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Intramolecular Aminolysis of Esters. Cyclization of Esters of (*o*-Aminophenyl)acetic Acid

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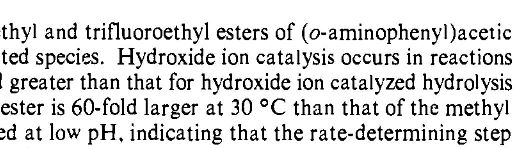
Abstract: Rate constants have been obtained for cyclization of the methyl and trifluoroethyl esters of (*o*-aminophenyl)acetic acid to 2-oxindole. Cyclization occurs via both the neutral and protonated species. Hydroxide ion catalysis occurs in reactions of the methyl ester with a second-order rate constant k_{OH} that is 100-fold greater than that for hydroxide ion catalyzed hydrolysis of methyl phenylacetate. The k_{OH} for cyclization of the trifluoroethyl ester is 60-fold larger at 30 °C than that of the methyl ester. The log k_0 vs. pH profile for the trifluoroethyl ester is bell shaped at low pH, indicating that the rate-determining step is changing with pH. Consequently, an intermediate is formed in the cyclization reaction that must be a tetrahedral addition product. This is also shown by curved plots of k_{obsd} vs. buffer concentration for cyclization of the methyl ester at pH less than 7, which indicate that the rate-determining step is changing with increasing buffer concentration. The rate-determining step at pH > 4 and low buffer concentration must be breakdown of a tetrahedral intermediate. The general base catalysis observed in the cyclization reaction of the methyl and trifluoroethyl esters is characterized by Brønsted β coefficients of 0.5 and 0.2, respectively. Thus, in the general base catalyzed reactions proton transfer is concerted with bond breaking, in contrast with the similar reactions of methyl 2-(aminomethyl)benzoate, in which a proton-transfer step is rate determining (β = 1.0). The decrease in Brønsted coefficient as the leaving group is improved indicates that the general base is partially removing a proton from the neutral tetrahedral intermediate as the C–O bond breaks. Several different mechanisms and/or rate-determining steps are possible in the intramolecular aminolysis of aliphatic esters; the key features in these aminolysis reactions in regard to mechanism are the pK_a of the nucleophile, the steric fit of the nucleophile to the carbonyl, and the ease of C–O bond breaking in decomposition of a tetrahedral intermediate to products.

The study of intramolecular catalysis in chemical reactions has been of great importance in attempts to understand the mechanism of enzyme action because of the striking resemblance of intramolecular reactions to corresponding enzymatic reactions proceeding through an enzyme–substrate complex.[2] Both intramolecular and bimolecular aminolysis reactions of phenolic esters have been extensively studied.[2-12] However, relatively few mechanistic investigations of aminolysis of aliphatic esters have been carried out.[13-17] The intramolecular reactions of methyl 2-(aminomethyl)benzoate proceed with striking mechanistic differences in comparison with bimolecular aminolysis of aliphatic esters.[15] General base catalysis is observed in the cyclization reactions of 2-substituted benzoate esters having poor leaving groups, and Brønsted β coefficients of 1.0[6,15,18] indicate that a proton transfer step is rate limiting. This step is most likely proton transfer from a neutral tetrahedral intermediate.

Kirby et al.[16] have recently studied cyclization reactions of methyl 3-(2-aminophenyl)propionate. In contrast with methyl 2-(aminomethyl)benzoate,[15] hydroxide ion catalysis was not observed below pH 10, and a rapid reaction of the protonated species was detected. General base catalysis was found which was not greatly affected by the pK_a of the catalyst. These mechanistic differences in comparison with the 2-substituted benzoate ester could be due to the much lower pK_a of the aniline nitrogen and/or the different ring size for nucleophilic attack (six vs. five). In view of the importance of understanding the factors that influence intramolecular reactions, we have investigated the cyclization of aliphatic esters of (*o*-aminophenyl)acetic acid (eq 1). These intramolecular reactions proceed via a five-membered ring, and the pK_a of the amine nucleophile is low. Aniline apparently does not act as a bimolecular nucleophile toward aliphatic esters,[16] but the intramolecular reactions of I proceed with facility. It has been found in this work that the reactions of I and II are mechanistically quite distinct from those of either methyl 3-(2-aminophenyl)propionate[16] or methyl 2-(aminomethyl)benzoate.[15]



(1)

R

I, CH_3
II, CH_2CF_3

Experimental Section

Materials. Methyl (2-aminophenyl)acetate (I) was prepared by esterification of (*o*-nitrophenyl)acetic acid followed by reduction of the nitro group. (*o*-Nitrophenyl)acetic acid (2 g) (Aldrich) was dissolved in 60 mL of dry methanol and benzene (v/v). Concentrated sulfuric acid (1.5 mL) was added, and the mixture was refluxed overnight. After cooling, 50 mL of ether was added, and the mixture was washed with dilute aqueous sodium carbonate solution and water. After the organic layer was dried over sodium sulfate, the ether was evaporated. The residue was taken up in methanol and hydrogenated for 2 h at 50 psi in the presence of 80 mg of PtO_2. The mixture was filtered, and the solvent was then removed by rotary evaporation. The resulting oil had peaks in the infrared spectrum at 3500, 1740, and 1160 cm^{-1}. Characteristic NMR peaks (Varian EM-360) relative to Me_4Si (0 ppm) were a multiplet (4 H) at 6.5–7.2, a broad singlet (2 H) at 4.2, a singlet (3 H) at 3.55, and a singlet (2 H) at 3.5. The hydrochloride salt was prepared by dissolving the oil in dry ether and bubbling in gaseous HCl. The white solid was removed by filtration and recrystallized from a chloroform–ether mixture, mp 105–108 °C. Anal. Calcd for $C_9H_{12}NO_2Cl$: C, 53.60; H, 5.96; N, 6.95. Found: C, 53.68; H, 6.04; N, 6.97.

2-Oxindole was obtained from the free base of I by heating a sample under reduced pressure for 20 min. A brown solid formed, which was

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(1) Postdoctoral Fellow, University of Southern California.
(2) (a) Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1966. (b) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969.
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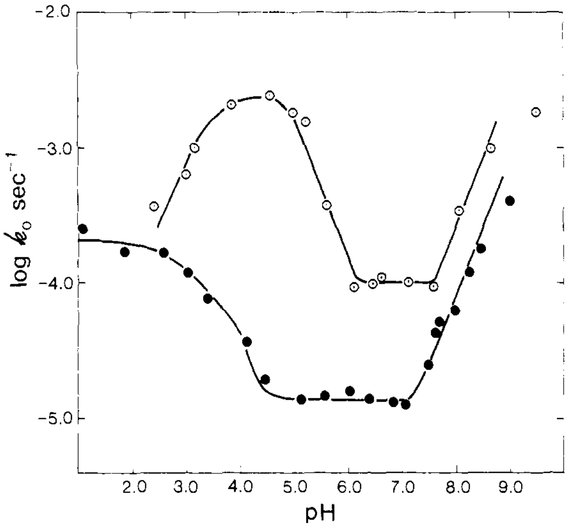


Figure 1. Plots of log k_0 vs. pH for cyclization of methyl (2-aminophenyl)acetate (●) and trifluoroethyl (2-aminophenyl)acetate (⊙) to 2-oxindole at 50 and 30 °C, respectively, in H_2O, $\mu = 0.5$ M with KCl.

recrystallized from chloroform–hexane. The material then melted at 123–125 °C and had IR and NMR spectra identical with those of the commercially available compound (Aldrich).

2,2,2-Trifluoroethyl (2-aminophenyl)acetate (II) was prepared in a manner similar to that used for I. (o-Nitrophenyl)acetic acid (10 g) was dissolved in 50 mL of benzene. 2,2,2-Trifluoroethanol and 2 mL of concentrated sulfuric acid were added, and the mixture was refluxed for 16 h. After cooling, 50 mL of ether was added, and the mixture was washed with a dilute aqueous sodium carbonate solution and water. The organic layer was dried over Na_2SO_4 and evaporated. The orange oil, in 100 mL of dry chloroform, was hydrogenated at 55 psi in the presence of 100 mg of PtO_2 and 2 g of trifluoroethanol for 4 h. The mixture was then filtered and rotary evaporated to yield an oil, which was converted to the hydrochloride in the same manner as I. After recrystallization from chloroform–ether, the material melted at 132–135 °C. Anal. Calcd for $C_{10}H_{11}NO_2ClF_3$: C, 44.53; H, 4.08; N, 5.19. Found: C, 44.32; H, 4.22; N, 5.15.

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 I and II to 2-oxindole were measured at 30 and 50 °C by following the absorbance increase at 250 nm, employing either a Beckman 25 or a Pye Unicam SP8-100 recording spectrophotometer. The spectrum of the product was invariably identical with that of an equivalent concentration of an authentic sample of 2-oxindole. Reaction solution pH values were measured with a Radiometer Model 22 pH meter and GK 2303 C combined electrode standardized with Mallinckrodt standard buffer solutions. Pseudo-first-order rate constants were computer calculated. In calculating second-order rate constants for OH^- catalysis, K_w values of 1.47×10^{-14} and 5.5×10^{-14} were employed at 30 and 50 °C, respectively.

pK_a Determination. The pK_a of methyl (2-aminophenyl)acetate was determined spectrophotometrically in H_2O at 30 °C ($\mu = 0.5$ M), employing a series of eight buffers and HCl solutions in the pH range 1.02–6.20. The value of the pK_a was found to be 3.7.

Results

A plot of log k_0 vs. pH for cyclization of methyl (2-aminophenyl)acetate (I) to 2-oxindole at 50 °C and $\mu = 0.5$ M (with KCl) is shown in Figure 1. The rate constants were obtained by extrapolation to zero buffer concentration or in 0.02 M total buffer, except in the case of imidazole buffers where the concentration of total buffer was 0.002 M. It was shown in separate buffer dilution experiments that such concentrations do not have an experimentally significant effect on the observed rate constants. The slope of the profile at pH > 7 is 1.0, indicating OH^- catalysis, whereas at pH 5–7 the rate constants are pH independent, due to a water-catalyzed reaction. At pH < 5 the rate constants increase with decreasing pH, indicating a reaction of the protonated ester. The data provide a good fit to eq 2, where k_p and

$$k_0 = \frac{k_p a_H + k_0' K_a + k_{OH} K_a (OH^-)}{K_a + a_H} \tag{2}$$

k_0' are rate constants for reaction of the protonated species and the pH-independent reaction of the neutral species, k_{OH} is the second-order rate constant for OH^- catalysis, and K_a is the dissociation constant of the neighboring amino group conjugate acid. At 50 °C these constants have the values $k_p = 1.8 \times 10^{-4}$ s^{-1}, $k_0' = 1.1 \times 10^{-5}$ s^{-1}, $k_{OH} = 14.4$ M^{-1} s^{-1}, and p$K_{app} = 3.4$. At 30 °C k_{OH} is 3 M^{-1} s^{-1}.

Table I. Rate Constants for General Base Catalyzed Cyclization of Methyl (2-Aminophenyl)acetate to 2-Oxindole at 30 °C in H_2O, $\mu = 0.5$ M

base	pK_a	$k_B \times 10^3$, M^{-1} s^{-1}
trimethylamine	9.86	5.12
2-methoxyethylamine	9.51	2.76
carbonate	9.45	14.5
morpholine	8.61	2.60
Tris	8.10	1.10
N-ethylmorpholine	7.60	0.113
imidazole	7.10	0.768[a]
Mes[b]	6.24	0.06[a]

[a] Calculated from the initial portion of the plot of k_{obsd} vs. buffer base concentration. [b] Mes = 2-(N-morpholino)ethanesulfonic acid.

Table II. Rate Constants for General Base (k_B) and General Acid (k_{HA}) Catalyzed Cyclization of Trifluoroethyl (2-Aminophenyl)acetate to 2-Oxindole at 30 °C in H_2O, $\mu = 0.5$ M

buffer	pK_a	$k_B \times 10^2$, M^{-1} s^{-1}	k_{HA}, M^{-1} s^{-1}
trimethylamine	9.86	8.10	
methoxyethylamine	9.51	4.88	
morpholine	8.66	4.08	
Tris	8.10	2.26	
N-ethylmorpholine	7.60	0.89	
imidazole	7.05	2.69	
cacodylate	6.45	3.88	
malonate	5.60	2.16	
acetate	4.60	0.87	0.025
glycolate	3.86		0.136

Also shown in Figure 1 is the plot of log k_0 vs. pH for cyclization of trifluoroethyl (2-aminophenyl)acetate (II) to 2-oxindole at 30 °C and $\mu = 0.5$ M (with KCl). The rate constants were obtained by extrapolation to zero buffer concentration. As was the case with I, a pH-independent reaction is discernible ($k_0' = 6.0 \times 10^{-5}$ s^{-1}), and a reaction of the protonated species occurs at pH < 6, but rate constants decrease with decreasing pH at pH less than 4.5. The rate constants k_{OH} and k_H at 30 °C have the values 171 M^{-1} s^{-1} and 150 M^{-1} s^{-1}, with k_H being the second-order rate constant for the apparent hydronium ion catalyzed reaction at pH 4.5–6.0 ($k_H = k_p/K_a$).

Pronounced buffer catalysis is observed in the cyclization reactions of both I and II. At pH > 7 general base catalysis occurs. Plots of k_{obsd} for cyclization of I vs. total morpholine concentration (B + BH$^+$) at three constant pH values (not shown) were nicely linear and gave the same second-order rate constant for morpholine catalysis. At pH less than 7 plots of k_{obsd} vs. buffer concentration were markedly curved in cyclization of I, as illustrated in Figure 2, where k_{obsd} is plotted vs. cacodylate concentration. Significant curvature was also obtained in imidazole and MeS buffers. However, such buffers gave nicely linear plots in cyclization of the trifluoroethyl ester (II), as shown in Figure 2. At pH < 5.5 general acid catalysis was also observed in cyclization of II. Rate constants for general acid and general base catalysis were separated by plotting k_B total (the slopes of plots of k_{obsd} vs. buffer base concentration) vs. $K_a/(K_a + a_H)$, where K_a is the dissociation constant of the amino group (assumed to be the same as determined spectrophotometrically for I). Catalysis by glycolic acid buffer was predominantly general acid. Rate constants for general base and general acid catalysis are given in Tables I and II. Brønsted plots of log k_B vs. pK_a are shown in Figure 3. The slopes β are 0.5 for I and 0.2 in the case of II. The use of statistical corrections produces only small changes, the slopes remaining 0.5

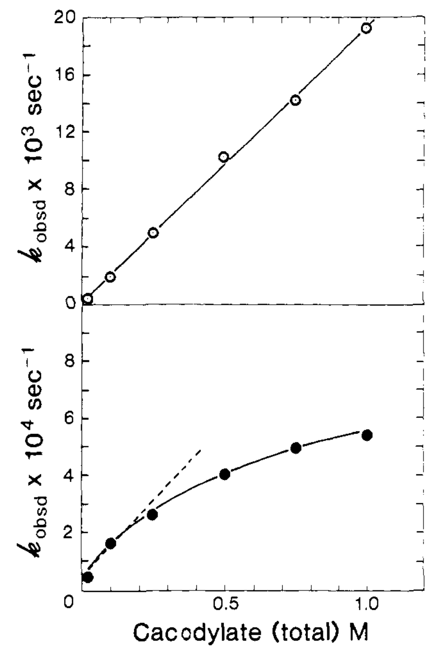


Figure 2. Plots of k_{obsd} vs. the total concentration of cacodylate buffer for cyclization of methyl (2-aminophenyl)acetate (●) and trifluoroethyl (2-aminophenyl)acetate (⊙) to 2-oxindole at 30 °C in H_2O, $\mu = 0.5$ M with KCl.

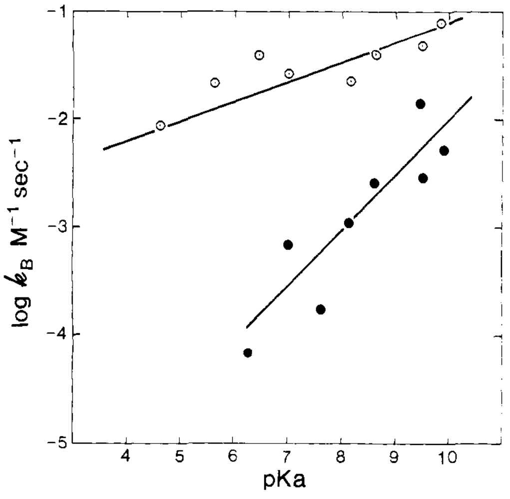


Figure 3. Brønsted plots of log k_B vs. the pK_a of the catalyzing general base in the cyclization of methyl (2-aminophenyl)acetate (●) and trifluoroethyl (2-aminophenyl)acetate (⊙) to 2-oxindole at 30 °C in H_2O, $\mu = 0.5$ M with KCl.

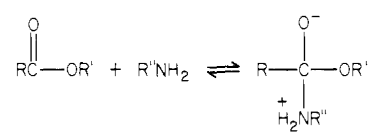
and 0.2. If only the amine bases are employed in the Brønsted plot for cyclization of II, the slope is 0.3.

Discussion

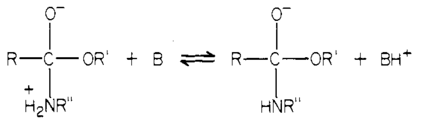
The pH-log (rate constant) profile in Figure 1 for cyclization of I to 2-oxindole (eq 1) at 50 °C shows OH^- catalysis at pH > 7 in reactions of the neutral species, a water-catalyzed reaction from pH 5 to 7, and an uncatalyzed or water-catalyzed reaction of the protonated species. The pK_{app} is 3.4, which is close to the measured pK_a of the amine group conjugate acid (3.7 at 30 °C). The second-order rate constant k_{OH} for I is 10^2 larger than that for OH^--catalyzed hydrolysis of methyl phenylacetate.[19,20] Therefore, the reaction of I represents OH^- enhancement of nucleophilic attack by the neighboring amine group similar to the OH^--catalyzed cyclization of methyl 2-(aminomethyl)benzoate,[15] although k_{OH} is 10^3-fold less with I.

The pH-log k_0 profile for the cyclization of the corresponding trifluoroethyl ester (II) is similar in shape to that of I, although the OH^--catalyzed reaction and the reaction of the protonated species of II are enhanced to such an extent that a pH-independent water reaction is restricted to the pH range 6-7.5. The profile at low pH is bell shaped, the downward bend indicating a change in rate-determining step. Consequently, an intermediate is formed in the reaction that is most likely a tetrahedral addition product.

A change in rate-limiting step with changing pH has been found in bimolecular aminolysis of esters with aliphatic alcohol leaving groups.[13,14] It was proposed[13] that formation of a tetrahedral intermediate is rate determining at high pH and breakdown is rate determining at lower pH. It was later suggested[14] that attack of neutral amine produces a zwitterion intermediate (eq 3). The


$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}OR'} + \mathrm{R''NH_2} \rightleftharpoons \mathrm{R{-}\overset{O^-}{\underset{H_2\overset{+}{N}R''}{C}}{-}OR'} \qquad (3)$$

rate-determining step at high pH was then considered to be a proton switch in the water-catalyzed reaction, giving a neutral tetrahedral intermediate, or proton abstraction from the zwitterion in the general base catalyzed reactions (eq 4). Such a rate-determining proton transfer should lead to a Brønsted β of 0 or 1.0, depending on whether the proton transfer is thermodynamically favorable or unfavorable.[21]


$$\mathrm{R{-}\overset{O^-}{\underset{H_2\overset{+}{N}R''}{C}}{-}OR'} + \mathrm{B} \rightleftharpoons \mathrm{R{-}\overset{O^-}{\underset{HNR''}{C}}{-}OR'} + \mathrm{BH^+} \qquad (4)$$

In intramolecular aminolysis reactions the rate-determining step has generally been found to be breakdown of a tetrahedral intermediate.[2,3,15,18] General base catalyzed reactions of 2-substituted benzoate esters are characterized by Brønsted β coefficients of 1.0.[6,15,18] The Brønsted plots are linear through the expected pK_a of a zwitterion. Thus, the rate-determining proton transfer is from a species of higher pK_a than the zwitterion. The reaction must involve proton abstraction from a neutral tetrahedral intermediate or a kinetic equivalent; i.e., formation of the tetrahedral intermediate is a preequilibrium process. In the intramolecular reactions of phenyl esters of γ-(4-imidazolyl)butyric acid, the equilibrium constant for intermediate formation is sufficiently large (greater than unity) that the apparent pK_a obtained kinetically is a composite constant.[3]

The decomposition of the tetrahedral intermediate into products is also very likely rate limiting in the intramolecular reactions of I and II at pH >4. The small β value for reaction of II (0.2) would be near that expected for proton abstraction from a zwitterion.[14] However, in bimolecular reactions the rate constants for OH^--catalyzed aminolysis were less than 10^2 larger than those for general base catalysis,[14] as would be expected in thermodynamically favorable proton-transfer reactions, whereas the corresponding ratio with II is 10^4 when the general base has a pK_a less than 8. Also, the β of 0.5 in cyclization of I indicates that the reactions are concerted, which is not in accord with proton transfer from a zwitterion. There is no reason to suspect that the rate-determining steps are not the same with I and II in view of the reasonably similar pH-rate constant profiles. The curved plots of k_{obsd} vs. total buffer for cyclization of I at pH less than 7 (Figure 2) show that the rate-determining step is changing as buffer concentration is increased, from one with a large dependence on buffer to one with little or no dependence on buffer concentration. Thus, it is again established that a kinetically important intermediate is being formed.[22] If the reaction of II at pH < 4 were

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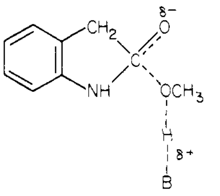
(19) Methyl phenylacetate has $k_{OH} = 2.97 \times 10^{-3}$ M^{-1} s^{-1} at 24.9 °C in 85% aqueous methanol. Acton, N.; Berliner, E. *J. Am. Chem. Soc.* **1964**, *86*, 3312.

(20) Extrapolation of second-order rate constants obtained in aqueous ethanol solutions at 24.8 °C to zero ethanol (Watkinson, J. G., Watson, W.; Yates, B. L. *J. Chem. Soc.* **1963**, 5437).

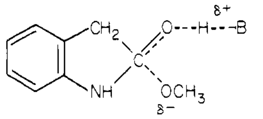
(21) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

considered to be OH^--catalyzed breakdown of an intermediate, the second-order rate constant would be 5×10^7 M^{-1} s^{-1}. This rate constant would necessarily be larger in the reaction of I (approaching diffusion control), since such a reaction is not observed even at pH 1. A larger rate constant for I than II in breakdown of the intermediate is, of course, quite unlikely. The rate-determining step will change when the rate of breakdown of the tetrahedral intermediate to products becomes greater than that for reversion to reactants. Thus, it is probable that the reaction at pH > 4 with both I and II and at low buffer concentration in the case of I involves breakdown of the tetrahedral intermediates;[23] the reaction of II at pH < 4 must then represent rate-determining formation of the intermediate (limited by free amine). Considering the pK_a values of the leaving group alcohols, 15.5 and 12.4,[27] the influence of the leaving group in the OH^--catalyzed reaction (k_{OH} for I and II differ by a factor of 60 at 30 °C) is consistent with significant, but far from complete, C–O bond breaking in the transition state.[28]

The linear Brønsted plots of Figure 3 for general base catalysis, with slopes β of 0.5 and 0.2, must reflect a rate-determining step involving proton transfer which is concerted with bond breaking in the cyclization of both I and II. Since breakdown of a tetrahedral intermediate must be rate determining in reactions of the neutral species, the most likely mechanisms involve proton transfer (III and IV) to or from the intermediate. These mechanisms are kinetically equivalent. However, the fact that the Brønsted coefficient β decreases greatly as the leaving group is improved from methoxide ion to trifluoroethoxide[27] shows that the mechanism is IV; i.e., general base catalysis involves proton transfer from a neutral tetrahedral intermediate. This will be an effective mechanism for breakdown of the tetrahedral intermediate in cases where the pK_a of the intermediate is high and/or the point for apparent OH^- catalysis lies below the Brønsted plot for general base catalysis.[30] As the leaving group becomes better, less proton transfer is required to attain the transition state, and as a consequence, β decreases. The kinetic equivalent III would demand that α for general acid catalysis would increase as the leaving group is improved ($\alpha = 1 - \beta$), which is not chemically reasonable. If the leaving group could be improved beyond trifluoroethyl, i.e., to phenyl, it would be predicted that β would decrease still further and might approximate zero. Buffer catalysis might not then be observed, depending on the fit of H_2O to the Brønsted line. This may be the case in certain intramolecular aminolysis reactions where the leaving group is good,[3,31,32] although with tertiary amine nucleophiles product must be formed via breakdown of the zwitterionic intermediate.[4,32] The point for H_2O ($k_0'/55.5$ M) fits reasonably well on the Brønsted plot for general base catalysis in cyclization of I, lying only slightly above the line. Therefore, it is quite probable that the mechanisms are the same with H_2O and the general bases in these reactions.

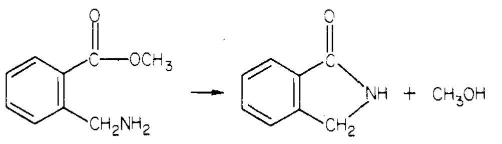


III

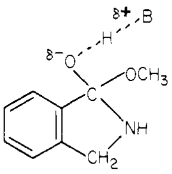


IV

The cyclization of methyl 2-(aminomethyl)benzoate (V) to phthalimidine (eq 5) gives rise to a pH–log (rate constant) profile that is linear with a slope of 1.0 at pH values greater than 8.6 and 2.0 at lower pH.[15] The inflection point at pH 8.6 must correspond with the pK_a of the neighboring amine group. Thus, the reaction involves apparent hydroxide ion catalysis at all pH values. When the leaving group is improved from methoxide to trifluoroethoxide, general base catalysis still gives a large β coefficient (0.7), but the pH–log (rate constant) profile is now linear with a slope of 1.0 at all pH values, i.e., both above and below the pK_a of the neighboring amine group.[33] Similar results were obtained when the pK_a of the nucleophile was reduced to 6.3 with a neighboring imidazolyl group in reactions of the trifluoroethyl, phenyl, and *n*-propyl thiol esters.[6,18] It is clear that the reactions of the 2-(aminomethyl)benzoate derivatives and I and II are different.



V (5)



VI

The large difference in the rate constants for apparent OH^- catalysis in cyclization of I and methyl 2-(aminomethyl)benzoate (>10^3) must be due in large part to a greater equilibrium concentration of the tetrahedral intermediate in the latter case resulting from the much higher pK_a of the neighboring amine group. The stepwise nature of the general base catalyzed reaction of the benzoate ester (mechanism VI) in comparison with the concerted reaction of I (mechanism IV) is possibly influenced by the pK_a value for the neutral tetrahedral intermediate from V, although in view of the completely linear Brønsted plot, this pK_a must be

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(22) Bender, M. L. "Mechanisms of Homogeneous Catalysis from Protons to Proteins"; Wiley-Interscience: New York, 1971; p 115.

(23) A concerted E2 elimination involving proton abstraction from the methylene group would not reasonably be expected in reactions of I and II in view of the poor leaving groups and the lack of strong electron withdrawal. Generation of the anion of ethyl substituted phenylacetates in highly basic media had no apparent effect on the rate of alkaline hydrolysis.[24] Malonate and acetoacetate esters[25] and carbamate esters[26] with very good phenolic leaving groups will undergo elimination, but only via an anionic species.

(24) Norman, R. O. C.; Ralph, P. D. *J. Chem. Soc.* **1963**, 5431.

(25) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993, 3003. Pratt, R. F.; Bruice, T. C. *Ibid.* **1970**, *92*, 5956.

(26) Bender, M. L.; Homer, R. B. *J. Org. Chem.* **1965**, *30*, 3975. Williams, A. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 808. Hutchins, J. E. C.; Fife, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 3786.

(27) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

(28) If the OH^--catalyzed reactions of I and II were considered to involve abstraction of a proton from a zwitterion intermediate, then since the reactions would be diffusion controlled and thermodynamically favorable ($k = 10^{10}$ M^{-1} s^{-1}), the equilibrium constant for cyclization of I to the zwitterion would be 1.4×10^{-9} while that for cyclization of II would be 1.7×10^{-8}. Employing these values the rate constant could only be 10^4 s^{-1} for the proton switch from the zwitterion in the water reaction of I (50 °C) and only 4×10^3 s^{-1} (30 °C) in reaction of II. These values are much too small for such a reaction; the rate constant for the proton switch would reasonably be expected to be 10^7–10^8 s^{-1}.[14,29]

(29) Grunwald, E.; Jumper, C. F.; Meiboom, S. *J. Am. Chem. Soc.* **1963**, *85*, 522. Luz, Z.; Meiboom, S. *Ibid.* **1963**, *85*, 3923.

(30) Significant buffer catalysis of this type may be seen when k_B (B) is comparable to or greater than k_3K_3/a_H, where K_3 is the dissociation constant of the neutral tetrahedral intermediate and k_3 is the rate constant for breakdown of the anionic intermediate. This is clearly the case with the buffers employed at pH <10. When the Brønsted β is less than 1.0, the percent of catalysis will become greater for constant base concentrations as pH is lowered, since k_3K_3/a_H will decline by a factor of 10 for every pH unit while that will not be the case for k_B (B). This situation will hold until the spontaneous reaction becomes pH independent. Thus, with II the point for k_{OH} on the Brønsted plot lies slightly above the line, but with a β of only 0.2 buffer catalysis is pronounced with the bases employed.

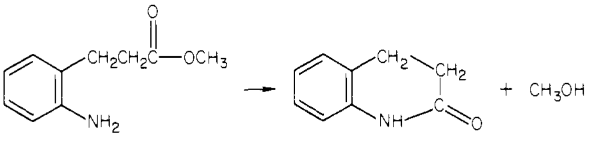
(31) Bruice, T. C. *J. Am. Chem. Soc.* **1959**, *81*, 5444.

(32) Fife, T. H.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4194.

(33) Fife, T. H.; Chauffe, L., unpublished data.

higher than 11. An important factor in these reactions must also be the relative ease of C–O bond breaking.

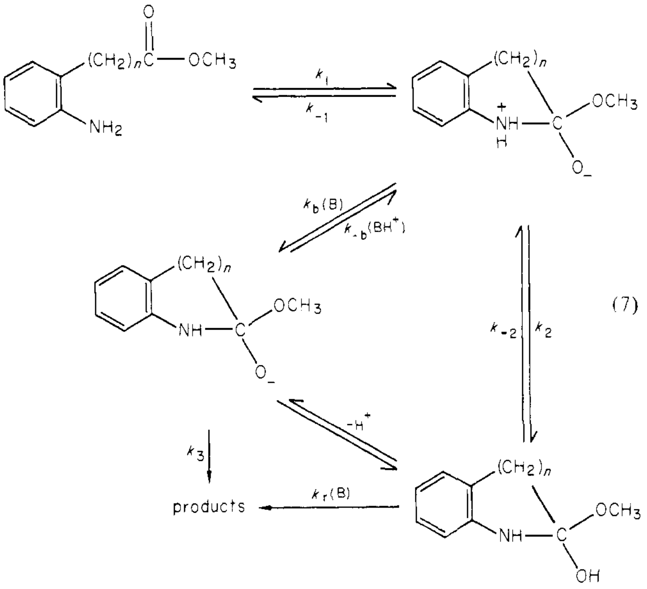
The cyclization of methyl 3-(2-aminophenyl)propionate (VII) (eq 6) is characterized by a pH–rate constant profile with pH-



VII

(6)

independent regions below pH 4 and above pH 6.[16] The difference between the pH-independent rate constants is only a factor of 3. Thus, the profile is quite different from that of methyl 2-(aminomethyl)benzoate or esters I and II. The reaction at low pH (similar to that of I) was considered to involve acid-catalyzed breakdown of a neutral tetrahedral intermediate. It was suggested that the pH-independent reaction at pH >6 represents a rate-determining proton switch, perhaps mediated by water molecules, similar to that postulated in bimolecular aminolysis reactions of aliphatic esters.[14] The general scheme, which could also be applicable to cyclization of I, is given in eq 7. General acid catalysis was found at low pH (α = 0.41), and general base catalysis was observed at higher pH that appeared not to be greatly affected by the pK_a of the catalyst. A striking difference in the cyclization reactions of I and methyl 3-(2-aminophenyl)propionate is the rapidity of the pH-independent reactions of the latter compound. The rate constants of the pH-independent reactions are 6×10^{-4} and 2×10^{-4} s^{-1} at 39 °C as compared with 1.8×10^{-4} and 1.1×10^{-5} s^{-1} for I at 50 °C. Thus, at pH 5–7, I cyclizes more than 10-fold more slowly than VII with an 11 °C difference in temperature. Rate constants for the two esters only become comparable at pH 8. Intramolecular reactions of phenolic esters proceed more rapidly through 5-membered-ring transition states,[4,32,34] and it might be anticipated that this would also be the case in reactions of aliphatic esters. However, the normal kinetic advantage of an intramolecular reaction via a 5-membered ring vs. a 6-membered ring[32,34] has been lost in the pH-independent reactions of I. On the other hand, the apparent OH$^-$-catalyzed reaction of I is at least 100-fold more favorable than that of VII.



(7)

It is clear that the mechanisms and/or rate-determining steps for cyclization of I and methyl 3-(2-aminophenyl)propionate are different even though the entering and leaving groups are the same and the pK_a values of the nucleophiles are quite similar. Rate-determining breakdown of a tetrahedral intermediate in one or both cases could lead to the differences observed in the rate constants. A difference would exist in the inductive electron withdrawal from the tetrahedral intermediate by the phenyl group, since there is one less methylene group interposed in the intermediate formed from I. This would make C–O bond breaking more difficult in breakdown of the intermediate to products in the case of I, which could in turn bring about a difference in rate-determining step in the reactions of the two esters. In cyclization of I either the proton switch occurs rapidly or formation of the neutral tetrahedral intermediate is totally concerted, without formation of a zwitterion.

If the proton switch (k_2 of eq 7) is rate determining in cyclization of VII, then k_0 will be given by eq 8 where K_1 is the

$$k_0 = k_2 K_1 \tag{8}$$

equilibrium constant for the formation of the zwitterionic intermediate. However, if breakdown of the neutral tetrahedral intermediate of I is rate determining, then k_0 at pH >5 for the pH-independent reaction is given by eq 9; k_0'' is the rate constant

$$k_0 = \frac{k_0'' K_1 K_2}{1 + K_1 + K_1 K_2} \tag{9}$$

for water catalyzed decomposition of the tetrahedral intermediate. If the equilibrium for nucleophilic attack (K_1) is unfavorable, i.e., $K_1 K_2 < 1$, eq 10 is obtained. Likewise in the apparent OH$^-$

$$k_0 = k_0'' K_1 K_2 \tag{10}$$

catalyzed reaction k_0 is given by eq 11 at $a_H > K_3$. In eq 9–11

$$k_0 = \frac{k_3 K_1 K_2 K_3}{a_H} \tag{11}$$

K_2 is the equilibrium constant for production of the neutral tetrahedral intermediate from the zwitterion, and K_3 is the dissociation constant of the neutral tetrahedral intermediate. Thus, if the scheme of eq 7 is applicable to both I and VII, then they differ only in that the proton-transfer steps that are rate determining in cyclization of VII are preequilibrium steps in cyclization of I. Kirby et al.[16] calculated with VII that K_1 was 10^{-11}, and therefore k_2 would be 2×10^7 s^{-1}. From the values estimated for the dissociation constant of the zwitterion (pK_B = 5.6) and the neutral tetrahedral intermediate (pK_3 = 12.3),[16] the equilibrium constant $K_2 = K_B/K_3$ can be estimated as 5×10^6, from which the value of k_{-2} can be calculated to be ~4 s^{-1}. The rate constant for the proton switch (k_2) could only be rate determining in reactions of VII if k_0'' and k_r(B) are greater than k_{-2}. A small relative decrease in k_0'' or k_r or increase in k_{-2} for cyclization of I would lead to rate-determining breakdown of the tetrahedral intermediate. From the differences in k_{obsd} for I and VII, it would appear that these compounds are near the borderline for a change in rate-limiting step. This is, of course, strongly supported by the downward curvature observed in plots of k_{obsd} vs. buffer concentration below pH 7 in the reaction of I.

Conclusions

When the pK_a of a neighboring amine group is high and the steric situation is very favorable for intramolecular nucleophilic attack, diffusion-controlled proton-transfer reactions in which a zwitterionic intermediate is stabilized would not necessarily be rate determining.[35] A step further along in the reaction sequence can then be rate limiting, e.g., breakdown of a neutral tetrahedral intermediate. This is the case in cyclization reactions of 2-substituted benzoate esters with which the tetrahedral intermediate is very likely at relatively high equilibrium concentration.[6,15,18] However, when the pK_a of the nucleophile is low and the steric situation is less favorable (6-membered ring), then the equilibrium

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(34) Bruice, T. C.; Pandit, U. K. J. Am. Chem. Soc. 1960, 82, 5858.

(35) Diffusion-controlled proton-transfer reactions that are thermodynamically favorable would not have an appreciable activation energy (ref 2b, pp 207–208). Therefore, the peak on a reaction coordinate diagram for proton transfer to or from a zwitterion should not be the highest point unless the preceding equilibrium (nucleophilic attack) is very unfavorable.

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concentration of zwitterionic intermediate may be small and a proton transfer involving this intermediate can be rate determining, as in the case of methyl 3-(2-aminophenyl)propionate;[16] i.e., the reaction will be similar to a bimolecular reaction rather than the intramolecular reaction of V. With esters I and II nucleophilic attack involves formation of a 5-membered ring so that the reactions are sterically more favorable than those of VII. Electron withdrawal from the carbonyl of II will also enhance nucleophilic attack. While the pK_a of the nucleophile is low, breakdown of the tetrahedral intermediate formed from I and II is rate determining, although I must lie close to the borderline for a change in rate-determining step.

Acknowledgment. This work was supported by research grants from the National Institutes of Health.

Registry No. I, 35613-44-6; I HCl, 49851-36-7; II, 82571-36-6; II HCl, 82571-38-8; V, 61088-45-7; 2-oxindole, 59-48-3; methyl phenylacetate, 101-41-7; (*o*-nitrophenyl)acetatic acid, 3140-52-1; methyl (*o*-nitrophenyl)acetate, 30095-98-8; 2,2,2-trifluoroethyl (*o*-nitrophenyl)-acetate, 82571-37-7; 2,2,2-trifluoroethanol, 75-89-8; methanol, 67-56-1; trimethylamine, 75-50-3; 2-methoxyethylamine, 109-85-3; Tris, 77-86-1; *N*-ethylmorpholine, 100-74-3; imidazole, 288-32-4; carbonate, 463-79-6; morpholine, 110-91-8; 2-(*N*-morpholino)ethanesulfonic acid, 4432-31-9; cacodylate, 75-60-5; malonate, 141-82-2; acetate, 64-19-7; glycolate, 79-14-1.

Optical Activity of β,γ-Enones: A Quantitative Chirality Rule

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Abstract: Generally the relation between molecular geometry and circular dichroism (CD) of an electronic transition is made via the rotational strength R, which contains the scalar product of the magnetic ($\vec{\mu}$) and electric ($\vec{r}$) dipole moment in that transition. It is assumed that with β,γ-enones the optical properties of the $n \rightarrow \pi^*$ transition derive from a perturbation of the local $n_{CO} \rightarrow \pi^*_{CO}$ transition in the carbonyl chromophore by the remaining part of the molecule. Since the $n_{CO} \rightarrow \pi^*_{CO}$ transition is strongly magnetic dipole allowed (along the C=O bond, z direction) but electric dipole forbidden, the rotational strength in β,γ-enones probes the z component of the admixed extraneous transition moment $\vec{r}$, whose magnitude is measured by the square root of the dipole strength D. It appears advantageous to express the optical activity as $R/(|\vec{\mu}|\cdot D^{1/2}) = \cos\theta$ since then it no longer contains the magnitude of $\vec{r}$ and is a direct measure of the angle θ between the C=O bond and the direction of the admixed electric dipole transition moment. For a series of rigid β,γ-enones, a surprisingly high correlation is found between $\cos\theta$ and the cosine of the angle ξ between the C=O bond and the C_γ=C_β bond: to a good approximation, $n \rightarrow \pi^*$ optical activity and enone structure are quantitatively related by the equation $\cos\theta = -(\text{sign } xy)\cdot(\cos\xi)$, where x and y are the coordinates of the olefinic C_β atom in the ketone reference frame and xy is positive in the upper-right quadrant. This transparant relationship indicates that the unique radiative properties of the $^1n\pi^*$ state of β,γ-enones derive from a small ethylenic $\pi_{CC}\pi^*_{CC}$ contamination in the carbonyl $n_{CO}\pi^*_{CO}$ state, which might be electrostatically brought in. Within limits, the chirality rule offers a quantitative tool in the study of β,γ-enone stereochemistry, as is illustrated for some examples.

In many respects $n \rightarrow \pi^*$ transition in β,γ-enones is an intriguing subject. Whereas position, width, and shape of the absorption band closely resemble those of the $n \rightarrow \pi^*$ band in saturated ketones, its intensity is often enhanced by more than an order of magnitude. With chiral enones, this increased dipole strength is sometimes, but not invariably, accompanied by enhanced circular dichroism (CD).[1] From the theoretical point of view, the situation with β,γ-enones is at the same time more simple and more complex than with saturated ketones. On the one hand, the large enhancement of intensity and optical activity in the $n \rightarrow \pi^*$ transition points to the ethylenic group as major perturber, suggesting a description in terms of a two-chromophore model. On the other hand, the ethylenic π orbitals (π_{CC}, π^*_{CC}) overlap those of the homoconjugated carbonyl bond (n_{CO}, π^*_{CO}), which renders the use of a simple electrostatic model admixing $\pi_{CC} \rightarrow \pi^*_{CC}$ character to the $n_{CO} \rightarrow \pi^*_{CO}$ transition questionable. Indeed, many investigators have invoked overlap effects as the main source of the enhanced optical activity[2-4] and absorption intensity.[5,6]

With respect to structure–CD relationship, the work of Moscowitz et al.[3] is of prime importance. These authors put forward a rule that for β,γ-enones of a specified (C=O)—(C=C) geometry (class A in their notation) allows the prediction of the sign of the longest wavelength Cotton effect: Due to n_{CO}–π_{CC} overlap the contribution to the $n \rightarrow \pi^*$ Cotton effect of a C=C group, situated in a rear octant, is consignate with the ketone octant rule, and for class A geometry, it is so large that it solely determines the sign of the CD (generalized octant rule, GOR). In the theoretical formalism underlying the GOR, the $n \rightarrow \pi^*$ electric-dipole transition moment was to result from both $\pi_{CC} \rightarrow \pi^*_{CC}$ and charge-transfer transitions, but the latter were judged to be relatively unimportant.[3] Later this was substantiated by MO–CI calculations[7] that showed that in the $n \rightarrow \pi^*$ transition of bicyclo[2.2.2]octenone the calculated dipole and rotational strengths derive exclusively from a $\pi_{CC}\pi^*_{CC}$ contamination in the $n_{CO}\pi^*_{CO}$ state which is electrostatically brought in.

Recently a major contribution in the field was given by Kuritani et al.[8] To explain the Cotton effect observed with some β,γ-enones, these authors explicitly took the view that the effects originate in the electrostatic admixture of $\pi_{CC}\pi^*_{CC}$ character in the $n\pi^*$ state. On this basis they proposed a new sector rule, complementing the GOR, claimed to predict correctly the sign of the $n \rightarrow \pi^*$ CD of β,γ-enones.[8]

Our interest in the subject was prompted when we observed for β,γ-enones large differences between the optical activities in

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