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KINETIC STUDY OF THE FORMATION AND RUPTURE OF STABLE TETRAHEDRAL INTERMEDIATES. C—O, C—N and C—S BOND FORMATION

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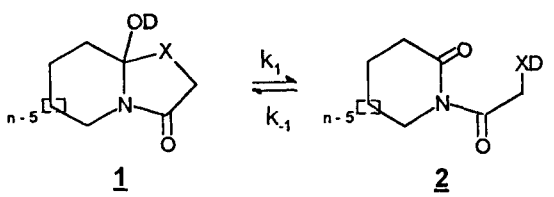
Measured pseudo-first-order rate constants for intramolecular formation of tetrahedral intermediates from *N*-2-hydroxyethylphthalimide, *N*-2-aminoethylphthalimide and *N*-2-thioethylphthalimide at pH > 6 are reported. The reaction is specific and general base catalysed, with β(Brønsted) values 0·44, 0·52 and 0·52 respectively. From a plot of log k_b (general base rate constants) vs γ' [the affinities of EtXH (X = O, NH, S) toward the carbonylic carbon], β'_{nuc} values of 0·01 (with OH^- as specific base), 0·25 (with imdidazole as general base) and 0·27 (with HPO_4^{2-} as general base were obtained). The observed relationships $p_{xy} = \vartheta\beta'_{nuc}/ - \vartheta pK_a = -\vartheta\beta(\text{Brønsted})/\vartheta\gamma' = 0{\cdot}03$ is supported by the predictions of an energy contour diagram, which, on extrapolation to a non-stable tetrahedral intermediate, predicts a late and slightly protonated transition state for the cleavage process. At pH < 3, these intermediates cleave to yield only the corresponding diacylimides. These reactions are general base and acid catalysed with $\beta > 0{\cdot}3$ and $\alpha < 0{\cdot}1$. A fast equilibrium between the intermediate and its *N*-protonated (amide) form is reached. The general base rupture of the latter is faster than that of the corresponding non-protonated intermediate by a factor of *ca* $10^9 - 10^{10}$-fold.

INTRODUCTION

As a direct method for studying the cleavage and formation of tetrahedral intermediates, we started a study of a series[1,2] of stable tetrahedral intermediates. The advantage of our approach over others[3–5] is that direct measurement of the process of rupture and formation of these intermediates can be achieved by dynamic NMR, based on the equilibrium shown in equation (1).

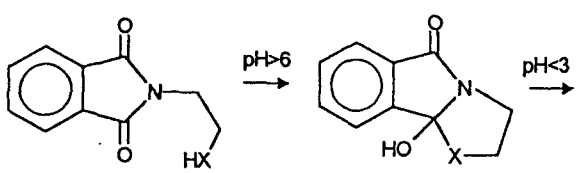


1 **2** (1)

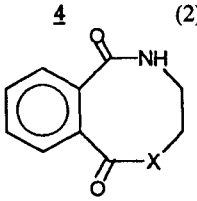
1a: X=O; n=6 (ring size)

1b: X=ND_2; n=5 (ring size)

The pseudo-first order rate constants k_1 and k_{-1}, over a wide pH range, were determined by ^{1}H NMR line-shape analysis of the methylene protons attached to **X**. For the rupture of **1a**[1,2] at 2·5 < pD < 9, both non-catalysed and specific and general base ($\beta = 0{\cdot}4$)-catalysed processes were observed. At pD < 2·5 an irreversible change is detected. For **1b**, however, the process of rupture to yield **2b** could be followed at pD = 2·5 where a specific acid catalysis occurs.[2] In order to cover other stable tetrahedral intermediates and in an effort to find an answer to the different chemistry between **1a** and **1b** at low pD, we prepared compounds **3a**, **3b** and **3c** [equation (2)].



3 **4** (2)



3a: X=O
3b: X=NH_2
3c: X=S

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As depicted in equation (2) and in contrast to compounds **1a** and **1b**, phthalimide derivatives **3** produce compounds **4** irreversibly. The tetrahedral intermediate **4** cleaves to produce only compounds **5** at pH < 3. Since these reactions are not in equilibrium, NMR lineshape analysis was discarded as the kinetic method; consequently, we used a conventional UV method to follow the conversions. The kinetic results and the consequences of the transformations **3** → **4** and **4** → **5** are discussed in this paper.

EXPERIMENTAL AND RESULTS

Syntheses

2-Hydroxyethylphthalimide (3a)

Following the method reported by Wenker,[6] **3a** was obtained in an 86% yield m.p. 128–130 °C (lit.[6] m.p. 129–131 °C). ^{1}H NMR, $CDCl_3$: δ 2·5 (s, 1H), 3·9 (s, 4H), 7·8 (m, 4H). UV (λ_{max}): 214, 240 and 300 nm ($\varepsilon = 2{\cdot}50 \times 10^3$ l mol^{-1} cm^{-1}).

2-Aminiumethylphthalimide (3b)

By hydrogenation with 10% Pd–carbon at 40 psi of 2-ethylazide–phthalimide, previously prepared according to Wolfe and Hasan,[7] **3b** was obtained in 71% yield. ^{1}H NMR, (D_2O): δ 3·3 (m, 2H), 4·0 (m, 2H), 7·8 (s, 4H). ^{1}H NMR, DMSO-d_6: δ 3·1 (t, 2H), 3·9 (t, 2H), 7·9 (s, 4H), 8·4 (m, 3H). UV (λ_{max}): 214, 240 and 300 nm ($\varepsilon = 1{\cdot}98 \times 10^3$ l mol^{-1} cm^{-1}).

2-Thioethylphthalimide (3c)

From phthalic anhydride (13·5 mmol) and 2-aminoethioethanol (40·5 mmol in benzene (20 ml) and pyridine (2 ml) (heated for 90 min at 100–110 °C) and separating the organic phase, **3c** was obtained in 58% yield, after recrystallization from diethyl ether–benzene, m.p. 68–70 °C. ^{1}H NMR, $CDCl_3$: δ 1·4 (t, 1H), 2·8 (dd, 2H), 3·9 (t, 2H), 7·8 (s, 4H). UV (λ_{max}): 214, 240 and 300 nm ($\varepsilon = 1{\cdot}67 \times 10^3$ l mol^{-1} cm^{-1}).

Identification of compounds 4 and 5

When compounds **3** were treated with NaOH (pH > 6), tetrahedral intermediates **4** were obtained. The ^{1}H NMR and UV spectra for **4a**, **4b** and **4c** are similar. ^{1}H NMR, D_2O: δ 3·30–3·45 (br, t, 2H), 3·55–3·75 (br, t, 2H), 7·30–7·60 (m, 4H). UV (λ_{max}): 214 and 240 nm. Tetrahedral intermediates **4** are transformed into the bicyclic compounds **5** when treated with acid (pH < 3). As for compounds **4**, the ^{1}H NMR and UV spectra of **5a**, **5b** and **5c** are very similar. ^{1}H NMR, D_2O: δ 3·40 (m, 2H), 3·60 (m, 2H), 7·80–8·00 (m, 4H). UV (λ_{max}): 214, 240 and 276 nm.

Kinetics

The kinetics were followed by UV measurements using an HP Model 8452A spectrophotometer. In reactions **3** → **4** the disappearance of the 300 nm absorption band corresponding to **3** was used. In reactions **4** → **5** the appearance of the 276 nm band corresponding to **5** was followed.

Reactions **3** → **4**

The solutions were prepared to give a final concentration of 10^{-4} M of substrate **3**, a buffer (imidazole or phosphate) concentration of 10^{-3} M and maintaining the ionic strength constant with a solution of 1 M KCl. The temperature was also kept constant at 25·0 °C with a circulating water-bath. The pseudo-first order rate constants were obtained from a plot of $\ln(A_t - A_\infty)$ vs t. The buffer-catalysed second-order rate constants were obtained from the slope of a plot of k_{obs} vs [B] (Figure 1; B = conjugate base of the buffer). The k_{OH^-} value was obtained by plotting the intercepts of the k_{obs} vs [B] plots vs [OH^-]. In Table 1 the second-order rate constants are reported. From a plot of log k_B vs. pK_a the β(Brønsted) values were obtained (Figure 2). A plot of log k_B vs γ' (affinity toward carbonylic carbon; see Discussion) gave the β'_{nuc} values (Figure 3). These β values are reported in Table 1.

Reactions **4** → **5**

Compounds **3** (10^{-4} M) were transformed completely (adjusting to pH > 6 with excess of NaOH) into **4**. The completeness of the reaction was verified by observing the total disappearance of the characteristic 300 nm UV band of **3**. The pH was reduced (<3) to the desired range and kept constant with 10^{-3} M buffer. The ionic strength was kept constant with 1 M KCl. The temperature of the bath was maintained constant at 25·0 °C with circulating water. The appearance of the 276 nm band characteristic of bicyclic compounds **5** was used to follow the kinetics. The pseudo-first-order rate constants were obtained from a plot of $\ln(A_\infty - A_t)$ vs t. From a plot of k_{obs} vs total concentration of buffer, different slopes at each pH were obtained. A plot of these slopes vs fraction of free acid of the buffer is shown in Figure 4. From the intercepts of these plots at $\alpha = 0$ and $\alpha = 1$ the second-order rate constants for the general acid and base catalysis were obtained. All these constants are reported in Table 2. The values of α(Brønsted) and β(Brønsted), obtained from a plot of log $k_{BH}(k_B)$ vs pK_a, are reported.

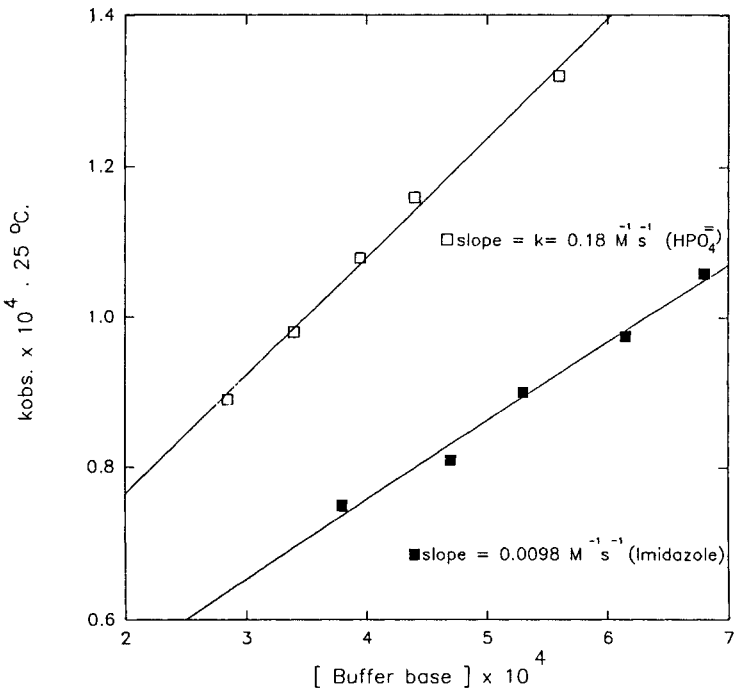


Figure 1. Plot of $k_{obs.}$ vs [buffer base] for compound **3c** at pH 6·7 and 25 °C

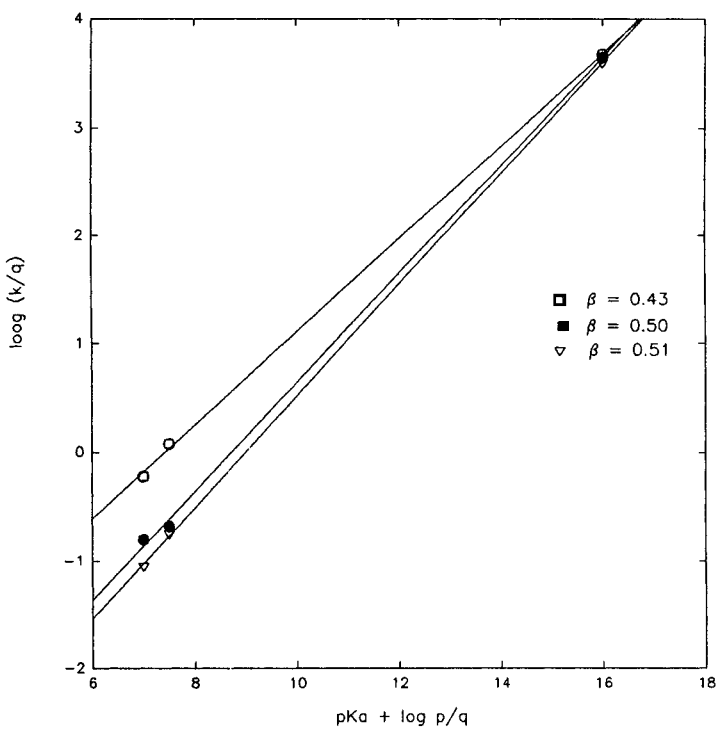


Figure 2. Plot of log k(base-catalysed second-order rate constants) vs pK_a of buffers (H_2O, imidazole and HPO_4^{2-}). Statistical correction is included

Table 1. k_B values, β(Brønsted) and β'_{nuc} for reactions **3** → **4**

Compound	k_{OH^-} (l mol^{-1} s^{-1})	$k_{imidazole}$ (l mol^{-1} s^{-1})	$k_{HPO_4^{2-}}$ (l mol^{-1} s^{-1})	β(Brønsted)
3a	4800 ± 66	0·6 ± 0·2	1·20 ± 0·5	0·43[a]
3b	4500 ± 34	0·16 ± 0·04	0·21 ± 0·08	0·50[a]
3c	4000 ± 54	0·09 ± 0·03	0·18 ± 0·06	0·51[a]
β'_{nuc}	0·01[b]	0·24[b]	0·26[b]	

[a] Obtained from a plot of the log of each value of this file vs pK_a (H_2O, imidazole and $H_2PO_4^-$). Statistical correction is included.
[b] Obtained from a plot of each value of this column vs γ' (**3a** 2·6, **3b** −0·2, **3c** −0·7), where γ' is the intrinsic affinity for carbonylic carbon.

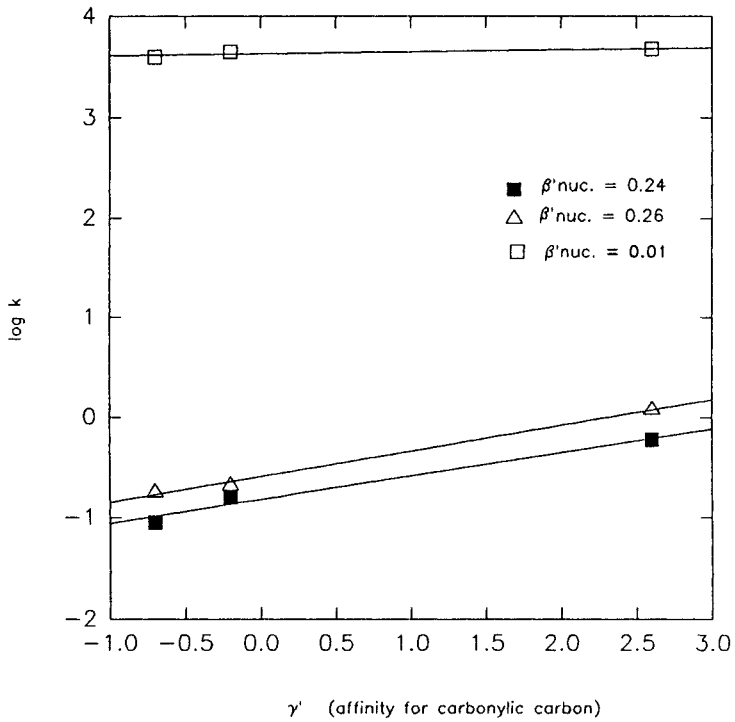


Figure 3. Plot of log k (base-catalysed second-order rate constants) vs γ' (affinity toward the carbonylic carbon): $\gamma' = 2·6$ (X = OH, **3a**), −0·2 (X = NH_2, **3b**) and −0·7 (X = SH, **3c**)

Table 2. Second-order rate constants, α, β and competition ratios of reactions **4** → **5**

	k_{BH} (l mol^{-1} s^{-1})[a]			K_B (l mol^{-1} s^{-1})			$k_{BH}/k_{B^-} = k_2/k_{B^-} \times 10^{-10}$[b]	
Compound	H_3PO_4	Oxalic acid	α(Brønsted)	$H_2PO_4^-$	Oxalate	β(Brønsted)	H_3PO_4, $H_2PO_4^-$	Oxalic, oxalate
4a	0·51	0·33	0·01	0·30	0·14	0·30	1·7	2·4
4b	0·34	0·21	0·03	0·49	0·07	0·94	0·69	3·0
4c	0·27	0·15	0·06	0·49	0·09	0·83	0·55	1·7

[a] Statistical correction is included.
[b] $k_{BH}/K_B = (k_2/k_{B^-})KK_{BH}$, where $K = 10^{-8}$ l mol^{-1} and $K_{BH} = 10^{-2}$ l mol^{-1}.

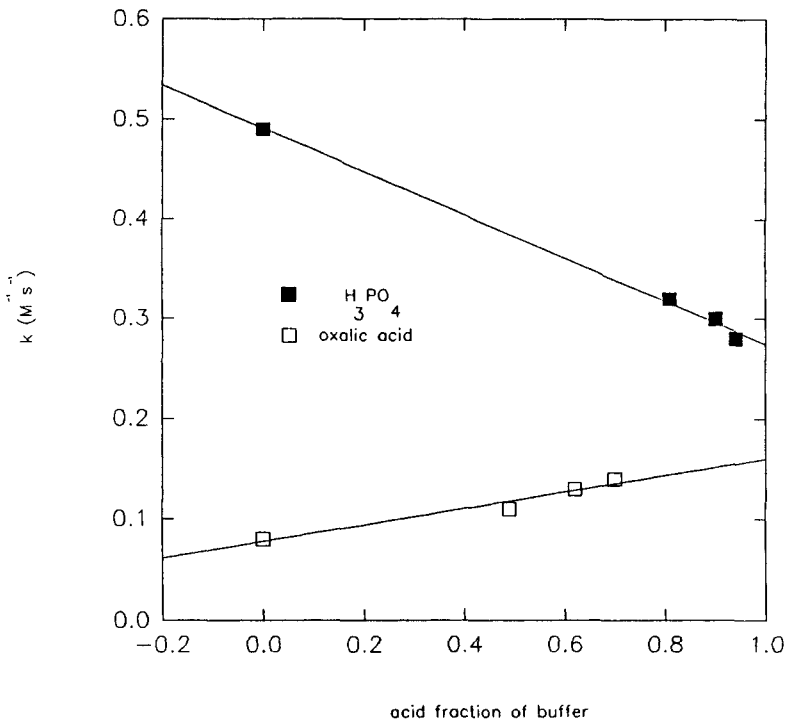


Figure 4. Plot of k (l mol^{-1} s^{-1}) of Figure 5 vs the acid fraction of buffers for compound **4c**. The k values were obtained from a plot of k_{obs} vs [total buffer] at different pH values

DISCUSSION

X—C bond formation (reaction 3 → 4)

In Table 1, the second-order rate constants of the general base catalysis for the intramolecular attack of the $-N(CH_2)_2XH$ groups to the phthalimide carbonylic carbon [equation (2), pH > 6] are reported. As shown, the β(Brønsted) values are similar, with values around 0·5. However, these values might be uncertain, since one of the plot points (OH^-) could be acting via a different mechanism to the other base catalyst. We discarded this alternative owing to the following evidence. Excluding the k_{OH^-} values from the calculations, the β(Brønsted) values obtained are in all cases $<0·6$. When they are included, the correlation coefficient $r^2 > 0·9996$. The β(Brønsted) values obtained[1,2] for compounds **1**, (0·4) and **2** (0·5) are also around the value of 0·5. Gravitz and Jencks[5] found β(Brønsted) = 0·57 in the general base catalysis (carboxylate buffers) for formation of compound **6′** from the phthalimide **6″**. In these systems, the point for water also fits the Brønsted plot, suggesting the same mechanism as that for the other catalyst.

In Table 1 are also given the β'_{nuc} values. They are completely different, with a maximum of 0·27 for the reaction catalysed by HPO_4^{2-}. When plotting k_B vs the pK_a of the $-N(CH_2)_2XH$ groups (slope = β_{nuc}), there is not a good linear correlation. However, when plotting k_B vs the affinities of the $-N(CH_2)_2XH$ groups towards carbonylic carbon ($\gamma'_{OH} = 2·6$, $\gamma'_{NH_2} = -0·2$ and $\gamma'_{SH} = -0·7$) a good correlation, the slope of which we have defined as β'_{nuc}, is found. These affinities were obtained from the following equilibrium:[8]

$$R{-}COH + HX \underset{}{\overset{K}{\rightleftharpoons}} R{-}\underset{X}{\overset{OH}{C}}{-}H \qquad (3)$$

The parameter γ, which is a measure of the ability of a given compound to add to the carbonyl group and, therefore, a measure of its affinity for carbon compared to hydrogen, is defined as $\gamma = \log(K_{RXH}/K_{MeNH_2})$. Sander and Jencks[8] obtained the γ values, evaluating the equilibrium constants of equation (3), and using pyridine-4-carboxaldehyde and different alcohols, amines and thiols as nucleophiles (HX). In our case, there is an intramolecular reaction [equation (2), pH > 6] between three different nucleophiles $-N(CH_2)_2XH$ (X = O, NH and S) and the phthalimide

Table 3. Affinity toward carbonyl carbon (γ')

Compound	γ[a]	pK_a	γ'[d]
3a	−2·5 (X = EtOH)	15·9[b]	2·6
3b	−0·3 (XH = $EtNH_2$)	10·8[b]	−0·2
3c	+0·35 (XH = $HOCH_2CH_2SH$)	10·2[c]	−0·7
CH_3NH_2	O (XH = CH_3NH_2)	10·6[b]	0

[a] $\gamma = \log(K_{HX}/K_{MeNH_2})$ from equilibrium RCOH + XH ⇌ RCH(OH)(X); values from Ref. 8.
[b] From Ref. 9.
[c] From Ref. 10.
[d] $\gamma' = \log$ [antilog $\gamma(K_{RX}/K_{RNH_2})$], where K_X and K_{RNH_2} are the equilibrium basicity constants.

carbonyl group. Therefore, we used the thermodynamic γ values to obtain the corrected γ' parameters, which are a measure of the intrinsic affinity for carbonylic carbon. Since the γ values of the $-N(CH_2)_2XH$ (X = -O,NH and S) groups have not been reported,[8] we used instead the values for ethylamine, ethanol and β-mercaptoethanol (Table 3).

The antilogarithm of γ is then defined according to

$$K_{HX}/K_{MeNH_2} = [RC(OH)(X)]\,[MeNH_2]\,/\,[RC(OH)(MeNH_2)]\,[XH] \quad (4)$$

In this equation, the affinity for carbon is given by the ratio $[RC(OH)(X)]/[RC(OH)(MeNH_2)]$ and the affinity for hydrogen by the ratio $[MeNH_2]/[XH]$. A good measure of the affinity for hydrogen of an X group is given by its basicity equilibrium constant, $K_X = K_W/K_{XH}$, in water. The reference used in the definition of γ is methylamine. However, under our experimental pH conditions, a correction of the methylamine contribution to the $[MeNH_2]/[XH]$ ratio is required, since methylamine would be in the form of $MeNH_3^+$ and not $MeNH_2$. This correction is given by the basicity equilibrium constant of $MeNH_2$, $K_{MeNH_2} = K_W/K_{MeNH_3^+}$, in water ($K_W = 10^{-14}$ mol^2 l^{-2}). We have defined γ' as the intrinsic affinity of the groups XH for carbon, where a correction for their affinity for hydrogen has been taken into account by multiplying the antilogarithm of γ [left-hand side of equation (4)] by the ratio of the equilibrium basicity constants, K_X/K_{RNH_2}, according to the expression $\gamma' = \log[\text{antilog } \gamma\,(K_X/K_{RNH_2})]$.

Plots of β'_{nuc} vs pK_a (buffer) and β(Brønsted) vs γ'

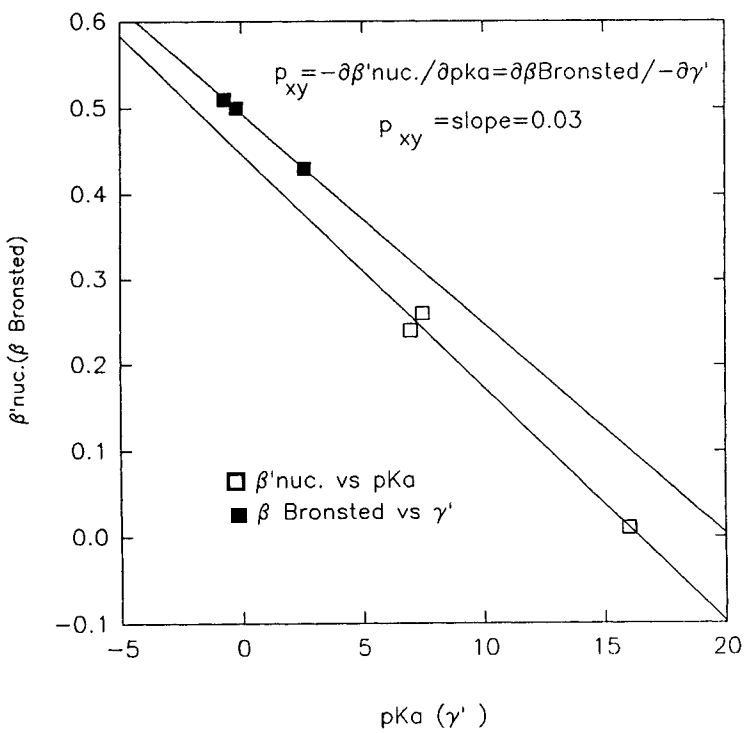


Figure 5. Plots of β'_{nuc} vs pK_a and β(Brønsted) vs γ' (affinity toward carbonylic carbon). The slope is the cross term p_{xy}

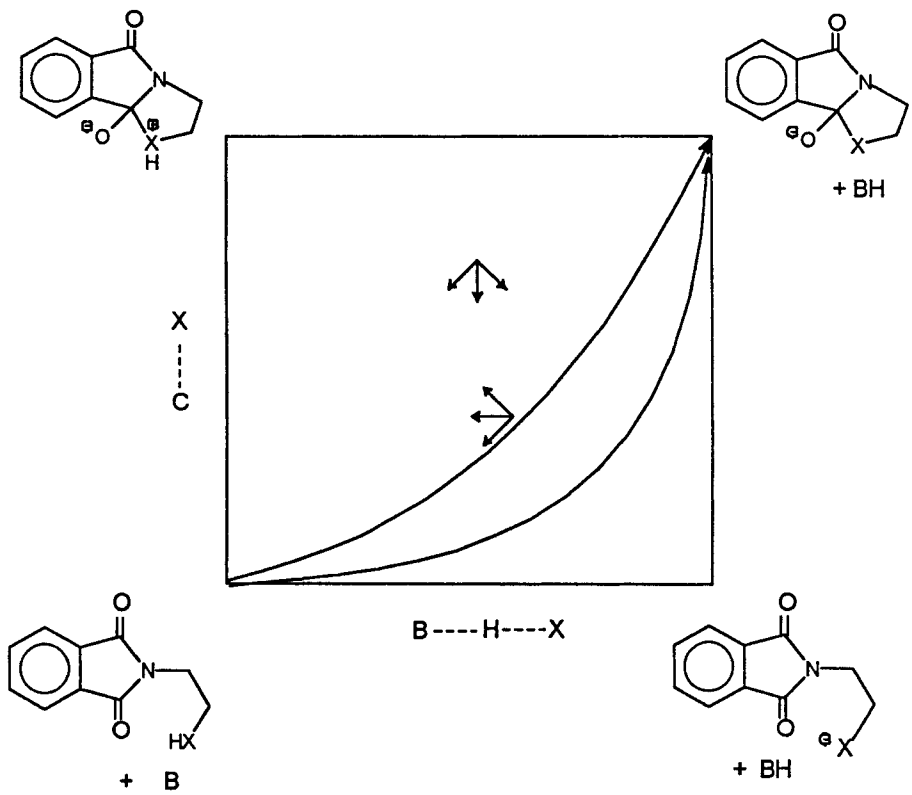
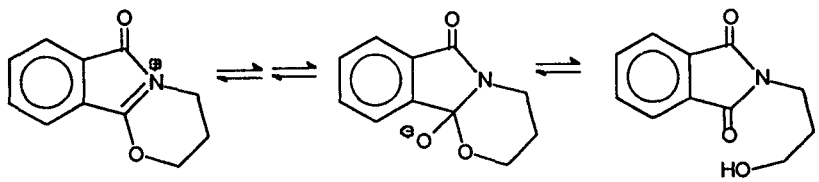


Figure 6. Contour diagram for reactions **4** → **5**. Solid lines: top, hypothetical symmetric reaction coordinate; bottom; reaction coordinate. Top arrows: predicted changes when the basicity of B is increased. Bottom arrows: predicted changes when the affinity toward the carbonyl carbon (γ') of XH groups is increased

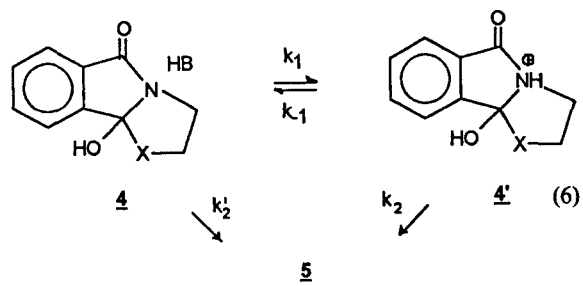
are shown in Figure 5. The average of the slopes for both lines is the cross-term $p_{xy} = \vartheta\beta'_{nuc}/-\vartheta$ pK_a $= -\vartheta\beta(\text{Brønsted})/\vartheta\gamma'$ and is equal to 0·03. This value is supported by the tendencies expected from the energy contour diagram of Figure 6 and the experimental measurements of β(Brønsted) and β'_{nuc}. When increasing the basicity of the buffer the two right corners are stabilized. This change introduces a movement toward the reactants on the parallel coordinate and towards the bottom right corner on the perpendicular coordinate, as shown by the arrows (top). The resultant movement is to decrease β'_{nuc} (bottom solid line in Figure 6) maintaining β(Brønsted) constant, as is observed experimentally (Table 1). Increasing the affinity of X toward the carbon (γ'), the top corners are stabilized. The resultant movement, as shown by the bottom arrows, is to decrease β(Brønsted). As is shown experimentally (Table 1), a small decreasee in β(Brønsted) is observed (from 0·52 to 0·43), changing from X = NH and X = SH ($\gamma' = -0{\cdot}2$ and $-0{\cdot}7$, respectively) to X = O with $\gamma' = 2{\cdot}7$. According to this mechanism, the X—C bond formation proceeds through a concerted mechanism with a transition in which the base has abstracted the proton half way, and the X—C bond is scarcely formed. The reverse reaction is the breakdown of the conjugate base of the tetrahedral intermediate (top right to bottom left corner in Figure 6). This reaction is then general acid catalysed with α(Brønsted) = 1 − β(Brønsted). The α(Brønsted) value for X = O is 0·57, which is similar to the value obtained by Gravitz and Jencks[5] [α(Brønsted) = 0·43] in the last step of the hydrolysis of phthalimidium cation **6** and by us[2] [α(Brønsted) = 0·6] in the rupture of compound **1a**. For X = NH, α(Brønsted) = 0·50 and we observe[2] for the rupture of intermediate **1b** α(Brønsted) = 0·4. The mechanism of cleavage proposed by Gravitz and Jencks[5] and by us[2] is one in which a pre-equilibrium between the tetrahedral intermediate and its conjugate base (T^-) is established. Then the rupture occurs from T^-; this last step is general acid catalysed and the rupture of the X—C bond and the protonation of the X group occur simultaneously. This is also the mechanism of the reverse of the reaction in Figure 6. The fact that the α(Brønsted)



(5)

6 6' 6''

values directly measured by Gravitz and Jencks and by us are very similar to those obtained from the β(Brønsted) values for compounds **3a** and **3b** reinforces the mechanism proposed in Figure 6. The mechanism of X—C formation is then general-base catalysed by direct abstraction of the proton by the base, in a concerted step with some X—C formation at the transition state. Further evidence in support of the concerted character of this mechanism the experimental observation in which there is a decrease in X—C formation as the basicity of the base decreases (Table 1, β'_{nuc} values).



(6)

4 5 4'

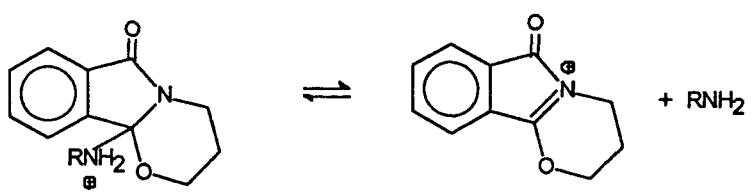
C—N cleavage (4 → 5)

General acid catalysis

Protonation of an amide nitrogen by water is a very slow process with a rate constant that can be estimated to be $k_{H_2O} = 10^{-14}$ l mol^{-1} s^{-1}, assuming diffusion-controlled reaction for the reverse interaction between the protonated amide ($pK_a = -8$ for $RCONH_3^+$)[11] and the hydroxide ion. However, protonation of the amide nitrogen by hydroxonium ion [k_1 in equation (6), $B = H_2O$] could be estimated to be, at least, $k_{H^+} = 10^4$ l mol^{-1} s^{-1}, assuming a rate constant $k_{-1}[H_2O]$ of 10^{12} s^{-1} for deprotonation of the amide by water (diffusion-controlled) and using the pK_a value of -8 estimated for primary amides, so that at pH < 2 protonation of the amide nitrogen of compounds **4** is a fast process (100 s^{-1}) compared with the values of $k_{obs} \approx 10^{-4}$ s^{-1} obtained for the formation of **5**. A fast equilibrium is then established between intermediates **4** and **4'** followed by the general base cleavage of **4'**. This mechanism is kinetically equivalent to the direct general acid catalysis (k_2') of the intermediate **4** that obviously could be ruled out due to the fast protonation by H^+ and the faster rupture from **4'** compared with **4**.

According to the proposed mechanism and as it is shown in equation (6), a pre-equilibrium, $4 + BH \rightleftharpoons 4' + B$, is established and the cleavage occurs from **4'**. The k_{obs} value is then given by $k_{obs} = [BH](k_2K_{BH}/K_a)$ so that the general acid rate constant is then given by $k_{BH} = k_{obs}/[BH] = k_2K_{BH}/K_a$ and $k_2 = k_{BH}K_a/K_{BH}$. This constant k_2 can be estimated from the observed general acid rate constant $k_{BH} \approx 10^{-1}$ l md^{-1}s^{-1} (Table 2, $BH = H_3PO_4$), the acidity constant for H_3PO_4, $K_{BH} \approx 10^{-2}$ mol l^{-1}, and the value of the acidity constant for the amide proton, $K_a = 10^8$ l mol^{-1}: $k_2 = 10^{-1}$ l mol^{-1} s^{-1}/10^{-8} l mol^{-1} $\times 10^{-2}$ l mol^{-1} = 10^9 l mol^{-1} s^{-1}. Since k_{-1} in equation (6) is diffusion controlled (10^{10} l mol^{-1} s^{-1}), k_2 is the rate-determining step with a partition factor (k_2/k_{-1}) equal to *ca* 10^{-1}.

It is interesting to compare the estimated value of k_2 (second-order rate constant) of (10^9 l mol^{-1} s^{-1}) for the rupture of tetrahedral intermediate **4'** with the estimated[12] first-order rate constant value (33 s^{-1}) for the rupture of compound **7** [equation (7)]. The effective



(7)

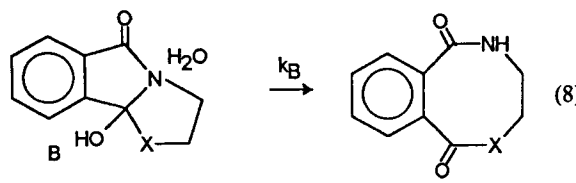
7

concentration, which is given by the ratio $33\ s^{-1}/10^9\ l\ mol^{-1}\ s^{-1}$, indicates what [BH] value is required in the intermolecular reaction in order to have equal intra- and intermolecular rates. This ratio is 3×10^{-9}. This low value implies that the intramolecular character for the process of rupture of **7** is more than compensated for by the additional driving force of an important negative charge on the oxygen developed in the rupture of **4'**, which is promoted by the general base catalysis of the k_2 step [equation (6)]. The value $\beta > 0{\cdot}97$ for this step, which was estimated from the relationship $\beta = 1 - \alpha$ ($\alpha = 0{\cdot}03$; see Table 1), reinforces the latter statement. Other factors[13] such as the difference in leaving and staying abilities of the protonated piperidine and an amide and the relative stabilities of the products (**6** + RHH_2 and **5a**) might also be influencing the relative reactivity of **7** and **4'**.

It has been found[12] that amines are 10^5 better leaving groups than alkoxides with similar pK_a values. We have observed that the intermediate **4** produces only compound **5** at pH < 3 [equation (2)]. Formation of compound **3** is not observed in any case (X = NH, S or O). This result is predicted based on the following considerations. For X = O, the protonation of X in the intermediate is very unfavourable at $0{\cdot}5 <$ pH < 3 owing to the low pK_a of the respective conjugate acid. For instance, the pK_a of $CH_3CH(S^+HEt)(OH)$ has been estimated[14] to be *ca* −7·91, so that in these cases the competition of leaving abilities is between the protonated amide and the corresponding alkoxide or thioxide. It has been pointed out by Gravitz and Jencks[12] that compound **7** is a good model for testing leaving abilities of protonated amines and alkoxide anions (RO instead of RNH_2^+ in **7**), since the driving force is identical in both systems. Therefore, the protonated amide must be cleaved much faster than the alkoxide (X = O) or thioxide (X = S). Conversely, for X = NH_2 in compound **4**, the amine is easily protonated since the $pK_a = 10{\cdot}81 - 5{\cdot}1 = 5{\cdot}7$, as predicted from $\rho_i \times \sigma_i$ correlation, using $\rho_i = 8{\cdot}5$ (Ref. 15) and $\sigma_i = 0{\cdot}60$ (Ref. 6) ($EtNH_2^+$). However, protonation of the nitrogen amide in **4** is also fast (see above). The competition for cleavage is then between both protonated amine and amide. The experimental result is that the rupture to yield compound **5** from **4'** is faster than cleavage of the amine. This observation is in agreement with the leaving abilities of the two nitrogens, which is given by the pK_a difference between the amide ($pK_a = -8$) and the amine ($pK_a = 5{\cdot}7$). The transition-state stability paralleled the product stability and since the protonation of the amine and amide nitrogens is fast, only the breakdown of the amide nitrogen is expected, according to the Curtin–Hammett principle.[17] Apparently, an extra stabilization of the 6–8-fused ring of **5** compared with the 6–5-fused ring of **3** may also be contributing. For instance, Glover *et al.*[18] found greater stability in 6,10-dioxo-1,5-diazacyclodecane and 5,10-dioxo-1,6-diazacyclodecane than in their open forms, *N*-(3-aminopropyl)glutarimide and 1-(4-aminobutyryl)one-2-pyrrolidin. We also detected[2] compounds similar to **5** at low pH. For instance, we observed this transformation for compounds **1b** and **1c** [X = NH_2, $n = 7$, equation (1)]. Atonov *et al.*[19] also found this rupture in caprolactam derivatives. Griot and Frey[20] observed the formation of a large ring system from *N*-(β-hydroxyiacyl)lactams.

General base catalysis

The scheme for the proposed general base catalysis is shown in equation (8).



(8)

4 **5**

A two-step mechanism where protonation of the amide nitrogen by water occurs in a slow step followed by the base catalysis and rupture of the C—N bond can be ruled out since no dependence on the concentration of the base will be observed. The estimated value of the rate constant for protonation of the amide nitrogen by water ($k_{H_2O} = 10^{-14}$, see above), is too low to afford a mechanism where the first step is fast compared with the cleavage; therefore, the general base catalysis must proceed through a concerted mechanism in which the negative charge on the oxygen (driving force) is well developed at the transition state, as supported by β(Brønsted) > 0·30 (Table 2). As shown in Table 2, the β(Brønsted) values for cleavage of **4** decrease in the order NH, S and O. This tendency is in agreement with the pK_a of the hydroxyl proton on **4**. The lower the pK_a the lower is β(Brønsted), since less abstraction of the proton is required. The process of proton abstraction, C—N bond cleavage and protonation of the amide nitrogen by water must then be concerted, since departure of nitrogen requires protonation to avoid the highly unstable amide anion —CON^-— intermediate.

Competition between general base and general acid mechanisms

The ratio k_{BH}/k_{B^-} describes the fraction of the product formed via general acid and base mechanisms. k_{B^-} is defined in equation (8) and, since $k_{BH} = Kk_2K_{BH}$ [equation (6)] where $K = 10^{-8}\ l\ mol^{-1}$ and $K_{BH} = 10^{-2}\ mol\ l^{-1}$ as described above, then $k_{BH}/k_{B^-} = k_2/k_{B^-} \times 10^{-10}$. From the ratio k_{BH}/k_{B^-} in

Table 2, it is found that $k_2 \gg k_{B^-}$ by a factor of 10^9–10^{10}.

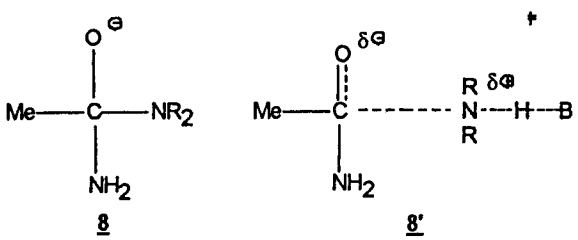
The k_2/k_B values for oxalate buffer are greater than those corresponding to $H_2PO_4^-$ for any X (**4a**, X = O; **4b**, X = NH; and **4c**, X = S). Since oxalic acid has a pK_a (1.19) lower than that of phosphoric acid (2·12), the effective reactivity of **4** [k_B, equation (8)] vs **4′** [k_2, equation (6)] is greater in the less basic buffer.

It has been pointed out[20] that the acid mechanism for rupture of tetrahedral intermediates is not clearly established. We are currently investigating the cleavage of different stable tetrahedral intermediates at low pH order to complete the results presented here.

CONCLUSIONS

From the results of the X—C bond formation an extrapolation to less stable tetrahedral intermediates can be made using the contour diagram of Figure 6. A destabilization of the two top corners of Figure 6 will result in a movement (opposite to the bottom arrows) of the transition state toward the right, increasing β(Brønsted). The transition state for such an intermediate will then have a β(Brønsted) near 1 and small β'_{nuc}. For the reverse reaction (rupture of the intermediate) a small α(Brønsted) [$\alpha = 1 - \beta$(Brønsted)] and a β'_{lg} ($\beta'_{lg} = 1 - \beta'_{nuc}$) near 1 are then predicted as depicted for transition state **8′**. These α and β'_{lg} values can be estimated. Assuming a conservative destabilization of the non-stable tetrahedral intermediates by a factor of 10^4 relative to the stable intermediate, and considering the experimental value of the obtained cross-term p_{xy} (0·03), a movement of β(Brønsted) of 0·2 unit is predicted. Even with this conservative value the β(Brønsted) for the rupture of **8′** is small, *ca* 0·3 ($\alpha = 1 - 0{\cdot}7$), with β'_{lg} near 1. Therefore, a late transition state is predicted where the driving force of the electron pair on oxygen is strong enough to promote the well developed departure of the leaving group. The last statement implies that the transition state resembles the reaction products. Therefore, factors such as product stability, entropy and leaving ability are more important than prototropic control, that is, the basicity of the heteroatom being cleaved from the carbon. This is the case for the cleavage of most of the tetrahedral intermediates.

In the basic hydrolysis of asymmetric acetamidines, it has been found that there is a preference for cleaving the more basic amine: secondary > primary ≫ ammonia. From this observation, it was concluded that basicity of the nitrogen in the intermediate **8** (prototropic control) is not relevant. Instead, it is the basicity of the cleaved amine itself that must be considered. The extrapolation that we have done to less stable tetrahedral intermediates, using Figure 6, might contribute to explaining the irrelevance of prototropic control. Having, as predicted, a late transition state, the basicity of the nitrogen at the intermediate **8** becomes irrelevant. It is the basicity of the already cleaved amine which counts. Ammonia having a lower basicity than primary and secondary amines, and consequently being less stable as a product, its rate of departure is lower. In this case and for most of the tetrahedral intermediates, transition-state stability is strongly paralleled by product stability, and other factors participating in the cleavage are overwhelmed by such an effect.



8 **8′**

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