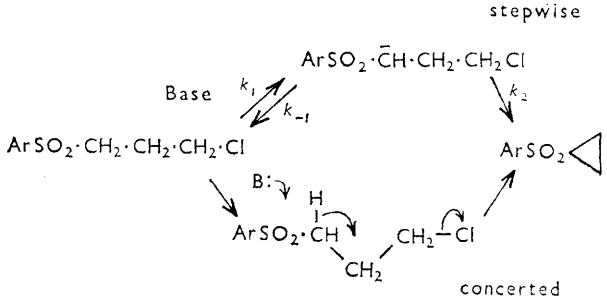
Intramolecular Reactions. Part VII.[1] Cyclisation of Aryl 3-Chloropropyl Sulphones

By **R. Bird** and **C. J. M. Stirling**, King's College, Strand, London W.C.2

Aryl 3-chloropropyl sulphones react with potassium t-butoxide in t-butyl alcohol to give aryl cyclopropyl sulphones in high yields. The effects of substituents in the aromatic nucleus upon the rate of the reaction have been determined, and a rectilinear Hammett plot with $\rho = +2{\cdot}32$ is obtained. Hydrogen atoms of the methylene group adjacent to the sulphonyl group are rapidly exchanged under basic conditions in deuteriated solvents, and the rate of cyclisation of 3-chloro-1,1-dideuteriopropyl *p*-tolyl sulphone in t-butyl [^{2}H]alcohol is twice that of the isotopically normal sulphone in t-butyl [^{1}H]alcohol. These results suggest that an intermediate carbanion is formed and that the ρ-value obtained for the reaction is a composite one which incorporates opposing effects upon the equilibrium concentration of the carbanion and its nucleophilicity in the subsequent ring-closure step. This finding is briefly discussed in relation to current views on cyclisation.

FORMATION of cyclopropyl sulphones from 3-halogenopropyl sulphones under strongly basic conditions was first observed by Zimmerman and Thyagarajan [2] and subsequently by Truce and Lindy.[3] More recently, the rate of formation of cyclopropyl *p*-tolyl sulphone from 3-bromopropyl *p*-tolyl sulphone has been measured in connection with a study [4] of the competition between cyclisation and external substitution and elimination reactions which occur when aryl ω-halogenoalkyl sulphones react with alkoxides.

In the latter investigation it was noticed that closure of a three-membered ring was much more rapid than that of a five-membered ring. Literature reports [4] indicated that in several reactions in which three-membered rings were more rapidly formed by intramolecular nucleophilic substitution than five-membered rings, an intermediate carbanion is involved. This is certainly true of cyclisations involving ω-halogenoalkyl malonic esters.[1] The relative rates of closure of rings of various sizes has been discussed [1] elsewhere, but in this connection we wished to know whether the high rate of closure of three- compared with five-membered rings was to be associated with a carbanionic intermediate. Formation of an aryl cyclopropyl sulphone from an aryl 3-chloropropyl sulphone in the presence of base can be (see Scheme) either



SCHEME

concerted or stepwise through an intermediate carbanion. In either event, of course, cleavage of the carbon–hydrogen bond adjacent to the sulphonyl group is involved.

In arylsulphonyl compounds, the effect of substituents in the aromatic nucleus upon reactions which involve the carbon–hydrogen bond adjacent to the sulphonyl group

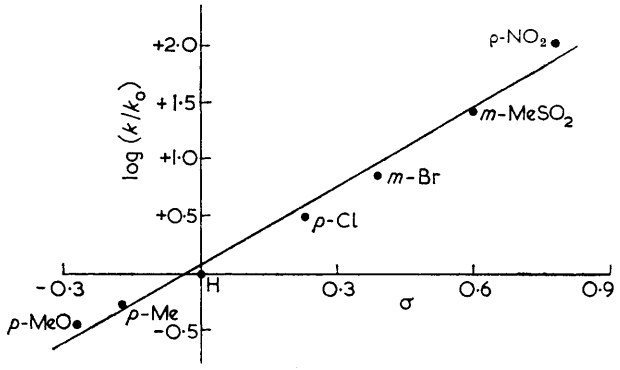
[1] Part VI, A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1968, 67.
[2] H. E. Zimmerman and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, 1960, **82**, 2505.
[3] W. E. Truce and L. B. Lindy, *J. Org. Chem.*, 1961, **26**, 1463.
[4] A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1967, 808.

has been examined for additions of amines to aryl vinyl sulphones [5] and for hydrogen–deuterium exchange under basic conditions.[6] The values of the Hammett ρ-parameter were +1·58 and +2·8 respectively. In the latter reaction, carbon–hydrogen bond extension in the transition state is considerable, and the value of ρ is probably near the maximum.

In the present work, a series of aryl 3-chloropropyl sulphones (Tables 2 and 3) has been synthesised using the sequence: 1-bromo-3-chloropropane ⟶ aryl 3-chloropropyl sulphide ⟶ aryl 3-chloropropyl sulphone. Treatment of the sulphones with potassium t-butoxide in t-butyl alcohol gives the aryl cyclopropyl sulphones (Table 4) in good yield.

The rate of reaction of each 3-chloropropyl sulphone with potassium t-butoxide in t-butyl alcohol at 30° was measured by determination, at intervals, of chloride ion released. Reactions were first-order in both sulphone and t-butoxide. Second-order rate constants are in Table 1.

The Hammett plot of log (k/k_0) against σ is shown in the Figure. Least-squares treatment of the data gives



ρ = +2·32 with $r = 0·994$ and $s = 0·104$. This value of ρ could be interpreted as indicating a concerted mechanism for the reaction, as its magnitude is much less than the largest value so far observed for a reaction which involves cleavage of a C–H bond adjacent to a sulphonyl group. Alternatively, the ρ-value may denote * the overall electronic effect of substituents differentially upon the pre-equilibrium and subsequent stage of a stepwise (carbanion) mechanism (see Scheme).

Rigorous distinction between concerted and stepwise anionic processes is not straightforward. 3-Chloropropyl *p*-tolyl sulphone, on dissolution in dimethyl sulphoxide and treatment with sodium deuteroxide in deuterium oxide, exchanges the methylene hydrogen atoms adjacent to the sulphonyl group much more rapidly than the cyclopropyl sulphone is formed. However, this result is evidence only that a carbanion may be formed; it does not place it on the pathway to product.[7] Accordingly, we have also estimated the primary deuterium isotope effect upon the cyclisation rate.

The rapid deuterium–hydrogen exchange which occurs under basic conditions complicates the determination of the primary isotope effect, as it requires that the cyclisation rate of α,α-dideuterio-γ-chloro-sulphone in heavy solvent is compared with that of the isotopically normal sulphone in light solvent. Any difference in rate between these systems comprises the primary and

TABLE 1

Rate constants for cyclisation of aryl 3-chloropropyl sulphones

Subst.	10^3k_2 (l. mole^{-1} sec.$^{-1}$)	Subst.	10^3k_2 (l. mole^{-1} sec.$^{-1}$)
p-MeO	1·23	*m*-Br	25·4
p-Me	1·85 (3·70 *)	*m*-$MeSO_2$	95·3
None	3·54	*p*-NO_2	379
p-Cl	11·1		

* For *p*-Me·C_6H_4·SO_2·CD_2·CH_2·CH_2·CH_2Cl in Bu^{t}OD.

TABLE 2

Aryl 3-chloropropyl sulphides

Subst.	Yield (%)	B. p./mm.	n_D^{25}	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
H	31	113°/1·6	1·5690 [a]	—	—	—	—
p-Cl	76	124/0·1	1·5850	48·5	4·7	48·9	4·6
p-Me	90	141/1·6	1·5637 [b]	—	—	—	—
p-MeO ...	61	124/0·3	1·5685	55·7	5·95	55·4	6·05
p-NO_2 ...	76	167/0·1 [c]	—	46·25	4·3	46·65	4·35
m-$MeSO_2$	62	220/0·6	1·5821	38·6 [d]	3·7	38·3 [d]	3·6
m-Br	77	141/1·5	1·6002	36·5 [e]	3·3	36·0 [e]	3·0

[a] Lit.,[3] b. p. 116°/4 mm., n_D^{20} 1·5752. [b] Lit.,[3] b. p. 118°/2 mm., n_D^{21} 1·5643. [c] M. p. 49—50° (G. M. Bennett and W. A. Berry, *J. Chem. Soc.*, 1927, 1666, give 50°). [d] Analysis for thiouronium picrate, m. p. 157—158°. [e] Analysis for thiouronium picrate, m. p. 169—170°.

TABLE 3

Aryl 3-chloropropyl sulphones

Subst.	Yield (%)	M. p.*	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
H	58	23—24° [a]	—	—	—	—
p-Cl	84	72·5	42·7	4·0	42·7	3·85
p-Me	86	72—73 [b]	—	—	—	—
p-MeO	87	70—71	48·8	5·3	48·3	5·3
p-NO_2	88	88·5	41·6	3·4	41·0	3·8
m-$MeSO_2$ ...	93	83	40·7	4·4	40·5	4·4
m-Br	82	44·5	36·4	3·2	36·3	3·4

* From MeOH. [a] B. p. 156—158°/0·7 mm., n_D^{18} 1·5489 (lit.,[3] b. p. 173—174°/2 mm., $n_D^{21·2}$ 1·5463). [b] Lit.,[3] 72—73°.

TABLE 4

Aryl cyclopropyl sulphones

Subst.	Yield (%)	M. p.	Cryst from	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
H	92·5	36°	*a*	—	—	—	—
p-Cl	89	72·5	MeOH	50·0	3·75	49·9	4·2
p-Me ...	96	65—66 [b]	MeOH	—	—	—	—
p-MeO ...	97	44—45	MeOH	56·2	5·9	56·6	5·9
p-NO_2 ...	85	147—148	MeOH	47·6	4·0	47·6	3·8
p-$MeSO_2$	97	156—157	PhH–Pet [c]	46·25	4·8	46·1	4·65
m-Br ...	98	72—73	MeOH	41·1	3·4	41·4	3·5

[a] B. p. 114—116°/0·1 mm. (lit.,[3] 130—135°/0·5 mm.). [b] Lit.,[3] 65—66°. [c] Light petroleum (b. p. 40—60°).

* Kindly pointed out to us by a referee.

[5] S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1967, 348.
[6] H. Hogeveen, G. Maccagnani, F. Montanari, and F. Taddei, *J. Chem. Soc.*, 1964, 4101.
[7] R. Breslow, *Tetrahedron Letters*, 1964, 399.

secondary deuterium isotope effects together with the solvent deuterium isotope effect.

The value of k_H/k_D was 0·5. Clearly, this is not compatible with a concerted mechanism for which k_H/k_D values of *ca.* 4 would be expected, even if allowance is made for the (almost certainly) small solvent isotope effect which a concerted mechanism would involve. We therefore suggest that an intermediate carbanion is formed.

For formation of a carbanion in t-butyl alcohol, the isotope effect cannot be predicted simply from consideration of the equilibrium

$$C{-}H + Bu^tO^- \rightleftharpoons C^- + Bu^tOH \qquad (1)$$

because the ratio of primary isotope effects on the forward and reverse reactions is unknown, and because the [^{1}H]- and [^{2}H]-acids have to be compared in isotopically different solvents. Two other equilibria in the system may be considered (by analogy with equilibria in water):

$$C{-}H + Bu^tOH \rightleftharpoons C^- + Bu^t\overset{+}{O}H_2 \qquad (2)$$

and

$$2Bu^tOH \rightleftharpoons Bu^tO^- + Bu^t\overset{+}{O}H_2 \qquad (3)$$

It follows that $K_2 = K_1 \cdot K_3$.

In aqueous systems, dissociation constants of acids (cf. K_2) are about four times as large in H_2O as in D_2O. Also, the autoprotolysis constant (cf. K_3) for D_2O is less than one-sixth of that for H_2O. If the same *trends* are followed for t-butyl alcohol as solvent, *i.e.*, $K_2 < K_3$, then $K_1 < 1$ for hydrogen compared with deuterium. The equilibrium concentration of carbanion is greater in the heavy isotope system and the inverse isotope effect is understandable.

These considerations apply to the pre-equilibrium only. The rate constant, k_2, for the cyclisation step must also be subject to a solvent isotope effect. As the transition state for cyclisation involves dispersal of charge, the reaction is probably slightly favoured by transfer to the heavy solvent, so that isotope effects on both stages are in the same direction, but this solvent isotope effect and the secondary isotope effect will both be small.

The general question (above), as to whether the rapid formation of three-membered rings involving intramolecular nucleophilic attack by carbon is necessarily to be associated with a discrete carbanion, must be left open.

EXPERIMENTAL

For general directions see Part VI.[1] Identities of starting materials and of products were checked by infrared and n.m.r. spectroscopy. *p*-Methoxy-,[8] *m*-bromo-,[9] and *m*-methyl-sulphonylbenzenethiol [10] were prepared by literature methods.

Aryl 3-Chloropropyl Sulphones.—The following preparation is typical. 1-Bromo-3-chloropropane (60 g., 1·3 mol.) was added to *p*-chlorobenzenethiol (36 g.) in 0·5N-ethanolic sodium ethoxide (500 ml.). The mixture was refluxed for 2 hr. and the resulting suspension poured into water (500 ml.) and extracted with dichloromethane. The extract was washed with dilute aqueous acetic acid and saturated aqueous sodium hydrogen carbonate, and evaporation and distillation gave the *chloro-sulphide* (41·9 g.), b. p. 124—125°/0·1 mm., n_D^{25} 1·5854 (Found: C, 48·5; H, 4·7; Cl, 32·3; S, 14·4. $C_9H_{10}Cl_2S$ requires C, 48·9; H, 4·6; Cl, 32·1; S, 14·5%).

3-Chloropropyl *m*-methylsulphonylphenyl and *m*-bromophenyl sulphides were characterised as the thiouronium picrates.[11]

The sulphide (30 g.) was kept with 30% aqueous hydrogen peroxide (63·5 g.) and acetic acid (200 ml.) at 100° for 2 hr. The mixture was poured into cold saturated brine, and filtration gave a residue of crude *sulphone* (27 g.), m. p. 72·5° (from methanol) (Found: C, 42·8; H, 3·85. $C_9H_{10}Cl_2O_2S$ requires C, 42·7; H, 4·0%).

The ^{1}H n.m.r. spectra of 3-chloropropyl *p*-methoxyphenyl and *p*-nitrophenyl sulphones showed traces of impurity, and infinity readings obtained in the kinetic work were 2 and 6% low respectively. Repeated crystallisation and chromatography failed to remove the impurities, and an alternative route through the 3-hydroxypropyl sulphide [3] was used in each case. The sulphones obtained still contained small amounts of the same impurity, and the rate constants for cyclisation of these compounds must be accepted with this reservation.

Cyclisation.—The following procedure is typical. 3-Chloropropyl *p*-chlorophenyl sulphone (3·417 g.) in t-butyl alcohol (110 ml.) was added to 0·25N-potassium t-butoxide in t-butyl alcohol (140 ml.). The mixture was set aside for 18 hr. at 25° and then ether and saturated brine were added. The organic layer was separated, washed with brine, and evaporated. The residue, on crystallisation from isopropyl ether, gave p-*chlorophenyl cyclopropyl sulphone* (89%), m. p. 72—72·5° (Found: C, 50·0; H, 3·75. $C_9H_9ClO_2S$ requires C, 49·9; H, 4·2%).

Kinetics.—Stock solutions of potassium t-butoxide in t-butyl alcohol were prepared by dissolution of potassium in the alcohol and subsequent dilution to ~0·2N. The solution was standardised against 0·1N-hydrochloric acid using Methyl Red as indicator. Solutions of the chloro-sulphone and of t-butoxide in t-butyl alcohol at 30·0° were mixed, and aliquot parts were transferred to tubes fitted with ground-glass stoppers. This procedure is made necessary by precipitation of potassium chloride. At suitable intervals, the contents of the tubes were poured into 0·5N-nitric acid which had previously been boiled to remove nitrous acid. An excess of aqueous 0·05N-silver nitrate was added and the excess was back-titrated with aqueous 0·005N-ammonium thiocyanate using ferric ammonium sulphate as indicator. At least seven determinations of each rate constant were made in separate runs. The variation in initial concentration of the chloro-sulphone was 0·05—0·1M, and in potassium t-butoxide 0·05—0·15M. A typical series of results is in Table 5.

The Hammett ρ-value was determined by the least-squares method using an Atlas computer.

Reactions with Deuteriated Compounds.—*3-Chloro-1,1-dideuteriopropyl p-tolyl sulphone.* Isotopically normal sulphone (1·7 g.) was dissolved in a mixture of perdeuteriodimethyl sulphoxide (8 ml.) and deuterium oxide (99·7% D_2O)

[8] C. M. Suter and H. L. Hansen, *J. Amer. Chem. Soc.*, 1932, **54**, 4100.
[9] H. F. Wilson and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 5200.
[10] F. G. Bordwell and H. M. Andersen, *J. Amer. Chem. Soc.*, 1953, **75**, 6019.
[11] A. I. Vogel, 'Practical Organic Chemistry,' 3rd edn., Longmans, London, 1956, p. 291.

(1·5 ml.). After 1 hr., the ^{1}H n.m.r. spectrum showed that no exchange had occurred. Addition of 30% sodium deuteroxide in deuterium oxide (0·06 ml.) to the solution caused the triplet at τ 6·75 (methylene protons adjacent to SO_2) to disappear rapidly, and a small peak appeared at 8·95, consistent with formation of a trace of cyclopropyl sulphone. Addition of deuterium oxide to the mixture precipitated the dideuterio-compound, which was filtered off and washed with deuterium oxide. It had m. p. 73—74° (from benzene–light petroleum) and the ^{1}H n.m.r. spectrum (in $CDCl_3$) confirmed the absence of methylene protons adjacent to the sulphonyl group.

TABLE 5

Rate of reaction of *p*-chlorophenyl 3-chloropropyl sulphone with potassium t-butoxide in t-butyl alcohol at 30°

Initial [Sulphone] = $1·5 \times 10^{-2}$M; initial [$Bu^tO^-K^+$] = $2·473 \times 10^{-2}$M.

Time (t) (min.)	10	20	30	40	50
0·05N-$AgNO_3$ consumed (ml.)	2·25	4·04	5·15	6·29	7·14
Log $(b - x)/(a - x)$ ...	0·246	0·276	0·297	0·326	0·355
Time (t) (min.)	60	80	100	120	∞
0·05N-$AgNO_3$ consumed (ml.)	7·97	9·32	10·60	11·20	14·83
Log $(b - x)/(a - x)$ ...	0·378	0·433	0·507	0·552	—

k_2, from plot of log $(b - x)/(a - x)$ against t, is $1·10 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ (duplicate, $1·11 \times 10^{-2}$).

t-Butyl [^{2}H]alcohol was prepared [12] from t-butyl alcohol and deuterium oxide. The azeotrope obtained after six equilibrations was dried (CaH_2), distilled, and then stored over Linde 4A molecular sieve for 3 days. Before use it was distilled in apparatus previously rinsed with deuterium oxide and dried. The ^{1}H n.m.r. spectrum of the product showed it to contain not less than 95% Bu^tOD.

Standard solutions of base were prepared by dissolution of twice-sublimed potassium t-butoxide in t-butyl [^{2}H]alcohol. Rate measurements were carried out as before except that the contents of the tubes were quenched in a 0·2M-aqueous acetate buffer (pH 4·6) and liberated chloride was determined by potentiometric titration.[13] Rates of cyclisation were known to be sensitive to the amount of water present in the solvent, and control runs were therefore carried out in which isotopically normal t-butyl alcohol was treated in exactly the same way as the 'heavy' solvent. The results were the same, within experimental error, as those obtained in the Hammett plot runs.

We thank Professor V. Gold for a valuable discussion of isotope effects, and the S.R.C. for a maintenance grant (to R. B.).

[7/1011 *Received, August 4th*, 1967]

[12] D. J. Cram and B. Rickborn, *J. Amer. Chem. Soc.*, 1961, **83**, 2178.
[13] V. J. Shiner and M. L. Smith, *Analyt. Chem.*, 1956, **28**, 1043