests a general acid catalysis mechanism (eq 101).



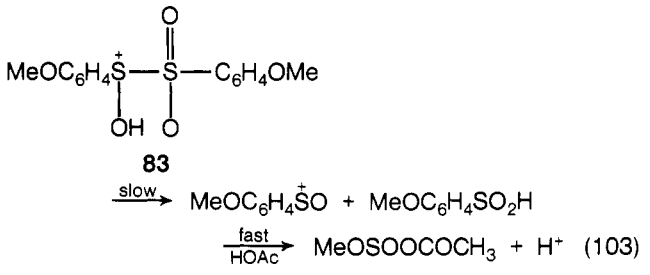
(101)

In aqueous acetic acid, aryl sulfinyl sulfones hydrolyze almost exclusively by an acid-catalyzed pathway.[193] The dependence of rate on aryl group structure is quite different from that observed for the spontaneous and the sulfide-catalyzed reaction. For most aryl groups a bimolecular mechanism involving nucleophilic assistance by the solvent was proposed (eq 102).



(102)

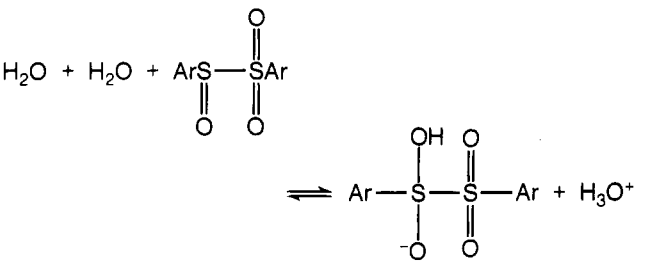
Although a unimolecular mechanism was originally proposed for the acid-catalyzed hydrolysis of the *p*-anisyl compound **83** (eq 103), Kice[194] has recently suggested that the hydrolysis of



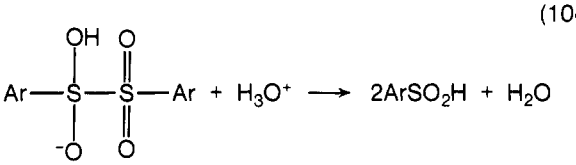
(103)

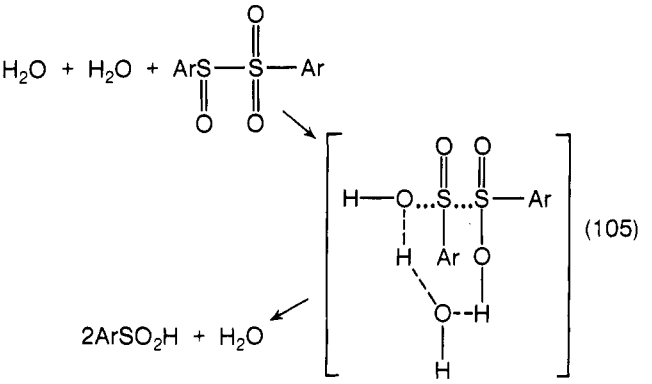
83 in aqueous acetic acid only differs from that of other aryl sulfinyl sulfones in that bond breaking is considerably in advance of bond forming in the transition state and that a free $ArSO^+$ ion is probably not obtained.

Whereas in aqueous acidic dioxane the hydrolysis of arylsulfinyl sulfones occurs almost exclusively by the spontaneous pathway, sulfide ion catalysis apparently requires hydrogen ion assistance. To explain this difference Kice and Guaraldi[192] suggested that neutral nucleophiles like H_2O or R_2S could not displace $ArSO_2^-$ from an arylsulfinyl sulfone. For spontaneous hydrolysis, water can itself provide the proton required by the leaving group either by a stepwise mechanism (eq 104) or in a concerted fashion (eq 105). For catalysis by sulfide ion a proton must be transferred to the $ArSO_2$ group as S–S bond fission occurs as provided by general acid catalysis. This is confirmed



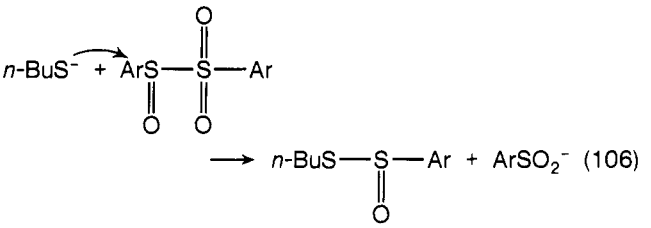
(104)





(105)

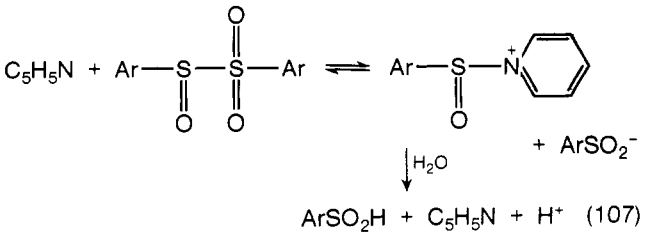
by the effect of added mercaptans on the hydrolysis of *p*-toluenesulfinyl sulfone in aqueous dioxane.[195] At low acidity (10^{-3} M), nucleophilic catalysis by *n*-BuS^- provides the predominant pathway (eq 106). At higher acidities, catalysis by *n*-BuSH occurs



(106)

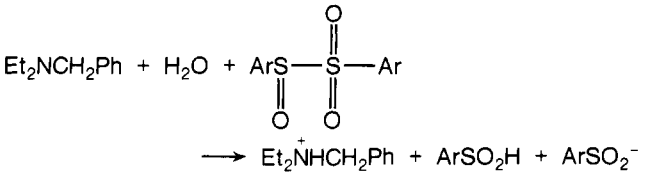
unaccompanied by acid catalysis because, unlike R_2S, *n*-BuSH can transfer a proton to the departing $ArSO_2^-$ group.

Tertiary amines can catalyze the hydrolysis of sulfinyl derivatives by either a nucleophilic or general base mechanism depending on the structure of the amine.[196] Thus while pyridine catalyzes the hydrolysis of *p*-anisyl *p*-methoxybenzenesulfinyl sulfone in aqueous dioxane or glyme by nucleophilic catalysis (eq 107), *N*-benzyldiethylamine acts as a general base as indi-



(107)

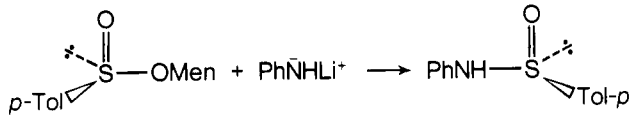
cated by the solvent isotope effect ($k_{R_3N}{}^{H_2O}/k_{R_3N}{}^{D_2O}$ = 2.4):



The greater catalytic reactivity of *N*-benzylpyrrolidine compared to that of *N*-benzyldiethylamine (although of similar base strengths) suggests that pyrrolidine acts as a nucleophilic catalyst.

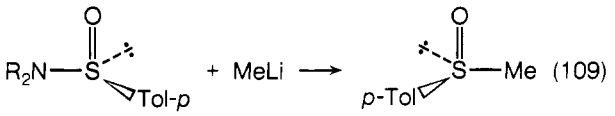
VIII. Sulfinamides

Cram and Nudelman[14] showed that the reaction of optically active menthyl *p*-toluenesulfinate with lithium anilides is highly stereospecific and proceeds with inversion at sulfur to form the corresponding sulfinamides (eq 108). The reaction of *p*-

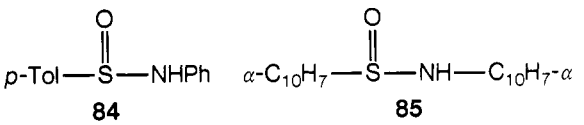


(108)

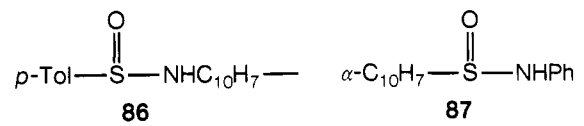
toluenesulfinamides with methyllithium has been shown to proceed with inversion[13,14] (eq 109).



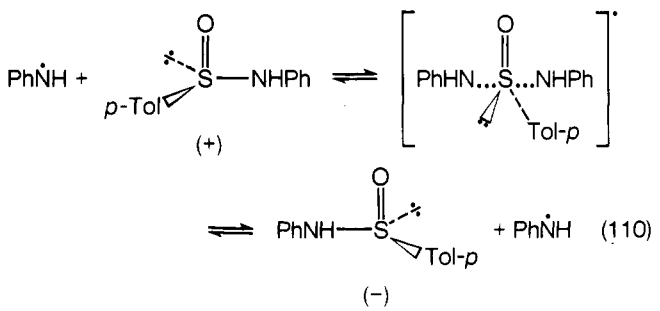
Cram and Booms showed[197] that the racemization of optically active sulfinamides **84** and **85** proceeded by a radical chain



mechanism. That S–N bond fission occurs in racemization was demonstrated by crossbreeding experiments in which racemization of a mixture of **84** and **85** was found to produce the cross-products **86** and **87**. It was suggested that the chain carrier



was ArN· and that racemization occurs via radical substitution at sulfur (eq 110).



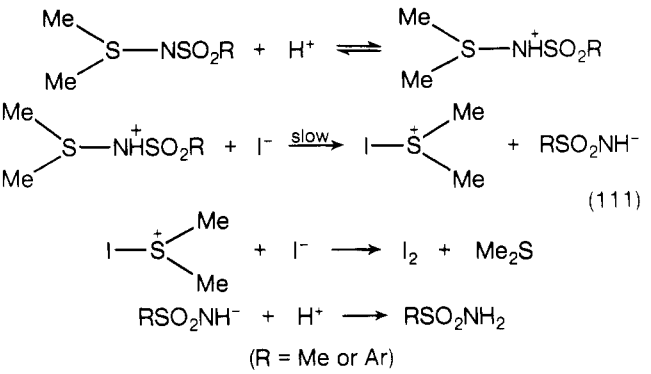
(110)

The alkaline hydrolyses of meta- and para-substituted *N*-mesitylbenzenesulfinamides correlate well with Hammett σ constants (ρ = 1.3).[198] The absence of any exalted resonance stabilization by the *p*-nitro group argues against the existence of a tetracoordinate sulfur intermediate. The absence of any oxygen-18 exchange in the partial hydrolysis of the amide in ^{18}O-enriched water is also consistent with such a view. However, as in the case of sulfite and sulfinate esters, such an intermediate if formed might be expected to decompose too rapidly for exchange to occur.

IX. Sulfimides

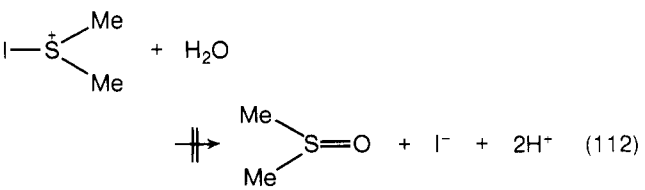
The stereochemistry of the sulfoxide–sulfimide–sulfoximide conversion reactions has been discussed in detail in section II. Kresze and Wustrow reported that[199] optically active *S*-methyl-*S*-(3-carboxyphenyl)-*N*-*p*-toluenesulfonylsulfimide underwent hydrolysis stereospecifically in 12 N hydrochloric acid. However, Cram and his co-workers[17] found that acidic hydrolysis of *N*-(*p*-tosyl)methyl-*p*-tolylsulfimide (**88**), both in 12 N sulfuric acid at 100° and 12 N hydrochloric acid at 25 °C, gave racemic sulfoxide as might be expected from the racemization of sulfoxides under such conditions.

N-Arylsulfonylsulfimides are reduced by iodide ion in aqueous perchloric acid.[200,201] A mechanism involving rate-determining



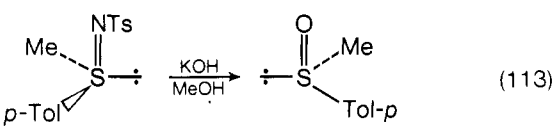
(111)

attack at sulfur by iodide ion (eq 111) was proposed. Under the conditions used no evidence could be detected of hydrolysis to sulfoxides which would involve competition of water with I^- for the dimethyliodosulfonium ion (eq 112).



(112)

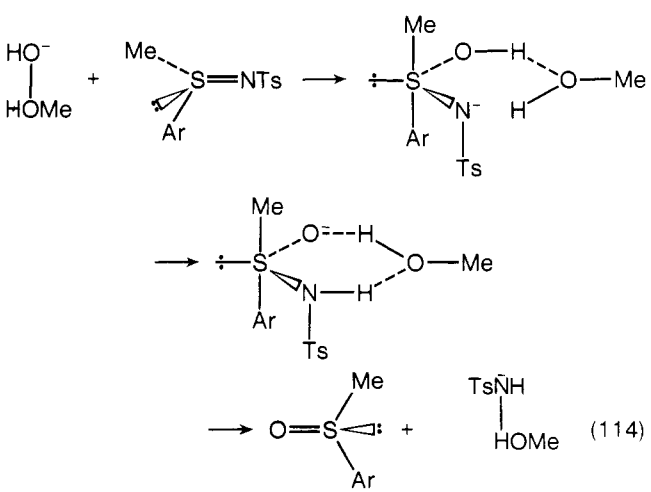
Cram and his co-workers[16–18] showed that the alkaline hydrolysis in methanol of **88** proceeds with inversion to the corresponding sulfoxide (eq 113). They proposed an e,e trigonal-



(113)

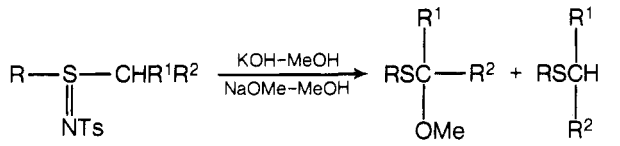
88

bipyramidal mechanism which provides bond angles between the entering and leaving group which can accommodate a six-membered ring and is consistent with inversion (eq 114).



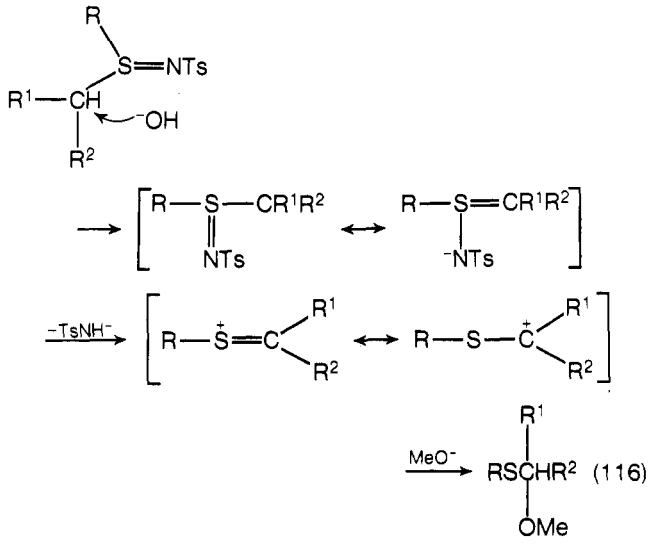
(114)

In a more general study Oae and his co-workers[202,203] found that *N*-*p*-tosylsulfimides can react with sodium hydroxide or sodium methoxide in methanol to form either the S-substitution product (sulfoxides as in eq 114) or Pummerer-type rearrangement products (α-methoxy sulfides or sulfides) (eq 115). The



R, R^1, R^2 = alkyl or aryl (115)

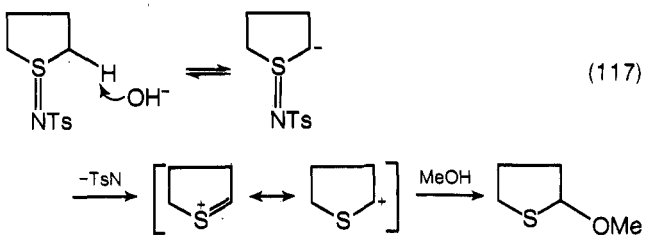
reaction products depend on the nature of the base, the solvent and the structure of the sulfimide. Most sulfimides except for diaryl-*N*-*p*-tosylsulfimides react with alkaline methanol to form either substitution or rearrangement products or a mixture of both. Steric effects on the rate of production of substitution products were found to be consistent with rate-determining nucleophilic displacement at sulfur (eq 114). An E1cb mecha-



(116)

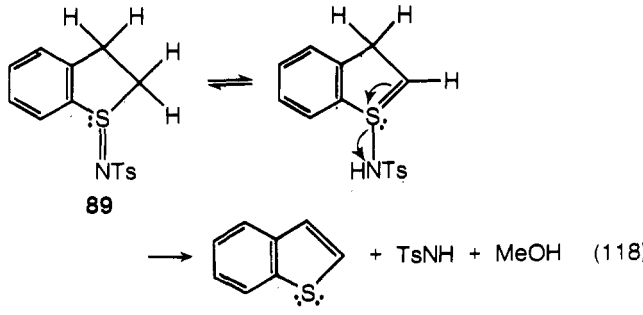
nism was proposed for the Pummerer reaction in which initial proton abstraction is followed by S–N bond cleavage (eq 116). The carbonium ion intermediate was found to be stabilized by alkyl or aryl groups attached to the α carbon.

Monocyclic sulfimides react with sodium hydroxide in methanol to form exclusively the corresponding α-methoxy sulfide (eq 117).[202] Cram and his co-workers,[18] however, found that the



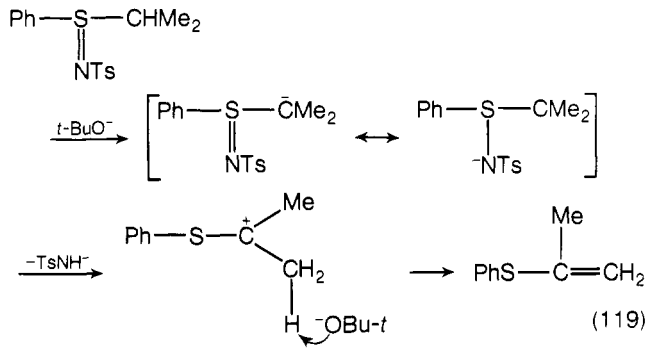
(117)

bicyclic sulfimide **89** reacted with potassium hydroxide in methanol to give benzo[*b*]thiophene (eq 118).



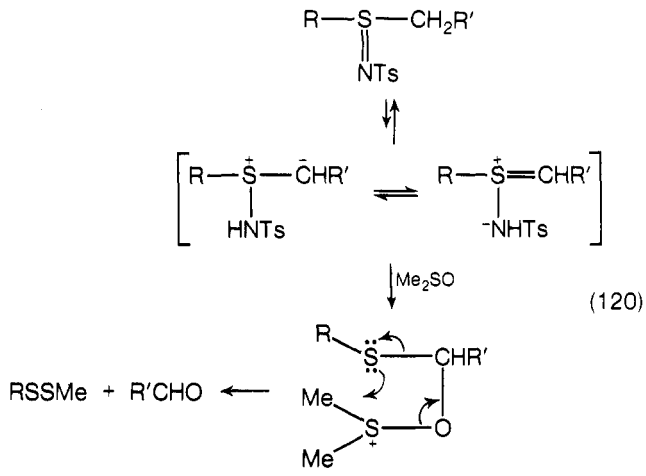
(118)

Oae and his co-workers[203,204] have recently shown that phenyl vinylene sulfides are obtained from the reaction of *N*-*p*-tosylsulfimides with potassium *tert*-butoxide in aprotic solvents. Neither the substitution nor Pummerer rearrangement products could be detected. A mechanism involving base-catalyzed α-proton removal from the Pummerer carbonium ion was proposed (eq 119).



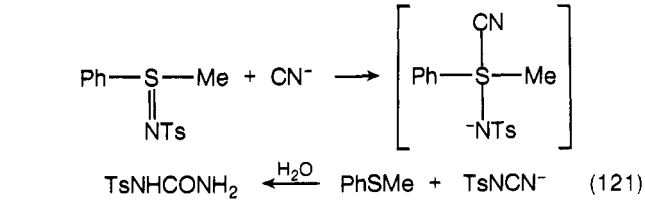
(119)

N-Sulfonylsulfimides having α-hydrogens react with dimethyl or diethyl sulfoxide at high temperature to form unsymmetric disulfides.[205] It was suggested that initial ylide–ylene formation is followed by nucleophilic attack by sulfoxide oxygen (eq 120).



(120)

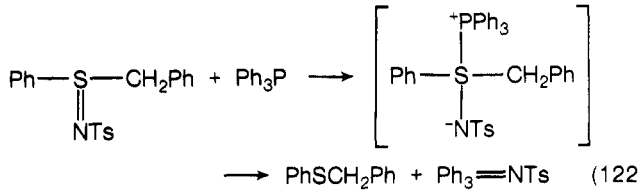
In contrast to this reaction, *N*-sulfonylsulfimides react with cyanide ion to form the corresponding sulfide and *N*-tosylurea.[206,207] Oae and his co-workers suggested that a tetracoordinate intermediate was formed (eq 121).



(121)

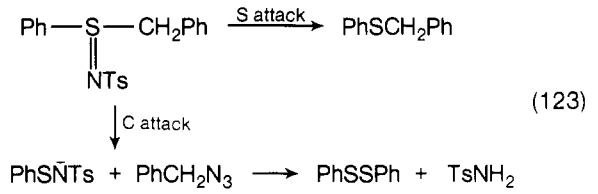
The relative reactivity toward cyanide ion of cyclic sulfimides fals in the order five- > seven- > six-membered ring. The lack of reactivity toward cyanide ion of 9-thiabicyclo[3.3.1]nonylsulfimide[207] is similar to that of the analogous bicyclic sulfoxide **46**[113] toward reduction and is consistent with a mechanism involving nucleophilic displacement at sulfur.

The reaction of other nucleophiles which are soft bases such as thiols or triphenylphosphine (eq 122) give similar reduction



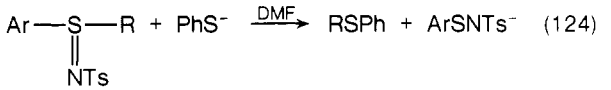
(122)

products to the cyanide ion reaction. On the other hand, harder nucleophiles like alkoxide, hydroxide, and azide give a mixture of products arising from attack at both sulfur and the benzylic carbon atom (eq 123).



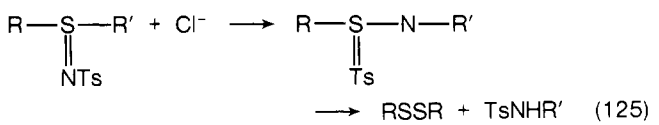
(123)

The reaction of alkyl aryl *N*-*p*-tosylsulfimides with thiophenoxide unexpectedly gives a sulfide by an SN2-type reaction on the carbon atom adjacent to sulfur (eq 124). However, in the case



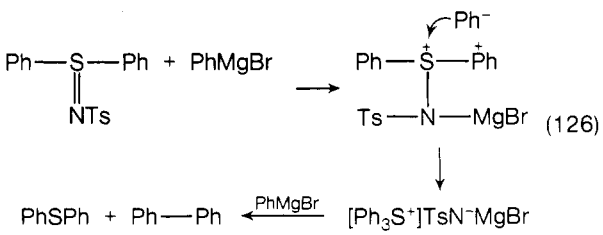
(124)

of diaryl or cyclic tetramethylene *N*-*p*-tosylsulfimides, the product obtained[208] is the original sulfide which suggests a mechanism similar to that for the reaction of sulfimides with triphenylphosphine and cyanide ion. In the presence of halide ions,[209] *N*-*p*-tosylsulfimides surprisingly rearrange to a disulfide and a sulfonamide (eq 125).



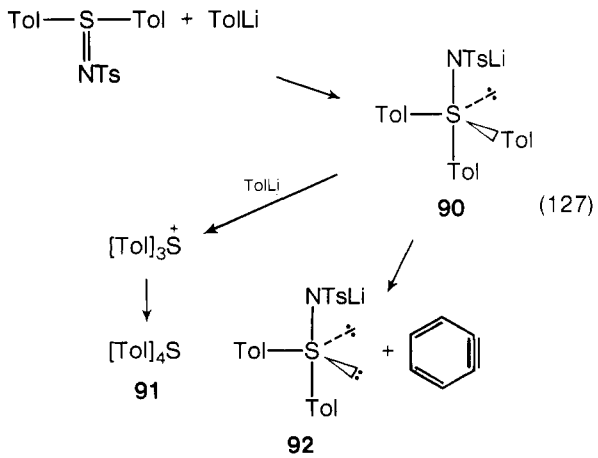
(125)

Diphenyl-*N*-*p*-tosylsulfimide reacts with phenylmagnesium bromide to form biphenyl and diphenyl sulfide.[210,211] Tracer experiments with diphenylsulfimine-*l*-^{14}C support a mechanism (eq 126) involving the formation of a sulfonium salt and rules out a benzyne mechanism.



(126)

Andersen and his co-workers[106] have suggested that the reaction of *S*,*S*-dimethyl-*N*-*p*-tosylsulfimide with *p*-tolyllithium follows a similar course to the reaction of *p*-tolyl sulfoxide with *p*-tolyllithium and occurs predominantly through a tetra-*p*-tolylsulfurane **91** which collapses to *p*-tolyl sulfide and *p*,*p*′-bitolyl (eq 127). Consistent with this view, the toluenesulfonamide anion



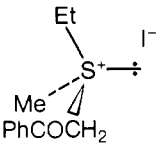
(127)

would be expected to be a better leaving group in **90** than the oxyanion in **36** (eq 51a), and the rate of formation of **91** is increased relative to that of **92** resulting in increased formation of *p*,*p*′-bitolyl and decreased formation of *m*,*p*′-bitolyl.

X. Sulfonium Compounds

A. Racemization

Carboxymethylethylmethylsulfonium chloroplatinate[1] (**1**) and phenacylethylmethylsulfonium ion[2] (**93**) were the first optically active sulfonium compounds to be prepared. Kenyon and his co-workers[212] suggested that racemization of **93** (as its iodide salt) involved a reversible nucleophilic displacement on carbon by iodide ion (eq 128). Optically active *tert*-butylethylmethyl-



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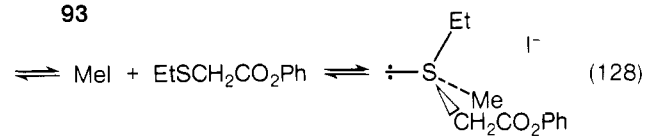
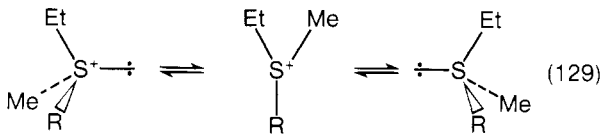


(128)

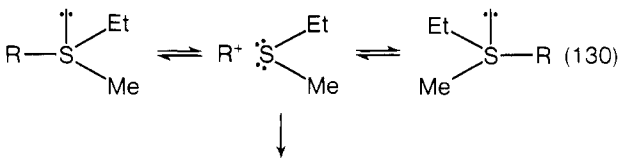
sulfonium perchlorate undergoes racemization about 10–15 times faster than it undergoes solvolysis in a variety of solvents.[213] The excess of racemization over solvolysis was interpreted by Darwish and Tourigny[213] as racemization occurring via pyramidal inversion of the sulfonium salt (eq 129).



(129)

A similar mechanism was proposed for the racemization of 1-adamantylethylmetylsulfonium,[214] benzylethylmethylsulfonium,[215] *p*-nitrobenzylethylmethylsulfonium,[215] and phenacylethylmethylsulfonium[215] perchlorate.

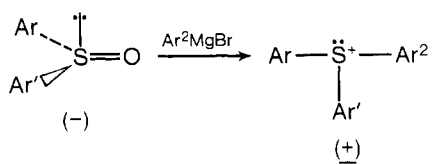
Darwish and Tourigny,[216] however, proposed that the racemization of *p*-methoxybenzylethylmethylsulfonium perchlorate occurred via carbon–sulfur heterolysis to give an unusual ion–neutral molecule pair which can react to give either solvolysis products or return to racemic sulfonium salt (eq 130). The rel-



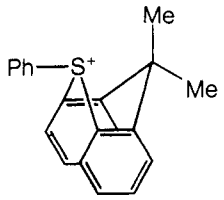
(130)

ative amounts of olefin and substitution product resulting from solvolysis vary considerably with the nature of the counterion. Brower and Wu[34] concluded that the volume of activation for the racemization of the phenacylethylmethylsulfonium ion ($\Delta v^{\ddagger} \sim 0$) is consistent with a pyramidal inversion mechanism while the value for the *tert*-butylethylmethylsulfonium ion ($\Delta v^{\ddagger} = +6.4$ ml/mol) is more compatible with a transition state in which partial dissociation has occurred.

Attempts to prepare optically active triarylsulfonium salts resulted in formation of a racemic mixture:[217]



Andersen and his co-workers[217] concluded that a triarylsulfonium ion undergoes rapid pyramidal inversion immediately after its preparation. This is totally unexpected in view of the lack of racemization of trialkylsulfonium salts at room temperature. The inversion of cyclic triarylsulfonium compounds was found to be slow even at high temperature. Thus **94** was sufficiently stable



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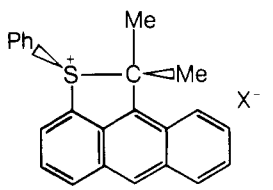
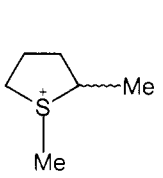


95

at 200° to study the coalescence of the *gem*-dimethyl doublet. Andersen and his co-workers concluded[217] that, since the transition state for pyramidal inversion is likely to be planar, the cyclic triarylsulfonium salt may be a poor model for the noncyclic compounds. The rate of cis–trans isomerization of the thioxiaaceanthrene **95** is comparable[218] to that reported for the racemization of **94**.

The rates of racemization of the cyclic sulfonium salts **96–98** are several orders of magnitude smaller than those of acyclic sulfonium salts.[219] This is again consistent with the high ring strain which would arise in such systems in attempting to reach a planar transition state for pyramidal inversion.



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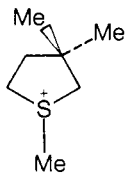

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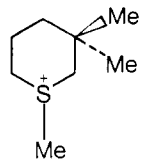
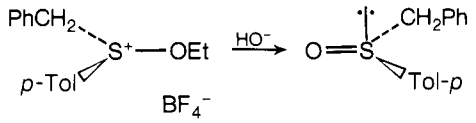


98

B. General Reactions

Johnson and McCants originally showed[6] that optically active sulfonium salts hydrolyze to the corresponding sulfoxide with inversion of configuration (eq 131). Consistent with this the hydrolysis of dimethylmethoxysulfonium perchlorate in oxygen-18 enriched water produced enriched dimethyl sulfoxide (eq 132).[220]



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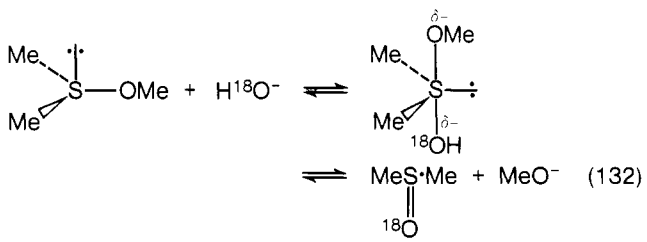
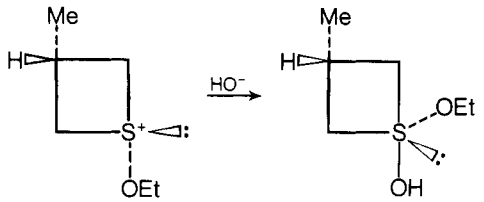


(132)

Tang and Mislow showed[7] that the base-catalyzed hydrolysis of both *cis*- and *trans*-1-ethoxy-3-methylthietanium ions proceeds with complete inversion (eq 4 and 5). This result is unexpected because if the thietanium ring takes up the anticipated a,e arrangement, axial attack by hydroxide ion of the cis isomer would give **99**. Pseudorotation about the lone pair of electrons as pivot to **100** would lead on to formation of the cis sulfoxide with *retention* of configuration at sulfur which is contrary to the experimental observation.

Mislow and Tang concluded, therefore, that if sulfur intermediates are formed and they undergo pseudorotation, they do so via high-energy intermediates of the type **101** or **102** in which either entering and leaving groups occupy equatorial positions (with the ring a,e) or the ring is constrained to occupy e,e positions with the entering and leaving groups axial. Either mechanism would result in inversion but such pseudorotation could be expected to proceed much less readily than that observed in phosphoranes.



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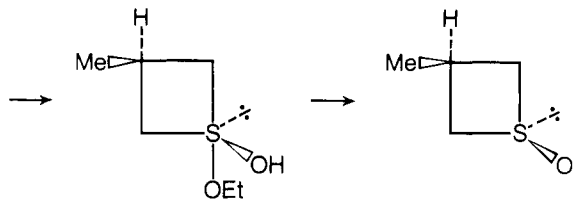

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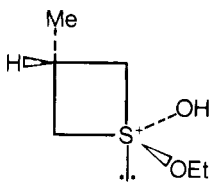

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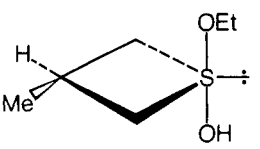
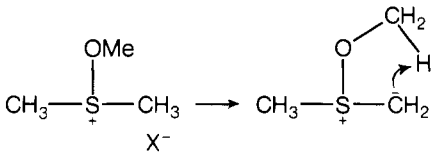


102

Many reactions of sulfonium compounds with bases involve nucleophilic displacement at carbon and/or an elimination and are outside the scope of this review.

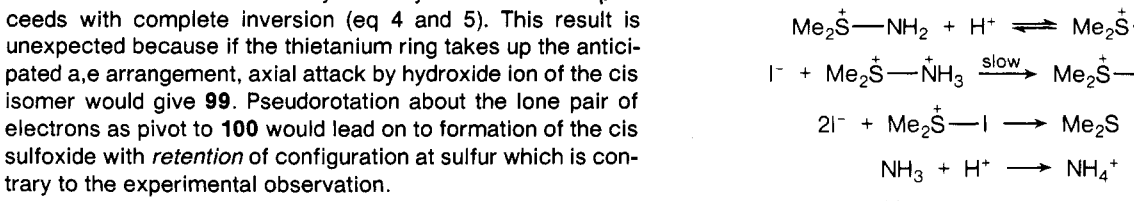
Alkoxysulfonium salts undergo rapid exchange with methoxide ion followed by either base-catalyzed collapse to carbonyl compounds and sulfides or α-rearrangement to monothioacetals.[221] Deuterium-labeling experiments suggest that the formation of carbonyl compounds occurs via a cyclic transition state involving a sulfur ylide (eq 133). Johnson and Phillips[222]



(133)

have compared the rearrangement reactions of acetoxy- and alkoxysulfonium salts with the analogous Pummerer rearrangement of sulfoxides in acetic anhydride which involves initial formation of an acetoxy sulfonium ion (eq 55).

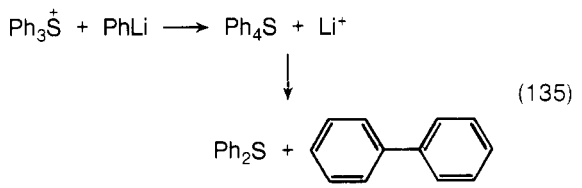
The concomitant acid and halide ion catalyzed racemization of sulfoxides involves attack by halide ion on a sulfonium ion (the conjugate acid of the sulfoxide) and has been discussed in section II. The acid-catalyzed iodide ion reduction of *S,S*-dimethylsulfinimium perchlorate[223] involves an analogous mechanism (eq 134). Kruger[223] has suggested that the sulfur



(134)

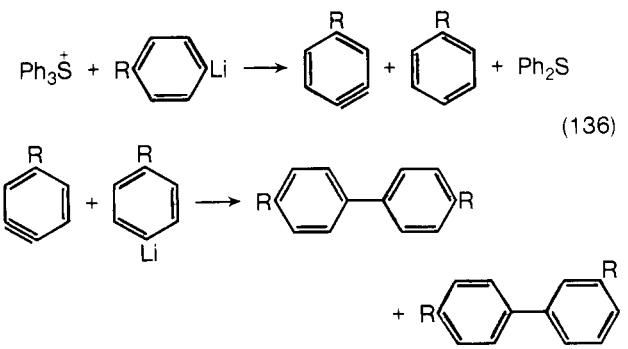
center in $Me_2SNH_3^{2+}$ is softer than that in $Me_2SOH_2^{2+}$ which is itself a borderline soft acid. Catalysis of this reaction by thiourea but not by chloride or bromide ions is consistent with the soft character of thiourea and iodide ions.

Both Wittig[224] and Franzen and his co-workers[225] showed that triarylsulfonium salts react with phenyllithium to form a sulfide and a biaryl. Wittig proposed that such reactions involved the formation of a tetraaryl sulfurane which was thermally unstable and collapsed to form the products (eq 135). Franzen, however,



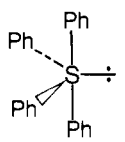
(135)

suggested that although this mechanism formed the major pathway, there was in fact a second minor pathway involving a benzyne intermediate which could lead to products (eq 136).



(136)

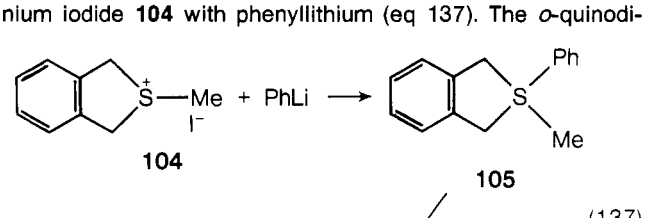
If the reaction of the tri-*p*-tolylsulfonium ion with phenyllithium proceeds solely via a benzyne intermediate, a 50:50 mixture of *p,p'*-bitolyl and *m,p'*-bitolyl products should be obtained.[226] Trost and his co-workers[105,227] were unable to detect any *m,p'*-bitolyl from the above reaction in THF at −78°, although Khim and Oae[228] reported the formation of both *p,p'* and *m,p'* isomers under reflux conditions in ether. Andersen and his co-workers[106] reinvestigated this reaction and obtained results in close agreement with those of Trost et al., but were able to detect a small amount (5%) of cross-coupling product which must originate from a benzyne mechanism. The different results of different groups of workers can probably be attributed to the different reaction conditions used. Jacobus and his co-workers[229] subsequently confirmed by carbon-14 labeling experiments that the major pathway for the reaction of triphenylsulfonium tetrafluoroborate and phenyllithium is via a tetraphenylsulfurane intermediate **103**; no evidence of a benzyne pathway



103

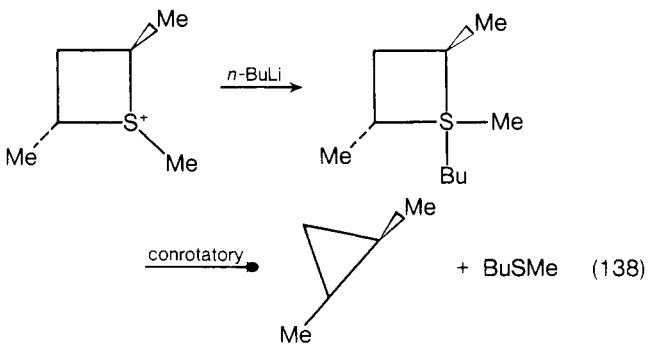
could be detected. Trost and his co-workers have studied the effect of substituents on the decomposition of both cyclic and acyclic sulfuranes.[105,227,230]

A cyclic sulfurane intermediate **105** has also been proposed[231] as an intermediate in the reaction of the cyclic sulfonium iodide **104** with phenyllithium (eq 137). The *o*-quinodimethane could not be observed but was thought to have polymerized. Trost and his group[232,233] have also studied the reaction of several cyclic sulfonium salts with *n*-butyllithium. *cis*-2,4-Dimethylthietanium borofluoride reacted to form the *cis*-dimethylcyclopropane with a high degree of stereospecificity while the cis salt produced the trans cyclopropane. A mechanism involving the formation of a cyclic sulfurane followed by its direct fragmentation in a conrotatory fashion was suggested (eq 138).



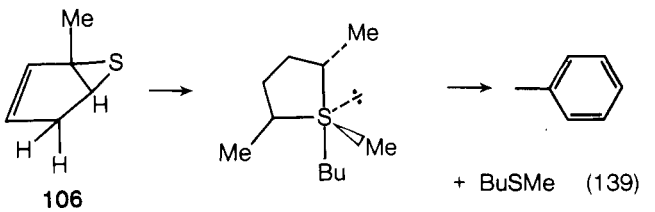
104 **105**

(137)



(138)

The reaction of 2,5-dihydrothiophenium salts with *n*-butyllithium produces both elimination and fragmentation products.[233] The complete stereospecificity of the fragmentation reaction is again attributed to the disrotatory fragmentation of a sulfurane intermediate; e.g., the trans salt **106** produces exclusively *cis,trans*-2,4-hexadiene (eq 139).

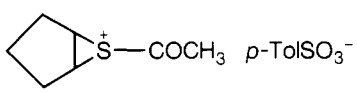


106

(139)

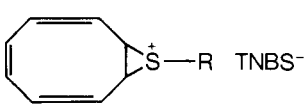
C. Episulfonium Salts

An early report[234] suggested that an episulfonium salt was formed on methylation of a terpene episulfide. The existence of cyclopentene-*S*-acetylepisulfonium *p*-toluenesulfonate (**107**)



107

was proposed on the basis of spectroscopic evidence.[235] Subsequently Helmkamp and Petit[236,237] isolated a series of episulfonium salts **108** from the reaction of cyclooctene and alkanesulfenyl 2,4,6-trinitrobenzenesulfonate (TNBS). Such salts



108

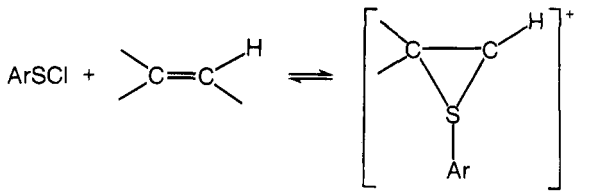
(R = alkyl)

can also be prepared by the alkylation of cyclooctene sulfide with either trimethyloxonium TNBS or with a tertiary halide and silver TNBS.

Kharasch and Buess suggested[238] that when vinyl sulfides or β-acetoxy sulfides as well as the 1:1 adduct were formed in the reaction of 2,4-dinitrobenzenesulfenyl halides with olefins, such products were formed via an intermediate episulfonium ion **109** (eq 140).

Several groups of workers have shown that addition to cis–trans olefin pairs is stereospecific and trans.[239,240] An ionic mechanism is supported by the effect of substituents ($\rho = -2.2$) on the addition of 2,4-dinitrobenzenesulfenyl chloride to para-substituted styrenes.[241] Solvent[242] and salt effects[242-244] are also consistent with such a mechanism.

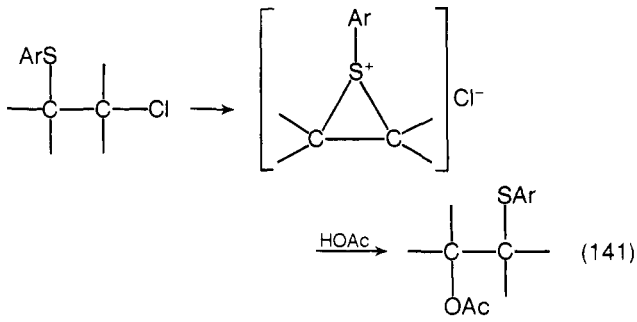
The existence of episulfonium ion intermediates has also been deduced from quite a different type of reaction—the solvolysis



109

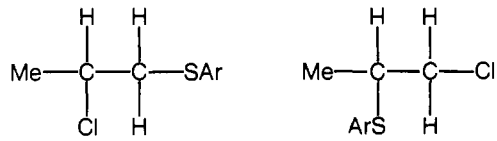
products (140)

of β-chloro sulfides (thioethers). Unusual rate accelerations have been attributed to the formation of cyclic sulfonium ions arising from neighboring group participation by sulfur[245] (eq 141). The



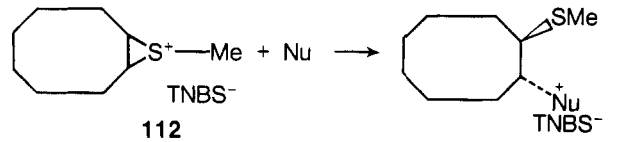
(141)

autoprotolysis of **110** and **111** gave identical product mixtures again suggesting a common cyclic intermediate. The various steric and electronic factors which control the direction of ring-opening of episulfonium ion intermediates in the addition of aryl and alkyl sulfenyl halides to olefins have been examined.[246-248]



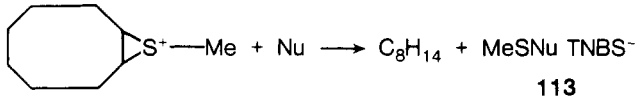
110 **111**

Helmkamp and his co-workers[249] have investigated the reaction of a variety of nucleophiles on *cis*-cyclooctene-*S*-methylepisulfonium TNBS (**112**) in the presence of excess cyclohexene. Nucleophilic attack on carbon occurs with both pyridine and acetate ion leading to the formation of 2-substituted cyclooctylthioethane (eq 142). In the case of acetate ion a



112 (142)

substantial amount of cyclooctene was also formed. Nucleophilic substitution at sulfur occurs with methyl mercaptide, thiourea, and tributylphosphine to form cyclooctene and a methanesulfenyl compound **113**, via transfer of the methanesulfenyl group to the

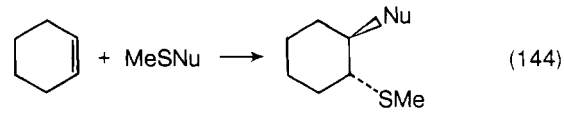


113

112 (143)

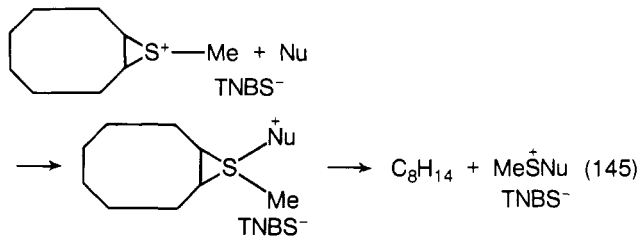
nucleophile (eq 143). With chloride ion, bromide ion, and dimethyl sulfide, nucleophilic attack also occurs at sulfur with the formation of a sulfenyl compound which adds on to cyclohexene (eq 144).

In some cases the sulfenyl compound arising from nucleophilic attack at sulfur is unstable. Thus the reaction of iodide ion



(144)

with **112** forms dimethyl sulfide. Fluoride ion was found to give cyclooctene as the only product. The yield of cyclooctene correlates with the softness of the nucleophile, the more highly polarizable nucleophiles giving high yields, while the less polarizable anions give lower yields of cyclooctene and attack carbon to open episulfonium ring. Thus the sulfonium sulfur of **112** is softer than a ring carbon atom in the same salt.

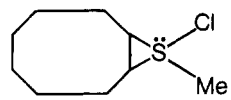


(145)

114

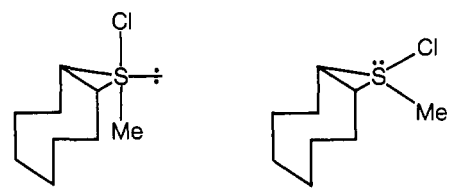
The desulfurization of **112** by nucleophiles such as tributylphosphine could occur via a tetracoordinate sulfur intermediate **114** (eq 145).

In a study of the reaction of the episulfonium ion **108** with tetraphenylarsonium chloride, Helmkamp and his co-workers[250] observed the rise and decay of an NMR signal which could be attributed to the *S*-methyl group of the intermediate **115**. This



115

was the first physical evidence for the existence of a tetracoordinate sulfur species. Models of **115** show that a trigonal-bipyramidal structure **116** would give rise to unfavorable van der Waals interactions between the hydrogen atoms bound to C-2 and C-7 and either the methyl group or the chlorine atom. Such constraints are absent in the square-planar structure **117**. Molecular orbital calculations are consistent with this view and Helmkamp and his co-workers[250] concluded that the exceptional stability of **115** arises from a combination of electronic and steric factors.



116 **117**

XI. Addendum

Further examples of the synthesis of chiral sulfimides,[251] sulfodiimides,[251] and thiosulfinate S-esters[252] have been reported. Thiosulfinate S-esters undergo stereospecific nucleophilic substitution at sulfinyl sulfur to yield the corresponding sulfinamides and sulfinates.[252]

Epoxides undergo ring-opening with Me_2SO in the presence of strong acids to form initially, in most cases, vicinal hydroxyalkylsulfonium salts.[253] These yield mixtures of 1,2-ketols and glycols on treatment with base.

Kaiser and his co-workers have shown that an α-effect operates at sulfinyl sulfur in a study of the nucleophile-catalyzed hydrolysis of diphenyl sulfite.[254] The synthesis of some azabicyclic amidosulfites has been reported.[255] The reaction of alkyl chlorosulfinates with tetrahydrofuran produced predominantly

4-chlorobutylalkyl ethers whereas with ethylene oxide the main products were β-chloroethylalkyl ethers.[256] In aqueous dioxane the equilibrium between naphthalene-1,8-disulfinic acid and the corresponding sulfinyl sulfone strongly favors the latter compound.[257]

A facile intramolecular transalkylation involving general-base-catalyzed attack of an alcohol on the sulfonium compound *S*-adenosyl-L-methionine has been observed.[258] The reaction of nucleophiles with sulfonium ions containing electron-withdrawing substituents leads to three different types of product.[259]

XII. References

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