Reaction of Amines and Oxygen Nucleophiles with 5-Nitrocoumaran-2-one: Nucleophilic and General Base Catalysis of Hydrolysis

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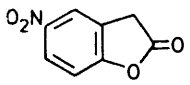
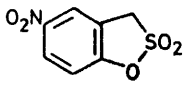
The reaction of nitrocoumaranone (1) with bases was studied using aqueous solution. Primary and secondary amines react to yield the 2-hydroxy-5-nitrophenylacetamide. A negligible deuterium oxide solvent isotope effect and a large Brønsted β_n confirm the nucleophilic pathway and a class II aminolysis. Carboxylic acids, phosphate, and heterocyclic amines yield the acid product, and the low Brønsted β, deuterium oxide solvent isotope effect of 2—3, and comparison with reactivity against 4-nitrophenyl acetate indicate a general-base catalysed path. Tertiary alkylamines (yielding acid) are more efficient than predicted from the general base Brønsted relationship, are less efficient than the primary amines of similar pK_a, and have negligible deuterium oxide solvent isotope effect; these data and comparison with 4-nitrophenyl acetate reactivity indicate a nucleophilic mechanism.

Consideration of frontier orbitals and stereoelectronic factors indicates that the *E*1cB mechanism is an ' allowed ' process which must be suppressed by the efficiency of trapping of the keten intermediate by the neighbouring hydroxy function.

PREVIOUS work has shown that the mechanism for alkaline hydrolysis of 5-nitrocoumaran-2-one (1) involves an addition–elimination (AE) process rather than an *E*1cB path.[1,2] The enhanced rate constant for alkaline hydrolysis of (1) over its acyclic analogue, 4-nitrophenyl 3-nitrophenylacetate,[3] is attributed [2] to increased accessibility of the carbonyl group in the rigid ring and the instability of *cis*-ester with respect to that of *trans*-esters.[4]



(1)



(2)

It is the purpose of this work to investigate the reactions of (1) with various nucleophiles in order to compare the results with those for 4-nitrophenyl acetate and for the sultone (2) from 5-nitro-2-hydroxyphenylmethanesulphonic acid.[5] The factors affecting the susceptibility of the lactone (1) to the observed nucleophilic and general base catalysed paths are considered.

EXPERIMENTAL

Materials.—The nitrocoumaranone (1) was prepared by the method of Tobias *et al.*[6] and had m.p. 186—187° (lit.,[6] 189—189.5°). The sultone (2) was from an earlier study.[5] Buffers were prepared from analytical grade materials or from recrystallised or redistilled bench grade products. All amines (except pyridine and 2,6-lutidine) were used in the form of hydrochlorides which were recrystallised from ethanol. Deuterium oxide (99.8% D) and a solution of deuterium chloride (DCl) in D_2O was obtained from the Ryvan Chemical Co. Ltd. Water used throughout the investigation was twice distilled from glass.

Methods.—Buffers were prepared with ionic strength 1.0M where necessary by the addition of KCl. The buffer solutions were diluted with 1M-KCl to vary the buffer concentration; in all cases studied here there was negligible pH variation on dilution. In some cases a less reactive buffer (for example 2,6-lutidine) had to be employed with a highly reactive species (for example ethylamine) in order to provide buffering capacity at a pH well below the p*K* of the conjugate acid of the species; in this case two buffer solutions were made up at the same pH, one containing the reactive species. These buffers were mixed to vary the concentration of the reactive species. The fraction of base (FB) of the reactive species was calculated from equation (1) where K_a is the ionisation constant of the conjugate acid of the reactive species.

The coumaranone (1) was dissolved in acetonitrile (2—4 mM) and 50 λ of this stock were added to 2.95 ml of buffer

$$FB = 1/(1 + a_H/K_a) \quad (1)$$

at 25° in a silica cell in the thermostatted cell compartment of a Beckman DBG, Unicam SP 600, or SP 800 instrument. Details of wavelength used and concentration range are recorded in Tables 1 and 2 together with thermodynamic

TABLE 1

Thermodynamic pK_a values [a]

Substrate	pK_a [b]	ε/l mol^{-1} cm^{-1} [c]
(2-Hydroxy-5-nitrophenyl) acetic acid	7.35 ± 0.05	17 900
N-(2-Hydroxy-5-nitrophenylacetyl)-piperidide	6.90 ± 0.05	17 300

[a] Ionic concentration maintained at 1M with KCl, 25° [b] Errors quoted are confidence limits. [c] This is similar to the extinction coefficient for the 4-nitrophenolate anion (F. J. Kezdy and M. L. Bender, *Biochemistry*, 1962, **1**, 1097).

pK_a values and extinction coefficient changes for substrate and product.

Rate constants (pseudo-first-order) were measured using a least-squares computer program or were obtained graphically. Values of absorption at infinite time, required for these methods, were observed experimentally or, in the case of slow reactions, calculated using equation (2) where

$$A_\infty - A_1 = (A_2 - A_1)^2/(2A_2 - A_3 - A_1) \quad (2)$$

A_1—A_3 are absorbances at times t_1—t_3 such that $t_2 - t_1 = t_3 - t_2$. In the latter case reactions were followed to at least 75% completion as judged from the absorbance change.

Product Analysis for the Reaction with Aniline.—The coumaranone (1) was dissolved in dioxan purified by passage through an alumina column to purge it from peroxides. This solution (1 ml containing 45 mg) was added dropwise to a mixture of dioxan (3 ml) and aniline buffer (4 ml, 0.5M, FB 0.5) over 2 h at room temperature. The solution was kept for 30 min to allow completion of the reaction; the rest of the lactone and further dioxan (0.7 ml) and aniline buffer (1 ml) were added and the mixture kept for 1 h. This procedure was necessary to avoid lactone precipitation.

TABLE 2

Rate data for attack of various species on 5-nitrocoumaranone (1) [a,m]

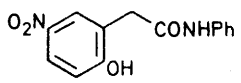
Species [h]	pK_a [b] ($pK_a^{D_2O}$)	k_B/l mol^{-1} s^{-1} [i,p]
Oxyanions		
1 Hydroxide [k]		1 050
2 Carbonate (4)	9.70 (10.37)	2.2 (400)
(4)		2.3 (D_2O)
3 Phenol (16)	10.03	40 [d]
4 Phosphate (6)	6.34 [e]	4.0×10^{-3} (350)
5 Acetate (4)	4.55 [e]	2.6×10^{-4} (340)
6 Formate (4)	3.55 [e] (3.97)	3.4×10^{-4} (340)
(3)		1.2×10^{-4}(D_2O)
7 Chloroacetate (7)	2.79 [e]	1.1×10^{-4}(340
8 Water [k]	−1.74 [e]	1.7×10^{-6}
Primary and secondary amines		
9 Piperidine (5) [i]	11.54	1.3×10^{4}
10 Ethylamine (15) [j]	10.94	1.9×10^{3}
11 β-Alanine (5) [i]	10.38	1.2×10^{3}
12 Glycine (5) [i]	9.81	620
13 Benzylamine (5) [i]	9.69	620
14 Morpholine (15) [j]	8.87	46
15 *N*-Glycylglycine (5) [j]	8.32	36
16 Methyl glycinate (5) [n]	7.73	11
17 Aminoacetonitrile (15) [f]	5.34	0.17(340) [m]
18 Aniline (6)	4.74 (5.33)	2.9×10^{-2}(340)
(4)		2.0×10^{-2}(D_2O)
19 TRIS(20)	8.23	0.27
Tertiary amines		
20 Triethylamine (22) [i,j]	10.96	650
21 *N*-Methylpiperidine (6) [i]	10.49	2.5
22 *NN*-Dimethylbenzylamine (4)	8.93	0.23
23 Triethanolamine (8)	8.12 (8.74)	0.34
(4)		0.32(D_2O)
24 *N*-Methylmorpholine (8)	7.41	3.7×10^{-2}
25 Imidazole (4)	7.20 (7.67)	5.5×10^{-3}
(3)		2.1×10^{-3}(D_2O)
26 Pyridine (9)	5.50 (5.88)	1.1×10^{-3}(340)
(3)		5.2×10^{-4}(D_2O)
27 Trimethylamine (4)	9.76	2.9 [g]

[a] 25°, ionic strength maintained at 1M with KCl; concentration of reactive species varied from 0.01 to 0.5M. [b] Except where stated, these values are from W. P. Jencks and J. Regenstein in ' Handbook of Biochemistry,' section J–187, ed. H. A. Sober, Chemical Rubber Company, Cleveland, 1970; ionisation constants for D_2O solvent are from this study. [c] Calculated assuming pK_w 14. [d] This value is a lower limit; the equilibrium constant, K_{eq}, for the nucleophilic reaction is 110 l mol^{-1}, and the lower limit for the reverse reaction (k_{-1} in Scheme 1) is 0.4 s^{-1}. [e] Value from ref. 5. [f] The value of k_3 for this substrate is 0.24 l mol^{-2} s^{-1}. [g] The upper limit for the reaction of trimethylamine with 5-nitrosultone (2) is 10^{-2} l mol^{-1} s^{-1}. [h] Value in parentheses is the number of determinations. [i] TRIS used as background buffer. [j] 2,6-Lutidine used as background buffer. [k] For data see Figure 1. [l] Except where stated in parentheses the wavelength for kinetics was 410 nm. [m] pK_a for the ionisation of the α-proton in (1) is 9.97 at 25°, 1M ionic strength. [n] Although hydrolysis of this buffer occurs at the pH corresponding to the buffering region of the species it is slow compared with the reaction in hand. Measurements of pH immediately before and after the aminolysis reaction were unable to detect significant decomposition. [p] Errors in k_B are $\leqslant \pm 10\%$ for the values quoted.

Water was then added till the crude product (3) separated. The precipitate was recrystallised from ethanol and had m.p. 195—197° (lit.,[7] 192°) (Found: C, 61.5; H, 4.5; N, 9.9. Calc. for $C_{14}H_{12}N_2O_4$: C, 61.8; H, 4.4; N, 10.3%). The i.r. and ^{1}H n.m.r. spectra are consistent with the amide structure.

N.m.r. spectra were measured with a JEOL 100 MHz instrument and microanalyses with a Hewlett–Packard 185 CHN analyser. M.p.s were determined using a Kofler Thermospan instrument and are corrected.

Determination of Ionisation Constants.—The acid (4) and amide product (3) were prepared *in situ* and used immediately for the pK_a determinations. The acid (4) was prepared by dissolving the coumaranone (0.7 mg) in acetonitrile (0.5 ml) and making up to 1 ml with aqueous KOH (1M). The piperidide (5) was prepared by dissolving the



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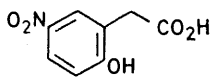

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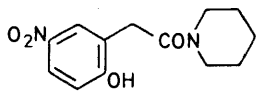


(5)

coumaranone (1) (1.4 mg) in acetonitrile (2 ml) containing piperidine (0.2 ml). The piperidide was chosen so that there could be no interference from the titration of excess piperidine over the pH range used to determine the pK_a. The pK_a values were measured after the solutions of the substrates had been allowed to stand for 30 min to allow for complete hydrolysis–aminolysis of the lactone. The following procedure was utilised. Substrate solution (50 λ) was added to 1M-KCl (2.5 ml) and the pH adjusted to between 9 and 10 using dilute HCl. This solution was equilibrated at 25° in a silica cell in the thermostatted cell compartment of a Pye–Unicam SP 500 spectrophotometer which had been modified such that: (a) a Radiometer pH-probe and micropipette could be inserted in the top of the cell without interfering with the light path and (b) stirring was possible in the silica cell with a small magnetic follower activated by a magnetic paddle wheel rotated by the thermostatting water. The pH was lowered by adding small portions of dilute HCl (0.02—0.1M) through the micropipette by manual operation of a Radiometer ABU 11 autoburette. A Radiometer digital pH-meter PHM 62 was utilised to measure pH to ±0.01 units. The absorbance was measured at 400 nm over a range of pH values encompassing the pK_a and a correction was applied, where necessary, to allow for the small volume of acid added. The results were fitted to a normalised curve using two-cycle semi-logarithmic graph paper according to the method of Brubacher *et al.*[8] We shall report full details of the modified cell housing in a future publication.

Ionisation constants of other species were measured potentiometrically using a Radiometer titration set comprising REC 61 Servograph, REA Titratigraph, PHM 62 pH-meter, TTT 60 titrator, and ABU 11 autoburette. Subtraction of the solvent titration curve gave data which were processed as above.

Deuterium Oxide Solvent Isotope Effects.—Sodium deuterioxide solution was prepared by dissolving small pieces of

sodium in deuterium oxide and was standardised with standard HCl. Deuterium chloride solution was standardised with standard KOH.

Pyridine buffers were prepared from analytical grade pyridine and DCl; formate buffers from sodium formate and DCl. In the case of imidazole, triethanolamine hydrochloride, and aniline hydrochloride which possess exchangeable protons, these reagents were initially dissolved in D_2O and the latter removed *in vacuo*. Imidazole buffers were then prepared using the deuteriated imidazole and DCl; aniline and triethanolamine buffers were prepared from DCl and NaOD. In the last cases the hydrogen content of the D_2O solvent was not increased by $>0.2\%$ H. Carbonate buffers from $NaHCO_3$ and Na_2CO_3 did not increase the hydrogen by $>0.4\%$ H.

The pH of the deuterium oxide buffers as recorded on the pH-meter was corrected to yield pD by equation (3).[9a]

$$\text{pD} = \text{meter reading} + 0.37 \qquad (3)$$

INDO calculations were carried out on the University of London CDC 7600 computer *via* the University of Kent Computer Centre. The program was modified from that of Pople and Beveridge [9b] by Drs. A. J. Lawson and K. A. F. Record of this laboratory. Angles and bond lengths are from ref. 9*c*.

RESULTS

Repetitive scanning of the spectrum over a wavelength range for the reactions of trishydroxymethylaminomethane (TRIS) (pH 8.4), phosphate (pH 6.7), acetate (pH 4.4), and 2,6-lutidine, ethylamine and morpholine (all pH 7.5, the latter two amines being buffered with 2,5-lutidine) indicated tight isosbestic points consistent with a simple 1 : 1 stoicheiometry. The absorbance changes observed at a pH value greater than the pK_a of the liberated nitrophenol were consistent with the release of the latter and were independent of buffer type and concentration. In the case of 2,6-lutidine at pH 7.5 the absorbance change at 400 nm was smaller than that for ethylamine and morpholine at the same pH consistent with the formation of a different product, presumably the acid (4) as opposed to the amide. Reference to Table 1 indicates that the pK_a of the acid (4) is 7.35 and that of the piperidide (5) is 6.90; variation in the latter value for a series of amides should not be significant. Thus at pH 7.5 a significantly larger amount of the nitrophenolate product would be protonated in the case of the acid (4) as opposed to the amide product.

Measurement of Second-order Rate Constants.—The rate law for release of the nitrophenolate absorption from (1) in all the buffers studied was pseudo-first-order over at least 90% of the reaction when infinity readings were directly obtained. The observed pseudo-first-order rate constants are a function of the concentrations of the varous nucleophiles present in the buffers and the general law is given in equation (4) where K_a is the ionisation constant of the

$$k_{obs}(1 + K_a/a_H) = k_{OH}[OH^-] + k_{H_2O}[H_2O] + k_B[\text{Nuc}] + k_3[\text{Nuc}]^2 + k_{buffer}[\text{Buffer}] \qquad (4)$$

coumaranone. The k_3 term was only observed in the case of reaction with aminoacetonitrile.

The bimolecular rate constants for attack of hydroxide ion and the water term were measured [together with the pK_a of (1)] by means of a ' grid-search ' least-squares computer program on k_{obs} data for zero buffer concentration. Rate constants at high pH were obtained with hydroxide buffer and lower pH data was from extrapolation from plots *versus* buffer concentration. The complete pH–profile is shown in Figure 1 and fits the theoretical equation (5).

$$k_{obs} = (k_{H_2O}[H_2O] + k_{OH}[OH^-])/(1 + K_a/a_H) \qquad (5)$$

Bimolecular rate constants (k_B) for the reaction of nucleophiles with (1) were obtained by plotting k_{obs} *versus* the total nucleophile concentration at a constant pH and fraction of base (FB). The slopes of these plots (k_2, see Figure 2) were plotted *versus* FB and extrapolation to FB 1 and zero gives the required k_B and k_A terms; k_A terms were not observed in this work. For many of the species (particularly of the amines) only one fraction of base was employed and k_B was obtained assuming no k_A term or other complication by dividing k_2 by FB.

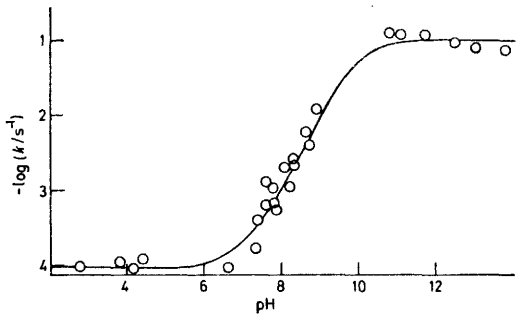


FIGURE 1 Dependence on pH of the hydrolysis of 5-nitrocoumaranone (1) at ionic strength 1M, 25°. Line is theoretical from equation (5) and parameters are from Table 2

Only in the case of aminoacetonitrile did plots of k_{obs} *versus* total amine concentration exhibit distinct upward curvature (Figure 3). No intercepts were observed at zero buffer concentration as expected from the pH profile for hydrolysis (Figure 1). Thus equation (4) reduces to equation (6); at these pH values there is no contribution from the conjugate base form of the lactone (1). A slight upward curvature is apparent in the curve for the aniline

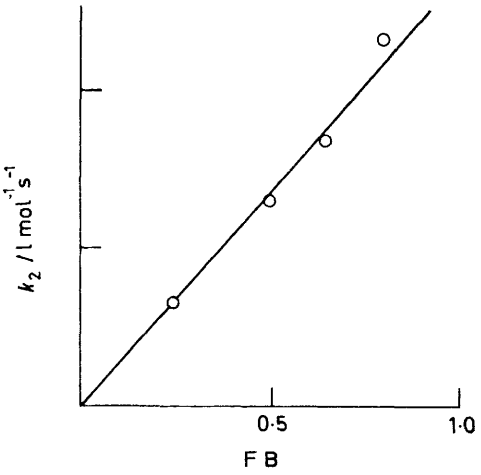


FIGURE 2 Dependence of k_2 for TRIS buffer on the fraction of free base (FB). Line is theoretical using data from Table 2; conditions as in Table 2

$$k_{obs} = k_B[\text{Nuc}] + k_3[\text{Nuc}]^2 \qquad (6)$$

case. The parameters k_B and k_3 were determined by plot-

ting k_{obs}/[total amine] *versus* [total amine] at constant pH. The intercepts of these plots at zero amine concentration when plotted *versus* FB give k_B and the slopes *versus* FB[2] give k_3.

The mechanism corresponding to the pH profile for hydrolysis of (1) has been elucidated from the evidence of a

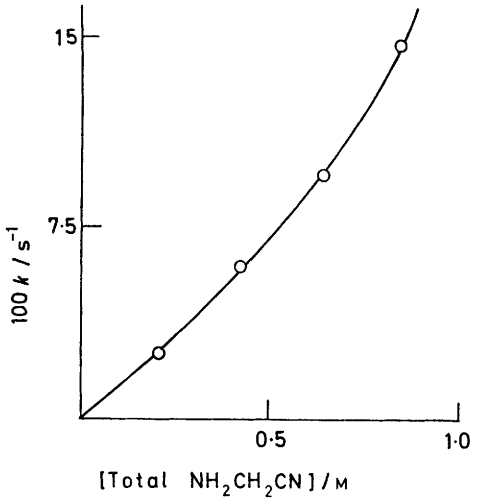
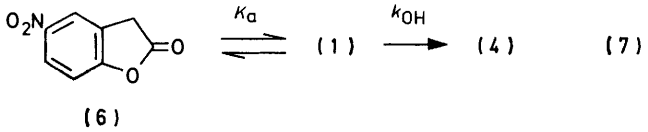


FIGURE 3 Dependence of k_{obs} on the total aminoacetonitrile concentration; lines are theoretical from parameters in Table 2

deuterium oxide solvent isotope effect [1] and is shown in equation (7). The present data agree with those of earlier workers, namely $k_{OH} = 1\ 290$ l mol^{-1} s^{-1} and p$K_a = 9.7$ [1] at ionic strength 0.2M; the value for k_{H_2O} has not previously been reported.

Determination of the Equilibrium Constant for the Reaction of (1) *with Phenolate Anion.*—The equilibrium constant for



reaction of phenolate anion with (1) was measured at three different pH values using TRIS buffer; details of the conditions used are recorded in Table 3. Adding the coumaranone to the buffer containing the phenol leads to a rapid initial increase in absorbance at 410 nm depending on the phenol concentration. The second stage of the reaction involves

TABLE 3

Equilibrium constants for reaction of phenolate anion with (1) [a]

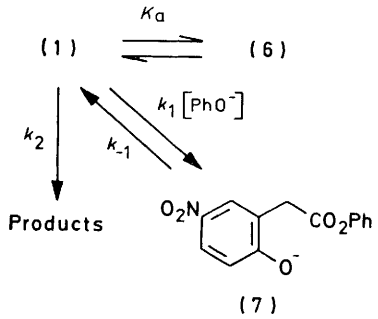
pH	FB	Concentration range/M	K'_{eq}/ l mol^{-1}	K_{eq}/ l mol^{-1}
8.34	0.02	0—0.15(5)	2.08	104
7.92	0.0077	0—0.24(5)	0.788	102
8.88	0.0661	0—0.15(6)	7.35	111

[a] TRIS buffer, 25°, wavelength 410 nm, ionic strength maintained at 1M with KCl.

a first-order increase in absorbance; the rate constant decreases with phenol concentration. Scheme 1 is proposed to account for these results. It is proposed that the initial absorbance increase is due to the production of ester (7) which decays through the lactone (1) to thermodynamically stable products, the acid (4) and *N*-acyl-TRIS. The equilibrium constant (K_{eq}) is given by equation (8). The concentration of (1) is directly related to the difference between absorbance at zero and infinite time (A_{eq}). We

$$K_{eq} = (7)/([(1)] \cdot [PhO]) \quad (8)$$

may assume that the extinction coefficients of the products and (7) are the same at the wavelength used [this is reasonable since the extinction coefficients of (4) and (5) are the



SCHEME 1

same within the limits of experimental error at 400 nm, see Table 1].

Equation (8) then reduces to (9) where A_i is the initial change in absorption. A correction must be made for the ionisation of (1) to give carbanion (6) which has significant

$$K_{eq} = A_i/(A_\infty - A_i)[PhO^-] \quad (9)$$

absorption at 410 nm.[1] This absorbance (A_x) may be measured in the absence of phenol and gives equation (10). A plot of $(A_i = A_x)/(A_\infty - A_i)$ *versus* total phenol concentration is shown in Figure 4 and the parameters recorded in Table 3.

$$(A_i - A_x)/(A_\infty - A_i) = K_{eq}FB([PhOH] + [PhO^-]) \quad (10)$$

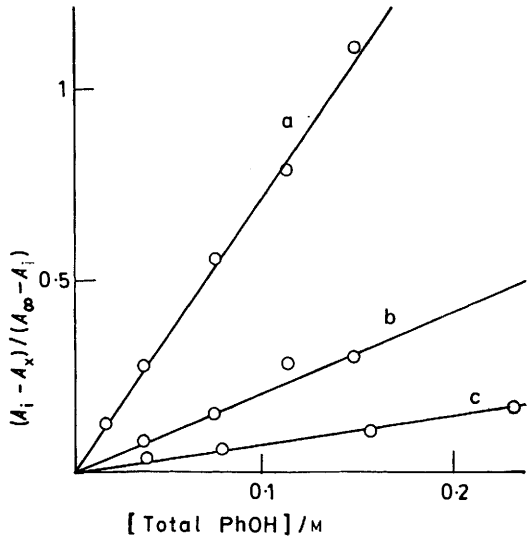


FIGURE 4 Reaction of 5-nitrocoumaranone with buffers containing phenol; dependence of the initial absorbance increase (410 nm) on phenol concentration. FB: a, 0.0661; b, 0.022; c, 0.0077. Lines are theoretical from parameters in Table 3

DISCUSSION

Figures 5 and 6 illustrate the Brønsted plots for the attack of various nucleophiles on (1); primary and

secondary amines except TRIS fall on a line of slope β_n 0.83. Product analysis in the case of the aniline nucleophile shows that the amide is formed to a major extent and, because of the good correlation, it is assumed that all the primary and second amines react through a nucleophilic mechanism. Further evidence for the

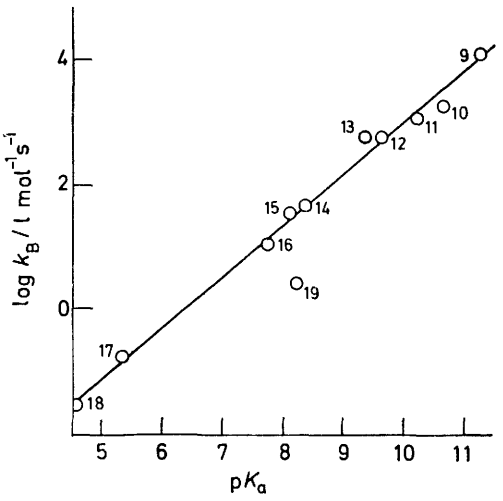


FIGURE 5 Brønsted plot for the reaction of primary and secondary amines with 5-nitrocoumaranone (1). Data and identification numbers are from Table 2 and the line is theoretical for β_n 0.83 (r 0.996); TRIS (19) has been excluded from the correlation

nucleophilic pathway is that the pK_a of the product (5) from reaction of piperidine with (1) differs from that of the acid product (4). The deuterium oxide solvent isotope effect (1.45, see Table 2) is also consistent with the nucleophilic pathway for the aniline.[10]

The open-chain analogue of (1), 4-nitrophenyl 3-nitrophenylacetate, should be an ester typical of Class II [11] in its aminolysis reactions. Thus the rate-limiting step should be breakdown of $T^{\pm}$ [11] to yield amide; in the present case the departure of nitrophenoxide ion should be slower than the entropically favoured analogous intermolecular reaction further substantiating rate-limiting $T^{\pm}$ decomposition.

The high β_n obtained here is in agreement with this pathway; previous studies have yielded β_n 0.9 $\pm$ 0.1 for esters of Class II.[12] On the basis of previous work, a break in the Brønsted line is expected for amines *ca.* 3—5 pK units more basic than the 4-nitrophenolate anion of (1).[13] This break corresponds to a change in rate-limiting step from breakdown of $T^{\pm}$ to its formation. In our system the most basic amine used, piperidine, is only *ca.* 4 pK units more basic than 4-nitrophenolate anion; consequently, it is not significant that a break is not observed in the Brønsted plot (Figure 5).

A Class II ester is expected not to possess second-order terms in amine for the aminolysis reaction because $T^{\pm}$ breakdown is rate-limiting (the rate-limiting step corresponds to $k^{\pm}$ defined by Satterthwait and Jencks' equation 5 in ref. 11; the product from this reaction is N-protonated amide which rapidly breaks down to amide); $k^{\pm}$ is larger than the rate constant for proton transfer from $T^{\pm}$ to a general base. Assistance by general base removal of a proton in the decomposition of $T^{\pm}$ might be expected for weakly basic amines where the acyl group transfer possesses ' Class II ' character.[11,12] The observation of a k_3 term [equations (4) and (6)] for aminoacetonitrile reaction with the coumaranone seems consistent with this explanation. The 4-nitrophenoxide anion is expected to be a relatively poor leaving group (from $T^{\pm}$) compared with aminoacetonitrile so that the system is close to, or may even enter, the Class III group of reactions.

Reactions of oxygen nucleophiles of low basicity, pyridine and imidazole, fall on a Brønsted line of slope β 0.4. In the case of imidazole, formate, and pyridine reactions deuterium oxide solvent isotope effects in the region 2—3 (Table 2) are strong evidence for general base catalysis.[10] The Brønsted exponent agrees closely with that obtained by Jencks and Carriuolo (0.47) for the reaction of a series of bases with ethyl dihalogenoacetates.[14] It may be significant that the water catalysis point for the coumaranone falls on the general base correlation line in the present work (Figure 6) and in that of the earlier work.[14] The mechanism for this reaction has been attributed to general base catalysis by a second

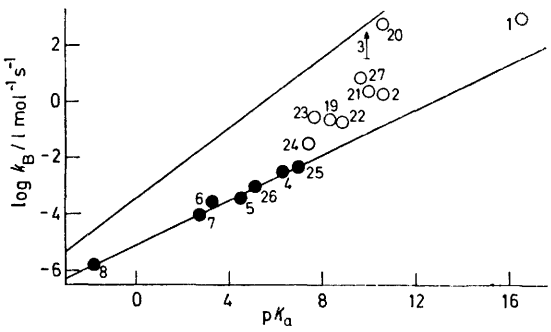


FIGURE 6 Brønsted plot for the reaction of species with 5-nitrocoumaranone (1); data and identification numbers are from Table 2. The upper line is for primary and secondary amines (Figure 5). The lower line is for β 0.4 (r 0.988) and refers to general base catalysis; the filled circles are the points used for this correlation

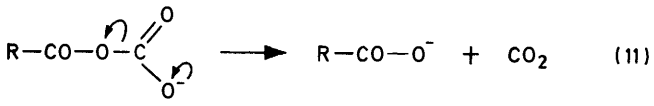
water molecule.[15] General base catalysis of water attack (a poor nucleophile) is consistent with the observation of general base catalysed aminolysis by weakly basic amines.

Tertiary amines of higher basicity than imidazole show enhanced reactivity against (1) compared with the general base correlation (Figure 6) but the Brønsted correlation for these species is poor with slope β_n 0.97 (r 0.861). This poor correlation, presumably due to steric effects, together with the small solvent deuterium oxide isotope effect for triethanolamine (Table 2) is consistent with a nucleophilic reaction. Rapid hydrolysis of the acylammonium salt yields the acid (4).

Reaction of carbonate dianion with (1) is consistent with a nucleophilic process in view of the small deuterium oxide solvent isotope effect (Table 2). It is possible that

the anhydride intermediate formed in this reaction decomposes rapidly to acid (4) *via* a unimolecular process [equation (11)].

The bimolecular rate constants of Table 2 may be compared with those for attack of the nucleophiles on 4-nitrophenyl acetate (Figure 7). An excellent cor-



(11)

relation is obtained and a line of unit slope goes through most of the points over a wide range of nucleophile structure. The coumaranone (1) is *ca.* 150-fold more reactive than the ester. It has been postulated that the higher rate constant for the alkaline hydrolysis of (1) over its open chain analogue 4-nitrophenyl 3-nitrophenylacetate (a factor of 11.7-fold) [3] could arise from increased accessibility of the carbonyl group in the rigid ring of the lactone (1).[2] If this were the case TRIS, a hindered nucleophile, would show less steric retardation in its reaction with (1) than with 4-nitrophenyl acetate. Hydroxide and carbonate which are bulky by virtue of extensive solvation fall below the amine correlation line (Figure 6); the close correlation (Figure 7) for all these nucleophiles indicates that the steric requirements of open chain ester and lactone are closely similar.

Significant deviations from the line (Figure 7) involve phosphate, acetate, pyridine, and imidazole which we

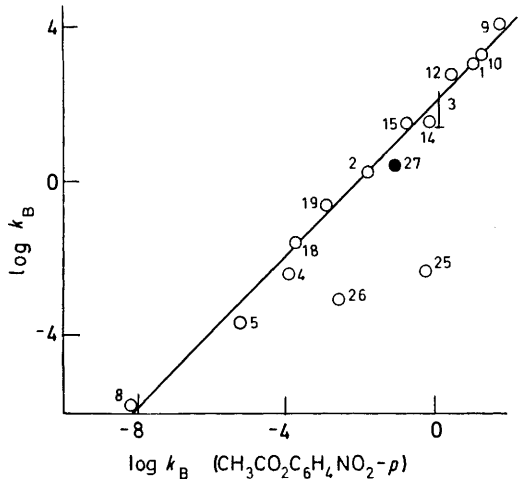


FIGURE 7 Comparison of bimolecular rate constants at 25° for attack of species on (1) and 4-nitrophenyl acetate. Data and numbers for identification are from Table 2 and from refs. 12*a*, 16, and 18*b*. The filled circle refers to the trimethylamine reaction (26.2° with 4-nitrophenyl acetate). The line is arbitrary of unit slope; units of k_B are in l mol^{-1} s^{-1}

have already concluded possess a general base path for attack on (1). Imidazole and pyridine are known to react with 4-nitrophenyl acetate *via* a nucleophilic path.[17,18] Reaction of acetate ion with 4-nitrophenyl acetate has both nucleophilic and general base pathways; the former accounts for *ca.* 70% of the reaction flux.[19] The acetate point lies near the line (Figure 7) and we believe this to be due to the significant contribution of the general base mechanism for the 4-nitrophenyl acetate reaction.

Evidence for nucleophilic attack on (1) by trimethylamine comes from a comparison of reactivities with 4-nitrophenyl acetate (Figure 7) and with the 5-nitrosultone (2) (Figure 8). The point in the former correlation only deviates to a minor extent from the line due presumably to slightly different conditions (5% dioxan–water and 26.2°) in the open chain ester case.[18b] Since trimethylamine acts as a nucleophile to the acetate [20] then the correlation indicates a nucleophilic path for its reaction with (1). A good correlation (slope 1.2) exists between lactone and sultone reactivities (Figure 8) although there is a deviation for some of these points on the corresponding Brønsted plots (see Figures 5 and 6

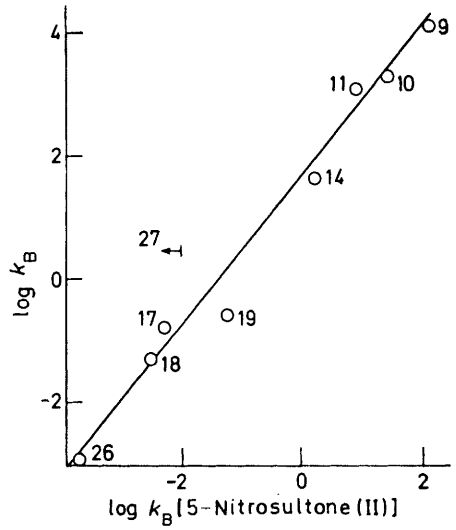


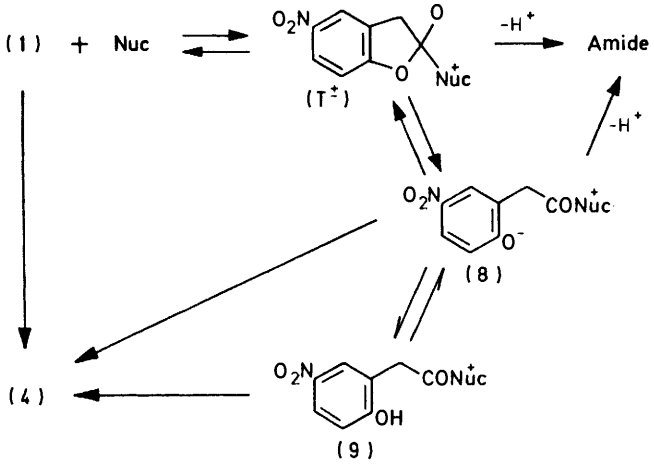
FIGURE 8 Comparison of bimolecular rate constants at 25° for attack of amines on (1) with attack on the 5-nitrosultone (2). Data and identity numbers are from Table 2 and ref. 5. The arrow represents an upper limit for the 5-nitrosultone reaction for trimethylamine estimated from this study. The line is arbitrary with a slope of 1.2; units of k_B are in l mol^{-1} s^{-1}

and ref. 5). The point for TRIS shows a slight enhancement for the sultone possibly reflecting a different steric requirement for the substrates. The reaction of trimethylamine and tertiary alkylamines with sultone (2) involves general base catalysis.[5] If general base catalysis operated in both sultone and lactone cases the point for trimethylamine should lie closer to the line for the other amines. However, the point deviates by a lower limit of *ca.* 10-fold indicating different mechanisms.

The low reactivity of hydroxide compared to its basicity (Figure 6) has been observed in other reactions including that with 4-nitrophenyl acetate.[15] This unusually low reactivity may be a result of the extensive solvation of the hydroxide ion.[10,15,21]

Nucleophilic versus *General Base Catalysis.*—The mechanism shown in Scheme 2 is postulated to explain the differences between nucleophilic and general base catalysis for (1). The major difference between 4-

nitrophenyl acetate and (1) is that the initial product (8) has an advantage in that return to reactants is intramolecular. The tetrahedral addition intermediate ($T^{\pm}$) formed by attack of the nucleophile on (1) should behave in a similar manner to that from 4-nitrophenyl acetate.

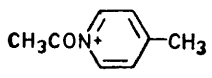


SCHEME 2

The reactions of primary and secondary amines with (1) show no mechanistic differences from their analogous reactions with 4-nitrophenyl acetate presumably because ($T^{\pm}$) can rapidly deprotonate and degrade to give a stable amide product. This path is not available for oxyanion or tertiary amine nucleophiles. It is possible that the decomposition of ($T^{\pm}$) is more favourable than the corresponding species in acyclic attack because model building for ($T^{\pm}$) indicates considerable *I* strain which would be released on cleavage. Rate-limiting addition induced by the fast decomposition step would explain the observation of only one amine with a substantial k_3 term but is inconsistent with previous arguments. The mechanism for aminolysis by the tertiary amines would require the participation of an *N*-protonated amide followed by fast proton transfer (Scheme 2) a pathway which is not now thought to be impossible.[11,22]

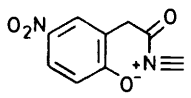
As the basicity of the oxyanion nucleophile is reduced, the equilibrium between (1) and (8) (Scheme 2) will lie almost entirely on the side of (1) so the formation of (8) and its breakdown cannot compete with the general base-catalysed reaction.

A value for the rate constant for intramolecular breakdown of (8) to (1) may be estimated for a pyridine-like nucleophile. *N*-Acetyl-4-methylpyridinium ion (10) reacts with 4-nitrophenolate anion with a rate constant 9.1×10^4 l mol^{-1} s^{-1} at 25°; allowing a factor of 10^5M as the effective molarity (see later) to estimate an intramolecular rate constant[23,24] yields 9.1×10^9 s^{-1} for the reverse process. Previous work on the decomposition of *N*-acylammonium ions[25,26] shows that the intermolecular decomposition of the intermediate (8) could not compete with the intramolecular attack (*N*-acetylpyridine has a decomposition rate constant 0.4—6.9 s^{-1}).[25,26]



(10)

The observation of a deuterium oxide solvent isotope effect of 1.09 for reaction of triethanolamine with (1) indicates that $k_2 > k_{-1}$ (as in Scheme 1 with a tertiary amine instead of phenolate anion as a nucleophile); we propose that for this amine and other tertiary alkylamines the reverse process (k_{-1}) is suppressed. An explanation for suppression of k_{-1} could be a process where the attacking anion ($^-O^-$) is held away from the carbonyl centre for the reverse step by attraction to the positive charge on the leaving group ($^-\overset{+}{N}$) and by steric repulsion by the leaving group (11). This explanation has precedent in a proposal of Young and his co-workers[27] to explain the absence of oxazolinone formation in peptide syntheses *via* aminoacyl azides; the oxyanion nucleophile (12) is proposed to be attracted to the central nitrogen of the azide. This type of interaction presumably does not occur in the pyridine and imidazole cases because the charge in the intermediate from these reagents is delocalised. In the triethanolamine case a substantial solvent isotope effect would be expected in the overall rate constant if k_2 were rate limiting because this step involves water attack.



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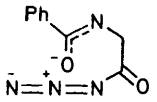


(12)

Rates and Equilibria.—Using the data of Figure 7 and a rate constant for phenolate anion attack on 4-nitrophenyl acetate[12a] we estimate k_1 to be 160 l mol^{-1} s^{-1} for phenolate anion attack on (1); from K_{eq} a value of 1.5 s^{-1} may be deduced for k_{-1}. Capon[23] estimated a rate constant k_{-1} of 7×10^3 l mol^{-1} s^{-1} for the cyclisation of phenyl 2-hydroxyphenylacetate. If we assume a reasonable Brønsted exponent for variation of the substituents on the aromatic ring of the acid to be —1 due to a product-like transition state, then k_{-1} for phenolate release from phenyl 2-hydroxy-5-nitrophenylacetate is *ca.* 7 s^{-1}. Both these estimates are in excess of the lower limit determined experimentally (Table 2, footnote *d*).

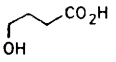
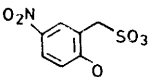
An estimate of the effective molarity may now be made for the cyclisation of phenyl 2-hydroxy-5-nitrophenylacetate compared with the attack of 4-nitrophenolate anion on phenyl acetate[12a] (see Table 4); using k_{-1} 1.5 s^{-1} the effective molarity is 3.8×10^4M comparable with that from Capon's work[23] for phenyl 2-hydroxyphenylacetate of 2.5×10^5M. These values are to be expected from a relatively 'tight' transition-state normally found in nucleophilic reactions at ester links.[24]

Table 4 compares equilibrium constants for reactions of five-membered ring species similar to lactones. The equilibria favour the five-membered ring with respect to the acyclic reaction as might be expected from entropy

considerations.[24,28] It is interesting to compare the 5-nitrocoumaranone (1) with the 5-nitrosultone (2) equilibrium constants for reaction with phenolate anion. The latter is *ca.* 1 000-fold larger than the former (Table 4). We attribute this to an increased ring strain in the reaction for coumaranones (Table 2) indicates that an *E*1cB process is not operating. The attack of amines on ketens is not expected as a rate-controlling step (as would be required by the kinetic results) because these rate constants are usually very large.

TABLE 4

Equilibria and rate constant data for the reactions of cyclic ester derivatives compared with the corresponding acyclic reactions [a]

Reaction	k_1	k_{-1}	K_{eq}
$PhO^- + (1) \rightleftharpoons (7)$	160 [j,b]	1.5 [h,b]	110 [i,b]
$PhO^- + CH_3CO_2C_6H_4NO_2\text{-}p \rightleftharpoons CH_3COOPh + p\text{-}NO_2C_6H_4O^-$	0.97 [j,c]	4.0×10^{-5} [j,c]	2.4×10^4
$H_2O +$  $\rightleftharpoons$ 			0.37 [d]
$H_2O + CH_3CO_2Et \rightleftharpoons CH_3CO_2H + EtOH$			16 [k,e]
$H_2O +$  $\rightleftharpoons$ Succinic acid	2.6×10^{-3} [h,f]	2.9×10^{-9} [h,]	9.1×10^5 [f]
$H_2O + (Ac)_2O \rightleftharpoons 2\ CH_3COOH$	2.7×10^{-3} [h,g]	8.1×10^{-15} [j,g]	3.3×10^{11} [k,g]
$PhO^- +$  $\rightleftharpoons$ 	62 [l,j]	5.2×10^{-4} [m,h]	1.4×10^5 [m,j]

[a] 25° in water; all data refer to water at unit activity where applicable. [b] This work. [c] From ref. 12*a*. [d] From ref. 31. [e] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1964, **86**, 4651. [f] Ref. 29. [g] Ref. 28 and J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837. [h] Units of s^{-1}. [i] Units of 1 mol^{-1}. [j] Units of 1 mol^{-1} s^{-1}. [k] Units of mol l^{-1}. [l] Ref. 5. [m] Ref. 29*c*.

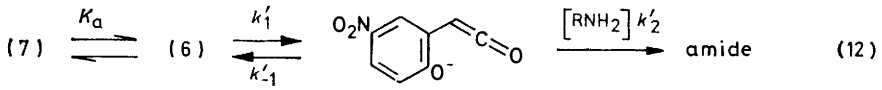
cyclic sulphonate ester [29] compared with that in the lactone.

Stereoelectronic Control.—Acyl-group transfer reactions of both coumaranone and sultone do not involve elimination–addition pathways; we believe that in the case of the sultone (2) this is due to the high energy of the sulphene-like transition-state which must take up a 'perpendicular' or skewed conformation (13) rather than the more stable planar form.[5,30] A further

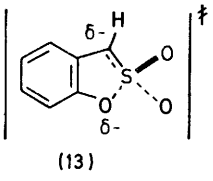
The rate constant for aminolysis if the major mechanism were rate limiting attack of amine on the keten [equation (12)] would be given by equation (13). Thus

$$\text{Rate} = \frac{k'_1 k'_2[\text{RNH}_2][(1)]}{k'_{-1}} \Big/ (1 + a_H/K_a) \quad (13)$$

at pH values below the pK_a of the lactone (1) such as in the reactions with TRIS buffers equation (13) reduces to (14) which predicts that the pseudo-first-order rate



stereoelectronic factor against the formation of the sulphene is that the frontier orbitals involved in the reaction are of the wrong symmetry (14) involving an



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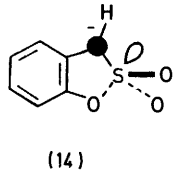


(14)

empty anti-bonding orbital in the plane of the sultone (in line with the S–O bond) and a filled *p*-orbital perpendicular to the plane at the α-carbon.

The observation that aminolysis is a bimolecular

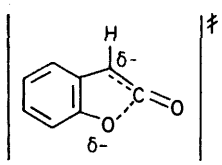
constants are inversely proportional to the hydrogen ion concentration; Figure 2 indicates no upward curvature as would be required by equation (14).

$$\text{Rate} = \frac{k'_1 k'_2}{k'_{-1}}[\text{RNH}_2][1]K_a/a_H \quad (14)$$

Moreover, Tobias and Kezdy [1] have already shown that the AE pathway for hydrolysis is favoured over the production of the keten; thus the observation of predominantly amide product in reaction of lactone with amine buffers would indicate a path *more* favourable than the hydrolysis, namely an AE mechanism.

No stereoelectronic control is apparent in the coumaranone case since the keten-like transition-state can take up a stable conformation (15); the frontier orbitals also

possess the correct symmetry for interaction (16) where a lone pair orbital on the oxygen is in the same plane (that of the five-membered ring) as the anti-bonding orbital on the carbon (in-line with the C–O bond). We conclude that a keten intermediate is captured very much more favourably by the intramolecular hydroxy group than



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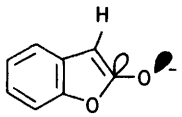

(16)

by another nucleophile thus suppressing the *E*1cB mechanism.

The question of the enhanced reactivity of the coumaranone over its acyclic analogue remains to be answered. The *I* strain [31] present in a γ-lactone is released on forming the tetrahedral intermediate but this enhancing effect is presumably balanced by the presence of unfavourable torsional forces in the transition state.[32] Release of strain on cleavage of the five-membered ring cannot be an accelerating factor because this step is post-rate limiting. We should point out here that the *cis*-effect contributes *ca.* 2.5 kcal mol^{-1} to the efficiency as estimated by Curl [4a] and Tabuchi [4c] which yields a rate constant ratio of the same order of magnitude as is observed for the cyclic–acyclic ester hydrolyses,[2] namely between one and two powers of ten. We estimate, using INDO calculations, that the *cis*-form of formic acid is less stable by *ca.* 0.8 kcal mol^{-1} than the *trans*-form. Our calculated dipole moments are 1.26 and 2.50 D respectively for *trans*- and *cis*-acids and some measure of confidence in the calculations may be had by comparison with the observed dipole moment (presumably for the *trans*-form) of 1.40 D.[33]

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