2-Halogeno-3-morpholinothietan 1,1-Dioxides. Kinetics of Base Catalysed *cis–trans*-Isomerization and Hydrogen–Deuterium Exchange

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The kinetics of base catalysed H–D exchange at position 2 and *cis–trans*-isomerization have beeen measured in CD_3CN–D_2O for a series of 2-halogeno-3-morpholinothietan 1,1-dioxides (1)—(6). The isomerization and exchange rates depend upon the nature of the halogen and are in the order I > Br > Cl. The results are rationalized in terms of electrostatic and/or steric effects. The values of the ratio k_{ex}/k_{is} are *ca.* 1 for compounds (1)—(3) and further support the known configurational instability of strained α-sulphonyl carbanions.

In a previous paper,[1] we reported the synthesis and stereochemistry of several *cis*- and *trans*-2-halogeno-3-morpholinothietan 1,1-dioxides. For the series of 4,4-dimethyl substituted derivatives (1)—(6) particularly, the *cis*-isomers are thermodynamically less stable than the *trans*-isomers as configurational isomerization easily and irreversibly occurs in mild basic medium.† During that work a qualitative dependence of the isomerization was also noted.

The above observations prompted us to make quantitative measures on base catalysed *cis–trans*-isomerization and H–D exchange in compounds (1)—(6) in order to evaluate which effects influence reaction rates.

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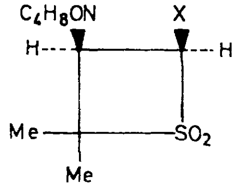
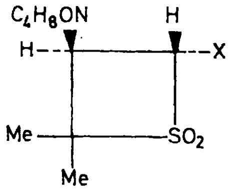
† No *cis*-isomer is present (by n.m.r. analysis) in the *trans*-somers produced by base catalysed isomerization.

[1] P. Del Buttero and S. Maiorana, *J.C.S. Perkin I*, 1973, 2540.



cis

(1) X = Cl
(2) X = Br
(3) X = I



trans

(4) X = Cl
(5) X = Br
(6) X = I

RESULTS

The isomerization and exchange kinetics were carried out in [$^2H_3$]acetonitrile–D_2O solution (4 : 1 v/v) at various pH values using $Na_4B_2O_7$ or $Na_4B_2O_7$–NaOD as buffer agents at 40° (Table). In all cases the products were *trans*-2-deuterio-2-halogeno-4,4-dimethyl-3-morpholinothietan 1,1-dioxides with an isotopic and isomeric purity of at least 95%.† The deuteriation and isomerization rates were followed simultaneously by careful integration of peaks due respectively to the protons in position 2 and to the methyl groups in position 4 (see Experimental section). The rates for both exchange and isomerization were first order in both base and sulphone (Table). Inspection of the Table also reveals that under our experimental conditions (i) in the *cis* series the k_{ex}/k_{is} values are *ca.* 1, (ii) isomerization and deuteriation rates depend upon the nature of the halogen and decrease in the order I > Br > Cl, and (iii) exchange is faster in the case of the *trans*-isomers though the reaction rate (*i.e.* exchange with inversion) of the *cis*-derivatives depends more on the nature of the halogen.

Exchange and isomerization rates of 2-halogeno-4,4-dimethyl-3-morpholinothietan 1,1-dioxides (1)—(6) (0·25M) in CD_3CN–D_2O (4 : 1 v/v) at 40 ± 0·1°

Compound	pH (±0·01)	10^3[Base]/M [c]	$10^5k_{is}/s^{-1}$ [d]	10^2k_{is}/l mol^{-1} s^{-1}	$10^5k_{ex}/s^{-1}$ [d]	10^2k_{ex}/l mol^{-1} s^{-1}
(1)	11·38 [a]	2·40	8·46	3·54	8·76	3·65
	12·95 [b]	88·6	310·0	3·50	330·0	3·72
	13·10 [b]	126·0	436·0	3·46		
(2)	11·38 [a]	2·40	21·6	9·02	21·8	9·08
(3)	11·38 [a]	2·40	59·3	24·7	62·0	25·8
(4)	11·38 [a]	2·40			148·2	61·8
(5)	11·38 [a]	2·40			292·1	121·7
(6)	11·38 [a]	2·40			383·6	159·8

[a, b] Apparent pH of buffer solutions of $Na_4B_2O_7$ and $Na_4B_2O_7$–NaOD respectively. [c] Calculated from pH values. [d] The rate constants are computer generated using the least squares method and are the average of at least three runs.

DISCUSSION

The first point that emerges from the results is the high configurational instability of these strained α-sulphonyl carbanions (k_{ex}/k_{is} *ca.* 1). The different optical stability of the open chain α-sulphonyl carbanions and those incorporating both the carbanionic centre and the sulphonyl group in a cyclic four- or five-membered ring structure has already been clearly pointed out.[2-4] Moreover a sharp decrease in the barrier to inversion has been shown for cyclopropyl carbanions substituted by a phenylsulphonyl group.[5] At the moment it is difficult to envisage a plausible explanation for this behaviour which does appear to be quite general. The other kinetic results [see points (ii) and (iii)] can be rationalized on the basis of steric and electronic factors in the light of the particular stereochemistry of the thietan dioxide ring and taking into account of the halogen atoms.

The stereochemistry of the isomers (1)—(6) have recently been studied by ^{1}H n.m.r. analysis.[1] The results, in accord with the crystal structures determined by *X*-ray analysis of the *cis*-derivative (1) [6] and of *r*-2-chloro-2,4,4-trimethyl-*t*-3-morpholinothietan 1,1-dioxide [7] as models, show that the thietan dioxide ring is puckered and that in the probably preferred conformation the halogen is in a pseudoaxial (*cis*-series) or in a pseudoequatorial (*trans*-series) disposition. Moreover in the former series stronger steric interactions between the ring substituents must be expected, since the chlorine atom is eclipsed by one of the oxygen atoms of the sulphonyl group and is in a 1,3-pseudoaxial relationship with one of the methyl groups in position 4. This steric hindrance is the driving force that through the formation of the carbanion, its inversion, and the consequent relief of strain, promotes exchange with isomerization in the *cis*-series.‡ These criteria, in line with the experimental results, are expected to have the greatest effect in the case of the iodo-derivative.

As for electrostatic effects, repulsion on the anionic, incoming base should reach a minimum in the case of

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† See footnote on p. 1676.

‡ The steric influence on the rate of the exchange with inversion can be related to the steric acceleration affecting the S_N1 nucleophilic substitutions.[8] Also the hypothesis of the intermediacy of a pyramidal carbanion with a very low barrier to inversion does not disprove the above considerations. An analogous effect is reported [9] to contribute to some degree in determining the H–D exchange rate in the halogenoforms ($CDI_3 \gg CDBr_3 > CDCl_3$).

[2] L. A. Paquette, J. P. Freeman, and M. J. Wyvratt, *J. Amer. Chem. Soc.*, 1971, **93**, 3216 and reference therein.

[3] E. J. Corey, H. Konig, and T. H. Lowry, *Tetrahedron Letters*, 1962, 515.

[4] D. J. Cram and T. A. Whitney, *J. Amer. Chem. Soc.*, 1967, **89**, 4651.

[5] A. Ratajczak, F. A. L. Anet, and D. J. Cram, *J. Amer. Chem. Soc.*, 1967, **89**, 2072.

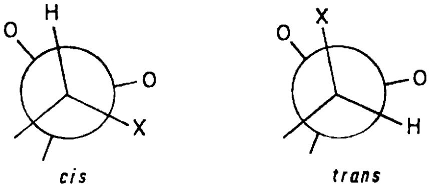
[6] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Gazzetta*, 1974, in the press.

[7] G. D. Andreetti, L. Cavalca, and P. Sgarabotto, *Gazzetta*, 1971, **101**, 440.

[8] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, London, 1969, ch. 8, p. 274.

[9] J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Amer. Chem. Soc.*, 1956, **79**, 1406.

iodine, which is the least electronegative and the most polarizable atom of the halogens. This effect is in accord with the observed order of reactivity (I > Br > Cl) in the *trans*- (exchange) and in the *cis*-series (exchange with inversion).† The less pronounced differences in reactivity observed in the *trans*-iodo-, -bromo-, and -chloro-derivatives (6), (5), and (4) (2·6 : 2 : 1), with respect to those of the *cis*-isomers (3), (2), and (1) (7 : 2·5 : 1) are in line with the above considerations. In fact, as shown before, only electrostatic factors control the exchange rates in the former case, whereas both electrostatic and steric effects operate in the latter. The greater H–D exchange rate of the *trans*-isomers with respect to the *cis*, cannot be accounted for by steric hindrance towards the incoming base since a scale of reactivity opposite to that found would be expected. In fact, 2-H is less sterically hindered in the *cis*-series.



FIGURE

A plausible explanation can be envisaged in the particular position of the exchanging proton with respect to the $\widehat{OSO}$ angle. In fact it is known that H–D exchange of a proton α to a sulphonyl or sulphinyl group depends markedly on its orientation with the groups.[12] In our cases, as pointed out previously, the ^1H n.m.r. data, the *X*-ray analysis, and the molecular models show that in the most probable ground state conformation, 2-H lies inside the $\widehat{OSO}$ angle in the *cis*-series and outside in the *trans* [1,6,7] (Figure). We presume that in the transition state, whatever it is, the two hydrogens should have a different orientation with respect to the $\widehat{OSO}$ angle, thus accounting for the differences in the H–D exchange rates.

EXPERIMENTAL

The ^1H n.m.r. spectra were taken with a Varian A 60A spectrometer with tetramethylsilane as internal standard. pH Measurements were performed on an Amel model 332 potentiometer.

Products.—The preparation and the physical properties of compounds (1)—(6) have been reported elsewhere.[1] However the m.p.s of compounds (1) and (4) reported therein should be inverted and are 157 and 132° respectively.

Reagents and Solvents.—Commercial [$^2H_3$]acetonitrile was used without further purification. A 0·01M solution of AnalaR grade sodium tetraborate (10 ml) in D_2O was diluted to the mark with [$^2H_3$]acetonitrile in a volumetric flask (50 ml) in a constant temperature bath (40 ± 0·1°). This solution showed a constant apparent pH of 11·38 ± 0·1 after four days. Solutions of higher pH were obtained by adding the appropriate amount of 0·1N-NaOD solution in D_2O to the buffer solution at pH 11·38.

Kinetics.—Substrates (1)—(6) (0·25 mmol) were dissolved in the buffer solutions (1ml) in an n.m.r. tube at constant temperature (40 ± 0·1°) and the tube was placed in the n.m.r. probe thermostatted at 40 ± 0·1°. H–D Exchange was followed by integration of the doublets centred at δ 4·63, 4·56, and 4·35 and 4·72, 4·69, and 4·53 [C*H*Cl of (1)—(3) and (4)—(6) respectively]. The isomerization rate was simultaneously measured through integration of the 4,4-dimethyl group signals. Pseudo-first-order rate constants were calculated on a UNIVAC 1106 computer using the least squares method. Average deviations from average values of *k* from at least triplicate runs were *ca.* ±6%.

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† The same reactivity scale has been found for H–D exchange in the case of the α-bromo- and chloro-acetone.[10] Moreover, the different polarizabilities of halogen atoms would affect the carbanion stabilities in such a way that the same order of reactivity would be expected. The same situation would be met if the destabilization factor (+*R* effect) on carbanions is operative.[11]

[10] R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.

[11] K. J. Klabunde and D. J. Burton, *J. Amer. Chem. Soc.*, 1972, **94**, 5985.

[12] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795 and references therein; R. R. Fraser and F. J. Schuber, *Chem. Comm.*, 1969, 1474.