Alkaline Hydrolysis of Substituted Phenyl *N*-Phenylcarbamates. Structure–Reactivity Relationships consistent with an *E*1cB Mechanism

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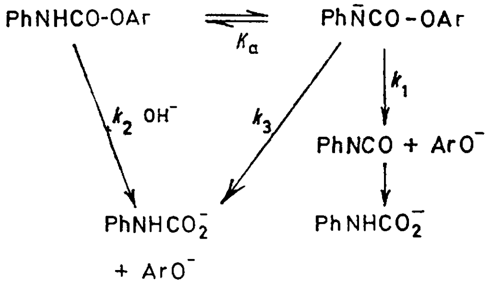
The rates of hydrolysis of substituted phenyl esters of *N*-phenylcarbamic acid have been measured over an alkaline pH-range at 25 °C, 0·1M ionic strength. The rate constant for unsubstituted phenyl ester was proportional to hydroxide ion concentration up to pH 12. The bimolecular rate constant for alkaline hydrolysis of the esters had a Hammett sensitivity of 2·86 and σ^- values were needed to fit the 4-nitro-, 4-cyano-, 4-acetyl, and 4-formyl substituents indicating resonance interaction with the transition state of the rate-determining step. The results are interpreted according to an *E*1cB mechanism for hydrolysis involving phenyl isocyanate intermediate. Bimolecular attack of hydroxide ion on neutral ester, bimolecular attack of water on anionic ester, and attack of hydroxide on the nitrogen proton concerted with departure of phenolate anion are excluded as possible mechanisms.

ESTERS with protons on atoms adjacent to the carbonyl function can hydrolyse in alkali by an *E*lcB mechanism as well as *via* the normal $B_{Ac}2$ pathway involving a tetrahedral intermediate.[1-3] Carbamates can hydrolyse *via* an isocyanate intermediate (Scheme). The existence of a sigmoid pH-dependence corresponding to an ionisation is not proof of the *E*lcB mechanism but points to the existence of an ionisation which may or may not be kinetically important. Analysis of the Scheme leads to equation (1). Thus k_1 and k_3 can be



SCHEME

$$\text{Rate} = [\text{ester}](k_2K_w/K_a + k_1 + k_3)/(1 + a_H/K_a)$$
$$= [\text{ester}]k'/(1 + a_H/K_a) \qquad (1)$$

negligible and the pH-dependence still involve an ionisation term.

Solvent deuterium oxide solvent isotope effects can be used as evidence for the *E*lcB mechanism; Tobias and Kézdy[2] suggested that k' had an isotope effect of 1·0 for *E*lcB and *ca.* 1·54 for $B_{Ac}2$. This method is not suitable for those esters where pK_a is greater than can be reached in water nor is it convenient when the rate constant in the pH region corresponding to ionisation is too high to measure by conventional methods. Pratt and Bruice[3] however have recently measured the isotope effect for known *E*lcB reactions and found it not unambiguously diagnostic. Bender and Homer[1a] utilised the inverse deuterium oxide solvent isotope effect as evidence for *E*lcB in the alkaline hydrolysis of 4-nitrophenyl *N*-methylcarbamate ($k_{OD}/k_{OH} = 1·8$). This figure has ambiguous interpretation as hydroxide is less nucleophilic (in H_2O) than deuterioxide (in D_2O)[4] and could arise from the $B_{Ac}2$ mechanism (k_2).

Trapping experiments are possible when the intermediate is common to a series and have been applied to the alkaline hydrolysis of aryl acetoacetates.[3] Gerrard and Hamer[5] used a stereochemical approach to the problem of phosphoramidate hydrolysis but this is not applicable generally as carboxyl esters are planar.

Hydrolysis of activated esters of carboxylic acids usually involves considerable buffer catalysis especially by imidazole which can act as a nucleophile. Bender and Homer[1a] observed that 4-nitrophenyl *N*-methylcarbamate hydrolyses with very little specific buffer catalysis by imidazole buffers whereas 4-nitrophenyl acetate hydrolysis ($B_{Ac}2$) in such buffers proceeds completely *via* *N*-acetylimidazole. Buffer catalysis would not be expected in the *E*lcB mechanism although it could act in the k_3 reaction involving attack of water on the anion.

Arrhenius parameters can be used to distinguish *E*lcB from $B_{Ac}2$ mechanisms[1a] where the former should show a considerably more positive entropy of activation than the latter.[6] The possibility of S_N2 attack of water on the anionic ester (k_3) is also recognised and the entropy of activation could be used to distinguish it from the *E*lcB type (k_1).

Alkaline hydrolysis of substituted phenyl esters shows a low sensitivity to leaving group ($\rho = ca.$ 1) and the rate-limiting step is addition of hydroxide to ester. Good Hammett relationships are observed where σ (as opposed to σ^-) is employed in agreement with no

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[1] (*a*) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975; (*b*) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, 1968, **90**, 7136; (*c*) J. Casanova and D. A. Rutolo, *ibid.*, 1969, **91**, 2347; (*d*) I. Christenson, *Acta Chem. Scand.*, 1964, **18**, 904. (*e*) L. W. Dittert, 'The Kinetics and Mechanisms of the Base-catalysed Hydrolysis of Organic Carbamates and Carbonates,' Ph.D. Dissertation, University of Wisconsin, 1961; *Diss. Abs.*, 1961, **22**, 1837; (*f*) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, 1965, **30**, 2910; (*g*) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 2993; (*h*) B. Holmquist and T. C. Bruice, *ibid.*, p. 3003.

[2] P. S. Tobias and F. J. Kézdy, *J. Amer. Chem. Soc.*, 1969, **91** ,5171.

[3] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.

[4] (*a*) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 675; (*b*) F. A. Long, *Proc. New York Acad. Sci.*, 1960, **84**, 596.

[5] A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1967, 1122; 1968, 539; 1969, 369; *Chem. Comm.*, 1966, 475.

[6] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

phenolate ion character in the transition state of the rate-limiting step. Neither k_2 nor k_3 (S_N2) should possess phenolate ion character in their transition states; thus, if alkaline hydrolysis possesses a proportion of *E*1cB character, substituents which mesomerically stabilise the departing oxyanion (4-nitro, 4-acetyl, 4-cyano, and 4-formyl) will deviate from the Hammett σ relationship. The presence of considerable negative charge on the leaving oxygen will give rise to a larger Hammett ρ value than is observed for the $B_{Ac}2$ mechanism.

We present here the results of a study of the alkaline hydrolysis of a series of substituted phenyl *N*-phenylcarbamates which could hydrolyse *via* an *E*1cB mechanism.

EXPERIMENTAL

Materials.—Substituted phenyl *N*-phenylcarbamates were prepared by heating on a water-bath phenyl isocyanate (2·5 g) with the equivalent amount of substituted phenol and pyridine (2·5 ml) as catalyst. The mixture liquefied and after a short time solidified. The products were recrystallised from ethanol and purity and structures were confirmed by m.p. and analysis (Table 1) and by i.r. spectroscopy. Acetonitrile was purified by the method of Lewis and Smyth [7] and buffers were prepared from AnalaR reagents with glass-distilled water.

TABLE 1

Analytical and physical properties of substituted phenyl *N*-phenylcarbamates [a]

			Found (%)				Calc. (%)		
Substituent	M.p. (°C)	Lit. m.p. (°C)	C	H	N	Formula	C	H	N
4-Methoxy	136—137		69·5	5·1	5·8	$C_{14}H_{13}NO_3$	69·2	5·3	5·7
4-Methyl	108—110	115 [b]	74·2	5·8	6·2	$C_{14}H_{13}NO_2$	74·0	5·7	6·1
Unsubst.	121—124	126 [b]	73·2	5·2	6·6	$C_{13}H_{11}NO_2$	73·2	5·4	6·6
4-Chloro	148—150	149 [b]	63·3	4·1	5·7	$C_{13}H_{10}ClNO_2$	63·0	4·0	5·7
3-Ethoxycarbonyl	98—99		67·7	5·5	4·9	$C_{13}H_{15}NO_4$	67·4	5·3	4·9
3-Formyl	168—170	159 [b]	69·9	4·8	5·7	$C_{14}H_{11}NO_3$	69·6	4·6	5·8
3-Chloro	125—127		63·1	4·0	5·7	$C_{13}H_{10}ClNO_2$	63·0	4·0	5·7
3-Nitro	132—135	129 [b]	60·3	4·0	10·7	$C_{13}H_{10}N_2O_4$	60·5	3·9	10·9
4-Cyano	153—155		70·9	4·4	12·0	$C_{14}H_{10}N_2O_2$	70·6	4·2	11·8
4-Acetyl	152—155		70·9	5·3	5·5	$C_{15}H_{13}NO_3$	70·6	5·1	5·5
4-Formyl	135—138	136 [b]	69·6	4·7	5·7	$C_{14}H_{11}NO_3$	69·6	4·6	5·8
4-Nitro	146—149	148 [b]	60·7	4·0	10·8	$C_{13}H_{10}N_2O_4$	60·5	3·9	10·9

[a] Analyses by Mr. G. Powell of this laboratory using a Hewlett–Packard–185 CHN analyser. M.p.s measured using a Kofler Thermospan instrument. [b] ' Organic Reagents for Organic Analysis,' Hopkin and Williams, London, 1949, pp. 155—160.

Methods.—The hydrolysis of the esters was initially followed at constant pH by repetitively scanning the u.v. spectrum during reaction with a Unicam SP 800 spectrophotometer equipped with a repetitive scanning attachment (SP 825). Kinetic observations were made at constant wavelength with a Beckman DBG or Unicam SP 600UV machine both equipped with a Smith's Industries Servoscribe recorder. In a typical measurement the ester (in acetonitrile solvent, 0·05 ml) was added on the tip of a glass rod to buffer (2·45 ml, 0·1M ionic strength final concentration) in a silica cell in the thermostatted cell compartment (25 °C) of the spectrophotometer and the change of optical density with time recorded. Pseudo-first-order rate constants were calculated by use of the infinity-time method. Occasionally the rate constants were checked *via* the Guggenheim method; [8] both methods gave identical results. Oxygen-18 was incorporated during base-catalysed hydrolysis of 4-nitrophenylcarbamate by dissolving sodium metal in enriched water. The ester (1 g) in dioxan (purified by passing AnalaR material through an alumina column to purge from peroxides) was added in small portions to a 1 : 1 (v/v) solution of the enriched water–dioxan and kept at room temperature overnight. The solution was acidified and extracted with chloroform and the chloroform layer dried and evaporated. The 4-nitrophenol product was recrystallised from benzene; the experiment was repeated with 4-nitrophenol (natural) instead of the ester. The products were subjected to mass spectral analysis (A.E.I. MS 902 high-resolution mass spectrograph) by Mr R. B. Turner under the supervision of Dr J. F. J. Todd.

Slopes and correlation coefficients for linear free-energy relationships were calculated from experimental data by use of ' Dartmouth Basic ' and the Kent ' On-line ' system with a central Elliott 4130 computer (the help of Dr N. J. Bridge is gratefully acknowledged).

RESULTS

Repetitive scanning of the u.v. spectra during base-catalysed hydrolysis of substituted phenyl *N*-phenylcarbamates revealed perfect isosbestic wavelengths between reactants and products indicating a simple 1 : 1 reaction.[9] Christianson [1d] observed that phenyl *N*-phenylcarbamate produced *N*-phenylcarbamate rapidly and during a longer period this anion decomposed to aniline. We observed spectroscopically that at pH values where the *N*-phenylcarbamate anion was expected to be fairly stable (from Christianson's work) [1d] a secondary slow reaction occurred after a stoicheiometric amount of phenol had been liberated. Thus the reaction being followed initially by spectroscopic means is the formation of the *N*-phenylcarbamate anion. Mohr [10] has shown that phenyl isocyanate is extremely rapidly decomposed at the pH values involved in this investigation so that decomposition of isocyanate is not a

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[7] G. L. Lewis and C. P. Smyth, *J. Chem. Phys.*, 1939, **7**, 1085.

[8] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[9] (*a*) H. L. Schläfer and O. Kling, *Angew. Chem.*, 1956, **68**, 667; (*b*) Ch. Chylewski, *ibid.*, 1971, **10**, 195; (*c*) G. Kortüm, ' Kolorimetrie, Photometrie, und Spektrometrie,' Springer, Berlin, 1962, p. 32.

[10] E. Mohr, *J. prakt. Chem.*, 1906, **73**, 177.

likely rate-determining step. Liberation of phenol from the unsubstituted phenyl ester had pseudo-first-order rate constants proportional to hydroxide-ion concentration (Table 2 and Figure 1) up to pH 12 and the results agreed with those of Christianson.[1d] Other hydrolyses obeyed pseudo-first-order kinetics up to *ca.* 90% of the total reaction and bimolecular rate constants were derived by division by the corresponding hydroxide-ion concentration (calculated from pH by use of the autoprotolysis constant).

TABLE 2

Dependence of hydrolysis rate constant on pH for phenyl *N*-phenylcarbamate [a]

pH	k/s^{-1} [b]
9	$5{\cdot}48 \pm 0{\cdot}2 \times 10^{-4}$
10	$5{\cdot}40 \pm 0{\cdot}3 \times 10^{-3}$
11	$5{\cdot}30 \pm 0{\cdot}1 \times 10^{-2}$
12	$5{\cdot}50 \pm 0{\cdot}1 \times 10^{-1}$

[a] 25 °C, 0·1M ionic strength. Rate constants from three measurements. Borate buffers at pH 9, carbonate at 10, and hydroxide at 11 and 12. [b] k_{OH} Derived from these figures, $54{\cdot}2 \pm 0{\cdot}8$ l mol^{-1} s^{-1}.

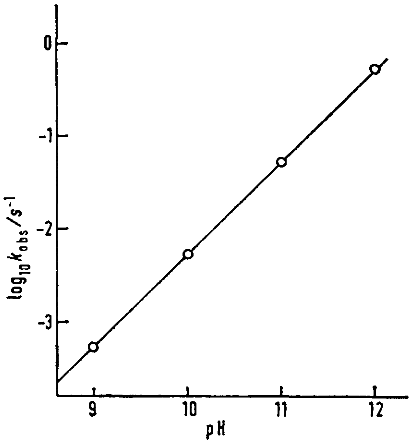


FIGURE 1 Variation of pseudo-first-order rate constant with pH for the hydrolysis of phenyl *N*-phenylcarbamate

TABLE 3

Rate constants for alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates [a]

Sub-stituent	λ_k/nm [g]	λ_i/nm [f]	k_{OH}/l mol^{-1} s^{-1}	pH	pK_a
4-Methoxy	240	274	$2{\cdot}52 \pm 0{\cdot}1 \times 10^{1}$	9·0	10·21
4-Methyl	280	260	$3{\cdot}62 \pm 0{\cdot}2 \times 10^{1}$	9·0	10·26
Unsubst.	290	257	$5{\cdot}42 \pm 0{\cdot}1 \times 10^{1}$	*h*	10·00
4-Chloro	285	250, 264, 226, 251	$3{\cdot}07 \pm 0{\cdot}2 \times 10^{2}$	9·0	9·38
3-Ethoxy-carbonyl	235	266, 273	$1{\cdot}26 \pm 0{\cdot}1 \times 10^{3}$	9·0	9·07 [d]
3-Formyl	235	225	$1{\cdot}64 \pm 0{\cdot}1 \times 10^{3}$	9·0	9·05 [d]
3-Chloro	240	260	$1{\cdot}83 \pm 0{\cdot}2 \times 10^{3}$	9·0	9·02
3-Nitro	350	277	$1{\cdot}32 \pm 0{\cdot}1 \times 10^{4}$	*e*	8·39
4-Cyano	290	213, 247	$4{\cdot}77 \pm 0{\cdot}2 \times 10^{4}$	*e*	7·95
4-Acetyl	300	213, 229, 267	$4{\cdot}23 \pm 0{\cdot}2 \times 10^{4}$	*e*	8·05
4-Formyl [c]	330	215, 232, 273	$6{\cdot}6 \pm 0{\cdot}3 \times 10^{4}$	*e*	7·66 [d]
4-Nitro	400	308	$2{\cdot}71 \pm 0{\cdot}3 \times 10^{5}$	*e*	7·15

[a] 25 °C, 0·1M ionic strength. Rate constants derived from three measurements. Buffers at pH 6·5 and 7·65 were phosphate, 9·00 were borate. [b] From G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75. [c] $\sigma = 0{\cdot}43$ from J. J. Ryan and A. A. Humffray, *J. Chem. Soc.* (*B*), 1966, 842. [d] Calculated from $-\mathrm{p}K_a = 2{\cdot}11\ \sigma - 9{\cdot}85$ (J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 178). [e] pH 7·65 and 6·5 employed. [f] Isosbestic wavelengths. [g] Kinetic wavelengths. [h] See Table 2 for pH values employed.

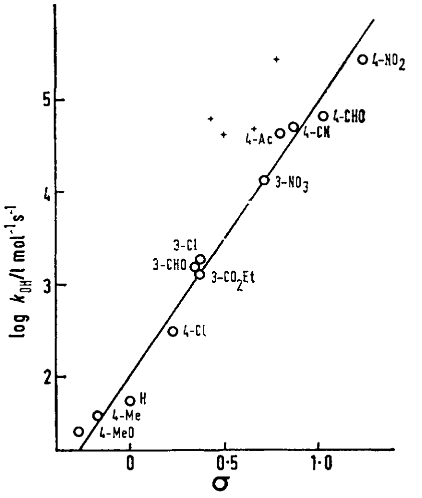


FIGURE 2 Dependence on σ (σ^-) of the rate constant for the alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates; σ and σ^- values from Table 2 footnotes *b* and *c*; + = σ values; line is theoretical ($\log_{10} k_{OH} = 2{\cdot}865\sigma^- + 2{\cdot}04$)

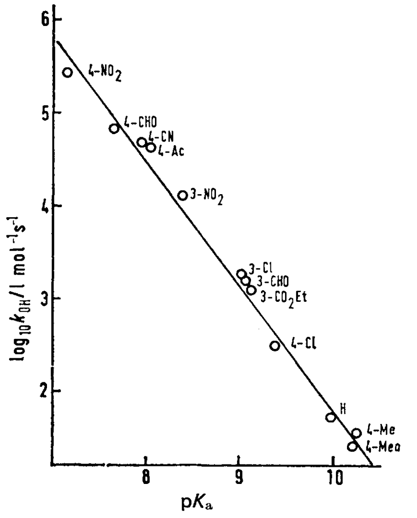


FIGURE 3 Brønsted plot of rate constant for alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates against pK_a of departing phenol (see Table 2); line is theoretical ($\log_{10} k_{OH} = 15{\cdot}2 - 1{\cdot}34\ \mathrm{p}K_a$)

No complication due to reaction of water with the un-ionised ester was encountered as bimolecular rate constants for two pH values for a number of carbamates were identical. Base-catalysed rate constants obeyed a good Hammett σ relationship ($\rho = 2{\cdot}95$, $r = 0{\cdot}985$) for substituents not able to interact mesomerically with the phenolate-like transition state (Figure 2). Substituents possessing σ^- values fitted the line when these values were employed ($\rho = 2{\cdot}86$, $r = 0{\cdot}991$). The bimolecular rate constants also fitted a Brønsted relationship when the pK_a values of the phenols were employed (Figure 3, $\beta = 1{\cdot}34$, $r = 0{\cdot}994$). The rate constants also fitted a Yukawa–Tsuno type equation[11] [equation (2)] with an R coefficient of $1 \pm 0{\cdot}2$. Oxygen-18

$$\log_{10} k/k_0 = \rho[\sigma + R(\sigma^- - \sigma)] \qquad (2)$$

incorporation studies showed that within the limits of the experiment CO–O cleavage occurred (Table 4).

TABLE 4

Mass spectral results for hydrolysis of 4-nitrophenyl *N*-phenylcarbamate in alkali[a,b,f]

	Natural		Control	Enriched	CO–O	Ar–O
Product	calc.[d]	obs.	obs.[c]	obs.	calc.[e]	calc.[e]
4-Nitrophenol	0·835	0·834	0·836	0·837	0·835	2·570

[a] Figures represent the abundance of the $M + 2$ ion as a percentage of the ion M^+. [b] An estimate of the errors can be obtained by comparing the observed and calculated natural abundance of the $M + 2$ ion. [c] Products treated with enriched water. [d] Calculated from the natural abundances (Handbook of Chemistry and Physics, Chemical Rubber Co., Cleveland, Ohio, 1966, vol. 47). [e] Calculation based on oxygen-18 enrichment of 1·94%. [f] For experimental details see text.

DISCUSSION

The base-catalysed hydrolysis of substituted phenyl *N*-phenylcarbamates exhibits a good Hammett σ relationship except for those substituents possessing σ^- values (Figure 2); when the latter values are employed a good correlation is observed for all substituents providing good evidence that the transition state for the rate-limiting step (*i.e.*, the expulsion of phenol from the ester) involves considerable phenolate ion character.

The absence of an inflexion in the rate constant up to pH 12 confirms the absence of an observable ionisation of the α proton in agreement with high pK_a values expected from other amide studies[12] (acetanilide has pK_a 17·59[12a] and back-bonding from the ester oxygen in phenyl *N*-phenylcarbamate would predict a higher pK_a). Thus equation (1) reduces to (3). Bimolecular attack of

$$\text{Rate} = [\text{ester}]\{k_2 + (k_1 + k_3)K_a/K_w\}[\text{OH}^-] \qquad (3)$$

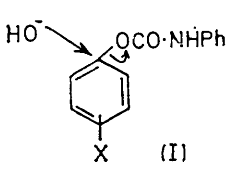
hydroxide ion on phenyl esters does not involve rate-determining breakdown of the tetrahedral intermediate;[13] thus phenolate ion character is not expressed. Alkaline hydrolysis of aryl *N*-phenylcarbamates does not therefore possess an important k_2 term.

The high selectivity of the hydrolytic rate constant to change in leaving group also excludes k_2 which generally has low values of ρ *ca.* 1.[13] The high observed ρ value is in agreement with that of Dittert[1e] for the *N*-methylcarbamates ($\rho = 2{\cdot}34$) as opposed to the *NN'*-dimethylcarbamates ($\rho = 1{\cdot}24$) and could reflect considerable build-up of negative charge in the transition-state. Hammett sensitivities from Dittert are based on only two points (phenyl and 4-nitrophenyl esters) and could therefore be suspect. Alkaline hydrolysis of *NN'*-disubstituted carbamates has not been investigated systematically but there seems no sound theoretical reason why this should have a higher sensitivity than phenyl esters of aliphatic carboxylic acids or should differ in selectivity to σ or σ^-. The Brønsted coefficient is too large for simple bond-breaking which should yield a value of <*ca.* 1·0 and is the result of a combination of an ionisation process (K_a), bond formation $(-\bar{\text{N}}\overset{\curvearrowright}{\text{---}}\text{C}-)$, and bond fission $(-\text{C}\overset{\curvearrowright}{\text{—}}\text{OAr})$.

A third mechanistic possibility not considered by Bender and Homer, by Christianson, or by Dittert is bimolecular attack of water on the ester anion (k_3); this mechanism should be less efficient than attack of hydroxide ion on neutral ester. If such a mechanism existed its selectivity towards phenyl substituent should be larger than for k_2. The more positive entropy of activation for phenyl *N*-phenylcarbamate hydrolysis than of the *N*-methyl homologue (by about 33 cal mol^{-1} K^{-1})[1d] points to a unimolecular process. If it is assumed that bimolecular attack of water on the anion of 4-nitrophenyl *N*-phenylcarbamate is the predominant mechanism its rate constant (k_3) can be calculated by use of an estimated pK_a for the carbamate[12] and the autoprotolysis constant ($k_3 = k_{\text{OH}} \,.\, K_w/K_a = 2{\cdot}71 \times 10^9$ s^{-1}). Reaction of water with the *neutral* carbamate would be expected to be faster than this but at pH 7·65 the observed hydrolysis rate constant for the ester is $1{\cdot}2 \times 10^{-1}$ s^{-1}. An argument not requiring an accurate estimated pK_a for carbamate is as follows: the phenyl ester has a pK_a >12 (see earlier), thus the water term is >*ca.* $54{\cdot}2 \times 10^{-14}/10^{-12} = 0{\cdot}542$ s^{-1} which is greater than the observed pseudo-first-order rate constant at pH 9 ($5{\cdot}48 \times 10^{-4}$ s^{-1}).

As the pK_a of the leaving group increases it is expected that the bimolecular mechanism (k_2) with its lower selectivity will become more efficient and in agreement with this the ethyl ester of mono-*N*-alkylated carbamates hydrolyse not very much more quickly than their disubstituted analogues.[1d,e]

Oxygen-18 incorporation studies with the 4-nitrophenyl ester exclude the possibility that the high selectivity and σ^- dependence arise from a mechanism involving nucleophilic aromatic substitution (I).



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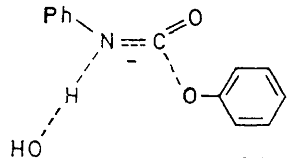

(II)

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[11] Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 971.

[12] (*a*) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266; (*b*) G. E. K. Branch and J. O. Clayton, *ibid.*, 1928, **50**, 1680; (*c*) K. Bowden, *Chem. Rev.*, 1966, **66**, 119; (*d*) P. M. Mader, *J. Amer. Chem. Soc.*, 1965, **87**, 3191; (*e*) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892.

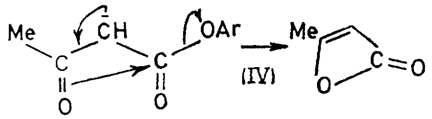
[13] (*a*) A. Williams and R. A. Naylor, *J. Chem. Soc.* (*B*), 1971, 1967; (*b*) J. J. Ryan and A. A. Humffray, *ibid.*, 1966, 842; (*c*) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, 1960, **82**, 3067; (*d*) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801.

A further mechanistic possibility for the expulsion of phenol by hydroxide ion is a concerted process involving a transition state (II) with charge spread over five atoms. This mechanism is not consistent with the *inverse* deuterium isotope effect observed for the alkaline hydrolysis of 4-nitrophenyl *N*-methylcarbamate[1a] in deuterium oxide nor with the extremely high β value indicating almost complete unit charge on the phenol oxygen in the transition state. The excellent fit of the data to a Hammett σ^- relationship which is reflected in a high Yukawa–Tsuno coefficient (*R*) also points to a stepwise mechanism. Finally, the absence of important buffer effects[1a] is not consistent with the concerted mechanism because other bases should be able to replace hydroxide as a catalyst.

We consider that the high selectivity for alkaline hydrolysis and correlation with a Hammett σ^- equation are useful tools for demonstration of the *E*1cB mechanism and are diagnostic of an isocyanate intermediate in monosubstituted carbamate aryl ester hydrolysis. Unfortunately, the other system where these tools have been applied, namely the alkaline hydrolysis of aryl acetoacetates,[3] can have two *E*1cB mechanisms: one involving a keten intermediate (III, analogous with isocyanate) and one involving a lactone (IV, diketen) intermediate. Distinction between the mechanisms could be difficult.

$\mathrm{AcCH{=}C{=}O}$

(III)



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