Transesterification versus Nucleophilic Displacement in Cyclic and Open-chain Organic Sulphites

By **P. A. Bristow** and **J. G. Tillett,*** Department of Chemistry, University of Essex, Wivenhoe Park, Colchester, Essex

The reactions of sodium methoxide and isopropoxide with dimethyl and ethylene sulphites have been investigated. The acid- and base-catalysed and thermal exchange reactions between methanol and ethylene sulphite and di-isopropyl sulphite have also been studied. The concurrent occurrence of nucelophilic substitution and transesterification in the presence of alkoxide is discussed.

GARNER and LUCAS[1] showed that the acid- or base-catalysed hydrolysis of (—)-1,2-dimethylethylene sulphite proceeded with complete retention of configuration. Subsequently, by using ^{18}O tracer techniques, it was established[2] that many simple cyclic and open-chain sulphites hydrolyse in this way. Foster, Hancock, Overend, and Robb[3] studied the hydrolyses of the cyclohex-1,2-ylene sulphites. The *trans*-sulphite hydrolysed to give the *trans*-diol. The *cis*-sulphite, however, whilst giving the *cis*-diol in acid solution, gave mainly the *trans*- with some *cis*-diol in alkaline solution. This implies that under the latter conditions some carbon–oxygen bond-fission occurs. Other cases are known in which the products of reaction with nucleophilic reagents require the conclusion that some carbon–oxygen bond-fission has occurred. Thus the reaction of ethylene sulphite with aryloxide ions[4] leads to products of the type $ArO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ in which ethylene sulphite has acted as a hydroxyethylating agent, and dialkyl sulphites undergo cleavage with iodide ions in acetone forming, among other products, alkyl iodides.[3] Similarly when cyclic sulphites of 1,3-diols are refluxed in acetone with sodium iodide, sodium iodoalkyl sulphites are formed. These are easily hydrolysed to the corresponding iodohydrins.[5] Besides the *O*-alkylation achieved with oxygen-containing nucleophiles the products of *N*-alkylation are obtained when dialkyl sulphites are heated with amines.[6] Thus dimethylaniline is formed in 96% yield from dimethyl sulphite and aniline. Recently Chapman, Isaacs, and Parker[7] showed that treatment of 5-piperidino-1,3,2-dioxathian 2-oxide hydrochloride with excess of sodium phenoxide gave 3-phenoxy-2-piperidinopropan-1-ol.

The position of bond-fission therefore seems to depend on the reaction conditions involved. Reactions in non-aqueous solvents seem to favour carbon–oxygen bond-fission and in order to study this further we have examined the reaction of a number of simple cyclic and open-chain sulphites with sodium methoxide or ethoxide in alcoholic media. Sulphur–oxygen bond-fission would result in alkoxy-exchange, or transesterification; carbon–oxygen bond-fission implies nucleophilic attack at carbon.

The transesterification of esters by alcohols is well known; the reaction is catalysed by both acids and bases. Bunnett, Robinson, and Pennington showed[8] that while the alkoxy-exchange reaction of methyl esters in methanol was fast, no nett reaction occurred. Attack at the alkyl group, however, resulting in alkyl–oxygen bond-fission, was much slower and gave dimethyl ether as a product.

In this work we show that dialkyl sulphites behave analogously. Alkoxy-exchange is rapid and is catalysed by both acids and bases; nucleophilic attack at carbon by alkoxide ions is slower and gives ethers as products. The reactions of cyclic sulphites are necessarily more complex and have also been examined.

---

[1] H. K. Garner and H. J. Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5497.

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

[3] A. B. Foster, E. B. Hancock, W. G. Overend, and J. C. Robb, *J. Chem. Soc.*, 1956, 2589.

[4] W. Carlson and L. Cretcher, *J. Amer. Chem. Soc.*, 1947, **69**, 1952.

[5] S. Wawzonek and J. T. Loft, *J. Org. Chem.*, 1960, **25**, 2068.

[6] W. Voss and B. Blanke, *Annalen*, 1931, **485**, 272.

[7] N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J. Chem. Soc.*, 1959, 1925.

[8] J. F. Bunnett, M. M. Robson, and F. C. Pennington, *J. Amer. Chem. Soc.*, 1950, **72**, 2328.

EXPERIMENTAL

The sulphites were prepared by standard methods and have been described elsewhere.[4,6,9–11] Diols were purified and dried by distillation. Alcohols were dried AnalaR reagents; methanol and ethanol were dried by Lund and Bjerrum's method. Sodium hydrogen sulphite was obtained by evaporation of an analytical grade solution until crystals appeared. These lost water rapidly in air to give sodium metabisulphite. Sodium methyl sulphite was prepared from methanol and sulphur dioxide.[12,13]

Di-isopropyl Sulphite–Methanol Exchange.—Di-isopropyl sulphite (0·1 mole) was added to methanol (0·2 mole) and the resulting solution heated to 80° until no further change in its n.m.r. spectrum occurred. The composition of the equilibrium mixture (Table 1) was estimated by proton summation of the n.m.r. spectra of the components.

TABLE 1

Equilibrium composition of the di-isopropyl sulphite–methanol system

Component	Mole %
MeOH	17
Pr^iOH	20
$MePr^iSO_3$	25
Me_2SO_3	23
$Pr^i{}_2SO_3$	15

Ethylene Sulphite–Methanol Exchange.—The approach to equilibrium in this system was studied from either side. Both ethylene sulphite (0·1 mole) and methanol (0·2 mole) on the one hand and dimethyl sulphite (0·1 mole) and ethanediol (0·1 mole) on the other were heated for 2 hr. in a sealed tube at 110°. The structure of the transesterification intermediate (II) was established from its n.m.r. spectrum.

TABLE 2

N.m.r. spectrum of the transesterification intermediate in the ethylene sulphite–methanol system

Proton type	Multiplicity	Relative intensity	τ
$CH_2·O·SO$	Complex	2	5·96 †
$\mathit{CH}_2·OH$	Complex *	2	6·21 †
OH	Singlet	1	Variable ‡
OCH_3	Singlet	3	6·31

* Broadened as catalyst reacts and hydroxy-proton exchange rates fall. † Centre value. ‡ Common with MeO*H* frequency.

Action of Sodium Methoxide on Dimethyl Sulphite.—Dimethyl sulphite (0·1 mole) was added to a solution of sodium methoxide (0·1 mole) in methanol (25 ml.) and the resulting solution refluxed for 8 hr. The white solid which separated out was centrifuged off, washed with methanol and dried *in vacuo*. *X*-Ray powder photographs of the precipitate showed it to be identical with authentic sodium metabisulphite. If, however, the reaction was left to proceed at room temperature and worked up under 'super dry' conditions in which the resulting solid was filtered off with the total exclusion of air, colourless needles separated out. *X*-Ray photographs of this material showed it to be sodium methyl sulphite. The gaseous products from the reaction were trapped in ice-cooled carbon tetrachloride, and the resulting solution examined by analysis of its n.m.r. spectrum. Dimethyl ether and a trace of methanol were detected.

Sodium ethoxide was allowed to react with diethyl sulphite under the conditions described above. The white solid formed was identified as sodium metabisulphite and the only gaseous product formed identified as diethyl ether by its n.m.r. spectrum.

TABLE 3

Equilibrium composition of the ethylene sulphite–methanol system

	Ethylene sulphite + methanol (mole %)	Dimethyl sulphite + ethanediol (mole %)
$MeO·SO·OCH_2·CH_2·OH$	7	7
MeOH	35	41
Me_2SO_3	11	11
$HO·CH_2·CH_2·OH$	17	25
Ethylene sulphite	30	16

Action of Sodium Isopropoxide on Dimethyl Sulphite.—Dimethyl sulphite (0·1 mole) was allowed to react with sodium isopropoxide (0·1 mole) in isopropanol (25 ml.) under the conditions described above. The main volatile product was distilled off and identified as isopropyl methyl ether (7·4 g., 95%). In addition some dimethyl ether was detected by examination of the n.m.r. spectrum of the distillate (see Discussion).

Action of Sodium Methoxide on Ethylene Sulphite.—This was carried out as above. The volatile products of the reaction were determined by analysis of the n.m.r. spectrum. Ethylene oxide and dimethyl ether were found to be present. The n.m.r. spectrum of the remaining reaction mixture after most of the solvent had been distilled off suggested that ethylene glycol remained. The white solid was again identified as sodium metabisulphite.

N.m.r. measurements were made on a Varian A-60A spectrometer with tetramethylsilane as internal reference and *X*-ray powder photographs were obtained on a Philips Debye–Scherrer-type powder camera.

DISCUSSION

Transesterification.—Alkoxy-exchange is subject to both acid and base catalysis, and is accelerated by heating. Mixed dialkyl sulphites tend to undergo thermal disproportionation (probably catalysed by sulphur dioxide from small amounts of thermal decomposition) into the two symmetrical compounds. Thus it is not possible to isolate and identify the frozen equilibrium components by distillation, or by g.l.c. as Davis[14] attempted. The use of n.m.r. spectroscopy, however, has enabled us to study some of these reactions *in situ* without disturbing the position of equilibrium.

A study of the simplest (uncatalysed) exchange system, dimethyl sulphite–methanol, showed that even on heating to 120° coalescence of the two methyl resonances occurred. Thus even at this temperature the rate of exchange is not fast enough to have a half-life of less than

---

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

[10] W. E. Bissinger and F. E. King, *J. Amer. Chem. Soc.*, 1947, **69**, 2158.

[11] C. C. Price and G. Berti, *J. Amer. Chem. Soc.*, 1954, **76**, 1213.

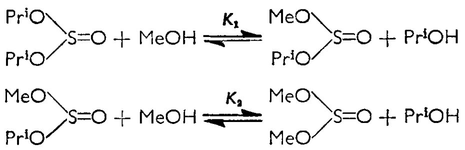
[12] A. Rosenheim and O. Liebknecht, *Ber.*, 1898, **31**, 405.

[13] A. Simon and H. Kriegsmann, *Z. phys. Chem. (Leipzig)*, 1955, **204**, 369.

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

a fraction of a second. This experiment indicated that it was unlikely to be possible to measure actual rates of exchange and subsequent investigations were confined to systems that had been allowed to reach equilibrium, or were in the process of equilibration.

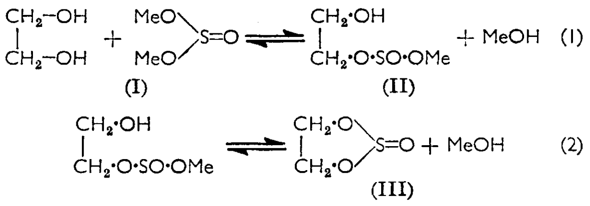
In the diethyl sulphite–methanol system it was not possible to distinguish clearly between the n.m.r. spectra of the three three sulphite species involved. A study of the di-isopropyl sulphite–methanol system proved more fruitful although there is still some overlap in the n.m.r.



spectra which makes the estimated concentrations of component species less precise. The results are indicated in Table 1 and lead to values of K_1 and K_2 which are both of the order of unity.

At probe temperature (*ca.* 35°) there was no discernible reaction until either a drop of a solution of methanolic HCl or NaOH (*ca.* 10^{-2}M) was added, when protons in the CH·O·SO group could be detected. Study of the influence of methoxide ion on the equilibrium was made more difficult by consumption of the catalyst (concurrent nucleophilic substitution) leading to reduction of the hydroxy-proton exchange rates and line-broadening of coupled-group proton resonances.

The exchange reaction of the ethylene sulphite–methanol system was investigated in a similar way.



The existence of the intermediate (II) was established from its n.m.r. spectrum (Table 2). The intermediate was observed when the equilibrium was approached from either side, and when the attainment of equilibrium was acid- or base- or thermally-accelerated. The use of catalysts is complicated by their consumption and does not correspond to that obtained thermally. The base-catalysed reaction of ethylene sulphite and methanol appeared to give a slightly anomalous result. The intermediate was found but only small amounts of dimethyl sulphite and ethanediol. This probably implies that the equilibrium (2) is more rapidly established under base catalysis than equilibrium (1). It is noteworthy that the reaction of ethanediol and dimethyl sulphite began to occur at much lower temperatures than for the cyclic sulphite and methanol.

The accuracy of the values of the equilibrium constants obtainable are again limited by spectral overlap; K_1 is *ca.* 1, and K_2 approximately 50. This means that the concentration of the intermediate is quite small, which argues even more strongly against strain in the ring than the evidence of transesterification provided by Davis.[14] The existence of the structurally related open-chain transesterification intermediate has also been established [15] for the ethylene carbonate–methanol system.

Study of other systems including trimethylene, tetramethylene, and *meso*-2,3-dimethylethylene sulphite and methanol revealed no evidence for the formation of a transesterification intermediate in these cases. However, this could reflect the experimental difficulties of detecting small concentrations of intermediates in cases where spectra are much more complex. The rate of alkoxy-exchange with five-membered cyclic sulphites was reduced by methyl substituents.

Nucleophilic Substitution in Dialkyl Sulphites.—Dimethyl sulphite reacts with sodium methoxide over several days at room temperature. Under reflux conditions (*ca.* 60°), however, reaction was substantially complete after *ca.* 8 hours. Under both sets of conditions a white solid eventually separated, which was identified as sodium metabisulphite, $Na_2S_2O_5$, by its *X*-ray powder photograph. It seems reasonable to suppose, as did Foster *et al.*,[3] that this is formed by the rapid hydrolysis of sodium methyl sulphite by traces of water:

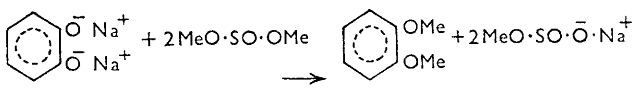
$$\mathrm{MeO{\cdot}SO{\cdot}O^- \, Na^+ + H_2O \longrightarrow HO{\cdot}SO{\cdot}O^- \, Na^+ + MeOH}$$
$$\mathrm{2HO{\cdot}SO{\cdot}O^- \, Na^+ \longrightarrow Na_2S_2O_5 + H_2O}$$

Under 'super dry' conditions colourless needles of sodium methyl sulphite separated out after leaving overnight at room temperature. In contrast, sodium hydroxide in methanol reacts with dimethyl sulphite to give sodium sulphite.

Gaseous products from reaction under reflux were collected in ice-cooled carbon tetrachloride. Examination of the n.m.r. spectrum of the resulting solution showed only the presence of dimethyl ether.

$$\mathrm{MeO^- + MeO{\cdot}SO{\cdot}OMe \longrightarrow MeOMe + {}^-O{\cdot}SO{\cdot}OMe}$$

Separate experiments have shown that sodium methyl sulphite does not react further with sodium methoxide. Thus one mole of alkoxide reacts with every mole of sulphite as suggested by the findings of Chapman *et al.*[7] and Voss and Blanke.[6] The latter workers also showed that phenols could be readily alkylated in good yield (89%) by heating their sodium derivatives with dialkyl sulphites in toluene.



It is particularly noteworthy that in this reaction two moles of dialkyl sulphites are consumed by every mole of 1,2-dihydroxybenzene, thus confirming the absence of any further reaction of the sodium methyl sulphite formed.

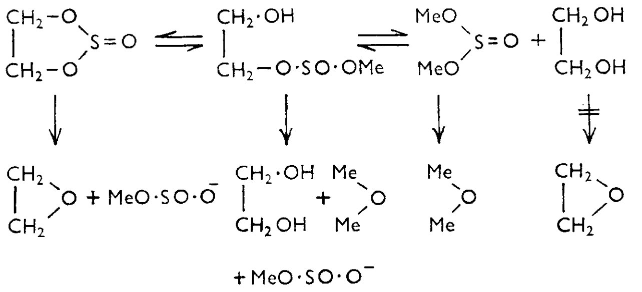
---

[15] P. A. Bristow and J. G. Tillett, *Tetrahedron Letters*, 1967, **10**, 901.

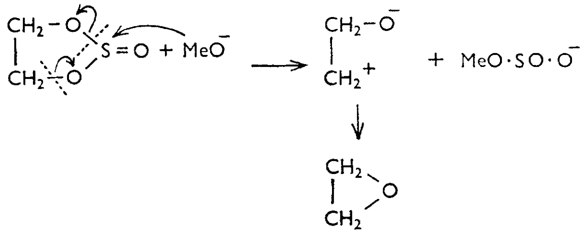
Under reflux conditions, diethyl sulphite reacted readily with sodium ethoxide in ethanol to give diethyl ether. Sodium metabisulphite was again formed. Isopropyl methyl ether was distilled almost quantitatively from the reaction of dimethyl sulphite and sodium isopropoxide. In addition, some dimethyl ether was detected by a methyl proton count of the n.m.r. spectrum of the distillate. This is formed by nucleophilic substitution following alkoxy-exchange of ester and alcohol:

$$\begin{tikzcd}
\mathrm{MeO{\cdot}SO{\cdot}OMe} + \mathrm{Pr^iOH} \arrow[r, shift left] \arrow[d, "\mathrm{MeO^-}"] & \mathrm{Pr^iO{\cdot}SO{\cdot}OMe} + \mathrm{MeOH} \arrow[l, shift left] \arrow[d, "\mathrm{MeO^-}"] \\
\mathrm{Me{\cdot}O{\cdot}Me} & \mathrm{MeO{\cdot}Pr^i}
\end{tikzcd}$$

Nucleophilic Substitution in Cyclic Sulphites.—The reaction of sodium methoxide with ethylene sulphite has been shown to form ethylene oxide, dimethyl ether, ethanediol, and sodium methyl sulphite or metabisulphite (depending on the conditions). Subsidiary experiments show that ethylene oxide is not formed from ethanediol under the conditions used. The possible reaction paths are outlined below:



The surprising absence of ethanediol mono- or di-methyl ether among the products indicates that nucleophilic substitution in cyclic sulphites occurs exclusively at sulphur probably *via* the reaction scheme below:



These results are in accord with those of Gillis[16] who obtained tetrahydrofuran from tetramethylene sulphite by using a tertiary nitrogen base as catalyst under more vigorous conditions (24 hr. at 180°). This led to charring and the occurrence of side reactions. He detected no cyclic ether formation from five- or six-membered cyclic sulphites. We have noticed that some tetrahydrofuran and sulphur dioxide are produced during the preparation of tetramethylene sulphite by transesterification. It is also noteworthy that ethylene sulphite may be produced by the high-pressure catalysed reaction of ethylene oxide and sulphur dioxide.[17]

These findings indicate that the rates of alkoxide reactions with organic sulphites must be considered in the context that any such measurements refer to the overall rate of reaction of all of the possible sulphite species which may be formed by exchange processes, since nucleophilic substitution and transesterification proceed concurrently.

We thank Dr. P. D. Greene for advice on the *X*-ray photographs and Mrs. M. Khowaja for information on unpublished work.

[7/1208 *Received, September* 18*th*, 1967]

[16] R. G. Gillis, *J. Org. Chem.*, 1960, **25**, 651.

[17] W. A. Rogers, U.S.P. 3,022,315 (*Chem. Abs.*, 1962, **57**, 5802).