Elimination–Addition Mechanism for the Hydrolysis of Carbamates. Trapping of an Isocyanate Intermediate by an *o*-Amino-group

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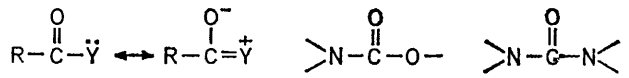
The hydrolytic conversion of aryl carbamates to amines is base catalysed and evidence is presented that the process involves an *E*1cB elimination with the formation of isocyanate intermediates. Substituents in the leaving group (*O*-aryl ring) have a larger effect (ρ = +3·17) on the observed rate of hydrolysis than those in the *N*-aryl ring (ρ = +0·64) where the effects of a substituent are compensatory. Using *N*-(*p*-nitrophenyl)carbamates, it was possible to measure both the acidity of the carbamate (K_{a_1}) and the rate of reaction of the carbamate anion (k_2); k_2 was sensitive to substituent effects (ρ = +2·90) for aryl carbamates indicating a high degree of acyl–oxygen bond cleavage in the transition state. A change in mechanism from *E*1cB to $B_{AC}2$ attack by hydroxide ion was noted for poorer leaving groups. The pH profile for the conversion of *p*-nitrophenyl *N*-(*o*-aminophenyl)carbamates to *o*-phenyleneurea was interpreted to show that the *o*-amino-group traps an isocyanate intermediate after the rate-determining *E*1cB elimination. Substituent effects for *NN*-disubstituted carbamates which hydrolyse *via* a $B_{AC}2$ mechanism are also discussed.

THE reactivity of the acyl function (1) is enhanced when the group Y is capable of electron withdrawal and may be markedly reduced when Y can donate electrons by resonance (2). When two electron-donating groups are



(1) (2) (3) (4)

present, as in the carbamates (3) or ureas (4) it is to be expected that nucleophilic attack on these systems would be very slow, reflecting the additive effect of both groups. This in general appears to be true since several reports are available on the slow alkaline hydrolysis of ureas [1] and alkyl carbamates.[2]

However several biologically related reactions, for example, the conversion of citrulline to arginosuccinate catalysed by arginosuccinate synthetase in the urea cycle [3] and the reactions of carbamoyl phosphate [4] involve apparent nucleophilic attack by nitrogen or oxygen centres on these unreactive systems. We present evidence in this report that an alternative mode of reaction for carbamates, elimination–addition, may be dominant under certain conditions and that in one instance at least, apparent nucleophilic attack by an amino-group on the carbamates may actually involve trapping by the nucleophile of a reactive isocyanate intermediate.[5]

[1] K. R. Lynn, *J. Phys. Chem.*, 1965, **69**, 687.
[2] P. Adams and F. A. Baron, *Chem. Rev.*, 1965, **65**, 567.
[3] O. Rochovansky and S. Ratner, *J. Biol. Chem.*, 1961, **236**, 2254.
[4] P. Reichard, *Acta Chem. Scand.*, 1957, **11**, 523.
[5] Preliminary communication, A. F. Hegarty and L. N Frost, *J.C.S. Chem. Comm.*, 1972, 500.

RESULTS AND DISCUSSION

The rates of hydrolysis of phenyl *N*-phenylcarbamate (5; $Ar^1 = Ar^2 = Ph$) have been investigated in water ($\mu = 1{\cdot}0$, KCl) at 25° (Table 1). The observed pseudo-first-order rate constants are proportional to the hydroxide ion concentration (even at high pH), as shown by the linearity of a plot of log k_{obs} *vs.* pH (Figure 1). Two possible mechanisms of hydrolysis, which are consistent with this kinetic behaviour are outlined in Scheme 1.

TABLE 1

Observed pseudo-first-order rate constants for the hydrolysis of phenyl *N*-phenylcarbamate (5; $Ar^1 = Ar^2 = Ph$) at 25° in water ($\mu = 1{\cdot}0$, KCl)

pH	$10^3 k_{obs}/s^{-1}$
10·02	4·0
10·42	9·3
10·98	44
11·32	115
11·55	160
12·40	1040
12·70	1700
13·40	7700
13·70	12,000

Path A involves direct hydroxide ion attack at the acyl function of the carbamate (5), leading to displacement of phenoxide ion (with or without the formation of a tetrahedral intermediate). In path B the conjugate base of (5), *i.e.* (8), is the reactive species. In this case the rate-determining step is elimination of phenoxide ion from the anion (k_2) to give the isocyanate intermediate (9). The latter then reacts rapidly either with water or at pH >8 with hydroxide ion [6] to yield the carbamate (6).

The unsubstituted carbamate (6) is thus an intermediate on both pathways. The further decarboxylation of carbamates such as (6; $Ar^2 = Ph$) to anilines (7) has been studied in detail;[7,8] the reaction is acid catalysed, even at high pH. Thus at pH >10 the carbamate (6; $Ar^1 = Ph$) is relatively long lived and can be detected spectrophotometrically. We have also measured the rates of further hydrolysis of the carbamate (6), formed from (5) at pH *ca.* 10—11 and the values obtained agree with those reported.[8] The carbamates (6) were shown to be intermediates in the hydrolysis of most of the aryl carbamates (5) which we have studied. However since the two reactions [(5) ⟶ (6) and (6) ⟶ (7)] have an opposite dependency on pH, the rates of the two reactions are comparable only over a very narrow pH range. In general therefore, the hydrolyses of (5) were characterised by tight isosbestic points, the products being substituted amines (7) at low pH, or the carbamates (6) at high pH. Where the two rates were comparable, it was possible to follow the first reaction [disappearance of substrate (5)] at an isosbestic point for the second reaction.

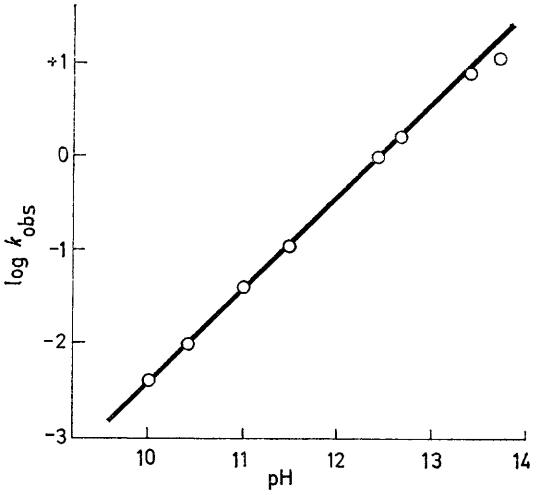


FIGURE 1 Plot of the log of the observed rate constants *vs.* pH for the hydrolysis of phenyl *N*-phenylcarbamate (5; $Ar^1 = Ar^2 = Ph$) in water at 25° ($\mu = 1{\cdot}0$, KCl)

From Scheme 1 equations (1) and (2) may be derived for paths A and B respectively. These two equations

$$k_{obs} = k_1 K_w/(K_{a_1} + a_H) \quad (1)$$

$$k_{obs} = k_2 K_{a_1}/(K_{a_1} + a_H) \quad (2)$$

are kinetically equivalent at all pH values and cannot be used to distinguish the two pathways.[9] When $a_H \gg K_{a_1}$, then in both cases k_{obs} is proportional to $1/a_H$ which is consistent with the observed kinetic behaviour of (5; $Ar^1 = Ar^2 = Ph$) (see Figure 1).

Several criteria have been used to distinguish between the two mechanistic pathways and to define the structural features of the carbamate which determine its mode of reaction. Broadly these methods involve (a) measurement of the response of the hydrolytic reaction to substituent effects in Ar^1 and in the leaving group Ar^2O^-; (b) identification of the presence or absence of the isocyanate (9) on the reaction pathway; and (c) blocking anion formation by *NN*-disubstitution.

Substituent Effects in Ar^1 *and* Ar^2.—The rates of hydrolysis of two series of carbamates 10 and 11 in which the *meta*- and *para*-substituents in the *N*- and *O*-aryl rings were varied are summarised in Tables 2 and 3.

SCHEME 1

[6] A. F. Hegarty, C. N. Hegarty, and F. L. Scott, unpublished results.

[7] S. L. Johnson and D. L. Morrison, *J. Amer. Chem. Soc.*, 1972, **94**, 1323.

[8] M. Caplow, *J. Amer. Chem. Soc.*, 1968, **90**, 6795.

[9] B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1968, **90**, 7136; 1969, **91**, 2993.

Since all of the carbamates, especially those with *m*- and *p*-nitro-groups, were not soluble in water, these measurements were carried out in 4 : 1 (v/v) water–dioxan at 25°,

TABLE 2

Summary of composite rate constants observed for the hydrolysis of phenyl *N*-(substituted phenyl)carbamates (10) in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl)

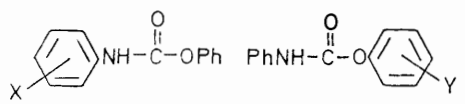
Substituent X	$10^3 k_2 K_{a_1}/s^{-1}$
H	1·78
p-Me	1·45
p-NO_2	5·75
p-Cl	3·00
p-Br	2·75

TABLE 3

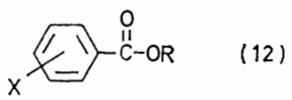
Summary of composite rate constants for the hydrolysis of substituted phenyl *N*-phenylcarbamates (11) in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl)

Substituent Y	$10^{13}\ k_2 K_{a_1}/s^{-1}$
p-Me	0·40
H	1·78
p-NO_2	39,000
p-Cl	12
m-Cl	26
m-Br	20

the ionic strength being maintained constant at 1·0M by the addition of potassium chloride. In each case the log of the observed pseudo-first-order rate constant for hydrolysis increased linearly with pH and the values quoted in Tables 2 and 3 are given as $k_2K_{a_1}$ (= k_1K_w). The individual observed rate constants were measured usually at four pH values over a pH range of at least one (and more usually two) pH units.



(10) (11)



(12)

From the summarised $k_2K_{a_1}$ values it is clear that electron-withdrawing substituents in both the *N*- and *O*-aryl rings enhance the reactivity of the carbamates, those in the leaving group having a markedly greater effect. A plot of log $k_2K_{a_1}$ (or log k_1K_w) *vs.* σ values [10] for the substituents X in (10) gave a ρ value of +0·64 (r 0·990) while the substituents Y in (11) gave ρ = +3·17 (r 0·989) (see Figure 2).

The relatively small substituent effect observed for the *N*-aryl ring could be consistent with either mechanistic pathway in Scheme 1. Thus Kirsch and his coworkers [11] have reported that the ρ value for hydroxide ion catalysed hydrolysis of the benzoates (12; R = Ph) is +2·02 (in 2 : 1 water–acetonitrile at 25°), similar to the value reported earlier (ρ = +1·93) for methyl benzoates (12; R = Me) in 2 : 1 water–dioxan.[12] Interpolation of an –NH– group between the acyl and aryl groups would

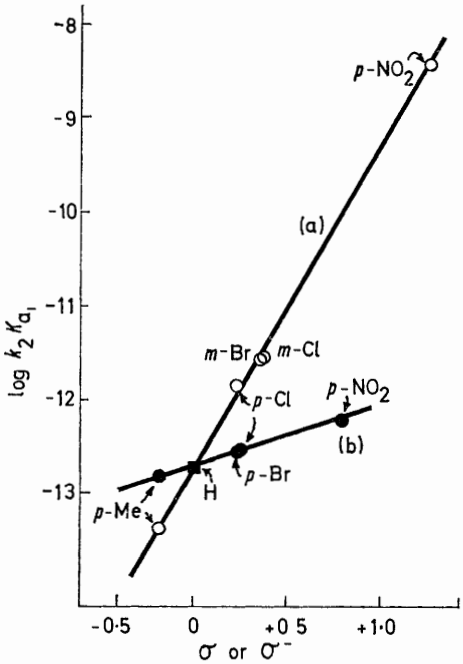


FIGURE 2 Hammett plots of log $k_2K_{a_1}$ for hydrolysis of (a) substituted phenyl *N*-phenylcarbamates (11) (open circles) and (b) phenyl *N*-(substituted phenyl)carbamates (10) (filled circles) in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl). The point for phenyl *N*-phenylcarbamate (■) is common to both correlations

be expected to reduce the sensitivity of the reaction to aryl group variation by up to 2·2-fold.[13] Thus direct hydroxide ion attack on (10) should yield a ρ value $\leqslant$ +1·0 (compared with the value of +0·64 observed).

In terms of the alternative mechanism (path B, Scheme 1) the values in Table 1 are composite. Electron withdrawal in the *N*-aryl ring would be expected to change K_{a_1} and k_2 in opposite directions: the acid strength of the carbamate (5) would be increased by stabilization of the anion (8), but the rate of decomposition of the stabilized anion would be decreased. The effect of substituent variation on K_{a_1} should be greater than on k_2 (the aryl ring being closer to the N–H than the acyl–oxygen bond), resulting in a small positive ρ value (as observed).

The large substituent effect [ρ = +3·17 for (11)] observed for the variation of the leaving group is less equivocal and undoubtedly favours the elimination (*E*1cB) pathway (path B, Scheme 1). A similar large value was also reported recently by Williams [14] (ρ = 2·86 in water at 25°), who also favoured an *E*1cB-type

[10] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.
[11] J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127.
[12] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4189.
[13] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1962, p. 98.
[14] A. Williams, *J.C.S. Perkin II*, 1972, 808.

mechanism, and may be inferred from the more limited data available from earlier studies on related substrates.[15] The $B_{AC}2$ mechanism (path A) would involve little acyl–oxygen bond cleavage in the transition state as judged from the low ρ values (*e.g.* ρ = +1·1 for aryl acetates [11,16]) obtained for substituent variation in the leaving group for hydroxide ion attack in the related aryl esters. On the other hand, it has been well established that the *E*1cB pathway is very sensitive to the nature of the leaving group, since the transition state is reached with almost complete acyl–oxygen bond cleavage.[17] However the constants quoted in Table 3 are again composite; but in this case an electron-withdrawing substituent will tend to increase both K_{a_1} and k_2 by providing a higher concentration of the anion *and* a better leaving group. Because of the remoteness of the substituent Y in (11) from the N–H group, it is expected (and this is confirmed below) that the ρ value for k_2 would not be a great deal less than +3·17. The clear necessity of using a σ^- value [18] (of +1·27) to correlate the data for Y = *p*-NO_2 adds further support to this; it is difficult to visualise how the *p*-NO_2 group could provide appreciable resonance stabilization of the anion of (11). The fact that there is a large degree of resonance interaction by the *p*-NO_2 group indicates, as has been pointed out,[14] considerable acyl–oxygen bond cleavage in the transition state in accord with the *E*1cB pathway. In the alternative $B_{AC}2$ mechanism of hydrolysis of *p*-nitrophenyl acetates and benzoates, the σ value used to correlate the data for the *p*-NO_2 substituent is close to the ' ordinary ' value of +0·778, *e.g.* +1·0,[19] +0·89,[11] and the degree of resonance as measured by the Yukawa–Tsuno *r* value is close to zero (*e.g.* $r \simeq 0{\cdot}2$ [20]).

As shown in Figure 1, the rate of hydrolysis of (5; $Ar^1 = Ar^2 = Ph$) is inversely proportional to hydrogen ion concentration, even up to 0·1M-hydroxide ion. Thus it is not possible to calculate individual k_2 and K_{a_1} values for this compound. However at the highest [HO^-] used (0·5M), it was apparent that the observed rate fell below that predicted by equation (2), assuming that $a_H \gg K_{a_1}$ (see Figure 1). This suggested that the pK_{a_1} value of (5; $Ar^1 = Ar^2 = Ph$) might be in the region 14—16. We have now found that by use of *N*-(*p*-nitrophenyl)carbamates (13) it is possible to bring the K_{a_1} values within measurable range. The presence of the nitro-group had the added advantage that stabilization of the anion (14) was such that the k_2 values (Scheme 1) were also reduced to a level where they could be estimated using conventional (stopped-flow) technique.

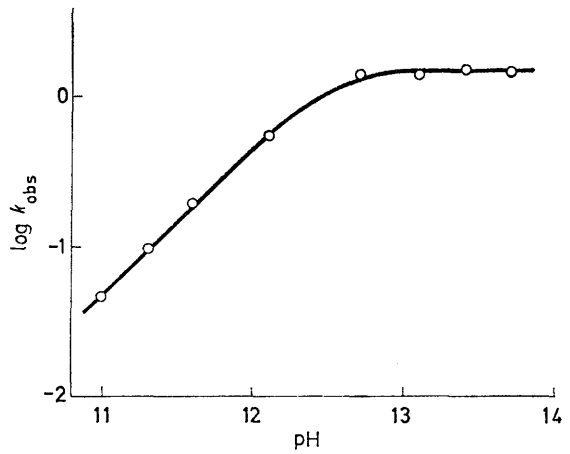
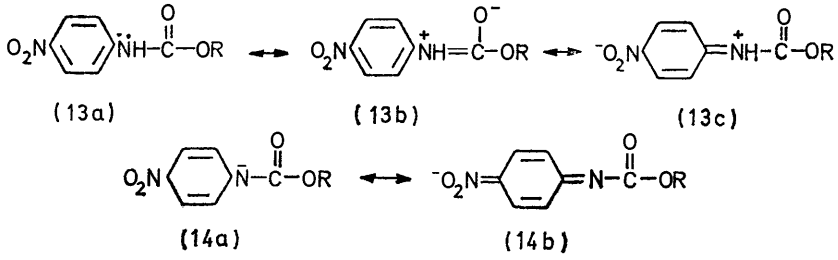


FIGURE 3 Plot of log k_{obs} *vs.* pH for the hydrolysis of phenyl *N*-(*p*-nitrophenyl)carbamate in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl). The points are experimental and the line is theoretical using equation (2) with k_2 = 1·54 s^{-1}, pK_a = 12·5



The data for the OPh compound (13; R = Ph) are presented in Figure 3; it is clear that in this case there is a high pH independent plateau as predicted by equation (2) [and (1)]. The line drawn in Figure 3 is theoretical, giving the best fit of the experimental data with k_2 = 1·54 s^{-1} and pK_{a_1} = 12·5 [using equation (2)].

Several other more reactive aryl and less reactive alkyl *N*-(*p*-nitrophenyl)carbamates (13) were also examined over a wide pH range in order to determine k_2 and K_{a_1} values. Table 4 summarises the data obtained. In each case a pH profile akin to that of Figure 3 was obtained and the values quoted in Table 4 are those which best fit the experimental data, using equation (2). In the case of the less reactive carbamates (13; R = Me, CH_2CH_2OMe, and CH_2CF_3) it was also possible to determine the pK_{a_1} of the carbamate by an independent spectrophotometric method. Since these substrates

[15] L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 1963, **52**, 852; I. Christenson, *Acta Chem. Scand.*, 1964, **18**, 904.
[16] T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, 1960, **82**, 3067.
[17] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.
[18] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.
[19] T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1964, **86**, 418.
[20] Z. S. Chaw, A. Fischer, and D. A. R. Harper, *J. Chem. Soc.* (*B*), 1971, 1819; A. A. Humffray and J. J. Ryan, *ibid.*, 1967, 468.

were hydrolysed (although slowly) at high pH, a sampling technique was used to determine the optical density at zero time.

As required by the mechanism in Scheme 1, where the

TABLE 4

Summary of calculated k_2 and K_{a_1} values for hydrolysis of aryl and alkyl *N*-(*p*-nitrophenyl)carbamates (13) in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl)

Carbamate (13) R	k_2/s^{-1}	pK_{a_1}	pK_a of HOR
Ph	1·54	12·5	9·95 [a]
p-ClC_6H_4	8·30	12·3	9·38 [a]
m-BrC_6H_4	28·2	12·0	9·11 [a]
m-$NO_2C_6H_4$	177	11·7	8·35 [a]
CF_3CH_2	0·00056	11·9	12·37 [b]
$MeOCH_2CH_2$	0·00013	13·0	14·82 [b]
Me	0·00015	13·0	15·09 [b]

[a] M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, 1959, **81**, 4226. [b] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1959, **81**, 1050; 1960, **82**, 795. [c] J. Murto, *Acta Chem. Scand.*, 1964, **18**, 1043.

K_{a_1} values could be measured spectrophotometrically, these correspond to the values required to fit the observed kinetics [using equation (1) or (2)].

A Hammett plot of the observed plateau rates, k_2, for the anions [(14; R = YC_6H_4) (Y = H, *p*-Cl, *m*-Br, and *m*-NO_2)] gave a ρ value of +2·90 (r 0·997). The *p*-nitro-substituted compound (14; R = *p*-$NO_2C_6H_4$)

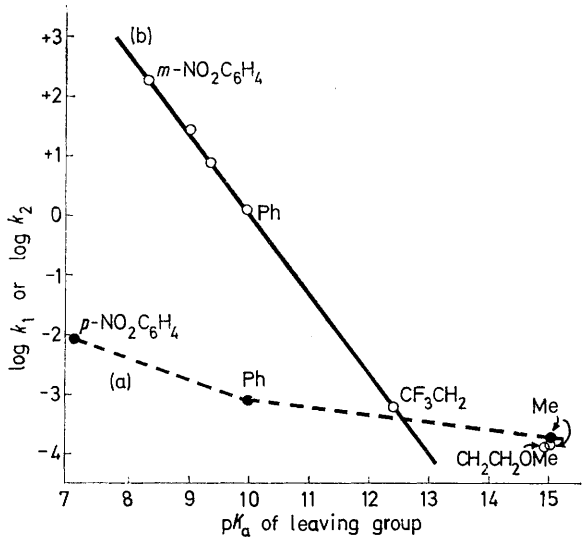
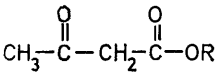


FIGURE 4 Plot of (a) the log of the ' plateau rates ' (k_2) for the hydrolysis of aryl and alkyl *N*-(*p*-nitrophenyl)carbamates (see Table 4) *vs.* pK_a of the conjugate acid of leaving group (open circles, solid line); also included is (b) a plot of log of second-order rate constants for hydroxide catalysed hydrolysis of the *N*-methyl analogues (24; Ar^1 = *p*-$NO_2C_6H_4$; R^2 = Me) *vs.* pK_a of the conjugate acid of the leaving group (closed circles, broken line)

reacted too rapidly at high pH to permit measurement. It thus appears that k_2 for these carbamates is very sensitive to the nature of the leaving group (much more so than is K_{a_1}) so that the transition state is reached with considerable acyl–oxygen bond cleavage, as expected for the *E*1cB pathway.

There is however a possible change-over in mechanism from *E*1cB as the leaving ability of $^-$OR in (13) is decreased. This is best seen in terms of a plot of the plateau rate k_2 *vs.* the pK_a of the conjugate acid of the leaving group (Figure 4). It is clearly seen that only substrates with good leaving groups (OR = *m*-nitro-, *m*-bromo-, *p*-chloro-phenoxy, phenoxy, and possibly trifluoroethoxy) show this high sensitivity to leaving group variation. In this case the plot of log k_2 *vs.* pK_a of HOR has a slope of −1·34 (solid line) close to the value previously reported,[17] −1·29, for *E*1cB mediated hydrolysis of the acetoacetate esters (15). The apparent



(15)

k_2 values for the carbamates with leaving groups poorer than trifluoroethoxy lie well above the solid line in Figure 4. The most likely explanation for this deviation from the linear free energy plot in Figure 4 is that a change-over in mechanism occurs from *E*1cB to $B_{AC}2$ (direct hydroxide ion attack, path A, Scheme 1) as the leaving ability is reduced. The existence of the change-over arises as a consequence of the sharp decrease in rate expected for the *E*1cB pathway as the leaving group ability is reduced. A similar change-over in mechanism was noted for the acetoacetate esters (15), the slope of the log k_2 *vs.* pK_a (of HOR) being close to zero when pK_a of HOR $\geqslant$ *ca.* 11. In the case of the carbamates (13) the change-over appears to occur when pK_a of HOR is *ca.* 12·5.

Trapping of Isocyanate Intermediate.—The *o*-aminophenylcarbamate (17; Ar^2 = *p*-$NO_2C_6H_4$) is smoothly converted to *o*-phenyleneurea (21) in aqueous solution at all pH values. The observed rates of cyclization of (17) to (21) in 4 : 1 water–dioxan are given in Table 5.

TABLE 5

Observed pseudo-first-order rate constants for the cyclization of *p*-nitrophenyl *N*-(*o*-aminophenyl)carbamate (17) to *o*-phenyleneurea (21) at 25° in 4 : 1 water–dioxan (μ = 1·0, KCl)

pH	2·7	3·0	3·2	3·6	4·05	4·55	4·8
10^4k_{obs}/s^{-1}	0·45	0·68	1·10	2·25	2·90	4·20	5·60
pH	5·05	5·35	5·86	6·22	6·52	6·93	7·22
10^4k_{obs}/s^{-1}	9·80	13·0	27·1	77·9	134	397	684

Since a good leaving group (*p*-$NO_2C_6H_4O^-$) is involved in these reactions, a *E*1cB type mechanism should be favoured; analysis of the data provdes good evidence of the existence of a reactive isocyanate intermediate on the reaction pathway.

The cyclization is base catalysed at low and at high pH, with a small region *ca.* pH 4—5 where the observed rate

is almost independent of pH (Figure 5). Several possible mechanisms can be envisaged for the cyclization; the most likely are summarised in Scheme 2. The favoured mechanism of cyclization involves rate-determining

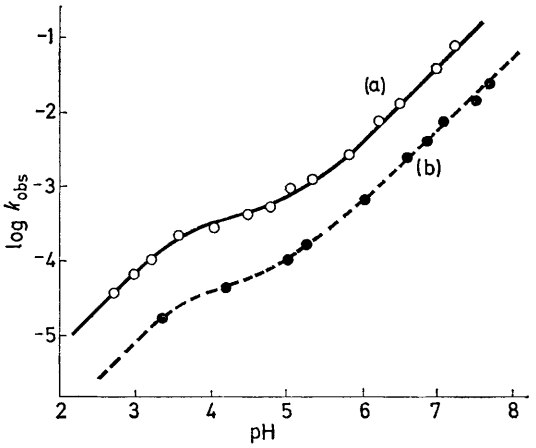


FIGURE 5 Observed rate constants and theoretical curves for (a) cyclization of *p*-nitrophenyl *N*-(*o*-aminophenyl)carbamate (17) to *o*-phenyleneurea (21) (open points, solid line) and (b) hydrolysis of *p*-nitrophenyl *N*-(*p*-aminophenyl)carbamate (5; $Ar^1 = p\text{-}NH_2C_6H_4$, $Ar^2 = p\text{-}NO_2C_6H_4$) (closed circles, broken line) in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl). The curves were drawn using equation (3) with the following values for the constants: (a) $k_2K_{a_1} = 4 \times 10^{-9}$; $k_2'K_{a_1}' = 6{\cdot}3 \times 10^{-8}$; $pK_{a_2} = 3{\cdot}87$; (b) $k_2K_{a_1} = 5{\cdot}7 \times 10^{-10}$; $k_2'K_{a_1}' = 9 \times 10^{-9}$; $pK_{a_2} = 3{\cdot}92$

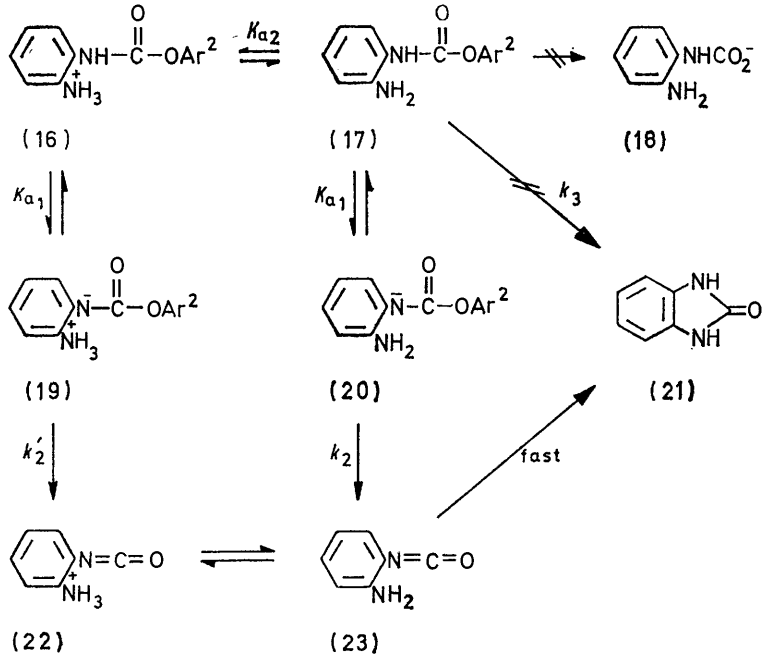
isocyanate (23) which rapidly cyclises to *o*-phenyleneurea (21). Using this mechanism expression (3) is obtained for the variation in the observed rate with pH (assuming that $a_H \gg K_{a_1}$ or K_{a_1}'). The solid line in

$$k_{obs} = \frac{k_2'K_{a_1}'a_H + k_2K_{a_1}K_{a_2}}{a_H(a_H + K_{a_2})} \qquad (3)$$

Figure 5 has been drawn using this equation with the following values for the constants: $k_2K_{a_1} = 4 \times 10^{-9}$; $k_2'K_{a_1}' = 6{\cdot}3 \times 10^{-8}$; $pK_{a_2} = 3{\cdot}87$.

The pK_{a_2} value of 3·87 is reasonable for the ionization of a substituted anilinium ion.[21] Moreover the ratio between the $k_2'K_{a_1}'$ and $k_2K_{a_1}$ values (15·8) is also consistent with the ρ value of +0·64 quoted above for substituents in this ring and an estimate of the difference in the σ values between the *o*-amino- and protonated *o*-amino-groups.[22]

A possible alternative mechanism involves direct nucleophilic displacement (k_3, Scheme 2) by the free amino-group on the carbamate (17) to form *o*-phenyleneurea (21) directly. Since the protonated form (16) would be unreactive on this basis at low pH ($< pK_{a_2}$) the log of the rate of cyclization would be proportional to pH and would then become independent of pH when $pH > pK_{a_2}$. A combination of such a mechanism together with hydroxide ion catalysed hydrolysis of (17) (either by *E*1cB or possibly $B_{AC}2$ pathways) would be kinetically indistinguishable from the *E*1cB followed by



SCHEME 2

*E*1cB type elimination from both the neutral carbamate (17) (at high pH) and from the protonated carbamate (16) at low pH, in both cases giving the *o*-aminophenyl trapping mechanism outlined above. Several features argue against the nucleophilic mechanism. Thus the *p*-amino-analogue of (17) [(5; $Ar^1 = p\text{-}NH_2C_6H_4$; $Ar^2 = p\text{-}NO_2C_6H_4$)] reacts in an exactly analogous manner to

[21] H. C. Brown *et al.*, in ' Determination of Organic Structures by Physical Methods,' eds. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955.

[22] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

(17; $Ar^2 = p\text{-}NO_2C_6H_4$) (see Figure 5). The observed rate constants at each pH are *ca.* 6-fold slower for the *p*-aminophenylcarbamate, but the profile (Figure 5) is of the same type. The ratio of $k_2K_{a_1}$ values for the protonated and free *p*-aminophenylcarbamates and the pK_{a_2} value calculated are also similar to those obtained for the *o*-aminophenylcarbamate. Since the *p*-amino-group in (5; $Ar^1 = p\text{-}NH_2C_6H_4$, $Ar^2 = p\text{-}NO_2C_6H_4$) is too remote to participate in the expulsion of the leaving group, it is also unlikely that the *o*-amino-group (which behaves similarly) is acting as a nucleophile in the rate-determining step. The $B_{AC}2$ mechanism, involving hydroxide ion displacement of phenoxide ion from (16) or (17) (which corresponds to path A in Scheme 1) can also be eliminated. The initial product formed in this case would be the unsubstituted *o*-aminophenylcarbamate (18). This carbamate (18) would not be expected to cyclise rapidly to give the observed product *o*-phenyleneurea (21), especially in view of the reluctance of (17) (with its better leaving group, *p*-nitrophenoxide ion) to form (21) directly.

If cyclization of (17) to (21) were occurring directly (k_3, Scheme 2) then one might expect a significant rate enhancement relative to the *p*-amino-analogue. However the rate enhancement is only 6-fold in this case and moreover is shown by *all* *N*-(*o*-substituted phenyl)-carbamates which we have examined, including those with non-nucleophilic substituents. This was shown by comparing the rates of hydrolysis of a series of *p*-nitrophenyl *N*-(*o*-substituted phenyl)carbamates (5; $Ar^1 = o\text{-}XC_6H_4$; $Ar^2 = p\text{-}NO_2C_6H_4$) (see Table 6). In each case the k_{obs} values were proportional to $1/a_H$ and the constants quoted in Table 6 are average values of $k_2K_{a_1}$ relative to the value for the unsubstituted material (5; $Ar^1 = Ph$; $Ar^2 = p\text{-}NO_2C_6H_5$). It is clear from these results (Table 6) that the *o*-amino (or protonated *o*-amino-groups) show little extra rate enhancement

TABLE 6

Summary of relative $k_2K_{a_1}$ values for the hydrolysis of *p*-nitrophenyl *N*-(*o*-substituted phenyl)carbamates at 25° in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl)

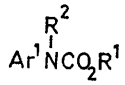
Substituent X	k_{rel}
H	1
o-Br	10
o-CH_3	4
o-NH_2	4
o-OMe	3

(relative to the *p*-substituted analogues) when compared to other *o*-substituted compounds. The nature of the general rate enhancement shown by *o*-substituted substrates has not been probed; however similar (and often much larger) effects have been attributed to the maintenance by the *o*-substituent of the reactive group in a conformation suitable for reaction.[23]

These results taken together imply that *E*1cB elimination from (16) and (17) is rate determining in the conversion of (17) to (21). Since the amino-group in (17) is not involved in the rate-determining step, the exclusive formation of the cyclic product must result from the trapping of an intermediate isocyanate (23) by the *o*-amino-group. The efficient trapping of the isocyanate by the *o*-amino-group is consistent with the well established reactivity of isocyanates towards amines;[24] since the reactive groups are adjacent in (23) the reaction should be especially rapid in this case.

The presence of the isocyanate intermediate could also be demonstrated by intermolecular trapping of the isocyanate by an amine. Thus when the hydrolysis of *p*-nitrophenyl *N*-phenylcarbamate was followed in 4 : 1 water–dioxan at pH 7·5 in the presence and absence of 0·01M-*p*-chloroaniline the observed rate constants were the same ($7·5 \pm 0·1 \times 10^{-2}$ s^{-1}), within experimental error. The absence of significant catalysis is not surprising in view of previous work with phosphate buffers.[25] However in the presence of 0·01M-*p*-chloroaniline 72% of the product obtained was *N*-*p*-chlorophenyl-*N'*-phenylurea. This was determined both by isolation and by spectrophotometric measurement of the reaction mixture. The formation of the urea without a rate enhancement indicates the presence of a reactive intermediate (phenyl isocyanate), formed after the slow step, which reacts preferentially with *p*-chloroaniline. The pH of the solution in this trapping experiment was maintained below 8 to minimize competition for the isocyanate by hydroxide ion (below pH 8 phenyl isocyanate reacts with water[6]); at high pH no urea is formed by trapping.

*Blocking the E*1cB *Pathway by* NN-*Disubstitution.*— When the nitrogen atom of the carbamate is disubstituted *e.g.* (24; R^2 = Me), the *E*1cB pathway for hydrolysis is no longer available, irrespective of the leaving ability



(24)

of R^1O^-. These compounds therefore constitute models for the direct hydroxide ion attack ($B_{AC}2$) mechanism. It has previously been reported that such *NN*-disubstituted carbamates hydrolyse very slowly, even in concentrated base.[15] We have confirmed this and have carried out a limited study on the effect of substituents. In the case of each of the carbamates (24; R^2 = Me) studied, the observed rate of hydrolysis was proportional to $[HO^-]$; where possible, measurements were made over the range 0·1—1·0M-HO^-. The average values of the second-order rate constants (k_1) obtained are summarised in Table 7.

The variation in k_1 when the leaving group (R^1O^-) is changed from methoxide to *p*-nitrophenoxide is *ca.* 37-fold; it can be estimated that a similar change in the

[23] K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, 1972, **94**, 8142.

[24] I. de Aguirre and J. C. Jungers, *Bull. Soc. chim. France*, 1965, 1316; and other papers in this series.

[25] M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975.

pK_a of the conjugate acid of the leaving group of *ca.* 8 units would bring about a rate difference in k_2 (*E*1cB mechanism) of $>10^{10}$-fold. This is clearly shown in Figure 5 where data for k_2 and k_1 values for similarly

TABLE 7

Second-order rate constants (l mol^{-1} s^{-1}) for the hydroxide ion catalysed hydrolysis of the *NN*-disubstituted carbamates, ArN(Me)CO_2R, in 4 : 1 water–dioxan at 25° (μ = 1·0, KCl)

Ar	R	10^4 k_1
p-$NO_2C_6H_4$	Me	2·1 (8·7) [a]
p-$NO_2C_6H_4$	Ph	7·2 (29) [a]
p-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	79 (213) [a]
Ph	Ph	0·17
Ph	*p*-$NO_2C_6H_4$	3·7

[a] In water at 25° (μ = 1·0, KCl).

substituted substrates (24; Ar^1 = *p*-$NO_2C_6H_4$) with R^2 = H and R^2 = Me are plotted together. This also demonstrates the sharp change-over in mechanism from *E*1cB to $B_{AC}2$ for the monosubstituted carbamates (24; R^2 = H) when the leaving ability of R^1O^- is reduced.

The $B_{AC}2$ mechanism is conversely characterised by a larger dependency on the nature of the substituent in the *N*-aryl (Ar^1) ring than that shown in the *E*1cB elimination. This is shown by comparing the change in the observed rate when Ar^1 is varied from Ph to *p*-$NO_2C_6H_4$ in both systems (Tables 2 and 7). This most likely reflects the important role of electron-withdrawing substituents (particularly those, like the *p*-NO_2 group capable of electron withdrawal by resonance) in reducing the electronic density on the carbamate nitrogen atom [see (13c)]. The contribution of structures such as (13b) to the stabilization of the carbamate is consequently reduced, making the substrate more reactive towards nucleophilic attack.

In conclusion, the hydrolysis of carbamates *via* an elimination–addition mechanism can be very rapid, even at neutral pH. This mechanistic pathway depends upon the carbamate (a) having a good leaving group and (b) being *N*-monosubstituted; otherwise slow $B_{AC}2$ hydrolysis by hydroxide ion occurs. In one case it was shown that apparent nucleophilic displacement by an *o*-amino-group at the acyl function of a carbamate involved in fact a prior elimination, with the formation of an isocyanate intermediate. This latter result may not, however, hold in general for all nucleophilic groups since it has recently been shown [26] that the ionized *o*-carboxy-group does act as a nucleophile towards carbamates, including those with good leaving groups.

EXPERIMENTAL

Materials.—All inorganic materials used were AnalaR grade. Dioxan was B.D.H. AnalaR grade, used without further purification. Deionized water was twice distilled from alkaline potassium permanganate.

The solvent used for most of the kinetic experiments, 4 : 1 (v/v) water–dioxan, was prepared at 25°.

[26] L. N. Frost and A. F. Hegarty, *J.C.S. Chem. Comm.*, 1973, 82.

M.p.s were measured using an Electrothermal capilliary apparatus and are uncorrected. I.r. spectra were measured using a Perkin-Elmer model PE257 spectrometer, the solids being examined as KBr discs.

Substrates.—Aryl N-phenylcarbamates. *p*-Chlorophenyl *N*-phenylcarbamate. A solution of *p*-chlorophenol (1·28 g, 0·01 mol) in dry benzene (10 ml) was added to a solution of phenyl isocyanate (1·19 g, 0·01 mol). A catalytic quantity (0·5 ml) of pyridine was added and the solution refluxed for 1 h. On evaporation of the solvent *in vacuo*, the carbamate precipitated (in near quantitative yield) and was recrystallised from chloroform–pentane, m.p. 148—150° (lit.,[14] m.p. 148—150°). The other substituted phenyl *N*-phenylcarbamates were prepared in an analogous manner and recrystallised from chloroform–pentane to constant m.p. (in each case C, H, and N analysis and i.r. spectra were consistent with carbamate structure): substituent 4-Me, m.p. 111—112° (lit.,[14] m.p. 108—110°); H, 125—127° (lit.,[14] 121—124°); 4-NO_2, 150—152° (lit.,[14] 146—149°) 3-Cl, 123—125° (lit.,[14] 125—127°).

Phenyl N-arylcarbamates. Phenyl *N*-(*p*-chlorophenyl)-carbamate. A solution of *p*-chloroaniline (1·25 g, 0·01 mol) in chloroform (10 ml) containing triethylamine (1·0 g, 0·01 mol) was added dropwise to a stirred solution of phenyl chloroformate (1·56 g, 0·01 mol) dissolved in chloroform (10 ml) at room temperature. The triethylamine hydrochloride was filtered off and the solvent evaporated *in vacuo*. The *carbamate* obtained was purified by recrystallisation from chloroform–pentane and had m.p. 148—150° (Found: C, 63·0; H, 4·0; N, 5·9. $C_{13}H_{10}ClNO_2$ requires C, 63·0; H, 4·0; N, 5·7%). The other phenyl *N*-(substituted phenyl)carbamates were similarly prepared from phenyl chloroformate and substituted anilines. They had the following m.p. and analytical data: substituent: 4-Me, m.p. 113—114° (Found: C, 73·8; H, 6·0; N, 6·2. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·9; N, 6·2%); 4-Br, 146—149° (Found: C, 53·7; H, 3·5; N, 4·9. $C_{13}H_{10}BrNO_2$ requires C, 53·4; H, 3·4; N, 4·8%); 4-Cl, 148—150° (Found: C, 63·0; H, 4·0; N, 5·9. $C_{13}H_{10}ClNO_2$ requires C, 63·0; H, 4·0; N, 5·7%); 4-NO_2, 152—154° (Found: C, 60·2; H, 3·8; N, 10·9. $C_{13}H_{10}N_2O_4$ requires C, 60·5; H, 3·9; N, 10·9%).

p-*Nitrophenyl N-(substituted phenyl)carbamates.* These were prepared by the following general method described for *p*-nitrophenyl *N*-(*o*-bromophenyl)carbamate. To a stirred solution of *o*-bromoaniline (3·44 g, 0·02 mol) dissolved in chloroform (20 ml) was added dropwise a solution of *p*-nitrophenyl chloroformate (2·01 g, 0·01 mol) dissolved in chloroform (10 ml). A solid precipitated after a short time; this was filtered off and shown to be *o*-bromoanilinium chloride. The filtrate was evaporated to dryness *in vacuo* and the residue recrystallised several times from chloroform–pentane to give p-*nitrophenyl* N-(o-*bromophenyl*)*carbamate*, m.p. 128—130° (Found: C, 46·5; H, 2·7; N, 8·6. $C_{13}H_9BrN_2O_4$ requires C, 46·3; H, 2·7; N, 8·3%). The other *p*-nitrophenyl *N*-(*o*-substituted phenyl)carbamates had the following m.p. and analytical data: *o*-Me, 151—153° (Found: C, 61·9; H, 4·6; N, 10·5. $C_{14}H_{12}N_2O_4$ requires C, 61·8; H, 4·4; N, 10·3%); *o*-NH_2, 121—123° (decomp.) (Found: C, 57·0; H, 4·2; N, 15·4. $C_{13}H_{11}N_3O_4$ requires C, 57·1; H, 4·0; N, 15·4%); *o*-Me, 131—133° (Found: C, 58·5; H, 4·4; N, 10·0. $C_{14}H_{12}N_2O_5$ requires C, 58·3; H, 4·2; N, 9·7%).

p-Nitrophenyl *N*-(*p*-aminophenyl)carbamate was prepared by the dropwise addition of a solution of *p*-nitro-

phenyl chloroformate (2·01 g, 0·01 mol) in chloroform (10 ml) to a stirred solution of *p*-nitrophenylenediamine (2·1 g, 0·02 mol) in chloroform (20 ml). The monohydrochloride of phenylenediamine which precipitated first was filtered and the carbamate was obtained by evaporation of the solvent to dryness. On purification by recrystallisation from chloroform–pentane the *carbamate* had m.p. *ca.* 180° (decomp.) (Found: C, 56·7; H, 4·1; N, 15·8. $C_{13}H_{11}N_3O_4$ requires C, 57·1; H, 4·0; N, 15·4%).

p-*Nitrophenyl* N-*methyl*-N-*phenylcarbamate*. The carbamate was prepared in chloroform solution by reaction of *p*-nitrophenyl chloroformate with *N*-methylaniline (2 equiv.) at room temperature (see above); recrystallisation (from chloroform–pentane) gave the *carbamate*, m.p. 60—62° (Found: C, 61·9; H, 4·4; N, 10·5. $C_{14}H_{12}N_2O_4$ requires C, 61·8; H, 4·4; N, 10·3%). *Phenyl* N-*methyl*-N-*phenylcarbamate* was similarly prepared, m.p. 57—59° (Found: C, 74·3; H, 6·0; N, 6·3. $C_{14}H_{12}NO_2$ requires C, 74·0; H, 5·7; N, 6·2%).

Alkyl N-(p-*nitrophenyl*)*carbamates*. 2,2,2-Trifluoroethyl *N*-(*p*-nitrophenyl)carbamate. To a stirred solution of 2,2,2-trifluoroethanol (4·4 g, 0·05 mol) in benzene (10 ml) at room temperature was added a solution of *p*-nitrophenyl isocyanate (8·2 g, 0·05 mol) in benzene (10 ml). A catalytic quantity of triethylamine was added (0·5 ml) and the solution was heated to 50° for 10 min. On cooling the *carbamate* precipitated as yellow crystals, m.p. 126—129° (from chloroform–pentane) (Found: C, 40·9; H, 2·65; N, 10·9. $C_9H_7F_3N_2O_4$ requires C, 40·9; H, 2·65; N, 10·6%). The following materials were similarly prepared: *methyl* N-(p-*nitrophenyl*)*carbamate*, m.p. 174—177° (Found: C, 48·9; H, 4·1; N, 14·4. $C_8H_8N_2O_4$ requires C, 49·0; H, 4·1; N, 14·3%); 2-*methoxyethyl* N-(p-*nitrophenyl*)*carbamate*, m.p. 99—101° (Found: C, 50·3; H, 5·0; N, 11·9. $C_{10}H_{12}N_2O_5$ requires C, 50·0; H, 5·0; N, 11·7%).

Methyl N-*methyl*-N-(p-*nitrophenyl*)*carbamate*. To a solution of *N*-methyl-*p*-nitroaniline (3·04 g, 0·02 mol) dissolved in tetrahydrofuran (20 ml) was added methyl chloroformate (0·95 g, 0·01 mol) and pyridine (0·5 ml). The mixture was refluxed (2 h) and the precipitated hydrochloride of *N*-methyl-*p*-nitroaniline filtered off on cooling. The filtrate was evaporated to dryness to give the *carbamate*, m.p. 100—102° (Found: C, 51·9; H, 5·05; N, 13·5. $C_9H_{10}N_2O_4$ requires C, 51·4; H, 4·85; N, 13·3%).

Phenyl N-*methyl*-N-(p-*nitrophenyl*)*carbamate*. *N*-Methyl-*p*-nitroaniline (1·52 g, 0·01 mol) and phenyl chloroformate (1·56 g, 0·01 mol) were dissolved in pyridine (20 ml) and stirred at room temperature for 12 h. The solution was poured onto crushed ice to precipitate the *carbamate*, m.p. 60—62° (from chloroform–pentane) (Found: C, 61·5; H, 4·7; N, 10·4. $C_{14}H_{12}N_2O_4$ requires C, 61·8; H, 4·4; N, 10·3%). p-*Nitrophenyl* N-*methyl*-N-(p-*nitrophenyl*)*carbamate* was similarly prepared and had m.p. 151—152° (Found: C, 52·55; H, 3·5; N, 13·1. $C_{14}H_{11}N_3O_6$ requires C, 53·0; H, 3·5; N, 13·2%).

Aryl N-(p-*nitrophenyl*)*carbamates*. The substituted phenyl *N*-(*p*-nitrophenyl)carbamates were prepared in benzene from equimolar quantities of *p*-nitrophenyl isocyanate and the substituted phenol as described above. The carbamates had the following m.p. and analytical data: substituent: 3-NO_2, m.p. 220—221° (Found: C, 51·9; H, 3·1; N, 14·4. $C_{13}H_9N_3O_6$ requires C, 51·5; H, 3·0; N, 13·9%); 4-NO_2, 193—196° (Found: C, 51·6; H, 3·2; N, 14·2. $C_{13}H_9N_3O_6$ requires C, 51·5; H, 3·0; N, 13·9%); 4-Cl, 199—201° (Found: C, 53·6; H, 3·0; N, 9·4. $C_{13}H_9ClN_2O_4$ requires C, 53·3; H, 3·1; N, 9·6%); 3-Br, 325—329° (decomp.) (Found: C, 46·6; H, 3·1; N, 8·2. $C_{13}H_9BrN_2O_4$ requires C, 46·3; H, 2·7; N, 8·3%).

Kinetic Method.—The kinetics of hydrolysis of alkyl and aryl *N*-arylcarbamates were studied in water or in 1 : 4 dioxan–water by following the change in optical density of the substrates at suitable wavelengths. Initial repetitive scans of the u.v. region established that these reactions held (except where otherwise specified) tight isosbestic points, indicating the absence of intermediates; normally for convenience the wavelength corresponding to the isosbestic point for the substituted phenol/phenolate released was used.

Those reactions which were buffered by the presence of hydroxide ion or by 10^{-2}M-phosphate or -borate buffers were followed using Unicam model SP 800 or SP 1800 spectrometers. Both instruments were equipped with thermostatted multiple cell compartments and external Unicam AR25 recorders. The substrate was made up as a concentrated solution (usually 10^{-2}M) in dioxan and reaction was initiated by addition of a drop of this substrate solution to the cell containing the equilibrated reaction solution. To ensure that pH drift was absent during a kinetic experiment, the pH of the solution was checked before and after reaction using a Radiometer model PHM 26 pH meter equipped with a Metrohm EA 125U electrode, which had been standardised using Radiometer aqueous buffer solutions. The pH values quoted for 4 : 1 water–dioxan solution are the measured values without further correction obtained using this technique.

For those reactions studied below pH 11 in the absence of added buffer, pH was maintained constant using a pH-stat assembly mounted in a Cary 14 u.v. spectrometer. A thermostatted cell (36 ml) (which was made of Pyrex glass with quartz windows) was mounted in the cell compartment of the spectrometer and the contents were stirred magnetically. Into the cell (but above the light beam) dipped a Metrohm EA 125U combined pH electrode, which both recorded the pH of the solution and controlled the addition of acid/base, and also a capillary Teflon tube (through which the acid/base was added). The Radiometer pH-stat assembly used consisted of a pH meter (type PHM 26), titrator (type TTT 11b) and an autoburette (type ABU 1C). The pH of the solution was maintained at a constant value by the addition of acid or base controlled by the titrator and the course of the reaction was followed (as above) by recording the change in optical density of the reaction solution at suitable wavelengths.

For the more rapid reactions ($t_{\frac{1}{2}} < 10$ s) a Durrum–Gibson model D-110 stopped-flow spectrometer, equipped with Kel-F components, was used. The apparatus had a log converter and the resultant absorbance *vs.* time plots were recorded on a Philips model storage oscilliscope. The absorbance *vs.* time plots were analysed in all cases to give the pseudo-first-order rate constants either (a) graphically, either by the method of Guggenheim, or more usually, using the experimental infinity value, or (b) using a weighted least squares programme written for the Olivetti–Underwood Programma 101. Good pseudo-first-order plots were obtained in all cases to $\geqslant$95% of reaction.

pK_a *Determinations*.—The dissociation constants of the less reactive alkyl *N*-(*p*-nitrophenyl)carbamates were determined at 25° in water (μ = 1·0, KCl) using the cell and pH-stat assembly already described. A known quantity of the carbamate was added to the reaction cell at high pH. Aliquot portions of 4N-hydrochloric acid were added and

the change in optical density was recorded at each 0·5 pH interval (0·1 pH interval near the pK_a). Since the total volume of base did not exceed 1% of cell volume, dilution corrections were not necessary. Since each determination was carried out over a short period, hydrolysis of the substrate was not appreciable. Theoretical titration curves were plotted from equation (4) and the plot of O.D. *vs.* pH was compared with the theoretical curves to give the pK_a.

$$\text{O.D.}_{obs} = \text{O.D.}_{max.} K_a/(a_H + K_a) \quad (4)$$

Trapping Experiments.—To an aqueous solution of potassium chloride (37·28 g dissolved in 400 ml at 25°) was added *p*-chloroaniline (0·6375 g) in dioxan (90 ml). The pH of the solution was adjusted to 7·5 and a solution of *p*-nitrophenyl *N*-phenylcarbamate (0·1299 g) dissolved in dioxan (10 ml) was added. The resulting 4 : 1 water–dioxan solution (μ = 1·0, KCl) contained a 0·01 mol *p*-chloroaniline and 0·001 mol *p*-nitrophenyl *N*-phenylcarbamate. The solution was stirred at room temperature for 30 min and the solid which precipitated (75 mg) was filtered off and identified as *N*-phenyl-*N'*-(*p*-chlorophenyl)urea by comparison with an authentic sample (i.r. spectrum, m.p. and mixed m.p. 140—143°). The aqueous filtrate was extracted with ether (3 × 70 ml). The extracts were first extracted with 3 × 50 ml portions of 20% sodium carbonate (to remove *p*-nitrophenol). Secondly the ether was extracted with 3 × 50 ml portions of 2N-hydrochloric acid. The ether was then dried (Na_2SO_4) and evaporated to give a further quantity of *N*-phenyl-*N'*-(*p*-chlorophenyl)urea (8·3 mg). The total recovery of urea represents 72% of the theoretical quantity if all the carbamate was converted to urea. In a control experiment using authentic *N*-phenyl-*N'*-(*p*-chlorophenyl)urea, the extraction procedure was shown to be essentially 100% efficient.

[3/561 *Received*, 16*th March*, 1973]