Structure–Reactivity Relationships and the Mechanism of General Base Catalysis in the Hydrolysis of a Hydroxy-amide. Concerted Breakdown of a Tetrahedral Intermediate

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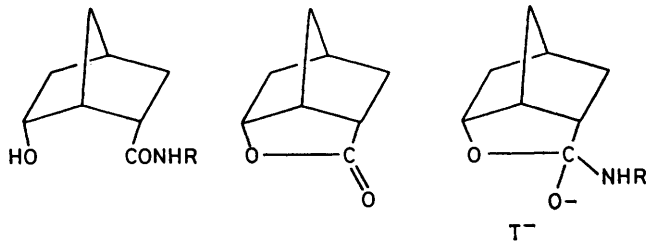
Kinetic general base catalysis is observed in the lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]-heptane-*endo*-2-carboxamides. The reaction mechanism is thought to involve the kinetically equivalent general-acid-catalysed breakdown of the tetrahedral intermediate, T^-. The Brønsted β values for the catalysed lactonisation of the *N*-propyl- and *N*-trifluoroethyl-amides are 0.70 and 0.50, respectively which are equivalent to α values of 0.30 and 0.50, respectively. These values are indicative of a concerted reaction in which proton transfer occurs synchronously with carbon–nitrogen bond fission. The dependence of the rate of reaction of *N*-substituted amides upon the acidity of the catalyst shows that β_{lg} decreases with increasing acidity of the catalyst. The behaviour of the observed structure–reactivity coefficients is discussed with the aid of energy diagrams and it is concluded that proton transfer makes a significant contribution to the reaction co-ordinate. The structure–reactivity coefficients also indicate a degree of charge imbalance in the transition state.

In the preceding paper [1] it was shown that the hydrolysis of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides (I) occurs with neighbouring group participation of the hydroxy-group. In alkaline solution



(I) (II) (III)

the intermediate lactone (II) is then hydrolysed to the corresponding hydroxy-acid.[1] A similar reaction occurs in the serine proteinases when a hydroxy-group of the enzyme attacks the amide group of the substrate.[2]

On the basis of structure–reactivity relationships it was suggested that the hydroxide-ion-catalysed hydrolysis of the hydroxy-amides (I) proceeds with rate-limiting breakdown of a tetrahedral intermediate. Proton transfer from water to the amine nitrogen of the tetrahedral intermediate T^- (III) facilitates fission of the carbon–nitrogen bond.[1] However, it was not possible on the basis of these data alone to distinguish between a stepwise mechanism of proton transfer and heavy atom reorganisation and a fully concerted mechanism.[3]

Herein is a report that kinetic general base catalysis is observed in the lactonisation of the hydroxy-amide (I) which corresponds to general-acid-catalysed breakdown of the tetrahedral intermediate T^- (III). Relationships between the rate of reaction and variations of the structure of the amine in the amide (I) and the catalyst indicate that the reaction proceeds through a concerted mechanism.

EXPERIMENTAL

The materials and methods were similar to those described previously.[1] The amines used as buffers were purified by crystallisation of the hydrochlorides or by distillation. Unless otherwise stated the reactions were carried out in aqueous solutions at 30.0° and at ionic strength 0.20M, maintained with potassium chloride.

RESULTS

The observed pseudo first-order rate constant for the lactonisation of hydroxyamides (I) increases linearly with

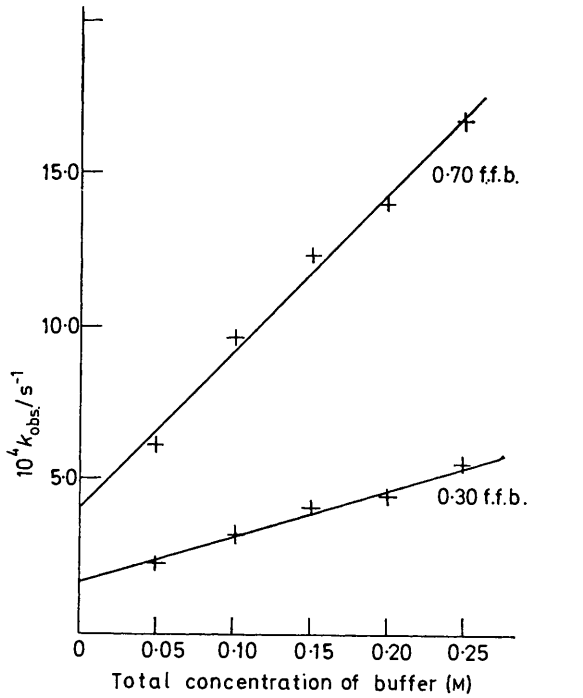


FIGURE 1 Plot of the observed pseudo-first-order rate constants for the lactonisation of *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-*N*-propylcarboxamide in water at 30 °C and *I* 0.20M (KCl) as a function of the total concentration of trifluoroethanol as buffer at the fraction of free base (f.f.b.) indicated

increasing concentration of buffer at constant pH [Figure 1 and Supplementary Publication No. SUP 22713 (4 pp.)†]. Plots of the slopes of these lines, k_{cat}, against the fraction of

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

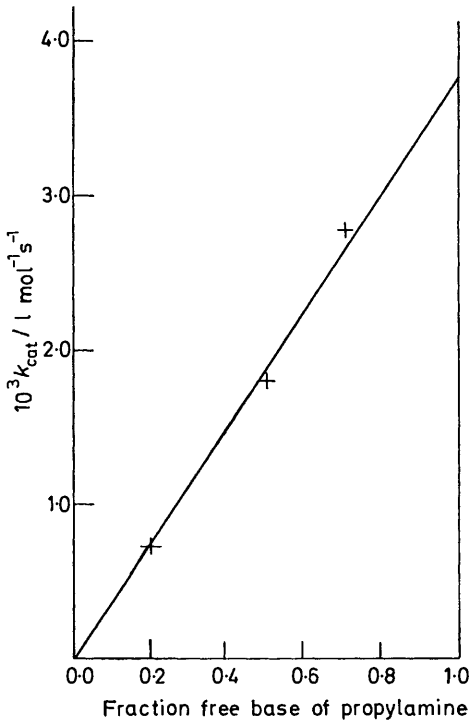


FIGURE 2 The dependence of the second-order rate constants, k_{cat}, for the lactonisation of *endo*-6-hydroxybicyclo[2.2.1]-heptane-*endo*-2-*N*-propylcarboxamide in water (from the slopes of graphs like those shown in Figure 1) upon the fraction of free base of the buffer, propylamine. The left and the right ordinate intercepts give the catalytic constants for the acidic and the basic species of the buffer, respectively

free base of the buffer show that catalysis is due to kinetic general base catalysis and that there is no significant general acid catalysis (right hand and left hand intercepts of Figure 2, respectively). The rate law for the lactonisation of the hydroxy-amide (I) is given by equation (1), where k_{obs} is the observed pseudo-first-order rate constant and

$$k_{obs} = k_H[H^+] + k_{OH}[OH^-] + k_B[B] \quad (1)$$

k_H, k_{OH}, and k_B are, respectively, the second-order rate constants for hydrogen ion, hydroxide ion, and general-base-catalysed conversion of the hydroxy-amide (I) into the lactone (II). The experimental conditions for the rate measurements and the observed rate constants are given in SUP 22713 and the derived rate constants are summarised in Table 1. Values of k_{OH} obtained from the kinetic runs in buffers agreed well (±10%) with those obtained in solutions of sodium hydroxide.[1]

DISCUSSION

The mechanism of the observed general base catalysis will be discussed initially followed by an examination of the multiple structure–reactivity relationships for the reaction.

1, *Mechanism of Catalysis.*—The observed (kinetic) general base catalysis is kinetically equivalent to mechanistic general acid–specific base catalysis [equation (2)] where B is the free-base form of the buffer and

$$k_{obs} = \text{Rate}/[(I)] = k_B[B] = k_B K_{BH}[BH^+][OH^-]/K_W \quad (2)$$

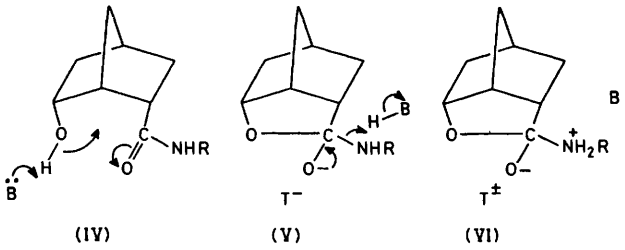
K_{BH} and K_W are, respectively, the dissociation constants of the conjugate acid of the base and water.

TABLE 1

Summary of the rate constants for the lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides in water at 30 °C and *I* 0.20M (KCl)

Base	pK_a	$10^4 k_B$/ l mol^{-1} s^{-1}
a *N*-Propylamide		
1 Hydroxide ion	13.83	4 800 ± 350
2 Trifluoroethoxide ion	12.31	520 ± 35
3 Propylamine	10.80	38.0 ± 3.0
4 2-Methoxyethylamine	9.74	4.25 ± 0.7
5 Hexafluoroisopropoxide ion	9.39	4.65 ± 0.6
6 Acetate	4.72	<0.09
b *N*-2,2,2-Trifluoroethylamide		
1 Hydroxide ion	13.83	290 ± 20
2 Trifluoroethoxide ion	12.31	68.0 ± 5.5
3 Propylamine	10.80	13.6 ± 1.8
4 2-Methoxyethylamine	9.74	5.20 ± 0.2
5 Hydrazine	8.23	0.54 ± 0.05
6 Acetate	4.72	<0.1

The observed general base catalysis cannot result from rate-limiting formation of the tetrahedral intermediate (IV) because this is inconsistent with the effect of the nature of the substituent R of the amine upon the rate of



the hydroxide-ion-catalysed reaction. Electron-releasing substituents *increase* the rate of reaction and the Brønsted β_{lg} value is +0.3 for hydroxide-ion catalysis.[1] It was suggested that the reaction proceeds by a rate-limiting step either involving concerted general-acid-catalysed breakdown of the tetrahedral intermediate T$^-$ (V) [proton transfer from water to the amine nitrogen is concerted with carbon-nitrogen bond fission (V; B = OH)] or a stepwise mechanism involving diffusion apart of T$^\pm$ and hydroxide-ion (VI; B = OH$^-$) or expulsion

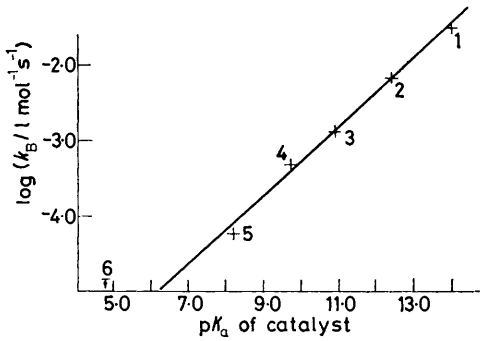


FIGURE 3 The dependence of the rate constants, k_B, for the general-base-catalysed lactonisation of *endo*-6-hydroxybicyclo-[2.2.1]heptane-*endo*-2-(*N*-2,2,2-trifluoroethyl)carboxamide upon the basicity of the catalyst. The numbers refer to the bases listed in Table 1

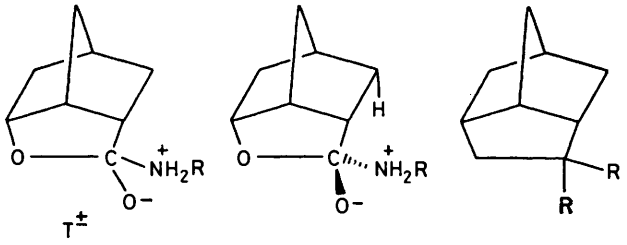
of amine from $T^{\pm}$ in the presence of hydroxide-ion as a ' spectator ' with little carbon–nitrogen bond fission.[1] The present results give information on the effect of variation of the structure of the catalyst B upon the rate of reaction and indicate that the reaction pathway involves the concerted mechanism (V).

The dependence of the second-order rate constants for the general-base-catalysed lactonisation of the hydroxy-*N*-trifluoroethylamide (I; R = CH_2CF_3) upon the basicity of the catalyst is shown in Figure 3. The slope of this line, the Brønsted β value, is 0.50 ± 0.06 and, from the limited data available, appears to be linear. As the Brønsted value is determined from catalysts covering a range of at least 4 pK_a units the observed β value is indicative of a concerted mechanism of proton transfer and a transition state in which the catalyst resembles an intermediate state between the free base form and its conjugate acid.[3] If general acid catalysis of the reaction occurred by a stepwise proton transfer mechanism then the catalyst in the transition state should either be fully protonated and resemble its conjugate acid [1] or be fully deprotonated and resemble its free base (*i.e.* display an ' Eigen curve ') and thus exhibit a Brønsted β value of 1.0 (α 0.0) or 0.0 (α 1.0), respectively. The observed β value is also inconsistent with a pre-association or a hydrogen-bonding mechanism of catalysis.[3] The proposed mechanism is shown in the Scheme. The initially formed tetrahedral intermediate T^- rapidly reverts to reactants (expulsion of alkoxide ion occurs much faster than expulsion of an amine anion [4]) and the reaction proceeds to products by general-acid-catalysed breakdown of this intermediate. Proton transfer is concerted with fission of the carbon–nitrogen bond.

Although general-base-catalysed formation of the tetrahedral intermediate in the lactonisation of hydroxyamides has been suggested [5] it has been shown from product analysis of iminolactones that, at high pH, the rate-limiting step is breakdown of the tetrahedral intermediate.[6] The rate of ^{18}O-exchange with the solvent is faster than that of the alkaline hydrolysis of anilides, which is also indicative of rate-limiting breakdown of the tetrahedral intermediate.[7] The decomposition of the tetrahedral intermediate formed by hydroxide-ion attack on *N*-methyltrifluoroacetanilide is general acid catalysed and shows a Brønsted exponent α of 1.0. This was interpreted in terms of complete proton transfer, the rate-limiting step being either diffusion apart of the intermediate and the conjugate base of the catalyst or cleavage of the carbon–nitrogen bond in the presence of the conjugate base within the solvent cage [8] [analogous to the decomposition of (VI) [1]].

The alcoholysis of amides is the microscopic reverse of the aminolysis of esters, a reaction which has been the subject of many investigations.[9] Heavy atom isotope effects in the hydrazinolysis of $HCO^{18}OMe$ indicate, assuming proton-transfer steps are fast, rate-limiting formation of the tetrahedral intermediate.[10] The microscopic reverse of this would, of course, correspond to rate-limiting breakdown of the intermediate in the alcoholysis of amides. In a comprehensive study Satterthwait nad Jencks [11] showed that the general-base-catalysed aminolysis of esters proceeds through a stepwise mechanism, the rate-limiting step being diffusion together of the base and the tetrahedral intermediate $T^{\pm}$ (VI). The microscopic reverse of this reaction would therefore have rate-limiting diffusion apart of the base catalyst and the intermediate (VI).[1] It was pointed out that a concerted mechanism must occur if the addition intermediate has no finite life-time.[11] The observed Brønsted β value of 0.5 for the general-base-catalysed lactonisation of the *N*-trifluoroethylamide (I; R = CH_2CF_3) in the present study is indicative of a concerted mechanism and therefore of an intermediate that does not exist or of a very limited lifetime.[3,12]

In Scheme 2 of the preceding paper the dependence of the mechanism upon the life-time of the intermediate $T^{\pm}$ (VI) was discussed.[1] A species must exist for longer than the period required for a vibrational motion,



(VII) (VIII) (IX)

10^{-13}—10^{-14} s, to be considered an intermediate. If the hypothetical tetrahedral intermediate, $T^{\pm}$ (VII) is too unstable to exist as an intermediate the reaction cannot proceed through this species by a stepwise mechanism and must proceed by a concerted mechanism.[3,13]

Although it has been suggested [14] that certain conformations of tetrahedral intermediates have life-times which are short compared with the times for intramolecular rotations [15] (*ca.* 10^{-12} s) a number of stable derivatives are known.[16] The rate of expulsion of amines from the tetrahedral intermediate, $T^{\pm}$, formed during the aminolysis of penicillin have been shown to be *ca.* 10^9—10^{10} s^{-1}.[17]

There are several *ad hoc* explanations for the relative instability of the tetrahedral intermediate $T^{\pm}$ (VII) and the negligible activation barrier for the expulsion of the amine from this hypothetical entity. According to the theory of stereoelectronic control [14] the breakdown of tetrahedral intermediates is facilitated by the lone pair of the heteroatoms [both oxygen [3] in (VII)] attached to the incipient carbonyl carbon being antiperiplanar to the leaving group. Presumably, the lone pairs of the ring oxygen eclipse the C–O– and C–$\overset{+}{N}H_2R$ bonds in (VII) (which itself may contribute to the relative instability of $T^{\pm}$) so that a lone pair has a dihedral angle of *ca.* 120° with the carbon–nitrogen bond, *i.e.* not the optimum antiperiplanar arrangement. On the other hand, the C(1), C(8), and ring O atoms of (VII)

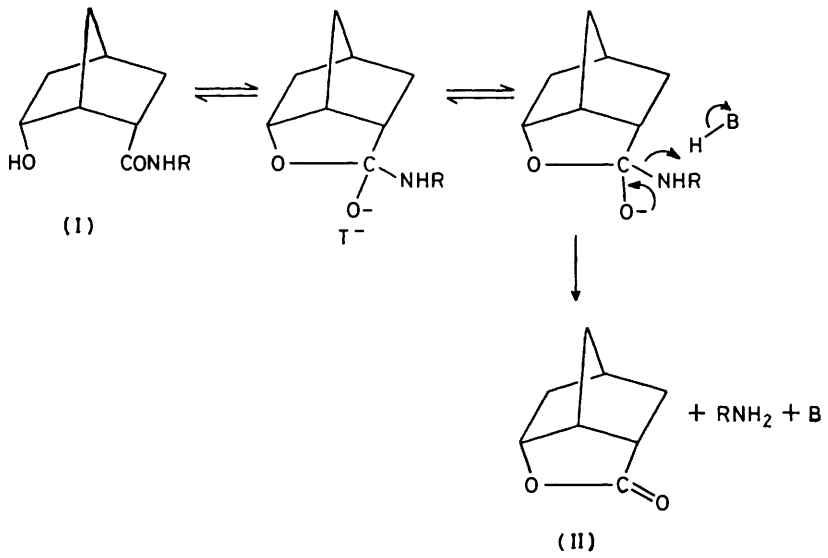
are, because of the conformational rigidity of the tricyclic system, approximately coplanar and conversion of (VII) to the lactone (II) probably requires little movement of these atoms. The ring oxygen in (VII) thus already has a very good geometry for conjugation between its lone pair and the incipient carbonyl group. According to the principle of least motion,[18] therefore, this may increase the rate of expulsion of amine from $T^{\pm}$ (VII).

Trigonal, approximately sp^2, centres in five-membered rings are less strained than tetrahedral, approximately sp^3, centres in the same ring size.[19] This may also contribute to the rapid expulsion of amine from $T^{\pm}$ (VII).

Another *ad hoc* explanation may be the unfavourable non-bonded interactions between the *endo*-3-hydrogen of the norbornyl system and either $\overset{+}{N}H_2R$ (VIII) (or O^- in its diastereoisomer) which are relieved upon conversion of $T^{\pm}$ (VII) into the lactone (II). The strain energy of the analogous hydrocarbon (IX; R = CH_3) is 7—11 kJ mol^{-1} greater than that of (IX; R = H).[20]

It is not possible to prefer exclusively one of these explanations to account for the rapid expulsion of amine from $T^{\pm}$ (VII).

2, *Structure–Reactivity Relationships*.—The dependence of the second-order rate constants for the general-base-catalysed lactonisation of the hydroxy-*N*-propylamide (I; R = $CH_2CH_2CH_3$) upon the basicity of the catalyst is shown in Figure 4. The slope of this line, Brønsted β value, is 0.70 ± 0.08 and appears to be linear over the pK_a range studied. This may be compared with the β value of 0.50 for the hydroxy-*N*-trifluoroethylamide. In view of the postulated mechanism of general-acid-catalysed breakdown of the tetrahedral intermediate (Scheme) the β values are equivalent to α values of 0.50 and 0.30 for the *N*-trifluoroethyl- and the *N*-propyl-amides, respectively. As the basicity of the leaving group increases (a poorer leaving group in the classic sense) the rate of reaction becomes *less* dependent upon the acidity of the proton donor. For example, with trifluoroethanol as the catalyst (pK_a 12.3) the catalytic rate constant for the *N*-propylamide is 8-fold *greater* than that for the *N*-trifluoroethyl derivative but with 2-methoxyethylamine as the catalyst (pK_a 9.7) the rate constants are very similar (Table 1).



SCHEME

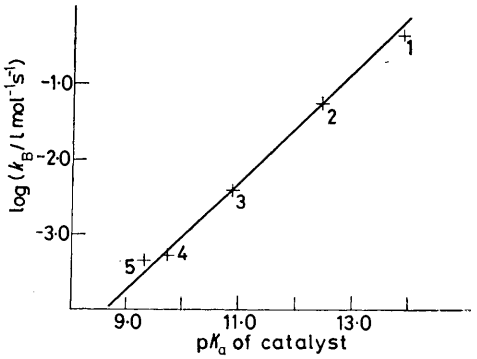


FIGURE 4 The dependence of the rate constants, k_B, for the general-base-catalysed lactonisation of *endo*-6-hydroxybicyclo-[2.2.1]heptane-*endo*-2-*N*-propylcarboxamide upon the basicity of the catalyst. The numbers refer to the bases listed in Table 1

Variation of the leaving group amine with hydroxide ion as the catalyst (water acting as proton donor) gives a β_{lg} value of +0.3.[1] Based on two-point Brønsted plots [rate constants for the hydroxy-amide of propylamine (pK_a 10.8) and for those of the hydroxy-amide of trifluoroethylamine (pK_a 5.8)] the dependence of β_{lg} upon the pK of the catalyst is shown in Table 2. The β_{lg} value *decreases* with decreasing basicity of the catalyst, *i.e.* with *increasing* acidity of the proton donor in the kinetically equivalent general-acid-catalysed mechanism.

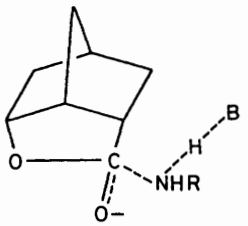
The general-base-catalysed lactonisation of the hydroxy-amide (I) corresponds to general-acid-catalysed

TABLE 2

Brønsted β_{lg} values from the dependence of the rate constants for the lactonisation of *N*-substituted *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides upon the basicity of the leaving group amine as a function of the basicity of the catalyst

Catalyst	pK_a	β_{lg}
Hydroxide ion	13.83	+0.30
Trifluoroethoxide ion	12.31	+0.20
Propylamine	10.80	+0.09
2-Methoxyethylamine	9.74	−0.02
Hexafluoroisopropoxide ion	9.39	−0.07

breakdown of the tetrahedral intermediate T^- (V) [1] and the observed Brønsted coefficients are consistent with a concerted mechanism (Scheme). The α values of 0.5 and 0.3 for the *N*-trifluoroethyl- and the *N*-propylamides, respectively, indicate that, in the transition state (X) the proton is *more* transferred to the departing nitrogen in the case of the more *weakly basic* amine. In a classic sense this is in agreement with the Polanyi–Bell–



(X)

Leffler–Hammond postulates [21] but in a truly concerted mechanism atomic motions in addition to proton transfer are taking place in the transition state. Electron-withdrawing substituents in the amine leaving group (X) will facilitate carbon–nitrogen bond fission but decrease the ease of protonation. Therefore the interpretation of the larger α value for the more weakly basic leaving amine in terms of *more* proton transfer in the transition state could be interpreted as ' anti-Hammond ' behaviour, *i.e.* the ' better ' leaving group requires more protonation.

Reactions in which more than two atoms are involved in the reaction co-ordinate require a multi-dimensional energy surface to understand the effect of substituents. The properties of a transition state have been described in terms of a three-dimensional energy contour diagram (Figure 5) in which the height of any point above some standard value represents the free-energy change (although the potential energy change is often used) for that point.[22-24] These are purely qualitative diagrams based on chemical intuition. Raising the energy of one side or corner of the diagram, by, for example, changing the p*K* of a reactant or product, is expected to introduce a perturbation across the energy surface that moves the transition state ' uphill ' along the direction of the reaction co-ordinate (' Hammond effect ') but ' downhill ' perpendicular to the reaction co-ordinate (' anti-Hammond effect ').[25]

For example, Figure 5 illustrates the two processes of carbon–nitrogen bond fission and protonation of nitrogen that occur when the tetrahedral intermediate T^- is converted into the lactone (II) (solvation changes are neglected or assumed to be linearly related to these processes). Movement along the left- and right-hand edges represents carbon–nitrogen bond fission with no proton transfer and movement along the top and bottom edges represents proton transfer with no carbon–nitrogen bond fission. *If*, for a given amine substituent and catalyst, the transition state is centrally placed as indicated in Figure 5 adding electron-withdrawing substituents to the leaving amine group should stabilise RNH^- and destabilise $T^{\pm}$. This will presumably move

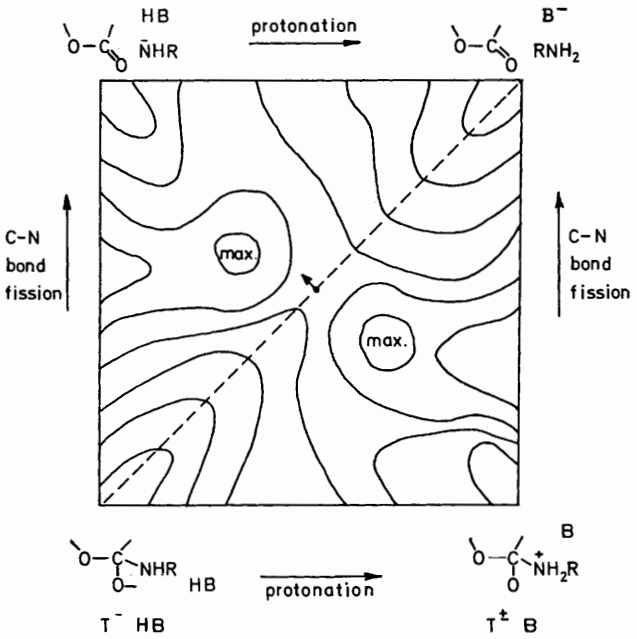


FIGURE 5 Contour diagram for the general-acid-catalysed breakdown of the tetrahedral intermediate T^- to an acyl group with a preferred concerted pathway. The reaction co-ordinate is shown by a dashed line. The arrow shows the expected change in the position of the transition state (perpendicular to the reaction co-ordinate) when an electron-withdrawing substituent is added to the leaving group amine

the transition state towards the top left corner of the diagram, *i.e.* the transition state will have *less* proton transfer and *more* carbon-nitrogen bond fission. Making the catalyst, BH, a stronger acid will stabilise B^- and destabilise BH. This will have two opposing effects: (i) an ' anti-Hammond ' effect by moving the transition state towards the bottom right corner causing *less* carbon–nitrogen bond fission but *more* proton transfer in the transition state, (ii) a Hammond effect by moving the transition state towards the bottom left corner causing *less* carbon–nitrogen bond fission and *less* proton transfer in the transition state.

Two, not unrelated, problems with the use of these three-dimensional energy diagrams are evident. First, the magnitude and the direction of a shift in the position of the transition state on the surface will be determined by the direction of the reaction co-ordinate and the

' starting ' position of the transition state (or, more rigorously, the curvature of the saddle point region, parallel and perpendicular to the direction of the reaction co-ordinate).[26] The amount of ' coupling ' between the atomic motions, in our case carbon–nitrogen bond fission and proton transfer, indicates the amount of ' concertedness ' of the reaction. A transition state occurring along the edges represents, of course, a stepwise reaction, *i.e.* carbon–nitrogen bond fission and protonation occur in separate steps and the reaction co-ordinate lies at 0 or 90° to the intermediates at the corners of the diagram. Hammond-type behaviour is expected for such a reaction mechanism. If the reaction co-ordinate is at 45° to T^- and products (bottom left and top right corners, respectively) carbon–nitrogen bond fission and proton transfer are ' coupled ' and this concerted reaction may give rise to Hammond and anti-Hammond type behaviour as described earlier. Reaction co-ordinates which have directions in between these angles represent varying amounts of ' coupling ' between the atomic motions or degree of ' concertedness ', and would show either Hammond, anti-Hammond, or neither type of behaviour. The second problem concerns the position of the transition state and the relative stabilities of the intermediates (real or hypothetical). It is not unreasonable to assume that the magnitude of the shift of the transition state depends greatly upon the stability of these intermediates. Intuitively, one would expect that changing the stability of a very unstable hypothetical intermediate would have less effect upon transition state geometry than that brought about by changes in the stability of an intermediate which is closer in energy to the transition state. In fact, a simple treatment of the effect of linear perturbations on the cross-over point of intersecting potential energy curves shows that the shift is smaller the greater the curvature of the unperturbed curve.[25,27] If, for example, the hypothetical intermediates, such as those in the top left and bottom right hand corners of Figure 5, are extremely unstable then it is expected that changes in their stability will have less effect upon the geometry of the transition state than similar energy changes in the structures of the bottom left and top right corners (' reactants ' and ' products '). Similarly, if the curvature of the potential energy surface is smaller for parallel than for perpendicular motion then, if the reaction co-ordinate is at 45°, ' Hammond effects ' will be more important than ' anti-Hammond effects '.[26]

The structure–reactivity relationships reported here are an attempt to map out the charge distribution in the transition state for the general acid catalysed breakdown of T^- (V) by comparing substituent effects upon the rate (assumed to reflect transition state stability) with their effects on equilibrium ionisation processes. Brønsted coefficients are assumed to reflect the *relative* amount of charge development that is ' seen ' by the substituent in the transition state or product and depend on the amounts of bond formation and cleavage that have occurred in the transition state.[28] For proton transfer reactions the Brønsted coefficient is often taken as a measure of the amount of proton transfer that has taken place in the transition state. This assumes that the amount of charge development as ' seen ' by the substituent changes monotonically with the amount of proton transfer. It is unlikely that this is the case when proton transfer is accompanied by other processes. Nonetheless, within a reaction series the Brønsted coefficient may be used to deduce that a reaction behaves *as if* there is a certain amount of charge development on a particular atom in the transition state.[3,23,26] This measure of charge development may be used to compare transition states with equilibria and with other transition states but it should *not* be used as an absolute measure of the charge on particular atoms and the transition state.[28]

The Brønsted α-value for the general-acid-catalysed

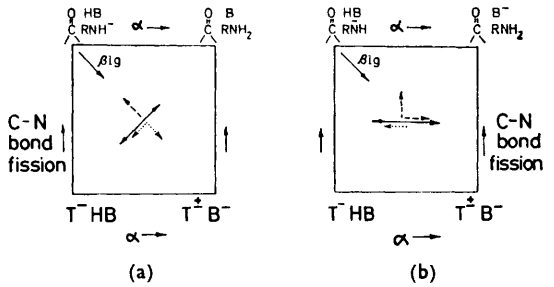


FIGURE 6 Energy diagram based on structure–reactivity coefficients for the general-acid-catalysed breakdown of the tetrahedral intermediate T^- to an acyl group. The x and y co-ordinates are defined by α and the amount of C–N bond fission, respectively. β_{lg} is defined by the diagonal arrow (top left to bottom right). The energy contours are not shown. (a) Diagonal reaction co-ordinate; (b) horizontal reaction co-ordinate (double-headed solid arrows). The expected change in the structure–reactivity coefficients upon the addition of an electron-withdrawing substituent to the amine leaving group is shown by the dashed line and the expected change upon making the proton donor BH a stronger acid is shown by the dotted line

breakdown of T^- (V) to the lactone (II) increases as the pK of the leaving group decreases. This may be taken to indicate that there is a change in the structure of the transition state for the reaction with changing substituents in the leaving group which corresponds to *more* proton transfer from the catalyst to the amine nitrogen (X) as the nitrogen becomes *less* basic but a better leaving group in terms of the ease of pro-acyl carbon–nitrogen bond fission. This change can be described by the coefficient [26] $P_{xy'} = \delta\alpha/\delta pK_{lg}$ with $P_{xy'}$ +0.039. A positive $P_{xy'}$ coefficient is consistent with a transition state for a concerted reaction mechanism that has a large component of proton transfer in the reaction co-ordinate.[26]

As the strength of the acid catalyst increases the Brønsted β_{lg} value decreases (Table 2) (the coefficient [26] $P_{xy'} = \delta\beta_{lg}/\delta pK_{HA} = +0.052$). This may be taken to indicate that there is a *decreasing* amount of positive charge on the departing amine nitrogen as the catalyst becomes a *stronger* acid. This could result from *less* proton transfer and/or *more* carbon–nitrogen bond fission in the transition state.

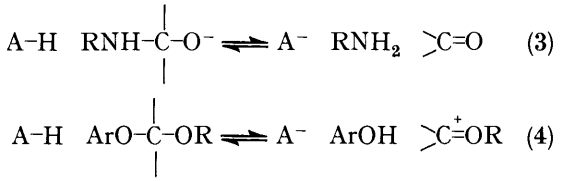
In Figure 6 is shown the three-dimensional reaction

co-ordinate diagram for the proposed mechanism. The Brønsted α coefficient for proton transfer is shown along the horizontal co-ordinate and the amount of C–N bond cleavage and formation along the vertical co-ordinate; the energy contour lines are omitted. Charge development on the leaving group measured by β_{lg} is shown along a diagonal co-ordinate and reflects the fact that β_{lg} may increase because of either increased amount of protonation or less C–N bond fission in the transition state, *i.e.* β_{lg} increases along the horizontal axis left to right and increases along the vertical axis, top to bottom.

A decrease in the basicity of the amine upon addition of an electron-withdrawing substituent will destabilise the tetrahedral intermediate $T^{\pm}$ and lower the energy of the upper left relative to the lower right of the diagram. For a diagonal reaction co-ordinate (Figure 6a) the position of the transition state will tend to slide ' downhill ' toward the upper left corner (perpendicular to the reaction co-ordinate). The horizontal axis of the diagram describes the amount of proton transfer, as measured by the Brønsted α value, so that this shift represents a *decrease* in α which is the *opposite* to that observed. The shift toward the upper left corner also corresponds to a decrease in β_{lg} along the diagonal axis, which is also not observed; the Brønsted plot (Figures 3 and 4) for β_{lg} is, within experimental error, indistinguishable from a linear relationship. However, if the reaction co-ordinate for this mechanism has an important horizontal component (Figure 6b shown as a completely horizontal reaction co-ordinate for display purpose only) then α would be expected to *increase* with increasing electron-withdrawing ability of substituents in the amine, *i.e.* display simple Hammond type behaviour with more proton transfer occurring to the less basic nitrogen in the transition state.

An increase in the acidity of the catalysing acid raises the energy of the left edge of the diagram relative to the right edge. For a diagonal reaction co-ordinate (Figure 6a) the transition state will then tend to slide downhill towards the bottom right, perpendicular to the reaction co-ordinate, and move uphill toward the bottom left, parallel to the reaction co-ordinate (' a Hammond effect '). The β_{lg} value may increase resulting from a motion perpendicular to the diagonal reaction co-ordinate because of more proton transfer and less C–N bond fission. A motion parallel to the reaction co-ordinate may either increase β_{lg} because of reduced C–N bond fission or, as is observed, *decrease* β_{lg} because of less proton transfer in the transition state. However, the net movement along the horizontal co-ordinate can be in either direction, depending on the direction and magnitude of the shifts perpendicular and parallel to the reaction co-ordinate, so that α can increase, decrease, or remain unchanged, as is observed, *i.e.* the Brønsted plots are linear over the acidity range of the catalysts studied. Again, a reaction co-ordinate with a predominant *horizontal* component (Figure 6b) will give the observed *decrease* in β_{lg} with increasing acidity of the catalyst. It appears, therefore, that the reaction co-ordinate has an important horizontal component, *i.e.* proton transfer makes a significant contribution, but there is little driving force from expulsion of the leaving group.

It is interesting to compare our observations with other reactions involving general-acid-catalysed expulsion of leaving groups. The general-acid-catalysed breakdown of T^{-}[equation (3)] is analogous to the general-acid-catalysed hydrolysis of substituted phenyl acetals [equation (4)] which shows an *increase* in β_{lg} with



increasing acidity of the acid catalyst and a *decrease* in α with the substitution of electron-withdrawing groups in the leaving phenol.[29] Similar observations have been made for the general-acid-catalysed formation of semicarbazones.[30] The major difference between these two reactions is that in the transition state for the acetal hydrolysis there appears to be significant bond cleavage between the leaving group and the incipient electrophilic centre [29] and that the acetal oxygen of the leaving group is much less basic than the nitrogen of the leaving group in equation (3). It is interesting to note that the structure–reactivity behaviour observed in our reaction has precedent in alkene-forming elimination reactions.[22,31] The primary process in elimination from β-*p*-nitrophenylethylquinuclidinium compounds is proton transfer, and there is little, if any, driving force from expulsion of the leaving group.[32] We can think of no reason why nitrogen should behave the same as carbon in this kind of reaction and differently from oxygen.

There is a degree of imbalance indicated by the observed α and β_{lg} values. The β_{lg} values are indicative of a transition state in which the nitrogen is almost completely protonated and in which there is little C–N bond fission.[1] On the other hand, the α-values are indicative of a transition state geometry in which proton transfer from the catalyst to the amine nitrogen (X) is partial and not complete. Previous observations of the imbalance between the charge development on the catalyst and on the amine nitrogen have been attributed to the localisation of some positive charge on the proton or an intervening water molecule.[3,28,33] It is conceivable that this imbalance reflects a fully concerted reaction in which the tetrahedral intermediate T^{-} is not formed.

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