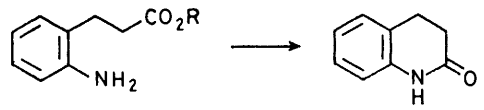
Anilide Formation from an Aliphatic Ester. The Mechanism of Cyclisation of Methyl 3-(2-Aminophenyl)propionate

By **Anthony J. Kirby** * and **Tasneem G. Mujahid**, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW
Patrick Camilleri, Chemistry Department, University of Malta, Msida, Malta

The cyclisation of methyl 3-(2-aminophenyl)propionate to dihydroquinolone is both general acid and general base catalysed. General base catalysis involves the diffusion-controlled, rate-determining removal of a proton from a zwitterionic tetrahedral intermediate, as observed for reactions with more basic amines. But the general acid catalysed proton transfer is concerted with heavy atom reorganisation, and a mechanism involving the rate-determining breakdown of a neutral tetrahedral intermediate is proposed. The kinetics require independent routes to the two tetrahedral intermediates, and it is shown that the cyclisation of the conjugate acid of the amino-ester is an important pathway for ester aminolysis by weakly basic amines.

To help us to resolve the kinetic ambiguities involved in the buffer-catalysed cyclisation of 3-(2-aminophenyl)-propionic acid (1; R = H) to the dihydroquinolone (2) [1] we have examined the corresponding reaction of the



(1) (2)

methyl ester (1; R = Me). Although ester aminolysis has been much studied,[2-4] no information is available about the reactions of anilines with ordinary aliphatic esters. The intermolecular reaction is known only with acyl-activated esters, and involves not aminolysis but general base catalysis of hydrolysis.[5] The intramolecular reaction has not been studied at all. The most closely relevant previous work is a study by Fife and DeMark [6] of the cyclisation of methyl 2-aminomethylbenzoate to phthalimidine. The cyclisation of (1) behaves quite differently.

EXPERIMENTAL

Methyl 3-(2-Aminophenyl)propionate (1; R = Me).—Methyl *o*-nitrocinnamate was reduced selectively to the *o*-aminocinnamate, m.p. 63—64°, using zinc dust,[7] and the amino-ester further reduced catalytically (using Adams catalyst, at atmospheric pressure in methanol) to the dihydrocinnamate. The compound cyclises on storage even at −20°, so fresh samples were prepared for each set of experiments. When the cyclisation was carried out in [$^2H_4$]methanol the n.m.r. spectrum of the solution obtained was identical to that of a solution of 3,4-dihydroquinolin-2(1*H*)-one (2) under the same conditions.

Methods are described in the following paper.[1]

RESULTS

The rate of cyclisation of (1) varies remarkably little with pH. The pH rate profile for the reaction (Figure 1) shows pH-independent reactions of both protonated and neutral forms, which differ in rate by a factor of only three in the pH range 0—10. Above pH 10 a rapid hydroxide-catalysed reaction sets in, which has a rate constant (0.4 dm^3 mol^{-1} s^{-1}) of the magnitude expected for alkaline hydrolysis of a methyl ester and has not been investigated further. Buffer catalysis of the reactions of both forms is pronounced, and the points on the pH–rate profile represent extrapolations to zero buffer concentration.

The kinetic data are summarised in Table 1. Least squares analysis of the pH–rate profile (k_0 values) gives an apparent pK_a for (1; R = Me) of 4.44 ± 0.06, in the region expected for an aniline. This value was used to calculate second-order rate constants for buffer catalysis (k_2) in terms of the free base form of the amino-ester. (The observed buffer constants, k_2', based on total buffer concentration, were divided by the fraction of substrate present in the free base form at the pH of the measurements.)

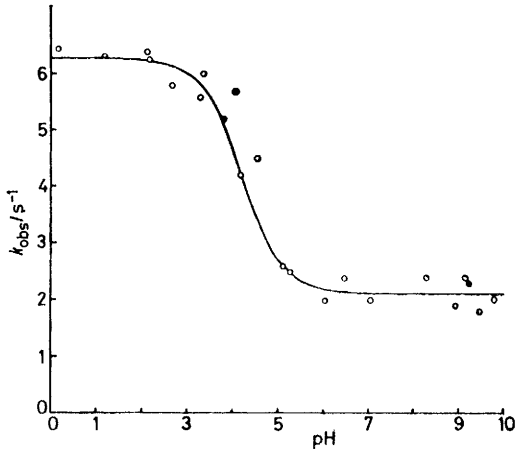


FIGURE 1 pH–Rate profile for the cyclisation of methyl 3-(2-aminophenyl)propionate, at 39° and ionic strength 1.0M. The points represent extrapolations in most cases, and are taken from Table 1. The curve is calculated, using plateau rates of 6.25 and 2.07 × 10^{-4} s^{-1} for the pH-independent reactions of the conjugate acid and neutral forms of (1), and a pK_a of 4.44

The k_2 values calculated for acid buffers (H_3O^+, chloroacetate, formate, and acetate) are very sensitive to the value taken for the pK_a of the substrate, since very little of the free base form is present at low pH. Thus, by far the largest uncertainty in these values arises from the uncertainty in the pK_a value derived from the pH–rate profile. The errors quoted for these cases represent 95% confidence limits, calculated in terms of two standard deviations of the pK_a (4.44 ± 0.12). The way the error limits depend on pH is readily apparent from the data shown in Figure 2.

When the second-order rate constants (k_2) for catalysis by buffers are plotted against the proportion of the buffer in

TABLE 1

Kinetic data for the buffer-catalysed cyclisation of methyl 3-(2-aminophenyl)propionate, at 39° and ionic strength 1.0M

Buffer	Concentration (M)	No. of runs	% Free base	pH	10^4k/ s^{-1}	$10^3k_2'$ [a]/ $dm^3\ mol^{-1}\ s^{-1}$	10^3k_2 [b]/ $dm^3\ mol^{-1}\ s^{-1}$
HCl	1	2			6.45		
HCl	0.1	2			6.33		
HCl	0.01	1			6.26		17 (22, 13)
Chloroacetate	0.1—0.5	5	20	2.12	6.4	1.16	244 (320, 185)
Chloroacetate	0.1—0.4	5	50	2.69	5.8	2.52	144 (189, 110)
Chloroacetate	0.1—0.5	6	80	3.30	5.6	2.98	44 (57, 34)
Formate	0.1—0.4	6	20	3.03	6.9	3.25	87 (113, 67)
Formate	0.1—0.4	3	40	3.37	6.0	5.57	71 (92, 55)
Formate	0.05—0.4	8	60	3.78	5.2	7.15	40 (50, 32)
Formate	0.1—0.4	6	80	4.17	4.2	5.55	16 (19, 13)
Acetate	0.1—0.4	6	20	4.06	5.7	10.5 ± 0.1	35 (43, 29)
Acetate	0.1—0.4	6	50	4.56	4.5	9.7 ± 0.1	17 (19, 15)
Acetate	0.1—0.4	3	75	5.10	2.6	5.7 ± 0.0	6.7 (7.0, 6.5)
Phosphate	0.05—0.2	3	20	6.02	2.0	21.6 ± 0.2	21.8
Phosphate	0.15—0.3	3	50	6.48	2.4	16.9 ± 0.4	17.0
Phosphate	0.05—0.2	3	80	7.05	2.0	10.7 ± 0.1	10.7
Triethylenediamine	0.1—0.5	5	20	8.29	2.4	2.21 ± 0.02	2.21
Triethylenediamine	0.1—0.5	4	50	8.93	1.9	4.66 ± 0.06	4.66
Triethylenediamine	0.1—0.4	3	60	9.16	2.4	5.61 ± 0.02	5.61
Triethylenediamine	0.1—0.5	4	80	9.48	1.8	8.39 ± 0.14	8.39
Carbonate	0.1—0.4	6	20	9.22	2.3	10.6 ± 0.1	10.6
Carbonate	0.1—0.4	3	50	9.78	2.0	12.2 ± 0.2	12.2
Carbonate	0.1—0.4	3	75	10.28	1.8	13.6 ± 0.1	13.6

[a] Errors quoted are standard deviations from least squares fit. [b] Error limits are either the same as those in k_2' (for phosphate, triethylenediamine, and carbonate), or, where these are negligible compared with the uncertainty introduced by the uncertainty in the pK_a (*i.e.* for chloroacetate, formate, and acetate), the 95% confidence limits, taking into account the uncertainty in the pK_a (see text).

the free base form, straight lines are obtained. The intercepts of these lines at zero and 100% free base give the rate constants for catalysis by the conjugate acid and free base forms of the buffer respectively. In the case of carboxylic acid buffers the lines give large positive intercepts at zero free base, and in every case a small negative intercept at 100% free base (Figure 2). For chloroacetate and acetate the upper 95% confidence limits are slightly negative, for formate slightly positive; and we conclude that catalysis by these anions is too small to measure within the accuracy of our experiments. Carboxylic acid buffers thus act exclusively as general acids.

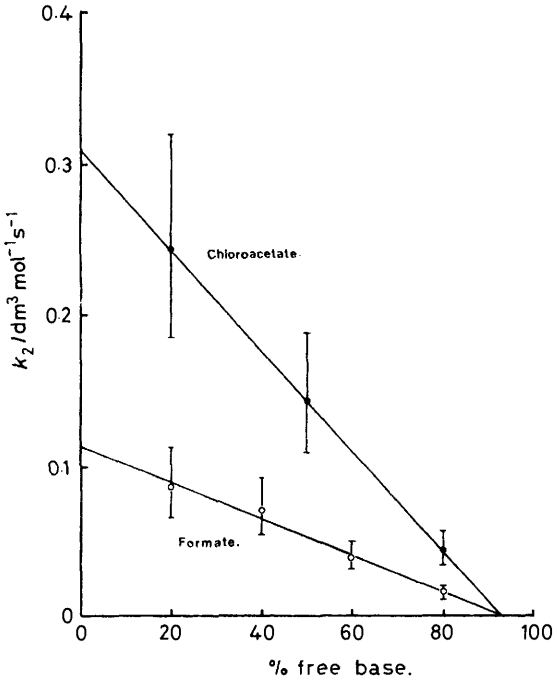


FIGURE 2 Plots of second-order rate constants for buffer catalysis (k_2) *versus* fraction of buffer present in free base form. The error bars mark 95% confidence limits (see text)

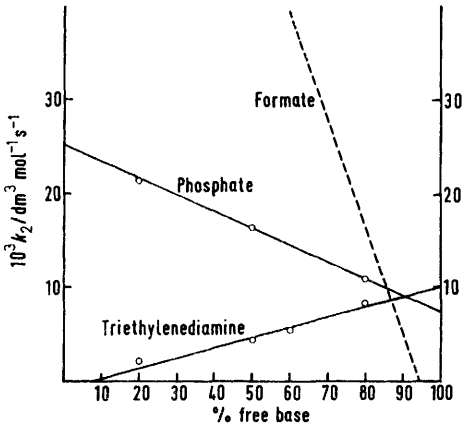


FIGURE 3 Plots of second-order rate constants (k_2) for catalysis by more basic buffers, *versus* fraction of buffer present in free base form. The dashed line, included for comparison, represents catalysis by formic acid, and is taken from Figure 2

Catalysis by strongly basic buffers, on the other hand, is characterised by large positive intercepts at 100% free base, and in the case of triethylenediamine (Figure 3) by a small negative intercept at zero free base. This amine thus acts exclusively as a general base. Carbonate and phosphate show large positive intercepts at both zero and 100% free base, showing that these buffers are active both as general acids and general bases. The intercepts of these plots at zero and 100% free base give second-order rate constants for general acid and general base catalysis by the buffer conjugate acid and free base forms, respectively. These are given in Table 2, and plotted against the pK_a of the conjugate acid form (Brönsted plot) in Figure 4.

Solvent deuterium isotope effects were measured in

TABLE 2

Derived constants for the general acid and general base catalysed cyclisation of methyl 3-(2-aminophenyl)propionate, at 39° and ionic strength 1.0M

Catalyst	pK_a [a]	k_{HA}/dm^3 mol^{-1} s^{-1} [b]	k_B/dm^3 mol^{-1} s^{-1} [b]
H_3O^+	−1.74	17.0 ± 0.9	
Chloroacetic acid	2.69	3.11 ± 0.00 × 10^{-1}	−2.2 ± 0.01 × 10^{-2} [c]
Formic acid	3.58	1.14 ± 0.03 × 10^{-1}	−7.6 ± 5.8 × 10^{-3} [c]
Acetic acid	4.56	4.57 ± 0.18 × 10^{-2}	−8.2 ± 3.8 × 10^{-3} [c]
Phosphate	6.48	2.55 ± 0.05 × 10^{-2}	7.3 ± 0.9 × 10^{-3}
Triethylenediamine	8.93	−0.8 ± 0.31 × 10^{-3} [c]	1.01 ± 0.05 × 10^{-2}
Carbonate	9.78	9.45 ± 0.02 × 10^{-3}	1.49 ± 0.01 × 10^{-2}
H_2O		3.76 ± 0.47 × 10^{-6}	

[a] Measured under the conditions of the experiments. [b] Errors quoted are standard deviations from least squares fit. [c] Catalysis too small to measure accurately. See text.

several buffers, on both limbs of the pH–rate profile. These results are summarised in Table 3. $k_H/k_D = 2.0$ for both high and low pH-independent reactions, and 2.5 for the general acid catalysed reactions of acetic and formic acids. The isotope effect is much reduced for the general base catalysed reaction. The gross value of $k_H/k_D = 1.5$ measured in 80% free base phosphate is made up of contributions from both general acid and general base catalysed reactions. If the general acid catalysed reaction is characterized by the value of $k_H/k_D = 2.5$ found for acetic and formic acid catalysis, then k_H/k_D for the general base catalysed reaction can be calculated as 1.1. The value for catalysis by triethylenediamine, which acts almost exclusively as a general base, is subject to some uncertainty (the second-order plot in D_2O appears to be very slightly curved at high buffer concentrations) but also lies between 1.1 and 1.5.

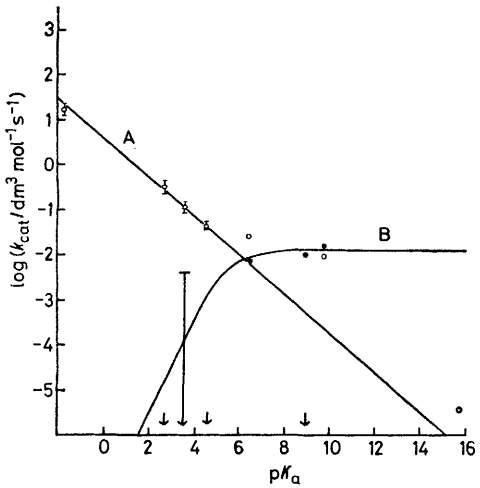


FIGURE 4 Brönsted plot for general acid (○, curve A) and general base (●, curve B) catalysis of the cyclisation of methyl 3-(2-aminophenyl)propionate. The data are taken from Table 2. The error bars mark 95% confidence limits, and for $pK_a < 6$ are determined by the uncertainty in the pK_a of the substrate (see text)

TABLE 3

Solvent deuterium isotope effects for the cyclisation of methyl 3-(2-aminophenyl)propionate, at 39° and ionic strength 1.0M

Buffer (% free base)	pH	10^4k_0 H_2O	10^4k_0 D_2O	k_H/k_D [a]	10^3k_2 H_2O	10^3k_2 D_2O	k_H/k_D [a]
1N-HCl		6.46	3.25	2.0			
0.1N-HCl		6.33	3.2	2.0			
Formate (80)	4.21	4.2	2.0	2.1	6.9	2.8	2.5
Acetate (50)	4.60	4.55	2.25	2.0	9.8	3.9	2.5
Phosphate (80)	7.05	2.0	1.0	2.0	10.8	7.1	1.5
Triethylene-diamine (50)	8.93	2.4	1.1	2.2	4.7	3.1	1.3 ±0.2 [a]

[a] The ratio is considered accurate to ±0.1, except for triethylenediamine, which is discussed in the text.

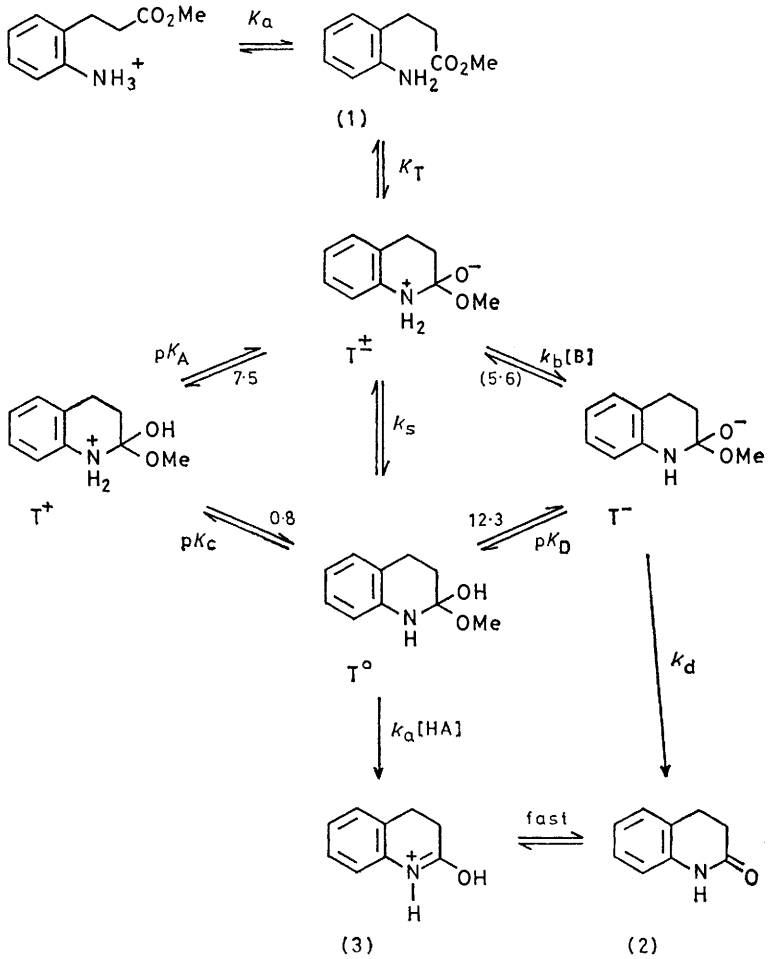
DISCUSSION

Intermolecular reactions of esters of aliphatic alcohols with anilines are observed only when the acyl group is activated, and then involve general base catalysis of hydrolysis, rather than direct attack of the aniline on the ester.[5] Aminolysis is observed only with strongly basic [8] or particularly reactive [4] amines. Thus amides, but not anilides, can readily be prepared by the reaction of ammonia or the amine with ethyl esters.[9] We can assume that the cyclisation of the aniline-ester (1) is rapid because of the high effective molarity of the amino-group: results for similar cyclisations, such as the lactonisation of an aryl 3-(2-hydroxyphenyl)propionate ester,[10] suggest that effective molarities of the order of 10^5M are to be expected in systems of this sort.

The cyclisation of (1) is unusual in being equally susceptible to general base and general acid catalysis. Buffers with $pK_a > 6.6$ act predominantly as general bases, whereas those with $pK_a < 6.6$ act exclusively as general acids. General base catalysis of aminolysis is well known, but general acid catalysis, if observed at all, normally makes only a minor contribution, and accurate data have proved difficult to obtain.[2-6,8,11] The low basicity of the aniline amino-group of (1) allows the intramolecular aminolysis to be studied at low pH, in the absence of competition from general base catalysis.

We discuss our results in terms of the detailed mechanism for ester aminolysis proposed by Satterthwait and Jencks.[4] This mechanism, as applied to the cyclisation of (1), is shown in Scheme 1. The realisation that proton transfer steps involved in the interconversion of the various ionic forms of the tetrahedral intermediate T can be kinetically significant [4] marked an important advance in our understanding of these reactions, and it is an essential part of the interpretation of our results.

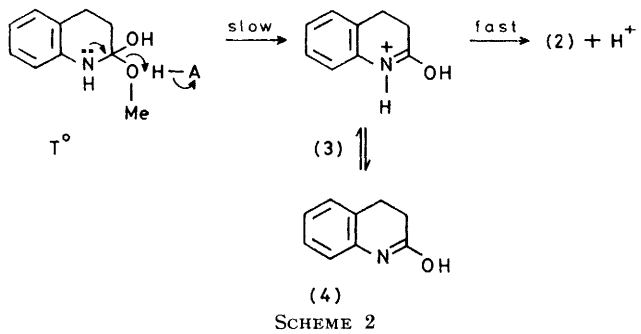
General Acid Catalysis.—The second-order rate constants for catalysis by carboxylic acids are correlated by the Brönsted equation. When the pH-independent reaction of the conjugate acid of (1), observed below pH 2, is treated as the kinetically equivalent H_3O^+-catalysed reaction of the free base (1), the second-order



SCHEME 1 Mechanism for the cyclisation of (1; R = Me). The pK_a values of the tetrahedral intermediates have been estimated by the method of J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 1436.

rate constant obtained falls on the same line (Figure 4). The Brönsted exponent α, based on these four points, is 0.41 $\pm$ 0.01. The points for phosphate and carbonate show positive deviations from the line, as frequently observed when these bifunctional general acid–base catalysts are involved in proton-transfer reactions of tetrahedral addition intermediates.[12-14]

Though one must be cautious when drawing straight lines through a small number of points on a Brönsted plot, the line (A, r 0.999 8) drawn in Figure 4 to connect the points for the four strongest general acids clearly represents the most acceptable correlation of the data.



SCHEME 2

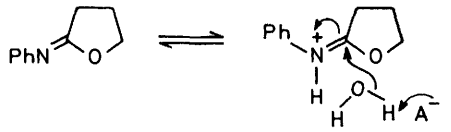
The substantial Brönsted exponent (α 0.41 $\pm$ 0.01) is not consistent with a diffusion-controlled proton transfer, but suggests that proton transfer is concerted with the making or breaking of other bonds. The large solvent deuterium isotope effect (k_H/k_D 2.5 for catalysis by acetic and formic acids, 2.0 for the H_3O^+ catalysed reaction) supports this conclusion.

The only step in the mechanism of Scheme 1 to fit this requirement is the breakdown of the neutral tetrahedral intermediate (T^0) to products. If this step is rate determining in the general acid catalysed aminolysis of (1) (Scheme 2), then its microscopic reverse, the general base catalysed hydration of the iminium cation (3), must be rate determining in the hydrolysis of the imine (4).

The intermediate (3), of course, will lose a proton faster than water can add, so the reaction concerned could only be observed for an imino-ester. Consistent with our interpretation, the rate-determining step in the hydrolysis of 2-phenyliminotetrahydrofuran (5) below pH 8 is the general base catalysed addition of water to the conjugate acid (6).[15]

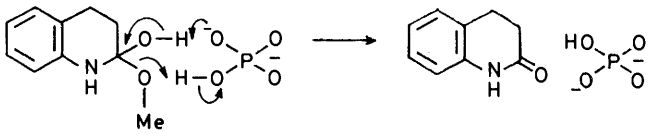
It is noteworthy that the bifunctional catalysts phosphate and carbonate show enhanced reactivity as general acids in this reaction. This is often observed in

cases where simple proton-switch processes are involved.[12-14] A similar explanation in terms of the mechanism of Scheme 2 is that the combination of acidic and basic groups in the catalyst molecule makes it



(5) (6)

possible to by-pass the protonated amide intermediate (3), so that T^0 can be converted directly to the amide product (2).



T^0 (2)

Also consistent with the mechanism of Scheme 2 are the effects of substituents in the benzene ring, measured for the corresponding reaction of the amino-acid.[1] The Hammett ρ value for the cyclisation of 3-(2-aminophenyl)propionic acid catalysed by H_3O^+ is 1.44,[1] corresponding to β_{nuc} *ca.* 0.5, consistent with a partial positive charge on aniline nitrogen in the transition state. A diffusion-controlled conversion of $T^{\pm}$ into T^+ by H_3O^+ would be thermodynamically favourable (see Scheme 1), and thus require a full positive charge on nitrogen in the transition state.

General Base Catalysis.—The second-order rate constants for general base catalysis by carbonate, triethylenediamine, and phosphate (Table 2) show only a very weak dependence on the pK_a of the catalyst (β 0.90 ± 0.02). Yet catalysis by acetate and other carboxylate ions is not detectable. These are data consistent with a diffusion-controlled proton transfer in the thermodynamically favourable direction, and a curve B of the general type demonstrated by Eigen [16] for simple proton transfer reactions is drawn to correlate the points in Figure 4. The solvent deuterium isotope effects for catalysis by triethylenediamine and phosphate are now small (1.3 ± 0.2), as expected [17] and observed [6] for diffusion processes.

General base catalysis of ester aminolysis has been interpreted [4] in terms of rate-determining removal of a proton by the general base from the first formed tetrahedral intermediate $T^{\pm}$ (Scheme 1). This form of the intermediate breaks down very rapidly to regenerate starting materials, but may go forward to products if it is ' trapped ' by protonation or deprotonation by a general acid or base. The proton transfer step is evidently not rate limiting for the general acid catalysed reaction, which involves the rapid formation of the more stable intermediate T^0 (see below). But proton removal by a general base generates the most basic form of the tetrahedral intermediate T^-, which can eliminate methoxide (k_d) to generate (2) directly. Mechanisms for the general base catalysed pathway involving T^0 can be excluded. Schmir and Cunningham [15] showed that the rate determining step in the hydrolysis of the closely analogous 2-phenyliminotetrahydrofuran at high pH is the uncatalysed addition of hydroxide ion to the conjugate acid, corresponding to the formation of T^0 from (3) in Scheme 1. The spontaneous elimination of methoxide from T^0 cannot be the rate-determining step of our reaction. Also, the removal of the OH proton from T^0 would be thermodynamically unfavourable, so that the Brönsted plot would have a slope close to unity if this step were rate determining (as it may be in the general base catalysed cyclisation of methyl 2-aminomethylbenzoate, studied by Fife and DeMark [6]). Given a pK_a of $T^{\pm}$ of 5.6 (Scheme 1), proton transfer to the three bases which show significant catalysis will be thermodynamically favourable, whereas proton transfer to carboxylate ions will not. This explains why the Brönsted plot (curve B of Figure 4) should change from the shallow, near zero slope apparent for bases of $pK_a > 7$, to unit slope for $pK < 5$, and thus accounts for the lack of observed catalysis by carboxylate anions. If we take the rate constant (k_b) for diffusion-controlled transfer of the proton from $T^{\pm}$ to the general base as 10^9 dm^3 mol^{-1} s^{-1} [16] the equilibrium constant for the formation of $T^{\pm}$ is readily calculated from the equation $k_{2(obs)} = k_b K_T$. Since k_2 is *ca.* 10^{-2} dm^3 mol^{-1} s^{-1} for the three general bases (Table 2), $K_T \simeq 10^{-11}$. This may be compared with a calculated value of 6×10^{-12} for the formation of $T^{\pm}$ by the addition of hydrazine to ethyl acetate.[4]

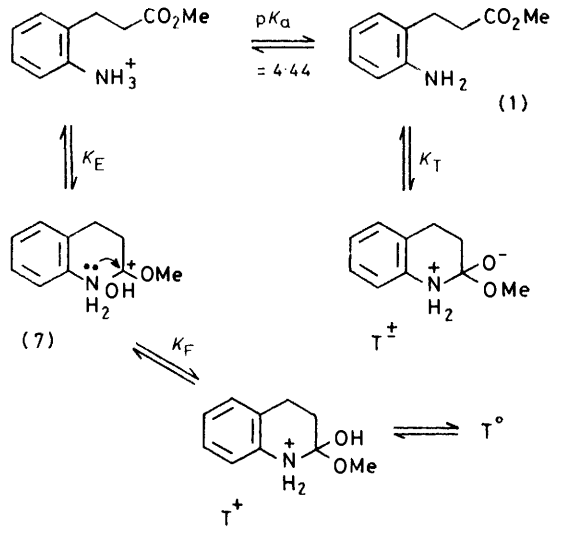
From this figure we can calculate a value of K_T for the intermolecular addition of an aniline of pK 4.44 to ethyl acetate, since the logarithm of the equilibrium constant should depend on the pK_a of the amine with a slope, $\beta = 0.6$.[4] Allowing a factor of 250 for the α-effect on the reactivity of hydrazine [3] (pK 8.3), but ignoring the difference between a methyl and ethyl ester, we obtain a value of $K_T = 9 \times 10^{-17}$ for the addition of the aniline to ethyl acetate. Clearly a tetrahedral intermediate $T^{\pm}$ as unstable as this constitutes an insurmountable barrier to ready intermolecular anilide formation. The comparison also allows an estimate of the effective molarity of the intramolecular amino-group of (1) in the equilibrium for the formation of $T^{\pm}$, as *ca.* 10^5M.

General Acid versus *General Base Catalysis.*—General acid and general base catalysis of the intramolecular aminolysis reaction (1) ⟶ (2) are equally efficient for a catalyst with pK_a *ca.* 6.5 (Figure 4). This would be expected if both reactions involved rate-determining proton transfer reactions of $T^{\pm}$, since this figure falls midway between the pK_a values estimated for the NH_2^+ and O^- groups of $T^{\pm}$ (Scheme 1). In fact the rate-determining step for the general acid catalysed reaction is the breakdown of T^0, so that this result is simply coincidental.

It is apparent from Figure 4 that the second-order

rate constants for general acid catalysis by strong general acids are greater than those for general base catalysis by strong general bases. Since the latter refer to diffusion-controlled proton transfers from $T^{\pm}$, in the thermodynamically favoured direction, the same upper limit must apply to the rate constants for the protonation of $T^{\pm}$ by strong general acids. The general acid catalysed reaction cannot therefore go *via* $T^{\pm}$, and we must look for an alternative mechanism for the rapid formation of T^0.

The simplest possibility is shown in Scheme 3. Under conditions where (1) is present as the conjugate acid it will be in equilibrium with a small concentration of the tautomer (7), with a free NH_2 in close proximity to the protonated ester group. Species (7) will cyclise very fast, to give T^+ directly, and it is readily demonstrated that this route provides the lowest energy path to T^0 at low pH.



SCHEME 3

The pK_a of the protonated ester group of (7) may be estimated as $-(3—4)$, on the basis of a pK_a for methyl propionate, measured in strong acid, of -3.1.[18] This means that K_E is of the order of 10^{-8}. At the pK_a of (1) the equilibrium constants for the formation of T^0 from (1) and its conjugate acid will be equal, $K_E K_F = K_T a_H / K_A$, thus $10^{-8} K_F = 10^{-11} \times 10^{-(4.44-7.5)} = 10^{-7.94}$. This calculation gives a value for K_F of *ca.* 1, and an equilibrium constant for the formation from (1), $K_E K_F$ of 10^{-8}. Since this is nearly 1 000 times more favourable than K_T, for the formation of $T^{\pm}$ from the neutral amino-ester (1), and since deprotonation of T^+ to give T^0 is thermodynamically favourable down to pH 1 (Scheme 1, pK_C 0.8), it is clear that the favoured route to T^0, at pH values up to and slightly above the pK_a of (1), is *via* the cyclisation of (7) to T^+ (Scheme 3).

The Uncatalysed Reaction.—The pH-independent reaction of the free base form of the ester (1), observed above pH 6, involves either a rate-determining proton switch through water, converting $T^{\pm}$ to T^0 directly, as suggested by Satterthwait and Jencks,[4] or the spontaneous elimination of methoxide from T^0. Simple deprotonation or protonation of $T^{\pm}$ by water would be thermodynamically unfavourable, and cannot account for the observed rate of the reaction (2×10^{-4} s^{-1}). General acid catalysis by water of the breakdown of T^0 (Scheme 2, HA = H_2O) is not a viable reaction [19] since this would merely generate hydroxide rather than methoxide, by an entropically less favourable route; the point calculated for catalysis by H_2O by this mechanism shows a positive deviation from the Brönsted plot for general acid catalysis (Figure 4).

The isotope effect (k_H/k_D 2.0) observed for the uncatalysed cyclisation suggests that proton transfer is involved in the rate-determining step, which is consistent with a pathway through $T^{\pm}$ to T^0, with k_s rate determining (Scheme 1).

Conclusions.—This new mechanism for ester aminolysis depends critically on the low basicity of the amino-group of (1). A low pK_a means that the free NH_2 group can exist at pH values where significant concentrations of protonated ester are formed, and that the general base catalysed route *via* $T^{\pm}$ is relatively unfavourable, since the equilibrium constant K_T for the formation of $T^{\pm}$ will be reduced for a less basic amine.

For each increase of one unit in the pK_a of the amine, the rate of the general acid catalysed reaction through T^+ is reduced ten-fold, because of the effect on K_E. There will be a similar increase in the pK_a of the ammonium group of $T^{\pm}$, so that its general base catalysed conversion to T^- becomes thermodynamically favourable one pK unit higher. This means that the curves (A and B of Figure 4) for the two catalytic reactions move apart by two units of pK for each increase of one in the pK_a of the amine, and explains why the general acid catalysed reaction is not observed in similar systems with more basic amino-groups.[6]

[8/612 *Received, 4th April,* 1978]

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