The Use of Radioisotopes in Studies of Reaction Mechanism. Part III.[1] Thiocyano-exchange and Azido-dethiocyanation of 2,4-Dinitro-1-thiocyanobenzene

By **Joseph Miller,*** Instituto de Química, Universidade Estadual de Campinas, 13,100 Campinas, S.P., Brasil
Frank H. Kendall,* Radioisotope Unit, University of Hong Kong, Hong Kong

The reactions of 2,4-dinitro-1-thiocyanobenzene with azide and thiocyanate ions in methanol and with thiocyanate ions in *NN*-dimethylformamide (DMF) have been studied using radioactive tracer techniques. The results are compared with those obtained previously for reactions of 2,4-dinitro-1-thiocyanobenzene with methoxide ion and for 1-iodo-2,4-dinitrobenzene with all three nucleophiles. The results show that thiocyano-exchange in methanol is a true S_NAr reaction in which the mobility of the thiocyano-group is similar to that of iodine. Both reactions exhibit a characteristic heavy nucleophile interaction in methanol but not in DMF. A significant increase in ease of displacement of the thiocyano-group in azido-dethiocyanation is speculatively ascribed to a favourable interaction between thiocyano- and azido-groups in the rate-limiting transition state. The much larger increase with methoxide ion in methanol, demonstrated in earlier studies, is linked with alternative attack at the cyano carbon atom. Thiocyano-exchange in DMF is very similar to thiocyano-deiodination in DMF. In both, the faster reaction in DMF than in methanol (solvent rate ratio <100) is a result of less negative $\Delta S^‡$ values, with $\Delta H^‡$ essentially unchanged.

SOME unpublished results mentioned in a recent monograph,[2,3a] indicated that 2,4-dinitro-1-thiocyanobenzene, in its reaction with sodium methoxide in methanol, had unexpectedly high reactivity in comparison with 1-halogeno-2,4-dinitrobenzenes (halogen = Cl, Br, or I). The latter react in what are virtually prototype reactions to give 2,4-dinitroanisole as product. This substance could also be isolated from the methoxide–thiocyano reaction mixture,† suggesting a corresponding reaction, although the reasons for high reactivity were in doubt.

The work now reported was undertaken to clarify uncertainties concerning the mobility of the thiocyano-group, for which radioisotope techniques offer particular advantages. The results show that the mobility is not abnormal.

EXPERIMENTAL

Materials.—2,4-Dinitro-1-thiocyanobenzene (Fluka puriss grade) was recrystallised from *NN*-dimethylformamide (DMF) and washed with dry methanol to constant m.p. 138° and then stored over magnesium perchlorate. Labelled 2,4-dinitro-1-[^{14}C]thiocyanobenzene was prepared by allowing 2,4-dinitro-1-thiocyanobenzene (4·0 g) to undergo exchange with potassium [^{14}C]thiocyanate (6 μCi) (Radiochemical Centre, Amersham), in methanol (1 ml) and DMF (30 ml) for 48 h at room temperature. 2,4-Dinitro-1-[^{14}C]thiocyanobenzene precipitated upon addition of ice–water; the precipitate was washed with water (5 × 5 ml), dried, and recrystallised from DMF, m.p. 137·5°. Potassium thiocyanate (reagent grade) was dried in a vacuum drier charged with phosphoric oxide, then recrystallised from dry methanol. Immediately before use the crystals were re-dried to constant weight. Sodium azide (reagent grade) was purified by recrystallisation from 50% methanol, rinsed with methanol, and stored in a vacuum desiccator. Scintillation grade PPO and POPOP were used as primary and secondary solutes for the liquid fluor solution. Methanol (AnalaR) and DMF (reagent grade) were purified immediately before use as described previously.[1]

Measurements of Radioactivity.—Carbon-14 radioactivity was measured by the liquid scintillation counting technique using a Nuclear Chicago liquid scintillation spectrometer and sample changer (type 720). The most suitable liquid fluor was found to be one based on 1,2-dioxan with ethoxyethanol and ethylene glycol as solubilisers.[4] A troublesome amount of colour quenching by 2,4-dinitro-1-thiocyanobenzene occurred and it was necessary to use a quenching calibration curve in conjunction with three quench standards which were counted with each batch of samples from a kinetic run. This procedure was found to be more reliable than the channels ratio method of quench correction. For potassium [^{14}C]thiocyanate, quench corrections were made by the internal standard method. The overall linearity of the counting procedure for each radioactive substance was established by counting a range of samples of known concentrations. In general, each sample was counted to give at least 10^4 counts.

Kinetic Rate Determination.—The rate of exchange between labelled thiocyanate ion and 2,4-dinitro-1-thiocyanobenzene was determined from equation (1) by measuring the rate of appearance of radioactivity in the initially unlabelled organic substrate. In equation (1) [A] = concentration of thiocyanate ion in the reaction mixture including the labelled ion, determined by weighing and checked

$$R = -\frac{[\mathrm{A}][\mathrm{B}]}{\beta[\mathrm{A}] + \alpha[\mathrm{B}]} \times \ln\frac{(1 - F)}{t} \qquad (1)$$

by titration against 0·01M-silver nitrate solution, [B] = concentration of organic substrate, determined by weighing the purified substance, α and β are constants representing the kinetic isotope effects in the two transfer reactions, and F = the exchange fraction occurring in time t. For these measurements the isotope effect terms are considered to be not significantly different from unity so that F is given by equation (2) where S = specific activity in counts s^{-1} mg^{-1}, and the subscripts refer to zero and infinite time.

$$F = (S_t - S_0)/(S_\infty - S_0) \qquad (2)$$

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† Reactions involving aromatic thiocyano-compounds characteristically give mixtures of products.

[1] (*a*) Part I, F. H. Kendall and J. Miller, *J. Chem. Soc.* (*B*), 1967, 119; (*b*) Part II, F. H. Kendall, J. Miller, and R. Wong, *ibid.*, 1971, 1521.

[2] K. W. Wong, M.Sc. Thesis, University of Hong Kong, 1963.

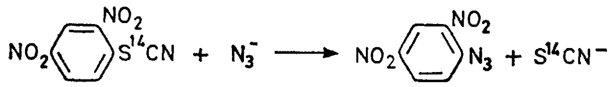
[3] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, London and New York, 1969 (*a*) p. 172; (*b*) pp. 142—143; (*c*) pp. 159, 161, 323; (*d*) pp. 152—155; (*e*) pp. 315—321; (*f*) p. 166.

[4] D. R. White, *Int. J. Appl. Radiation Isotopes*, 1968, **19**, 49.

The exchange reaction in methanol was carried out in sealed tubes following the procedure described previously.[1b] After opening, the contents of each tube were discharged into ice–water (10 ml), and left to stand in a refrigerator for 15 min. The precipitated 2,4-dinitro-1-[^{14}C]thiocyanobenzene was filtered off in a demountable filter. After drying, samples of the substrate (10 mg) were accurately weighed directly into glass counting vials containing scintillation fluor (5 ml).

The exchange in DMF was more conveniently carried out in a twin-cell reaction vessel specially designed to permit preheating of each reactant before mixing.[5] The course of the reaction was followed by taking samples (1 ml), at timed intervals, these being discharged into water (10 ml). The precipitated substrate was then processed as described above. At each stage of manipulation every possible care was taken to exclude moisture from the reaction. The specific activity of the potassium [^{14}C]thiocyanate used in each reaction was chosen to give *ca.* 0·25 μCi in each sample taken from the mixture.

For the reaction between azide ion and 2,4-dinitro-1-thiocyanobenzene in methanol the rate was followed by measuring the rate of appearance of labelled thiocyanate ion in the reaction medium when initially labelled organic substrate reacted with azide ion, the reactants being present in equimolar amounts.



The possibility of rapid solvolysis of the organic substrate was investigated by measuring the appearance of labelled thiocyanate ion in solution. This was shown to be negligible even after 4 h at 42°.

The reaction was carried out in glass stoppered tubes immersed in a refrigerated temperature-controlled water-bath. Samples (1 ml) were removed and introduced into ice-cold 0·01M-potassium thiocyanate solution (10 ml). After stirring and standing in a refrigerator to permit complete precipitation of the organic substrate the samples were filtered through two No. 42 Whatman paper discs in a specially made micro-filter unit which permitted the filtrate and washings to be collected quantitatively. Portions (1 ml) of the filtrate were transferred to a counting vial containing fluor (10 ml). In separate experiments it was shown that by controlling the conditions of precipitation strictly, the solubility in water of 2,4-dinitro-1-[^{14}C]thiocyanobenzene was very small, and the counts due to this could easily be accommodated in the calculations as a background subtractive term.

The rate data obtained for over 50% of the reaction conformed to the second-order rate equation (3) where a is the

$$k_2t = 1/(a - x) - 1/a \qquad (3)$$

initial concentration and x is the concentration reacted after time t.

Reaction order and activation energies were determined by the methods reported previously; [1a] for activation energy determination, four or more temperatures were used. Results are summarised in Tables 1 and 2.

DISCUSSION

Earlier studies [6,7] of the reactivity of cyano- (and formyl) aromatic substrates with methoxide, azide, and thiocyanate ions showed that, together with the expected nucleophilic substitution at activated aromatic carbon, attack also occurred at cyano (and formyl) carbon with methoxide ion. No such alternative attack occurred with thiocyanate ion, and it seemed also to be of small importance with azide ion. These facts guided our present studies, designed to clarify the ease of displacement of the thiocyano-group from aromatic carbon.

TABLE 1

Reaction order of thiocyanate exchange

Reaction, solvent, temperature (°C)	[A]/M *	[B]/M *	10^7R/mol l^{-1} s^{-1}	Reaction order † a	b
SCN⁻ exchange, methanol, 96	0·0286	0·0248	3·22		
	0·0287	0·0499	6·01		
	0·0100	0·0760	3·60		
	0·0252	0·0760	9·24		
	0·0521	0·0760	19·4	1·0	0·92
SCN⁻ exchange, DMF, 55	0·1579	0·1600	249		
	0·2485	0·1600	362		
	0·1579	0·2377	363		
	0·1688	0·0600	93	0·85	1·0

* [A] = Thiocyanate ion, B = 2,4-dinitro-1-thiocyanobenzene. † Reaction order with respect to each reactant evaluated by plotting log R against log [A] and against log [B].

On the basis of the common two-step S_N2 Ar mechanism, which has been particularly studied with 2,4-dinitrophenyl compounds, the electronegativity of the leaving group plays a key role where the formation of the first transition state (T.St.1) is rate-limiting.[3b,8,9] This is illustrated by the high mobility of fluorine in such reactions. There is ample evidence that T.St.1 formation is characteristically rate limiting in reactions with nucleophiles in which the nucleophilic atom is in the first row of the Periodic Table; and especially so in protonic solvents.[3c] However, where the formation of the second transition state (T.St.2) is rate limiting, rupture of the bond to the leaving group affects rates and obscures the electronegativity effect.

For the thiocyano-group the combination of cyano with sulphur is expected to give the thiocyano-group an electronegativity value close to that for chlorine. Thus the ease of displacement of the thiocyano-group should be in or near the relatively small range encompassed by the heavy halogens.[3c] From these assumptions and the results from earlier work,[6,7] it was possible to predict approximate kinetic data for the azido- and thiocyanodethiocyanation reactions.

The experimental results in Tables 1 and 2 show that as for the exchange reactions studied previously,[1a,b] the SCN⁻ reaction follows second-order kinetics and the exchange rate is faster in DMF than in methanol.

In Table 3 the new data are compared and contrasted

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[5] F. H. Kendall and T. Henshall, *J. Amer. Chem. Soc.*, 1960, **82**, 1853.

[6] (*a*) J. Miller, *J. Amer. Chem. Soc.*, 1954, **76**, 448; (*b*) R. L. Heppolette, J. Miller, and V. A. Williams, *ibid.*, 1956, **78**, 1975; (*c*) J. Miller, A. J. Parker, and B. A. Bolto, *ibid.*, 1957, **79**, 93.

[7] N. S. Bayliss, R. B. Heppolette, L. R. Little, and J. Miller, *J. Amer. Chem. Soc.*, 1956, **78**, 1978.

[8] J. Miller, *Rev. Pure Appl. Chem.*, 1951, **1**, 171.

[9] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

with those previously obtained for 1-iodo-2,4-dinitrobenzene.

From the rate ratio ArSCN/ArI the mobility of the thiocyano-group relative to iodine at 100° is 0·17 for the reaction with thiocyanate ion in methanol. This relatively small difference is dependent on $\Delta S^\ddagger$, the $\Delta E^\ddagger$ values being identical within experimental error. The similarities in the values of the Arrhenius parameters are more significant, demonstrating in both reactions what we have called the heavy nucleophile interaction.[1b,3,10] The resemblance between the thiocyano- and iodo-groups is still further demonstrated by the comparison in DMF as solvent. The relative mobility is 0·28; and the Arrhenius parameters are again similar. Significantly, in this solvent, the heavy nucleophile interaction is not noticeable, in accord with our earlier discussion.[1b] The solvent rate ratios, which are $\leqslant 100$, result from less negative $\Delta S^\ddagger$ values in DMF. This contrasts with the considerably larger ratios observed when the anionic nucleophile is small.[1b,3,11] In such cases there are large reductions in $\Delta E^\ddagger$ ($\simeq \Delta H^\ddagger$) on transfer from protic to aprotic solvents.

TABLE 2

Activation parameters

Reaction, concentrations, solvent	T/K ($\pm$0·1)	$10^4 k_2$/ l mol^{-1} s^{-1}	$\log_{10}(B$/ l mol^{-1} s^{-1})	$\Delta E^\ddagger$/ kJ mol^{-1}	$\Delta G^\ddagger$/ kJ mol^{-1}	$\Delta H^\ddagger$/ kJ mol^{-1}	$\Delta S^\ddagger$/ J mol^{-1} K^{-1}
SCN^- exchange, methanol, $[C_6H_3SCN(NO_2)_2] = 0{\cdot}0486$M, $[SCN^-] = 0{\cdot}0488$M	342·4	0·4842	8·46	83·6 [a]	115·4	80·7	−93·3
	351·3	1·047	8·45				
	357·9	1·698	8·45				
	366·6	3·235	8·45				
	371·2	4·624	8·45				
SCN^- exchange, DMF, $[C_6H_3SCN(NO_2)_2] = 0{\cdot}1600$M, $[SCN^-] = 0{\cdot}1579$M	314·1	2·299	11·10	88·2 [b]	101·2	85·3	−42·9
	319·8	4·362	11·10				
	328·0	9·873	11·10				
	333·0	15·80	11·10				
Azido-dethiocyanation, methanol, $[C_6H_3SCN(NO_2)_2] = 0{\cdot}0140$M, $[N_3^-] = 0{\cdot}0141$M	277·5	9·030	10·12	69·8 [c]	89·5	66·5	−61·5
	286·8	24·18	10·12				
	295·0	54·61	10·12				
	303·4	119·3	10·11				

[a] Graphical slope error ±0·4 kJ mol^{-1}. [b] Graphical slope error ±1·25 kJ mol^{-1}. [c] Graphical slope error ±0·8 kJ mol^{-1}.

TABLE 3

Comparative kinetic data for some reactions of 1-iodo- and 1-thiocyano-2,4-dinitrobenzenes at 100°

X in 1-X-2,4-dinitrobenzene	Reagent/ solvent	k_2/ l mol^{-1} s^{-1}	$\Delta E^\ddagger$/ kJ mol^{-1}	$\log_{10}(B$/ l mol^{-1} s^{-1})	Substrate rate ratio (ArSCN/ ArI)	Reagent rate ratio ($SCN^- = 1$)	Solvent rate ratio (DMF/ MeOH)
I	OMe^-/MeOH	3·61	79·3	11·7	1	$1{\cdot}09 \times 10^3$	
I	N_3^-/MeOH	$2{\cdot}00 \times 10^{-1}$	79·3	10·4	1	$6{\cdot}04 \times 10$	
I	SCN^-/MeOH	$3{\cdot}31 \times 10^{-3}$	83·9	$9{\cdot}2_5$	1	1	
I	SCN^-/DMF	$1{\cdot}94 \times 10^{-1}$	82·8	10·9	1		58·5
SCN	OMe^-/MeOH	$1{\cdot}59 \times 10^3$	57·3	$11{\cdot}2_5$	440	$2{\cdot}88 \times 10^6$	
SCN	N_3^-/MeOH	2·09	69·8	10·1	10·5	$3{\cdot}81 \times 10^3$	
SCN	SCN^-/MeOH	$5{\cdot}50 \times 10^{-4}$	83·6	$8{\cdot}4_5$	0·17	1	
SCN	SCN^-/DMF	$5{\cdot}50 \times 10^{-2}$	88·2	11·1	0·28		100

With azide ion as reagent in methanol the relative ease of displacement of the thiocyano-group is significantly raised. The ArSCN/ArI rate ratio which is 10·5 at 100° is essentially dependent on $\Delta E^\ddagger$. Even at this higher value the mobility of the thiocyano-group is still close to that of the heavy halogens (Cl, Br, or I).[3] It is quite different from the much larger ArSCN/ArI rate ratio with methoxide ion in methanol (440 at 100°) [2,3a] which is ascribed to predominant alternative attack at the cyano carbon atom.

Our method of measuring azido-dethiocyanation, and our earlier studies with methoxide and azide ions,[6,7] do not support the possibility that the higher mobility of the thiocyano-group in azido-dethiocyanation is due to a proportion of attack by azide ion at cyano carbon. We speculate instead that the reason is the existence in the transition state of azido-dethiocyanation of a favourable interaction between the thiocyano- and azido-groups, which can reasonably be postulated. We link the difference in behaviour between methoxide ion and the two pseudohalide ions with relative kinetic electrophilicities of cyano and aryl carbon, and nucleophilicities of reagents toward them. These in turn are related to the structure and reactivity of 2,4-dinitro-1-thiocyanobenzene (I). It has five electrophilic centres with leaving groups (Ia—e). However, combining ease of displacement of these potential leaving groups with intrinsic electrophilic strengths at their points of attachment, only two of these electrophilic centres, *viz*. (Ia and b) are highly reactive in S_N reactions. At both, the leaving group is

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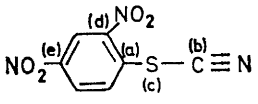
[10] J. Miller, *J. Amer. Chem. Soc.*, 1963, **85**, 1628; D. L. Hill, K. C. Ho, and J. Miller, *J. Chem. Soc.* (*B*), 1966, 299; K. C. Ho, J. Miller, and J. W. Wing, *ibid.*, p. 310; J. Miller, *Austral. J. Chem.*, 1969, **22**, 921.

[11] J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 117.

very similar, consisting of a strongly electron-withdrawing system linked to the electrophilic carbon through bivalent sulphur. Substitution at (a) is an aromatic S_N reaction with the thiocyano-leaving group; substitution at (b) is an S_N reaction at heteropolar unsaturated carbon with the 2,4-dinitrophenylthio-leaving group.



(I)

Assessment of the relative facility of reactions at (a) and (b) must include consideration of the relative ease of displacement of these two groups. However, consideration of structural factors suggests that the mobility will be similar for both groups and this resemblance is supported by experimental evidence.[3f,12]

This leaves the relative electrophilic strength of aryl and cyano carbon towards the different reagents as the controlling factor. Clearly this is strongly dependent on the substituents in the aromatic ring which must have a much larger effect on the reactions at aryl than at cyano carbon: we plan to study this further. In 2,4-dinitro-1-thiocyanobenzene the relative electrophilic strengths are such that predominant reaction is expected to be at aryl carbon with thiocyanate ion; but at cyano carbon with methoxide ion azide ion should be close to thiocyanate ion in behaviour.

In terms of the hard and soft acids and bases concept,[13] which is often stretched to include organic reactions, one could say that aryl carbon is ' softer ' than cyano carbon. This simply rephrases the problem, though it has the value of relating to other reactions more easily.

Our view is that cyano carbon, linked directly to nitrogen by a triple bond should have a higher fractional positive charge than the 1-carbon of the 2,4-dinitrophenylthio-group which is linked only to carbon atoms. Thus the transition state of substitution at cyano carbon should have a considerably greater electrovalent contribution to the order of the bond between the reagent and electrophilic carbon. This would not only lead to the large observed difference between the light and heavy nucleophiles, methoxide and thiocyanate ions, but also to that between azide ion, with its distributed negative charge, and methoxide ion.

[4/269 *Received*, 12*th February*, 1974]

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[12] A. L. Beckwith and J. Miller, unpublished work.

[13] R. G. Pearson, ' Survey of Progress in Chemistry,' Academic Press, New York, 1969, vol. 5, p. 1.