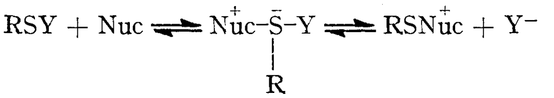
Nucleophilic Substitution at Bivalent Sulphur. Part V.[1] A Study of Exchange Reactions at Bivalent Sulphur using ^{19}F Nuclear Magnetic Resonance Spectroscopy

By **Donald R. Hogg*** and **Joseph Stewart**, Department of Chemistry, University of Aberdeen, Aberdeen AB9 2UE

Exchange broadening is observed in the ^{19}F n.m.r. spectrum of a solution of bis-(2-nitro-4-trifluoromethylphenyl) disulphide and the corresponding thiolate ion. The rate of exchange is dependent on concentration and solvent composition. A rate constant of $1{\cdot}5 \times 10^4$ l mol^{-1} s^{-1} is calculated for exchange at 70°. A rapid exchange leading to line broadening is also obtained with an equimolar mixture of potassium cyanide and 2-nitro-4-trifluoromethylphenyl thiocyanate. These compounds react to give the thiolate ion which then gives the monosulphide by reaction with starting material. No exchange was observed with 2-nitro-4-trifluoromethylbenzenesulphenanilide and aniline, nor with the corresponding sulphenyl thiocyanate and potassium thiocyanate, although potassium cyanide reacted with this compound to give the aryl thiocyanate. No evidence was obtained for the formation of an intermediate during substitution at sulphur.

MOST of the existing evidence [2] concerning nucleophilic substitution at bivalent sulphur can be accommodated by an S_N2 type mechanism similar to that at saturated carbon. In one reaction [2a] the partial charge on the sulphur atom in the transition state was calculated to be $+0{\cdot}6$. More recently evidence has been advanced [3] for an S_AN mechanism in which the sulphur atom in the intermediate carries a negative charge [reaction (1)].



$$\mathrm{RSY + Nuc \rightleftharpoons \overset{+}{Nuc}\text{-}\underset{\underset{R}{|}}{\overset{-}{S}}\text{-}Y \rightleftharpoons RS\overset{+}{Nuc} + Y^-} \qquad (1)$$

As the positions of the ^{19}F n.m.r. signals from the 2-nitro-4-trifluoromethylbenzenesulphenyl group are highly sensitive to charge variation at the sulphur atom,[1] exchange reactions at sulphur were studied using compounds containing this group in an attempt to detect a possible intermediate.

Thiolate Ion–Disulphide Exchange.—The ^{19}F n.m.r. spectrum of equimolar solutions of bis-(2-nitro-4-trifluoromethylphenyl) disulphide and the sodium salt of the corresponding thiol in 30% v/v aqueous dioxan were measured at various concentrations and temperatures. At 30° the spectrum of a $0{\cdot}1$M solution consisted of a very broad signal centred at *ca.* 1225 Hz downfield from trifluoroacetate ion, the internal standard. This signal lies between the sharp singlets given separately by the starting materials at 1179 and 1284 Hz respectively and close to the weighted average of these signals (1214 Hz). As the temperature was increased in stages to 85° the broad signal sharpened (Figure 1) and became broad again when the temperature was decreased, thus showing that the broadening was due to a kinetic effect, presumably exchange between the thiolate ion and the disulphide, and that this exchange is fast on the n.m.r. time scale. The position of the time-averaged signal shifted slightly to higher field as the temperature increased. A small singlet at 1156 Hz at 30° was also observed and found to increase in intensity with time. This signal, which occurred in all similar systems, was assigned, by comparison with an authentic specimen, to bis-(2-nitro-4-trifluoromethylphenyl) sulphide. The formation of this compound presumably involves an irreversible nucleophilic substitution at the activated aromatic carbon atom of the disulphide by the thiolate ion, the reaction occurring simultaneously with the reversible exchange at sulphur.

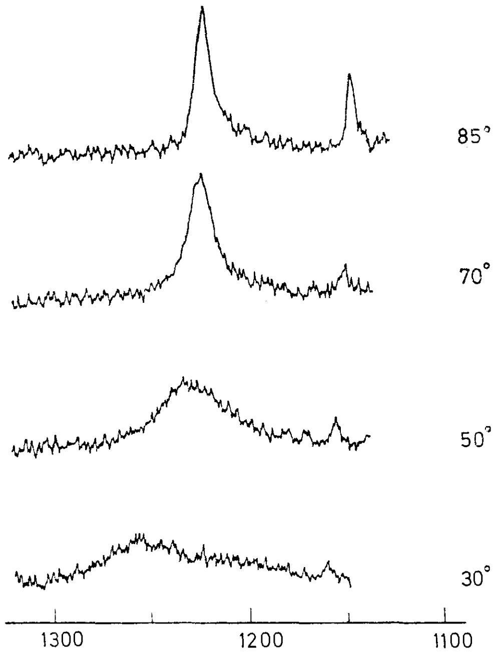


FIGURE 1 ^{19}F N.m.r. spectra (Hz from $CF_3CO_2^-$ ion) of a solution of bis-(2-nitro-4-trifluoromethylphenyl) disulphide ($0{\cdot}1$M) and the corresponding thiolate ion ($0{\cdot}1$M) in 30% v/v aqueous dioxan at various temperatures

For a very rapid exchange, where the signals coalesce

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[1] Part IV, D. R. Hogg and J. Stewart, *J.C.S. Perkin II*, 1974, 436.

[2] (*a*) L. Senatore, E. Cuiffarin, and A. Fava, *J. Amer. Chem. Soc.*, 1970, **92**, 3035; (*b*) J. L. Kice and J. M. Anderson, *J. Org. Chem.*, 1968, **33**, 3331; C. Brown and D. R. Hogg, *Chem. Comm.*, 1967, 38; A. Fava and A. Iliceto, *J. Amer. Chem. Soc.*, 1958, **80**, 3478.

[3] E. Cuiffarin and G. Guaraldi, *J. Amer. Chem. Soc.*, 1969, **91**, 1745, *J. Org. Chem.*, 1970, **35**, 2906; E. Cuiffarin and L. Senatore, *J. Chem. Soc.* (*B*), 1970, 1680; E. Cuiffarin, L. Senatore, and M. Isola, *ibid.*, 1971, 2187; E. Cuiffarin and F. Griselli, *J. Amer. Chem. Soc.*, 1970, **92**, 6015.

to give a single line the exchange rate can be obtained[4] from expression (2) where P_a and P_b are the relative

$$1/2\tau = 2\pi P_a P_b (\delta\nu)^2 W^{-1} \qquad (2)$$

populations of the states between which exchange occurs (1/3, 2/3), $\delta\nu$ the separation of the signals in the absence of exchange (105 Hz), and W is the linewidth at half peak-height due to exchange broadening. This expression is applicable if $1/\tau$ and $\delta\nu \gg W''$, the effective linewidth in the absence of exchange, and if $1/\tau \gg 2\pi\delta\nu$. At 70 and 85° both conditions apply and $1/2\tau$ equals 1500 and 2600 s^{-1} respectively. Division by the concentration of disulphide gives values of $1{\cdot}5 \times 10^4$ and $2{\cdot}6 \times 10^4$ l mol^{-1} s^{-1} for the second-order velocity constants at these temperatures and hence a value of 37 kJ mol^{-1} for the activation energy. By extrapolation, the second-order velocity constant at 25° equals 2×10^2 l mol^{-1} s^{-1}. At 50° the temperature of measurement is too close to the coalescence temperature for the above expression to hold and the rate of exchange cannot readily be calculated in this case where $P_a \neq P_b$.

Reducing the concentration of the reactants or increasing the relative volume of water in the solvent reduces the rate of exchange and hence increases the coalescence temperature. Thus reducing the concentration of the reactants to $1{\cdot}7 \times 10^{-2}$M gave two broad singlets at *ca.* 1290 and 1185 Hz with a coalescence temperature between 60 and 70°, showing that the apparent first-order velocity constant is concentration dependent. At this concentration the broad singlet obtained above 70° was centred at *ca.* 1210 Hz. Similar results were obtained in 36·3% v/v aqueous dioxan at a concentration of $1{\cdot}5 \times 10^{-2}$M except that the coalescence temperature was *ca.* 70°. Conversely decreasing the relative amount of water increased the rate of exchange and in 17·6% v/v aqueous dioxan at a reagent concentration of 3×10^{-2}M, second-order velocity constants of $6{\cdot}5 \times 10^4$ and $3{\cdot}0 \times 10^4$ l mol^{-1} s^{-1} were obtained at 85 and 70° respectively, and the coalescence temperature was well below room temperature. The high rate of exchange and its sensitivity to solvent composition indicate that it involves a nucleophilic substitution at one of the sulphur atoms of the disulphide by the thiolate ion rather than a radical process of the type described by Gur'yanova.[5] In confirmation no exchange broadening was observed in a solution of the thiol and the disulphide to which an equivalent amount of sodium hydroxide had not been added. The spectrum consisted only of sharp singlets at 1188 and 1179 Hz attributed to the two components.

The rate constant [6] for the hydrolysis of this disulphide by sodium hydroxide in 50% v/v aqueous dioxan at 25·0° is 1·15 l mol^{-1} s^{-1}. Changing the nucleophile from hydroxide ion to thiolate ion in this case causes an increase in the rate of nucleophilic substitution at bivalent sulphur of *ca.* 10^4 if, as expected, the effect of changing the medium is comparatively small. This increase seems reasonable as benzenethiolate ion, a much stronger nucleophile, is *ca.* 10^4 times more reactive [7] at saturated carbon than hydroxide ion and the relative reactivity should be greater for reaction at a ' softer ' acidic centre such as sulphur. No evidence could however be obtained concerning possible intermediates in the exchange reaction.

Cyanide Ion–Thiocyanate Exchange.—An equimolar solution of 2-nitro-4-trifluoromethylphenyl thiocyanate and potassium cyanide was reddish brown. The ^{19}F n.m.r. spectrum of a freshly prepared solution showed a broad signal centred at *ca.* 1160 Hz and a small singlet at 1284 Hz assigned to the thiolate ion. With increasing time the latter signal became more intense and then diminished. The former signal became steadily more sharp and after 24 h the spectrum consisted of one singlet at 1159 Hz, assigned by comparison with an authentic specimen to bis-(2-nitro-4-trifluoromethylphenyl) sulphide (Figure 2). When a three-fold excess of potassium cyanide was used, the thiolate ion signal and the sulphide signal were both present after 69 h. In this system the centre of the broad signal lies very close to the singlet at 1164 Hz produced by the starting material in the absence of cyanide ion. This suggests that the environment of the fluorine in the exchanging system is very similar to that in the thiocyanate. Such a situation would be created by a rapid exchange of cyanide ion by an S_N2 type substitution at sulphur or by a rapid equilibrium between the thiocyanate and the intermediate formed by the addition of cyanide ion at carbon [reaction (3)]. The charge on the nitrogen in the

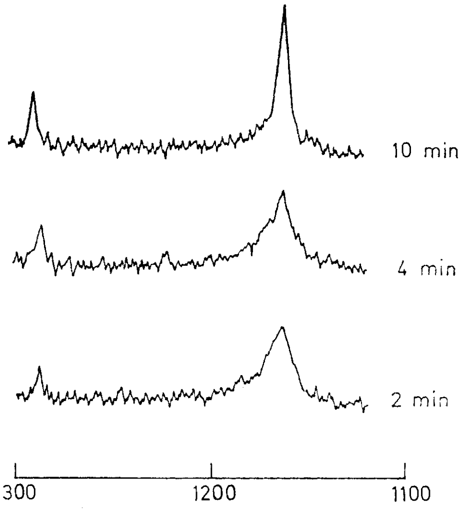

FIGURE 2 ^{19}F N.m.r. spectra (Hz from $CF_3CO_2^-$ ion) of a solution of potassium cyanide and 2-nitro-4-trifluoromethylphenyl thiocyanate in 30% v/v aqueous dioxan at various times after mixing

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[4] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 1966, **88**, 3185.

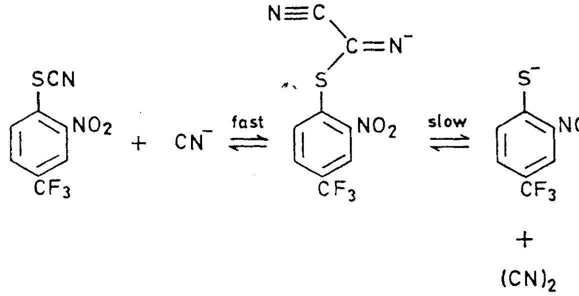
[5] E. N. Gur'yanova, *Quart. Reports Sulphur Chem.*, 1970, **5**, 113.

[6] D. R. Hogg and J. Stewart, *J.C.S. Perkin II*, 1974, 43.

[7] R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, 1968, **90**, 319; I. R. Alet and B. D. England, *J. Chem. Soc.*, 1961, 5259.

intermediate is not in conjugation with the benzene ring and its effect will be reduced by the electron-withdrawing effect of the added cyano-group. Exchange cannot involve the thiolate ion as the broad signal does not occur far enough downfield and the thiolate ion signal is always sharp. If the broadening is due to exchange at sulphur then this must occur simultaneously with a reaction similar to (3) giving the thiolate ion. Aryl thiocyanates react similarly [1,8] with other nucleophiles to give the thiolate ion.

The final product of this reaction, bis-(2-nitro-4-trifluoromethylphenyl) sulphide, is considered to be formed



(3)

by the nucleophilic displacement of the thiocyanate ion by the thiolate ion [reaction (4)]. The monosulphide

$$\mathrm{ArS^- + ArSCN \longrightarrow ArSAr + SCN^-} \qquad (4)$$

and thiocyanate ion were formed from an equimolar mixture of the aryl thiocyanate and thiolate ion but the reaction did not go to completion owing presumably to hydrolysis [1] of the aryl thiocyanate. An increase in the proportion of cyanide ion in the original reaction also gives a mixture of thiolate ion and monosulphide. In this latter case the increased concentration of reagent will increase the rate of formation of thiolate ion and thus produce an excess of this intermediate. This type of reaction has been postulated [9] to account for the presence of lanthionine residues in proteins which have been treated with cyanide ion and for the products from the reaction [10] of certain disulphides with cyanide ion but has not been observed previously with aryl thiocyanates.

Other Systems.—The ^{19}F n.m.r. spectra of equimolar solutions of aniline and 2-nitro-4-trifluoromethylbenzenesulphenanilide, and of potassium thiocyanate and 2-nitro-4-trifluoromethylbenzenesulphenyl thiocyanate, showed only one singlet identical with that of the starting material at 1203 and 1180 Hz respectively. These exchange reactions must be slow or negligible and if an intermediate is formed its concentration is too low for detection. In contrast to the previous reactions these nucleophiles should have a low thiophilicity.[9] As expected from the relatively high thiophilicity of cyanide ion, it reacted rapidly with an equimolar quantity of sulphenyl thiocyanate to form the aryl thiocyanate [reaction (5)]. The n.m.r. spectrum contained a minor

$$\mathrm{ArS{\cdot}SCN + CN^- = ArSCN + SCN^-} \qquad (5)$$

signal assigned to starting material which presumably remains unchanged owing to further reaction of cyanide ion with the aryl thiocyanate.

EXPERIMENTAL

Materials.—Bis-(2-nitro-4-trifluoromethylphenyl) sulphide, m.p. 145—146° (lit.,[11] 142—143°), was prepared from sodium sulphide nonahydrate and two equiv. of 4-chloro-3-nitrobenzotrifluoride in ethanol. 2-*Nitro*-4-*trifluoromethylbenzenesulphenanilide*, orange crystals from carbon tetrachloride, m.p. 88—88·5°, was prepared (68%) from the sulphenyl chloride and aniline, τ 1·41br (1H, s), 2·21br (2H, s), 2·60—3·10 (5H, m), and 4·78br (1H, s) (Found: C, 49·4; H, 3·1; N, 9·0; S, 10·5. $C_{13}H_9F_3N_2O_2S$ requires C, 49·7; H, 2·9; N, 8·9; S, 10·2%). Other reactants and solvents were as previously described.[1,6]

^{19}F *N.m.r. Spectra.*—Spectra were measured in a 10% solution of sodium trifluoroacetate in aqueous dioxan immediately after mixing and then at various intervals using a Varian model A100 n.m.r. spectrometer operating at 94·1 MHz. Signals are expressed in Hz downfield from trifluoroacetate as internal standard. Except where stated the concentration of substrate was *ca.* 0·1M and the medium was 30% v/v aqueous dioxan. In some cases solubility difficulties were experienced and some of the solutions may have been supersaturated.

One of us (J. S.) thanks the S.R.C. for the award of a maintenance grant.

[4/222 *Received*, 5*th February*, 1974]

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[9] A. J. Parker and N. Kharasch, *Chem. Rev.*, 1959, **59**, 583.

[10] R. G. Hiskey and F. I. Carroll, *J. Amer. Chem. Soc.*, 1961, **83**, 4647.

[11] A. Roe, J. A. Montgomery, W. A. Yarnall, and V. A. Hoyle, jun., *J. Org. Chem.*, 1956, **21**, 28.