vacuum, yielding the oxonium salts which are stable at room temperature.

Tetramethylene[(trimethylsilyl)methyl]oxonium Tetrafluoroborate. A mixture of silver tetrafluoroborate, (trimethylsilyl)methyl bromide, and tetrahydrofuran (1:1:1 mole ratio) in dichloromethane was stirred for 3 days under exclusion of light and atmospheric moisture. The reaction mixture was worked up as described above.

Acidic (Trimethylsilyl)oxonium Ions. The ions **10**–**13** were prepared by the dropwise addition of the corresponding alcohol, ether, or siloxane in SO_2 into a $FSO_3H–SbF_5$ (1:1) solution in SO_2 at −78 °C.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No. **1**, 98704-62-2; **2**, 98704-64-4; **3**, 98704-66-6; **4**, 77871-44-4; **5**, 98704-67-7; **6**, 98719-89-2; **7**, 89909-23-9; **8**, 98704-68-8; **9**, 89909-27-3; **10**, 98704-69-9; **11**, 98704-70-2; **12**, 98704-71-3; **13**, 98704-72-4; $(CH_3)_3SiO^+(CH_3)_2$, 80754-55-8; $(CH_3)_3SiCH_2Cl$, 2344-80-1; $(CH_3)_3SiCH_2Br$, 18243-41-9; $(CH_3)_3SiCH_2I$, 4206-67-1; $(CH_3)_3SiCH_2OH$, 3219-63-4; $(CH_3)_3SiCH_2OCH_3$, 14704-14-4; $(CH_3)_3SiCH_2OCH_2Si(CH_3)_3$, 51264-54-1; CH_3I, 74-88-4; CH_3CH_2I, 75-03-6; THF, 109-99-9; $(CH_3)_3SiOCH_3$, 1825-61-2; $(CH_3)_3SiCH_2OSi(CH_3)_3$, 18297-68-2; $(CH_3)_3SiOSi(CH_3)_3$, 107-46-0; $(CH_3CH_2)_3SiOH$, 597-52-4; $CH_3CH_2O^+H_2$, 18639-79-7; $CH_3CH_2O^+HCH_3$, 52067-06-8; $(CH_3CH_2)_2O^+H$, 17009-83-5; $(CH_3)_2O^+CH_2CH_3$, 44209-06-5; $(CH_3CH_2)_2O^+CH_3$, 44387-70-4; $(CH_3)_2O^+H$, 17009-82-4; $(CH_3)_3O^+$, 43625-65-6; CH_3CH_2OH, 64-17-5; $CH_3CH_2OCH_3$, 540-67-0; $CH_3CH_2OCH_2CH_3$, 60-29-7; $(CH_3)_2O$, 115-10-6.

2-*endo*-[(Dimethylamino)methyl]-3-*endo*-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene. A Model for Serine Esterases in the Aqueous Cleavage of *p*-Nitrophenyl Acetate

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The nucleophilic reactivity of the title amino alcohol (**1**) toward the carbonyl carbon of *p*-nitrophenyl acetate (PNPA) reveals the attack by both the free dimethylamino group and the internally hydrogen-bonded hydroxy group of **1**. The amino ester formed in the reaction of **1** with PNPA hydrolyzes ~53 times faster than the ethyl acetate under essentially similar conditions. This enhanced reactivity is attributed to the probable intramolecular general acid-catalyzed expulsion of the leaving alkoxy group from the tetrahedral intermediate formed by the addition of hydroxide ion to the carbonyl carbon of amino ester. The reaction of **1** with PNPA giving the acetate of **1** as an intermediate and its subsequent enhanced hydrolysis to lose the acyl group again is taken as a model for the action of serine esterases.

There is strong evidence that the action of serine enzymes involves the attack on the carbonyl group of the substrate by the hydroxylic oxygen atom of a serine residue which has had its nucleophilicity increased by hydrogen bonding too and then proton transfer to an imidazole nitrogen atom from a histidine residue.[1-5] Jencks and Carriuolo[6] found that $(HOCH_2)_3CNH_2$ (TRIS) cleaves *p*-nitrophenyl acetate about $^1/_{15}$ as rapidly as *tert*-butylamine does although it is only about $^1/_{250}$ as basic. This was attributed to the nucleophilic attack largely by hydroxy groups on the basis of the observation that an intermediate, most likely an ester, was formed in the reaction. Bruice and York[7] studied the reaction of TRIS with aryl acetates, from which they got good Hammett equation correlations, with a ρ of 0.58 for the rate constant k_n for neutral TRIS and a ρ of 0.55 for the hydroxide ion catalyzed reaction. Although these values are much smaller than those obtained for reactions with ammonia (1.8) or imidazole (1.7–1.9), these authors preferred the amino group as the position of greatest nucleophilicity toward acyl carbon. Hersey et al.[8] have recently presented spectral evidence for ester formation in the reaction of TRIS with activated carbonyl compound 4-*trans*-benzylidene-2-phenyloxazolin-5-one.

Page and Jencks[9] found that ethanolamine and 3-quinuclidinol reacted with acetylimidazole some five times as rapidly as amines of comparable basicity that lacked hydroxy groups. They explained these observations by proposing a mechanism that involved the nucleophilic attack by anionic oxygen of zwitterion form of the amino alcohol. Werber and Shalitin[10] studied the reactions of tertiary amino alcohols with active esters, and they appeared to be probably the first to estimate the extent of reaction via the zwitterion forms of their amino alcohols. In almost all the studies where the amino alcohols brought about the efficient cleavage of esters, it could not be determined whether this cleavage had occurred by the attack of only amino or hydroxy group or of both the groups. The present study was initiated with an aim to explore the possibility of the existence of the internally hydrogen-bonded form of the title alcohol by reacting it with *p*-nitrophenyl acetate. The detailed kinetic studies and the analysis of the observed data are described in this manuscript.

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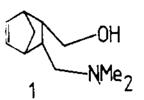
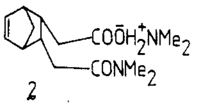
Experimental Section

Materials. The 2-*endo*-[(*N*,*N*-dimethylcarbamoyl)methyl]-3-*endo*-(carboxymethyl)bicyclo[2.2.1]hept-5-ene–dimethylamine salt (**2**) and its lithium aluminum hydride reduction product 2-*endo*-[(dimethylamino)methyl]-3-*endo*-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**1**) were prepared by procedures that have been published for these compounds.[11] The melting points and spectral data (NMR) for recrystallized compounds were found to be same as those obtained by Nelson et al.[11] The GLC of white recrystallized compound **1** dissolved in benzene revealed only one peak. *p*-Nitrophenyl acetate (PNPA) was commercial product and was recrystallized from hexane before use.



1



2

All other reagents used were of reagent grade. Glass-distilled water was used throughout the kinetic studies. Amine buffers of desired pH were freshly prepared just before the start of the kinetic runs by addition of appropriate amounts of hydrochloric acid to the concentrated solutions of free amine.

The thermodynamic pK_a of the conjugate acid of **1** (**1**H$^+$) was determined potentiometrically at 25 °C in the presence of potassium chloride (with its initial concentration of 1.0 M), and the value obtained is 9.88. The value of pK_a of 9.55 was obtained in the absence of potassium chloride salt. The pH value was taken as $-\log a_{H^+}$, and the activity coefficient, ν, was calculated as described elsewhere.[12]

[(2-*endo*-3-*endo*-(Hydroxymethyl)bicyclo[2.2.1]hept-5-enyl)methyl]trimethylammonium Bromide (3). To 1.6 g (8.8 mmol) of **1** in 50 mL of anhydrous acetone was added ~3–4 mL (~52–70 mmol) of methyl bromide with stirring at room temperature using a dry ice cooled condenser. The white precipitate that had separated after ~15 h was collected on a filter and washed several times with anhydrous acetone to give 2.5 g (98%) of product, mp 210.5–211 °C.

Kinetic Measurements. The aqueous cleavage of PNPA in the presence of buffer solution of **1** was followed by monitoring the increase in absorbance at 400 nm of *p*-nitrophenolate ion with the progress of the reaction. The ionic strength of each reaction mixture was kept constant at 1.0 M by using a concentrated solution of KCl. The initial concentration of PNPA was kept constant at 2.0×10^{-5} M in all kinetic runs. The temperature of the reaction mixture was maintained at 25 °C in the sample compartment of a Cary-16 UV–vis spectrophotometer. The pH values of the reaction mixtures before the start and at the end of the kinetic runs were found to be same. All the kinetic runs were carried out under pseudo-first-order kinetic conditions. The observed pseudo-first-order rate constants, k_{obsd}, were determined from eq 1 by the use of the nonlinear least-squares technique.

$$A_{obsd} = X_0 E_{app}(1 - \exp(-k_{obsd}t)) + A_0 \qquad (1)$$

In eq 1 all the symbols have their usual meanings as described elsewhere.[13] Almost all the kinetic runs were carried out for more than four half-lives of the reaction. The fitting of the observed data to eq 1 was reasonably good in all the kinetic runs. Duplicate kinetic runs were carried out at every total buffer concentration, and the average values of k_{obsd} were found to have mean deviations of less than 1% at most of the total buffer concentrations.

While the effect of the total concentration of **3** at different pH on the cleavage of PNPA was studied, the pH of the reaction medium was maintained by the use of 0.1 or 0.06 M *N*,*N*-dimethylbenzylamine buffer solutions. The ionic strength was kept constant at 1.0 M.

Detection and Kinetics of the Formation and Decay of the Intermediate 2-*endo*-[(Dimethylamino)methyl]-3-*endo*-(acetoxymethyl)bicyclo[2.2.1]hept-5-ene (4) in the Reaction Mixture of PNPA and 1. To a solution of 182.25 mL of 0.001 M PNPA was added 20.25 mL of water. This solution was kept at a constant temperature of 25 °C for a few minutes, and then the reaction was initiated by adding 22.5 mL of 0.1 M buffer solution of **1** containing ~25% free base. Various samples of 20 mL were withdrawn from the reaction mixture at different time intervals, and each sample was quickly extracted for four to seven times with cyclohexane, ~20–25 mL being taken of it each time. The volume of the collected organic layer for each sample was reduced to ~<1 mL under vacuum by using the microdistilling equipments. The organic mixture of volume of <1 mL was then diluted to 5 mL with cyclohexane solvent. The initial concentration of PNPA in each sample turned out to be 3.24×10^{-3} M. The absorbance values at two wavelengths 5.65 and 5.75 μm of these samples were obtained from their recorded IR spectra. The 3-mm path lengths IR cells were used in the entire studies. The observed results are shown graphically in Figure 1. The wavelengths of 5.65 and 5.75 μm are the characteristic wavelengths for maximum absorption of carbonyl group of PNPA and **4**, respectively.[14] The pH of the reaction mixture was found to drop from 8.99 (at the beginning of the reaction) to 8.60 (at the completion of the reaction) possibly because of the low concentration of buffer and comparatively high concentrations of products formed during the course of the reaction.

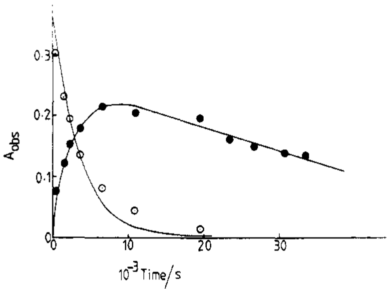
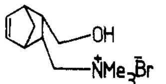
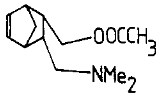


Figure 1. Plots showing the dependence of A_{obsd} vs. time for the reaction of PNPA with (1). The progress of the reaction was monitored at 5.65 (⊙) and 5.75 μm (●). The solid lines are drawn through the least-squares-calculated points as described in the text.



3



4

Results and Discussion

During the course of the reaction the absorbance at 5.75 μm appeared to increase in the initial phase of the reaction and then attained a maximal value before it started decreasing in the final phase of the reaction (Figure 1). This indicates the formation of a stable intermediate on the reaction path. This intermediate is apparently formed by the attack of both the internally hydrogen-bonded and completely deprotonated hydroxy group of **1** and **1**H$^+$, respectively, at the carbonyl carbon of PNPA. The complete reaction could be expected to follow the reaction scheme as shown in eq 2, where A, C, D, and E represent PNPA, *p*-nitrophenolate ion, **4**, and acetic acid, respectively. In eq 2, k_0 represents the pseudo-first-order rate constant for the reaction in which aqueous cleavage of A

$$A \xrightarrow{k_0} C + E$$
$$A \xrightarrow{k_n^{OH}[1]} C + D \qquad (2)$$
$$D \xrightarrow{k_2} E + 1$$

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(14) In the studies on the aqueous cleavage of PNPA under the buffer solution of *o*-[(dimethylamino)methyl]benzyl alcohol, we observed that the maximum absorption peak of carbonyl group had appeared at 5.65 μm for PNPA and at 5.75 μm for *o*-[(dimethylamino)methyl]benzyl acetate.[15]

is catalyzed by water, hydroxide ion, and the tertiary amino group of 1. Since the total concentration of buffer is more than 12 times larger than that of PNPA, it may be assumed that the reaction has occurred under pseudo-first-order kinetic condition. Equation 3 may be easily derived from eq 2. In eq 3, $k_1 = k_n^{OH}[B]_T$, where $[B]_T$ is

$$A_{obsd} = E^A[A]_T \exp(-k_{obsd}t) + \frac{E^D[A]_Tk_1}{k_{obsd}-k_2}(\exp(-k_2t) - \exp(-k_{obsd}t)) \quad (3)$$

the total buffer concentration prepared from 1, k_n^{OH} is the bimolecular rate constant for the reaction of A with 1 when reacting site in 1 is the hydroxy group rather than the tertiary amino group, $k_{obsd} = k_0 + k_1$, where k_{obsd} is the observed pseudo-first-order rate constant obtained by measuring the rate of production of C, $[A]_T$ is the total concentration of A, A_{obsd} is the observed absorbance at any time t, and E^A and E^D are the molar extinction coefficients of A and D, respectively.

The value of k_{obsd} of $(3.02 \pm 0.04) \times 10^{-4}$ s^{-1} was obtained spectrophotometrically by monitoring the increase in absorbance at 400 nm due to the production of C. The values of E^A at both wavelengths 5.65 and 5.75 μm were found to be 118.1 M^{-1} (3 mm)$^{-1}$ and 10.0 M^{-1} (3 mm)$^{-1}$, respectively. The values of E^D at 5.65 and 5.75 μm were considered as 1.0 M^{-1} (3 mm)$^{-1}$ and 164.0 M^{-1} (3 mm)$^{-1}$, respectively. These values were obtained for *o*-[(dimethylamino)methyl]benzyl acetate and thus the assumption made in the present analysis is that the values of E^D for both *o*-[(dimethylamino)methyl]benzyl acetate and 4 at the respective wavelengths of 5.65 and 5.75 μm are same. The values of k_1 and k_2 were calculated from eq 3 with nonlinear least-squares technique. The observed data at both wavelengths (5.65 and 5.75 μm) were used in the least-squares regression analysis with known values of $[A]_T$ (3.24×10^{-3} M), k_{obsd} (3.02×10^{-4} s^{-1}), and E^A and E^D (at the appropriate wavelength). The calculated values of k_1 and k_2 were found to be $(1.54 \pm 0.09) \times 10^{-4}$ and $(2.45 \pm 0.36) \times 10^{-5}$ s^{-1}, respectively. The fitting of the observed data to eq 3 is evident from the plots shown in Figure 1 where the solid lines are drawn through the least-squares-calculated points. Although the observed values of k_1 and k_2 are not very reliable for (a) the fact that they are derived from a kinetic run where pH was dropped from 8.99 to 8.60 as the reaction reached to the completion and (b) the assumption that E^D for both *o*-[(dimethylamino)methyl]benzyl acetate and 4 at respective wavelengths of 5.65 and 5.75 μm are same, the ratio of k_1/k_2 of ~6 is conceivable for the reaction scheme shown in eq 2.

A series of kinetic runs were carried out at different total amine 1 buffer concentrations ($[B]_T$) and at three different pH's ranging from 9.75 to 9.11, by monitoring the increase in A_{obsd} at 400 nm due to the appearance of C as a function of time. The observed data are shown graphically in Figure 2. The rate of the aqueous cleavage of A in the presence of buffer components of 1 may be shown as eq 4, where

$$\text{rate} = -\mathrm{d}[A]_T/\mathrm{d}t = (k_w + k_{OH}[O^-H] + k_n[B])[A]_T \quad (4)$$

$[A]_T$ represents the total concentration of A and $k_n = k_n^{NMe_2} + k_n^{OH}$, where $k_n^{NMe_2}$ represents the bimolecular rate constant for the cleavage of A catalyzed by the tertiary amino group of 1. It can be shown that the observed rate law (rate = $k_{obsd}[A]_T$) and eq 4 may lead to eq 5, where ν represents the activity coefficient of protonated amine ($1H^+$). The value of ν of 0.708 was obtained at 1.0 M ionic

$$k_{obsd} = k_w + k_{OH}[O^-H] + \frac{k_n\nu K_a}{a_H + \nu K_a}[B]_T \quad (5)$$

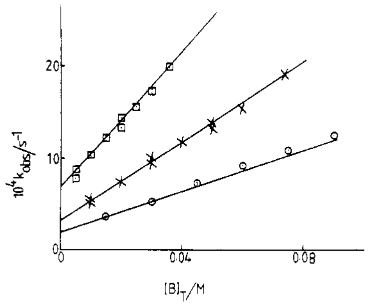

Figure 2. Plots showing the dependence of k_{obsd} vs. $[B]_T$ for the aqueous cleavage of PNPA in the buffer solutions of (1) at pH 9.12 ± 0.01 (⊙), pH 9.43 ± 0.01 (×), and pH 9.74 ± 0.02 (⊡). The solid lines are drawn through the least-squares-calculated points as described in the text.

strength and 25 °C is comparable with that of 0.67 obtained by Kirsch et al.[16] under similar conditions. The observed data (40 k_{obsd} obtained at various $[B]_T$ and pH) were used to calculate k_n from eq 5 with known values of k_w[16] and k_{OH}[16] and the weighted least-squares fit resulted the value of k_n as $(10.1 \pm 0.1) \times 10^{-2}$ M^{-1} s^{-1}. The fitting of observed data to eq 5 is evident from the plots shown in the Figure 2 where solid lines are drawn through the least-squares-calculated points.

In order to find out the effect of the presence of zwitterions of 3 on the cleavage of PNPA, a series of kinetic runs were carried out at two different pH (9.17 and 9.79) and at various total concentrations of 3 ($[Z]_T$) ranging from 0.020 to 0.156 M. The observed data obtained at 25 °C were treated with eq 6 and the value of k_z of 27.4 ± 3.5 M^{-2}

$$k_{obsd} = k_w + k_{OH}[O^-H] + k_z[Z]_T[O^-H] \quad (6)$$

s^{-1} was obtained by the use of the weighted least-squares analysis. The literature values[15] of k_w and k_{OH} were used in the calculation of k_z from eq 6. The fitting of the observed data to eq 6 is evident from the standard deviation of the value of k_z and from the least-squares-calculated rate constants k_{calcd}. A table of observed data and k_{calcd} is available as supplementary material.

It is apparent from the infrared spectrophotometrically monitored kinetics of the cleavage of PNPA in a buffer solution of 1 that a significant amount of 4 is formed during the course of the reaction. The formation of 4 could be ascribed to the nucleophilic attack at carbonyl carbon by both the internally hydrogen-bonded hydroxyl group of 4 (5 and 5′) and the anionic oxygen of the zwitterion form (6) as shown in Scheme I. Although it is difficult to estimate quantitatively the contribution due to catalysis by tertiary amino group of 1 ($k_n^{NMe_2}$) and by the hydroxyl group of 5, 5′, and 6 (k_n^{OH}) to the observed value of k_n, a qualitative estimate of these contributions could be carried out as follows. The observed values of k_n for $CH_3(CH_2)_3NMe_2$ (k_n = 0.066 M^{-1} s^{-1}, pK_a 10.37),[15] $MeOCH_2CMe_2CH_2NMe_2$ (k_n = 0.0083 M^{-1} s^{-1}, pK_a 9.69),[15] $MeOCH_2CH_2NMe_2$ (k_n = 0.0072 M^{-1} s^{-1}, pK_a 9.31),[15] and for some other relatively less hindered tertiary amines lead to a Brønsted plot of slope (β_{nuc}) of 0.8.[15] If we assume that $CH_3(CH_2)_3NMe_2$, $MeOCH_2CH_2NMe_2$, and 1 fall on a Brønsted plot of β_{nuc} of 0.8 then the estimated value of $k_n^{NMe_2}$ for 1 will be 0.02 M^{-1} s^{-1}. Thus, the observed value of k_n of 0.10 M^{-1} s^{-1} and the estimated value of $k_n^{NMe_2}$ of 0.02 M^{-1} s^{-1} resulted the value of k_n^{OH} of 0.08 M^{-1} s^{-1}. The value of k_n^{OH} of 0.08 M^{-1} s^{-1} is not significantly different from the corresponding value of 0.050 M^{-1} s^{-1} obtained for

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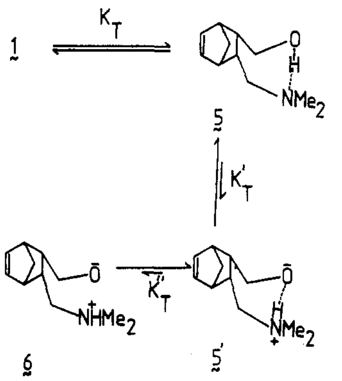
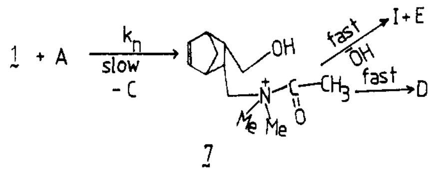
(15) Unpublished observations.

(16) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

Scheme I



Scheme II



the reaction of A with *o*-[(dimethylamino)methyl]benzyl alcohol.[17]

One might argue that the initial attack at the carbonyl carbon of A could be exclusively due to tertiary amino group of **1** and the ester D formation might result from instantaneous cleavage of intermediate product **7** by the intramolecular nucleophilic attack of its hydroxy group at carbonyl carbon as shown in Scheme II. Although such a possibility is conceivable in principle, it may be ruled out for the following reasons. (i) On the basis of the Brønsted plot of slope 0.8, the estimated value of k_n for **1** will be 0.02 M^{-1} s^{-1}, which is nearly five times smaller than the observed one (0.10 M^{-1} s^{-1}). The observed value of k_n of 0.10 M^{-1} s^{-1} thus reveals that the tertiary amino group is not the only reacting site of **1** for the nucleophilic attack at carbonyl carbon of A. (ii) The observed and estimated values of pK_a of $1H^+$ have been found to be 9.88 and 10.27 (see Appendix), respectively. The decrease in observed pK_a by 0.4 pK units compared to the estimated one could be attributed to the consequence of relatively increased stability of conjugate base of $1H^+$ due to internal hydrogen bonding as shown in **5**. This kind of internal hydrogen bonding will apparently make the partially deprotonated hydroxy group a more effective nucleophilic compared to the partially protonated tertiary amino group of **1**.

It has been well demonstrated in a few nucleophilic addition elimination reactions involving hydroxy amine nucleophiles that the zwitterion forms of these nucleophiles have also revealed the significant nucleophilic reactivity toward the carbonyl carbon of various esters. Thus, it is conceivable to assume that $k_n^{OH} = k_{n_1}^{OH} + k_{n_2}^{OH}$ where $k_{n_1}^{OH}$ and $k_{n_2}^{OH}$ represent the apparent bimolecular nucleophilic rate constants for the reactions of A with **5**, **5′**, and zwitterion form of **1** (**6**), respectively. Although it is certainly difficult to resolve quantitatively $k_{n_1}^{OH}$ and $k_{n_2}^{OH}$ from k_n^{OH} because kinetically $k_{n_1}^{OH}$ is indistinguishable from $k_{n_2}^{OH}$, a qualitative approach as described below has been considered to determine $k_{n_1}^{OH}$ and $k_{n_2}^{OH}$ from k_n^{OH}.[10,17]

It is apparent that

$$k_n^{OH}[1] = k_{n_1}[5] + k_{n_2}[6] \qquad (7)$$

where k_{n_1} and k_{n_2} are specific bimolecular rate constants for the nucleophilic cleavage of A catalyzed by hydroxyl group of **5**, **5′** and **6**, respectively. From Scheme I and by introducing the ionization constant, K_a' of hydroxylic hydrogen atom of the conjugate acid of **1** ($1H^+$), eq 7 may be reduced to eq 8.

$$k_n^{OH}[1] = k_{n_1}K_T[1] + \frac{k_{n_2}K_a'}{K_a}[1] \qquad (8)$$

or

$$k_n^{OH} = k_{n_1}K_T + \frac{k_{n_2}K_a'}{K_a} \qquad (9)$$

Also if

$$k_n^{OH} = k_{n_1}^{OH} + k_{n_2}^{OH} \qquad (10)$$

then from the characteristic definitions of k_{n_1}, k_{n_2}, $k_{n_1}^{OH}$, and $k_{n_2}^{OH}$ one can get eq 11. Now if we assume that the

$$k_{n_2}^{OH} = k_{n_2}K_a'/K_a \qquad (11)$$

ionization constants of the hydroxylic hydrogen atoms of $1H^+$ and the quaternary ammonium compound of **1** (**3**) are of equal magnitude and that the rate constants for attack of the two zwitterions on the carbonyl substrate are the same, then

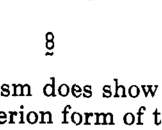
$$k_{n_2}[6] = \frac{k_{n_2}K_a'}{K_w}[Z]_T[O^-H] = k_z[Z]_T[O^-H] \qquad (12)$$

because under the experimental conditions, $a_H \gg K_a'$. In eq 12, $[Z]_T$ represents the total concentration of **3**, and $k_z = k_{n_2}K_a'/K_w$. From eq 11 and 12 it could be shown that

$$k_{n_2}^{OH} = k_zK_w/K_a \qquad (13)$$

The value of k_z of 27.4 M^{-2} s^{-1} and the known values of K_w (10^{-14} M^{-2}) and K_a (1.33×10^{-10} M) were used to calculate $k_{n_2}^{OH}$ from eq 13, and the value thus obtained is 2.1×10^{-3} M^{-1} s^{-1}. The observed value of k_n^{OH} of 80×10^{-3} M^{-1} s^{-1} thus reveals the value of $k_{n_1}^{OH}$ of $\sim 78 \times 10^{-3}$ M^{-1} s^{-1}. This analysis indicates that $k_{n_1}^{OH}$ is nearly 39 times larger than $k_{n_2}^{OH}$. Similarly, the value of $k_{n_1}^{OH}/k_{n_2}^{OH}$ of ~ 40 was found in *o*-[(dimethylamino)methyl]benzyl alcohol catalyzed cleavage of A.[17] It is worth mentioning that the intrinsic reactivity of **6** (i.e., k_{n_2}) must be much larger than that of **5**, **5′** (i.e., k_{n_1}). But the apparent bimolecular rate constant, $k_{n_1}^{OH}$ ($=k_{n_1}K_T$) is ~ 39 times larger compared to $k_{n_2}^{OH}$ ($= k_{n_2}K_a'/K_a$, where $K_a' = K_TK_T'K_T''[1]a_{H^+}/[1H^+]$). These results indicate that the contribution due to the zwitterion form is negligible compared to that of the internally hydrogen-bonded form of these hydroxy amines.

A skeptic might doubt the reliability of our estimate of the rate constant for reaction via the zwitterion form on the basis of assuming that the hydroxy groups of the protonated amine $1H^+$ and the quaternary ammonium cation **3** are equally acidic. As shown in **8** the dimethylammonio substituent may be a more strongly acidifying substituent than the trimethylammonio substituent because of its possibility for internal hydrogen bonding. We think that this criticism does show that in allowing for reaction via the zwitterion form of the amino alcohol we did neglect the hydrogen-bonded form of the zwitterion



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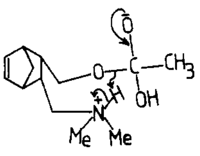
[17] Hine, J.; Khan, M. N. *J. Am. Chem. Soc.* **1977**, *99*, 3847.

J. Org. Chem. 1985, 50, 4855–4861 4855

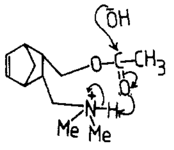
(5′). Actually, the internally hydrogen-bonded amine should have its hydrogen-bonding proton lying nearer the oxygen (5) or the nitrogen atom (5′). But the form 5′ is also a form of the zwitterion. When we refer to nucleophilic attack by the internally hydrogen-bonded alcohol we are including reaction via both species (5 and 5′). It is not possible to know which of the two will be responsible for most of the attack on A. The species 5′, while less abundant, should be much reactive in attacking by its oxygen atom. Hence there may be a significant amount of reaction via a hydrogen-bonded form of a zwitterion (5′), but we include this in the kind of process that can take place with the serine enzymes. We think that the factor of 39 by which the rate of such reaction exceeds that estimated for reactions via non-hydrogen-bonded zwitterion 6 is a good deal larger than the uncertainty of the estimate and, therefore, shows that the reaction by the proposed mechanism is occurring.

It is interesting to note that the ratio of $k_{n_1}{}^{OH}/k_w'$ is of the order of 10^6, where $k_w' = k_w/[H_2O]$ and $k_w(=5.5 \times 10^{-7}$ $s^{-1})$[6] is the pseudo-first-order rate constant for water-catalyzed cleavage of A. The ratio $k_{n_1}{}^{OH}/k_w'$ gives at least a qualitative measure of the enhancement caused by internally tertiary amine assisted hydroxy group catalyzed compared to unassisted hydroxy group catalyzed cleavage of A. Jersey et al.[8] have also observed the ratio of $k_{\mathrm{TRIS\ hydroxy}}/k_{H_2O}$ hydroxy of the order of 10^6 for TRIS- and water-catalyzed cleavage of 4-*trans*-benzylidene-2-phenyloxazolin-5-one.

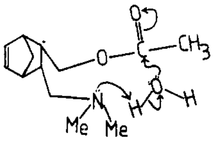
The value of k_2 of 2.45×10^{-5} s^{-1} at pH 8.80 may be used to calculate the hydroxide ion catalyzed bimolecular rate constant, k_{OH}, for the cleavage of 4. Assuming that water-catalyzed cleavage of 4 is negligible compared to the hydroxide ion catalyzed one at pH 8.80, the k_{OH} was found to be ~4 M^{-1} s^{-1}. This value is nearly 53 times larger than k_{OH} (4.5 M^{-1} min^{-1}) obtained for aqueous cleavage of ethyl acetate.[5] The significantly larger reactivity of 4 compared to that of ethyl acetate toward hydroxide ion could be attributed to the intramolecular general acid catalysis involving either transition-state TS1 (if expulsion of leaving group is the rate-determining step) or TS2 (if nucleophilic attack is the rate-determining step). TS2 is kinetically indistinguishable from TS3, which involves intramolecular general base catalysis. Furthermore, the possibility of the formation of TS1 via TS3 may be considered to be less likely for such a possibility could be expected to result in an enhanced reactivity of *o*-[(dimethylamino)methyl]benzyl alcohol toward less active esters such as methyl formate and acetylcholine. But no enhanced reactivity could be observed in these reactions.[15] However, the present data are not sufficient to differentiate between TS1, TS2, and TS3.



TS1



TS2



TS3

Although the present model is certainly an incomplete one, at least for the acylation step, because of the proposed involvement in this step of an aspartic acid residue in the "charge relay system",[18] it does display the major aspects of the mechanism involved in acylation and deacylation steps of the reactions catalyzed by serine esterases.

Acknowledgment. I express my appreciation and gratitude to Professor Jack Hine of the Ohio State University for suggesting this problem and for his hospitality in providing laboratory space and facilities and a postdoctoral fellowship in the completion of this work. This investigation was supported in part by NIH Grant GM 18593 granted to Professor Jack Hine.

Appendix

Estimation of p*K* Value of 1H⁺. Fox and Jencks[19] have reported that the acidities of substituted aliphatic tertiary ammonium ions, $XCH_2N^+HR_1R_2$, could be satisfactorily correlated with a value of $\rho_I = -8.4$. After correction by a factor of 2.5 per methylene group for transmission of substituent effect through the carbon atom, the value of $\rho_I = -0.54$ was considered for $XCH_2CH_2CH_2CH_2N^+HMe_2$. The pK_a of $CH_3(CH_2)_3N^+HMe_2$ has been found to be 10.37. The substitution of OH ($\sigma_I{}^{OH} = 0.25$) for H lowers the pK_a of $CH_3(CH_2)_3N^+HMe_2$ by -0.14 ($=-0.54 \times 0.25$). Thus, the esimated pK_a of $HO(CH_2)_4N^+HMe_2$ is 10.27.

Registry No. 1, 56679-25-5; 2, 98540-23-9; 3, 98540-24-0; 4, 98540-25-1; p-$NO_2C_6H_4OAc$, 830-03-5.

Supplementary Material Available: A table of observed data including k_{calcd} for the effect of the concentration of 3 on the cleavage of PNPA at different pH (1 page). Ordering information is given on any current masthead page.

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(19) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* 1974, *96*, 1436.

Preparation of Mesoionic Dipyrido[1,2-*a*:1′,2′-*c*]imidazolium-11-thiolates from the Binz–Marx Reaction[1]

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The reaction of a mixture of pyridine and 2-picoline with sulfur dioxide in the presence of benzoyl chloride, followed by treatment with aqueous potassium hydroxide, affords the mesoionic compound 1 in a one-pot reaction. Variously substituted derivatives of 1 may be obtained by similar reactions starting with appropriately substituted pyridines and/or 2-picolines. In hot concentrated hydrobromic acid these compounds extrude elemental sulfur and yield the parent heterocyclic cations. Their solvatochromy makes them useful indicators of solvent polarity.

In 1907 Binz and Marx[2] reported that reaction of a mixture of benzoyl chloride and pyridine with sulfur dioxide, followed by treatment with aqueous potassium hydroxide, gave a deep red compound having the empirical

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