*E*1cB Mechanisms. Part III.[1] Effect of Ionisation of Amido-NH on Reaction of Hydroxide Ion with Methyl 3- and 4-Benzamidobenzoates

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Rate constants for hydrolysis of methyl 4-(substituted benzamido)benzoates and the corresponding 3-isomers have been measured over a range of hydroxide-ion concentrations (20% dioxan–water. v/v) spanning the ionisation of the amido-NH group. The pseudo-first-order rate constants obeyed a kinetic law (i) derived from a mechanism

$$k = k_2\{1 + (K_a/K_w)(k_4/k_2)[OH^-]\}[OH^-]/(1 + (K_a/K_w)[OH^-]) \qquad \text{(i)}$$

involving bimolecular attack ($B_{Ac}2$) of hydroxide ion on both neutral and ionised ester. Neutral ester reacted five times more rapidly than conjugate base with hydroxide ion. Ionisation of the amido-NH functions were measured separately by spectrophotometric titration and the pK_a values varied from 12 to 14·5. Values of K_a for the methyl 4-(substituted benzamido)benzoates and the 3-isomers had Hammett sensitivities of +1·53 ($r = 0·999$) and +1·37 ($r = 0·993$) respectively. Sensitivity of k_2 and k_4 (hydroxide on neutral ester and hydroxide on conjugate base respectively) to Hammett σ values were very small, in agreement with other workers' results for sensitivities for ionisation of substituted benzamidophenols and anilines.

CONTINUING our investigations on the hydrolysis of esters which are weak acids [1] we have observed that at a concentration of 0·2M-NaOH the alkaline hydrolysis of
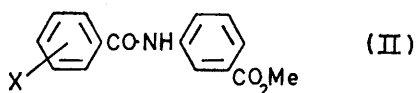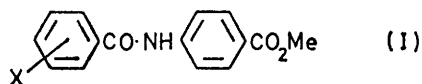
methyl 4-(substituted benzamido)benzoates (I) possessed a substantial negative Hammett sensitivity. As it was not expected that the amido-NH group would be substantially ionised at the hydroxide-ion concentration used these results were difficult to explain. Further investigation of the alkaline hydrolysis of the *para* (I) and *meta* (II) series over a range of hydroxide-ion concentration provides an explanation of the initial results. Hydroxide ion reacts with both neutral and conjugate base of the ester and least inhibition occurs with the 4-methoxy-derivatives because these are the least ionised at the given hydroxide ion concentration.

EXPERIMENTAL

Materials.—Reagent-grade dioxan was purified by Vogel's method [2] and immediately before use was purged from

[1] Part II, A. Williams and K. T. Douglas, *J.C.S. Perkin II,* 1972, 1454.
[2] A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 1956, p. 177.

peroxides by passage through an alumina column (potassium iodide solution was used to test for absence of peroxides). The methyl (substituted benzamido)benzoates were synthesised from the corresponding methyl aminobenzoate (prepared from the acid *via* the Fischer–Speier method): methyl aminobenzoate (1·51 g) was dissolved in redistilled pyridine (15 ml) and to this solution was added the substituted benzoyl chloride (10 mmol) in small portions during

dioxan–water media were not kept for more than a day and were protected from light during use with aluminium foil.

Ionisation of the amido-NH group was measured spectrophotometrically (Table 2) and by use of data of Harned and Fallon [4b] for dioxan–water mixtures the ' hydroxide-ion concentration for half ionisation ' (K_w/K_a) was dissected into its component K_a value. Owing to reactivity of the substrates the optical density at a given wavelength had to

TABLE 1

Analytical and physical properties of substrates [a]

Compound	M.p. (°C)	Found (%)			Formula	Calc. (%)		
		C	H	N		C	H	N
(If)	217—220	52·1	3·2	12·1	$C_{15}H_{11}N_3O_7$	52·2	3·2	12·2
(Ia)	170—171	70·6	5·1	5·5	$C_{15}H_{13}NO_3$	70·9	5·3	5·3
(Ig)	205—206	67·8	5·2	4·8	$C_{16}H_{15}NO_4$	67·8	5·2	4·9
(Ic)	239—241	60·2	4·2	9·5	$C_{15}H_{12}N_2O_5$	60·0	4·0	9·3
(Id)	207—210	62·2	4·5	4·8	$C_{15}H_{12}ClNO_3$	62·2	4·1	4·8
(IIc)	193—195	60·1	4·3	9·3	$C_{15}H_{12}N_2O_5$	60·0	4·0	9·3
(IIb)	162—163	59·9	4·1	9·3	$C_{15}H_{12}N_2O_5$	60·0	4·0	9·3
(IIe)	124—125	71·5	5·6	5·1	$C_{16}H_{15}NO_3$	71·4	5·6	5·1
(IIa)	130—131	70·5	5·3	5·5	$C_{15}H_{13}NO_3$	70·9	5·1	5·5
(IId)	137—138	62·7 [b]	4·1	4·8	$C_{15}H_{12}ClNO_3$	62·2	4·1	4·8

[a] Analyses by Mr. G. M. Powell of this laboratory using a Hewlett–Packard 185 analyser. M.p.s were determined with a Kofler Thermospan instrument. [b] Mass spectral and t.l.c. evidence confirm structure and purity of this compound.

0·5 h with vigorous stirring. The mixture was stored overnight at room temperature, evaporated to dryness *in vacuo*, and the solid partially dissolved in ice–water. The product was filtered off and recrystallised from methanol. M.p.s and analytical data are in Table 1.

Kinetics.—Hydrolyses were followed by observing the change in the u.v. absorption (Table 2) by the species initially

TABLE 2

Spectral data for substrates [c]

Compound	λ_t[e]/nm	$10^{-4}\Delta\varepsilon/\lambda_t$	λ_k[d]/nm	λ_i[b,e]/nm
(If)	350	0·560	330	277
(Ic)	350	0·398	300	272
(Id)	330	1·06	300	277
(Ia)	340	0·994	300	274
(Ig)	335	1·05	300	284
(IIe)	295	0·206	315	295, 278
(IIb)	325	0·431	315	275
(IId)	320	0·320	325	290, 264
(IIa)	300	0·344	315	None [f]
(IIc)	350	0·420	350	None [f]

[a] 20% Dioxan–water (v/v), 25 °C. [b] Measured at 0·02M-NaOH; the isosbestic points vary according to the hydroxide-ion concentration. [c] Titration wavelength. [d] Kinetic wavelength. [e] Wavelength for isosbestic points. [f] In the u.v. range studied.

by spectral scan with a Unicam SP 800 spectrophotometer and finally with a Beckman DBG spectrophotometer at constant wavelength. Hydroxide-ion concentration was in large excess over substrate and first-order kinetics were analysed by the Guggenheim [3] or infinity methods. Stock solutions of the esters were in dioxan and owing to the ease of peroxidation of dioxan and the high nucleophilicity of a peroxide ion compared with a hydroxide ion (α-effect) [4a] the

[3] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.
[4] (a) T. C. Bruice and S. J. Benkovic, ' Bio-organic Mechanisms,' Benjamin, New York, 1966, vol. I, p. 45; (b) H. S. Harned and L. D. Fallon, *J. Amer. Chem. Soc.*, 1939, **61**, 2374.

be extrapolated to zero time. The dependence of ionisation on hydroxide-ion concentration is identical with that for the velocity–substrate concentration dependence in enzyme reactions and a previously used mathematical technique was employed to evaluate K_w/K_a.[1] Computer programmes were written in Dartmouth Basic and run on the Kent ' On-line ' system with a central Elliott 4130 computer.

RESULTS

Reaction of the methyl esters with hydroxide ion exhibited good first-order kinetics with respect to ester concentration. The observation of excellent isosbestic wavelengths during repetitive scanning of the u.v. spectrum during hydrolysis points to a 1 : 1 stoicheiometry and the known rates of alkaline hydrolysis of benzanilides and methyl benzoates [5] suggest that the observed reaction is a simple ester hydrolysis. Comparison of product spectra, in a limited number of cases, with the spectra for the expected products confirms this conclusion. The dependence of the first-order rate constant for hydrolysis on hydroxide ion concentration is illustrated in Figure 1 for some *para*-esters. This dependence can be explained by the kinetic Scheme 1 where

$$AH \underset{}{\overset{K_a}{\rightleftharpoons}} A^- + H^+$$

$$\downarrow k_2[OH^-] \qquad \downarrow k_4[OH^-]$$

$$product$$
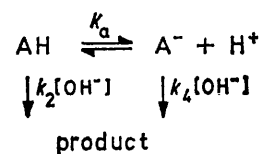
SCHEME 1

both neutral substrate *and* conjugate base react with hydroxide ion. Steady-state analysis of Scheme 1 yields equation (1) which can be rearranged to equation (2). Fit of the data to the latter equation is illustrated in Figure 2

[5] National Bureau of Standards, Circular 510, Tables of Chemical Kinetics.

where k_2 and k_4 are obtained by plotting a function of $k_{(observed)}$, K_w/K_a, and hydroxide-ion concentration [left-
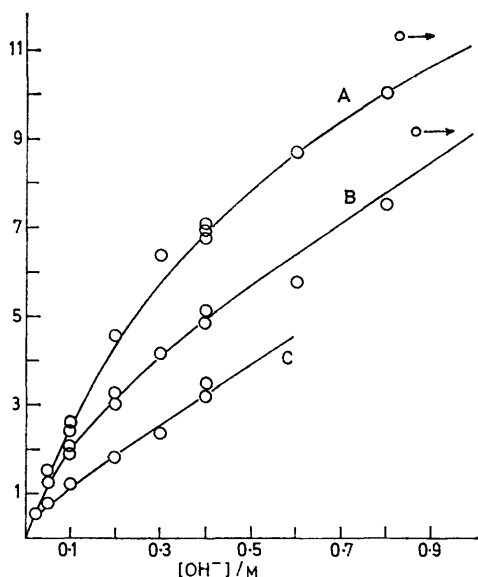

FIGURE 1 Plot of $k_{(observed)}$ aginst [OH⁻] for hydrolysis of methyl 4-(substituted benzamido)benzoates: A, 4-OMe; B, 4-Cl; C, 4-NO₂. Lines are theoretical [equation (1)] and parameters are taken from Table 3; conditions as in Table 3
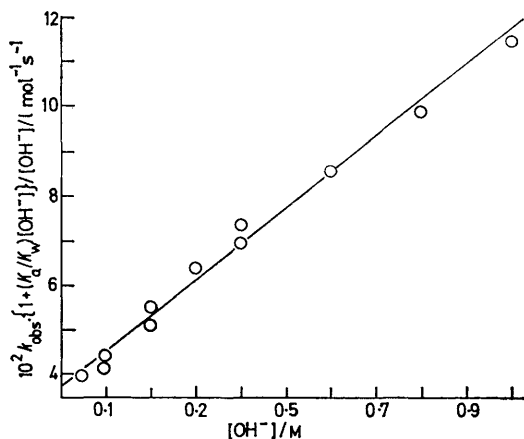

FIGURE 2 Plot of $k_{(observed)} \cdot \{1 + (K_a/K_w)[OH^-]\}/[OH^-]$ against [OH⁻] for methyl 4-(4-chlorobenzamido)benzoate. Line is theoretical from parameters in Table 3; conditions as in Table 3.

hand side of equation (2)] against hydroxide ion concentration.

$$k_{(observed)} = k_2\{1 + (K_a/K_w)k_4[OH^-]/k_2\}[OH^-]/ \{1 + (K_a/K_w)[OH^-]\} \quad (1)$$

$$k_{(observed)} \cdot \{1 + (K_a/K_w)[OH^-]\}/[OH^-] = k_2 + (K_a/K_w)k_4[OH^-] \quad (2)$$

Values of k_2 and k_4 are in Table 3. Ionisation constants (K_w/K_a) utilised in these calculations and obtained by spectrophotometric titration are also in Table 3 and a

* J. Hine and M. Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.

typical fit of the data to the ionisation parameters is illustrated in Figure 3. Fit of the theoretical lines to the ' raw ' experimental data for kinetics is illustrated in Figure 1 for the *para*-series.

Accuracy in the measurements of k_2 is least for the electron-withdrawing substituents because the ionisation occurs at hydroxide-ion concentrations lower than those used here (*e.g.*, the 3,5-dinitro-substituent). Errors in k_4 occur when the ionisation occurs at concentrations higher than those used here (*e.g.*, the 4-methoxy-substituent). In determining the Hammett sensitivity for the ionisation for the *meta*-series
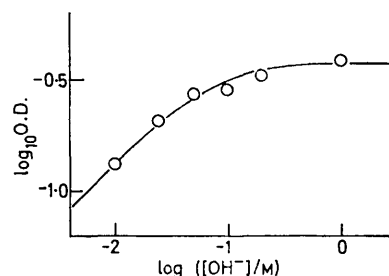

FIGURE 3 Spectrophotometric titration of methyl 3-(4-nitrobenzamido)benzoate. Line is theoretical from parameters in Table 3; conditions as in Table 3

the 4-methyl derivative was omitted from the calculations. K_w/K_a for the *para*- and *meta*-esters were calculable from the equations $\log K_w/K_a = -1.53\sigma - 0.658$ and $\log_{10} K_w/K_a = -1.37\sigma - 0.560$ respectively. Correlation coefficients were 0.999 and 0.993 respectively.

DISCUSSION

The change in spectrum (at zero time) for esters (I) and (II) in increasing concentrations of hydroxide ion cannot be easily explained except by ionisation of the benzamido-NH group. If K_w is 2.399×10^{-15} (ref. 4b) for 20% dioxan–water (v/v) then pK_a ranges from *ca.* 12 [for the 3,5-dinitro-derivative (If)] to *ca.* 14.5 [for the 4-methoxy-ester (Ig)]. These are reasonable values compared with that for acetanilide (pK_a 17.59) [6] which does not possess activating ester and phenyl groups.

Alkaline hydrolysis of the esters (I) and (II) in the hydroxide-ion concentration range where ionisation is prevalent should give non-linear plots of rate constant against hydroxide-ion concentration. The general kinetic scheme for alkaline hydrolysis of the ionisable ester is shown in Scheme 2 and the kinetic equation
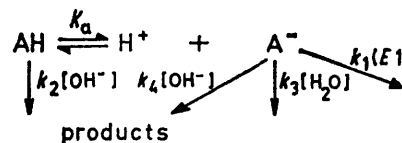
SCHEME 2

derived from this by the steady-state treatment is similar to that of equation (1) except that k_2 is composite [equation (3)]. It is likely that bimolecular attack of

$$k_2 \text{ [in equation (1)]} = k_2 + (K_a/K_w)(k_1 + k_3) \quad (3)$$

water (k_3) on the ionised ester is not a significant factor as the rate constant for reaction of water with methyl benzoate-type esters although not reported in the literature can be estimated from data of Jencks and Carriuolo [7] for reaction of water with methyl acetate. The known reactivity ratio of methyl acetate to methyl benzoate to attack of hydroxide ($ca.$ 11) [8a] gives a value of $ca.$ 2 × 10^{-11} s^{-1} for hydrolysis of methyl benzoate in water at 25 °C; this value is negligible for our system and

are as expected since the former is attack of anion on neutral ester whereas the latter is anion–anion attack; there is clearly considerable spreading of the negative charge over the complete system as other ratios for anion–neutral : anion–anion rate constants where charge is at a similar distance from the electrophilic atom are considerably larger than these.[9] Table 3 shows that the values for k_2 for both 3- and 4-isomers are closely similar but those for k_4 are larger in the 3-series. The

TABLE 3

Ionisation constants and kinetic parameters for alkaline hydrolysis of methyl benzamidobenzoates [a]

Compound	$(K_w/K_a)/(l\ mol^{-1})$	$k_2/l\ mol^{-1}\ s^{-1}$	$10^3 k_4/l\ mol^{-1}\ s^{-1}$	pK_a
(IIb)	0·0339 ± 0·0032	0·0499 ± 0·0147 [b]	20·2 ± 0·8	13·15
(IIe)	0·187 ± 0·070	0·0740 ± 0·0041	26·2 ± 1·5	13·89
(IId)	0·124 ± 0·016	0·0699 ± 0·0042	21·6 ± 0·9	13·71
(IIa)	0·286 ± 0·052	0·0583 ± 0·0043	27·7 ± 2·0	14·16
(IIc)	0·0204 ± 0·0035	0·0653 ± 0·0493 [b]	21·4 ± 2·26	12·93
(Id)	0·0838 ± 0·0155	0·0370 ± 0·0031	7·03 ± 0·54	13·54
(Ia)	0·251 ± 0·051	0·0327 ± 0·0008	5·80 ± 0·34	14·02
(Ic)	0·0140 ± 0·0035	0·0440 ± 0·0069	6·92 ± 0·38	12·77
(Ig)	0·564 ± 0·065	0·0284 ± 0·0005	1·6 ± 0·5 [b]	14·37
(If)	0·00159 ± 0·00018	0·113 ± 0·075 [b]	8·20 ± 0·43	11·82

[a] 25 °C, 20% dioxan–water (v/v), 1M ionic strength.   [b] Refer to Results section for discussion of these large uncertanties.

$K_a/K_w × k_3$ is very small compared with the observed value for k_2 [from equation (1)].

The $E1$ mechanism involving an intermediate of the type (III) is not possible in the case of the 3-isomers (II) and is probably not operative in the case of the 4-isomers (I) since resonance energy must be destroyed in forming the quinone methide-type intermediate. A further

(III)
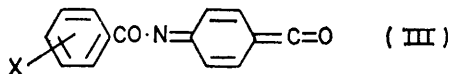
disadvantage of the $E1$ mechanism is that the conjugate base of the ester is not strong enough to expel the more strongly basic alkoxide ion. In the case of the carbamate esters the conjugate base is clearly strong enough to expel the weaker 4-nitrophenolate anion.[8b,c] There is much evidence that the $E1cB$ mechanism does not operate with alkaline hydrolysis of alkyl carbamates [8d,e,f] [ester (I) is a vinylogue of an acylated carbamate]. The k_2 parameter calculated from the data by use of equation (1) thus refers to bimolecular attack of hydroxide ion on the neutral ester carbonyl group.

The nature of the k_4 parameter is probably attack of hydroxide ion on the ester carbonyl of the conjugate base. The relative magnitudes of k_2 and k_4 (Table 3)

latter effect is probably due to a contribution to the ground state structure (IV) of the canonical form for the 4-ester which is not possible with the 3-isomer.

(IV)
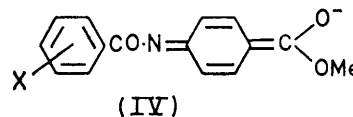
Sensitivities to substituent on the benzamido-function are on the whole not easily distinguished from zero for k_2 and k_4 for both *meta*- and *para*-series; agreement is observed with the results of Donohue, *et al.*[10] for ionisation of 4-(substituted benzamido)-phenols and -anilines. The parameter K_w/K_a has a Hammett sensitivity greater than unity for both esters (I) and (II) indicating a greater ' linkage ' than in the ionisation of benzoic acids.

Kinetically and spectroscopically observed ionisation constants are identical as illustrated by the good fit of the theoretical curves (derived in part from spectroscopic ionisation constants) and the experimental kinetic data (Figure 1); ionisation of tetrahedral adducts as postulated in the case of activated acyl anilides [11] is not therefor necessary to explain the kinetics.

[7] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743.

[8] (a) A. Williams and G. Salvadori, *J. Chem. Soc.* (*B*), 1971, 2401; (b) A. Williams, *J.C.S. Perkin II*, 1972, 808; (c) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975; (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) L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 1963, **52**, 852.

[9] E. A. Halonen, *Acta Chem. Scand.*, 1955, **9**, 1492.

[10] J. A. Donohue, R. M. Scott, and F. M. Menger, *J. Org. Chem.*, 1970, **35**, 2035.

[11] (a) R. L. Schowen and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1966, **88**, 1223; (b) S. S. Biechler and R. W. Taft, *ibid.*, 1957, **79**, 4927; (c) A. Bruylants and F. J. Kézdy, *Rec. Chem. Progr.*, 1960, **21**, 213; (d) P. M. Mader, *J. Amer. Chem. Soc.*, 1965, **87**, 3191.