precipitate was isolated. It was heated with 150 mL of acetic acid for 1 h and then cooled and isolated. Recrystallization from acetic acid yielded 3.5 g (84%) of colorless needles: mp 250–255 °C dec; ^{1}H NMR (Me_2SO-d_6, Me_4Si) δ 9.31 and 8.67 (NH_2), 8.78 (6-H), 4.77 (CH_2), 3.89 (NCH_3), 2.68 (CH_3). Anal. Calcd for $C_7H_{11}N_3Br_3$ (M_r 297.00): C, 28.31; H, 3.73; N, 14.15. Found: C, 28.37; H, 3.76; N, 13.82.

Sodium Salt of 3-Cyano-1-(4-nitrobenzyl)-1,4-dihydropyridine-4-sulfonic Acid (2a). To 0.4 g (1.45 mmol) of 3-cyano-1-(4-nitrobenzyl)pyridinium chloride[20] dissolved in 2.5 mL of water was added 0.18 g (1.45 mmol) of sodium sulfite. The water was removed on a freeze dryer, and the residue was extracted with three portions of 5 mL of 2-propanol. The solvent was removed, and the yellow residue (4.6 g, 92%) was dried at 100 °C in vacuo: mp 156–159 °C dec; ^{1}H NMR (D_2O, DSS) δ 8.08 and 7.46 (Ar), 7.30 (2-H, d, $J_{2,6}$ = 1.3 Hz), 6.34 (6-H, dd, $J_{6,2}$ = 1.3 Hz, $J_{6,5}$ = 8.4 Hz), 5.19 (5-H, dd, $J_{5,4}$ = 5.7 Hz, $J_{5,6}$ = 8.4 Hz), 4.64 (CH_2), 4.22 (4-H, d, $J_{4,5}$ = 5.7 Hz). Anal. Calcd for $C_{13}H_{10}N_3NaO_5S$ (M_r 343.29): C, 43.22; H, 2.79; N, 11.63. Found: C, 42.50; H, 3.19; N, 10.99.

4-Amino-5-cyano-2-methyl-1-(4-nitrobenzyl)pyrimidinium Bromide (3a). A mixture of 1 g (7.5 mmol) of 4-amino-5-cyano-2-methylpyrimidine[21] and 2.16 g (10 mmol) of 4-nitrobenzyl bromide was stirred and heated in 30 mL of 2-propanol for 24 h. After isolation, the precipitate was treated with three portions of 3 mL of water and the combined filtrates were concentrated to a volume of about 1 mL. The yield was 0.4 g (15%), mp 228–230 °C dec. By addition of 0.5 g of sodium iodide, an additional 1.2 g of crude material could be recovered: ^{1}H NMR (D_2O, DSS) δ 8.83 (CH), 8.32 and 7.46 (Ar), 5.56 (CH_2), 2.60 (CH_3). Anal. Calcd for $C_{13}H_{12}BrN_5O_2 \cdot H_2O$ (M_r 343.29): C, 42.41; H, 3.83; N, 19.02. Found: C, 42.10; H, 3.87; N, 19.00.

4-Amino-5-cyano-1,2-dimethylpyrimidinium Iodide (3b). 4-Amino-5-cyano-2-methylpyrimidine[21] (1 g, 7.5 mmol) and 5 g (35 mmol) of iodomethane were dissolved in 20 mL of dimethylformamide. After 18 h, the precipitate was isolated and washed repeatedly with ether. The yield was 1.8 g (87%) of colorless crystals: mp 185–187 °C dec; ^{1}H NMR (D_2O, DSS) δ 8.80 (CH), 3.91 (NCH_3), 2.72 (CH_3). Anal. Calcd for $C_7H_9IN_4 \cdot H_2O$ (M_r 276.07): C, 30.45; H, 3.29; N, 20.29. Found: C, 29.83; H, 3.24; N, 19.94.

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Effect of Distortion on the Hydrolytic Reactivity of Amides. 2. N-Pyramidalization: Decomposition of *N*-Benzoylaziridines in Aqueous Media

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The decomposition of para-substituted *N*-benzoylaziridines (H, OCH_3, NO_2, Br) in buffered aqueous media is studied at 25 °C as a function of pH in order to assess the effect of *N*-pyramidalization on the hydrolytic reactivity of the amide bond. Overall, the reaction shows three dominant terms: OH^- and H_2O attack on the neutral form and H_2O attack on the protonated form of the amide. In base, the exclusive reaction is rate-limiting and irreversible attack of OH^- on the C=O unit leading to normal hydrolytic products. This is shown by the first-order dependence on [OH^-] from pH 8 to 14 of the hydrolysis rate and by the fact that ~50% ^{18}O-enriched amide recovered from the hydrolysis medium as a function of time shows no ^{18}O loss. Relative to *N*,*N*-dimethylbenzamide ($k_{OH^-}^{25°C}$ = 6.0 × 10^{-6} M^{-1} s^{-1}), *N*-benzoylaziridine is ~200 000-fold more susceptible to OH^- attack ($k_{OH^-}^{25°C}$ = 1.1 M^{-1} s^{-1}). The k_{OH^-} terms follow a $\sigma\rho$ relationship with ρ = 1.68. In acid, the products are not the expected hydrolytic ones of benzoic acid and aziridine. Rather, exclusive ring opening occurs to give *p*-X-$C_6H_4C(=O)NHCH_2CH_2OX$. In acetate buffers, product analysis by ^{1}H NMR indicates that the ring-opened material consists of alcohol and acetate (X = H and $C(=O)CH_3$).

I. Introduction

An attractive hypothesis for enzyme-mediated amide hydrolysis suggests that a share of the exothermicity of substrate binding is utilized in a productive way to induce stress or strain in the substrate, enzyme, or enzyme–substrate complex, which is relaxed as the transition state for the acyl transfer reaction is approached.[1] In effect, this notion is equivalent to the widely held view that enzymes bind transition states better than they bind substrates,[1g] the net effect being to lower the activation energy for the catalyzed process. As far as amide hydrolysis is concerned, at some point along the catalyzed hydrolytic pathway, the conjugation between the N: and C=O π-bond in the amide must be significantly reduced in order to allow nucleophilic attack. As part of an on-going program to evaluate the influence of geometric distortion of the amide bond on its hydrolytic reactivity, we recently reported[2a] the syntheses and kinetic studies of the hydrolysis of anilides **1a–d**[2b] and **2**.

Both skeletons render the amide portion extremely reactive toward hydrolysis, the second-order rate constants for OH^- attack on **1a** and **2** at 25 °C being 262 and 60 M^{-1}

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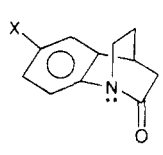
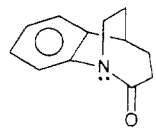
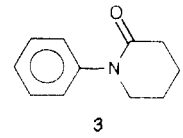




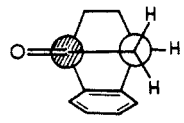


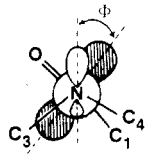
3

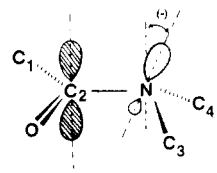
1a, X = H
b, X = CH_3
c, X = Cl
d, X = OCH_3

2

s^{-1}, respectively.[2] By comparison, the value for an unstrained counterpart **3** at 25 °C is 2.0×10^{-5} M^{-1} s^{-1}.[3] As illustrated in the Newman projection of **1** (**4**), two modes of distortion are present: pyramidalization of the N toward



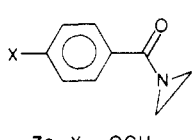


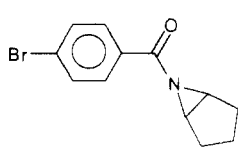


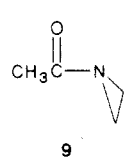
4 (N shaded) 5 6

an sp^3 geometry *and* twisting of the lone pair from maximal overlap with the C–O π-bond. While it is not necessarily true that these two modes can be separated in a real sense,[4] formally this can be done in terms of the twist angle (ϕ) and tilt angle (θ) pictured as in **5** and **6**, respectively. Values for either of these angles in excess of 0° lead to a reduction in the N—C=O overlap, the net effect being to activate the C=O group toward nucleophilic attack.

Molecular models suggest that the ϕ and θ values for **1** are 90° and ~20°, respectively.[5] The X-ray crystallographic structure of **2** indicates ϕ and θ values of ~30° and 20°, respectively.[6] We were therefore surprised to see that in terms of OH^- attack, the much smaller twist angle of **2** than **1** did not lead to the expected large reduction in rate for the former, the difference being only a factor of ~4.[1] The question to be asked is What is the relative importance to the rate of OH^- attack of the twisting and tilting modes of distortion? which cannot be answered in a straightforward fashion with **1** and **2** since both deformations are present. Fortunately, a series of test amides exists in which one of the distortions is dominant, namely the *N*-acylaziridines. X-ray crystallographic structures of (*p*-bromobenzoyl)aziridines **7c**[7] and **8**[8] as well as gas-phase electron diffraction studies of *N*-acetylaziridine **9**[9] indicate that in all cases the N is pyramidalized, with tilt angles of 34°, 27°, and 30°, respectively, and twist angles of 0 ± 10°. Surprisingly, no kinetic data are available for the hydrolyses of such species.







7a, X = OCH_3
b, X = H
c, X = Br
d, X = NO_2

8 9

With the above in mind, we undertook a study of the hydrolysis rates and products of **7a–d**. It will be seen that pyramidalization of the N in **7** leads to ~10^5-fold enhancement of the attack of OH^- on the acyl unit relative to a comparison material, *N*,*N*-dimethylbenzamide.

II. Experimental Section

a. Syntheses. *N*-Benzoylaziridine (7b). A 10-mL benzene solution containing 0.01 mol each of aziridine and triethylamine was added dropwise to a 10-mL solution of benzoyl chloride in benzene kept at 0–5 °C. The mixture was filtered and solvent removed from the filtrate under reduced pressure at 5 °C. Recrystallization of the residue from ether at −20 to −25 °C gave a 30% yield of low-melting solid: mp 5 °C; mass spectrum, *m/z* (intensity) 147 (7.8), 105 (100.0), 77 (75.8), 51 (22.9); ^1H NMR (D_2O) δ 2.45 (s, 4 H), 7.65 (m, 5 H); IR ($CHCl_3$) 1674.9, 1601.0, 1582.3, 1474.6, 1451.0, 1340.0, 1226.6, 1212.2, 1149.7, 1053.6, 1023.6 cm^{-1}. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.15. Found: C, 73.31; H, 6.11; N, 9.52.

The other para-substituted benzoylaziridines (**7a,c,d**) were prepared according to a modification of the procedures of Woods, Borkovec, and Hart.[10] To a mixture of 10 g of ice, 10 g of benzene, 0.4 g of NaOH, and 0.1 mol (0.435 g) of aziridine was added over 20 min 0.1 mol of the appropriate substituted benzoyl chloride in 10 mL of benzene. The mixture was stirred at 0 °C for 30 min, the benzene layer was separated, and the aqueous layer was washed with ether. The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was recrystallized (Me_2SO for **7d**, CH_3CN for **7a,d**[7]).

7d: faint yellow crystals, yield 85%; mp 117–118 °C; ^1H NMR (D_2O) δ 2.6 (s, 4 H), 8.3 (m, 4 H); IR ($CHCl_3$) 1683.8, 1606.6, 1529.7, 1339.7, 1225.9, 1212.2, 1149.7, 1054.6, 1014.4 cm^{-1}; mass spectrum, *m/z* (intensity) 192 (5.12), 151 (7.93), 150 (100.0), 120 (6.76), 104 (31.7), 92 (11.0), 76 (24.1). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.19; N, 14.57. Found: C, 56.08; H, 4.21; N, 14.42.

7a: white crystals, 90%; mp 74–75 °C; ^1H NMR (D_2O) δ 2.5 (s, 4 H), 3.9 (s, 3 H), 7.05 and 8.05 (AA′BB′, 4 H); IR ($CHCl_3$) 1668.5, 1603.9, 1578.3, 1511.1, 1463.0, 1419.7, 1338.8, 1259.0, 1238.8, 1210.2, 1168.1, 1055.2, 1027.9; mass spectrum, *m/z* (intensity) 178 (4.7), 177 (21.8), 136.05 (8.7), 135 (100), 107 (4.9), 92 (7.2), 77 (10.4). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.43; H, 6.26; N, 7.90.

N,*N*-Dimethylbenzamide was prepared according to the procedure of Bunton, Nayak, and O'Connor.[11] Fifty percent ^{18}O-labeled *N*-benzoylaziridine was prepared from the corresponding half-labeled benzoic acid (from hydrolysis of benzoyl chloride in $H_2{}^{18}O$) by first converting the acid to half-labeled benzoyl chloride[12] and then treating with aziridine as above.

b. Kinetics. Reaction rates were determined by observing the rate of decrease of absorbance of amides at the wavelength of maximum change (**7a**, 275 nm; **7b**, 250 nm; **7c**, 260 nm; and **7d**, 270 nm) on a Cary UV–vis spectrophotometer interfaced to a microcomputer as previously described.[13] Aqueous buffer solutions at three to five concentrations between 0.02 and 0.1 M (μ = 0.1 M KCl) were employed (formate, pH 3.4–3.7; acetate, pH 4.0–5.0; MES (morpholinoethanesulfonic acid), pH 6.0–6.5; MOPS (morpholinopropanesulfonic acid), pH 7.0; EPPS (*N*-(2-hydroxyethyl)piperazine-*N*′-3-propanesulfonic acid), pH 8.0–8.5; CHES ((cyclohexylamino)ethanesulfonic acid), pH 9.0–10.0; CAPS ((cyclohexylamino)propanesulfonic acid), pH 10.5–11.5; NaOH, pH 12–13).

Stock solutions of 3×10^{-2} M amide were prepared in CH_3CN. Reactions were initiated by injecting 10 μL of stock into a 1.0-cm quartz cuvette containing 3.0 mL of buffer that had been thermally equilibrated at 25.0 ± 0.2 °C in the spectrophotometer cell holder for 15 min. Pseudo-first-order rate constants for the disappearance of starting material (k_{obsd}) were determined by fitting of the absorbance vs. time curves for the decomposition of the amides to a standard exponential model ($A_t = A_{t_\infty} + (A_{t_0} - A_{t_\infty})e^{-kt}$). In

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all cases, reactions followed excellent first-order kinetics to at least 85% completion. Buffer catalysis was not observed except with EPPS (for **7b** and **7a**) and MOPS (for **7d**). Faster reactions (k_{obsd} > 0.1 s^{-1}) were followed with a Durrum-Gibson Model 115 stopped-flow spectrophotometer interfaced into a microcomputer.[13] Into one drive syringe was placed a 0.1 N HCl (or 0.02 N HCl + 0.08 M KCl) solution while the second syringe was charged with a 0.1 M aqueous KCl solution containing 2×10^{-4} M amide. Both syringes were thermostated at 25 °C for 20 min prior to determining the kinetics. Values reported are the averages of 8–10 determinations.

c. ^{18}O Exchange. A typical experiment involved addition of a stock solution of 48% ^{18}O-enriched amide (3×10^{-2} M in CH_3CN) to 60 mL of buffer (0.1 M acetate, pH 4.5; CAPS, pH 10.5), thermostated at 25 °C. Ionic strength was kept constant at 0.1 M (KCl), and the final amide concentration was 2×10^{-4} M. After $^1/_2\tau_{1/2}$, $1\tau_{1/2}$, and $1^1/_2\tau_{1/2}$ for hydrolysis, 20 mL of the reaction mixture was directly extracted with 2 × 20 mL of $CHCl_3$. The organic layers were immediately drained onto $MgSO_4$, after which the mixture was filtered and stripped of solvent and the residue analyzed directly by low-resolution mass spectrometry.[14] Percent ^{18}O enrichment was determined as % $^{18}O = [(I_{M+2})/(I_M + I_{M+2})] \times 100$ where I_M and I_{M+2} are the absolute intensities of the ^{16}O and ^{18}O parent peaks. Reported values are the averages of four to five mass spectral determinations.

Experimental data for kinetics and ^{18}O exchange are given as Tables 1S and 2S, respectively, supplementary material.

d. Product Analysis. Reaction products were analyzed by ^1H NMR (Bruker WH-200 FTNMR) under the kinetic reaction conditions at pH 12.0, 4.5, and 2.0. Solutions of 1–3 mg of amide (depending upon solubility) in 0.3 mL of D_2O were prepared in NMR tubes and the NMR spectra monitored periodically.

pH 12.0. An appropriate amount of NaOD was added to D_2O to attain pH 12.0. Upon addition of amide, an instantaneous reaction occurred, producing a singlet at δ 1.6, characteristic of free aziridine, and a multiplet at δ 7–8 identical with that of the authentic carboxylic acid in the same medium. In the case of the product **7a**, a singlet at δ 3.9 for the *p*-CH_3O group in *p*-methoxybenzoate was observed.

pH 2.0. To a DCl/D_2O solution was added amide. The resulting spectrum showed two triplets at δ 3.70 (2 H) and δ 3.55 (2 H), characteristic of the pattern for $RC_6H_4C(=O)NHCH_2CH_2OH$. Control experiments establish that no peaks characteristic of free amino ethanol under these conditions are present.

pH 4.5. The medium was buffered at pH 4.5 by the addition of NaOD to CD_3COOD (0.1 M solution). The NMR spectrum of **7a** was monitored over a time equivalent to $3\tau_{1/2}$. At t = 0, only peaks at δ 2.45 and 7.7 were present, characteristic of starting material. As time progressed, these gave way to four triplets at δ 3.55 (δ 3.60) and 3.70 (4.2), consistent with products containing a $RC_6H_4C(=O)NHCH_2CH_2X$ moiety, with X being OH and $OC(=O)CH_3$ (values in parentheses). Experiments conducted with CD_3COOD, pH 4.5, 5.0 M, showed the product to be exclusively acetate ring opened material. In neither acid experiment is aziridine observed. Hence, product analyses show that in base the reaction proceeds by normal hydrolysis but the acid-catalyzed reaction involves exclusively ring opening.

Results and Discussion

Shown in Figure 1 is the log k_{obsd} vs. pH profile for the decomposition of **7b**. Also plotted on the figure at the lower right and left corners for comparison purposes are the acid-[15] and base-catalyzed-hydrolysis pH-dependent rate constants for the hydrolysis of *N*,*N*-dimethylbenzamide. The profiles for the other para-substituted *N*-benzoylaziridines essentially follow the same pattern as for **7b** and for that reason are not included in the figure.

The appearance of the pH-dependent profile is indicative of the three processes for which k_{obsd} adheres to the expression given in eq 1.[16] Inclusion of the small H_2O term (or its kinetic equivalent of OH^- attack on 7-H^+) appears

$$k_{obsd} = k_H[H_3O^+] + k_O + k_{OH}[OH^-] = (k_H[H_3O^+]^2 + k_O[H_3O^+] + k_{OH}K_w)/[H_3O^+] \quad (1)$$

justified by the better fits of the data by nonlinear least-squares treatment to eq 1 than to the corresponding equation without a k_O term. Also, in the neutrality region, slight buffer catalysis is evident for **7a**,**b**,**d** with MOPS or EPPS buffers, which likely stems from general catalysis of the attack of H_2O.

The lines drawn through the data of the figure are those calculated on the basis of the nonlinear least-squares fitting of the data to eq 1, with the derived parameters being given in Table I. (Given in Table 1S, supplementary material, are the primary rate constants.)

In the base region, the reaction proceeds by irreversible rate-limiting attack of OH^- on the amide C=O leading to normal hydrolysis products. This is supported by ^{18}O-labeling experiments in which ~48% labeled **7b** is reisolated at various times from the hydrolysis medium. For example, **7b** reisolated from hydrolysis in CAPS buffer, pH 10.1, μ = 0.1 M (KCl), T = 25 °C at 0, $^1/_2$, 1, and $1^1/_2$ half-times of hydrolysis ($\tau_{1/2}$ = 29 min) contained 48.6 ± 0.3%, 48.7 ± 0.3%, 48.5 ± 0.4%, and 48.6 ± 0.3% ^{18}O enrichment. (Primary data are given in Table 2S, supplementary material.) In addition, the log k_{OH} values for **7a–d** can be correlated with the σ-values of the para substituents giving a ρ of 1.68 (r = 0.993, 4 data) suggestive of a rate-limiting step involving nucleophilic addition to the C=O unit. ^1H NMR data for the hydrolysis products of NaOD/D_2O-promoted reactions indicate the exclusive presence of aziridine and the appropriate para-substituted sodium benzoate: no ring-opened material is present.

In the acid region, the reaction does not proceed to give the normal hydrolytic products of benzoic acid and aziridine but rather an acid-catalyzed ring opening. ^1H NMR analysis of the products formed from **7b** in pH 2.0 DCl/D_2O indicates that the aziridine ring is not present, the NMR spectrum being identical with that of authentic **10** (X = H). When the course of the reaction is followed at pD 4.5 in CD_3CO_2D buffer, two sets of chemical-shift-inequivalent pairs of triplets are observed to be formed at the expense of the signals of **7b**. These arise from **10** and **11** (X = H), the CH_2OAc signals of the latter being ~ 15–20% intensity and downfield of those of **10** by 0.5 unit (δ 4.20), as expected for the acetylated methylene. The same general phenomenon of formation of **10** and **11** in

Table I. Second-Order Rate Constants for Decomposition of Amides 7a–d and *N*,*N*-Dimethylbenzamide Determined at 25 °C

amide	k_H,[a,b] M^{-1} s^{-1}	10^6k_O, s^{-1}	k_{OH},[b] M^{-1} s^{-1}
7a	50.3	1.04	0.27
7b	42.6	0.56	1.1
7c	26.5	2.03	2.8
7d	1.0	7.06	16.9
N,*N*-dimethylbenzamide	1.8×10^{-7}[c]		6.0×10^{-6}[d]

[a] $k_H = k_{H_2O}/K_a^7$ (ref 16). [b] Error limits ±5% of quoted number. [c] Reference 15. [d] Determined in 2 N NaOH solution assuming first-order dependence on $[OH^-]$.

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(16) A more complete mechanism for decomposition of starting material is that involving pre-equilibrium protonation of 7 followed by H_2O attack on 7-H^+. In this instance, eq 1a holds. However, since the profile gives no indication of leveling off at high $[H_3O^+]$, then $K_a^7 \gg [H_3O^+]$ so that the kinetic expression in eq 1a reduces to that in eq 1 where $k_H = k_{H_2O}/K_a^7$.

$$k_{obsd} = k_{H_2O}[H_3O^+]/(K_a^7 + [H_3O^+]) + k_O + k_{OH}[OH^-] \quad (1a)$$

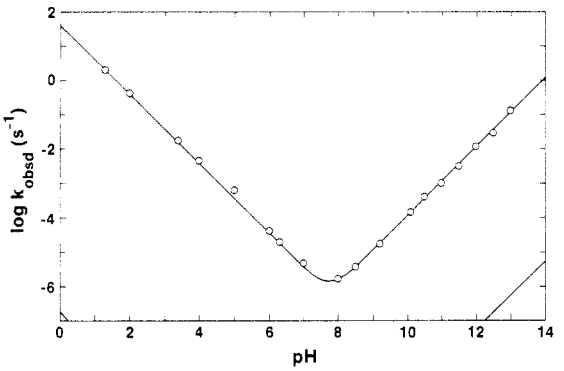


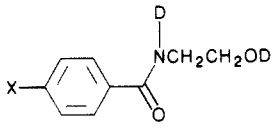
Figure 1. Plot of log k_{obsd} vs. pH for the decomposition of *N*-benzoylaziridine in aqueous media (T = 25.0 °C, μ = 0.1 M (KCl)). Also shown in the lower left and right corners, respectively, are the acid and base dependencies for hydrolysis of *N,N*-dimethylbenzamide under comparable conditions.

Table II. Observed Pseudo-First-Order Rate Constants for the Decomposition of 7b in Acetate Buffer at pH 4.75,[a] T = 25 °C, μ = 0.2 M (KCl)

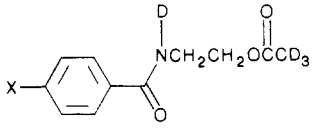
$[acetate]_{total}$, M	$10^3 k_{obsd}$, s^{-1}	$[acetate]_{total}$, M	$10^3 k_{obsd}$, s^{-1}
0.02	1.01 ± 0.01	0.3	1.10 ± 0.01
0.1	1.05 ± 0.02	0.4	1.15 ± 0.02
0.2	1.07 ± 0.01		

[a] pK_a value of HOAc.

CD_3CO_2D buffers is also noted for the ring opening of **7a** and **7d**.



10



11

Finally, the competetive formation of OH and OAc products requires that the kinetically observed rate constants be linearly dependent upon [acetate]. Indeed, as is shown in Table II, there is a small but significant increase in k_{obsd} as [acetate] increases; the second-order rate constant for acetate attack is 3.9×10^{-4} M^{-1} s^{-1}. The rate constant data suggests that at [acetate] = 0.4 M, roughly 15% of the product should be **11**, which corresponds with the NMR-determined ratios of **11**/**10** measured above.

Although the acid-catalyzed process is quite rapid, the values of k_H given in Table I do not correlate in any straightforward way with any σ-values for the para substituents. This is explained by opposing effects of the substituent on the pK_a of 7-H^+ and the rate constant for subsequent H_2O attack. There is also no evidence for reversible attack of H_2O on the C=O unit of 7-H^+ in acid since this would be anticipated to lead to loss of ^{18}O from enriched starting material during the course of reaction. For example, when 48% ^{18}O-enriched **7b** is recovered from 0.1 M acetate (pH 4.5, T = 25.0 °C, μ = 0.1 M (KCl)) after $^1/_2$, 1, and $1^1/_2$ half-times of reaction ($\tau_{1/2}$ = 7.7 min), the amount of ^{18}O is invariant at 48.2 ± 0.3%, 48.2 ± 0.3%, and 48.1 ± 0.3%, respectively. The reason for the sharp change in reactivity of **7** from hydrolysis to ring opening in passing from the base to acidic regions is not immediately clear, although it is well-known that aziridine ring opening is catalyzed by the presence of Lewis and Brønsted acids.[17] However, acyl-activated aziridines generally undergo ring opening with nucleophiles even in the absence of (Lewis) acid catalysis.[18] Nevertheless, the present study indicates that nucleophilic attack of OH^- does not promote ring opening but a "normal" addition to the C=O unit.

Finally, we wish to point out the marked acceleration toward OH^- attack that is induced by N-pyramidalization, which was the original purpose of the investigation. Comparison of the k_{OH^-} data in Table I indicates **7b** undergoes attack (2.2×10^5)-fold more rapidly than does *N,N*-dimethylbenzamide. The reason for this is related partly to the greater accessibility of the attacking nucleophile to the C=O unit of **7b** since the aziridine carbons are tied back relative to those in dimethylbenzamide.[19] More importantly, the N-pyramidalization in **7** is expected to lead to a marked reduction in the importance of N^+=C—O^- resonance forms since an sp^2-hybridized N in a three-membered ring is unfavorable.[20] This is also reflected in the infrared stretching frequencies of 1674.9 cm^{-1} and 1624.9 cm^{-1} for **7b** and *N,N*-dimethylbenzamide, respectively. Indeed, that such pyramidalization of the adjacent N leads to significant reduction in p–p overlap is best appreciated when one considers that rehybridizing one carbon unit in ethylene from $sp^2 \rightarrow sp^3$, which corresponds to a tilt angle of 19.5°, leads to a reduction in the overlap with the adjacent p orbital of 50%.[21] [**Note Added in Proof**: Apparently the same situation obtains for **7b** since the NMR-determined NC=O rotational barrier (normally 16–22 kcal/mol[22]) is markedly reduced to <6 kcal/mol.[20a,c]] Whether a twisting or tilting deformation is more important in terms of increasing the susceptibility of an amide toward nucleophilic addition is somewhat difficult to judge in general. Nevertheless, a simplistic analysis on the basis of overlap[21] suggests that a 20° tilt angle exerts a more profound perturbation than a 20° twist angle since overlap for the latter mode adheres to a cos ϕ relationship.

The above study clearly indicates that tilting distortions can cause a major activation toward nucleophilic addition to an amide. Should favorable contacts between an enzyme and its bound substrate stress the scissile bond in an analogous way during the catalyzed hydrolysis of a peptide, then it is apparent that considerable enhancement of the rate is to be realized.

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Registry No. **7a**, 15269-50-8; **7b**, 7646-66-4; **7c**, 18292-63-2; **7d**, 19614-29-0; PhCOCl, 98-88-4; MeO-*p*-C_6H_4COCl, 100-07-2; Br-*p*-C_6H_4COCl, 586-75-4; O_2N-*p*-C_6H_4COCl, 122-04-3; aziridine, 151-56-4.

Supplementary Material Available: Pseudo-first-order rate constants for decomposition of **7a–d** under various conditions (Table 1S) and percent ^{18}O incorporated in recovered **7b** reisolated from aqueous buffered media (Table 2S) (8 pages). Ordering information is given on any current masthead page.

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(21) Streitweiser, A. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961; pp 11–20. In this treatment, the overlap integral (S) between a pure p orbital and an adjacent aligned sp^3 hybrid orbital is given as $S = \int p^*y \cdot (^1/_2 (s + px + py + pz))\, d\tau = {}^1/_2 \int p^*y \cdot py\, d\tau$. Similarly, the overlap between two py orbitals twisted by a dihedral angle (ϕ) is given as $S = \int p^*y \cdot py\, d\tau \cdot \cos\phi$.

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