The Kinetics of Hydrolysis of Methyl and Phenyl Isocyanates

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The hydrolysis of phenyl isocyanate is subject to general base catalysis by tertiary amines and the point for water falls on the Brønsted plot, which indicates that the uncatalysed reaction involves two molecules of water, one acting as a nucleophile and the other as a general base. The rather small solvent isotope effect, $k_w^{H_2O}/k_w^{D_2O} = 1.65$, and the proton inventory, are discussed. The hydrolysis of methyl isocyanate (unlike phenyl isocyanate) is acid-catalysed, probably proceeding with pre-equilibrium protonation. Methyl isocyanate reacts with hydrogenphosphate dianion and with hydrogensulphate ion, forming mixed anhydride species. The formal reaction with hydrogensulphate ion may proceed by pre-equilibrium protonation followed by nucleophilic attack by sulphate ion.

The hydrolysis of isocyanates is a two-stage reaction [(i) and

$$RNCO + H_2O \longrightarrow RNHCO_2H \qquad (i)$$

$$RNHCO_2^- + H^+ \longrightarrow RNH_2 + CO_2 \qquad (ii)$$

(ii)]. Depending on the conditions there can also be some reaction (iii) of the product amine with the reactant. Aminolysis

$$RNCO + RNH_2 \longrightarrow RNHCONHR \qquad (iii)$$

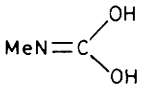
of isocyanates as in reaction (iii) has been the subject of detailed mechanistic study[1,2] and the decomposition of carbamate anions [reaction (ii)] has also been extensively investigated.[3,4] This paper reports a study of reaction (i). Such studies are aided by conditions of relatively low pH, because (ii) becomes a fast subsequent stage, and (iii) is retarded by amine protonation.

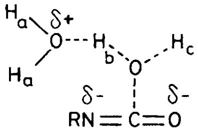
The first reported kinetic study of the hydrolysis of an organic isocyanate in water was that of Mader.[5] The buffer-independent hydration of unprotonated 4-dimethylaminophenyl isocyanate was shown to take place by hydronium ion-catalysed, hydroxide ion catalysed, and uncatalysed pathways. The buffers (oxygen acids) formed mixed carbamic acid–oxygen acid anhydrides,[6] and the only significant buffer catalysis observed was due to the rapid breakdown of one such anhydride (that formed from arsenate).

There have been several studies of the hydrolysis of methyl and aryl isocyanates in aqueous dioxane,[7–11] including a study of solvent deuterium isotope effects.[11] A Hammett ρ-value for hydrolysis of substituted phenyl isocyanates of 2.6 has been reported.[8] The acid catalysis observed in the case of methyl isocyanate[11] has been correlated with H_0; no such catalysis was found for phenyl isocyanate.

A surprising observation was that the hydrolysis of methyl isocyanate in dioxane containing water enriched in $H_2{}^{18}O$, under conditions which lead to substantial formation of *NN'*-dimethylurea as in reaction (iii), gave some ^{18}O incorporation into the urea product.[10] Pre-equilibrium formation of a hydrated intermediate (**1**) has been suggested.

The aims of this work were to study the hydrolysis of methyl and phenyl isocyanates in aqueous solution, to seek general base and general acid catalysis, to obtain a proton inventory[12] for uncatalysed hydrolysis, and to re-examine the question of whether or not oxygen exchange during hydrolysis occurs.


(**1**)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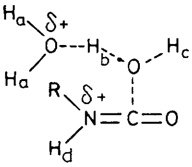
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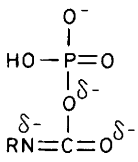
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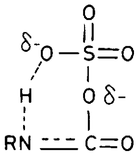
(**5**)

Experimental

Materials.—Phenyl and methyl isocyanates, and acetonitrile, were purified by distillation from P_2O_5. Acetonitrile was stored over type 3A molecular sieves. *N*-Ethylmorpholine and *N*-methyldiethanolamine were purified by distillation, trimethylamine hydrochloride by recrystallisation from ethanol, and *O*-methylhydroxylamine by recrystallisation from ethanol–ether. *NN'*-Dimethylurea was prepared by dropwise addition of methyl isocyanate to an aqueous solution of methylamine, and recrystallised from chloroform–ether, m.p. 108.5—109 °C (lit.,[13] 106 °C). Other materials were normally of AnalaR grade and used as supplied.

Kinetics.—Reactions were initiated by the addition by syringe of 10—60 μl of a solution of the isocyanate to 2—4 cm^3 of an aqueous solution. For the hydrolyses, the absorbance decrease at 220—225 (methyl isocyanate) or 230 nm (phenyl isocyanate) was monitored, using an SP 1800 spectrophotometer or in later runs a Gifford 252 spectrophotometer linked to a microcomputer. First-order rate coefficients were computed from readings taken over at least three half-lives. Hydrolyses of *N*-methylcarbamoyl phosphate dianion (δ 2.56) and *N*-methylcarbamoyl sulphate monoanion (δ 2.57) were followed by ^1H n.m.r. (Hitachi–Perkin-Elmer R600 spectrometer). Following injection of methyl isocyanate into the phosphate or sulphate buffer in D_2O, rapid disappearance of the signal due to the

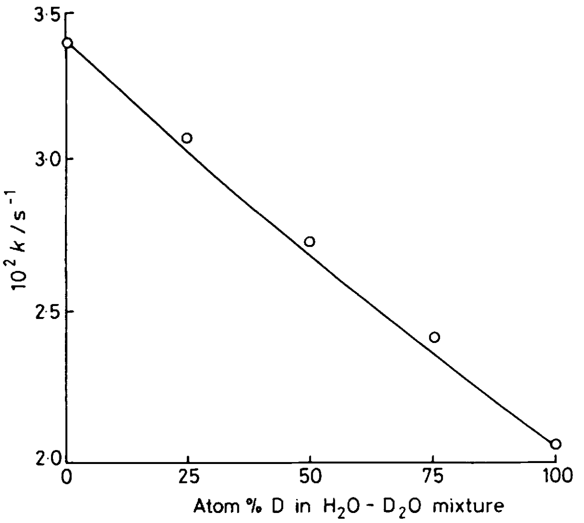

Figure 1. Proton inventory plot for the uncatalysed hydrolysis of phenyl isocyanate. The curve is theoretical[12] for transition state (2) with Φ_a 0.89, Φ_b 0.77, and Φ_c 1

Table 1. Mean values of first-order rate coefficients, k_{obs}, for hydrolysis of phenyl isocyanate in dilute aqueous HCl[a]

t/°C	[LCl][b]/ mol dm^{-3}	Atom% D in H_2O–D_2O	n[c]	10^2 k_{obs}/ s^{-1}
4.9—5.0	0.20	0	7	0.49—0.51
15.0—15.1	0.20	0	3	1.36—1.39
34.8—35.0	0.20	0	5	7.44—7.61
25.0	0.20	0	12	3.37
25.0	0.10	0	7	3.38
25.0	0.02	0	5	3.44
25.0	2.00	0	5	2.66[d]
25.0	1.50	0	5	2.66[d]
25.0	0.50	0	5	2.64[d]
25.0	0.20	25.0	5	3.07
25.0	0.20	50.0	6	2.73
25.0	0.20	75.0	5	2.40
25.0	0.20	100	3	2.06

[a] The initial concentration of phenyl isocyanate was 1—4 × 10^{-4} mol dm^{-3}. The ionic strength was 0.2 mol dm^{-3} maintained with KCl, unless otherwise noted. [b] L = H or D. [c] Number of runs. [d] The ionic strength in these runs was 2.0 mol dm^{-3}, maintained with LiCl.

reactant and appearance of signals with the chemical shifts mentioned above, was followed by slow decay of those signals and appearance of a signal due to methylammonium ion. Rate coefficients for this process were obtained from plots of ln(A/A_r) *versus* time, where A and A_r are the integrated signals due to the intermediate and the reference [3-(trimethylsilyl)propanesulphonic acid], respectively.

Oxygen Exchange.—Methyl isocyanate (30 μl) was added to $H_2{}^{18}O$ (5 cm^3; 20 atom % ^{18}O) and maintained 25 °C for 30 min. Solvent was removed under vacuum. The solid residue was purified by vacuum sublimation, and analysed by mass spectrometry (VG Micromass model MM16F). The value of 100 $h_{M+2}/(h_M + h_{M+2})$, (where h_M is the height of the molecular ion peak at m/e 88 and h_{M+2} is the height of the peak at m/e 90) was found to be 0.38 (±0.04) (mean of eight determinations) compared with 0.45 (±0.15) (mean of six determinations) for a control sample. Thus there was no measurable ^{18}O enrichment of the *NN'*-dimethylurea formed.

Results

The Hydrolysis of Phenyl Isocyanate in Aqueous Hydrochloric Acid.—The observed rate coefficients for reaction (i), k_{obs}, for hydrolysis in 0.02—0.20 mol dm^{-3} hydrochloric acid (the ionic strength being maintained at 0.2 mol dm^{-3} with KCl) confirm the absence of catalysis by hydronium ion in water, as in aqueous dioxane.[9,11] The mean value of the rate coefficient at 25 °C is 3.39 × 10^{-2} s^{-1}, and this is the value of k_w used in the studies of general base catalysis reported below. The value is reduced to 2.66 × 10^{-2} s^{-1} when the ionic strength is increased to 2 mol dm^{-3}, but again no acid catalysis is discernible* in solutions containing up to 2.0 mol dm^{-3} HCl. The reaction in 0.2 mol dm^{-3} HCl is therefore the pure uncatalysed reaction with water. Results of a proton inventory study under these conditions are shown in Figure 1. Activation parameters derived from the results in the first four rows of Table 1 and relating to k_w are: $\Delta H^\ddagger$ 62.1 (±0.3) kJ mol^{-1}; $\Delta S^\ddagger$ −65.1 (±1) J K^{-1} mol^{-1}.

The Hydrolysis of Phenyl Isocyanate in Aqueous Buffers.—In *N*-ethylmorpholine, *N*-methyldiethanolamine, trimethylamine, and borate buffers the observed rate coefficients for reaction (i) were found to vary with the pH and with [B], the concentration of the basic form of the buffer, according to equation (iv).

$$k_{obs} = k_w + k_{OH}[OH^-] + k_B[B] \qquad (iv)$$

Difficulties in the determination of the values of k_{OH} and k_B (Table 2) arose from interference from reactions (ii) and (iii). Interference from reaction (ii) for the runs with borate and trimethylamine buffers was avoided by the use of the isosbestic wavelength of phenylcarbamate ion and aniline at 270 nm, but with the earlier runs with the other buffers, this procedure was not used. Analysis of the final spectra revealed also the presence of small amounts (1—9%) of diphenylurea, showing that reaction (iii) had proceeded to some extent. A detailed kinetic analysis revealed that in no case was the error in k_B arising from interference from reactions (ii) and (iii) greater than *ca.* 10%. The rather large error associated with k_{OH} (Table 2) reflects the fact that the contribution from the hydroxide term equation (iv) was always small under the conditions of its determination using borate buffers. For the other buffers, k_B was determined as the mean of values of ($k_{obs} - k_w - k_{OH}[OH^-]/[B]$). The errors quoted are standard deviations and are rather larger than normal because in addition to the difficulties mentioned, the rather fast rate of the uncatalysed (k_w) reaction (half-life of 20 s) limits the range of accessible rate constants to a factor of *ca.* 3.

The Hydrolysis of Methyl Isocyanate in Aqueous Acid, and its Reaction with Phosphate and Sulphate Buffers.—In these studies, conditions were sufficiently acidic to preclude complications arising from reactions (ii) and (iii). Acid catalysis of hydrolysis is marked, and the observed rate coefficient for disappearance of methyl isocyanate also increases linearly with the total concentration of phosphate or sulphate buffer at constant [H$^+$]. Experiments at several values of pH in each case revealed that it is the basic form of the phosphate buffer ([A] = [$HPO_4{}^{2-}$]) but the acid form of the sulphate buffer ([A] = [$HSO_4{}^-$]) which must be used in equation (v) (Figures 2 and 3). Rate

$$k_{obs} = k_w + k_H[H^+] + k_A[A] \qquad (v)$$

constants k_w, k_H, and k_A are in Table 3.

The contribution of k_w to the right-hand side of equation (v) was small, and the uncertainties in the value quoted are esti-

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* We thank N. A. Cooley for these measurements.

Table 2. Rate constants k_B for buffer base-catalysed hydrolysis of phenyl isocyanate in water at 25 °C^a

No.	Buffer base	pK_a of buffer acid	Range of pH	Range of total buffer concentration mol dm^{-3}	Number of runs	k_B/dm^3 mol^{-1} s^{-1}
1	H_2O	−1.74				6.1×10^{-4} ^{b}
2	*N*-Ethylmorpholine^c	7.67^d	7.4—7.9	0.02—0.10	72	0.66 (±0.10)
3	*N*-Methyldiethanolamine^c	8.57^d	7.7—8.3	0.02—0.11	52	0.94 (±0.26)
4	Borate^e	9.24^f	7.7—8.9	0.02—0.20	57	0.71 (±0.09)
5	Trimethylamine^e	9.81^d	8.9—9.0	0.05—0.20	24	2.4 (±0.4)
6	OH^-	15.74	*g*	*g*	*g*	1 170 (±580)^h

[a] The initial concentration of phenyl isocyanate was 1×10^{-4} mol dm^{-3}. The ionic strength was 0.2 mol dm^{-3}, maintained with KCl. [b] Value of $k_w/[H_2O]$ [equation (iv) and Table 1]. [c] Wavelength used was 282 nm. [d] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solutions,' IUPAC Analytical Division, Butterworths, London, 1965. [e] Wavelength used was 270 nm. [f] B. B. Owen, *J. Am. Chem. Soc.*, 1934, **56**, 1695. [g] As for borate. [h] Value of k_{OH} [equation (iv)].

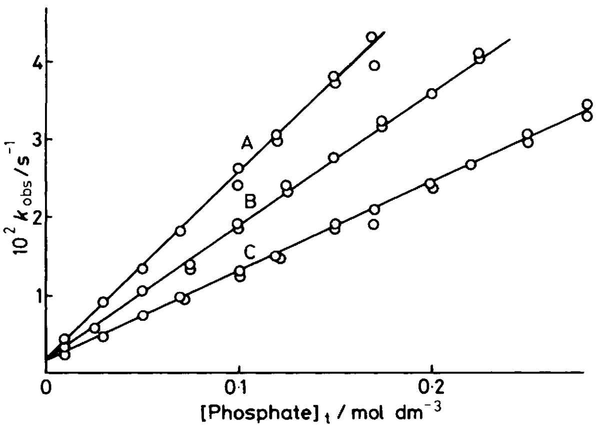


Figure 2. Observed rate coefficient for disappearance of methyl isocyanate in phosphate buffers, plotted against total buffer concentration. Curve A, $F_A = 0.67$; curve B, $F_A = 0.50$; curve C, $F_A = 0.33$ $\{F_A = [HPO_4^{2-}]/([HPO_4^{2-}] + [H_2PO_4^-])\}$

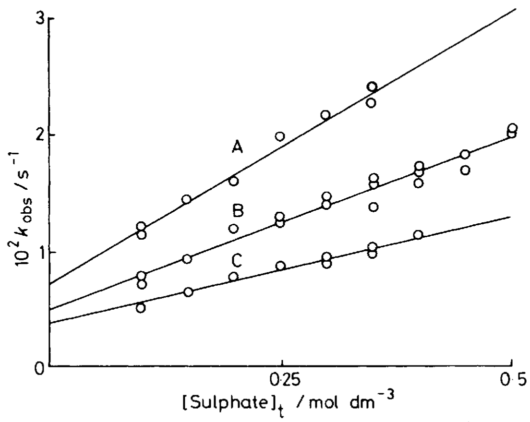


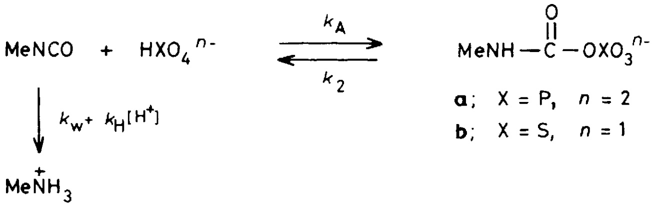
Figure 3. Observed rate coefficient for disappearance of methyl isocyanate in sulphate buffers, plotted against total buffer concentration. Curve A, $F_A = 0.58$; curve B, $F_A = 0.43$; curve C, $F_A = 0.29$ $\{F_A = [HSO_4^-]/([HSO_4^-] + [SO_4^{2-}])\}$

mated to be ±20%. They are in satisfactory agreement with a literature value[14] of 1.47×10^{-3} s^{-1}. The latter value was used in the calculations of F_A described in the footnotes to Table 3.

Investigations by ^{1}H n.m.r. showed that the reactions in phosphate and sulphate buffers did not give the methylammonium ion directly. In each case a new signal arose which then decayed slowly to give the signal due to the methylammonium ion. In the light of similar reactions,[5,14] we consider the initial products in the two buffer media to be *N*-methylcarbamoyl phosphate dianion and *N*-methylcarbamoyl sulphate monoanion respectively.

The rate constant for reaction of phosphate dianion with methyl isocyanate (0.36 mol^{-1} dm^3 s^{-1}; Table 3) is 27 times slower than its reaction with isocyanic acid under the same conditions.[14] Activation parameters for the reaction of methyl isocyanate with HPO_4^{2-} are: $\Delta H^\ddagger$ 62 (±1) kJ mol^{-1}; $\Delta S^\ddagger$ −47 (±2) J K^{-1} mol^{-1}.

The Kinetics of the Decomposition of the Intermediates formed from Methyl Isocyanate and HPO_4^{2-} *or* HSO_4^-.—Only preliminary studies have been made, using ^{1}H n.m.r. and solvent D_2O (Table 4). Deuterium isotope effects are ignored in the semi-quantitative treatment which follows. *N*-Methylcarbamoyl phosphate dianion (reasonably assumed to be the prevailing form of the intermediate at pH 7.2, and to decompose by C–O rather than P–O fission, by analogy with carbamoyl phosphate[15]) decomposes very slowly, which means that following the formation of this species methyl isocyanate may be treated as a steady state intermediate in its decomposition [Scheme a and equation (vi)]. Using the data of Tables 3 and 4, the value of



Scheme.

$$k_{obs} = k_2\,(k_w + k_H[H^+])/(k_w + k_H[H^+] + k_A[HPO_4^-]) \quad \text{(vi)}$$

k_2 (Scheme a) is 3.5×10^{-5} s^{-1}, which may be compared with the value[15] of 2.7×10^{-4} s^{-1} for the similar reaction of carbamoyl phosphate dianion at 37 °C. The equilibrium constant for formation of *N*-methylcarbamoyl phosphate dianion (k_A/k_2; Scheme a) is *ca.* 1×10^4 mol^{-1} dm^3.

In a similar manner, using equation (vi) but with $[HSO_4^-]$ in place of $[HPO_4^{2-}]$, Scheme b and the data of Tables 3 and 4

Table 3. Rate constants[a] for uncatalysed and acid-catalysed hydrolysis of methyl isocyanate, and for reaction of methyl isocyanate with HPO_4^{2-} and HSO_4^-

Buffer	$[A]_t$[b]/ mol dm^{-3}	F_A[c]	t/°C	Range of $10^2\ k_{obs}$/s^{-1}	Number of runs	$10^3 k_w$/s^{-1}	k_H/mol^{-1} dm^3 s^{-1}	k_A/mol^{-1} dm^3 s^{-1}
HCl	0.06—0.240		25.0	1.11—4.05	17	1.34	0.16	
DCl	0.05—0.225		25.0	1.38—6.34	9	*d*	0.29	
HPO_4^{2-}	0.01—0.05	0.33	15.0	0.11—0.30	7	0.59	*d*	0.15
	0.01—0.28	0.33	25.0	0.24—3.46	24	1.30[e]	*d*	0.36[e]
	0.01—0.25	0.50	25.0	0.33—4.47	20			
	0.01—0.25	0.67	25.0	0.37—6.54	20			
	0.01—0.035	0.33	35.0	0.63—1.29	12	3.35	*d*	0.82
	0.01—0.030	0.33	45.0	1.33—2.77	10	7.55	*d*	1.88
HSO_4^-	0.10—0.40	0.58	25.0	1.17—2.56	10	(7.2)[f]		0.075[e]
	0.10—0.50	0.43	25.0	0.74—2.05	21	(5.1)[f]		
	0.10—0.40	0.29	25.0	0.53—1.13	13	(3.9)[f]		
DSO_4^-	0.10—0.50	0.64	25.0	1.32—3.16	9	(9.2)[f]		0.065[e]
	0.10—0.50	0.48	25.0	0.91—2.07	8	(6.8)[f]		
	0.10—0.40	0.32	25.0	0.49—1.08	7	(3.1)[f]		

[a] Ionic strength 1.0 mol dm^{-3}, maintained with KCl. [b] Total buffer concentration, $HPO_4^{2-} + H_2PO_4^-$ or $HSO_4^- + SO_4^{2-}$. [c] $F_A = [A]/[A]_t$ where A is the active form of the buffer (see text). Values of F_A for sulphate buffers were estimated as follows: acidities being too high for the use of a pH meter, $[H^+]$ was calculated from $k_o = k_w + k_H[H^+]$ where k_o is the intercept of the plot of k_{obs} *versus* $[A]_t$. F_A was then obtained by solving the equations $[A]_t = [HSO_4^-] + [SO_4^{2-}]$, $[NaOH]_{total} + [H^+] = [HSO_4^-] + 2[SO_4^{2-}]$, and $F_A = [HSO_4^-]/[A]_t$, where $[NAOH]_{total}$ is the stoicheiometric concentration of alkali added in order partially to neutralise the H_2SO_4 initially present. From the values of F_A, concentration pK_a values relating to 1 mol dm^{-3} ionic strength for HSO_4^- and DSO_4^- of 1.51 and 1.75, respectively, were deduced, which are related satisfactorily to the thermodynamic values of pK_a, 1.99 (A. Albert and G. P. Serjeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971) and 2.33 (M. H. Leitzke and R. W. Stoughton, *J. Phys. Chem.*, 1963, **67**, 652). respectively. [d] The contribution of this term to the right-hand side of equation (v) was too small for a value to be estimated. [e] Average value. [f] Value of $10^3(k_w + k_H[H^+])$.

Table 4. Observed rate coefficients for the decomposition of intermediates formed in the reactions of methyl isocyanate with HPO_4^{2-} and HSO_4^- in D_2O

Intermediate	$[B]_{total}$[a]/ mol dm^{-3}	F_A[b]	$[S]_o$[c]/ mol dm^{-3}	t/°C	I[d]/ mol dm^{-3}	pH[e] (approx)	$10^3 k_{obs}$[f]/ s^{-1}
$MeND-CO-OPO_3^{2-}$	0.25	0.5	0.04	25	0.5	7.2	0.001
$MeND-CO-OSO_3^-$	0.20	0.5	0.05	35	0.4	1.8	0.35

[a] Concentration of total buffer during the formation of the intermediate. The buffer was either sulphate or phosphate. [b] Molar fraction of DPO_4^{2-} or DSO_4^- in total buffer. [c] Initial concentration of methyl isocyanate. [d] Ionic strength. No external electrolyte was added. [e] pH Value for the decomposition of the intermediate. [f] Psuedo-first-order rate constant observed for decomposition of the intermediate.

give rise to a value of k_2 for decomposition of *N*-methylcarbamoyl sulphate monoanion, when allowance is made for the difference in temperature, of *ca.* 5 × 10^{-4} s^{-1} at 25 °C. The equilibrium constant for formation of *N*-methylcarbamoyl sulphate monoanion from methyl isocyanate and HSO_4^- is *ca.* 130 mol dm^{-3} (this assumes that *N*-methylcarbamoyl sulphate monoanion breaks down by C–O and not S–O fission, a fact which has not yet been established).

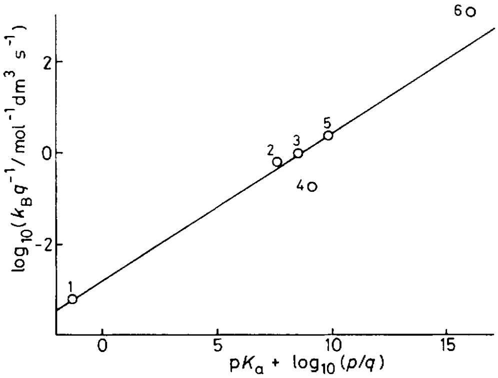


Figure 4. Brønsted plot for base-catalysed hydrolysis of phenyl isocyanate in aqueous buffers. The numbers of the bases are as in Table 2. Statistical correction factors, *p* and *q*, are as described in R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Sect. A*, 1966, **291**, 297.

Discussion

Uncatalysed Hydrolysis.—We found no incorporation of ^{18}O into the *NN'*-dimethylurea product when methyl isocyanate was hydrolysed in unbuffered water containing $H_2{}^{18}O$ (see Experimental section) and therefore we cannot support the view[10] that there is pre-equilibrium formation of the hydrated intermediate (**1**), at least under our conditions.

The reaction is probably best seen as one in which two molecules of water are involved, one acting as a nucleophile and one as a general base, with a transition state as in (**2**).

This picture is consistent with current views regarding water attack at many electrophilic centres.[16] It receives support in the present work from the observation that the point for water falls on the Brønsted plot for general base catalysis by tertiary amines of the hydrolysis of phenyl isocyanate (Figure 4). It is also consistent with the observation that the point for water falls above the Brønsted plot for attack of aryl oxide ions on isocyanic acid.[14] It is noteworthy also that the necessary conditions for general catalysis[17] appear to be met. A similar transition state has been considered likely in the direct hydration of carbon dioxide, a reaction which resembles the hydrolysis of phenyl isocyanate both in absolute rate, and in solvent isotope effect.[16b]

However, there is some difficulty in reconciling the observed rather modest solvent isotope effect with transition state (**2**). Consideration of the slope of the Brønsted plot, β 0.33 (Figure 4), leads[12] to the fractionation factor for H_a in (**2**), $\Phi_a = 0.69^{0.33} = 0.89$. Making the usual assumption that $\Phi_c = 1$, it follows from the requirement $k_w^{D_2O}/k_w^{H_2O} = \Phi_a^2\Phi_b\Phi_c$ that, for phenyl isocyanate hydrolysis, $\Phi_b = 0.77$. This value is too high[18] for a proton 'in flight' and suggests[19] that the proton is not being transferred as part of the reaction co-ordinate motion in the transition state (**2**). A similar suggestion has been made regarding the hydrolysis of ammonium ions,[18] but it is not clear at present why it should apply in some cases but not in others. This difficulty apart, transition state (**2**) accounts satisfactorily for the observations regarding the uncatalysed hydrolysis of isocyanates. It leads to the prediction of a proton inventory with slight curvature, but which is just within experimental error of the observed straight line (Figure 1).

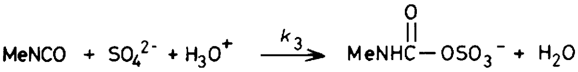
Hydronium Ion-catalysed Reaction.—Our failure to observe acid catalysis with phenyl isocyanate allows us to state that the rate constant for hydronium ion-catalysed hydrolysis must be less than *ca.* 0.01 mol^{-1} dm^3 s^{-1}. This may be contrasted with the rate constant reported[5] for acid-catalysed hydrolysis of unprotonated 4-dimethylaminophenyl isocyanate of 7.35×10^3 mol^{-1} dm^3 s^{-1}. The substituent effect of the 4-dimethylamino group is impossibly large, showing that the reaction observed by Mader[5] at low pH was in fact uncatalysed hydrolysis of 4-dimethylaminophenyl isocyanate protonated on the amino group. The effect of the 4-$\overset{+}{N}Me_2H$ substituent on the uncatalysed reaction (raising the rate constant from 0.034 to 0.16 s^{-1}) is in the expected direction.[8]

The hydrolysis of methyl isocyanate does exhibit hydronium ion catalysis, and the rate constant, 0.16 mol^{-1} dm^3 s^{-1} (Table 2), is clearly much greater than that for phenyl isocyanate, consistent with some development of positive charge on nitrogen in the transition state. The solvent isotope effect, k_H/k_D 0.56 (Table 2), suggests pre-equilibrium protonation. It would be inconsistent not to suggest that the subsequent attack of water involves two water molecules giving a transition state (**3**), analogous to (**2**), but a similar problem arises regarding the fractionation factor of the proton being transferred from nucleophilic water to general base water in the transition state. If Φ_a is taken to be in the range 0.8—0.9, Φ_d 0.9—1, and Φ_c as unity, then Φ_b must be in the range 0.72—1.0, which again is too large for a proton 'in flight' and recourse must be had to a similar explanation as for uncatalysed hydrolysis. Consideration of alternative cyclic transition states involving protonation of the nitrogen in the rate-determining step and more than one proton being transferred, fails to resolve the problem.

General Base-catalysed Hydrolysis.—The sensitivity of the substrate to nucleophilic attack by primary and secondary amines and oxyanions, and the need for buffers which do not absorb in the u.v. region, limited the number of general bases studied. In the Brønsted plot (Figure 4) deviation by borate is expected because of its unusual mode of ionisation.[20] The general base-catalysed reaction can hardly be other than one with a transition state like (**2**), because nucleophilic attack by tertiary amines is unlikely to lead to catalysed hydrolysis.[1] General base catalysis has not previously been observed in the hydrolysis of isocyanates, and should possibly be taken into account when considering the kinetics of aminolysis,[1,2] though its contribution would be small.

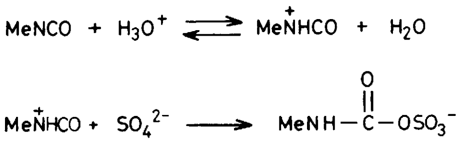
Reaction of Methyl Isocyanate with Oxyacid Anions.—The reaction of isocyanates with HPO_4^{2-} has been reported previously[5,14,15] and there is good evidence[14] that the reaction takes place by straightforward nucleophilic attack, with the non-cyclic transition state (**4**).

Reaction with hydrogensulphate ion has not previously been observed and was unexpected (general acid-catalysed hydrolysis had been sought). The reaction cannot proceed analogously to (**4**), because hydrogensulphate is an extremely weak base and could not be expected to compete as a nucleophile with water and sulphate ion, or be only five times less reactive than phosphate dianion (Table 3) from which it differs in basicity by at least 10 pK_a units. A cyclic transition state such as (**5**) cannot be ruled out, but poses the question: why should it be involved in this reaction but not[14] in that of hydrogenphosphate? More likely alternatives involve not HSO_4^- but the kinetically equivalent combination of H_3O^+ and SO_4^{2-} [equation (vii)]. Rate constants for this process in H_2O and D_2O are (from Table 3) 2.43 and 3.66 mol^{-2} dm^6 s^{-1} respectively, giving an isotope effect, $k_3^{H_2O}/k_3^{D_2O}$, of 0.66.

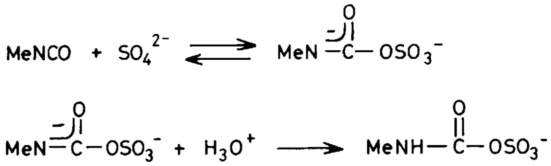


$$\mathrm{MeNCO} + SO_4^{2-} + H_3O^+ \xrightarrow{k_3} \mathrm{MeNH}\overset{\displaystyle O}{\overset{\|}{\mathrm{C}}}-\mathrm{OSO_3^-} + H_2O \qquad \text{(vii)}$$

Two stepwise processes, equations (viii) and (ix), can be considered for reaction (vii).



$$\begin{aligned}&\mathrm{MeNCO} + H_3O^+ \rightleftharpoons \mathrm{Me\overset{+}{N}HCO} + H_2O\\&\mathrm{Me\overset{+}{N}HCO} + SO_4^{2-} \longrightarrow \mathrm{MeNH}-\overset{\displaystyle O}{\overset{\|}{\mathrm{C}}}-\mathrm{OSO_3^-}\end{aligned} \qquad \text{(viii)}$$



$$\begin{aligned}&\mathrm{MeNCO} + SO_4^{2-} \rightleftharpoons \mathrm{MeN}{=}\overset{\displaystyle O^-}{\overset{|}{\mathrm{C}}}-\mathrm{OSO_3^-}\\&\mathrm{MeN}{=}\overset{\displaystyle O^-}{\overset{|}{\mathrm{C}}}-\mathrm{OSO_3^-} + H_3O^+ \longrightarrow \mathrm{MeNH}-\overset{\displaystyle O}{\overset{\|}{\mathrm{C}}}-\mathrm{OSO_3^-}\end{aligned} \qquad \text{(ix)}$$

The stepwise process (ix) is analogous to the mechanism of general acid-catalysed aminolysis of isocyanates by weakly basic amines.[1] However, the solvent isotope effect seems to rule out this possibility because the final proton-transfer step would certainly be diffusion controlled and the solvent isotope effect would therefore be expected to be close to unity.

This leaves the stepwise process (viii) as the more likely, although a concerted process avoiding both the high-energy intermediates, $\mathrm{Me\overset{+}{N}HCO}$ and $\mathrm{Me\overset{-}{N}{-}CO{-}OSO_3^-}$, cannot be ruled out at present.

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References

1 A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1753, 1760.
2 A. F. Hegarty, C. N. Hegarty, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1258; 1975, 1166.
3 S. P. Ewing, D. Lockshon, and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 3072.
4 R. B. Moodie and P. J. Sansom, *J. Chem. Res.* (*S*), 1979, 390.
5 P. M. Mader, *J. Org. Chem.*, 1968, **33**, 2253.
6 C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, 1934, **17**, 931; 1935, **18**, 142; C. Naegeli, A. Tyabji, L. Conrad, and F. Litwan, *ibid.*, 1938, **21**, 1100.

7 R. P. Tiger, I. G. Badeva, S. P. Bondarenko, and S. J. Entelis, *Kinet. Katal.*, 1977, **18**, 117.

8 R. P. Tiger, L. S. Bekhli, and S. G. Entelis, *Vysokomol. Soedin., ser. B*, 1969, **11B**, 460.

9 R. P. Tiger, L. S. Bekhli, and S. G. Entelis, *Kinet. Katal.*, 1970, **11**, 1347.

10 R. P. Tiger, I. V. Kumpanenko, and S. G. Entelis, *Zh. Org. Khim.*, 1971, **7**, 63.

11 R. P. Tiger, L. A. Bekhli, and S. G. Entelis, *Kinet. Katal.*, 1971, **12**, 318.

12 R. L. Schowen, 'Isotope Effects in Enzyme Catalysed Reactions,' Proc. 6th Annual Harry Steinbeck Symposium, 1976, p. 64.

13 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, 4th edn.

14 H. Al Rawi and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 2671.

15 C. M. Allen and M. E. Jones, *Biochemistry*, 1964, **3**, 1238.

16 (*a*) G. Gopalakrishnan and J. L. Hogg, *J. Org. Chem.*, 1983, **48**, 2038, and references cited therein; W. Karzign and J. F. Engberts, *Tetrahedron Lett.*, 1978, 1787; F. M. Menger and K. S. von Katasubban, *J. Org. Chem.*, 1976, **41**, 1868; J. L. Kurz and G. J. Ehrhardt, *J. Am. Chem. Soc.*, 1975, **97**, 2259; M. Komiyama and M. L. Bender, *Bioorg. Chem.*, 1980, **9**, 288; M. Hegazi, J. F. Mata-Sagreda, and R. L. Schowen, *J. Org. Chem.*, 1980, **45**, 307; (*b*) Y. Pocker and D. W. Bjorkquist, *J. Am. Chem. Soc.*, 1977, **99**, 6537.

17 W. P. Jencks, *J. Am. Chem. Soc.*, 1972, **94**, 4731.

18 R. Lynn Ehrhardt, G. Gopalakrishnan, and J. L. Hogg, *J. Org. Chem.*, 1983, **48**, 1586.

19 W. Palaitis and E. R. Thornton, *J. Am. Chem. Soc.*, 1975, **97**, 1193; M.-C. Choi and E. R. Thornton, *ibid.*, 1974, **96**, 1428.

20 R. P. Bell, J. O. Edwards, and R. B. Jones in 'The Chemistry of Boron and its Compounds,' ed. E. L. Muetterties, Wiley, New York, 1967.

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