Nucleophilic Substitution at Sulphinyl Sulphur. Kinetics and Oxygen-18 Tracer Studies of the Alkaline Hydrolysis of Some Sulphinate Esters

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The rates of alkaline hydrolysis of some simple aliphatic sulphinate esters have been studied at various temperatures. The enthalpies and entropies of activation have been determined. The main difference in reactivity between the five- and six-membered rings is shown to be due to entropy strain. Oxygen-18 experiments demonstrate that 1,2-oxathiolan 2-oxide does not undergo ^{18}O exchange with solvent during hydrolysis.

VARIOUS examples have been reported of extraordinary differences between the rates of alkaline hydrolysis of the esters of five-membered cyclic inorganic oxy-acids of phosphorus and sulphur and their six-membered and open-chain analogues. Five-membered cyclic phosphates,[1-5] phosphonates,[6] aromatic sulphates,[7] and sulphonates [8] all hydrolyse 10^5—10^7 times more rapidly than their open-chain analogues. The kinetic acceleration observed for the hydrolysis of both aliphatic [9-11] and aromatic [12,13] sulphites is *ca.* 10^3.

The cause of kinetic acceleration in cyclic esters has been the subject of much speculation and was originally thought to arise from some form of ring strain. Recently, however, the importance of both enthalpy and entropy contributions to the increased rates of reaction of five-membered cyclic esters has been recognised. Thus whilst entropy strain is the main cause of the observed kinetic acceleration in the hydrolysis of cyclic sulphites,[12] the high reactivity of five-membered cyclic phosphonyl compounds arises from a combination of both effects.[14,15]

The observed kinetic acceleration for attack at sulphonyl sulphur is very similar for both cyclic sulphates [7] and the analogous cyclic sulphonates [8] in which one ring oxygen has been replaced by a methylene group. Whilst the effect of ring size on the alkaline hydrolysis of cyclic sulphites has been studied in some detail [9-11] no similar comparison between sulphite and sulphinate esters has been reported. In an attempt to investigate further kinetic acceleration in cyclic sulphinyl compounds we now report a study of the rates and activation parameters for the alkaline hydrolysis of some simple aliphatic sulphinate esters.

One of the most important questions regarding the mechanism of nucleophilic substitution at sulphinyl sulphur concerns the timing of bond breaking and formation in the rate-determining step. Is bond formation complete before bond breaking starts to occur or are formation and breaking synchronous? The former situation would imply the existence of an actual intermediate along the reaction pathway. Bender demonstrated [16] the existence of a tetrahedral intermediate in the hydrolysis of a carbonyl ^{18}O-labelled carboxylic ester by showing that the ester recovered after partial hydrolysis had undergone oxygen-18 exchange with the solvent. We have adapted this procedure to see if any evidence can be found for the existence of an intermediate in nucleophilic attack at sulphinyl sulphur by investigating the partial hydrolysis of 1,2-oxathiolan 2-oxide in ^{18}O-enriched water.

EXPERIMENTAL

Materials.—The sulphinates were prepared by standard methods. 1,2-Oxathiolan 2-oxide had b.p. 33° at 0·15 mmHg (lit.,[17] 48—49° at 0·2 mmHg); 1,2-oxathian 2-oxide had b.p. 31° at 0·1 mmHg (lit.,[17] 60—61° at 0·5 mmHg); methyl methanesulphinate had b.p. 38° at 12 mmHg (lit.,[18] 38° at 12 mmHg); methyl benzenesulphinate had b.p. 58° at 0·15 mmHg (lit.,[18] 88—89° at 0·3 mmHg).

Kinetic Measurements.—The rates of alkaline hydrolysis were measured by a pH-stat technique using a Radiometer TTT2 automatic titrator assembly with a titration cell thermostatted to ±0·1°. The first-order rate coefficients, k_1, were determined at a number of different pH values for each compound studied at each temperature. Values of k_1 were calculated graphically from plots of alkali consumed *versus* time. Values of the second-order rate coefficients, k_2, were calculated from plots of k_1 *versus* $[HO^-]$. Values of $[HO^-]$ were derived from measured pH values, the activity coefficient, f_{OH^-}, of the hydroxide ion being taken as unity.

Influence of Temperature.—The entropies ($\Delta S^{\ddagger}$) and enthalpies ($\Delta H^{\ddagger}$) of activation were calculated from the equation $k = \mathbf{k}T/h\exp(\Delta S^{\ddagger}/R)\exp(-\Delta H/RT)$ by a least-squares procedure.

Isotopic Experiments.—1,2-Oxathiolan 2-oxide was hydrolysed in alkaline solutions of water enriched with oxygen-18. The reaction was interrupted after partial hydrolysis and the unhydrolysed ester was isolated by ether extraction,

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[1] J. Kumamoto, J. Cox, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 4858.

[2] J. Lecocq, *Compt. rend.*, 1956, **242**, 1902.

[3] P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1961, **83**, 1102.

[4] F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1963, **85**, 1773.

[5] E. T. Kaiser and K. Kudo, *J. Amer. Chem. Soc.*, 1967, **89**, 6725.

[6] A. Eberhard and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1965, **87**, 253.

[7] E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *J. Amer. Chem. Soc.*, 1965, **87**, 3781.

[8] E. T. Kaiser, K. Kudo, and O. R. Zaborsky, *J. Amer. Chem. Soc.*, 1967, **89**, 1393.

[9] C. A. Bunton, P. B. D. de la Mare, A. Lennard, D. R. Llewellyn, R. B. Pearson, J. G. Pritchard, and J. G. Tillett, *J. Chem. Soc.*, 1958, 4761.

[10] J. G. Tillett, *J. Chem. Soc.*, 1960, 37.

[11] R. E. Davis, *J. Amer. Chem. Soc.*, 1962, **84**, 599.

[12] P. A. Bristow, J. G. Tillett, and D. E. Wiggins, *J. Chem. Soc.* (*B*), 1968, 1360.

[13] P. B. D. de la Mare, J. G. Tillett, and H. F. Van Woerden, *Chem. and Ind.*, 1961, 1533; *J. Chem. Soc.*, 1962, 4888.

[14] G. Aksnes and K. Bergeson, *Acta Chem. Scand.*, 1966, **20**, 2508.

[15] R. F. Hudson and C. Brown, *Accounts Chem. Res.*, 1972, **5**, 204.

[16] M. L. Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

[17] D. N. Harpp, J. G. Gleason, and D. K. Ash, *J. Org. Chem.*, 1971, **36**, 322.

[18] I. B. Douglass, *J. Org. Chem.*, 1965, **30**, 633.

purified by distillation, and analysed for oxygen-18 by conversion to carbon dioxide.

Analysis for ^{18}O.—In all experiments carbon dioxide was analysed with an A.E.I. MS12 mass spectrometer equipped with a digital ion current meter. The vacuum line and pyrolysis tubes used were a modification of those of Williams and Hager.[19] Samples were converted to carbon dioxide by heating with mercury(II) chloride. To obtain reproducible results it was found necessary to use a $HgCl_2$: sulphinate ratio of $\geqslant$100 as previously observed by Shain and Kirsch.[20] Typically, sulphinate (5—10 mg) together with mercury(II) chloride were placed in a breakseal ampoule which was evacuated, sealed, and heated for 1—1·5 h at 400—500°. After cooling, the ampoule was placed in the vacuum line, the seal broken, and the hydrogen chloride generated was trapped by passage through benzoquinone.[21] The gaseous products were distilled through a series of traps at −72, −135, and −196°. Before the trap at −196° was put in place, a small amount of non-condensible gas was pumped from the −135° trap and discarded. The reproducibility of the analysis procedure was checked using tank carbon dioxide before and after each analysis.

TABLE 1

Second-order rate-coefficients k_2 (l mol^{-1} s^{-1}) for the alkaline hydrolysis of sulphinate esters

T (°C)	20·0	30·0	40·0	50·0	61·0
Sulphinate					
1,2-Oxathiolan 2-oxide	24·0	34·0	47·1	57·8	78·1
1,2-Oxathian 2-oxide	2·65	3·37	4·46	5·21	7·00
Methyl methanesulphinite	10·7		20·1	32·0	46·7
Methyl benzenesulphinate		26·5	33·9	45·2	16·2

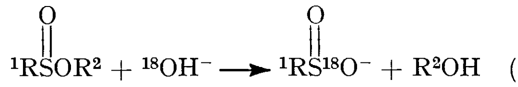
TABLE 2

Partial hydrolysis of 1,2-oxathiolan 2-oxide in ^{18}O-enriched water

		^{18}O Abundance (atoms % excess)	
Conditions	% Hydrolysis	Solvent H_2O	Recovered ester
N-NaOH	50	3·35	0·00
N-NaOH	50	10·0	0·01

DISCUSSION

Kinetic Studies.—Our kinetic results are consistent with those of Bunton and Hendy [22] who showed that the alkaline hydrolysis of simple sulphinate esters follows second-order kinetics. Bunton and Hendy also showed that the rate-determining step involves bimolecular nucleophilic attack at the sulphur atom with cleavage of the sulphur–oxygen bond [equation (**1**)]. This mechanism is formally analogous to the $B_{AC}2$ mechanism



$$^{1}\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}\mathrm{OR}^{2} + {}^{18}\mathrm{OH}^{-} \longrightarrow {}^{1}\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}{}^{18}\mathrm{O}^{-} + \mathrm{R}^{2}\mathrm{OH}$$

(1)

observed in the hydrolysis of carboxylic esters and to that of the alkaline hydrolysis of cyclic sulphites.

The relative reactivity (at 20°) towards hydroxide ion attack on going from the five- and six-membered cyclic sulphinates to the open-chain methyl methanesulphinate changes in the order 2·4 : 0·3 : 1·1 (Table 1). The kinetic results are surprising for two reasons. Both the close similarity in rates of hydrolysis along the series and the observed order of reactivity are unexpected. Thus this order of reactivity is quite different to that observed for the hydrolysis of other cyclic esters of phosphorus and sulphur, *i.e.* five-membered ring $\gg$ six-membered ring $\approx$ open-chain ester, or for the hydrolysis of cyclic carbonates [23,24] and lactones [25] where the six-membered ring is more reactive than the five because of destabilisation of the six-membered ring by the *exo*-carbonyl group.[26] Values obtained for the Arrhenius parameters for the alkaline hydrolysis of sulphinates are shown in Table 3.

TABLE 3

Arrhenius parameters for the alkaline hydrolysis of sulphinate esters

Sulphinate	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} *
1,2-Oxathiolan 2-oxide	4·9 ± 0·2	−35·3 ± 0·6
1,2-Oxathian 2-oxide	3·9 ± 0·2	−43·1 ± 0·6
Methyl methanesulphinate	6·4 ± 0·5	−31·9 ± 1·6
Methyl benzenesulphinate	4·7 ± 0·2	−36·6 ± 0·6

* Calculated at 20°.

The values of $\Delta H^{\ddagger}$ are all quite similar indicating the absence of any ‘ enthalpy ’ or ring strain although the values are much smaller than those observed for the analogous cyclic sulphites [12] (10—12 kcal mol^{-1}). The values of $\Delta S^{\ddagger}$ are also considerably more negative than observed for sulphite esters. The main cause of the difference in reactivity between the five- and six-membered cyclic sulphinates is seen to lie in the entropy of activation. In the transition state for hydrolysis the molecule takes up a more ordered structure and molecular motions at the reaction site are suppressed. This loss of entropy increases the free energy of activation. The relatively rigid five-membered cyclic sulphinate is already constrained much more than its conformationally mobile six-membered analogue and far less energy is required to reach the transition state. The reactivity of methyl methanesulphinate is anomalous. It is much more reactive than would be expected by comparison with the corresponding sulphite ester, the major contribution to this high reactivity coming from a more favourable entropy of activation. The exact cause of this enhanced reactivity is not clear.

Oxygen-18 *Studies.*—The results of subjecting 1,2-oxathiolan 2-oxide to partial hydrolysis in water enriched in oxygen-18 are shown in Table 2. The sample of ester recovered from hydrolysis in 3·35% $H_2{}^{18}O$ showed no isotopic enrichment. The very slight enrichment observed for hydrolysis in water of quite high

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[19] F. R. Williams and L. P. Hager, *Science*, 1958, **128**, 1434.

[20] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, 1968, **90**, 5848.

[21] D. R. Henberg and L. Ponticorvo, *Internat. J. Appl. Radiation Isotopies*, 1956, **1**, 208.

[22] C. A. Bunton and B. N. Hendy, *J. Chem. Soc.*, 1962, 2562.

[23] S. Sarel, I. Levin, and L. A. Pohoryles, *J. Chem. Soc.*, 1960, 3082.

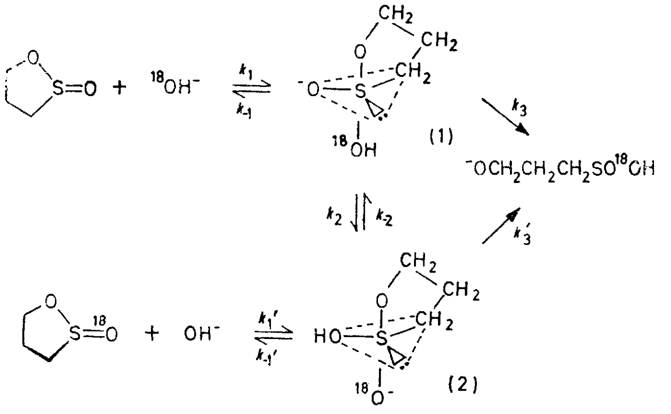
[24] J. G. Tillett and D. E. Wiggins, *J .Chem. Soc.* (*B*), 1970, 1359.

[25] C. W. Matuzak and H. Schechter, Abs. Papers. Amer. Chem. Soc. Meeting, New York, 1957, p. 12p.

[26] H. C. Brown, J. H. Brewster, and H. Schecter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

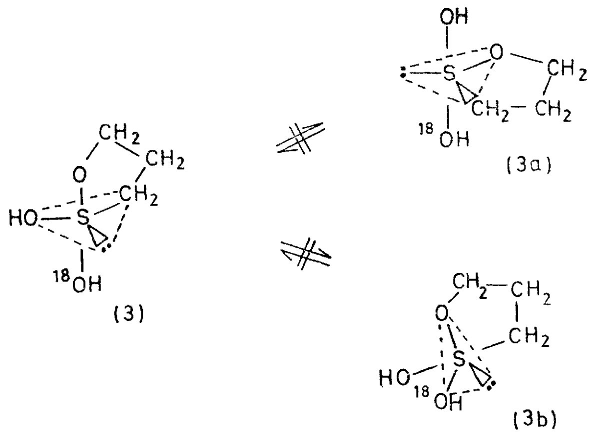
oxygen-18 abundance (10%) can be attributed to contamination of the isolated sample by enriched solvent. There is therefore no evidence of back exchange of the ester with the solvent in the alkaline hydrolysis of this sulphinate ester. Bunton and his co-workers [27] were also unable to detect any significant back exchange in the hydrolysis of ethylene sulphite. In neither case, however, do such observations necessarily rule out the existence of an intermediate. As Bender originally pointed out,[16] the rate of oxygen equilibration of an intermediate might be much slower than its rate of decomposition and hence oxygen exchange might not be observed. If an intermediate were formed in the alkaline hydrolysis of a cyclic sulphinate, it seems reasonable to assume by analogy with substitution reactions at phosphorus that it would have a trigonal bipyramidal geometry. According to the preference rules [28] the 1,2-oxathiolan ring would prefer to span an apical and an equatorial position with the methylene group of the ring equatorial. This would allow the sulphinyl oxygen and the lone pairs of electrons to occupy equatorial positions. The simplest pathway for oxygen equilibration (Scheme) would be by proton transfer (1) ⟶ (2).

Kice and Walters have suggested [29] in the analogous situation for cyclic sulphites that since O^- probably has a considerable energetic preference for an equatorial position, equilibration of oxygen atoms in a trigonal bipyramidal intermediate *via* such a simple proton transfer as in (1) ⟶ (2) which would place an O^- group in an apical position would be very slow compared to the breakdown of the intermediate in either the forward or reverse directions, *i.e.* $k_2 \ll k_{-1}$ or k_3. It seems likely therefore that even if an intermediate were formed, there is good reason to suppose that oxygen exchange might not occur during its lifetime and hence no incorporation of oxygen-18 into the unhydrolysed ester would be observed.



Scheme

Kice and Walters [29] also considered a more favourable route for oxygen exchange for ethylene sulphite involving first protonation of O^-, pseudorotation about the electron pair as pivot, followed by deprotonation. Such a mechanism is, however, not possible for 1,2-oxathiolan 2-oxide. The trigonal-bipyramidal intermediate (3) derived from (1) by protonation cannot readily undergo pseudorotation because pseudorotation about the ring carbon atom as pivot [(3) ⟶ (3a)] would expand the ring angle to 120°, whereas pseudorotation about the lone pair of electrons [(3) ⟶ 3b) would push the ring methylene group into an unfavourable apical position. The conjugate acid of (1) is therefore ' frozen ' in the trigonal bipyramidal (3). The situation is similar to that observed with the methyl ester of propylphosphonic acid which hydrolyses with 99·8% ring-opening but with $<$0·2% exocyclic cleavage.[30] If (3) cannot pseudorotate it cannot place the OH group in an apical position required for a leaving group and so oxygen exchange cannot occur by this mechanism. Even if a mechanism were available for pseudorotation of the intermediate in the alkaline hydrolysis of sulphinates, it has been suggested that such a process would be much slower than at phosphorus.[31] Thus the absence of oxygen exchange in the alkaline hydrolysis of 1,2-oxathiolan 2-oxide does not exclude the possibility of the formation of an intermediate in nucleophilic substitution at sulphinyl sulphur in this system.



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[27] C. A. Bunton, P. B. D. de la Mare, P. M. Greasley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 1958, 4751.

[28] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 1.

[29] J. L. Kice and C. A. Walters, *J. Amer. Chem. Soc.*, 1972, **94**, 590.

[30] E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1966, **88**, 3432.

[31] R. Tang and K. Mislow, *J. Amer. Chem. Soc.*, 1969, **91**, 5644.