(Scheme I). This is reasonable since RCO_2H should be more highly solvated than RCO_2R making its formation more favored by pressure because of a smaller molar volume.

However, we are comparing our data with those determined by others, and in view of the ca. 3 cm^3/mol difference in ΔV^*_{obsd} for ethyl acetate from two different groups (Table V), the values of $\Delta\Delta V^*$ may not remain the same when all data that are compared come from the same laboratory. We propose to test this by determining values of ΔV^*_{obsd} for a variety of acetates **3** where R is varied from alkyl through phenyl and finally again to *p*-nitrophenyl to obtain a spectrum of results as the stability of the $R'O^-$ varies.

Experimental Section

Materials. The esters *p*-nitrophenyl acetate, dimethylacetate, and trimethylacetate used in this study were those described in our earlier report.[6] *p*-Nitrophenyl propionate was prepared from *p*-nitrophenol and propionyl chloride in pyridine.[22,23] Recrystallization from chloroform–hexane gave crystals, mp 63–64 °C (lit.[23] 62.5–63 °C). The purity of the esters was checked by monitoring the absorption spectrum at 400 nm before and after basic hydrolysis in 0.1 M NaOH. A stoichiometric amount of *p*-nitrophenoxide ion was formed.

Tris buffers were prepared from "Tris·HCl" and "Tris Base" obtained from the Sigma Chemical Co. The weights of "Tris·HCl" and "Tris Base" were carefully determined so as to permit good calculations of "Tris" concentrations. The 0.005 M Tris buffers were prepared by tenfold dilution of stock solutions of 0.05 M buffers. pH values at atmospheric pressure were determined at the reaction temperatures. The pH values at high pressures were calculated from the atmospheric pressure pH values, the known compression of water at high pressures, and the pressure dependences of the ionizaton constants of Tris·HCl and water.[3,6,24,25]

Ester Hydrolysis. The esters were hydrolyzed in 0.005 M Tris buffers at 24.5 °C. Hydrolysis was monitored by observing the change in absorbance at 400 nm due to the pseudo-zero-order production of *p*-nitrophenoxide ion at less than 5% conversion.

To a 5-ml volumetric flask was added 200 μl of ester stock solution. The stock solution of *p*-nitrophenyl propionate was 2.9×10^{-3} M in the solvent acetonitrile; the other ester stock solutions were the same as previously reported.[6] This was then diluted volumetrically with 0.005 M Tris buffer maintained at constant ionic strength with sodium chloride. The kinetics were followed by the procedures previously reported.[3,6]

High-Pressure Optical Cell. Complete details of the high-pressure apparatus and techniques have been reported.[3,6]

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Intramolecular Nucleophilic Aminolysis of Aliphatic Esters. Cyclization of Methyl 2-Aminomethylbenzoate to Phthalimidine

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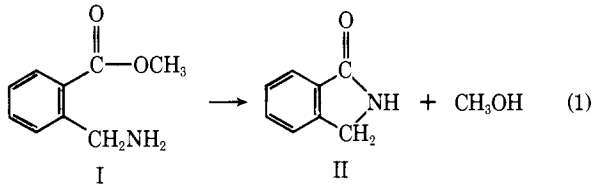
Abstract: Methyl 2-aminomethylbenzoate cyclizes at 30 °C in H_2O to phthalimidine with apparent hydroxide ion catalysis. The value of the second-order rate constant k_{OH} (7×10^3 M^{-1} s^{-1}) is ~10^5-fold greater than that for hydrolysis of methyl benzoate. The slope of a plot of log k_0 vs. pH is 1.0 at pH values above 8.60 and 2.0 at pH values less than 8.60. Pronounced general-base catalysis is observed in the cyclization reaction. The Brönsted coefficient β for a series of general-base catalysts is 1.0, which is the value expected for a proton-transfer reaction in the thermodynamically unfavorable direction. Thus, it is probable that the rate-determining step in the general-base-catalyzed cyclization is proton transfer which is not concerted with bond making or breaking. The k_{OH} values are closely similar for the cyclization of methyl 2-aminomethylbenzoate, ethyl 2-hydroxymethylbenzoate, and *tert*-butyl 2-mercaptomethylbenzoate, even though the nucleophilic groups differ greatly in basicity.

Chemical intramolecular reactions bear a striking resemblance to corresponding enzymatic reactions proceeding through an enzyme–substrate complex.[1,2] Consequently, the study of intramolecular catalysis has been of great importance in attempts to understand the mechanism of enzyme action. In determining the relative efficiency of intramolecular nu-

cleophiles, a common structural basis is desirable. Esters and amides of 2-hydroxymethylbenzoic acid serve as models for the acylation of α-chymotrypsin, since general-base catalysis of cyclization to phthalide takes place with various bases, including imidazole.[3,4] The cyclization reactions are quite rapid, k_{OH} being enhanced by 10^5 in comparison with hydroxide ion catalyzed hydrolysis of ethyl benzoate or benzamide. Thus, the 2-substituted benzoate system provides an excellent opportunity for comparing intramolecular nucleophiles of various types.

Bimolecular aminolysis of phenolic[5] and aliphatic esters[6,7] has been extensively studied. Intramolecular aminolysis of substituted phenyl γ-dimethylaminobutyrates and δ-dimethylaminovalerates proceeds with effective molarities of 1000–5000 M for the neighboring dimethylamino group, in comparison with bimolecular aminolysis of *p*-nitrophenyl acetate by trimethylamine.[8] The neutral amine group of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate is a highly efficient intramolecular nucleophile with an effective molarity of at least 10^8 M, in comparison with bimolecular attack of amines on the unsubstituted ester.[9] The rearrangement of *O*-acetylethanolamine to *N*-acetylethanolamine has been investigated.[10] However, there have been no previous studies of intramolecular aminolysis reactions of aliphatic esters where the nucleophile and the ester carbonyl are constrained in proximity and the leaving group breaks away from the remainder of the molecule. Therefore, in order to compare the efficiency of an amine with sulfhydryl and alcohol nucleophiles[3] in intramolecular nucleophilic displacement of aliphatic alcohol leaving groups, we have determined the rates of cyclization of methyl 2-aminomethylbenzoate (I) to phthalimidine (II) (eq 1).



I II

Experimental Section

Materials. Methyl 2-cyanobenzoate was obtained from Aldrich. Methyl 2-aminomethylbenzoate hydrochloride was prepared by catalytic reduction of the nitrile in ethanol–chloroform using platinum oxide as the catalyst by the method of Secrist and Logue.[11] Hydrogenation was carried out on a Parr apparatus for 11 h at 55 psi of H_2. After filtration, the solvent was removed by rotary evaporation. The product was recrystallized from a methanol–ethyl acetate mixture, yielding white crystals melting at 173–175 °C.

Anal. Calcd for $C_9H_{12}NO_2Cl$: C, 53.60; H, 6.01; N, 6.95. Found: C, 53.36; H, 6.20; N, 6.65.

Buffers were prepared from reagent-grade materials. Amine buffer components were freshly distilled or recrystallized prior to use.

Kinetic Methods. The rates of cyclization of methyl 2-aminomethylbenzoate to phthalimidine were measured by following the absorbance decrease at 285 nm or the increase in absorbance at 271 nm. The spectrum of the product was invariably identical with that of an equivalent concentration of synthetically prepared phthalimidine.[12,13] At pH values below 9, a Gilford 2000 recording spectrophotometer was employed. A 60-μl sample of I in methanol was injected into 3 ml of buffer (μ = 0.5 with KCl) to initiate the reactions. At pH values above 9, a Durrum D110 stopped-flow apparatus was employed. In the stopped-flow determinations, substrate in 10^{-3} M HCl solution in one syringe was rapidly mixed with an equal volume of buffer from the other syringe to give the appropriate reaction solution. The drive syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 30 ± 0.1 °C. Optical density changes after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207B). With each buffer, four to six pairs of reactions with overlapping oscilloscope traces were tabulated. Infinity points were stable.

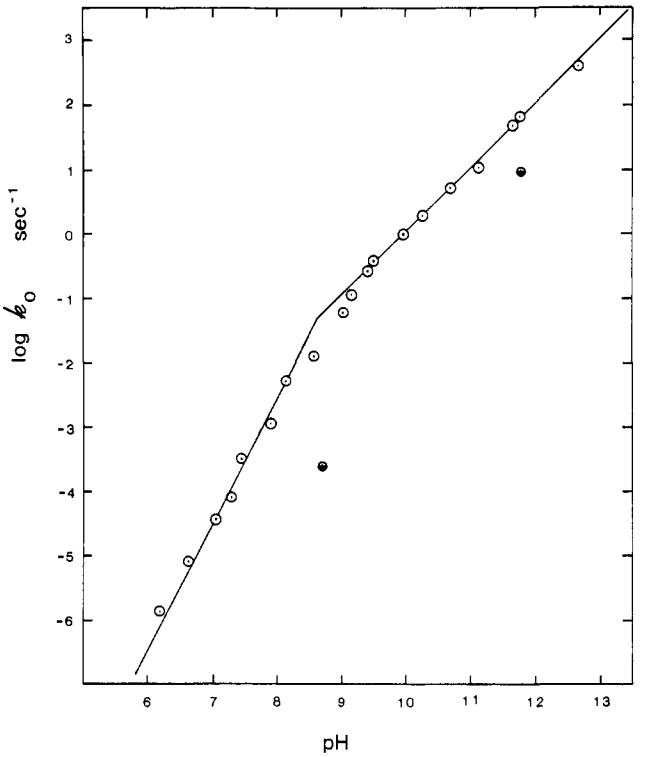


Figure 1. Plot of log k_0 vs. pH for the cyclization of methyl 2-aminomethylbenzoate to phthalimidine at 30 °C and μ = 0.5 with KCl in H_2O (⊙) or D_2O (◒) (pH = pD). The points were obtained at zero buffer concentration, except in hydroxide ion solutions, and pH 6.19, where the point represents the rate constant in 0.1 M total phosphate buffer.

Reaction solution pH values were measured with a Radiometer pH meter Model 22 and GK 2303C combined electrode standardized with Mallinckrodt standard buffer solutions. Pseudo-first-order rate constants were calculated with an Olivetti-Underwood Programma 101.

Product Isolation. A 0.15-g sample of methyl 2-aminomethylbenzoate in 35 ml of pH 10 solution was allowed to stand at 25 °C until the reaction was complete. The mixture was extracted with ether and the ether extracts were dried over anhydrous sodium sulfate. Removal of the ether yielded material with an identical melting point (mp 148–150 °C) and uv spectrum as an authentic sample of phthalimidine.[12,13]

Results

In Figure 1 is presented a plot of log k_0 vs. pH for cyclization of methyl 2-aminomethylbenzoate (I) to phthalimidine at 30 °C, where k_0 is k_{obsd} at zero buffer concentration. From pH 12 to 9 the plot is linear with a slope of 1.0, indicating apparent hydroxide ion catalysis (k_{OH} = 7.2 × 10^3 M^{-1} s^{-1}). At pH 8.6 a unit change in slope occurs to 2.0. As seen in Figure 1, the reaction is slower in D_2O than in H_2O. The value of k_{OD} is 5.8 × 10^3 M^{-1} s^{-1}, giving a ratio k_{OH}/k_{OD} = 1.2. In calculating second-order rate constants, the ion product of water (K_w) and K_{D_2O} at 30 °C were taken to be 1.47 × 10^{-14} and 0.2 × 10^{-14}, respectively.[14]

Pronounced general-base catalysis is observed in the cyclization reaction. The minimum equation for k_{obsd} is given in eq 2,

$$k_{obsd} = [k_{OH}(OH^-) + k_B(B) + k_B'(B)(OH)]\left[\frac{K_{app}}{K_{app} + a_H}\right] \quad (2)$$

where K_{app} is the apparent dissociation constant of the conjugate acid of I. A plot of $k_{obsd}/K_{app}/(K_{app} + a_H)$ vs. ethanolamine free base concentration at three pH values is given in Figure 2. The slopes increase as the pH increases, indicating hydroxide ion catalysis in the general-base reaction. A plot of the slopes of Figure 2 vs. hydroxide ion concentration (Figure

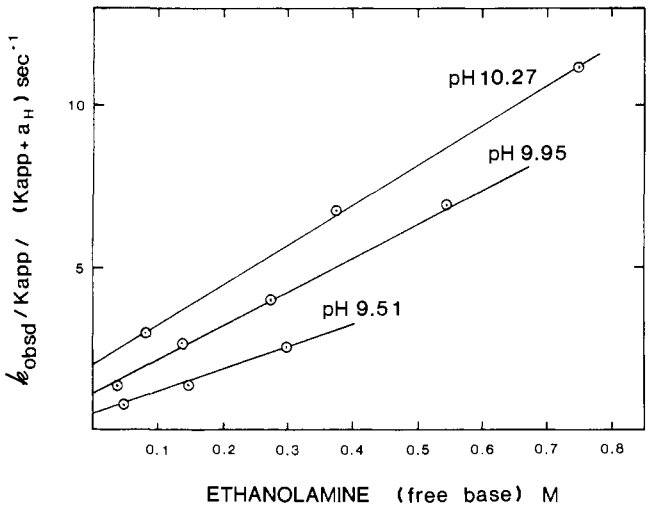


Figure 2. Plot of $k_{obsd}/K_{app}/(K_{app} + a_H)$ for the cyclization of methyl 2-aminomethylbenzoate to phthalimidine at 30 °C (μ = 0.5) vs. ethanolamine free base concentration (M).

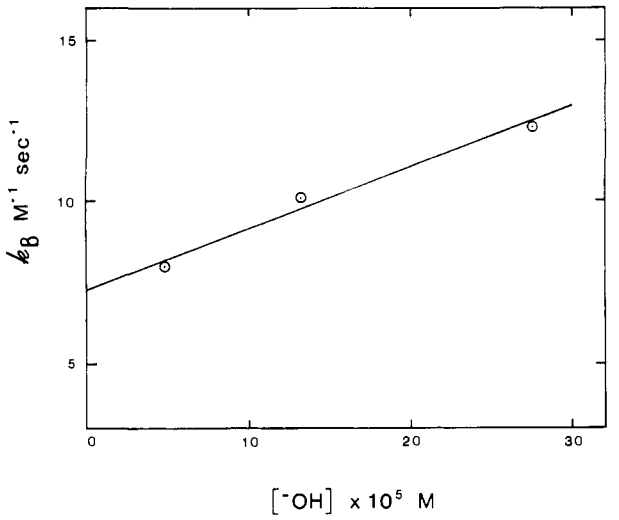


Figure 3. Plot of the slopes of Figure 2 vs. hydroxide ion concentration.

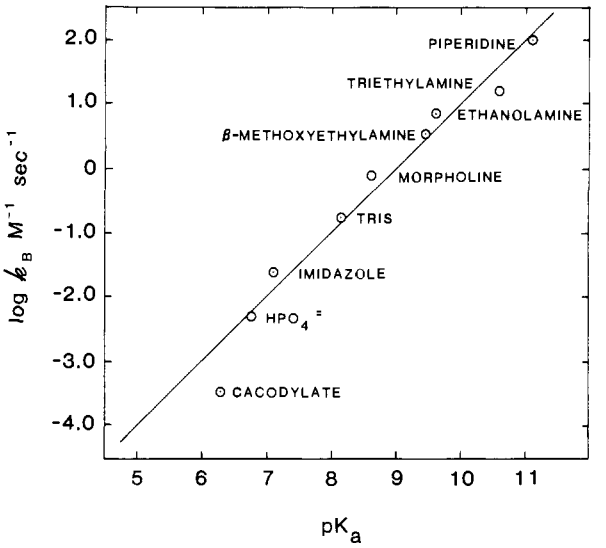


Figure 4. A Brönsted plot of log k_B for general-base-catalyzed cyclization of methyl 2-aminomethylbenzoate to phthalimidine at 30 °C vs. the pK_a of the conjugate acid of the general-base catalyst.

Table I. Rate Constants for Catalysis of the Cyclization of Methyl 2-Aminomethylbenzoate to Phthalimidine at 30 °C in H_2O (μ = 0.5 M with KCl)

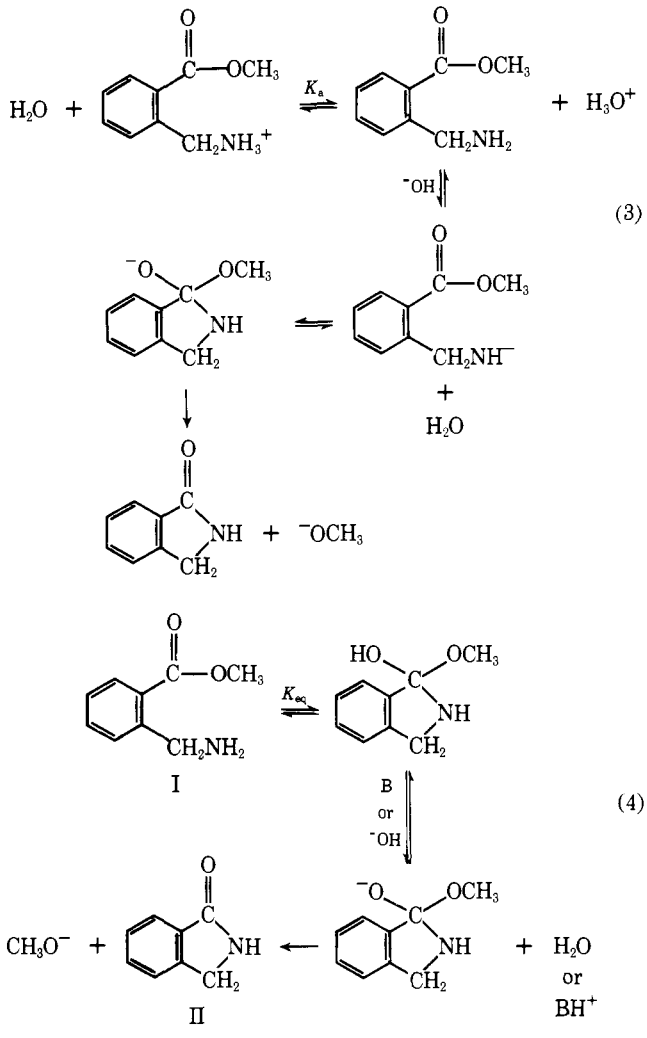
Base	pK_a	k_B, M^{-1} s^{-1}	$k_B^1 \times 10^{-4}$, M^{-2} s^{-1}	$k_{OH} \times 10^{-3}$, M^{-1} s^{-1}
^-OH				7.2
Piperidine	11.1	105.4		
Triethylamine	10.6	15.7		
Ethanolamine	9.60	7.25	1.9	
β-Methoxyethylamine	9.45	3.99		
Morpholine	8.60	0.79		
Tris	8.15	0.172		
Imidazole	7.05	0.0249		
HPO_4^{2-}	6.75	0.0052		
Cacodylate	6.28	0.00034		

3) is linear and extrapolates to an intercept at zero (^-OH). Consequently, with ethanolamine there is a term in the rate expression for both uncatalyzed and hydroxide ion catalyzed general-base reactions. The latter term very likely results from catalysis of the cyclization by the anionic species of ethanolamine ($^-OCH_2CH_2NH_2$). This would lead to the term in the equation for k_{obsd} corresponding to $k_B^1(HOCH_2CH_2NH_2)(OH^-)$. The second-order rate constant for catalysis by β-methoxyethylamine, an amine of similar basicity but without the hydroxyl group substituent of ethanolamine, did not vary significantly as pH was increased in the range 9.06–9.93. Hydroxide ion catalysis of the general-base reaction was also not observed in piperidine, Tris, imidazole, phosphate, morpholine, or cacodylate buffers. Values of the rate constants are given in Table I. The rate constant for Tris catalysis is 2.80-fold less in D_2O than H_2O. A Brönsted plot of log k_B vs. pK_a of the catalyzing base is presented in Figure 4. The slope is 1.02 with a correlation coefficient of 0.980. Cacodylate deviates negatively from the line established with amines. If cacodylate is omitted from the correlation, the least-squares slope is 0.93 (r = 0.990). The point for hydroxide ion falls 2.7 log units below the line in Figure 4.

Discussion

Methyl 2-aminomethylbenzoate cyclizes to phthalimidine in a reaction for which the pH–rate constant profile (Figure 1) shows only apparent hydroxide ion catalysis in the reaction at zero buffer concentration. There is no evidence for a change in rate-determining step with pH, such as has been observed in the bimolecular aminolysis of aliphatic esters.[6,7] At pH 8.60 the slope of the plot in Figure 1 changes from 1.0 to 2.0. Protonation of the amine group would cause such a change in slope at the pK_a of the amine. It was not possible to measure the thermodynamic pK_a of I because of the extremely rapid rates of cyclization at pH values close to pK_{app}, but a pK_a of 8.6 would be reasonable for an aliphatic amine. From the linear plot of log k_0 vs. pH with slope of 1.0, an apparent second-order rate constant k_{OH} may be calculated (7×10^3 M^{-1} s^{-1}), which is ~10^5-fold greater than the second-order rate constant for hydroxide ion catalyzed hydrolysis of methyl benzoate (0.125 M^{-1} s^{-1}) at 30 °C.[15] A reasonable reaction scheme is given in eq 3. At pH values above 6 there is no uncatalyzed cyclization of the neutral species, whereas such a reaction is an important feature of the bimolecular aminolysis of esters.[5-7] An alternative to the scheme of eq 3 would involve rapid and reversible attack of the neutral amine on the carbonyl, followed by hydroxide ion or general-base-catalyzed decomposition of a tetrahedral intermediate (eq 4) or a kinetic equivalent.

Pronounced general-base catalysis is observed in the cyclization of I. This catalysis involves proton transfer in the transition state, as shown by the large D_2O solvent isotope effect ($k_B^{H_2O}/k_B^{D_2O}$ = 2.80), in the case of Tris catalysis. The



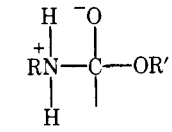
(3)

(4)

Brönsted plot of Figure 4 shows that bases of widely varying charge and type (cacodylate, phosphate, imidazole, and various amines) fit reasonably well on a single line. This appears to be a characteristic of general-base-catalyzed reactions,[16,17] in contrast with nucleophilic reactions where nucleophiles of different type have separate lines.[18] The Brönsted coefficient β is, within error, 1.0, the value expected for a proton-transfer reaction in the thermodynamically unfavorable direction.[19] Thus, it is probable that the rate-determining step in the general-base-catalyzed cyclization reaction is proton transfer, which is not concerted with bond making or breaking. A Brönsted coefficient of 1.0 has also been obtained in the cyclization of ethyl 2-hydroxymethyl-4-nitrobenzoate to 5-nitrophthalide[20] and 2-hydroxymethylbenzamide to phthalide.[4] At high pK_a the Brönsted slope for the latter reaction changes to 0.2, indicating a change in rate-limiting step.

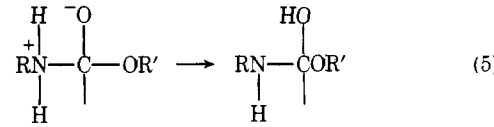
Nucleophilic cyclization reactions of aliphatic 2-substituted benzoate esters appear to be characterized by Brönsted coefficients near 1.0 in cases where bimolecular general-base catalysis is observed. To the extent that these reactions represent reasonable models for the action of α-chymotrypsin on ester and amide substrates (aminolysis of an ester is the microscopic reverse of alcoholysis of an amide), it can be surmised that in chymotrypsin catalysis proton-transfer reactions play an important role.

Satterthwait and Jencks[7] have proposed a mechanism for intermolecular aminolysis of esters in which, with most alkyl and aryl esters, attack of amine to form a labile dipolar intermediate (III) is rapid and reversible, the rate-determining step at high pH being abstraction of a proton from this intermediate by a general base, a proton transfer through water (alkyl esters,



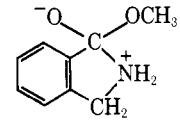
III

eq 5), or direct breakdown of the intermediate to products



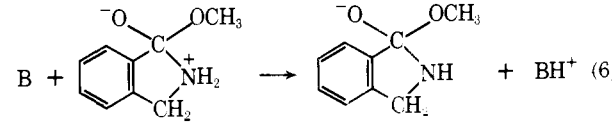
(5)

(phenyl esters). While it is possible that a dipolar intermediate IV is being formed in the cyclization of I, it is clear that a



IV

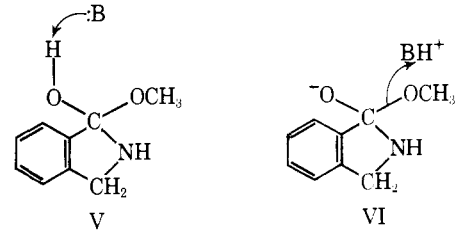
proton switch through water similar to eq 5 cannot be rate determining at any pH investigated. Such a mechanism would give rise to a pH-independent region in the pH–rate constant profile, whereas hydroxide ion catalysis is observed at all pH values. General-base catalysis could involve rate-determining proton abstraction from the intermediate IV (eq 6), analogous



(6)

to the Satterthwait and Jencks[7] mechanism for general-base-catalyzed bimolecular aminolysis. Removal of a proton from IV or a neutral tetrahedral intermediate by hydroxide ion should be a diffusion-controlled reaction with a rate constant of $\sim 10^{10}$ M^{-1} s^{-1}. Thus, from the k_{OH} value of 7×10^3 M^{-1} s^{-1} it can be calculated that if nucleophilic attack is by the neutral amine in the cyclization of I, then the equilibrium constant K_{eq} for ring closure is at least 7×10^{-7}. This is considerably greater than the K_{eq} of 6×10^{-12} calculated for addition of hydrazine ($pK_a = 8.3$) to ethyl acetate[7] and reflects the advantage of an intramolecular reaction.

There is no break in the pH–log k_0 profile (Figure 1) at pH values as high as 12.7. Likewise, there is no curvature in the Brönsted plot of Figure 4 even with bases of high pK_a such as piperidine ($pK_a = 11.1$). Curvature in these plots at the pK_a of the intermediate would be expected if proton transfer is rate determining. Thus, it is likely that the pK_a of the critical intermediate from which rate-determining proton transfer takes place is greater than 11.1, which would be greater than the pK_a expected for IV. The pK_a of the addition intermediate of ethyl acetate and hydrazine has been estimated[7] to be 9.6. Therefore, the most likely mechanisms for general-base-catalyzed cyclization are rate-determining proton abstraction from the amine group in the formation of a tetrahedral intermediate, removal of a proton from a neutral tetrahedral intermediate (V), or the kinetically equivalent proton donation to the leaving group (VI).[21]

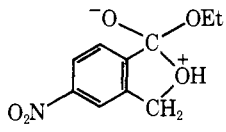


V VI

The cyclization reactions of 2-hydroxymethylbenzoate esters and I are similar not only in regard to the magnitude of the

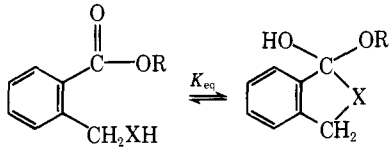
Brönsted coefficients (1.0), but also with respect to the absolute values of the rate constants.[20] For example, the values of k_{Im}, the second-order rate constants for imidazole-catalyzed cyclization, are 8.75×10^{-3}, 2.29×10^{-2}, and 2.49×10^{-2} M^{-1} s^{-1} with ethyl 2-hydroxymethylbenzoate, ethyl 2-hydroxymethyl-4-nitrobenzoate, and I, respectively, even though the neighboring alcohol and amine groups must differ greatly in basicity. The closely similar Brönsted coefficients and rate constants in the cyclization reactions might imply a common mechanism and rate-determining step in the general-base-catalyzed reaction.

Proton abstraction from an intermediate VII in the cyclization of ethyl 2-hydroxymethyl-4-nitrobenzoate, analogous to intermediate IV in the cyclization of I, should, because of the great acidity of VII, be diffusion controlled with all bases, including water. The structure of VII is similar to that of an orthoester, so pK_a would be ~ -8,[22] but the Brönsted coefficient is 1.0,[20] indicating proton transfer in the thermodynamically unfavored direction. It can be calculated from the magnitude of the rate constants that formation of a tetrahedral intermediate cannot be rate determining if proton transfer is a stepwise process. Thus, equilibrium conditions must prevail for the formation of a tetrahedral intermediate and the rate-determining step in the general-base-catalyzed reaction must be removal of a proton from a neutral tetrahedral intermediate or a kinetically equivalent general-acid catalysis analogous to V and VI.



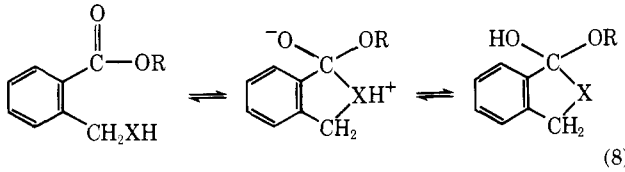
VIII

The corresponding k_{OH} values for cyclization of I (7×10^3 M^{-1} s^{-1}), ethyl 2-hydroxymethylbenzoate[3] (10^4 M^{-1} s^{-1}), ethyl 2-hydroxymethyl-4-nitrobenzoate[20] (5×10^4 M^{-1} s^{-1}), and *tert*-butyl 2-mercaptomethylbenzoate[23] (3.5×10^3 M^{-1} s^{-1}) might also imply a common rate-determining step in the hydroxide ion catalyzed reactions. The k_{OH} values in the cyclization of these compounds with aliphatic alcohol leaving groups of similar basicity may reflect a rate-determining step that is diffusion controlled following an equilibrium step, or, since proton abstraction by hydroxide ion from any of the various tetrahedral intermediates should be diffusion controlled and thermodynamically favorable, the hydroxide ion catalyzed reaction might involve rate-determining C–O bond breaking. In either case, the equilibrium constants K_{eq} for cyclization (eq 7) must be nearly the same regardless of the nature of X.



(7)

This might be the case if two or more sequential steps occur which compensate in their effects on the overall equilibrium, i.e., if nucleophilic attack by the neutral species is followed by rapid reversible proton transfer from X to O (eq 8). If it is the anionic species X^- that acts as the nucleophile, then the acidity of XH and the nucleophilic ability of X^- must almost exactly compensate. An alternative that cannot at present be eliminated is that the reactions proceed with different mechanisms which, coincidentally in these examples, give rise to similar rate constants.



(8)

Intramolecular aminolysis in I is strikingly different in several aspects than bimolecular aminolysis reactions of the aliphatic esters that have previously been studied.[6,7] Mechanism is, of course, a function of transition-state structure and there appears to be no a priori reason why they should be the same in the intramolecular and bimolecular reactions. In view of the close correspondence of an enzyme reaction proceeding through an enzyme substrate complex and a chemical intramolecular reaction, it is clear that one should employ intramolecular catalysis as the model from which to gain insight into analogous enzymatic reactions.

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References and Notes

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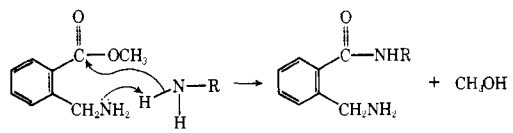
(21) Another mechanism which could lead to an enhanced rate of ester disappearance, but which would give different products would have the neighboring amine function acting as an intramolecular general base. However,



product spectra were invariably qualitatively and quantitatively identical with that of phthalimidine. Amides of 2-aminomethylbenzoic acid have spectra that are quite different from that of phthalimidine.[23] Consequently, if amino amides are being formed, they can only be present in trace amounts.
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