The Reaction of Some Cyclic and Open-chain Disulphides with Methyl Trifluoromethanesulphonate

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The rates of reaction of methyl trifluoromethanesulphonate with a number of cyclic and open-chain disulphides have been studied at various temperatures. The main products of the reactions have been identified as the corresponding methylsulphonium salts. The difference in reactivity between the five-membered and other disulphides arises from a combination of both enthalpy and entropy effects.

The reactivity of cyclic disulphides has attracted considerable attention because of their importance in biological systems. In almost all reactions to date, the five-membered 1,2-dithiolans are more reactive than open-chain disulphides towards nucleophilic, electrophilic or radical reactions at the disulphide bond. Thus Fava and his co-workers showed that 1,2-dithiolan reacts with thiobutoxide [equation (1)] *ca.* 10^4 times faster than does the open-chain dibutyl disulphide [equation (2)] for the corresponding ^{34}S-exchange reaction.[1] Similarly 1,2-dithiolans react much more readily towards electrophilic persulphate oxidation than dithians. Open-chain disulphides and the seven-membered dithiepans do not react with this reagent.[2,3]

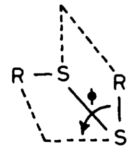
It has generally been assumed that the major cause of the high reactivity of dithiolan is the presence of strain in the five-membered ring. This has been determined by a variety of methods to lie in the range 4—25 kcal mol^{-1},[2,4–6] but is more likely to be at the lower end of this range. The optimum strain-free dihedral angle, φ, between the two substituents attached to the S–S bond in open-chain disulphides is *ca.* 90°.[7,8] In this conformation (A), repulsion between the non-bonding lone-pairs of the sulphur atoms is minimised and maximum overlap of these orbitals with the *d*-orbitals of adjacent sulphur atoms is permitted, leading to an S–S bond with considerable double bond character and restricted rotation.[8,9] Incorporation of the disulphide group into a cyclic disulphide leads to a decrease of the dihedral angle with decreasing ring size Thus φ is reduced to *ca* 70° in dithian [10] and to 27° in dithiolan.[7] As the ring size is reduced, the double bond character of the S–S bond decreases, and lone-pair–lone-pair repulsions increase, leading to an increase in ring strain.

Hudson and Filippini have shown that the enhanced reactivity of cyclic sulphides towards methyl fluorosulphonate (' magic methyl ') [equation (3)] can be correlated with the dihedral angle φ.[11] The rate of reaction increases regularly with the energy of orbital splitting, which is proportional to $\cos^2\varphi$ and gives a measure of the destabilization of the nucleophile arising from p_π–p_π lone-pair repulsions, suggesting that torsional strain is an important factor in the enhanced reactivity of the five-membered ring.

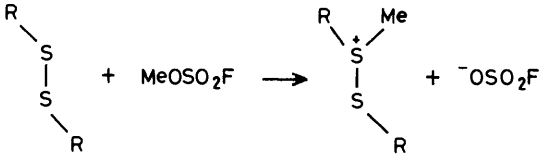
In recent years, however, it has become increasingly recognised that entropy strain as well as enthalpy strain can contribute to kinetic acceleration in cyclic systems.[12] Thus the enhanced reactivity towards hydroxide ion of both cyclic phosphates [13,14] and cyclic carbonates [15] arises from a combination of both effects, whilst that observed in cyclic sulphites arises exclusively from entropy strain.[16] Schmidt and his co-workers have suggested that the high reactivity of the dithiolan ring towards electrophilic attack may arise partly from entropy strain.[17] Davis has made a similar suggestion for nucleophilic reaction of disulphides.[18]

(1)

$$Bu^{*}S^{-} + BuSSBu \longrightarrow Bu^{*}SSBu + BuS^{-} \qquad (2)$$



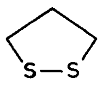
(A)



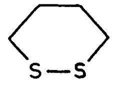
$$RSSR + MeOSO_2F \longrightarrow R\overset{+}{S}(Me)SR + {}^{-}OSO_2F \qquad (3)$$

MeSSMe
(1)

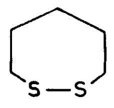
EtSSEt
(2)



(3)



(4)



(5)

In an attempt to determine experimentally the relative importance of entropy and enthalpy strain on kinetic acceleration in cyclic disulphides, we now report a detailed study of the activation parameters for the reaction of methyl trifluoromethanesulphonate (triflate) with a number of cyclic and open-chain disulphides (1)—(5).

Experimental

Materials.—Dimethyl and diethyl disulphides were commercially available samples which after fractionation had b.p. 110° (lit.,[19] 110°) and 48—49° at 15 mmHg (lit.,[19] 45° at 13 mmHg), respectively. Cyclic disulphides were prepared *via* the corresponding dithiolate lead salt [20,21] using dichloromethane (dithian, dithiepan) and benzene (dithiolan) as solvents. 1,2-Dithian purified by sublimation had m.p. 31—32° (lit.,[2] 32—33°), $M^{\cdot+}$ 120. 1,2-Dithiepan had b.p. 53—55° at 2 mmHg (lit.,[20] 55—60° at 1.7 mmHg), $M^{\cdot+}$ 134. 1,2-Dithiolan cannot be isolated from benzene solution due to its instability.[2,5] The concentration of dithiolan in this solution was determined using the extinction coefficient at 330 nm (ε 147).[2] Dimethyl sulphide and ethyl methyl sulphide were commercial samples used without further purification. Methyl triflate prepared by the methylation of trifluoromethanesulphonic acid with dimethyl sulphate had b.p. 98—99° (lit.,[22] 98—99°), δ (CCl_4) 4.23 (s, CH_3), *m/e* 69 ($M^{\cdot+}$ − $MeSO_3$).

Product Analyses.—M.p.s and b.p.s were uncorrected. ^1H N.m.r. resonance spectra were obtained on a Varian EM-360 spectrometer; chemical shifts are expressed relative to tetramethylsilane as internal standard. Mass spectra were determined with an A.E.I. MS 12 spectrometer operated at 70 eV. G.l.c. was carried out on a Perkin-Elmer F17 gas chromatograph equipped with a flame ionization detector using a 2 m × 1/8 in column packed with 15% Carbowax on Chromosorb W, and operated at a column temperature of 50°.

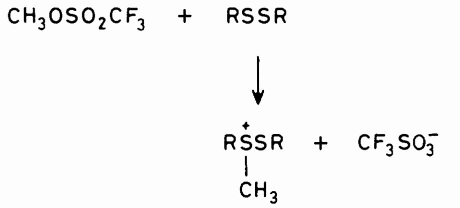
Reaction of Dimethyl Disulphide (1) *with Methyl Triflate.*—Dimethyl disulphide (0.24 g) in dichloromethane (5.0 ml) was added to an equimolar solution of methyl triflate (0.41 g) in dichloromethane (5 0 ml) with stirring at 25°, and the mixture allowed to stand for 48 h. The product was precipitated out of solution by the addition of ether to give crystals of dimethyl(methylthio)sulphonium triflate, m.p. 28—36° (0.62 g, 91%), δ (CH_2Cl_2) 3.27 (6 H, s) and 2.92 (3 H, s); *m/e* 94 (100%). The product was generally unstable and liquified overnight.

Reaction of Diethyl Disulphide (2) *with Methyl Triflate.*—Similar conditions were used as for dimethyl disulphide. The product was thrown out of solution by the addition of ether to give diethyl(methylthio)sulphonium triflate as an oil (*ca.* 0.7 g, 85%); *m/e* 122 (67%).

Reaction of 1,2-*Dithian* (4) *with Methyl Triflate.*—A solution containing equimolar amounts (0.25M) of dithian and methyl triflate in dichloromethane (10 ml) was allowed to stand at 25° for 24 h. The product was precipitated from solution to give methylthiodithian-1,2-diylsulphonium triflate, m.p. 172—178° (decomp.) (<0.1 g) as a solid, *m/e* 135 (13%) and 88 (100). The sulphonium salt was treated with potassium iodide in acetone and shaken with sodium thiosulphate to remove iodine. The resulting solution was extracted with ether, the extract dried ($MgSO_4$), and the solvent evaporated off to give a small quantity (*ca.* 0.1 g) of an oily product. This was purified by column chromatography on alumina, eluting first with benzene and then ethyl acetate to produce *bis-*(4-*methylthiobutyl*) *disulphide* as a pale yellow liquid (Found: C, 44.5; H, 8.4; S, 47.3. $C_{10}H_{22}S_4$ requires C, 44.4; H, 8.2; S, 47.4%), δ (CCl_4) 2.55br (8 H, m, SCH_2), 2.05 (6 H, s, CH_3S), and 1.75br (8 H, m, CH_2), *m/e* 270 ($M^{\cdot+}$, 11%).

Reaction of 1,2-*Dithiepan* (5) *with Methyl Triflate.*—Similar conditions were used as for 1,2-dithian. Portions of the resulting slightly yellow solution were withdrawn and treated with methanolic potassium iodide. The reaction solution after titration with sodium thiosulphate was extracted with ether. The extract was dried ($MgSO_4$) and the solvent evaporated off to give a trace of bis-(3-methylthiopropyl) disulphide as a liquid, *m/e* 242 ($M^{\cdot+}$, 19%) and 121 (100).

Kinetic Measurements.—(a) *By* ^1H *n.m.r. spectroscopy.* The disulphide stock solution (0.5 ml, 0.1M) was pipetted into an n.m.r. tube standing in a thermostatted bath (±0.1°). After thermal equilibration had occurred, methyl triflate (*ca.* 5.6 μl) was added, and the mixture thoroughly shaken. At appropriate times, the n.m.r. tube was withdrawn from the thermostat and the n.m.r. spectrum recorded rapidly several times over the region δ 2.0—4.5. Equal concentrations of disulphide and methyl triflate were used. The relative areas of the peak of the product (at δ 3.27) and the methyl triflate reactant (at δ 4.33) were used to determine the relative concentration of reactant to product. Second-order rate constants were calculated from the equation $k_2t = (1/a)(i_p/i_r)$, where a is the initial concentration of both reactants, i_p and i_r are the integral heights of product and reactants respectively. Plots of i_p/i_r as a function of time gave good straight lines, from the slope of which values of k_2 were determined. Rate constants obtained by this method were reproducible to ±10%.



(4)

(6)
a; R = Me
b; R = Et

(b) *By u.v. spectroscopy.* This method was used to study the reaction between methyl triflate and 1,2-dithiolan. Dithiolan (stock solution in benzene) was added to dichloromethane (3.0 ml) in a thermostatted u.v. cell. (The concentration of disulphide used was *ca.* 4 × 10^{-3}M.) After thermal equilibration, methyl triflate (20 μl) was added and the resulting mixture shaken. The decrease in absorption at 330 nm was continuously monitored. The reaction was studied under both second-order and pseudo-first-order conditions. Second-order rate constants were reproducible to ±7%.

(c) *Quenching method.* This method was used to study the reaction of methyl triflate with diethyl disulphide and dithiepan in acetonitrile. Methyl triflate was injected into a thermostatted solution of the disulphide (2.0 ml, 0.260M) in acetonitrile in a small stoppered tube. The final concentration of methyl triflate was 0.10—0.20M to maintain pseudo-first-order conditions. Portions (30 μl) were withdrawn at intervals and quenched in a solution of potassium iodide (3.0 ml, 0.1M) in methanol. The absorption at 360 nm of the resulting solution was then determined and the concentration of sulphonium salt obtained from a standard calibration curve. Rate constants were reproducible to ±8%.

Influence of Temperature.—The entropy ($\Delta S^\ddagger$) and enthalpy ($\Delta H^\ddagger$) of activation were calculated from the equation $k_2 = kT/h \exp(\Delta S^\ddagger/R) \exp(-\Delta H^\ddagger/RT)$ by a least squares procedure.

Results and Discussion

Products of Reaction.—When a solution of dimethyl disulphide in solvent dichloromethane is treated with an equimolar quantity of methyl triflate, the n.m.r. spectrum initially consists of two singlets at δ 4.33 and 2.55 with an intensity ratio of 1 : 2 due to methyl triflate and dimethyl disulphide respectively. These signals decrease rapidly and simultaneously two new signals appear, a six-proton singlet at 3.27 and a three-proton singlet at δ 3.92 consistent with the formation of dimethyl(methylthio)sulphonium triflate (6a). The n.m.r. spectrum of the corresponding 2,4,6-trinitrobenzenesulphonate [23] and hexafluorophosphate [24] consists of two singlets at δ 3.12, 2.83, and 3.10, 2.80 respectively.

Table 1. Values of the second-order rate constants (10^3k_2/l mol^{-1} s^{-1}) for the reaction of methyl triflate with diethyl disulphide and dithiepan in acetonitrile at different temperatures

	T/°C				
Disulphide	25.0	30.0	34.9	39.9	45.5
10^3k_2 (EtSSEt) [a]	1.6	2.5	3.6	5.6	8.6
10^3k_2 (Dithiepan) [a]	2.3	2.9	4.8	6.4	9.6
k_{rel}	1.4	1.2	1.1	1.4	1.1

[a] Quenching method. Mean value of k_{rel} 1.2 ± 0.1.

Table 2. Values of the second-order rate constants (10^4k_2/l mol^{-1} s^{-1}) for the reaction of methyl triflate with disulphides in dichloromethane at different temperatures

	T/°C				
Disulphide	15.0	20.0	25.0	30.0	35.0
MeSSMe (1) [a]	0.73	1.2	1.8	2.2	3.2
EtSSEt (2) [a]	2.3	3.5	4.8	6.3	8.7
1,2-Dithiolan (3) [b]	36	53	83	120	190
1,2-Dithian (4) [a]	2.8	4.8	7.3	12	19
1,2-Dithiepan (5) [c]	2.9	4.3	6.0	7.9	11

[a] By n.m.r. [b] By u.v. [c] Calculated from values of k_2 in acetonitrile using k_{rel}.

Table 3. Iodometric analysis of sulphonium salts after KI treatment

Disulphide	% I_2 Found	
MeSSMe	96 [a]	
EtSSEt	90 [a]	80 [b]
1,2-Dithiolan	82 [a]	
1,2-Dithian	79 [a]	
1,2-Dithiepan		78 [b]

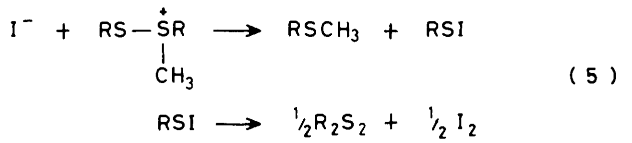
[a] By titration with $Na_2S_2O_3$ (0.001M), average of several determinations. [b] For runs in solvent acetonitrile.

Further evidence for the formation of the sulphonium salt came from its isolation in excellent yield (91%) by precipitation out of solution by the addition of ether. The salt was a rather unstable crystalline solid, m.p. 28—36°, tending to liquefy on standing. It was possible, however, to obtain its mass spectrum and the detailed fragmentation pattern was consistent with the expected product. The salt was relatively stable in dichloromethane solution and could be left standing at ambient temperature for several days with only negligible changes in its n.m.r. spectrum.

Similar changes were observed in the n.m.r. spectrum of mixtures of methyl triflate with diethyl disulphide and 1,2-dithian. In these cases also, the corresponding sulphonium salts (6b) and (7b) could be precipitated by the addition of ether and were identified by their mass spectra.

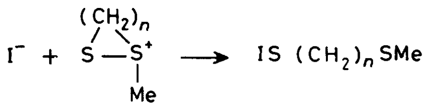
It is interesting to note that electrophilic attack of methyl triflate, on the disulphides studied here, fails to result in scission of the S–S bond. This would suggest that the presence of a nucleophile is required to effect cleavage of the methylated disulphide link. The triflate anion appears to be too weak a nucleophile to react in this way, although Kice has observed the existence of ready acid-catalysed concomitant S–S bond cleavage involving protonation of one sulphur atom and nucleophilic attack at the other[25] and Bach and Rajan have recently observed similar concomitant metal-assisted disulphide cleavage.[26]

Helmpkamp has shown that cleavage with iodide ion produces iodine *via* disproportionation of the intermediate sulphenyl iodide [equation (5)] and confirmed that for dimethyl(methylthio)sulphonium salts the ratio of methyl sulphide to dimethyl sulphide found is 2 : 1.[27] The iodine produced can be determined with thiosulphate and this method has been used in the present work to determine the extent of methylation. The results are shown in Table 3.



$$I^- + RS-\overset{+}{S}(CH_3)R \longrightarrow RSCH_3 + RSI \qquad (5)$$

$$RSI \longrightarrow \tfrac{1}{2}R_2S_2 + \tfrac{1}{2}I_2$$



(7) (6)

$$IS(CH_2)_nSMe \longrightarrow \tfrac{1}{2}MeS(CH_2)_nSS(CH_2)_nSMe + \tfrac{1}{2}I_2$$

(8)

a; n = 3
b; n = 4
c; n = 5

The products of the reaction of methyl triflate with both dimethyl and diethyl disulphides were treated with potassium iodide and the further decomposition products formed by disproportionation of the sulphenyl iodides identified by g.l.c. as dimethyl and diethyl disulphides respectively.

An analogous reaction scheme to that for the decomposition of sulphonium salts derived from open-chain disulphides [equation (5)] is shown in equation (6) for cyclic 1,2-disulphides. The three disulphides (8a—c) were isolated and identified by n.m.r. and/or mass spectrometry (see Experimental section).

Kinetic Studies.—The second-order rate constants for the reaction of methyl triflate with dimethyl and diethyl disulphides and 1,2-dithian were determined by an n.m.r. method. The rate of reaction of dithiolan was determined by following the decrease in the characteristic u.v. absorbance at 330 nm. The reaction between methyl triflate and 1,2-dithiepan in dichloromethane gave inconsistent results because of the low solubility of the product in this solvent. To permit comparison of relative rates, the rates of reaction of both diethyl disulphide and 1,2-dithiepan were determined in acetonitrile using a quenching method. It was then assumed that the rates of reaction of these two sulphides would be affected to the same extent by change of solvent. The rate data for dithiepan in acetonitrile could then be ' corrected ' to give calculated values for solvent dichloromethane. It has been reported that methyl triflate solvolyses slowly in solvent acetonitrile [k_2 (extrap) at 25° 2.0 × 10^4 l mol^{-1} s^{-1}].[28] No correction had to be made for this, since experiments in this solvent were carried out under pseudo-first-order conditions with an excess of disulphide, and the rates of reaction of diethyl disulphide and dithiepan are an order of magnitude greater than the rate constant for solvolysis.

The kinetic results (Table 2) show that the differences in the rates of reaction of the various disulphides with methyl triflate are relatively small. The five-membered dithiolan reacts *ca.* 13 times faster than either dithian or dithiepan which in turn react slightly faster than dimethyl or diethyl disulphide. Values for the Arrhenius parameters are shown in Table 4. Both 1,2-dithiolan and 1,2-dithian have a much more favourable entropy of activation than the other disulphides. The

Table 4. Arrhenius parameters [a] for reactions of disulphides with methyl triflate in dichloromethane

Disulphide	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}
MeSSMe (1)	11.9 ± 1.3	35.8 ± 5.7
EtSSEt (2)	10.9 ± 1.1	37.3 ± 5.6
Dithiepan (5)	10.7 ± 1.1	37.1 ± 5.6
Dithian (4)	16.2 ± 0.9	18.5 ± 1.7
Dithiolan (3)	13.6 ± 0.5	22.2 ± 1.6

[a] Calculated at 25.0 °C.

expected large rate enhancement is, however, offset by the corresponding increase in the enthalpy of activation. The reaction of methyl triflate with disulphides, whilst not entirely relieving ring strain by cleavage of the sulphur–sulphur bond, does cause a reduction in the lone-pair–lone-pair repulsions as a result of methylation of one of the sulphur atoms of the disulphide bond. Such relief of ring strain should be largest for those disulphides in which the torsional angle φ [see (A)] is <90°. The relative values of $\Delta H^{\ddagger}$ for 1,2-dithiolan and 1,2-dithian are consistent with this view. We are currently investigating in other related alkylation reactions the apparently anomalous position of dithiane for which a more negative value of $\Delta S^{\ddagger}$ would have been expected on the basis of its greater flexibility compared to that of dithiolan.

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