24 h. An additional 0.200 g of ethylene oxide was added and the solution stirred at room temperature for an additional 24 h. The solvent was then evaporated to produce a brown oil. Trituration with anhydrous Et_2O gave 0.625 g (86%) of **22** as a tan solid which was not further purified: mp 45–48 °C; IR (neat) 3370 cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.30 (12 H, m), 2.65–3.05 (4 H, m), 3.45 (2 H, t, J = 5 Hz); mass spectrum, for M^+, m/e 181.1462 (calcd for $C_{11}H_{19}NO$ m/e 181.1467.

2-(2-Chloroethyl)-2-azaadamantane (8). A 5.187-g (43.6 mmol) quantity of $SOCl_2$ was added dropwise to 350 mg (1.90 mmol) of **22** with stirring at 0 °C. After the addition was complete, the ice bath was removed, and the solution was brought to reflux for 2.5 h. Excess $SOCl_2$ was then distilled off, leaving a brown residue which solidified upon standing. The solid was washed with several portions of anhydrous ether and then dried under reduced pressure to produce 231 mg (61%) of **8**·HCl after recrystallization from CH_2Cl_2–C_6H_6: mp 232–233 °C dec; IR (Nujol) 2560, 2485, 1100 cm^{-1}; NMR ($CDCl_3$) δ 1.50–3.15 (13 H, m), 3.35–3.82 (4 H, m), 4.19 (2 H, t, J = 5.5 Hz).

Anal. Calcd for $C_{11}H_{18}NCl$·HCl: C, 55.94; H, 8.11; N, 5.93. Found: C, 55.74; H, 7.92; N, 6.12.

2-Chloroadamantane (23). A 1.00-g (6.58 mmol) portion of 2-adamantanol (Aldrich) was treated with 5.0 mL of freshly distilled $SOCl_2$. The mixture was stirred at reflux for 3 h. The excess $SOCl_2$ was removed by heating under a stream of N_2. Residual $SOCl_2$ was destroyed by addition of ca. 2 mL of dry MeOH. Evaporation of solvent produced 1.073 g (95.7%) of crude **23**, which was recrystallized from MeOH; mp 183–185 °C (lit.[27] mp 186–188 °C).

Solvolysis Product Studies. An approximately 1.0 mM solution of the substrate was prepared by dissolving it in a solution of 480 mL of 0.02 M NaOH and 120 mL of MeOH. The reaction vessel was flushed with N_2 and stirred at a constant temperature (25 °C) for a minimum of 8 half-lives. After evaporation of the MeOH in vacuo, the basic aqueous layer was saturated with NaCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to produce the mixture of products.

Kinetic studies were performed by following the liberation of Cl^- with an Orion 94-17 chloride ion electrode and an Orion 90-02 double-junction reference electrode connected to an Orion 701A ion analyzer. A typical procedure for the β-halo amines follows. Into a jacketed titration cup maintained at 20.00 (±0.01) °C were placed 6.2 mL of 0.010 N NaOH, 1.50 mL of MeOH, and 0.20 mL of 5.0 M $NaNO_3$ (ionic strength adjustor). The stirred solution and electrodes were allowed to equilibrate, after which time a 0.100-mL aliquot of the halo amine in dry MeOH was added at t = 0. The rate of reaction of the test compound was followed by plotting ln ($Cl_\infty - Cl_t$) vs. time. All reactions showed good first-order kinetic behavior through 3–4 half-lives when fitted by using linear least-squares regression techniques on a Hewlett-Packard HP41C calculator. Each rate value is based on 10–15 points per run. Most rates represent averages of three determinations. Arrhenius values were determined from a plot of (log k) vs. $1/T$ for each reaction.

The kinetic study of **23** was run in an identical manner, except that modifications were made to accommodate the required higher temperatures. Thus, 1.6-mL aliquots of a 5.0 mM solution of **23** in absolute MeOH were added to breakseal ampules, each containing 6.4 mL of 0.02 M NaOH that was also 3.2×10^{-4} M in NaCl. The ampules were sealed and immersed in an isothermal bath. At appropriate intervals, an ampule was withdrawn, cooled in ice–H_2O, and opened, and the contents were assayed as above. After the initial Cl^- present was corrected for, the rates were determined as above.

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Registry No. 1, 79191-36-9; 1·HCl, 79254-04-9; 3, 79191-37-0; 8, 79191-38-1; 8·HCl, 14578-33-7; 9a, 53092-72-1; 9b, 79191-39-2; 10, 79191-40-5; 11, 40810-53-5; 12, 3015-16-5; 13, 79191-41-6; 13·HCl, 79191-42-7; 14, 79191-43-8; 15, 79191-44-9; 16, 79191-45-0; 17, 79191-46-1; 18, 79191-47-2; 19, 770-15-0; 20a, 3015-19-8; 20b, 3632-95-9; 21, 768-41-2; 22, 14578-32-6; 23, 7346-41-0; 24, 100-35-6; 1,3-dibromoadamantane, 876-53-9; 2-adamantanol, 700-57-2.

Differentiation of Nucleophilic and General Base Catalysis in the Hydrolysis of *N*-Acetylbenzotriazole Using the Proton Inventory Technique[1]

Ganesa Gopalakrishnan and John L. Hogg*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

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The hydrolysis of *N*-acetylbenzotriazole is catalyzed by acetate and imidazole by two different modes as shown by the proton inventory technique. Acetate acts as a general base catalyst to abstract a proton from the attacking water molecule. The unexpected upward curvature in the proton inventory plot can be attributed to a reactant-state isotopic fractionation factor contribution from acetate ion. The proton inventory for imidazole catalysis exhibits downward curvature and is shown to be consistent with a nucleophilic catalysis role for imidazole. The intermediate, 1-acetylimidazole, then undergoes rate-determining water-catalyzed hydrolysis via the expected mechanism.

Introduction

The neutral, water-catalyzed hydrolysis of esters, amides, and carbonates has, in many instances, been shown to involve a transition-state structure in which one water molecule acts as a base to abstract a proton from the attacking water molecule.[2-5] For the general-base-catalyzed reactions the general base (e.g., imidazole) acts to abstract a proton from the attacking water molecule.[6-9] The two

(1) This work was supported by the National Institutes of Health (Grant No. 1 R01 GM 25433) and, in part, by the Robert A. Welch Foundation.

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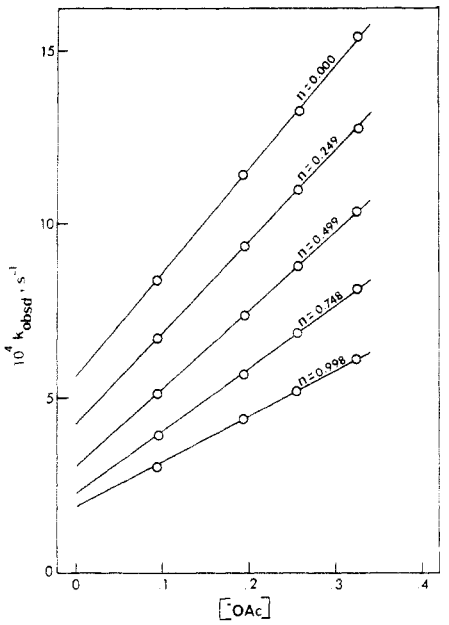
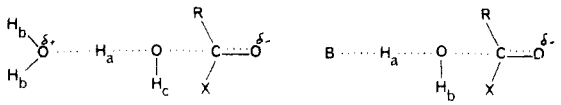


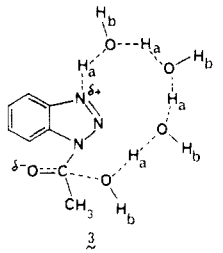
Figure 1. Plot of k_{obsd} vs. acetate ion concentration for the hydrolysis of *N*-acetylbenzotriazole in H_2O–D_2O mixtures of atom fraction deuterium, *n*, at 50.00 ± 0.05 °C. The runs were done at pH 5.01 or the equivalent pD. Each point represents the average of two runs. The circles encompass the error bars.

transition-state structure types are shown in **1** and **2**, respectively.



1 2

Recently, the water-catalyzed hydrolysis of *N*-acetylbenzotriazole was investigated at several different ionic strength values by using the proton inventory technique.[10] These results, coupled with those of Reboud-Ravaux,[11] led us to suggest the cyclic transition state (**3**) involving four water molecules for this reaction.[10] A similar transition state has been proposed for the neutral, water-catalyzed hydrolysis of 1-acetyl-1,2,4-triazole.[12]



3

The nature of the transition-state structures for the *N*-acetylbenzotriazole and 1-acetyl-1,2,4-triazole systems seemed to be a departure from the expected structures so we chose to investigate the general-base-catalyzed hydrolysis of *N*-acetylbenzotriazole as well. The general bases chosen were imidazole and acetate ion. The results of proton inventory investigations of these hydrolysis reactions are reported here.[13]

Table I. Second-Order Rate Constants for the Acetate-Catalyzed Hydrolysis of *N*-Acetylbenzotriazole in Mixtures of H_2O–D_2O of Atom Fraction Deuterium *n* at 50.00 ± 0.05 °C[a]

atom fraction of D (*n*)	$10^6 k_2$, M^{-1} s^{-1}	$10^6 k_2$(calcd),[b] M^{-1} s^{-1}
0.000	3035[c]	3035
0.249	2645	2647
0.499	2263	2239
0.748	1830	1822
0.998[d]	1355	1354

[a] Ionic strength was maintained at 0.5 M with KCl. [b] Calculated on the basis of the model of eq 2 with $\phi_a^* = 0.40$ and $\phi_{-OAc} = 0.90$. [c] These values were obtained as the slopes of the k_{obsd} vs. acetate concentration plots shown in Figure 1. [d] Atom fraction of deuterium in "100%" deuterated buffer solution as determined by Mr. Josef Nemeth.[34]

Table II. First-Order Rate Constants for the Spontaneous Hydrolysis of *N*-Acetylbenzotriazole in Mixtures of H_2O–D_2O of Atom Fraction Deuterium *n* Buffered with Acetic Acid–Acetate at 50.00 ± 0.05 °C[a]

atom fraction of D (*n*)	$10^7 k_1$, s^{-1}	$10^7 k_1$(calcd),[b] s^{-1}
0.000	5417[c]	5417
0.249	4163	4145
0.499	2998	3107
0.748	2203	2281
0.998[d]	1696	1629

[a] Ionic strength was maintained at 0.5 M with KCl. [b] Calculated on the basis of the cyclic transition-state model obtained in the previous study[10] with $\phi_a^* = 0.74$. [c] These values were obtained as the intercepts of the k_{obsd} vs. acetate concentration plots shown in Figure 1. [d] Atom fraction of deuterium in "100%" deuterated buffer solution as determined by Mr. Josef Nemeth.[34]

Results

The hydrolysis of *N*-acetylbenzotriazole was studied in acetic acid–sodium acetate buffers at pH 5.01 or the equivalent point on the pD–rate profile. The ionic strength was maintained at 0.5 M with potassium chloride at 50.00 ± 0.05 °C. Figure 1 shows the plots of the observed pseudo-first-order rate constants as a function of acetate concentration in buffers of atom fraction deuterium *n* in this pH (pD)-independent region. The second-order rate constants, k_2, for acetate catalysis and the first-order rate constants, k_1, for the spontaneous hydrolysis were determined as the slopes and intercepts of these plots, respectively. These values are collected in Tables I and II. The solvent deuterium isotope effects were determined to be $k_1^{H_2O}/k_1^{D_2O} = 3.20$ and $k_2^{H_2O}/k_2^{D_2O} = 2.24$. A plot of k_1 vs. *n* (figure not shown) exhibits downward curvature quite similar to that observed in the neutral, water-catalyzed hydrolysis of *N*-acetylbenzotriazole determined previously.[10] The proton inventory plot of k_2 vs. *n* (Figure 2) exhibits a rather uncommon upward curvature not expected for a classical general-base-catalyzed mechanism.[8,9]

The hydrolysis of *N*-acetylbenzotriazole was also studied in imidazole–imidazolium ion buffers at pH 5.95 or the equivalent point on the pD–rate profile. At 50.00 ± 0.05 °C the hydrolysis was too fast to study with use of our technique so the study was conducted at 25.00 ± 0.05 °C at 0.5 M ionic strength with concentrations of free imid-

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(13) For a discussion of the proton inventory technique and the significance of the curvature parameter γ, see ref 14–21.

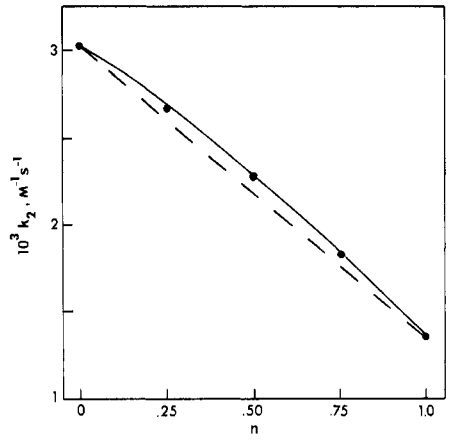

Figure 2. Dependence of the second-order rate constants for the acetate ion catalyzed hydrolysis of *N*-acetylbenzotriazole on the atom fraction of deuterium in the solvent at 50.00 ± 0.05 °C. The data are taken from Table I. The solid line was calculated on the basis of the transition-state model described by eq 2 with $\phi_a^* = 0.4$ and $\phi^-_{OAc} = 0.90$. The dashed line is present to emphasize the curvature.

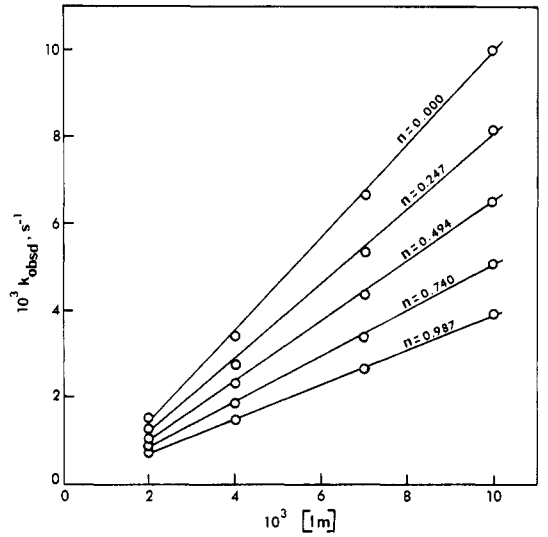

Figure 3. Plot of k_{obsd} vs. imidazole concentration for the hydrolysis of *N*-acetylbenzotriazole in H_2O–D_2O mixtures of atom fraction deuterium, *n*, at 25.00 ± 0.05 °C. The runs were done at pH 5.95 or the equivalent pD. Each point represents the average of two runs. The circles encompass the error bars.

azole less than 10^{-2} M in the buffer. Even under these conditions the reaction was orders of magnitude faster than the acetate- or water-catalyzed reactions. The pseudo-first-order rate constant increases linearly with imidazole concentrations up to 10^{-2} M but shows a greater dependence at higher concentrations. Thus, all proton inventory studies were done with buffers containing free imidazole in the concentration range 10^{-3} to 10^{-2} M. Plots of the observed rate constant as a function of imidazole concentration in buffer solutions of atom fraction deuterium *n* are shown in Figure 3. The second-order rate constants, k_2, obtained as the slopes of these lines are plotted as a function of *n* in Figure 4 and are collected in Table III. This plot exhibits significant curvature ($\gamma = 0.36 \pm 0.07$),[18] which is again in contrast with what one would expect for a classical general-base mechanism.[12,13] Furthermore, the plots of k_{obsd} vs. *n* (not shown) at the various imidazole concentrations all exhibit downward curvature with similar γ values (Table IV).

When the imidazole-catalyzed reaction was followed at 245 nm, the absorption maximum of 1-acetylimidazole,[3] a sudden burst in absorbance followed by a slow absorbance decrease was observed. The magnitude of the burst was dependent upon imidazole concentration but the rate of decrease in absorbance did not correspond to the rate of the overall reaction.

The reaction in imidazole buffers was also followed in the presence of initially added benzotriazole. A plot of log $(A_t - A_\infty)$ vs. time exhibited two distinct slopes—a fast first-order decrease in absorbance followed by a slower first-order decrease. The initial slope gave a rate constant equivalent to k_{obsd}, while the second slope exhibited an inverse dependence on benzotriazole concentration.

Table III. Second-Order Rate Constants for the Imidazole-Catalyzed Hydrolysis of *N*-Acetylbenzotriazole in Mixtures of H_2O-D_2O of Atom Fraction Deuterium *n* at 25.00 ± 0.05 °C[a]

atom fraction of D (*n*)	$10^3 k_2$, $M^{-1} s^{-1}$	$10^3 k_2$(calcd),[b] $M^{-1} s^{-1}$
0.000	1074[c]	1074
0.247	865	863
0.494	679	681
0.740	530	526
0.987[d]	395	395

[a] Ionic strength was maintained at 0.5 M with KCl. [b] Calculated on the basis of the model of eq 3 with $\phi_a^* = 0.62$ and $\phi_b^* = 0.77$. [c] These values were obtained as the slopes of the k_{obsd} vs. imidazole concentration plots shown in Figure 3. [d] Atom fraction of deuterium in "100%" deuterated buffer solution as determined by Mr. Josef Nemeth.[34]

Table IV. γ Values[18] at Each Individual Imidazole Concentration Used in Figure 3 for the Imidazole-Catalyzed Hydrolysis of *N*-Acetylbenzotriazole in H_2O-D_2O Mixtures at 25.00 ± 0.05 °C[a]

[imidazole],[b] M	γ value[c]
0.002	0.33 ± 0.21
0.004	0.37 ± 0.00
0.007	0.34 ± 0.05
0.010	0.37 ± 0.05

[a] These values, in essence, represent a separate proton inventory of k_{obsd} at each different imidazole concentration. [b] Concentration of free imidazole in the buffer. [c] Calculated by using the computer program GAMIS01.

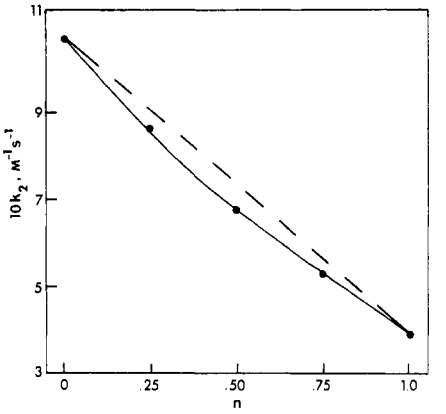

Figure 4. Dependence of the second-order rate constants for the imidazole-catalyzed hydrolysis of *N*-acetylbenzotriazole on the atom fraction of deuterium, *n*, in the solvent at 25.00 ± 0.05 °C. The data are taken from Table III. The solid line was calculated on the basis of the transition-state model described by eq 3 with $\phi_a^* = 0.62$ and $\phi_b^* = 0.77$. The dashed line is present to emphasize the curvature.

Discussion

The linear dependence of k_{obsd} on acetate concentration (Figure 1) coupled with the solvent deuterium isotope

effects suggest a general-base mechanism for acetate catalysis. Such general-base mechanisms are generally exemplified by linear proton inventories since a single "in-flight" proton is responsible for the observed solvent deuterium isotope effect.[8,9] Hence, the upward bowing in the proton inventory (Figure 2) for acetate catalysis of *N*-acetylbenzotriazole is an unusual observation.

Upward curvature in proton inventories occurs in two instances: (i) when one or more exchangeable hydrogenic sites has an isotopic fractionation factor other than unity or (ii) when there are inverse isotope effect contributions to the observed solvent isotope effect.[18-20] The present case can be interpreted in terms of reactant-state fractionation factor contributions to the observed solvent isotope effect.

The general form of the equation which describes the dependence of the rate constant k_n on the atom fraction of deuterium n in the solvent and the rate constant in pure protium oxide k_0 is shown in eq 1.[14-21] The parameters

$$k_n = k_0 \frac{\prod_i^{TS}(1 - n + n\phi_i^*)}{\prod_i^{RS}(1 - n + n\phi_j)} \quad (1)$$

ϕ_i^* and ϕ_j are isotopic fractionation factors for exchangeable hydrogenic sites in the transition state (TS) and reactant state (RS), respectively. These isotopic fractionation factors measure the deuterium to protium preference for the exchangeable site relative to the deuterium to protium preference for an exchangeable solvent site.

The reactants involved in the expected transition state for general-base catalysis by acetate are *N*-acetylbenzotriazole, water, and acetate ion. Salomaa and Aalto[22] and Albery[18] suggested the fractionation on solvent sites surrounding a negatively charged ion is much more pronounced than those surrounding positive ions or neutral sites. This is probably because the orientation of water molecules places the isotopically substituted site close to negatively charged ions but not to positively charged ions. From the measurements of Gold and Lowe,[23] Albery[18] arrived at a fractionation factor of 0.90 for transfer of acetate ion from protium oxide to deuterium oxide.

If we write the form of eq 1 for a system including a single "in-flight" transition-state proton (H_a in **2**) and include the reactant-state fractionation factor of 0.90 for acetate, we arrive at eq 2. Substitution of the values for

$$k_n = k_0 \frac{(1 - n + n\phi_a^*)}{(1 - n + n\phi^{-}_{OAc})} \quad (2)$$

the rate constants in pure protium oxide and pure deuterium oxide and the value for n in "pure" deuterium oxide along with the value of 0.90 for ϕ^{-}_{OAc} allows one to calculate a fractionation factor of 0.40 for ϕ_a^*. These values account for the observed solvent deuterium isotope effect since $k_2^{H_2O}/k_2^{D_2O} = 2.24$, while $(1/\phi_a^*)\cdot\phi_{AcO^-} = 2.25$. Furthermore, the solid line of Figure 2 is generated from eq 2 with these values. The numerical values may also be compared in Table I. This analysis shows that the acetate catalysis of *N*-acetylbenzotriazole hydrolysis can be accounted for by a classic general-base transition state once the reactant-state fractionation factor for acetate is included.

The proton inventory for the spontaneous hydrolysis (k_1 vs. n) is not shown but is the same as that obtained earlier for *N*-acetylbenzotriazole at pH 3 or the equivalent pD.[10] This is additional support for the previous study since the same fractionation factor of 0.74 used in the previous study generates the proton inventory obtained in the present study.

The downward curvature observed in the proton inventory for imidazole catalysis (Figure 4) suggests the involvement of multiple protons in the transition state, the source of such curvature. The curvature parameter γ has a value of 0.36, which implicates three protons in the transition state.[18] One would have expected a linear proton inventory as in previous studies of general-base catalysis by imidazole (e.g., the imidazole-catalyzed hydrolysis of 1-acetylimidazole).[8] Several factors must be considered when formulating a transition state for this reaction: (i) there is a sudden increase in absorbance at 245 nm followed by a slow decrease, (ii) initially added benzotriazole inhibits the reaction, (iii) there is a nonlinear dependence on imidazole, and (iv) the imidazole-catalyzed hydrolysis is orders of magnitude faster than the acetate-catalyzed hydrolysis. All of these facts disfavor a general-base role for imidazole in the hydrolysis of *N*-acetylbenzotriazole and point to a role as a nucleophilic catalyst.

The distinction between nucleophilic and general-base catalysis is often difficult to make.[24] Nucleophilic catalysis by imidazole and similar bases has been reported in the hydrolysis of substrates of the type RCOXR′ where R is an alkyl or an aryl group and HXR′ is a good leaving group such as a thiol, phenol, or a substituted phenol.[25-27] Jencks and Kirsch showed that imidazole acts only as a nucleophilic catalyst whenever the pK_a of the leaving group is less than 10.[28] In the present case, the pK_a of the leaving group, benzotriazole, is 8.32.[11]

Nucleophilic catalysis, recognized first by Bender and Turnquest[27] and Bruice and Schmir,[29] involves the addition of the nucleophile to generate an intermediate followed by unimolecular decomposition of the intermediate and regeneration of the catalyst. The small solvent isotope effects observed in such cases have been attributed to solvent reorganization accompanying the activation process. The imidazole-catalyzed hydrolysis of *N*-acetylbenzotriazole exhibits a reasonably large solvent isotope effect of $k_{H_2O}/k_{D_2O} = 2.72$.

The observed burst in absorbance at 245 nm, the characteristic absorption maximum of 1-acetylimidazole, and its slow decrease suggest the buildup of 1-acetylimidazole as an intermediate. The neutral, water-catalyzed hydrolysis of 1-acetylimidazole has been previously shown to exhibit a downwardly curved proton inventory with a γ value of 0.36,[3] a value identical with that observed in the

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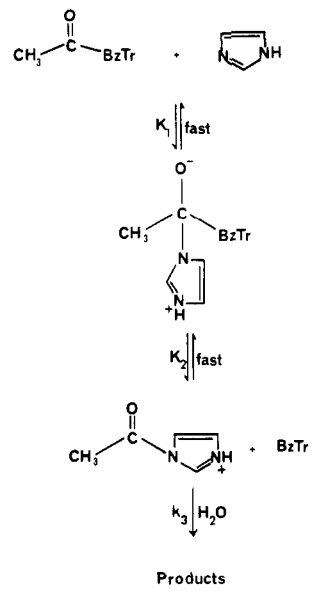
Scheme I



imidazole-catalyzed hydrolysis of *N*-acetylbenzotriazole. This suggests that 1-acetylimidazole is formed as an intermediate in the present study.

Two pieces of evidence which initially seem contradictory to this proposal are: (i) the rate of decrease of the absorbance at 245 nm after the initial burst does not correspond to the overall rate, and (ii) the directly measured rate of hydrolysis of 1-acetylimidazole is fast in comparison to the rate of the present reaction. The first piece of evidence is easily explained by the fact that the increasing concentration of benzotriazole causes an increase in absorption at 245 nm. The slower rate of hydrolysis is probably due to the slow rate of initial acylation which affects the steady-state concentration of the intermediate.

The mechanism shown in Scheme I which involves nucleophilic attack on *N*-acetylbenzotriazole by imidazole to give 1-acetylimidazole followed by its rate-determining, water-catalyzed hydrolysis is consistent with all of the experimental data.

The transition-state structure for the water-catalyzed hydrolysis of 1-acetylimidazole has previously been established as that shown in **1**.[3] The proton inventory was shown to be consistent with eq 3 with $\phi_a^* = 0.55$ and ϕ_b^*

$$k_n = k_0(1 - n + n\phi_a^*)(1 - n + n\phi_b^*)^2 \qquad (3)$$

$= 0.83$. The present system, when analyzed in the same fashion, gives values of $\phi_a^* = 0.62$ and $\phi_b^* = 0.77$ for a fit to eq 3. These values are within experimental error of the original values and generate the solvent deuterium isotope effect of 2.72. Thus, eq 3, along with these fractionation factors, values of n, and $k_{1.0}$ can be used to generate the calculated values in Table III and the solid line in Figure 4.

Figure 5 shows the linear relationship between the directly measured rate constants for the neutral, water-catalyzed hydrolysis of 1-acetylimidazole from the previous study[3] and the second-order rate constants for the imidazole-catalyzed hydrolysis of *N*-acetylbenzotriazole. The observed solvent deuterium isotope effects are 2.58 and 2.72, respectively, for the two systems.

The proposed mechanism is similar to the generally accepted mechanism of α-chymotrypsin-catalyzed reactions represented by eq 4.[30] It is also quite similar to the im-

$$E + S \overset{K_s}{\rightleftharpoons} E{\cdot}S \overset{k_2}{\rightleftharpoons} E\text{–acyl} \xrightarrow[H_2O]{k_3} E + P_2 + P_1 \qquad (4)$$

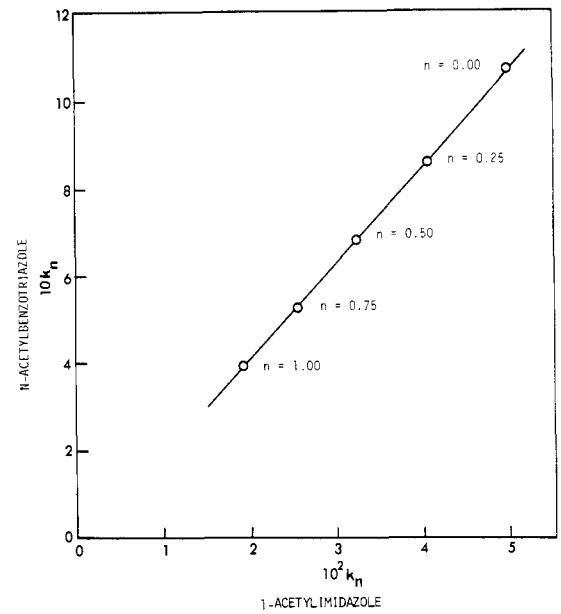


Figure 5. Comparison of the second-order rate constants (Table III) observed in the imidazole-catalyzed hydrolysis of *N*-acetylbenzotriazole and the directly measured first-order rate constants of the neutral, water-catalyzed hydrolysis of 1-acetylimidazole at 25.00 ± 0.05 °C.[3] The k_n values corresponding to $n = 0.25$ and 0.75 for hydrolysis of 1-acetylimidazole were calculated from the k_0 value.

idazole-catalyzed reactions of *p*-nitrophenyl acetate.[31] These reactions differ in rate-limiting steps. The *p*-nitrophenyl acetate reaction has as its rate-limiting step the nucleophilic attack of imidazole, while the rate-limiting step in the present study is the water-catalyzed hydrolysis of the acyl intermediate.

Conclusion

The proton inventory technique has been shown to be extremely useful in differentiating transition-state structures for general-base catalysis and nucleophilic catalysis of *N*-acetylbenzotriazole hydrolysis. The unusual reactant-state contributions to the observed solvent deuterium isotope effect in the case of acetate catalysis have been readily identified by using the technique.

Experimental Section

Materials. *N*-Acetylbenzotriazole was prepared by the method of Staab.[32] Imidazole was purified by repeated recrystallization from benzene. Imidazole-*1-d* was prepared by the method of Garfinkel and Edsall.[33] Deuterium oxide (99.75 atom % deuterium; Bio-Rad) was used as obtained. Deuterium chloride (20% solution in D_2O; Aldrich) and acetic acid-*d* (98 atom % deuterium; Aldrich) were used as obtained. Potassium chloride and sodium acetate were oven dried before use.

The stock acetic acid–sodium acetate buffer solutions (0.5 M total buffer) adjusted to pH 5.01 or the equivalent pD were prepared by dissolving appropriate amounts of sodium acetate and acetic acid or acetic acid-*d*, in either H_2O or D_2O. The ionic strength was adjusted to 0.5 M with potassium chloride. Solutions of lower buffer concentration were prepared from the stock buffer solutions by dilution with 0.5 M potassium chloride solution. The pH(D) of the solutions was maintained by using a Corning pH meter 130 equipped with a combination electrode.

(30) Jencks, W. P. In "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; p 45.
(31) See page 67 and references therein of ref 30 for an excellent discussion of this type of reaction.
(32) Staab, H. A. *Chem. Ber.* **1957**, *90*, 1320.
(33) Garfinkel, D.; Edsall, J. T. *J. Am. Chem. Soc.* **1958**, *80*, 3807.

The stock 1:10 imidazole/imidazolium ion buffer solution was prepared by dissolving the amount of imidazole (imidazole-*1-d*) to give 0.11 M imidazole in 0.1 M HCl(DCl). The ionic strength was maintained at 0.5 M with potassium chloride. Solutions of lower buffer concentration were prepared by dilution with 0.5 M potassium chloride solution. The atom fraction of deuterium was determined by Mr. Josef Nemeth.[34]

(34) Urbana, IL 61801.

Kinetics. The hydrolysis of *N*-acetylbenzotriazole was monitored by observing the decrease in absorbance at 300 nm, using a Cary 118C ultraviolet-visible spectrophotometer equipped with a constant-temperature cell compartment and interfaced with a computerized data acquisition system. The absorbance values at 1- or 10-s intervals were collected and analyzed by using a nonlinear-least-squares computer program. Plots of log $(A_t - A_\infty)$ vs. time were used in a confirmatory fashion.

Registry No. *N*-Acetylbenzotriazole, 18773-93-8.

Effect of Inverse Micelles on the Competition between Lactonization and Polymerization Reactions of an ω-Hydroxy Carboxylic Acid[1]

David A. Jaeger* and J. Thomas Ippoliti

Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071

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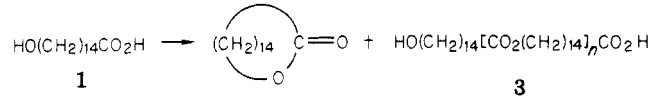
The ability of inverse micelles to influence the competition between carbodiimide-mediated lactonization and polymerization of 15-hydroxypentadecanoic acid (1), yielding pentadecanolide (2) and polymer (3), respectively, has been investigated by using inverse micellar systems in benzene based on di-*n*-dodecyldimethylammonium bromide (DDABr) and on bis(2-ethylhexyl) sodium sulfosuccinate (AOT) with and without water pools. Two ionic carbodiimides, 1-cyclohexyl-3-[2-(*N*-methylmorpholinio)ethyl]carbodiimide *p*-toluenesulfonate (4) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5), were used. The inherent ability of carbodiimide 4 to effect lactonization of 1 is inhibited moderately by DDABr inverse micelles without water pools and completely by AOT inverse micelles without water pools. Carbodiimide 4 did not effect esterification when these inverse micellar systems contained water pools; carbodiimide 5 apparently did not do so under any of the conditions used.

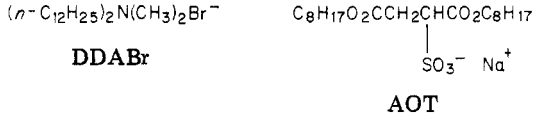
Under esterification conditions an ω-hydroxy carboxylic acid undergoes competing intra- and intermolecular reactions to yield lactone and polymer, respectively.[2] The formation of medium (8–11 membered) and large (12 membered and above) rings is entropically unfavorable,[3] and synthetic procedures have used high-dilution[2] and/or special activation techniques[4,5] to promote lactonization relative to polymerization. Inverse micelles in nonpolar aprotic solvents have been used to catalyze numerous reactions;[6] their catalytic ability is believed to result, in part, from the fact that they can bind substrates strongly in specific orientations.[6] We herein report the ability of inverse micelles to influence the competition between lactonization and polymerization for 15-hydroxypentadecanoic acid (1), yielding pentadecanolide (2) and



1 2 3

polymer 3, respectively, when mediated by carbodiimides. Carbodiimides have been used previously to effect esterification/lactonization in other systems.[7]

Several inverse micellar systems based on di-*n*-dodecyldimethylammonium bromide (DDABr) and on bis(2-ethylhexyl) sodium sulfosuccinate (AOT) in benzene



DDABr AOT

were used with and without dissolved water pools.[8] When 1 is solubilized by an inverse micelle containing a water pool, it is likely that its hydroxyl and carboxyl groups are hydrogen bonded to the pool. Within an inverse micelle even in the absence of a water pool it is assumed that these two functional groups are localized at the ionic core due to ion–dipole interactions.[8] Thus, association with an inverse micelle, with or without a water pool, should bring the hydroxyl and carboxyl groups of 1 closer together on a time-averaged basis than they would be otherwise in bulk solution. If a carbodiimide is also solubilized in an inverse micelle containing a single molecule of 1, it might be expected to effect lactonization as the result of the proximity of the hydroxyl and carboxyl groups. Two ionic carbodiimides, 1-cyclohexyl-3-[2-(*N*-methylmorpholinio)-ethyl]carbodiimide *p*-toluenesulfonate (4)[9a] and 1-[3-(di-

(1) Some of these results were presented at the International Symposium on Solution Behavior of Surfactants—Theoretical and Applied Aspects, June 30–July 3, 1980, Potsdam, NY.

(2) Stoll, M.; Rouvé, A. *Helv. Chim. Acta* **1935**, *18*, 1087.

(3) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 198.

(4) For reviews, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, *33*, 3041.

(5) For specific pertinent examples, see: (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. (c) Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.* **1980**, *45*, 1535.

(6) (a) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975; Chapter 10. (b) Fendler, J. H. *Acc. Chem. Res.* **1976**, *9*, 153.

(7) For examples, see: (a) Neelakantan, S.; Padmassani, R.; Seshadri, T. R. *Tetrahedron* **1965**, *21*, 3531. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Ibid.* **1958**, *2*, 1.

(8) (a) For a general discussion of the ability of inverse micelles in nonpolar solvents to dissolve water and polar solubilizates, see ref 6. (b) Even without added water there were certainly traces present. It is apparently impossible to prepare *completely* anhydrous inverse micellar solutions even with due care (Eicke, H. F.; Christen, H. *Helv. Chim. Acta* **1978**, *61*, 2258. Djermouni, B.; Ache, H. J. *J. Phys. Chem.* **1979**, *83*, 2476).

(9) (a) Sheehan, J. C.; Hlavka, J. J. *J. Org. Chem.* **1956**, *21*, 439. (b) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *Ibid.* **1961**, *26*, 2525.

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