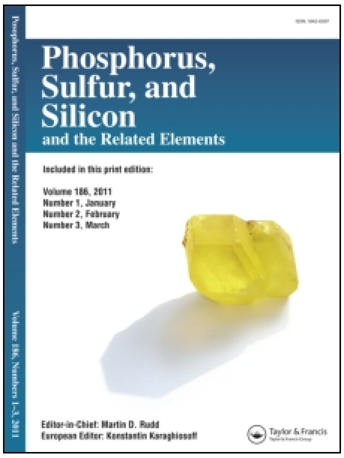

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# REACTIVITY OF SULFUR HETEROCYCLES

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# REACTIVITY OF SULFUR HETEROCYCLES

by

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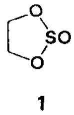
The relationship between ring strain and the reactivity of alicyclic compounds has been of fundamental importance in the development of modern organic chemistry. Because of their biological interest, the reactivity and stereochemistry of cyclic phosphorus compounds have been extensively studied.[1,2] In recent years the reactivity of cyclic sulfur compounds has also begun to attract considerable interest. In 1966 it was pointed out that the common feature of sulfur-containing heterocycles is that nucleophilic attack at sulfur, be it di-, tri-, or tetra-coordinated, is always faster than the corresponding open-chain analogues.[3] The present review attempts to discuss some of the factors which affect the reactivity of cyclic sulfur compounds towards nucleophilic attack and to draw attention to some of the recently observed exceptions to this generalization.

## I. Sulfates and Sulfonates

One of the earliest systematic studies of the effect of ring size on the reactivity of sulfate esters was carried out by Westheimer and his co-workers who showed[4] that ethylene sulfate (1) hydrolyses in alkaline solution some twenty times faster than dimethyl sulfate (3) and approximately one hundred times faster than the six-membered analogue, trimethylene sulfate (2). However, whilst ethylene sulfate hydrolyses partially by sulfur–oxygen bond-fission, (2) and (3) hydrolyze exclusively with carbon–oxygen bond-fission so that relative rates of attack at sulfur in these systems could not be accurately determined. To overcome this problem Kaiser and co-workers[5] compared the rates of hydrolysis of catechol cyclic sulfate (4) and diphenyl sulfate (5) which hydrolyze exclusively with sulfur–oxygen fission. The relative rates of hydrolysis ($2 \times 10^7$) are an accurate measure of the difference in the rate of attack at sulfur in the five-membered heterocycle (4) compared to its open-chain analogue (5). In the corresponding sulfonate esters, the sultone (6) hydrolyzes some $7 \times 10^5$ times faster than phenyl α-toluene sulfonate (8).[6] Furthermore the rate of hydrolysis of the six-membered cyclic sulfonate (7) is about $10^4$ times less than that of (6).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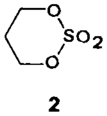
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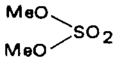
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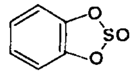
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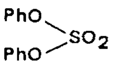
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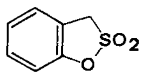
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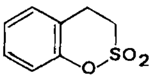
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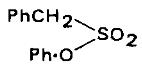
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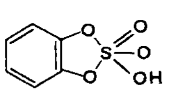
This leads to the most commonly observed order of reactivity of sulfur heterocycles viz. 5-membered ring ≫ six-membered ring > open-chain analogue. This order of reactivity is observed in the hydrolysis of both sulfate and sulfonate aromatic esters. The difference in reactivity between the five-membered ring and its open-chain analogue (the so-called kinetic acceleration) for both sulfates and sulfonates ($10^5$-$10^7$ times) is of a similar order of magnitude to that observed in the hydrolysis of phosphonates and phosphates.[1] Thermochemical measurements show that the chief driving force for the rapid ring-opening of five-membered sulfur heterocycles is ring strain. Thus the heat of hydrolysis of ethylene sulfate is *ca.* 5-6 K cal mol$^{-1}$ more than for dimethyl sulfate.[4] The heat of hydrolysis of methyl ethylene phosphate exceeds that of trimethyl phosphate by a similar amount.[7] Westheimer showed that such enthalpy strain accounts for most but not all of the kinetic acceleration observed in five-membered cyclic phosphate esters.[8] The important observation that kinetic acceleration is observed for five-membered cyclic phosphates, not only for ring-opening saponification but also for reactions not involving ring-fission such as oxygen-exchange and cleavage of groups external to the ring, led to the suggestion that such reactions proceed via a trigonal bipyramidal intermediate which can undergo pseudo-rotation allowing strain in the five-membered ring to decrease without ring-opening.[1]

The existence of pentacovalent intermediates in alkaline hydrolysis of sulfate and sulfonate esters could not be detected by partial hydrolysis in oxygen-18 enriched water followed by isolation of the unhydrolyzed ester.[9] However, the absence of oxygen–exchange does not rule out the possibility of the formation of such an intermediate since the rate of oxygen–equilibration of the intermediate might be much slower than its decomposition. This might well be expected if oxygen equilibration involves pseudorotation amongst trigonal bipyramidal intermediates because it has been suggested that such a process would be much slower at sulfur than at phosphorus.[10] It seems reasonable to assume that if the hydrolyses of sulfate and sulfonate esters proceed via a pentacoordinate intermediate of the type (9) for the alkaline hydrolysis of catechol sulfate, then strain would be relieved on going from the ester to such an intermediate if it has the trigonal-bipyramidal structure (10) in which the five-membered ring spans an apical and a basal position.

Ring strain in alicyclic systems has been discussed primarily in terms of bond angle deformations, bond stretching, torsion about the dihedral angles and non-bonding interactions.[11,12] The origin of ring strain in cyclic esters has been the subject of much discussion which has centred around three possible causes viz. (a) angle strain,[13] (b) strain-induced changes in the 2p-3d $\pi$-character of the endocyclic oxygen-hetero-atom bonds[14,15] and 1,3-non-bonding interactions between the oxygen atoms.[4]



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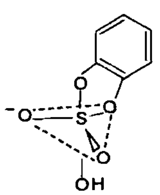
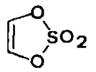


**10**

X-ray structure analysis shows the presence of considerable ring-strain in five-membered cyclic sulfates and sulfonates. The internal O–S–O bond in catechol sulfate (4) is only 97.1°[15] and the corresponding C–S–O angle in the sultone (6) is 96.1°.[16] The six-membered sultone (7) which undergoes alkaline hydrolysis only ten times faster than its open-chain analogue (8) is much less strained than the five-membered ring having a much larger internal C–S–O bond angle of 101.4° and a larger C–O–S bond angle (116.9° compared to 108.9°).[17] Boer and Flynn have shown[18] that all the angles in catechol sulfate are strained. The O–C–C angles are distorted to values of 112.5° and 110.7°, well below the normal angle for sp$^2$-hybridized carbon. The two S–O–C angles (108.6° and 108.7°) are also considerably less than the values expected for an acyclic diester.[18] The internal O–S–O bond in ethylene sulfate (98.4°) is similar to that for catechol sulfate and is again indicative of considerable ring-strain.[16] A particularly interesting compound is vinyl sulfate (11) which is extraordinarily reactive and has an O–S–O bond angle of 93.6°, very close to that required for a trigonal-bipyramid intermediate for alkaline hydrolysis.[15] Another interesting feature of the geometry of (11) is that the C–O bond distance falls from 1.46 Å in (1) to the very short distance of 1.24 Å in (11), whereas the internal S–O bond length increases from 1.53 Å in (1) to 1.62 in (11).



**11**

The earlier proposal that 2p-3d $\pi$-bonding between the endocyclic oxygen atoms and the heteroatom could induce strain in cyclic phosphate esters has now been largely abandoned. Although nmr studies have shown that phosphorus nuclei in strained cyclic phosphoranes seem to be more shielded than their unstrained open-chain counterparts,[14] this does not appear to arise from ring-strain because X-ray analysis could detect no difference in the corresponding endo- and exocyclic P–OC bond lengths.[19] Boer and Flynn have suggested that any changes in multiple bond characters of sulfur and phosphorus cyclic esters are more likely to be electronic in origin.[18]

X-ray studies of catechol sulfate (6) have shown that the five-membered ring is unexpectedly distorted to a non-planar envelope structure where the sulfur atom lies 0.249 Å above a plane through the six carbon and two oxygen atoms.[18] The most likely cause of such an effect lies in 1,3-interactions between the lone pairs of the ring oxygen atoms and the exocyclic oxygens. Such interactions in the five-membered ring could be minimized by bending into a non-polar conformation. Davis has predicted theoretically[20] that whereas such interactions are negligible in the five-membered ring of ethylene sulfite with only one exocyclic oxygen atom, they could be larger in a cyclic ester with four oxygens attached to phosphorus or sulfur as in phosphates or sulfates.

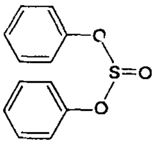
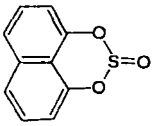
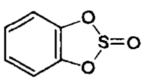
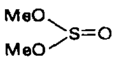
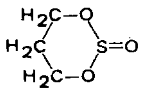
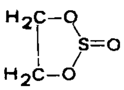
It seems likely therefore that although the major cause of enthalpy strain observed in the alkaline hydrolyzes of sulfate and sulfonate esters from angle strain, lone-pair-lone-pair repulsions may also contribute to the observed destabilization of the five-membered ring. There is also another important factor which could influence the kinetic acceleration. Determination of the Arrhenius parameters for the alkaline hydrolysis of cyclic and open-chain phosphoryl compounds has demonstrated that some of the high reactivity of five-membered cyclic phosphates arise from a more favourable entropy of activation.[21] There is no comprehensive data available at present, however, to indicate the importance of such entropy-strain effects in the hydrolyzes of sulfate and sulfonate esters.

## II. Sulfites

It has been shown by oxygen-18 labelling studies that the hydrolyzes of organic sulfites (with only one or two unusual exceptions) proceed entirely with sulfur-oxygen bond-fission.[22] The rates of alkaline hydrolysis which therefore reflect the rates of attack at sulfur are shown in Table I. Although the differences in reactivity between the cyclic and open-chain esters are less dramatic than for the corresponding sulfates and sulfonates, the relative order of reactivity viz: five-membered ring ≫ six-membered ring > open-chain ester is still the same.

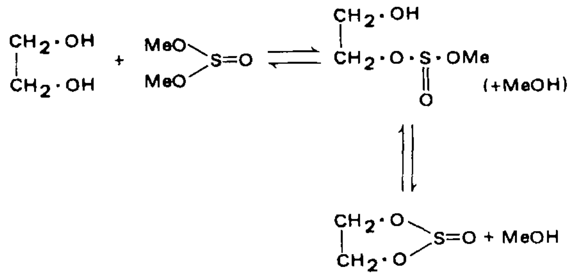
TABLE I

Relative Rates of Alkaline Hydrolysis of Organic Sulfites[a] [23]

| | | |
|---|---|---|
|  |  |  |
| $1.3 \times 10^6$ | $16 \times 10^6$ | $2.0 \times 10^9$ |
|  |  |  |
| 1.0 | 30 | 8000 |

[a] In aqueous (1%) dioxane at 25°.

Thermochemical data for the hydrolysis of sulfate esters shows that the observed kinetic acceleration does not arise from relative strain in the initial states because the heats of hydrolysis of the five-membered cyclic esters and their open-chain analogues are identical within experimental error.[20,24] The absence of strain in the five-membered cyclic sulfite ring has also been confirmed by transesterification studies.[25] Mixtures of dimethyl sulfite and ethylene glycol or ethylene sulfite and methanol in the presence of traces of acids or bases readily form an equilibrium mixture suggesting that ring-opening and ring-closure occur readily.



The Arrhenius parameters for the alkaline hydrolysis of sulfites (Table II) throw some light on the origin of the observed kinetic acceleration.

In the aliphatic series it is clear that the main cause of kinetic acceleration lies in the entropy of activation. This increases with ring size, the value for the seven-membered ring being almost identical to that for the open-chain sulfites. The aromatic sulfites show similar behaviour. The main cause of the difference in activity

TABLE II

Arrhenius Parameters for the Alkaline Hydrolysis of Organic Sulfites[26]

| Sulfite | $\Delta H^\ddagger$ (k cal mol$^{-1}$) | $\Delta S^\ddagger$ (eu) |
|---|---|---|
| Ethylene | 10.2 | −14.7 |
| Trimethylene | 12.3 | −18.1 |
| Tetramethylene | 12.3 | −23.7 |
| Dimethyl | 11.2 | −23.9 |
| Catechol | 5.6 | −6.2 |
| 1,8-Naphthylene | 8.1 | −6.7 |
| Diphenyl | 6.6 | −17.4 |

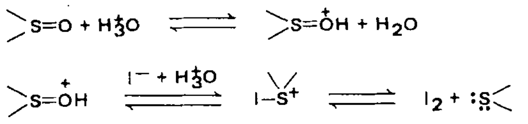
between catechol sulfite and diphenyl sulfite is the dramatic fall in the value of $\Delta S^{\ddagger}$. The role of entropy contributions to the kinetic acceleration of five-membered cyclic sulfites has been discussed[26,27,28] in terms of Taft's "*entropy-strain*" principle.[29] Both the open-chain and larger rings (>5 atom) sulfites have relatively mobile forms whereas five-membered cyclic sulfites like ethylene sulfite and catechol sulfite have relatively rigid structures. This does not mean, however, that they are strained as shown by the thermochemical data.[20,24] In the transition state for hydrolysis the ester takes up a more ordered structure and the molecular motions of the alkyl or aryl groups and the larger ring sulfites are suppressed. This loss of entropy increases the free energy of activation. For the five-membered cyclic sulfites the molecule is already constrained and far less energy is required to reach the transition state, resulting in a lower free energy of activation.

It has been suggested that the alkaline hydrolyses of sulfite esters proceed via the formation of a trigonal bipyramidal intermediate.[30] Unlike the hydrolysis of sulfate esters, however, such a process is not required to be associated with relief of ring strain. A model of ethylene sulfite shows an internal O–S–O bond-angle if 102° which is some way from the 90° required in such a transition state.[31] Bunton and his co-workers[22] were unable to detect any significant oxygen-exchange in the hydrolysis of ethylene sulfite. As in the case of sulfates and sulfonates, however, such evidence does not exclude the possibility of the formation of an intermediate. Kice has discussed some of the reasons which lead to the conclusion that oxygen-exchange in a trigonal-bipyramidal intermediate for the hydrolysis of cyclic sulfites would be slow.[32]

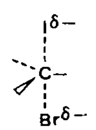
In acid solution sulfite esters show quite a different reactivity sequence. The open-chain dimethyl sulfite hydrolyzes about twenty times faster than ethylene sulfite.[33,34] It is not known whether the rate differences in acid solution arise from differences in basicity of the sulfates or in the relative reactivity of their conjugate acids. The site of protonation is not known unequivocably either.

### III. Sulfoxides

The effect of ring size on the acid catalyzed reduction of cyclic sulfoxides by iodide ion has been studied by Oae and co-workers.[35] This reaction involves nucleophilic displacement at the sulfur atom by iodide ion:



For alicyclic sulfoxides the rates of reduction fall over a 700-fold range in the sequence 5- > 4- > open-chain > 7- > 6-membered cyclic sulfoxide. This sequence does not parallel the relative order of basicity suggesting that other factors control the overall rate of reaction. This order of reactivity is identical to that observed for nucleophilic substitution in carbocyclic compounds involving a hybridization change from $sp^3 \rightarrow sp^2$ (except for the four-membered ring which is known to hydrolyze by a different mechanism).[36] It has been assumed that both reactions proceed via similar trigonal bi-pyramidal transition states, viz. (12) and (13).



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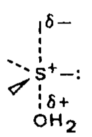


**13**

This would imply a high-energy transition state for the sulfoxide reaction (13) in which the thietane ring spans basal-basal positions.[10]

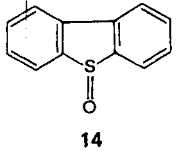
Analysis of the Arrhenius parameters for the reduction of sulfoxides (Table III) leads to some interesting conclusions.

**TABLE III**

**Reduction of Aliphatic Sulfoxides[35]**

| Sulfoxide | Rel. rate | $\Delta H^{\ddagger}$ (k cal mol$^{-1}$) | $\Delta S^{\ddagger}$(eu) |
|---|---|---|---|
| thietane-1-oxide | 34.7 | 20.0 | −6.7 |
| thiolane-1-oxide | 717. | 15.7 | −15.1 |
| thiane-1-oxide | 1.00 | 17.6 | −21.6 |
| thiepane-1-oxide | 9.9 | 16.1 | −22.2 |
| dimethyl sulfoxide | 32.6 | 17.4 | −15.2 |

The greater reactivity of the five-membered sulfoxide compared to either the six- or seven-membered analogues is due primarily to its more favourable entropy of activation. Its rigid structure in the ground state must be such that it closely resembles the geometry required in the transition state and can reach this with little loss of entropy. Dibenzothiophene oxide (14), which has an even more rigid structure has a still lower value of $\Delta S^{\ddagger}$ (−10.4 eu). Thietane-1-oxide provides an interesting extension of these ideas. The small value of $\Delta S^{\ddagger}$



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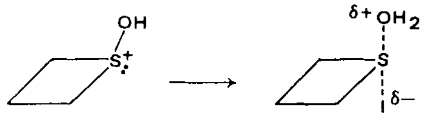
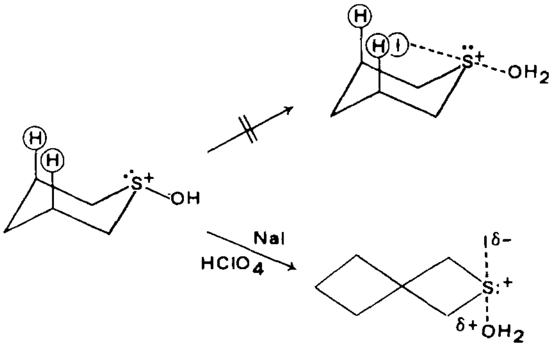
again indicates there is little change of rigidity on reaching the transition state whilst Oae has suggested that[35] the relatively large activation energy reflects the energy required to overcome the unusual angle strain present in the transition state (**15**) for this compound.



**15**

It is possible that in this case, however, direct nucleophilic attack of iodide ion at sulfur occurs to produce the ring cleavage product instead of the reduction product.

Oae and co-workers[35] have suggested that attack of sulfur by iodide ion is hindered by steric effects of β-axial hydrogens in six- and seven-membered sulfoxides and that such interactions can be minimized by twisting of the ring into a half-chair form (**16**). Some confirmation of this view comes from the extremely low reactivity towards reduction of the bicyclic (3.3.1)-9-sulfoxide, (**17**), which is so rigid that it cannot bend to minimize steric effects.



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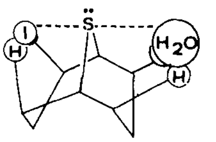


**17**

Sulfoxides can also be reduced with sodium hydrogen sulfite. The rates of reduction using this method again reach a maximum for the five-membered thiolane-1-oxide as for acid-catalyzed iodide ion reduction.[37] What appears to be the typically high reactivity of the five-membered sulfoxide ring also shows up in the hydrochloric acid-catalyzed stereomutation of sulfoxides where thiolane-1-oxide has been found to react about four hundred times faster than the six-membered thiane-1-oxide.[38]

## IV. Sulfides and Disulfides

There has been considerable interest in the reactivity of cyclic disulfides because of the importance of α-lipoic acid in biological systems.[39] In most reactions observed to date 1,2-dithiolanes are more reactive than open-chain disulfides in nucleophilic, electrophilic and radical reactions at the S–S bond. Thus Fava and his co-workers showed that 1,2-dithiolane reacts with thiobutoxide [eq (1)] about $10^4$ times faster than does the open-chain n-butyldisulfide [eq (2)].[40]

(1)

$$n\text{-Bu}^{*}\text{S}^{-} + n\text{-BuS–S-Bu-}n \longrightarrow n\text{-Bu}^{*}\text{S–S–Bu-}n + n\text{-Bu S}^{-} \quad (2)$$

In contrast to six-membered ring dithianes, unsubstituted 1,2-dithiolanes undergo a rapid ring-opening polymerization.[39,40] The order of reactivity towards cyanopropyl radicals is 5-membered > 6-membered > open-chain disulfide.[42] Similarly 1,2-dithiolanes are much more readily oxidized by persulfate than dithianes. Open-chain disulfides and the seven-membered dithiepanes do not react with this reagent.[39,41]

One of the major causes of the high reactivity of dithiolane is undoubtedly the strain present in the five-membered ring. The optimum strain-free dihedral angle, $\phi$ between the two substituents attached to the S–S bond in open-chain disulfides is about 90°.[43,44] In this conformation, repulsion between the non-bonding lone-pairs of the sulfur atoms is minimized and maximum overlap of these orbitals with the d-orbitals of adjacent sulfur atoms is permitted, leading to an S–S bond with considerable double bond ($d_\pi$-$p_\pi$) character and inhibiting restricted rotation.[44,45] Incorporation of the disulfide group into a cyclic disulfide leads to a decrease of the dihedral angle with decreasing ring size. Thus $\phi$ is reduced to about 70° in dithiane[46] and to 27° in dithiolane.[43] With reduction in ring size, the double bond character of the S–S bond decreases and lone-pair-lone-pair repulsions increase leading to an increase in ring strain.

Although the subject of earlier controversy more recent thermochemical and kinetic measurements establish that the ring strain in the dithiolane ring is about 4 k cal $\text{mol}^{-1}$.[40,47] Hudson and Filippini[48] have elegantly demonstrated that the enhanced nucleophilic reactivity of cyclic sulfides towards methyl fluorosulfonate [eq (3)] is related to the dihedral angle, $\phi$. The rate of reaction (Table IV) increases regularly with the energy of orbital splitting which is related to $\phi$ and gives a measure of the destabilization

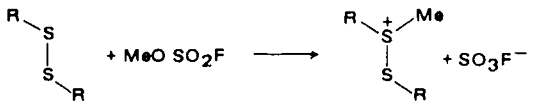
TABLE IV

Comparison of Reactivity of Disulfides with Dihedral Angle $\phi$

| Disulfide | Cos $^2\phi$ | log $k_c/k_a$† |
|---|---|---|
| EtS–S Et | 0.01 | 0 |
| 1,2-dithian | 0.25 | 0.52 |
| α-lipoic acid | 0.67 | 1.57 |

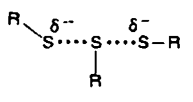
† $k_c/k_a$ is ratio of rates of cyclic and acyclic disulfide.

of the nucleophile (and hence an increase in its reactivity) due to pπ-pπ lone-pair repulsions.



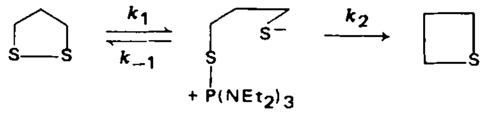
(3)

These observations suggest that in electrophilic reactions at the sulfur atom of disulfides, orbital splitting is the main cause of the enhanced reactivity of the five-membered dithiolane ring although other factors such as bond angle deformations may also contribute to the ring strain. Schmidt and his co-workers have suggested,[49] however, the entropy strain is the predominant cause of the kinetic acceleration ($10^4$ times) observed in the reaction of mercaptide ions with disulfides [eqs (1) and (2)]. It is generally assumed that the transition state for nucleophilic attack at di-coordinate sulfur proceeds through a transition state in which the incoming and outgoing groups are collinear.[40,50] In the transition state for attack of 1,2-dithiolane by thiobutoxide, the three sulfur atoms would be collinear, the S–S bond would be stretched and to minimize repulsions the valency angle at the attacked sulfur atom would be decreased to 90° (18). Schmidt and co-workers[42] have pointed out that the ground state of 1,2-dithiolane (valency angle S atom 92°; S–S bond length, 2.1 Å) is more similar in its geometry to the transition state than is the ground state of an open-chain disulfide (valency angle at S, 107°; S–S bond distance, 2.05 Å). Hence far less energy is required to reach the transition state for the reaction of 1,2-dithiolane than for an open-chain disulfide. Davis has similarly argued[51] that entropy strain is the main cause of kinetic acceleration for nucleophilic reactions of disulfides.



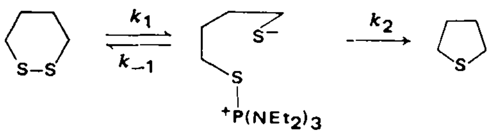
**18**

In the ionic cleavage of cyclic disulfides by tris-(diethylamino) phosphine, 1,2-dithiolane reacts about 10,000 times faster than its open-chain analogue, diamyl disulfide.[52] Surprisingly, however, 1,2-dithian reacts [eq (5)] about twice as rapidly as the "more strained" 1,2-dithiolane [eq (4)].



(4)

**19**

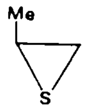


(5)

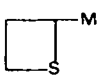
**20**

Harp and Gleason have suggested[52] how this apparent paradox can arise from the relative magnitudes of $k_1$, $k_{-1}$ and $k_2$. Ring-opening ($k_1$) of the strained five-membered cyclic disulfide is rapid whereas the reverse cyclizaton of the phosphonium salt (**19**) will be slow because it involves formation of a four-membered ring. On the other hand 1,2-dithiane is less strained than 1,2-dithiolane and its ring-opening will be slower. Forward cyclization of (**20**) leading to a five-membered sulfide will be more rapid than the corresponding reaction of (**20**) leading to thietane. Thus for 1,2-dithiolane the kinetic acceleration for ring-opening due to enthalpy strain is offset by a decrease in $k_2$ because of the high energy required to form a four-membered transition state.

No systematic studies of the effect of ring size on the reactivity of cyclic sulfides have been reported. However, under carefully controlled conditions alkyl lithiums attack sulfur-heterocycles exclusively at sulfur if severe bond-angle distortions are present.[53]



**21**

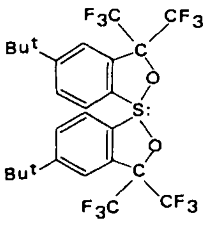


**22**

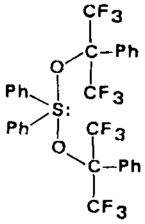
Both 2-methylthiocyclopropane (**21**) and 2-methylthietane (**22**) react with ethyl lithium to form carbanion intermediates which rapidly polymerize to linear polymers, whereas thiolane and thiepane fail to react.

## V. Sulfuranes

Martin and his co-workers have recently made some remarkable observations about the reactivity of spirocyclic sulfuranes in which a sulfur atom forms part of a bicyclic system.[34] The five-membered bicyclic system (23) is very unreactive towards base hydrolysis compared to its open-chain analogue 24, the general order of reactivity observed for sulfuranes was acyclic $>$ monocyclic $>$ spirocyclic and very probably acyclic $\gg$ spirocyclic for sulfurane oxide hydrolysis. This order of reactivity is completely opposite to that observed in other sulfur heterocycles. Martin and his co-workers have rationalized the low reactivity of 23 on the basis that considerable ring strain would arise as the trigonal-bipyramidal sulfurane attempts to take up the tetrahedral shape of an oxosulfonium ion in the transition state for hydrolysis. Spirophosphoranes show a similar reduction in reactivity when phosphorus in part of a bicyclic system.[55]



**23**



**24**

## Summary

The reactivity of sulfur heterocycles arises from a subtle interplay of both enthalpy and entropy effects. The importance of the latter effect has only recently been appreciated. Enthalpy strain in sulfur heterocycles arises primarily from a combination of both conventional angle strain and non-bonding interactions.

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*Note added in proof.*

Scorrano and his coworkers [R. Curci, D. Di Furia, A. Levi and G. Scorrano, *J. Chem. Soc. Perkin II.*, 408 (1975)] have recently shown that whilst the dependence on acidity of the rate of reduction of thietane 1-oxide and thiolane 1-oxide is quite similar to that of dimethyl sulfoxide, the acid dependence of thian 1-oxide is quite different. These authors have therefore pointed out that considerable care should be taken in interpreting reactivity data determined at a single acid concentration. This observation throws some doubts on earlier observations of the relative rates of stereomutation[38] and reduction[35] of cyclic sulfoxides.