The Kinetics and Mechanism of Addition of Water and Alcohols to *p*-Nitrophenyl Isothiocyanate. The Effects of Added Dimethyl Sulphoxide

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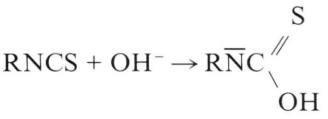
Isothiocyanates, *p*-Nitrophenyl

The second order-rate constants for the addition of water and ethanol to *p*-nitrophenyl isothiocyanate are larger in dimethyl sulphoxide solution than in pure water or ethanol. The detailed behaviour over a wide composition range suggests that H-bonding by the hydroxylic reactant to the solvent favours reaction, whereas H-bonding to this reactant retards reaction. The behaviour and relative reactivities of isocyanates and isothiocyanates suggest that proton-transfer concurrent with nucleophilic attack at carbon, is less important in additions of hydroxylic compounds to isothiocyanates than to isocyanates. Branched-chain alcohols react more slowly with isothiocyanates than do primary alcohols. An excess of ethoxide ions reacts relatively rapidly with *p*-nitrophenyl isothiocyanate in ethanol to give the ionized thiourethane. The kinetics of this process, and the equilibrium constant for proton transfer between thiourethane and ethoxide ions, have been determined.

Few mechanistic studies exist concerning additions of compounds HX to isothiocyanates [1]. The rate of reaction (1) has been measured for numerous isothiocyanates using aqueous solutions, the ionized thiocarbamic acid product (**1**)



$$\mathrm{RNCS + OH^- \longrightarrow R\overline{N}C(\!=\!S)OH} \qquad (1)$$

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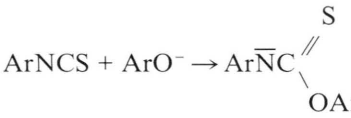
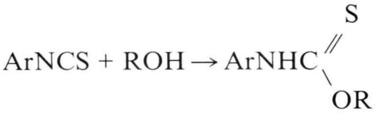
being stable in sufficiently alkaline solutions [1–3]. Substituent effects on the rate of reaction (2) have been thoroughly studied in aqueous buffer solutions [3]. The (slow)



$$\mathrm{ArNCS + ArO^- \longrightarrow Ar\overline{N}C(\!=\!S)OAr} \qquad (2)$$

rates of the uncatalyzed alcoholyses (3) of aryl isothiocyanates have been examined with (i) pure aliphatic alcohols [4] at 40–50 °C, and (ii) 1-octanol (*ca.* 2–8 M) in *o*-dichlorobenzene [5] at 90–120 °C. In these processes the reaction order is unity in isothiocyanate, unity in hydroxide and phenolate ions, but uncertain for the alcohols.



$$\mathrm{ArNCS + ROH \longrightarrow ArNHC(\!=\!S)OR} \qquad (3)$$

2

We have now studied the kinetics of the uncatalyzed reactions of *p*-nitrophenyl isothiocyanate with water, and with a series of aliphatic alcohols in dimethyl sulphoxide; we have also examined the reaction with ethoxide ions in ethanol solution.

Experimental

p-Nitrophenyl isothiocyanate was the Aldrich product. Dimethyl sulphoxide (DMSO) was dried with calcium hydride, distilled, and stored over a molecular sieve. The alcohols were the purest available commercial products, and were used without further purification. Stock solutions of sodium ethoxide were prepared by dissolution of sodium metal. Reactions were monitored using UV spectrophotometry; good isosbestic points for loss of reactant and formation of product were obtained. In DMSO, reaction with an alcohol leads to the corresponding thiourethane (**2,** $\lambda_{\max}$ 340–350 nm), but the reaction with water (eq. (7)) yields *p*-nitroaniline ($\lambda_{\max}$ 386 nm). Both reactions proceed in effectively quantitative yield. Reaction with an excess of $\mathrm{EtO^-}$ in ethanol (eq. (4)) leads to the thiourethane anion (**3,** $\lambda_{\max}$ 361 nm). Addition of acid to solutions of **3** leads to formation of the corresponding unionized compound (**2,** $\lambda_{\max}$

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Table. Rate constants for alcoholysis of *p*-nitrophenyl isothiocyanate.

$[\mathrm{RNCS}]_{\mathrm{init}} \simeq 3 \times 10^{-5}$ M; k_2 = second-order rate constant; for k_{obs} see test; k_{obs} values are averages of two measurements.

(a) Reaction in ethanol at 31.0 °C

(i) Order in EtONa

10^4 [EtONa]/M	0.0	6.0	8.0	11.2	16.0	40.0	80.0	
$10^3\ k_{obs}/s^{-1}$	0.10	2.7	3.4	5.0	6.7	18.6	36.1	
$k_2/mol^{-1}\ dm^3\ s^{-1}$		4.5	4.3	4.5	4.2	4.6	4.5	Av = 4.4

(ii) Effect of temperature (10^4 [EtONa] = 8.0 M)

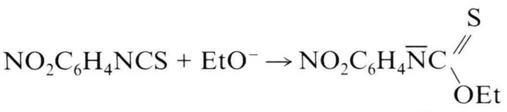
Tp/°C	20.0	30.0	40.0
$10^3\ k_{obs}/s^{-1}$	1.9	3.2	4.4

(b) Reaction with alcohols in DMSO at 31.0 °C

Alcohol	Methanol	Ethanol	*n*-Hexanol	Cyclohexanol
$10^5\ k_2/mol^{-1}\ dm^3\ s^{-1}$	30.1	11.1	12.0	6.2
Alcohol	Propan-2-ol	Pentan-3-ol	*t*-Butanol	
$10^5\ k_2/mol^{-1}\ dm^3\ s^{-1}$	4.6	3.4	1.4	

k_2 for ethanol from initial slope of curve A in Figure, for other alcohols from average k_{obs} values obtained at [ROH] = 0.20 and 0.50 M.

334 nm). Our reaction conditions are in the Table and Figure.



$$\mathrm{NO_2C_6H_4NCS} + \mathrm{EtO^-} \longrightarrow \mathrm{NO_2C_6H_4\overline{N}C}{\overset{\textstyle S}{\underset{\textstyle OEt}{\lessgtr}}} \qquad (4)$$

3

The observed first-order rate constants, k_{obs}, were rectilinear over three half-lives and reproducible to within ±15%. At low alcohol concentrations ($\lesssim$0.2 M) in DMSO a small correction was made to k_{obs} to allow for the concurrent reaction with residual water in the dried solvent.

Results and Discussion

(i) Reaction with EtO⁻ in ethanol solution

p-Nitrophenyl isothiocyanate is one of the most reactive isothiocyanates yet studied kinetically, but its spontaneous reaction with ethanol is rather slow at 31 °C (Table). The presence of sodium ethoxide leads, however, to a marked increase in rate. Our results show that reaction (4) is first-order in both isothiocyanate and ethoxide (Table). This behaviour is analogous to that reported for addition of hydroxide and phenolate ions to isothiocyanates in water [2, 3]. Competition experiments [6] and other data [1] predict that $k_2 \simeq 7\ dm^3\ mol^{-1}\ s^{-1}$ at 25 °C for the second-order reaction between ethoxide ions and *p*-nitrophenyl isothiocyanate in aqueous solution. The reaction is therefore (Table) about 2-fold slower in ethanol (in which sodium ethoxide is probably [7] >75% dissociated at the concentrations used). We find $\Delta H^{\neq}$ = 29.1 kJ mol^{-1} and $\Delta S^{\neq}$ = −138 J K^{-1} mol^{-1}. These results are compatible with a simple bimolecular attack by ethoxide ions at the thiocarbonyl carbon atom.

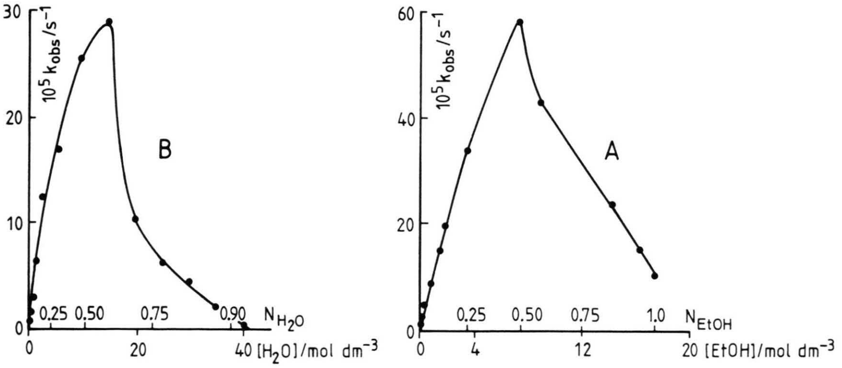
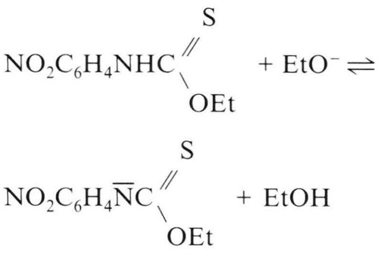


Figure. Effect of solvent composition on k_{obs}. Cosolvent DMSO; tp 30 °C; $[\mathrm{RNCS}]_{\mathrm{initial}} \simeq 3 \times 10^{-5}$ mol dm^{-3}; N = mole fraction.

Addition of sodium ethoxide ($0.5-5.0 \times 10^{-4}$ M) to a solution of the thiourethane (3.0×10^{-5} M) in ethanol permits estimation of the equilibrium constant, $K = [(\mathbf{3})]/[EtO^-][NO_2C_6H_4NHC(S)OEt]$ for reaction (5). We find $K = 6.0 \times 10^3$ mol^{-1} dm^3 at 30 °C.



$$NO_2C_6H_4NHC(=S)OEt + EtO^- \rightleftharpoons NO_2C_6H_4\overline{N}C(=S)OEt + EtOH \quad (5)$$

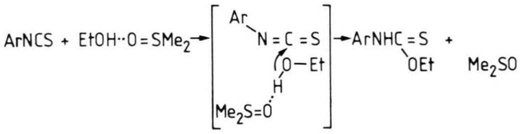
3

(ii) Reaction with alcohols in DMSO

A previous comparison [4] of the reactivities of aliphatic alcohols towards *p*-bromophenyl isothiocyanate did not involve a fixed solvent environment (the different alcohols serving as solvents). These spontaneous reactions were also inconveniently slow. We find that the spontaneous reactions (3), with Ar = $NO_2C_6H_4$, are faster in DMSO solution than in the pure alcohols, k_{obs} passing through a sharp maximum for ethanol at *ca.* 8 M ethanol ($N_{EtOH} \simeq 0.5$, Figure). DMSO is known [8] to undergo strong hydrogen bonding with H-donors, and this no doubt increases notably the nucleophilicity of the alcohol oxygen atom in DMSO-rich solutions compared to the situation in alcohol-rich solutions. The shape of the Figure (curve A) suggests to us a sharp and significant change in the H-bonding structure of ethanol-DMSO mixtures at $N_{EtOH} \simeq 0.5$. If a 1:1 EtOH-DMSO complex dominates at low ethanol concentrations, surplus ethanol molecules will begin to become available when $N_{EtOH} > 0.5$. These may be less or non-activated by DMSO, may H-bond to each other, and may also serve to deactivate the 1:1 complexes by H-bonding to either of its O-atoms. Hence the observed rate constant might be expected fall at high alcohol concentrations, as found. Thus for this reaction we consider that the solvent effects (as opposed to the concentration effects) arising from changes in solvent composition stem primarily from changes in the nucleophilicity of ethanol, rather than from any effect on the stability of the isothiocyanate [9] or the bulk dielectric constant (see below).

For ethanol concentrations between 0.1–0.8 M the alcoholysis is first-order in ethanol. In this region, and at lower concentrations, the addition probably takes place *via* a slow, predominantly nucleophilic, attack by the 1:1 complex, as in eq. (6).

Whether the proton transfers to nitrogen simultaneously, or subsequently *via* reaction of the anion with the protonated solvent, is not known, although the latter seems the more likely (see below).



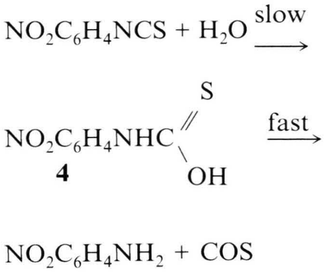
(6)

At high ethanol (low DMSO) concentrations the reaction will be expected to be approximately first order in DMSO but with a smaller slope than that observed in the first order in ethanol region (at low alcohol concentration). This is found (Figure). The lower slope arises because in an excess of alcohol the DMSO-alcohol complexes are less reactive. These facts determine to a large extent the shape of the plot in the Figure.

Our comparison (in the first-order region) of the reactivities of different alcohols (Table) leads to a sequence similar to that obtained using the pure alcohols as solvents [4]. It immediately suggests that steric effects are more important than polar substituent effects in these alcohol additions, although the effects of the substituents on the polarities of the H-bonds are uncertain. Addition in the molecular plane is more likely to lead to steric hindrance and our results are therefore compatible with Williams' conclusions concerning additions of phenolate ions in water [3].

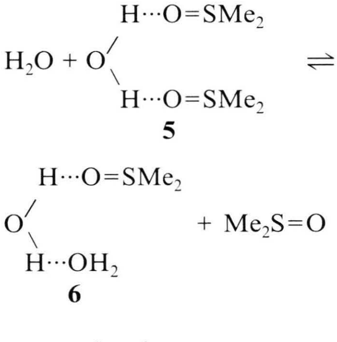
(iii) Reaction with water in DMSO

The spontaneous reactions of isothiocyanates with water are even slower than those with alcohols (water on balance being more deactivated by its extensive H-bond structure) but, as for alcohols, we find the rate is substantially increased in DMSO solutions. The reaction will lead initially to a thiocarbamic acid (**4**), but such acids are known to be unstable under acidic, neutral, or mildly alkaline conditions, when they decompose to give the amine [1]. In our systems the intermediate thiocarbamic acid is not detected, and must decompose relatively very rapidly compared to its rate of formation (eq. (7)).



$$NO_2C_6H_4NCS + H_2O \xrightarrow{slow} \underset{\mathbf{4}}{NO_2C_6H_4NHC(=S)OH} \xrightarrow{fast} NO_2C_6H_4NH_2 + COS \qquad (7)$$

The Figure (curve B) shows that the dependence of k_{obs} on $[H_2O]$ is somewhat similar to that found for the ethanolysis, except that the maximum rate is more pronounced and occurs at a slightly higher mol fraction of the hydroxylic compound. The reaction is first order in water when $[H_2O] \lesssim 3$ M. The results are compatible with the presence of reactive water molecules solvated as in eq (8), species **6** being less nucleophilic than **5,** and being progressively deactivated by further H-bonding to oxygen as the water content rises. The pattern of our results is very similar to those obtained by Menninga and Engberts for the deprotonation of arylsulphonylmethyl perchlorates in dioxan–water, and in acetonitrile–water mixtures [10]. Our explanations are similar in outline to theirs, and also analogous to ideas of Symons [11].



$$H_2O + \underset{\mathbf{5}}{O(H\cdots O{=}SMe_2)_2} \rightleftharpoons \underset{\mathbf{6}}{(Me_2S{=}O\cdots H)O(H\cdots OH_2)} + Me_2S{=}O \qquad (8)$$

The second-order rate constant at low water concentrations, $k_2 = 4.1 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} at 31 °C, is *ca.* 3-fold and 7-fold smaller than those for the ethanol and methanol reactions, respectively (Table). Since steric effects will be minimal for water itself, these results suggest that the active water- and alcohol-DMSO complexes may be significantly different, as postulated above. Whatever the true explanation, water is less nucleophilic towards the isothiocyanates in DMSO than are primary alcohols. The water reaction becomes especially slow in water-rich mixtures (Figure). The fact that the rate is comparatively slow in both pure ethanol and water compared with DMSO-rich mixtures suggests that solvent bulk dielectric constant is of minor importance compared with H-bonding factors in influencing the reaction rate. The reactions of OH^- and EtO^- with the isothiocyanate in DMSO are too fast for conventional measurement.

(iv) Comparison with isocyanate reactions

Isothiocyanates are much less reactive than isocyanates towards spontaneous hydrolysis and alcoholysis. For example, in pure water *p*-nitrophenyl isothiocyanate has $t_{1/2} \gtrsim 20$ h at 30 °C, whereas the corresponding isocyanate will have [12] $t_{1/2} \lesssim 5$ sec. For isothiocyanates hydrolysis and alcoholysis are facilitated by a solvent that reduces self-association of the hydroxylic species and increases the nucleophilicity of the attacking oxygen atom; conditions that favour self-association have a decelerating effect. For isocyanates the opposite is true [13]. These facts suggest different detailed mechanisms operate. For isocyanates the nitrogen atom is believed by some authors [13–17] to receive a proton concurrently with the nucleophilic attack by oxygen on carbon in a low-energy, cyclic transition state involving polymeric alcohol or water. For isothiocyanates the nitrogen atom is almost certainly less basic [3, 18], and it seems this cyclic mechanism will be energetically less advantageous; the reactions are consequently disadvantaged unless circumstances provide a much enhanced nucleophilicity for the oxygen atom. But this is not all. Whether, for isothiocyanates, the nucleophile adds in the molecular plane or perpendicular to it, H-bonding stabilization of the developing negative charge in the transition state will be feeble because neither the N nor the S atom will readily accept protons. These circumstances may partly account for the much lower reactivities of isothiocyanates compared with their O-analogues. Since the C=S bond is weaker [19] (more readily opened) than the C=O bond, another major factor in determining the lower reactivity is presumably the charge on the carbonyl carbon atom which some calculations [20] suggest is lower for RNCS than for RNCO. Williams' discussion [3] suggests the reverse; if this is so the absence of synchronous addition for the isothio compounds must account for a great deal.

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