

Kinetics and Mechanism of Nucleophilic Addition of Hydroxide to Aromatic Isocyanides

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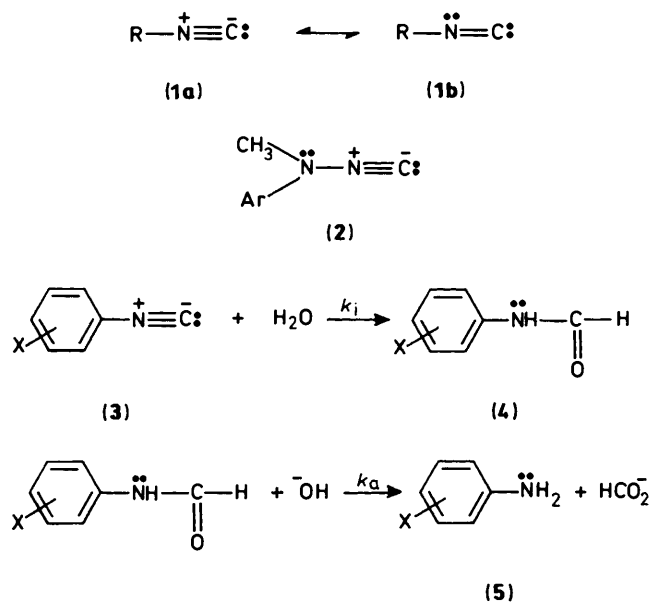
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para- and *meta*-substituted aromatic isocyanides have been found to react in alkaline aqueous dioxane yielding the corresponding formamides. From a kinetic analysis of the reaction, the observed rate constants were found to be linearly dependent upon hydroxide concentration; this observation, together with the positive value of ρ , was taken as evidence of direct nucleophilic attack. Decreasing values of ΔH^\ddagger were observed as electron-withdrawing substituents were introduced, whereas ΔS^\ddagger was fairly constant at $-57 \text{ J K}^{-1} \text{ mol}^{-1}$; this indicates little variation in transition-state geometry across the range of isocyanides studied. The kinetic evidence is discussed in terms of two mechanisms: nucleophilic attack of hydroxide with concerted proton transfer from water to the isocyano carbon, and nucleophilic attack of hydroxide to yield a carbanion intermediate, with protonation occurring in a rapid subsequent step. The reaction rate increases with increasing water content in the solvent; this observation appears to favour the concerted mechanism. In dioxane-deuterium oxide the reaction showed a small inverse isotope effect; the apparent lack of an appreciable primary isotope effect is consistent with a concerted mechanism only if minimal proton transfer from water to carbon has occurred in the transition state.

Isocyanides are unusual in that they are stable organic compounds containing a formally divalent carbon atom (**1b**). However, microwave^{1a,b} and electron diffraction^{1c} studies have shown them to be linear dipolar molecules better described by the triple-bonded resonance form (**1a**). Isocyanides are susceptible to 1,1-addition at the isocyano carbon atom, either in the presence or in the absence of metal catalyst, to yield substituted imines. Consistent with form (**1a**), the initial attack on the isocyanide tends to be electrophilic, involving either a proton or an electrophilic reagent such as an acid chloride, a halogen, or a metal.² The reaction between isocyanide and a nucleophilic amine or alcohol, catalysed by compounds of group 1B and group 2B, metals, has been extensively studied²⁻⁴ and appears to involve attack of the nucleophile upon either a carbene-metal complex³ or an isocyanide-metal complex with a pseudo-nitrilium ion structure.⁴ In the absence of metal or acid catalyst, isocyanides are generally considered to be inert towards nucleophilic attack. Recent theoretical studies of anionic⁵ and neutral⁶ 1,1-addition to isocyanides have dealt mainly with stereochemical aspects. In the case of the neutral nucleophiles water and ammonia, *ab initio* calculations⁶ suggest that solvent (water) molecules catalyse the addition, although activation energies were calculated to be prohibitively high. There are, however, isolated examples where isocyanides appear to undergo nucleophilic 1,1-addition in the absence of metal catalyst;³ in particular, the very reactive isocyanide (**2**) (Ar = 2,4-dinitrophenyl) undergoes direct nucleophilic attack by amine and hydroxide.⁷ This suggested that simple aryl isocyanides might be more susceptible to nucleophilic attack than had been supposed previously. Therefore, a systematic study of the kinetics and mechanism of the nucleophilic addition of hydroxide to a range of *para*- and *meta*-substituted phenyl isocyanides was undertaken, the results of which are presented and discussed in this paper.

Results

The reactions of the isocyanides (**3a-g**) under pseudo-first-order conditions in a range of 1:4 dioxane-water solutions containing from 0.02 to 0.80M-NaOH were studied at 70 °C. For



Scheme 1.

each isocyanide only one product, the corresponding aniline (**5**), was obtained on completion. However, when the reaction mixture was analysed prior to completion a small amount of an intermediate material was detected, as was unchanged isocyanide. The intermediate was identified as the *N*-arylfarmide (**4**) [usually by t.l.c., but in the case of (**4f**) by isolation]. A typical repetitive scan of the u.v. spectral change for the overall transformation of (**3**) into (**5**) [specifically that of (**3c**) in 0.8M-NaOH at 70 °C] is shown in Figure 1. This repetitive scan can be divided into four areas: (1) 275–278 nm, where an initial rapid increase in absorbance is followed by a slow decrease; (2) 279–281 nm (point A), where there is a rapid increase in absorbance which follows first-order kinetics and is complete after 15 min ($k_{\text{obs}} 2.74 \times 10^{-3} \text{ s}^{-1}$ at 280 nm); (3) 282–299 nm, where an initial rapid increase in absorbance is followed after about 15 min by a slower increase; and (4) 300–330 nm, where

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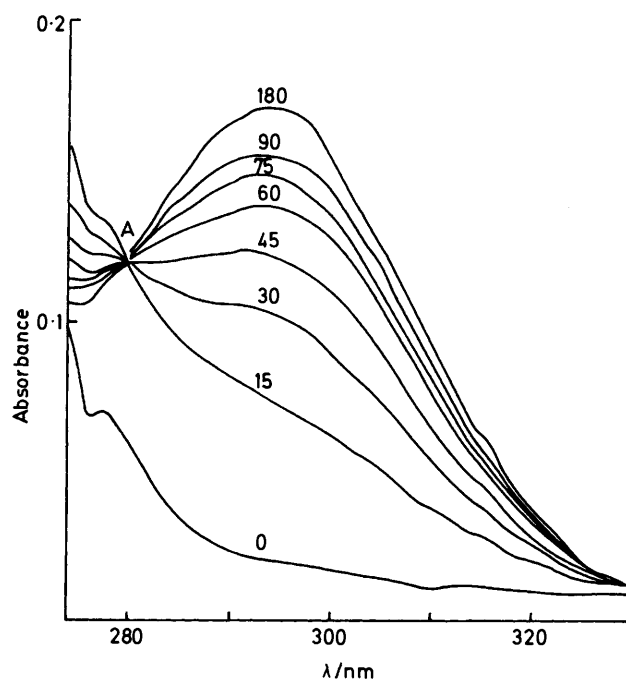


Figure 1. Electronic spectra of *p*-chlorophenyl isocyanide (3c) in 0.8M-NaOH in 1:4 dioxane-water at 70 °C, at intervals of 15 min; $[\text{isocyanide}]_0 = 1.4 \times 10^{-4}\text{M}$

there is a slow increase in absorbance which follows first-order kinetics throughout the reaction ($k_{\text{obs.}} = 3.54 \times 10^{-4} \text{ s}^{-1}$ in the region 300–330 nm). An investigation of the alkaline hydrolysis of the observed intermediate, the formamide (4c), under identical conditions revealed the area 300–330 nm to be an isosbestic region for the conversion of (4c) into (5c), *i.e.* a region where $\epsilon_4 = \epsilon_5$.

Similar behaviour was observed for all the isocyanides (3a–g) with $[\text{NaOH}]$ in the range 0.02–0.80M at 70 °C, and with $[\text{NaOH}] = 0.8\text{M}$ at 60, 65, or 75 °C. In particular, in a region of the spectrum where $\epsilon_4 \approx \epsilon_5$, the absorbance change for the overall transformation of (3) into (5) was found to follow good first-order kinetics from $t = 0$, over several half-lives, and for up to 250-fold variation in substrate initial concentration. From the absorbance change in the appropriate region of the spectrum therefore, it was possible to obtain a pseudo-first-order rate constant $k_{\text{obs.}}$ for the overall transformation of (3) into (5) under any particular set of conditions. Furthermore, for the isocyanides (3b–g) plots of $k_{\text{obs.}}$ for reactions at 70 °C in solutions of different $[\text{NaOH}]$ against $[\text{NaOH}]$ were linear ($r > 0.996$) (Figure 2). Second-order rate constants k were determined from the slopes of these plots and are listed in Table 2. All plots extrapolated to zero at $[\text{NaOH}] = 0$. In order to maintain the ionic strength constant at 0.8, NaCl was added. However, plots of $k_{\text{obs.}}$ against $[\text{NaOH}]$ when no NaCl was added [reactions of (3b) and (3f)], or where the ionic strength was maintained with Na_2SO_4 [(3f)], were also linear and gave values of k identical with those obtained when NaCl was added.

Values of k obtained from $k_{\text{obs.}}$ measured at other temperatures, along with the activation parameters ΔH^\ddagger and ΔS^\ddagger , are also listed in Table 2. The values of ΔH^\ddagger show a steady decrease as the substituent on the phenyl ring becomes more electron-withdrawing, while ΔS^\ddagger remains fairly constant at around $-57 \text{ J K}^{-1} \text{ mol}^{-1}$ with the exception of the value for (3a).

Values of k for the reaction of phenyl isocyanide (3b) to give the aniline (5b) in solutions containing various ratios of dioxane to water are collected in Table 3.

For the isocyanides (3a, d, and f), values of k for the reaction

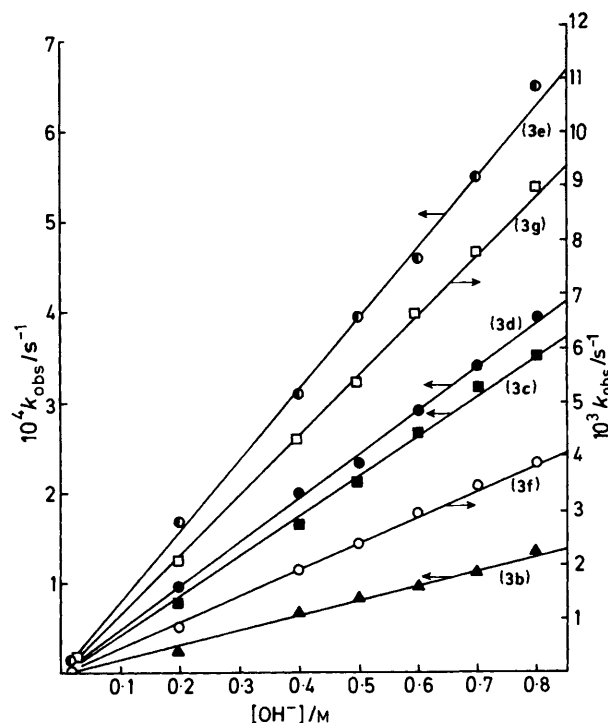


Figure 2. Plots of $k_{\text{obs.}}$ for the reactions of isocyanides (3) in 1:4 dioxane-water containing NaOH [$\mu = 0.8$ (NaCl)] at 70 °C vs. $[\text{NaOH}]$

Table 1. Values of $k_{\text{obs.}}$ for alkaline hydrolysis of formamides (4a–g) in 1:4 dioxane-water at 70.0 °C

Formamide	X	$10^3 k_{\text{obs.}}/\text{s}^{-1}$	
		$[\text{NaOH}] = 0.8\text{M}$	$[\text{NaOH}] = 0.2\text{M}$
(4a)	<i>p</i> -Me	2.70	
(4b)	H	3.41	0.56
(4c)	<i>p</i> -Cl	2.89	0.55
(4d)	<i>p</i> -Br	2.80	
(4e)	<i>m</i> -Cl	2.60	0.60
(4f)	<i>m</i> -NO ₂	10	1.50
(4g)	<i>p</i> -NO ₂	260 ^a	

^a Extrapolated from values at 20–30 °C.

with ⁻OD in 1:4 dioxane-deuterium oxide were obtained (Table 4). In each case an inverse isotope effect was found.

A Hammett plot of $\log k$ against σ showed a good correlation ($r = 0.99$) and a ρ value of +2.25 (Figure 3).

The values of $k_{\text{obs.}}$ for the alkaline hydrolysis of the formamides (4a–g) to give the anilines (5a–g) at $[\text{NaOH}] = 0.8$ and 0.2M were determined separately and are collected in Table 1.

Discussion

The product analysis clearly suggests a reaction scheme in which the isocyanide (3) is converted into the formamide (4), which reacts further to give formate and the aniline (5) (Scheme 1). The absorbance A at any time t , at any wavelength, for such a reaction is given by equation (i), where $p = k_i/(k_a - k_i)$, ϵ

$$A = \{(\epsilon_3 - \epsilon_5) + p(\epsilon_4 - \epsilon_5)\}[(3)]_0 \exp(-k_1 t) - \{p(\epsilon_4 - \epsilon_5)\}[(3)]_0 \exp(-k_a t) + A_\infty \quad (\text{i})$$

Table 2. Second-order rate constants (k) for reactions of isocyanides (3) with hydroxide at various temperatures, and activation parameters

Isocyanide	X	$10^4 k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}{}^a$			$\Delta H^\ddagger/\text{kJ mol}^{-1}{}^b$	$\Delta S^\ddagger/\text{J mol}^{-1} \text{ K}^{-1}{}^b$
		60 °C	65 °C	70 °C		
(3a) ^c	<i>p</i> -Me		0.38	0.70	102.4 ± 6.5	-28 ± 19
(3b)	H	0.59	0.97	1.64	93.2 ± 1.0	-47 ± 3
(3c)	<i>p</i> -Cl	1.73	2.77	4.40	85.3 ± 1.0	-62 ± 3
(3d)	<i>p</i> -Br	1.87	3.08	4.87	87.6 ± 1.0	-54 ± 3
(3e) ^d	<i>m</i> -Cl	3.29	5.70	7.95	83.8 ± 5.0	-61 ± 15
(3f)	<i>m</i> -NO ₂	20.8	34.3	48.4	77.2 ± 7.0	-65 ± 20
(3g)	<i>p</i> -NO ₂	47.6	70.6	110.6	77.5 ± 3.6	-57 ± 10

^a Solvent 1:4 dioxane–water [$\mu = 0.8$ (NaCl)]. ^b Errors are standard deviations. ^c $10^4 k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1} = 1.12$ at 75 °C. ^d $10^4 k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1} = 13.25$ at 75 °C.

Table 3. Rate constants (k) for reaction of phenyl isocyanide (3b) with hydroxide in various dioxane–water mixtures at 70 °C

% dioxane–water (v/v)	$10^4 k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
0	2.32
20	1.64
30	1.01
40	0.61

Table 4. Solvent isotope effect for reaction of isocyanides with OH⁻ (OD⁻) in 1:4 dioxane–H₂O (D₂O) at 70 °C

Isocyanide	X	$k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$
(3a)	<i>p</i> -Me	1.15 ± 0.06
(3d)	<i>p</i> -Br	1.21 ± 0.07
(3f)	<i>m</i> -NO ₂	1.40 ± 0.10

refers to the extinction coefficient for (3), (4), or (5), and k_i and k_a are the pseudo-first-order constants for the individual steps.⁸ The values of k_a can be obtained from the observed experimental pseudo-first-order rate constants for the independent alkaline hydrolysis of the formamides (4) (Table 1).

Consideration of equation (i) shows that the observed changes in absorbance with time for the overall transformation of (3) into (5) are entirely consistent with the proposed Scheme 1. Most importantly, at wavelengths where $\epsilon_4 = \epsilon_5$ (or indeed where $\epsilon_4 - \epsilon_5$ is small), equation (i) reduces to (ii); therefore in

$$A = \{(\epsilon_3 - \epsilon_5)[(3)]_0\} \exp(-k_i t) + A_\infty \quad (\text{ii})$$

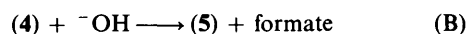
this area of the spectrum the absorbance change would be expected to follow first-order kinetics. Furthermore, the observed pseudo-first-order rate constant k_{obs} will reflect only variations in the first step [(3) to (4)] and will not depend on k_a . This is just what is observed in all cases, *i.e.* a region of the spectrum (a) where $\epsilon_4 - \epsilon_5$ is approximately zero, (b) where first-order kinetics for the transformation of (3) into (5) are observed throughout the reaction, and (c) where the observed rate constants for this transformation are generally an order of magnitude lower than those for alkaline hydrolysis of (4) (*i.e.* k_{obs} does not appear to reflect k_a). In other regions of the spectrum a more complex variation in absorbance described by equation (i) would be expected and is indeed observed [*e.g.* regions (1) and (3) of the spectrum in Figure 1]. If k_i can be obtained from k_{obs} , measured as described, a point where $\epsilon_3 - \epsilon_5 = -p(\epsilon_4 - \epsilon_5)$ may be found. In the repetitive scan of (3c) (Figure 1) such a point is A , and here equation (i) will reduce to (iii). First-order kinetics should also be followed at this

$$A = -\{p(\epsilon_4 - \epsilon_5)\}[(3)]_0 \exp(-k_a t) + A_\infty \quad (\text{iii})$$

point and the observed pseudo-first-order rate constant for the transformation of (3c) into (5c) should yield k_a . As already seen, first-order kinetics were followed at this point, and the value of k_a determined in this way ($2.74 \times 10^{-3} \text{ s}^{-1}$ at $[\text{NaOH}] = 0.8\text{M}$ and 70 °C) agreed well with that obtained from direct measurement of the reaction of (4c) to give (5c) ($2.89 \times 10^{-3} \text{ s}^{-1}$ at $[\text{NaOH}] = 0.8\text{M}$ and 70 °C). This provides further evidence that the proposed scheme is correct.

On the basis of the foregoing discussion it can be seen that by monitoring the overall reaction at the isobestic point of the second step, it is possible to study independently the first. Since all values of k listed in Table 2, and all the values of k_{obs} plotted against $[\text{NaOH}]$ in Figure 2, were obtained from measurements in regions where $\epsilon_4 - \epsilon_5 \approx 0$, it can be concluded that any variations in these constants due to temperature, substituents, *etc.* reflect factors affecting conversion of the isocyanide (3) into the formamide (4) only.

If we consider the results for the transformation of (4) into (5) in Table 1 (along with results obtained by other workers⁹), and the linear variation of k_{obs} for the overall transformation of (3) into (5) with hydroxide ion concentration (Figure 2), it can be concluded that the processes involved are reactions (A) and (B).

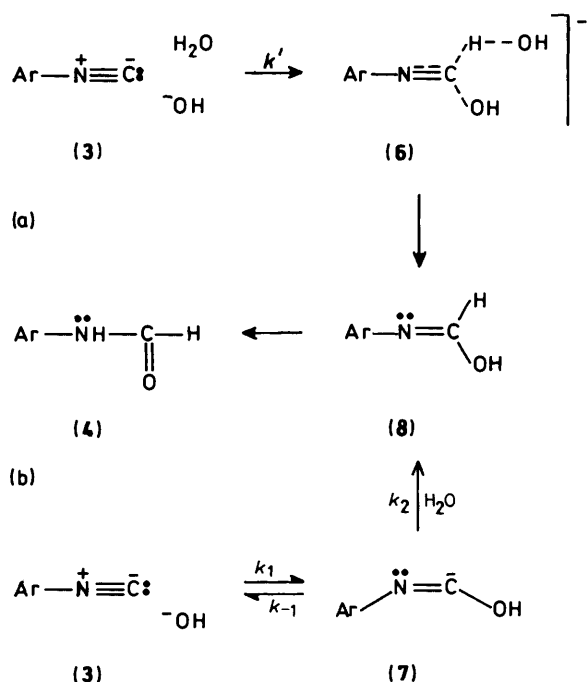


Since the alkaline hydrolysis of formamides has been the subject of much study by other workers,⁹ the following discussion will concentrate on the first step of the scheme, the conversion of the isocyanide (3) into the formamide (4).

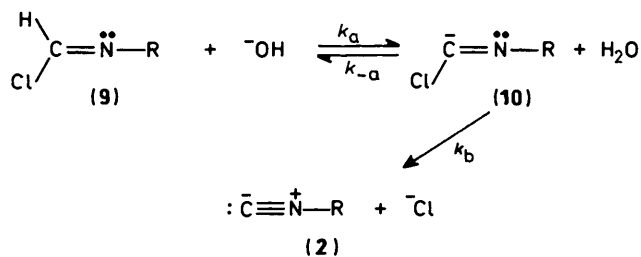
The linear dependence of k_{obs} on $[\text{NaOH}]$ and the positive value of ρ support the proposition of direct nucleophilic attack of OH⁻ on the isocyanide. A mechanism involving attack of OH⁻ or H₂O on an isocyanide initially protonated by H₂O or H₃O⁺ would be either acid-catalysed or pH-independent. Furthermore, the zero value of k_{obs} at $[\text{NaOH}] = 0$ shows that such reactions are negligible.

These observations are consistent with two mechanisms (Scheme 2); (a) concerted attack of OH⁻ and one or more water molecules to give a transition state generalised as (6), or (b) stepwise formation of an intermediate carbanion (7) followed by protonation by water. In either case the product would be the imidic acid (8). Both mechanism (a) and step 2 of (b) would be irreversible by virtue of the rapid tautomerisation of (8) to the formamide (4), and the probability that (8) would exist mostly as its conjugate base from which the reverse reaction is most unlikely.

In mechanism (a), k (Table 2) will be a pseudo-second-order constant, containing a term reflecting the involvement of water in the transition state. Assuming a steady-state concentration of (7), the expression (iv) holds for mechanism (b). The relative



Scheme 2.



Scheme 3.

$$k_{\text{obs.}} = k_1 k_2 [\text{OH}^-] / (k_{-1} + k_2) \quad (\text{iv})$$

magnitudes of k_{-1} and k_2 can be estimated by considering the base-catalysed hydrolysis of the formimidoyl chloride (9) [R = 2,4-(NO₂)₂C₆H₃NMe] (Scheme 3).⁷ The rates of protonation of, and of loss of Cl⁻ from, the intermediate (10) [which is analogous to (7)] were comparable. To compare (7) with (10), the much lower nucleofugality of OH⁻ relative to Cl⁻ would make elimination of OH from (7) much slower than protonation to give (8), and thus for (b) $k_{\text{obs.}} = k_1[\text{OH}^-]$ and $k = k_1$. Thus it can be seen that k refers to a concerted OH⁻/H₂O attack on (3) if (a) is correct, and to attack of OH⁻ only, if (b) is correct.

From the activation parameters in Table 2 it can be seen that the increase in k with increasing electron-withdrawing ability of X is due mainly to the decrease in ΔH^\ddagger . As the nucleophile approaches the carbon atom, the electrons in the second π -bond [see (1a)] move onto the N, forming a lone pair; this is clearly favoured by electron-withdrawing substituents.

The negative values of ΔS^\ddagger point to a transition state that is more ordered than the starting materials, as would be expected of a bimolecular or a higher order reaction. Since k , the rate constant from which ΔS^\ddagger is derived, is second order, the values of ΔS^\ddagger refer to a standard state of 1 mol dm⁻³. This being so, ΔS^\ddagger appears rather small for a bimolecular reaction in solution. On a simple level, it seems reasonable to assume that charge dispersion will occur on going to the transition state [in either

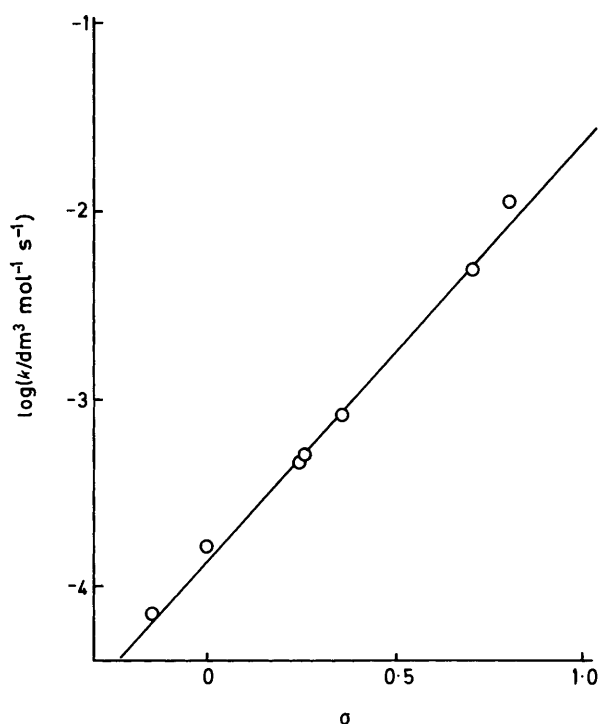


Figure 3. Plot of $\log k$ for the reactions of isocyanides (3) in 1:4 dioxane-water at 70 °C vs. σ .

mechanism (a) or (b)] and that there will be a decrease in solvation, particularly if the highly solvated OH⁻ is 'removed' from the solvent on joining the carbon. This would result in a 'desolvation ΔS^\ddagger ' contribution which is positive. Allowing for this factor, the overall value of ΔS^\ddagger is not inconsistent with the postulated mechanism and the relatively constant value for (3b-g) suggests that transition state shows little variation across the range of isocyanides studied.

In the Hammett plot, the good correlation ($r = 0.99$) supports the assumption that the same mechanism holds for all the substrates (3a-g), while the positive sign of ρ reflects an increase in negative charge on the N atom as the lone pair forms on it. Since this formation occurs in response to attack of OH⁻, the magnitude of the ρ term (2.25) suggests that a high degree of HO-C bonding exists in the transition state.

The decrease in k for (3b) with decreasing water content in the solvent is shown in Table 3. No clear simple relationship is observed between k and either water content or any solvent polarity parameter. It may reflect the involvement of water in the rate-limiting step (*i.e.* k may be a pseudo-second-order constant, $k = k'[\text{H}_2\text{O}]^x$), or a solvation/polarity effect, or a combination of both. Since mechanism (b) does not involve attack by water in the rate-limiting step, such a variation would be expected to be due to the solvent/polarity effect only. Once again, it seems reasonable to assume that a reaction in which the dipolar isocyanide and negatively charged OH⁻ are transformed into a transition state leading to (7) would result in charge dispersion giving a transition state less polar and less solvated than the starting materials. Thus mechanism (b) would lead to an increase in k with decrease in solvent polarity and solvating ability, the converse of what is observed. In mechanism (a) solvation/polarity factors would be of secondary importance to the stoichiometric involvement of water, and k would be expected to decrease with decreasing water content. Clearly, the results favour mechanism (a). However, a more comprehensive study of solvent effects would be more informative.

The solvent isotope effect (Table 4) is a combination of three

separate factors: solvation, the relative nucleophilicity of OD^- and OH^- , and a primary effect. Assuming that the following qualitative arguments hold equally in 1:4 dioxane- D_2O and in pure D_2O ,¹⁰ each factor can be treated as follows. The solvation factor, due to charge dispersion in the transition state, will lead to a small (10–30%) rate enhancement in D_2O .^{11–13} Schowen¹⁴ has shown that $k_{\text{OD}^-}/k_{\text{OH}^-}$ varies from 1 to 2¹⁵ depending on the extent of bond formation in the transition state. The magnitude of any primary isotope effect will depend on the extent of proton transfer from water, up to a maximum $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ of about 10, and it will offset the first two factors. Clearly, even assuming maximum $k_{\text{OD}^-}/k_{\text{OH}^-}$ and solvent effects, the values in Table 4 indicate a primary effect of not more than 2.3. For mechanism (a) this implies only slight transfer of H from water in the transition state.

The lack of an appreciable primary isotope effect appears to favour mechanism (b). However, the observed trend [$k(\text{D}_2\text{O})/k(\text{H}_2\text{O})$ decreases from (3f) to (3a)] is not consistent with this; a more 'product-like' transition state with a larger $k_{\text{OD}^-}/k_{\text{OH}^-}$ would be expected for the less reactive (3a) than for (3f). For mechanism (a) this trend suggests an increased, though still small, extent of H transfer from water in the transition state for (3a) relative to (3f).

Finally, it is of interest that $\log k$ correlates with σ rather than σ^- in the Hammett plot (Figure 3), as shown in the case of the *p*-nitrophenyl isocyanide (3g). This implies that the lone pair forming on the N does not conjugate with the aromatic ring, but that conjugation presumably occurs between the ring and the C=N bond.

Conclusions

The results reported show that direct attack of the nucleophile OH^- on the isocyanato group occurs under moderate conditions. The attack is favoured by electron-withdrawing groups on the isocyanide, and the rate variation is due mainly to electronic factors reflected in ΔH^\ddagger . Despite some remaining uncertainty about solvent influences, a concerted mechanism involving a transition state with a high degree of HO–C bonding and a low degree of H (from water)–C bonding is favoured over a stepwise mechanism.

The results obtained contrast with the previously supposed lack of reactivity of isocyanides towards direct nucleophilic attack (in particular by alkali¹⁶).

The success of nucleophilic addition in the present case can be ascribed to several factors. First, the low concentrations reduce the likelihood of isocyanide polymerisation,¹⁷ which occurs readily at higher concentrations. Secondly, the highly aqueous solvent clearly favours the reaction, although the specific reason for this has not been established. Thirdly, the use of aromatic isocyanides having electron-withdrawing substituents favours nucleophilic attack; commonly used alkyl isocyanides have electron-donating substituents and are generally less reactive. Finally, the desolvation (particularly of OH^-) on going to the transition state appears to be important in offsetting what would otherwise be a rather unfavourable ΔS^\ddagger .

Experimental

Materials.—The isocyanides (3a–g) were prepared by the method of Ugi¹⁸ from the corresponding anilines, and were purified by distillation, recrystallisation, sublimation, or chromatography. The purity was checked by g.l.c. in the case of liquids, and by t.l.c. in the case of solids; no impurities were detected except in the case of *p*-tolyl isocyanide (3a) which contained <4% of *p*-toluidine (5a). The formamides (4a–g) were prepared from the corresponding anilines and formic acid, and the recrystallised solids were found to be pure by t.l.c.

The water used was de-ionised and distilled and dioxane was purified according to the method of Vogel.¹⁹ Deuterium oxide (Aldrich) was used as supplied. Inorganic materials were of Analar grade.

Kinetics.—Reaction solutions were prepared by injecting 1–5 μl of 0.06–0.7M-solutions of the isocyanides in dioxane into 2.6 cm^3 of the solvent [giving solutions $(0.3\text{--}8.0) \times 10^{-4}\text{M}$ in isocyanide], contained in thermostatically controlled, stoppered silica cuvettes. The rate for each reaction was measured by monitoring the u.v. absorbance change at a wavelength corresponding to an isosbestic point for the hydrolysis, under identical conditions, of the intermediate formamide (4) with a Pye Unicam SP8-100 or SP1800 spectrophotometer. Reactions were run in 1:4 dioxane–water containing 0.8, 0.7, 0.6, 0.5, 0.4, 0.2, or 0.02M-sodium hydroxide, generally with added sodium chloride to maintain the ionic strength at 0.8, but in some cases with sodium sulphate added and in others with no added salt. The value of k_{obs} was determined from a least-squares plot of $\ln(A_\infty - A)$ against time. The value of A_∞ was determined experimentally after about 10 half-lives, but for some of the slower reactions ($k < 0.6 \times 10^{-4} \text{ s}^{-1}$) it was calculated by a computer program designed to give the best straight-line plot of $\ln(A_\infty - A)$ against time. When higher concentrations ($> 1 \times 10^{-2}\text{M}$) of isocyanide were used, the absorbance change was measured by using diluted samples. Rate constants obtained by all methods were in excellent agreement with one another. The appropriate wavelength for monitoring each reaction was determined by preliminary repetitive scans of the isocyanide reaction, and of the corresponding formamide hydrolysis reaction under identical conditions. The second-order rate constants (k) were calculated from a linear plot of k_{obs} against hydroxide concentration using the method of least-squares (reactions at 70 °C), or by dividing k_{obs} (a mean of at least three determinations at one hydroxide concentration) by the hydroxide concentration (reactions at 60, 65, and 75 °C). Standard deviations were less than $\pm 5\%$. Activation parameters were determined from plots of $\ln k$ against $1/T$ and quoted errors are standard deviations.

Reaction rates for the pseudo-first-order alkaline hydrolysis of the formamides (4) were measured by monitoring the absorbance change in the u.v. spectrum of (4) with time at a suitable wavelength. Rate constants were calculated as already described.

Product Analysis.—In kinetic runs the products were identified by a comparison of the spectra obtained after about 10 half-lives with those of reference compounds. For larger-scale reactions, products and intermediates were identified by t.l.c. analysis after extraction with dichloromethane or chloroform. In the case of *m*-nitrophenyl isocyanide (3f) a portion of the preparative-scale reaction mixture was subjected to work-up after 3 min to yield, in addition to the aniline (5f) and unchanged isocyanide (3f), a small amount of *N*-(*m*-nitrophenyl)formamide (4f), which was isolated by preparative t.l.c. When this reaction was allowed to go to completion (55 min), work-up yielded *m*-nitroaniline (5f) in 97% yield.

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Received 28th May 1987; Paper 7/941