The Pyridine-catalysed Reaction of Methanol with Phenyl Isocyanate in Tetrachloromethane

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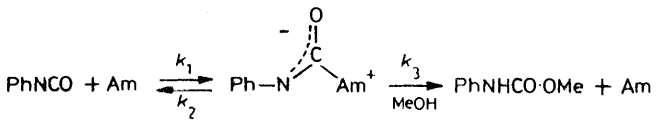
The title reaction is first order in catalyst and each reactant. Several 3- and 4-substituted pyridine catalysts generate a Brönsted plot with slope β of 0.49. This, the steric effect of 2,4,6-trimethylpyridine, the deuterium isotope effect, and the solvent effect are consistent with the general base mechanism of catalysis. The nucleophilic mechanism is considered relatively unlikely. 2-Pyridylmethanol reacts with phenyl isocyanate faster than does 4-pyridylmethanol, indicating intramolecular general base catalysis in the former case.

THE industrial importance of the reaction between alcohols and isocyanates has led to many studies of kinetics and mechanism.[1] It has been pointed out [2] that in much of the early work, hydrogen-bonded associations were not properly taken into account. Current recognition [3] of the enormous changes in relative basicities between aqueous solution and the gas phase makes it clear also that, when diverse bases are considered, the use of aqueous basicities for correlating amine catalytic constants determined in non-polar organic solvents [4,5] may be misleading.

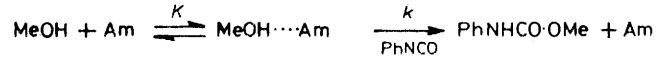
Two mechanisms have been proposed to account for tertiary amine catalysis, corresponding to catalytic activation of the isocyanate [4,6] (nucleophilic catalysis, Scheme 1) and of the alcohol [7] (general base catalysis, Scheme 2), respectively. Both mechanisms, provided



SCHEME 1

that in each case the second step is rate determining, are in accord with the first-order dependence of the reaction rate on the concentration of each species, alcohol, isocyanate, and tertiary amine.

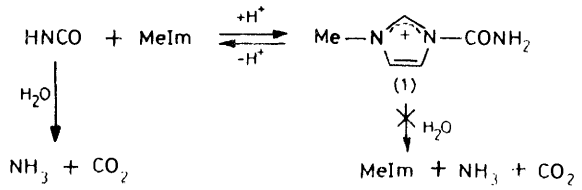
Scheme 1 has been widely accepted [5,8] but indirect evidence against this mechanism comes from the work



SCHEME 2

of Williams and Jencks [9] on the reaction of 1-methylimidazole with cyanic acid in water. They found that nucleophilic attack occurred but that rather than acting as a catalyst for its decomposition 1-methylimidazole merely diverted the cyanic acid temporarily from the reaction path. Although (I) with its extra proton, would be expected to be more susceptible to nucleophilic attack than the zwitterionic intermediate of Scheme 1, its breakdown was simply the reverse of its formation (Scheme 3). The fact that 1-dimethylcarbamoylpyridinium is hydrolysed in water very much more slowly [10] than methyl isocyanate [9] is a second contraindication for nucleophilic catalysis.

In this paper we report a study of the reaction in tetrachloromethane of methanol with phenyl isocyanate catalysed by substituted pyridines, together with related studies of deuterium isotope effects, solvent effects, and the kinetics of related reactions of 2- and 4-pyridylmethanols, in an attempt to clarify the mechanism. The availability of equilibrium constants for amine–alcohol hydrogen bonding [11] dictated the choice of alcohol



SCHEME 3

and solvent. 3- And 4-substituted pyridines were chosen as catalysts because hydrogen-bonding association constants [12] and gas-phase proton affinities [13] correlate with aqueous pK_a values, giving confidence that the latter are for this restricted set of tertiary amines satisfactory measures of basicity for correlation purposes.

It has been claimed [14] that there is some degree of self-association of pyridines in tetrachloromethane. The association is weak and if, as seems likely, no stronger than in cyclohexane [15] can be safely ignored. Weak interactions between pyridines and tetrachloromethane [16] are also unlikely to provide serious complications.[12b]

RESULTS

For kinetic studies, concentrations of methanol were sufficiently low (5×10^{-3}M) for the extent of dimerisation to be negligible. Phenyl isocyanate was present in >10-fold excess over methanol. The reactions, monitored by g.l.c.

TABLE 1

The dependence of observed rate constant upon the concentration of phenyl isocyanate in its reaction with methanol catalysed by pyridine (concentration 0.094M) in tetrachloromethane at 25 °C

[PhNCO]/M	$10^4 k_{obs.}$/s^{-1}	$(10^3 k_{obs.}/[PhNCO])$/l mol^{-1} s^{-1}
0.0703	1.06	1.51
0.0912	1.37	1.50
0.108	1.64	1.52
0.134	2.01	1.50
0.146	2.32	1.59

TABLE 2

Kinetic results for the reaction of phenyl isocyanate with methanol catalysed by substituted pyridines in tetrachloromethane at 25 °C

Catalyst, alcohol, and association constant (K/l mol^{-1})	[PhNCO]/M	10^2[py]/M [a]	$10^4 k_{obs}$/s^{-1} [b]	10^3 ($k_{obs.}$/[PhNCO]) (1 + K[Py]) l mol^{-1} s^{-1}
3-Chloropyridine, methanol, 1.35 [c]	0.130		0.0130	0.0101
	0.200	12.4	0.235	0.137
	0.156	16.3	0.315	0.247
	0.151	18.6	0.323	0.268
	0.174	20.8	0.433	0.319
	0.168	26.1	0.474	0.381
	0.178	30.6	0.616	0.489
Pyridine, methanol, 2.9 [c]	0.132	3.94	1.03	0.868
	0.138	7.87	1.80	1.61
	0.126	12.0	2.51	3.68
	0.128	16.5	2.85	3.30
	0.142	18.7	3.29	3.57
	0.0582	19.9	1.48	4.00
Pyridine, methan[^{2}H]ol, 2.3 [c]	0.150		0.004 61	0.003 07
	0.150	7.04	1.14	0.884
	0.136	8.82	1.28	1.13
	0.132	10.6	1.42	1.35
	0.140	12.3	1.46	1.34
	0.128	13.8	1.62	1.67
	0.153	14.1	1.60	1.38
	0.140	15.9	1.96	1.91
	0.141	17.6	2.49	2.49
	0.136	19.5	2.24	2.39
4-Methylpyridine, methanol, 3.1 [d]	0.119	3.95	2.16	2.03
	0.126	5.07	3.15	2.90
	0.0717	7.58	2.46	4.23
	0.0781	10.1	2.91	4.89
	0.0772	12.6	3.52	6.34
	0.0726	15.1	3.92	7.92
	0.0962	17.6	5.60	9.00
	0.0957	20.3	6.18	10.5
4-Methoxypyridine, methanol	0.148	0.0551	0.0929	0.0629 [e]
	0.172	0.0854	0.206	0.118 [e]
	0.152	0.123	0.214	0.141 [e]
	0.152	0.136	0.208	0.137 [e]
	0.134	0.991	1.58	1.18 [e]
	0.135	2.41	3.30	2.45 [e]
	0.138	3.21	4.52	3.27 [e]
	0.111	3.61	3.81	3.45 [e]
	0.134	4.04	5.96	4.46 [e]
2,4,6-Trimethylpyridine, methanol, 3.32 [c]	0.132	2.71	2.44	2.01
	0.132	4.15	3.13	2.71
	0.144	5.18	4.07	3.30
4-Dimethylaminopyridine, methanol	0.133	0.0833	1.45	1.09 [e]
	0.142	0.188	3.09	2.17 [e]
	0.134	0.226	3.52	2.62 [e]
	0.137	0.313	4.90	3.58 [e]
	0.150	0.374	6.81	4.06 [e]
	0.118	0.408	5.95	5.05 [e]
	0.130	0.438	7.02	5.40 [e]
	0.139	0.476	8.74	6.28 [e]
	0.149		0.002 [f,g]	0.0014 [e,g]
	0.141	0.112	1.78 [f]	1.26 [e]
	0.164	0.186	3.57 [f]	2.18 [e]
	0.135	0.304	4.92 [f]	3.66 [e]
	0.139	0.348	5.88 [f]	4.23 [e]
	0.126	0.440	6.78 [f]	5.40 [e]
4-Dimethylaminopyridine, methan[^{2}H]ol	0.149	0.121	1.16	0.780 [e]
	0.148	0.174	1.86	1.26 [e]
	0.151	0.250	2.81	1.87 [e]
	0.174	0.332	4.73	2.72 [e]
	0.132	0.419	4.42	3.35 [e]
	0.140	0.481	4.88	3.49 [e]
	0.159	0.542	7.58	4.77 [e]

[a] Total catalyst concentration. [b] Observed first-order rate constant. [c] Values taken from ref. 11. [d] Estimated, assuming the deuterium isotope effect on the pyridine–methanol association constant to be the same as that observed for the pyridine–phenol association constant, using data from ref. 11. [e] K[Py] assumed small compared with unity; see text. [f] Runs in the presence of acetonitrile, [MeCN] = 3.49M. [g] Estimated from the small extent of reaction after 79 h.

analysis of samples for the product methyl *N*-phenylcarbamate, always followed a first-order course. Monomeric methanol was therefore the reactive species in both catalysed and uncatalysed reactions. (With higher concentrations of alcohols, the uncatalysed reactions of *p*-chlorophenyl isocyanate in diethyl ether proceed mainly through dimers and higher aggregates of the alcohols.[2])

The second-order rate constant, obtained by dividing the observed first-order constant by the isocyanate concentration, is effectively constant when the isocyanate concentration is changed (Table 1), confirming that the reaction is first order in phenyl isocyanate.

When account is taken of the equilibrium extent of hydrogen bonding between methanol and substituted pyridine [equation (1)] both Schemes 1 and 2 lead to equation (2). (The fraction of substituted pyridine which is hydrogen bonded to methanol is negligible.) k_0 Is the

$$\mathrm{MeOH} + \mathrm{XPy} \rightleftharpoons \mathrm{MeOH\cdots PyX} \qquad (1)$$

$$k_{\mathrm{obs.}} = \left(\frac{k_0 + k_{\mathrm{cat}}[\mathrm{XPy}]}{1 + K[\mathrm{XPy}]}\right)[\mathrm{PhNCO}] \qquad (2)$$

second order rate constant for the uncatalysed reaction between methanol and phenyl isocyanate. If Scheme 1 is correct (necessarily with $k_2 \gg k_3[\mathrm{MeOH}]$ to account for the first-order dependence upon methanol concentration) then $k_{\mathrm{cat}} = (k_1k_3/k_2)$. If Scheme 2 applies, then $k_{\mathrm{cat}} = kK$.

The observed rate constants (Table 2) vary with the concentration of catalyst according to equation (2). k_0 Is taken as $k_{\mathrm{obs.}}/[\mathrm{PhNCO}]$ in the absence of catalyst (Table 2, first entry). Values of k_{cat}, calculated as the mean of $(\{(k_{\mathrm{obs.}}/[\mathrm{PhNCO}])(1 + K[\mathrm{XPy}])\} - k_0)/[\mathrm{XPy}]$, are in Table 4. Literature values [11] of K were used, except that for 4-methoxy- and 4-dimethylamino-pyridine K is not known. In these two cases estimated values from a log K *versus* pK_a plot led to the conclusion that for the low catalyst concentrations used $K[\mathrm{XPy}] \ll 1$. This was confirmed from the linear nature of plots of $k_{\mathrm{obs.}}/[\mathrm{PhNCO}]$ *versus* [XPy]. For these two catalysts k_{cat} was therefore calculated as the mean of $\{(k_{\mathrm{obs.}}/[\mathrm{PhNCO}]) - k_0\}/[\mathrm{XPy}]$.

TABLE 3

Kinetic hydrogen isotope effects on the addition of methanol to phenyl isocyanate

Catalyst	$k_{\mathrm{cat}}^{\mathrm{H}}/k_{\mathrm{cat}}^{\mathrm{D}}$
None	3.27 [a]
Pyridine	1.70 (±0.19)
4-Dimethylaminopyridine	1.58 (±0.19)

[a] $k_0^{\mathrm{H}}/k_0^{\mathrm{D}}$: due to the slowness of these uncatalysed reactions the error in this value may be relatively large.

TABLE 4

Catalytic constants for the reaction of phenyl isocyanate with methanol in tetrachloromethane at 25 °C

Catalyst	pK_a	k_{cat}/l[2] mol^{-2} s^{-1} [a]
3-Chloropyridine	2.84 [b]	1.39 (±0.19) × 10^{-3}
Pyridine	5.18 [b]	2.05 (±0.11) × 10^{-2}
Pyridine	5.18 [b]	1.21 (±0.12) × 10^{-2} [c]
4-Methylpyridine	6.01 [b]	5.22 (±0.29) × 10^{-2}
4-Methoxypyridine	6.52 [b]	0.105 (±0.011)
2,4,6-Trimethylpyridine	7.43 [b]	6.75 (±0.56) × 10^{-2}
4-Dimethylaminopyridine	9.41 [b]	1.20 (±0.08)
4-Dimethylaminopyridine	9.41 [b]	6.37 (±0.21) [d]
4-Dimethylaminopyridine	9.41 [b]	0.762 (±0.077) [c]

[a] Calculated as mean of $(k - k_0)/[\mathrm{py}]$ where k is $(k_{\mathrm{obs.}}/[\mathrm{PhNCO}])$ $(1 + K[\mathrm{py}])$: errors are standard deviations. [b] From ref. 26. [c] With methan[^{2}H]ol. [d] In the presence of acetonitrile, [MeCN] = 3.49M.

Rate constants for the reactions of MeOD, uncatalysed and catalysed by pyridine and 4-dimethylaminopyridine, are in Table 2. Deuterium isotope effects are summarised in Table 3. For the association between pyridine and MeOD, K was calculated on the assumption that the deuterium isotope effect on the association constant for pyridine and methanol is the same as it is for pyridine and phenol.[11]

In order to examine solvent effects, kinetic runs were carried out in a mixture of tetrachloromethane and acetonitrile (3.49M) with 4-dimethylaminopyridine as catalyst. The effect of acetonitrile could be threefold: it increases the polarity of the medium, it enters into hydrogen-bonded association with methanol [reaction (3)], and it could act as a catalyst itself [reaction (4)]. Recognition of these complications converts equation (2) into (5).

$$\mathrm{MeCN} + \mathrm{MeOH} \overset{K_{\mathrm{MeCN}}}{\rightleftharpoons} \mathrm{MeCN\cdots HOMe} \qquad (3)$$

$$\mathrm{PhNCO} + \mathrm{MeOH} \xrightarrow{k_{\mathrm{cat}}^{\mathrm{MeCN}}} \mathrm{PhNHCO_2Me} \qquad (4)$$

$$\frac{k_{\mathrm{obs.}}}{[\mathrm{PhNCO}]} = \frac{k_0' + k_{\mathrm{cat}}'[\mathrm{XPy}] + k_{\mathrm{cat}}^{\mathrm{MeCN}}[\mathrm{MeCN}]}{1 + K[\mathrm{XPy}] + K_{\mathrm{MeCN}}[\mathrm{MeCN}]} \qquad (5)$$

The primes are introduced because the rate constants may have been affected by solvent polarity. From the reported value [11] for 28 °C, a value for K_{MeCN} of 1.25 l mol^{-1} at 25 °C can be estimated. $K[\mathrm{XPy}]$ is small compared with unity, so the value of the bottom line of the right hand side of equation (5) is *ca.* 5.4. A plot of $(5.4\ k_{\mathrm{obs.}}/[\mathrm{PhNCO}])$ *versus* [XPy] is shown in Figure 1. The intercept measured in the

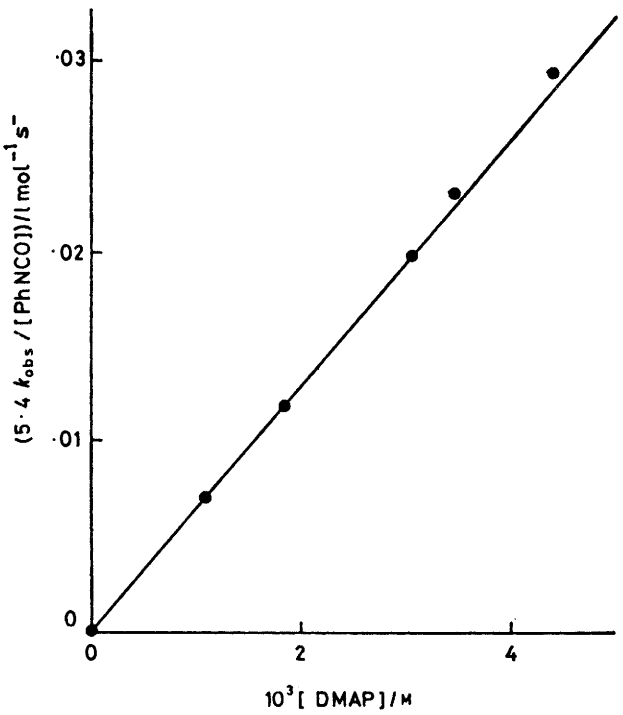


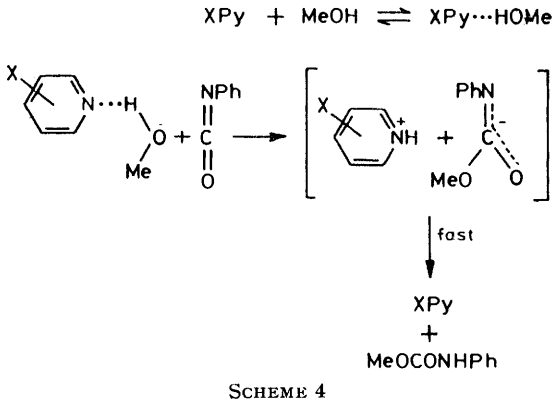
FIGURE 1 Plot of $(5.4\ k_{\mathrm{obs.}}/[\mathrm{PhNCO}])$ *versus* the concentration of 4-dimethylaminopyridine (DMAP) for the catalysed addition of methanol to phenyl isocyanate in tetrachloromethane containing 3.49M-acetonitrile

absence of catalyst, $k_0' + k_{cat}^{MeCN}[MeCN] = 7.2 \times 10^{-6}$ l mol^{-1} s^{-1}, is in fact slightly less than k_0. It seems likely therefore that there is no significant catalysis by MeCN and little solvent effect upon the uncatalysed reaction. The slope $k_{cat}' = 6.4 (\pm 0.2)$ l^2 mol^{-2} s^{-1}. Thus increased solvent polarity has increased the catalytic constant by a factor of 5.4. The slope of the plot of $k_{obs.}/[PhNCO]$ *versus* [XPy] is almost identical with that for pure tetrachloromethane which illustrates the ease with which hydrogen bonding can mask other effects if ignored.

The Reactions of 2- and 4-Pyridylmethanol with Phenyl Isocyanate.—These alcohols were studied at concentrations close to their solubility limit. Conditions and results are in Table 4. The thermal instability of the carbamates led to the use of h.p.l.c. rather than g.l.c. for analysis of reaction mixtures. The results are less accurate; estimated errors are given.

DISCUSSION

The Reaction Catalysed by Substituted Pyridines.—All the data are consistent with the mechanism of Scheme 2, an expanded version of which is Scheme 4. The Brönsted plot (Figure 2) has a slope β of 0.49. This shows that the positive charge development on pyridine nitrogen in the transition state is partial. Comparison can be made with other reactions involving substituted pyridines in tetrachloromethane in which there has been a partial transfer of positive change to the pyridine nitrogen in the transition state. In the acylation of phenols with anhydrides, general base catalysed by pyridines,[17] β lies in the range 0.85—0.96. Acyl group exchange of 4-nitrophenyl acetate,[18] with the same type of catalysis has β 0.94. Quaternisation of substituted pyridines in some dipolar aprotic solvents [19] (an S_N2 reaction) has β values between 0.33 and 0.44.



SCHEME 4

The point for 2,4,6-trimethylpyridine falls below the Brönsted line for the other catalysts (Figure 2) by 0.47 log units. This steric effect comes within the (rather large) range of steric effects reported for reactions involving rate-determining proton transfers to pyridine nitrogen. In diazo-coupling with rate-determining proton removal, 2,6-dimethylpyridine is one-tenth as reactive as expected from its basicity.[20] On the Brönsted plot for nitroethane deprotonation,[21] 2,6-dimethylpyridine falls below the line by 0.4 units. The nitramide decomposition shows no such steric effect.[22] On the other hand steric effects in nucleophilic reactions are usually large. 2-Methylpyridine is less than one-hundredth as reactive as pyridine in its nucleophilic attack on acetic anhydride [23] and 4-nitrophenyl acetate.[24] It is clear that the magnitude of the steric effect is more

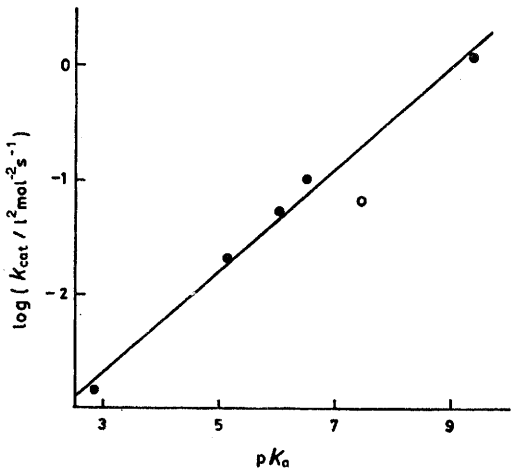


FIGURE 2 Brönsted plot for the addition of methanol to phenyl isocyanate in tetrachloromethane catalysed by substituted pyridines. Slope β = 0.49. The point for 2,4,6-trimethylpyridine, not included in the correlation, is shown as an open circle

consistent with the general base than with the nucleophilic mechanism, even though this was Baker's chief reason for preference for the latter.[4]

The deuterium isotope effect (Table 3) could be a rather large secondary effect, but isotope effects on proton transfers between electronegative centres, and those in which the proton transfer is not the only covalency change occurring in the transition state, are expected to be modest; [25] the observed isotope effect is consistent with the transition state in Scheme 4.

An observation [5] that the deuterium isotope effect increases with increasing basicity has been used as support for the nucleophilic mechanism. However, in that work hydrogen-bonding associations were not taken into account, even though, taking typical conditions, it is likely that (on the basis of equilibrium constants for similar associations [11]) *ca.* 10% of the alcohol was dimerised and 30% hydrogen-bonded to catalyst. Our results suggest (Table 3) that the solvent isotope effect decreases with increase in catalyst basicity, though the results for pyridine and 4-dimethylaminopyridine are within experimental error.

The effect of an increase in solvent polarity is to increase the catalytic constant. This is not surprising because it is hard to imagine a transition state for the reaction which is not more polar than the ground state. The previous puzzling observation [7] that an increase in solvent polarity decreased the rate constant, can now be attributed to a failure to take into account the effect of hydrogen bonding equilibria.

2-Pyridylmethanol reacts with phenyl isocyanate

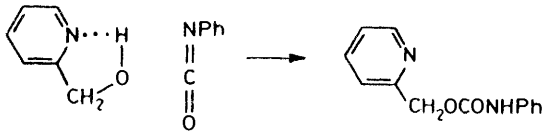
significantly faster than does 4-pyridylmethanol (Table 5). Since the polar effect of the substituent on methanol should in both cases be similar, it seems reasonable to conclude that the difference is due to intramolecular general base catalysis (Scheme 5).

TABLE 5

Rate constants for the reaction of 2- and 4-pyridylmethanol with phenyl isocyanate in tetrachloromethane at 25 °C

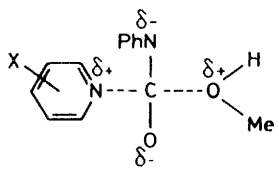
	2-Pyridylmethanol	4-Pyridylmethanol
$[Alcohol]_4$M [a]	4.90×10^{-3}	4.97×10^{-3}
[PhNCO]/M [a]	0.131	0.130
$k_{obs.}/s^{-1}$ [b]	$1.3 (\pm 0.2) \times 10^{-4}$	$1.1 (\pm 0.2) \times 10^{-5}$
$k_{obs.}[PhNCO]^{-1}$/l mol^{-1} s^{-1}	9.6×10^{-4}	8.1×10^{-5}

[a] Initial concentration. [b] Observed first-order rate constant.

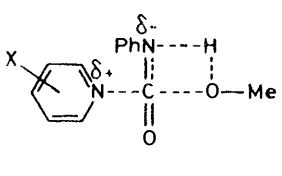


SCHEME 5

The present results are therefore consistent with the general base mechanism. They do not rule out the nucleophilic mechanism, but the Brönsted slope is not consistent with a transition state in which the pyridine nitrogen bears a full positive charge. Pyridine loss from a tetrahedral intermediate is unlikely to be rate determining [26] which leaves concerted displacements like (II)



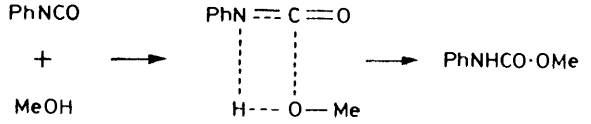
(II)



(III)

or (III) as the only possible transition states for the nucleophilic mechanism. For reasons mentioned in the introduction nucleophilic catalysis seems relatively unlikely.

The Uncatalysed Reaction.—The order in methanol, deuterium isotope effect, and solvent effect show that the transition state contains one molecule of methanol, with a proton in flight, and is relatively non-polar. A four-centre process (Scheme 6) is indicated.



SCHEME 6

EXPERIMENTAL

Materials.—Tetrachloromethane was distilled from calcium hydride and stored over 4A molecular sieves. Acetonitrile was distilled from phosphoric oxide, then from calcium hydride, and stored over 3A molecular sieves. Methanol was dried.[27] Methan[^{2}H]ol (Aldrich) was used as supplied. 2-Pyridylmethanol was distilled and 4-pyridylmethanol recrystallised. Phenyl isocyanate was distilled from phosphoric oxide. Substituted pyridines were purified, and 4-methoxypyridine prepared, as previously.[26] Methyl *N*-phenylcarbamate, m.p. 47 °C, was prepared by a standard method.[28] 2-Pyridylmethyl and 4-pyridylmethyl *N*-phenylcarbamate were prepared by the addition of phenyl isocyanate to 2-pyridylmethanol in diethyl ether and 4-pyridylmethanol in acetone, respectively. After refluxing for 1 h and removing the solvent the products were recrystallised from heptane and benzene, respectively, m.p.s 99—100 (lit.,[29] 99.5) and 129.5—130 °C (lit.,[29] 125—126 °C), respectively.

The Kinetic Method.—Exclusion of moisture was the major problem; vessels into which solvent and reagents came into contact were silanised by rinsing with dichlorodimethylsilane. Stock solutions were dispensed from enclosed burettes through greaseless stopcocks under a pressure of dry air. The two-limbed reaction vessel had facilities for removing samples under a pressure of dry nitrogen without ingress of moisture. Solvent, catalyst, methanol, and chromatographic internal standard were placed in one limb, phenyl isocyanate and solvent in the other. The contents of the two limbs were mixed after thermal equilibration. Samples were taken at time intervals, quenched, and analysed chromatographically; details are in Table 6.

Pyridines [30] (as other amines [31]) react with tetrachloromethane and it was necessary to exclude light from their solutions, and to use them as soon as possible after pre-

TABLE 6

Details of quenching and analysis for the reaction of phenyl isocyanate with alcohols

Alcohol	Internal standard	Method of quenching	Peak area [a] ratio measured	Response [b] factor	Method	Chromatographic systems: Column	Chromatographic systems: Conditions
Methanol and methan[^{2}H]ol	*p*-Nitrotoluene	Hydrochloric acid, 1M, 4 cm^3, stir 5 min	prod. (560) std. (345)	0.914	G.l.c.	10% SE 30 on Chromosorb W-HP 1.5 m, 4 mm i.d.	Nitrogen, 30 cm^3 min^{-1}, 160 °C
4-Pyridylmethanol	Nitrobenzene	Octanol, 2 cm^3	alc. (235) std. (560)	0.306	H.p.l.c.	Spherisorb ODS 5μ, 25 cm, 4.5 mm i.d.	Methanol–water 1 : 1, 1.2 cm^3 min^{-1}
2-Pyridylmethanol	2-Bromo-4-nitrotoluene	Methanol, 2 cm^3	prod. (960) std. (2600)	1.010	H.p.l.c.	Spherisorb ODS 5μ, 25 cm, 4.5 mm i.d.	Methanol–water 1:1, 1.5 cm^3 min^{-1}

[a] The figures in parentheses are typical retention times, *t*/s. [b] Slope of calibration plot of peak area ratio against concentration ratio.

paration. For the reaction of phenyl isocyanate with methanol the identity of the product, methyl *N*-phenylcarbamate was checked by g.l.c.–m.s. The spectrum was as published.[32]

Preliminary studies showed that over the period of a kinetic run any reaction of the isocyanate with the product, with itself, or with water if present, is negligible. Although great care was taken to exclude water, traces were present in a few runs giving rise to *NN'*-diphenylurea which was identified by i.r. and by mixed m.p. The effect of the urea, as observed in these cases and confirmed by runs in which either water or the urea was deliberately added, was to accelerate the reaction. Fortunately the urea is practically insoluble in tetrachloromethane; small quantities were detectable as suspensions of crystals in the reaction mixture. Any runs in which such crystals were visible were discarded.

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