The Mechanism of Hydrolysis and Ethylaminolysis of *N*-Benzoylglycine and *N*-Benzoylsarcosine Esters

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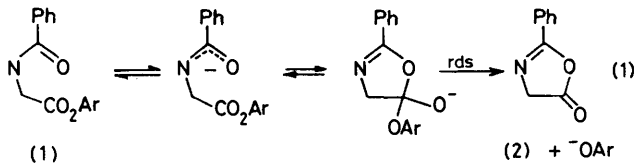
The hydrolysis and ethylaminolysis of *N*-benzoylglycine and *N*-benzoylsarcosine esters have been studied for a range of leaving hydroxy-functions with pK_a from 5.45 to 15.5. Ethylaminolysis of *N*-benzoylglycinate esters involves kinetic terms in $[EtNH_2]$ and $[EtNH_2][OH^-]$. The mechanism of ethylaminolysis of the glycinates does not involve the oxazolinone intermediate as a major contributor to the reaction flux; more than 99% of oxazolinone formed is partitioned to amide. The reactions studied encompass Class I, II, and III mechanisms as demonstrated by characteristic 'S-shaped' Brønsted profiles. The absence of kinetic terms in $[EtNH_2]^2$ is taken as evidence for a concerted formation of anionic tetrahedral intermediate (T^-) from hydroxide-assisted attack of ethylamine on *N*-benzoylglycinate ester. The hydrolysis of 2-chloro-4-nitrophenyl *N*-benzoylsarcosinate in neutral solution involves an intermediate; this is shown not to be the *N*-methylphenyloxazolinone cation but results from intramolecular attack of the neutral amide on the activated aromatic nucleus.

STUDIES of the alkaline hydrolysis of *N*-benzoylglycinate (hippurate) esters led to the conclusion that an oxazolinone intermediate is formed with rate-limiting expulsion of the phenolate group [equation (1)].[1,2] Esters with poor leaving groups such as methanol hydrolyse *via* the normal AE (addition-elimination) mechanism in alkali.[1-3]

In a recent report we showed that aminolysis of 4-nitrophenyl hippurate proceeds *via* the AE mechanism; the rate constant for release of 4-nitrophenol is linearly dependent on the amine concentration and with 0.4M ethyl glycinate the rate constant is some 10-fold larger than the rate constant for oxazolinone formation. Using data from McCarthy and Hegarty[4] for the attack of glycine on phenyloxazolinone and from de Jersey, Kortt, and Zerner on hydroxide attack it may be shown that in 0.02M-glycine buffer at a fraction of base (FB) of 0.5 that the product ratio amide/acid is *ca.* 600. McCarthy and Hegarty[4] have shown that an activated



O-(*N*-benzoylglycyl)-1-hydroxypyrazole ester undergoes transamination to glycine (0.01M, pH 9.8) *via* the oxazolinone. It is the purpose of this investigation to study the effect of leaving-group variation on the aminolysis reaction of *N*-benzoylglycinates and *N*-benzoylsarcosinates.

EXPERIMENTAL

Materials.—Hippurate esters were prepared as follows. Methyl and 2-chloroethyl hippurates were prepared from hippuric acid and the corresponding alcohol by refluxing for 16 h with benzene; Dowex acid resin was used as a catalyst and water removed with a Dean and Stark apparatus.[2] Filtration and evaporation of the solvent gave the crude ester. 2-Chloroethyl hippurate was recrystallised from benzene–light petroleum and had m.p. 56.5—58 °C (lit.,[5] m.p. 59 °C). The methyl ester was recrystallised from methanol–water and had m.p. 80—82 °C (lit.,[6] m.p. 80—81.5°).

2-Nitrophenyl, 2-chloro-4-nitrophenyl, and 3-nitrophenyl hippurates were prepared by stirring the appropriate phenol with hippuric acid and dicyclohexylcarbodi-imide in equimolar quantities in ethyl acetate at room temperature for 5 h. The urea product was filtered off and the solvent evaporated to yield the crude esters which were recrystallised from methanol. The 3-nitrophenyl ester had m.p 120—123 °C (lit.,[7] m.p. 118—122°) and the 2-chloro-4-nitrophenyl had m.p. 151—153° (Found: C, 54.0; H, 3.2; N, 8.2. $C_{15}H_{11}ClN_2O_5$ requires C, 53.8; H, 3.3; N, 8.4%). The 2-nitrophenyl ester had m.p. 107.5—109.5 °C (lit.,[8] m.p. 108—110 °C).

Phenyl and 4-nitrophenyl hippurates were prepared from hippuryl chloride,[7] pyridine and the corresponding phenol in methylene chloride by stirring the mixture at 0 °C for 1 h.[7] The suspension was stirred overnight at room temperature and the crude ester obtained by filtration, washing of the filtrate with dilute HCl followed by $NaHCO_3$ solution, drying of the filtrate with $MgSO_4$, and evaporation. The phenyl ester was recrystallised from benzene and had m.p. 102—104 °C (lit.,[7] m.p. 104 °C). The 4-nitrophenyl ester was recrystallised from methanol and had m.p. 168—170 °C (lit.,[7] m.p. 170—171 °C).

2,2,2-Trifluorethyl hippurate was prepared by slowly adding hippuryl chloride to the alcohol cooled in ice. Pyridine was then added (equimolar quantity) and the mixture stirred for 30 min. Dilute HCl was added to the solid residue and the crude ester recovered by filtration. The ester was recrystallised from benzene and had m.p. 133.5—136 °C (lit.,[2] m.p. 134—135 °C).

4-Nitrophenyl *N*-benzoylsarcosinate was prepared from the phenol and *N*-benzoylsarcosine (prepared by the method of O'Brien and Niemann)[9] using dicyclohexylcarbodi-imide and ethyl acetate as solvent. The ester was recrystallised from ethanol and had m.p. 116—117 °C (lit.,[8] m.p. 113 °C). 2-Chloro-4-nitrophenyl and 3-nitrophenyl *N*-benzoylsarcosinates were prepared as above and recrystallised from ethanol. The 3-nitrophenyl ester had m.p. 68—69 °C (Found: C, 61.3; H, 4.7; N, 8.7. $C_{16}H_{14}N_2O_5$ requires C, 61.1; H, 4.5; N, 8.9%). The 2-chloro-4-nitrophenyl ester had m.p. 113—115 °C (Found: C, 55.3; H, 4.1; N, 7.8. $C_{16}H_{13}ClN_2O_5$ requires C, 55.1; H, 3.8; N, 8.0%).

The structures of the substrates synthesised above were confirmed by satisfactory i.r. and n.m.r. spectra. We are grateful to Dr. D. O. Smith for running n.m.r. spectra on a

JEOL 100-MHz instrument. Melting points were determined using a Kofler Thermospan machine and are corrected. Analyses were carried out by Mr. G. Powell of the University's Microanalytical Laboratory using a Hewlett-Packard Model 185 CHN analyser.

Buffer materials and amines were of analytical grade where available or were recrystallised or redistilled from bench-grade reagents. Ethylamine was from the hydrochloride recrystallised from ethanol. Water was doubly distilled from glass apparatus.

Methods.—Preparation of ethylamine buffers. In the case of the least-reactive hippurate esters ethylamine buffers were prepared with ionic strength at 1.0M and fractions of free base (FB) of the order 0.1—0.9. For the highly reactive esters lower pH values were employed using buffers from carbonate, trishydroxymethylaminomethane (TRIS) or phosphate. These were mixed with similar buffers containing ethylamine hydrochloride (1M) to obtain varying concentrations of ethylamine at a constant FB. The latter value (FB) was calculated from the pH of the solution and the pK_a for the ethylammonium acid using equation (2); the pK_a was estimated titrimetrically at 25 °C and 1M ionic strength using a Radiometer titration set

$$FB = 1/(1 + a_H/K_a) \quad (2)$$

comprising REC 61 Servograph, REA Titratigraph, PHM 62 digital pH-meter, TTT 60 Titrator and ABU 11 Autoburette. Subtraction of the solvent titration curve gave data which were analysed to give the pK_a.

Kinetics.—The reactions of the aryl hippurates and *N*-benzoylsarcosinates were followed spectrophotometrically at fixed wavelengths which were determined from repetitive scanning of the spectrum during a trial hydrolysis experiment. The substrate (50 λ), in acetonitrile stock solution, was added to 2.5 ml buffer in a silica cell in the thermostatted cell compartment of a Unicam SP 800, SP 500 or Beckman DBG spectrophotometer. The change in absorbance was measured using a Servoscribe recorder.

The reactions of the alkyl hippurates were measured using a hydroxamic acid assay procedure modified from that described by Satterthwait and Jencks.[10] The ester (0.5 ml, 0.2M in acetonitrile or, for 2 chloroethyl hippurate, ethanol) was incubated at 25 °C with ethylamine buffer (9.5 ml). Samples (1 ml) were withdrawn at known times and incubated with hydroxylamine buffer (1 ml of a solution of 4 ml 4M-NH_3OHCl and 6 ml 3.5M-NaOH) for 4 min. The hydroxylamine buffer was prepared within 2 h of use since it oxidises rapidly.[11] Ferric chloride (4 ml; 6% in 2.5M-HCl) was then added and the absorbance measured after 20 min at 540 nm with a Pye-Unicam SP 600UV spectrophotometer. The reference cell contained 1 part ethylamine buffer, 1 part hydroxylamine buffer and 4 parts (by volume) of the ferric chloride solution. Under the above conditions the colour produced (at pH ~ 1) was stable over a period of several hours.[12a]

The pH of the buffer solution was measured at the end of the reaction and an average value for different ethylamine concentrations at constant FB was used to determine the hydroxide ion concentration. Variation in the measured pH was only *ca.* ±0.02 units; the ionic product for water at 1M ionic strength was determined as 13.97.

An infinity value was measured after at least 5 half-lives and the pseudo-first-order rate constants obtained by plotting $A_t - A_\infty$ *versus* time on two-cycle semi-logarithmic graph paper.

The above recipe for the hydroxamic acid method gave precipitates with the trifluoro-ester and a slight variation in the concentration was employed. The ester was made approximately M/15 in ethanol and the stock (1.5 ml) was incubated at 25 °C with ethylamine buffer (28.5 ml). Aliquots (3 ml) were withdrawn at known times and added to the hydroxylamine buffer (1 ml) and incubated for 4 min. Ferric chloride solution (2 ml, 12% in 5M HCl) was added and the absorbance measured as above.

RESULTS AND DISCUSSION

Good first-order kinetics were obtained over at least 90% of the reaction for all substrates with ethylamine and hydroxide ion at the pH values and wavelengths studied. In the case of the 3-nitrophenyl, 4-nitrophenyl, 2-chloro-4-nitrophenyl, and 2-nitrophenyl hippurates the alkaline hydrolysis involves the 2-phenyloxazolin-5-one which can be observed at wavelengths below *ca.* 360 nm [1,8] when its decomposition is rate limiting. The wavelengths used for the esters in this work (400—420 nm) ensure no interference from the absorbance due to the oxazolinone intermediate. Under conditions where breakdown of the oxazolinone is not rate limiting, repetitive scanning of the spectrum during hydrolysis gives good isosbestic points which is good evidence for an overall 1 : 1 stoicheiometry. Good isosbestic wavelengths were obtained for the hydrolysis of the 3- and 4-nitrophenyl *N*-benzoylsarcosinate esters. In the case of phenyl hippurate the use of high wavelengths to avoid oxazolinone absorbance is not possible. However, at the individual wavelengths employed for kinetics excellent first-order rate constants are obtained in the ethylamine buffers; this is probably due to rate-limiting oxazolinone formation. Repetitive scanning of the spectrum during the hydrolysis of 2-chloro-4-nitrophenyl *N*-benzoylsarcosinate over a range of pH values from 7.6—9.1 in TRIS buffer indicates the build-up and decay of an intermediate absorbing in the region 290—360 nm; in the present work the wavelength for the kinetics (400 nm) is not affected by absorbance due to the intermediate.

Evaluation of k_{OH}, k_B *and* k_3.—Equation (3) is the rate law for the reaction of ethylamine buffers with hippurate

$$k_{obs} = k_{OH}[OH^-] + k_B[EtNH_2] + k_3[OH][EtNH_2] + k_{buffer.}[buffer] \quad (3)$$

esters. The bimolecular rate constants for the attack of hydroxide ion on the various substrates (k_{OH}) was measured using high pH (>11) buffers where no buffer component was present. A second method, for the most reactive esters, involved plotting the rate constants (extrapolated to zero buffer concentration) *versus* the pH. Division of the buffer independent rate constants by the hydroxide ion concentration gives the k_{OH} term.

The second-order rate constants for the reaction of ethylamine with the substrate (k_B) were obtained by plotting k_{obs} against total amine concentration at constant FB. The slopes of these plots (k_2) were replotted *versus* FB. These plots all gave zero intercept at FB = 0 and where they were linear the intercept at

FB = 1 gives k_B. In the case of curved plots the parameter k_2/FB plotted against hydroxide ion concentration gives a linear relationship with a slope (k_3) and in intercept (k_B).

Reference to equation (3) indicates that if hydroxide ion and free ethylamine concentration are small then the third-order term ($k_3[OH^-][EtNH_2]$) might not be observable. In the case of 4-nitrophenyl hippurate we may estimate an upper limit for k_3 (from the Brønsted plot for k_3 for the other substrates as described later) close. This variation is probably due to the high ionic strength used in this work (1.0M with KCl) compared with zero or 0.1M ionic strength in the case of the literature values.[2,8]

The hydrolysis of 2-chloro-4-nitrophenyl *N*-benzoylsarcosinate proved to be interesting in that at relatively low pH values (7—8) spectroscopic studies indicate the presence of an intermediate. Following the reaction at 400 nm, the absorption corresponding to the 2-chloro-4-nitrophenolate anion, gave pseudo-first-order rate constants over 90% of the reaction. Allowing for the effect of buffer on the rate constants for phenolate release yields a rate constant for zero buffer concentration and the pH-dependence of the latter indicates a pH-independent term as well as a hydroxide one [equation (4)]. The parameters for this equation are collected in Table 2.

$$k = k_{H_2O} + k_{OH}[OH^-] \quad (4)$$

It is not possible that the plateau region of the pH-dependence (k_{H_2O}) corresponds to formation of an *N*-methylphenyloxazolinone intermediate (3) because the acid-catalysed hydrolysis at pH 6 [12] of the parent phenyloxazolinone ($pK_a \geqslant \overset{+}{N}H$ <1.6) [12] is 140-fold faster than the rate constant for decomposition of the intermediate (Table 2). We favour a mechanism involving a '7-exo-trig' ring cyclisation process [12c] where the neutral amide oxygen of the sarcosinate attacks the activated aromatic nucleus to yield an imidate ester intermediate (see below). Reference to Satterthwait and Jencks [13] shows that the rate constant for decomposition of the proposed imidate ester intermediate (1.2×10^{-3} s^{-1}

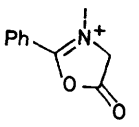


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TABLE 1

Kinetic data for the hydrolysis and aminolysis of hippurate esters[a]

Ester	λ/nm [b]	pK_a [c]	pH-range	N [g]	k_{OH}/l mol^{-1} s^{-1} [e]	$k_B \times 10^3$/l mol^{-1} s^{-1} [e]	k_3/l mol^{-2} s^{-1} [e]
Methyl [f]		15.54	10.3—11.4	15	0.76 ± 0.04	1.5 ± 0.6	2.0 ± 0.3
2-Chloroethyl		14.31	10.6—11.3	10	1.8 ± 0.1	12 ± 1	3.2 [d]
2,2,2-Trifluoroethyl		12.43	9.9—11.0	18	11 ± 0.5	62 ± 30	170 ± 40
Phenyl	275—287	9.95	9.9—10.9	17	19 ± 0.4	160 ± 10	210 ± 10
3-Nitrophenyl	350	8.35	8.0—9.2	13	820 ± 50	4.5 ± 0.2 10^3	2.6 10^4 [d]
4-Nitrophenyl	400	7.14	6.6—9.2	34	6 200 ± 300	5.1 ± 0.3 10^4	4.2 10^3 [d]
2-Chloro-4-nitrophenyl	400	5.45	6.8—8.5	10	4.4 ± 0.2 10^4	1.1 ± 0.1 10^5	
2-Nitrophenyl	400	7.23	8.3—9.0	9	1.1 ± 0.1 10^4	6.5 ± 0.6 10^4	

[a] Ionic strength maintained at 1M with KCl, 25 °C. [b] Wavelength for kinetic measurements. [c] Values for pK_a values of alcohols and phenols from the compilation of W. P. Jencks and J. Regenstein, in 'Handbook of Biochemistry,' ed. H. A. Sober, Chemical Rubber Co., Cleveland, Ohio, 1970, 2nd edn., section J–87. [d] These values are upper limits. [e] Errors quoted are confidence limits. [f] 22 °C. [g] Number of points.

as 10^5 l mol^{-2} s^{-1}. At the highest pH studied for this substrate (8.5) and the highest ethylamine concentration (FB = 0.003 16, 0.45M total amine) the k_3 term has an upper limit of 4.5×10^{-4} s^{-1}. The value of k_3 may not be measured for this ester since the observed rate constant is 9.52×10^{-2} s^{-1}.

Tables 1 and 2 collect the rate constant parameters for the decay respectively of hippurate and *N*-benzoylsarcosinate esters in ethylamine buffers. Reference to

TABLE 2

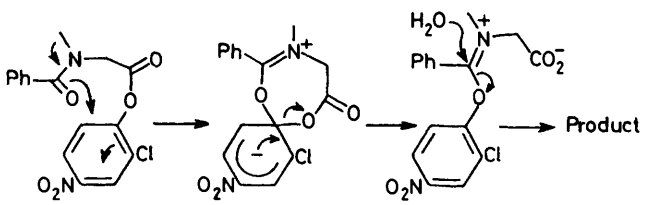
Kinetic data for the hydrolysis and ethylaminolysis of *N*-benzoylsarcosine esters [a]

Substrate	pK_a	pH-range	N [e]	k_{OH}/l mol^{-1} s^{-1} [b]	k_B/l mol^{-1} s^{-1} [b]
4-Nitrophenyl	7.14	8.4—11.6	14	68 ± 4	15 ± 1
3-Nitrophenyl	8.35	9.9—11.7	11	48 ± 5	2.3 ± 0.2
2-Chloro-4-nitrophenyl [c,d]	5.45	8.35—10.1	14	240 ± 10	67 ± 6

[a] Ionic strength maintained at 1M with KCl, 25 °C, wavelength for kinetic studies = 400 nm. [b] Errors quoted are confidence limits. [c] $k_{H_2O} = 1.0 \times 10^{-3}$ s^{-1}, $k_{CO_3^{2-}} = 0.47$ l mol^{-1} s^{-1}, $k_{TRIS} = 2.3 \times 10^{-2}$ l mol^{-1} s^{-1}. [d] The rate constant for the decomposition of the intermediate species (TRIS buffer, 0.0517M at FB = 0.25, pH 7.72) is 1.19×10^{-3} s^{-1}. [e] Number of points.

Table 1 indicates that the confidence limits for k_B for methyl and 2,2,2-trifluoroethyl hippurates are larger than the limits for the other esters. The reason for this error is the accumulation of errors in the protocol for obtaining k_B values.

The present parameters, where comparable, are lower by a factor of approximately two than those of other workers [8] and from this laboratory [2] except for methyl hippurate where the temperature is lower and 4- and 2-nitrophenyl hippurate where the agreement is quite



in TRIS buffer at 0.052M, FB = 0.25) is close to that observed for water hydrolysis of phenyl *N*-methylacetimidate (1.03×10^{-4} s^{-1}).

Figure 1 illustrates the Brønsted plot for the alkaline hydrolysis of hippuric acid and *N*-benzoylsarcosinate esters as a function of the pK_a of the leaving hydroxy-group. Correction of the alkyl hippurate data for steric hindrance in the case of attack on the aryl esters (the factor used is an 8.7-fold correction determined using isopropyl and cyclohexyl esters as models for the

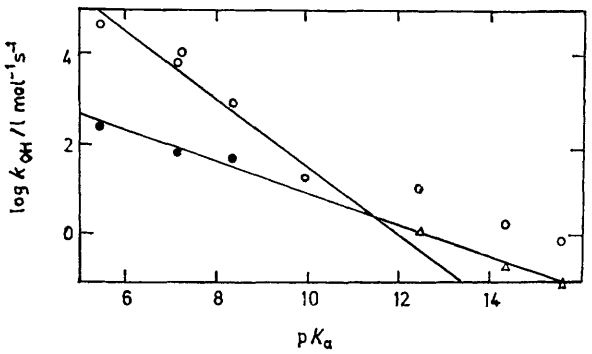


FIGURE 1 Brønsted plot for the alkaline hydrolysis of *N*-benzoylglycine (○) and *N*-benzoylsarcosinate (●) esters. The values for the alkyl hippurate esters (△) are corrected as described in the text. The data and conditions are in Tables 1 and 2

phenyl ester) [2] then gives an excellent fit ($\beta = -0.35$, $r = 0.997$) with the rate constants for the *N*-benzoylsarcosinate esters studied. The aryl hippurates lie on a line of higher slope ($\beta = -0.76$, lit.,[2] $\beta = -0.8$). The possible steric effect caused by the *N*-methyl group in the case of the sarcosinates has been ignored for the purpose of this comparison. The slope of the combined aryl *N*-benzoylsarcosine and alkyl hippurate plot agrees with that of earlier work using a smaller pK_a range ($\beta = -0.35$).[2] This β value is of the order expected for the normal addition–elimination pathway of ester hydrolysis ($\beta = -0.32$ for alkaline hydrolysis of substituted phenyl and alkyl acetates) [14] where the phenyl esters fall on a parallel line approximately one order of magnitude below that of the alkyl ester line.

The Brønsted relationship for the uncatalysed reaction (k_B) is illustrated in Figure 2. Alkyl hippurates fall on a line of slope $\beta = -0.46$ whereas phenyl hippurates fall on a line of slope $\beta = -0.9$. The phenyl ester line is about an order of magnitude lower than expected from the alkyl ester line and we attribute this to the steric hindrance of the bulky phenyl groups as in the hydroxide hydrolysis.[2] 2-Chloro-4-nitrophenyl hippurate deviates some 16-fold below the phenyl ester correlation. The mechanism for ethylaminolysis involves direct attack of amine at the ester; variation of base type cannot alter the equilibrium formation of the anion. As a comparison the rate constant for ethylaminolysis of 4-nitrophenyl hippurate is of the same order of magnitude as that for 4-nitrophenyl acetate (51 and 16 l mol^{-1} s^{-1} respectively at 25 °C and 1M ionic strength) for which the addition–elimination mechanism applies. Hippurates show only a two- to three-fold acceleration over their *N*-benzoylsarcosine analogue (see Tables 1 and 2) for attack by ethylamine where oxazolinone formation is not possible.

Reference to Table 1 reveals that the rate constants for attack on the 2- and 4-nitrophenyl hippurates are similar (51 and 65 l mol^{-1} s^{-1} respectively). The difference between their leaving group pK_a values is only 0.09 (Table 1) so that if there were no steric effect requirement by the *ortho*-nitro-group the reactivities would be expected to be the same, as they are. Recent work has shown that the rate constants for the reaction of imidazole with aryl trimethylacetates with *ortho*-substituents obey a good Brønsted-type line down to esters with leaving phenols of $pK_a = 4$.[15] This reaction involves direct attack of imidazole on the ester carbonyl.[16] The observation that the rate constant for ethylaminolysis of 2-chloro-4-nitrophenyl hippurate lies below the line for other phenyl esters cannot be due to steric effects on the basis of the above evidence; we regard the deviation as arising from a change in rate-limiting step for ethylaminolysis around a pK_a of the leaving group of *ca.* 6—7.

We believe that the mechanism shown below (Scheme 1) for ethylaminolysis of phenyl hippurates is consistent with the present results. A similar mechanism has been proposed by Satterthwait and Jencks [13] for the aminolysis of phenyl acetates. On the basis of Scheme 1 the Brønsted plot for the reaction of ethylamine with phenyl hippurates (Figure 2) may be divided into three sections. The alkyl hippurate portion has a rate-limiting proton switch at high pH (k_5) followed by rapid loss of a proton

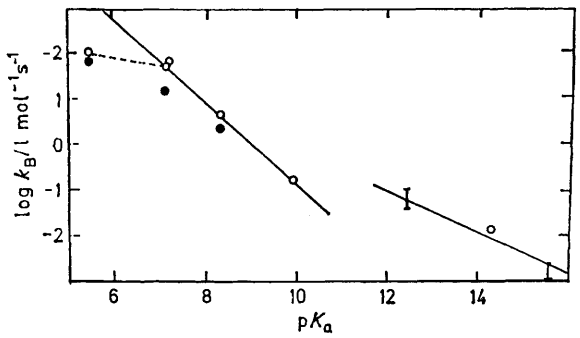
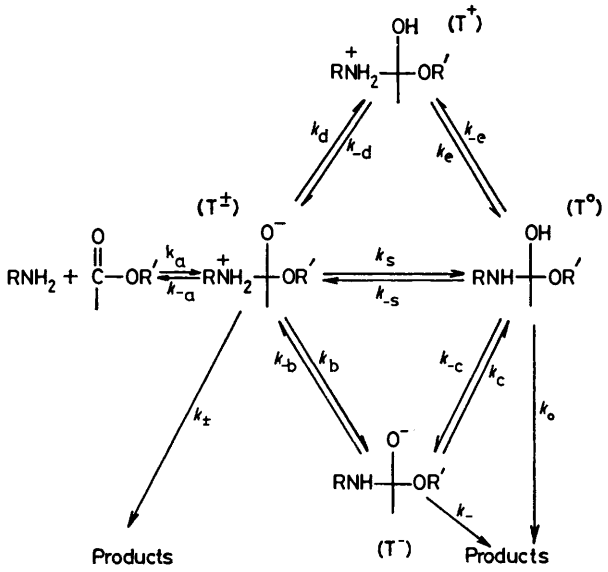


FIGURE 2 Brønsted plot for the attack of ethylamine on *N*-benzoylglycine (○) and *N*-benzoylsarcosinate (●) esters. Data are taken from Tables 1 and 2 and the lines are theoretical with slopes $\beta = -0.90$ and -0.46

from oxygen (k_{-c}) and the expulsion of an alcoholate ion from the anionic intermediate T^- (k_-), which should become rate limiting at lower pH. This mechanism predicts only a small sensitivity to electron-withdrawing substituents on the leaving group as is observed ($\beta = -0.46$). The phenyl hippurates should possess as rate-limiting step the departure of the leaving group ($k_\pm$) from the addition intermediate ($T^\pm$). A requirement of this mechanism is a large β and this is observed ($\beta = -0.9$) consistent with considerable bond cleavage in the transition-state.

Only when the leaving group becomes sufficiently acidic does the rate-limiting attack of amine occur in

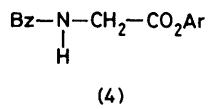
Scheme 1 ($k_{\pm} > k_{-a}$). In the present case the break appears to occur for phenolate groups about 4 pK units lower than ethylamine, consistent with previous work. The aminolysis of 1-acetoxy-4-methoxypyridinium ions has a break in the structure reactivity correlation some 6 units of pK (Δ pK) above that of the leaving group;[17] this is consistent with amine leaving groups being *ca.*



SCHEME 1

10^5-fold more reactive than alkoxide ions of comparable pK_a.[18,19] Recent work has revealed a Δ pK of *ca.* 4 for the reaction of pyridines with 2,4-dinitrophenyl methyl carbonate.[20]

We attribute the factor of 2 between the reactivity of ethylamine with hippurate (4) and *N*-benzoylsarcosinate (5) esters to the differing steric requirements. A comparison of the rate constants for imidazole attack on



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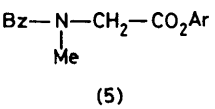

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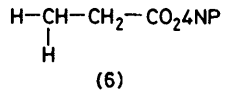

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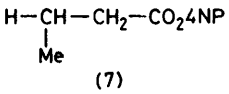

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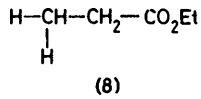

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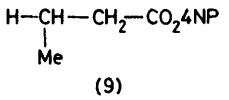


(9)

esters (6) and (7) which are steric models for (4) and (5) respectively indicates that the methyl-substituted species (7) is 1.8-fold less reactive than (6) in water at 30°.[16] That this is not due to an inductive effect is borne out by the possession of identical σ_I values for methyl and ethyl substituents (−0.05).[21]

The ratio of ethylamine reactivity for 2-chloro-4-nitrophenyl esters of (4) and (5) is close to that for the other ester ratios (1.6); this indicates that if in the latter esters rate-controlling attack [equation (5)] is occurring then there is little steric effect on the $k_{\pm}/k_{-a}$ ratio for

$$k_B = k_a \quad (5)$$

$$k_B = k_a \cdot k_{\pm}/k_{-a} \quad (6)$$

esters where breakdown of $T^{\pm}$ is rate-limiting [equation (6)].

The esters (8) and (9) may also be used as steric models of (4) and (5), and (8) is more reactive than (9) by 2.3-fold *versus* hydroxide ion attack. The rate-controlling step in these cases is hydroxide addition.

It is perturbing that, despite the change in mechanism for alkaline hydrolysis of hippurate esters, there is a good linear free-energy relationship between $k_{\text{ethylamine}}$ and $k_{\text{hydroxide ion}}$ with a unit slope (Figure 3). The good correlation is due to a cancelling of factors: (*a*) the break in the structure–reactivity correlation for hydroxide and ethylamine occur at roughly the same pK_a; (*b*) the slopes of the different portions of the Brønsted correlations are similar (−0.35 and −0.76 for hydroxide and −0.46 and −0.9 for ethylamine); (*c*) the steric requirements for the alkaline hydrolysis and aminolysis of the alkyl hippurates compared with the aryl esters for the addition–elimination reaction are similar. These factors illustrate the dangers of drawing conclusions from such relationships alone, where both ordinate and abscissa are allowed to vary in a way that the different factors involved may complement each other and thus cancel.

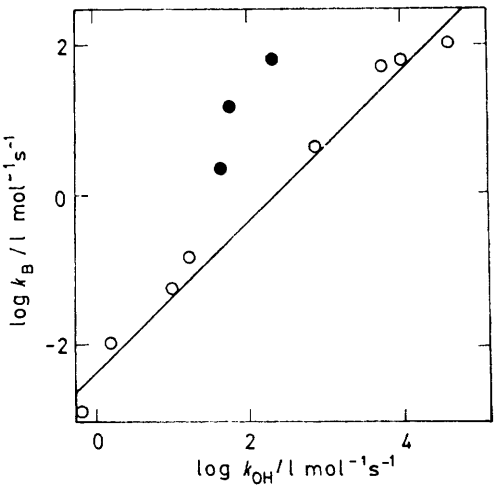
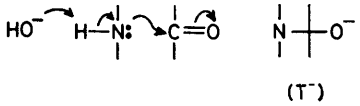


FIGURE 3 Plot of ethylamine *versus* hydroxide ion reactivity for hippurate esters (○) and *N*-benzoylsarcosinate esters (●). Data are from Tables 1 and 2 and the line is arbitrary with unit slope

Ethylaminolysis Catalysed by Hydroxide Ion.—The ethylaminolysis of methyl hippurate has a non-linear k_2 *versus* FB plot illustrating the influence of the third-order term involving amine and hydroxide. For this ester the proportion of the reaction passing through the 'third-order' mechanism is 28%, through direct aminolysis 50% and through hydrolysis 22% for an ethylamine buffer of 1M concentration at FB = 0.5. The k_3 term could arise from a general base-catalysed

removal by hydroxide ion of a proton from an attacking ethylamine group as in Scheme 2 to yield T^- directly. A kinetically equivalent alternative involves removal of a proton from $T^\pm$ (Scheme 1, k_b) to yield T^-.

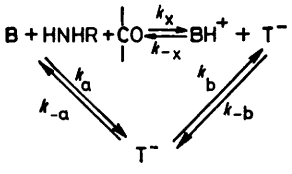
Consider Scheme 1 for alkyl hippurates (and acetates);[10] it has been postulated that the rate-limiting step is proton transfer from $T^\pm$, and this could involve one or more molecules of water (k_s in Scheme 1) which would not appear in the resultant kinetic expression.



SCHEME 2

Proton transfer from $T^\pm$ in the hydroxide catalysed reaction would give T^- and either this step or a subsequent one could be rate limiting for hydroxide ion to appear in the kinetic expression. Proton transfer to the hydroxide from $T^\pm$ will be thermodynamically favourable (k_{-b}) and diffusion controlled (Scheme 1).[22] Either mechanism is possible since although expulsion of the fully protonated amine (k_{-a}) would be faster than the expulsion of the partly protonated amine (k_{-x} in Scheme 3), this would be offset by the equilibrium (k_b/k_{-b}) which will favour T^- at high pH. We estimate pK_b to be 9.3 for phenyl hippurate (see Appendix). The concerted process would have to provide a sufficient free-energy advantage to overcome the requirements for the freezing of three molecules in the transition-state.[23]

When the base (B) is weaker than $T^\pm$ as in the hydrazine-catalysed hydrazinolysis of phenyl acetates[10] the concerted process may be ruled out since proton transfer to T^- from BH^+ is now thermodynamically favourable



SCHEME 3

and expulsion of amine will take place *via* k_{-a} and not k_{-x}.

The observed Brønsted $\beta_{l.g.}$ of *ca.* 0.5 for the k_3 term (Figure 4) is expected for a stepwise mechanism with decomposition of $T^\pm$ catalysed by base; however, a similar $\beta_{l.g.}$ would be expected for the concerted mechanism if the breakdown of T^- (for class II aminolysis) were rate limiting.

No [ethylamine]^2 term was observed in this work and such a term is expected on the basis of the rate constants obtained by earlier workers.[10,24] For this reason we are inclined to believe in the concerted pathway; the absence of concerted ethylamine-catalysed removal of a proton from attacking ethylamine would be due to the difficulty in observing it because of an expected Brønsted exponent close to unity. A similar absence of an [amine]^2 term is observed in the reaction of amines with carbon dioxide; the hydroxide ion-catalysed term could also be due to a concerted[25] process. The absence of a k_3 term in the *N*-benzoylsarcosine work is due to the low concentrations of ethylamine employed and the consequent difficulty in observation.

The mechanism involving attack of amine on oxazolinone [equation (7)] is not a likely contender for the k_3

$$\text{Ester} \overset{OH^-}{\rightleftharpoons} (2) + \bar{O}Ar \xrightarrow{RNH_2} \text{Amide} \qquad (7)$$

term in equation (3) because the aminolysis of the oxazolinone would need to be rate limiting. This is not possible since the concentration of amine is well in excess of the phenolate concentration produced from the reactant; thus this mechanism should be independent of amine concentration.

McCarthy and Hegarty's observation[4] that *O*-(*N*-benzoylglycyl)-1-hydroxypyrazole undergoes aminolysis *via* the oxazolinone intermediate is interesting in that in

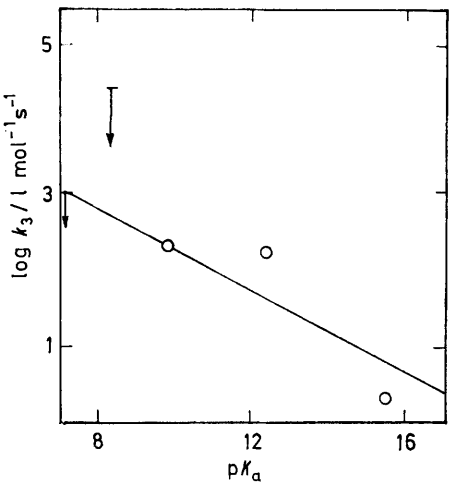


FIGURE 4 Brønsted plot of k_3 against the ionisation of the leaving hydroxy-group. The data are from Table 1 and the line is arbitrary with slope −0.5

the amine concentrations used (0.01M) the bimolecular mechanism is not favoured. The mechanistic change-over (from EA to AE) occurs as the concentration of amine increases. The level at which this change will occur depends on the relative reactivities of ester to react with amine or to eliminate phenol to yield oxazolinone. The Brønsted β value for the former reaction is low especially when the leaving group improves and the reaction changes from Class II to Class III. The EA reaction has a high β value and therefore the concentration of amine necessary to change the mechanism from EA to AE increases as the leaving group ability increases.

Appendix.—The pK_a values of the intermediates T^+, T^0, $T^\pm$, and T^- (Scheme 1) may be estimated using the method of Fox and Jencks;[26] values of ρ_I are taken as −8.4 for both $R_2NH_2^+$ and ROH.[26] Values of σ_I are from Charton[21] or Ritchie and Sager.[27] The σ_I value for $PhCONHCH_2^-$ is taken to be the same as that for

$MeCONHCH_2^-$ (0.07) [21] since MeCONH- ($\sigma_I = 0.28$) and PhCONH- ($\sigma_I = 0.27$) have similar values.[21]

pK_e: Starting with dimethylamine ($pK_a = 10.64$) using σ_I for CH_3, OH, and PhO $pK_e = 5.1$.

pK_d: Starting with methanol ($pK_a = 15.54$) using σ_I for $EtNH_2^+$ and PhO $pK_d = 6.6$.

pK_c: Starting with methanol and σ_I for PhO and EtNH $pK_c = 10.8$.

pK_b: $pK_b = pK_e + pK_c - pK_d = 9.3$.

The error in the pK_a values calculated in the above way is estimated to be no more than ± 1 unit.[26]

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