Participation of an Elimination Mechanism in Alkaline Hydrolyses of Alkyl *N*-Phenylcarbamates

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Second-order rate constants for alkaline hydrolysis of alkyl *N*-phenylcarbamates and alkyl and aryl *N*-methyl-*N*-phenylcarbamates have been measured. Together with results from an earlier paper the alkaline hydrolysis of aryl and alkyl *N*-phenylcarbamates is related linearly with pK_a (7—16) of the leaving alcohol and phenol ($\beta = -1{\cdot}15$); the fully substituted carbamates have $\beta = -0{\cdot}25$. These results are interpreted to mean that alkyl *N*-phenylcarbamates hydrolyse in alkali *via* an elimination type of process. It is estimated that a changeover from an elimination (*E*1cB) to a bimolecular substitution (S_N2) mechanism occurs when the pK_a of the leaving alcohol exceeds ~17. A discussion of the factors favouring S_N2 or *E*1cB mechanisms in alkaline hydrolysis is given.

It is now well established that some esters with protons on the atom adjacent to the ester group undergo alkaline hydrolysis *via* an elimination mechanism (*E*lcB).[1] Such a mechanism has only been proved, so far, in esters where the leaving group has a pK_a of *ca.* 10 and less. The possession of a good leaving group is not the only criterion for an elimination type of mechanism as there are many such esters possessing an ' α-proton ' which are known to hydrolyse *via* an S_N2 process.[1g] The changeover from elimination to a substitution mechanism will not occur at a constant pK_a for the leaving group. Although there is doubt as to the nature of the elimination mechanism in the hydrolysis of aryl acetoacetates,[1c] a clear change in mechanism (to S_N2) is observed as the pK_a of the leaving group rises above *ca.* 11. Thus, most alkyl acetoacetates hydrolyse *via* an S_N2 mechanism. Increasing the stability of the intermediate in the elimination process should allow even these alkyl esters to hydrolyse *via* the *E*1cB mechanism.

This study sets out to investigate the mechanism of alkaline hydrolysis of alkyl *N*-phenylcarbamates with leaving alcohols of pK_a from 12 to 16.

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EXPERIMENTAL

Materials.—The alkyl esters of *N*-phenylcarbamic acid were prepared by the following general method: alcohol (10 mmol) was mixed with acetonitrile (*ca.* 2 ml) and cooled in an ice-bath. Phenyl isocyanate (10 mmol) was then added and the mixture thoroughly swirled. Addition of triethylamine (0·5 ml) caused an evolution of heat due to the reaction between isocyanate and alcohol. The mixture was kept at room temperature for *ca.* 3 h and the carbamate precipitated with dilute hydrochloric acid. The crystalline precipitate was filtered, washed thoroughly with water, and then dried in the air. Recrystallisation from light petroleum (b.p. 60—80°) gave analytically pure carbamate.

Esters of *N*-methyl-*N*-phenylcarbamate were prepared in the following manner: *N*-methylaniline (10 mmol) was dissolved in dichloromethane (10 ml) containing triethylamine (10 mmol). The solution was cooled in ice and the appropriate chloroformic ester (10 mmol) added

[1] (*a*) R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956; (*b*) A. F. Hegarty and L. N. Frost, *Chem. Comm.*, 1972, 500; (*c*) A. Williams, *J.C.S. Perkin II*, 1972, 808; (*d*) A. Williams and K. T. Douglas, *ibid.*, p. 1454; (*e*) A. J. Kirby and C. J. Lloyd, *Chem. Comm.*, 1971, 1538; (*f*) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, 1968, **90**, 7136; (*g*) 1969, **91**, 3003; (*h*) K. D. Kopple, *ibid.*, 1957, **79**, 6442; (*i*) J. F. Bunnett and M. B. Naff, *ibid.*, 1966, **88**, 4001; (*j*) I. Christianson, *Acta Chem. Scand.*, 1964, **18**, 904; (*k*) L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 1963, **52**, 852; (*l*) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975.

with swirling. The mixture was kept at room temperature for *ca.* 2—3 h and extracted with N-HCl, sodium hydrogen carbonate solution, and water. It was evaporated after drying (Na_2SO_4). Recrystallisation from light petroleum (b.p. 60—80°) gave analytically pure crystals. The ethyl ester, an oil, was obtained pure by vacuum distillation of a 50 mmol preparation.

Structures of the substrates in Table 1 were confirmed using i.r. and n.m.r. spectroscopy.

Methods.—At alkaline pH (0·01—1M-NaOH) the alkyl carbamates showed little change in u.v. spectrum on hydrolysis but possessed intense absorption maxima in the 235 nm regions. Since the product, aniline, does not absorb strongly at this wavelength in acid solution the hydrolyses were followed by acidifying aliquot portions of the reacting solutions and measuring the decrease in absorbance at 235 nm due to unchanged ester. The same procedure was used for the ethyl *N*-methyl-*N*-phenylcarbamate except that the acidified portion was measured at 230 nm. The 4-nitrophenyl and phenyl ester hydrolyses were followed directly utilising the change in absorbance at 400 and 240 nm respectively. Instruments and kinetic techniques employed were those of a previous report.[1c]

RESULTS

Reactions obeyed first-order kinetics (with respect to ester) up to *ca.* 90% of the total reaction and the derived rate constants were proportional to hydroxide ion concentration within the limited range studied. The rate constants were insensitive to change in ionic strength from 0·1 to 1M and division by the hydroxide ion concentration gave the second-order rate constant for reaction of hydroxide ion with esters, and these are collected in Table 2.

TABLE 1

Analytical and physical properties of substrates

Substrate	M.p. (°C) [a]	Lit. m.p. (°C)
N-Phenylcarbamates		
2,2,2-Trichloroethyl	86—87	87 [2]
2,2,2-Trifluoroethyl	69—71	70 [3]
2,2-Dichloroethyl	69—70 [c]	
2-Chloroethyl	51—52	51 [4]
Propargyl	62—63	63 [5]
Ethyl	52—53	52 [1j]
Methyl	47—48	47 [8]
N-Methyl-*N*-phenylcarbamates		
4-Nitrophenyl	60—61	69—70 [6]
Phenyl	57—58	58 [6]
Ethyl	115 [b] (at 30 mmHg)	99—100 [b,7] (at 2 mmHg)

[a] M.p.s determined using a Kofler Thermospan instrument. [b] B.p. [c] Analysis (by Mr G. M. Powell of this laboratory using a Hewlett–Packard 185 C, H, and N analyser) (Found: C, 46·1; H, 4·0; N, 5·8. $C_9H_9Cl_2NO_2$ requires C, 46·2; H, 3·9; N, 6·0%).

Studies by Christianson [1j] and by Dittert and Higuchi [1k] show that the hydrolysis of carbamate esters yields carbamate ion which decomposes slowly in alkali but fast in acid to amine and carbon dioxide. The above methods of following the hydrolysis ensure that the observed reaction is that from ester to carbamate ion.

A plot (Figure 1) of $\log_{10} k_{OH}$ *versus* pK_a of the leaving moiety for the *N*-phenylcarbamates encompassing results for phenyl [1c] and alkyl esters has a high Brønsted β (−1·15) and a high correlation coefficient (0·996). A similar plot for the *N*-methyl-*N*-phenylcarbamates (Figure 1) has a

TABLE 2

Kinetic parameters for substrates

Substrate	pK_a [c]	k_{OH}/ l mol^{-1} s^{-1} [a]	[OH$^-$]/M
N-Phenylcarbamates			
2,2,2-Trichloroethyl	12·24	3·16 ± 0·06 × 10^{-1}	0·005—0·01
2,2,2-Trifluoroethyl	12·43	1·00 ± 0·05 × 10^{-1}	0·005—0·01
2,2-Dichloroethyl	12·89	5·00 ± 0·11 × 10^{-2}	0·01—0·1
2-Chloroethyl	14·31	1·59 ± 0·08 × 10^{-3}	0·05—0·1
Propargyl	13·55	7·25 ± 0·17 × 10^{-3}	0·05—0·1
Ethyl [b]	16·0	3·20 ± 0·13 × 10^{-5}	0·1—1·0
Methyl [b]	15·54	5·50 ± 0·20 × 10^{-5}	0·1—1·0
N-Methyl-*N*-phenylcarbamates			
4-Nitrophenyl	7·15	7·98 ± 0·21 × 10^{-4}	0·1—1·0
Phenyl [b]	10·00	1·41 ± 0·06 × 10^{-4}	0·1—1·0
Ethyl [b]	16·0	3·98 ± 0·15 × 10^{-6}	0·1—1·0

[a] Ionic strength 0·1M, 25° except where stated. [b] Kinetic parameter measured at 1M ionic strength. Ionic strength has little effect on the rate constants up to 1M. [c] Values from P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1959, **81**, 1050; 1960, **82**, 795.

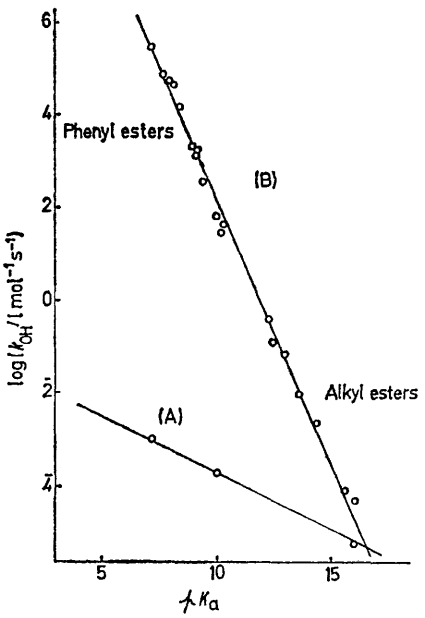

FIGURE 1 Dependence of k_{OH} on pK_a of leaving group for alkyl and phenyl esters of (A) *N*-methyl-*N*-phenylcarbamic and (B) *N*-phenylcarbamic acid. Lines are theoretical. Phenol pK_a values from G. F. A. Kortum, W. Vogel, and K. Andrussow, 'Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961

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[6] E. Lelbmann and E. Benz, *Ber.*, 1891, **24**, 2108.
[7] R. L. Dannley, M. Lukin, and J. Shapiro, *J. Org. Chem.*, 1955, **20**, 92.
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much lower slope (−0·250; $r = 0·963$) and all the points lie well below those for the monosubstituted carbamates.

DISCUSSION

Recent work from this laboratory [1c] and from that of Hegarty [1b] utilising linear free energy relationships indicates that *N*-phenylcarbamates with good leaving groups hydrolyse in alkali *via* an *E*1cB mechanism (Scheme 1).

$$PhNHCOX \underset{}{\overset{K_a}{\rightleftharpoons}} PhNCOX \xrightarrow{k_2} PhN{=}C{=}O + X^- \xrightarrow{} \text{products}$$

SCHEME 1

The most convincing evidence that alkyl *N*-phenylcarbamates hydrolyse *via* an *E*1cB pathway is that their second-order rate constants for reaction with hydroxide ion fit the same linear free energy relationship ($\log_{10} k_{OH}$ *versus* pK_a of leaving alcohol) that encompasses the phenyl esters (Figure 1). Fully *N*-substituted carbamates fit a similar relationship but their reactivity and the slope (β) is much lower than for the monosubstituted esters. The high slope of the relationship for the leaving phenols and the dependence on Hammett σ^- was considered to stem from a rate determining C–OAr cleavage [1c] in a mechanism involving ionisation of the NH group followed by an *E*1 expulsion of the aryloxide anion. It is now accepted that alkaline hydrolysis (S_N2) of phenyl esters involves rate determining attack of hydroxide ion on the ester to give the 'tetrahedral' intermediate (T^-) which decomposes rapidly to products ($k_{-1} < k_2$) so that cleavage of the

$$RCO{-}OAr + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T^- \xrightarrow{k_2} \text{products}$$

SCHEME 2

C–OAr bond is not involved in the transition state of the rate-determining step.[9] For this reason the sensitivity of the hydrolysis rate constant to change in substituent on the phenol leaving group or to change in the leaving group, as measured by the pK_a of its conjugate acid, is small. Carbamates, fully substituted on the nitrogen atom, are no exception to this rule.

Although the observation of a high β value for the hydrolysis of *N*-phenylcarbamates is explained by the *E*1cB mechanism, it is impossible at this stage to dissect the β value into contributions from ionisation and *E*1 reaction. This dissection has been possible in phosphoramidate [1d] and aminosulphonate [10] ester hydrolysis because the overall reactivity of the corresponding elimination steps are not high and the pK_a values of the α-NH groups are considerably less than that for water. In these esters the β values for the separate steps combine to yield a large β for the apparent hydroxide ion reaction.

Changeover in Mechanism.—In the plot of $\log_{10} k_{OH}$ *versus* pK_a of leaving group in the hydrolysis of acetoacetate esters [1a] a distinct break is observed at $pK_a \sim 11$ which indicates a changeover in predominant mechanism from *E*1cB (low pK_a range, high β) to S_N2 (high pK_a range, low β). No evidence for a change in mechanism (in the form of a break) is seen in the *N*-phenylcarbamate series (Figure 1) but we can determine the pK_a at which a changeover in mechanism should occur. We can estimate the alkaline hydrolysis rate constants for *N*-phenylcarbamates (for the S_N2 mechanism) from those for the *N*-methyl-*N*-phenylcarbamates. Steric and polar differences can be eliminated approximately by multiplying the latter rate constants by the ratio of rate constants for attack of hydroxide on ethyl propionate ($2·20 \cdot 10^{-2}$ l mol^{-1} s^{-1}) [11] and ethyl 2-methylpropionate ($0·55 \cdot 10^{-2}$ l mol^{-1} s^{-1}); [11] strictly, the 2-phenyl derivatives should be employed but the

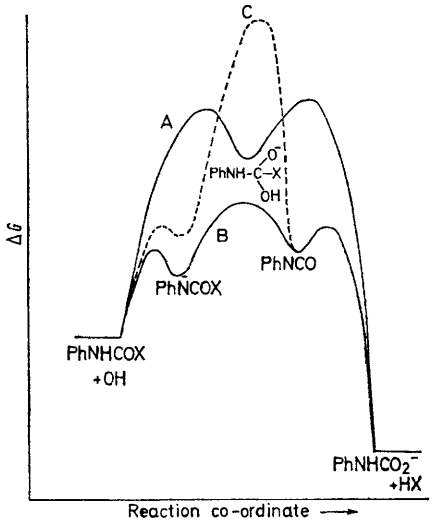

FIGURE 2 Free energy diagram for alkaline hydrolysis of *N*-phenylcarbamates

data is not available. Thus, k_{OH} (S_N2) for *N*-phenylcarbamates is approximately four-fold that for *N*-methyl-*N*-phenylcarbamates. Since ethyl *N*-phenylcarbamate is 10-fold more reactive than the fully substituted ester, we conclude that a small proportion of the ethyl ester hydrolysis proceeds *via* an S_N2 pathway; *N*-phenylcarbamate derivatives with leaving groups with pK_a values greater than that of ethanol hydrolyse in alkali *via* S_N2 mechanism involving a 'tetrahedral' intermediate (T^-).

The changes in conditions leading to a change in mechanism are best understood with the use of a free energy diagram (Figure 2). Path A represents the S_N2 type mechanism (with T^- intermediate) and B the *E*1cB mechanism (with two intermediates). Let us consider an ester with a good leaving group which hydrolyses in alkali *via* pathway B: as the leaving group ability decreases (pK_a of the leaving group conjugate

[9] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

[10] K. T. Douglas and A. Williams, *J.C.S. Chem. Comm.*, 1973, 356.

[11] G. Davies and D. P. Evans, *J. Chem. Soc.*, 1940, 339.

acid increases), the decomposition of the conjugate base of the ester (PhN̄COX) becomes progressively more difficult till the transition-state free energy equals that for the rate-limiting step of path A (the addition step to give T^-). As the pK_a of the conjugate acid of the leaving group increases further, path A becomes the predominant mechanism because the decomposition of PhN̄COX will be more sensitive to leaving group than will the addition step to give T^- (the centre of reaction is more remote from substituent in the formation of T^-). If the intermediate (in this case phenyl isocyanate) is sufficiently stable, the transition state for elimination can be stabilised sufficiently for even alkyl esters to follow the *E*1cB pathway in hydrolysis.

In an S_N2 reaction of a constant nucleophile with an ester of varying leaving group there is a changeover in the rate-determining step as the pK_a of the leaving group increases to, and then exceeds, the pK_a of the nucleophile as it leaves T^- to regenerate starting ester.[12] When the nucleophile leaves T^- more readily than the leaving alcohol, the overall rate constant becomes strongly dependent on pK_a of the leaving group. It is not conceivable that $k_{-1} > k_2$ in an S_N2 mechanism in the hydrolysis of *N*-phenylcarbamates in the total pK_a range studied because the hydroxide ion is such a poor leaving group compared with the other alkoxide and phenoxide anions.

The entropy of activation for alkaline hydrolysis of phenylurethane was observed to be large and negative and 14 cal mol^{-1} K^{-1} more positive than that for the *N*-methyl-*N*-phenylurethane.[1j] It was concluded that both esters hydrolysed *via* the usual S_N2 type mechanism. The enthalpy of activation for the phenylurethane (15·9 kcal mol^{-1}) was close to that for phenyl *N*-phenylcarbamate hydrolysis (16·6 kcal mol^{-1}) suggesting that in the *N*-phenylcarbamate series the change in reactivity is largely entropy controlled. It is difficult to use entropy and enthalpy data to argue against an *E*1cB mechanism where two steps are involved because the Arrhenius parameters for the ionisation step are not known.

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[12] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837.