Intramolecular Nucleophilic Attack by Imidazole on Aliphatic and Phenolic Esters of *o*-(2-Imidazoyl)benzoic Acid. Relationship of Anion and Neutral Species Attack

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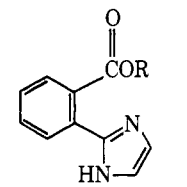
Abstract: The rate constants for hydrolysis of a series of esters of *o*-(2-imidazoyl)benzoic acid have been measured as a function of pH in H_2O at 30 and 50 °C. The pH–rate constant profile for the methyl ester shows hydroxide ion catalysis at pH values >8 with a second-order rate constant k_{OH} that is similar to that of methyl benzoate. Thus, the neighboring imidazoyl group does not participate in the hydrolysis reaction at high pH. At pH 6–8 there is a pH-independent reaction which is 3.6 times slower in D_2O than in H_2O. The pH–log rate constant profile for the trifluoroethyl ester is a straight line with a slope of 1.0 in the pH range 4–12 even though the pK_a of the imidazoyl group is 6.3. The value of k_{OH} is 10^3 greater than that for hydrolysis of trifluoroethyl benzoate. Hydrolysis of the phenyl ester occurs in two observable steps. The first step is cyclization accompanied by phenol release. The second step is hydrolysis of the tricyclic acylimidazole intermediate. The first step has a linear pH–rate constant profile with slope of 1.0 in the pH range 4–10 ($k_{OH} = 1.2 \times 10^5$ M^{-1} s^{-1} at 30 °C). At a pH corresponding to pK_1 of the imidazoyl group, the nucleophilic reactions of the neutral and anionic species contribute equally to k_{obsd}. Thus, at pK_1 there is no kinetic advantage from reaction of the anionic species of the nucleophile rather than the neutral species, formation of a tetrahedral intermediate being an equilibrium process. The cyclization step is catalyzed by general bases with a Brønsted β of 1.0, indicating that a proton-transfer step in the thermodynamically unfavorable direction is rate determining. This step is most likely proton transfer to or from a tetrahedral intermediate.

Histidine-57 is located at the active site of α-chymotrypsin and presumably is directly involved in both the acylation and deacylation steps.[2,3] Therefore, an understanding of the manner in which imidazole can participate in ester and amide hydrolysis is of great importance in attempts to understand the mechanism of action of the enzyme. The imidazole ring of substituted phenyl γ-(4-imidazoyl)butyrates functions as an intramolecular nucleophile,[4] but does not participate in the hydrolysis of the corresponding methyl ester. In fact, imidazole has been found to act only as a general base when the leaving group is poor ($pK_a > 12.5$).[5,6] Intramolecular general base catalysis by imidazole takes place in the hydrolysis of 4-(2′-acetoxyphenyl)imidazole.[7]

Intramolecular nucleophilic attack by hydroxymethyl,[8] aminomethyl,[9] and mercaptomethyl[10] nucleophiles has been studied in the cyclization of 2-substituted benzoate esters of aliphatic alcohols. These reactions are catalyzed by hydroxide ion with second-order rate constants that are closely similar for all compounds in the series. Thus, in these examples where the steric situation is reasonably constant, the rate constants are nearly independent of the basicity of the attacking nucleophile. The second-order rate constants for apparent hydroxide ion catalysis are $\sim 10^5$ larger than for hydroxide ion catalyzed hydrolysis of the corresponding unsubstituted benzoate esters. The pK_a of the aminomethyl group in this series is 8.6 which is only ~ 2 pK_a units higher than might be expected for a neighboring imidazole group. Thus, in view of the small dependence of the rate constants for cyclization on basicity of the nucleophile, it is possible that a neighboring imidazole might in this series, where it is restricted in close proximity to the reaction center, act as a nucleophile toward an aliphatic ester. In order to compare the efficiency of imidazole with that of amine, alcohol, and sulfhydryl nucleophiles in intramolecular nucleophilic displacement of poor leaving groups, we have studied the hydrolysis of the methyl, trifluoroethyl, and phenyl esters I, II, and III where the pK_a of the leaving group varies from 10 to 16. Unlike the other nucleophiles, an imidazole group offers the opportunity of observing intramolecular reactions in which the nucleophile can exist in the protonated, neutral, or anionic form at accessible pH values, so that the relative reactivities of these species may be determined.



I, R = $-CH_3$
II, R = $-CH_2CF_3$
III, R = 

Experimental Section

Materials. 2-Carboxybenzaldehyde and glyoxal were obtained from Aldrich. 2,2,2-Trifluoroethyl benzoate was prepared by the method of Sam and Bej.[11] Buffers were prepared from reagent grade materials. Amine buffers were freshly distilled or recrystallized prior to use. D_2O (99.8 at. % D) was purchased from Bio-Rad Laboratories and used without further purification.

***o*-(2-Imidazoyl)benzoic acid** was prepared by a method based on that of Radziszewski.[12] 2-Carboxybenzaldehyde (0.194 mol) was added to 150 mL of concentrated aqueous ammonia. Glyoxal, as a 40% solution in water, was added dropwise over 2 h at room temperature. The mixture was heated at reflux for 3 h and was allowed to stand over night. After filtration, the filtrate was acidified to form a thick precipitate which was collected and washed twice with dilute acid and with successive 50-mL portions of ethanol until the precipitate was nearly colorless. The precipitate was suspended in ethanol, and HCl gas was bubbled in until most of the precipitate had dissolved. After filtration, the solvent was removed from the filtrate by rotary evaporation leaving a white solid. Recrystallization from ethanol and ethyl acetate gave colorless crystals, mp 264–267 °C.

***N*,2-(2′-Benzoyl)imidazole** (IV) was prepared by heating *o*-(2-imidazoyl)benzoic acid (10 mmol) and 30 mL of thionyl chloride at reflux overnight. The excess thionyl chloride was removed by distillation leaving a yellow solid, the hydrochloride salt of the acylimidazole. After the solid was washed several times with benzene to remove the last traces of thionyl chloride, it was suspended in dry tetrahydrofuran. To this suspension was added 1.2 equiv of triethylamine,

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and the slurry was allowed to stir overnight at room temperature. The suspension was then filtered, and the solvent was removed from the filtrate by rotary evaporation. The bright yellow solid was taken up in dry benzene and filtered to remove any material which did not dissolve. Upon removal of the benzene on a rotary evaporator, a solid residue (IV) was obtained. For analytical purposes the solid was sublimed to give yellow crystals, mp 239–240 °C. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.14; H, 3.76; N, 16.47.

The hydrochloride salts of the esters of *o*-(2-imidazoyl)benzoic acid were prepared by heating at reflux 2.0 g of cyclic acylimidazole IV with the appropriate alcohol or a concentrated solution of the alcohol in tetrahydrofuran for 6 h. The solvent and excess alcohol was removed by distillation under high vacuum, and the resulting solid was taken up in chloroform. After filtration, HCl gas was bubbled into the filtrate for 5 min. The solvent was removed from the brown solution by rotary evaporation, and the solid residue was washed with 50-mL portions of hexane and ether until the washes were colorless. Further purification was effected by taking up the solid in a minimum amount of dry chloroform and adding it to five times its volume of dry ether. The solvent was decanted from the white precipitate which formed. The hydrochloride salts were recrystallized from methanol–ethyl acetate or chloroform–ether. The methyl ester I hydrochloride had mp 198–200 °C. Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.35; H, 4.65; N, 11.74. Found: C, 55.55; H, 4.72; N, 11.67. The 2,2,2-trifluoro ester II hydrochloride had mp 163–164 °C. Anal. Calcd for $C_{12}H_{10}ClF_3N_2O_2$: C, 46.99; H, 3.29; N, 9.13. Found: C, 46.82; H, 3.56; N, 9.42. The phenyl ester III (mp 119–121 °C) was highly unstable in air. Therefore, that compound was not submitted for analysis. However, the IR, UV, and NMR spectra were consistent with the assigned structure. The NMR spectrum (Varian Model EM-360A) was taken in Me_2SO-d_6 with Me_4Si as an internal standard (δ ppm). It had three distinct absorption patterns in the aromatic region: a broad multiplet at δ 7.38, a complex pattern between 7.60 and 7.85, and a third complex pattern between 8.10 and 8.35, in the ratio of 3:6:2. Another broad singlet at δ 12.0, assigned to the imidazolium nitrogen protons, was in a ratio of 2/11 to the aromatic protons. The IR (KBr) showed a strong absorption at 5.75 (ester C=O), two strong absorptions at 7.98 and 8.44, and the distinctive W-shaped absorption pattern at 3.50 and 3.68 μ. The UV maximum, in acetonitrile, was at 262 nm. The reasonably sharp melting point, taken in a sealed capillary tube, indicates the purity of the material.

Kinetic Methods. The rates of hydrolysis of the esters I, II, and III at 30 and 50 ± 0.1 °C were determined spectrophotometrically with either a Beckman 25 or a Gilford 2000 recording spectrophotometer. Identical rates were obtained by following the absorbance increase at 265–270 or the absorbance decrease at 305 nm. Aliquots (10–50 μL) of the substrate dissolved in anhydrous acetonitrile were injected into 2-mL solutions of the buffer (μ = 0.5 M with KCl). The rates of hydrolysis of cyclic acylimidazole IV were similarly obtained at 30 ± 0.1 °C by following an absorbance decrease at 240 or an absorbance increase at 270 nm. The UV spectra of the products of the hydrolyses were identical with those of *o*-(2-imidazoyl)benzoic acid and the appropriate alcohol or phenol.

In determination of rate constants for hydrolysis of the trifluoroethyl ester at pH values above 8.5, a Durrum D110 stopped-flow apparatus was utilized. The substrate, dissolved in 10^{-3} M HCl, was placed in one drive syringe and the appropriate buffer was placed in the other. The syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 50.0 ± 0.1 °C. The absorbance changes after mixing at either 270 or 305 nm were recorded on a Hewlett-Packard Model 1207B storage oscilloscope. For each buffer four to six runs were tabulated. Infinity points were stable. Rate constants for hydrolysis of the phenyl ester III at pH values >7.0 were similarly determined at 30 ± 0.1 °C by following the absorbance changes at 270 nm.

Reaction solution pH values were measured with either a Radiometer Model 22 pH meter with a GK 2303C combination electrode or a Beckman Model 3500 pH meter with a combination electrode standardized against Mallinckrodt standard buffer solutions. The pH of buffer solutions was measured at the same temperature as the rate measurements. The pD was determined by using the glass electrode correction equation of Fife and Bruice.[13] Pseudo-first-order rate constants were calculated with an IBM 370-158 computer using a rigorous least-squares procedure.

Spectrophotometric pK_a Determinations. The pK_a of methyl *o*-(2-imidazoyl)benzoate at 50 °C and μ = 0.5 M was determined spectrophotometrically by measuring the absorbance at 270 nm of identical aliquots of the substrate in various buffers over the pH range of 4.12–8.98. The pK_a was found to be 6.08. However, the rates of hydrolysis at 50 °C of the trifluoroethyl ester II (μ = 0.5 M) were too rapid at pH values >7.75 to determine accurately the top portion of the titration curve. In that case equation

$$\mathrm{pH} = \mathrm{p}K_a + \log (A - A_a)/(A_b - A) \qquad (1)$$

where A is the absorbance at any pH, A_a is the absorbance of the protonated ester at pH values of 4.12 and less, and A_b is the absorbance of the neutral ester at pH values of 8.98 and greater, was rearranged to give

$$a_H(A_a - A) = K_aA - K_aA_b \qquad (2)$$

A value of 4.79×10^{-7} for K_a was thereby determined from the slope of a plot of $a_H(A_a - A)$ vs. A. The rate of cyclization of the phenyl ester III was much too fast to permit an accurate determination of the pK_a.

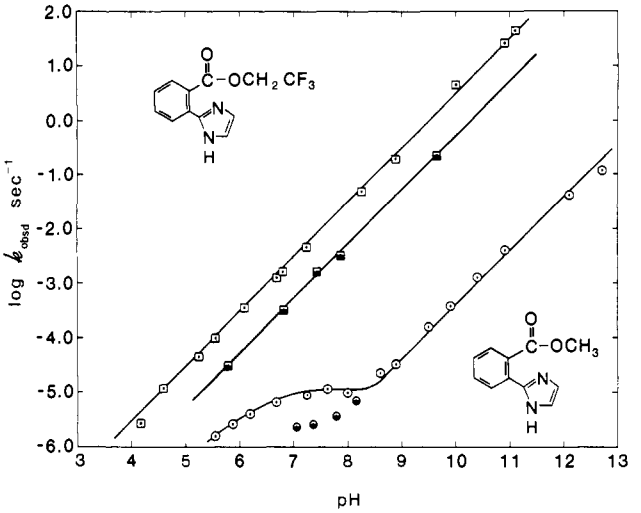


Figure 1. Plots of log k_{obsd} vs. pH or pD for hydrolysis of methyl *o*-(2-imidazoyl)benzoate (⊙) and trifluoroethyl *o*-(2-imidazoyl)benzoate at 50 °C and μ = 0.5 in H_2O (□) or D_2O (■).

Results

In Figure 1 is shown a plot of log k_{obsd} vs. pH or pD for hydrolysis of the methyl (I) and trifluoroethyl (II) esters of *o*-(2-imidazoyl)benzoic acid in H_2O at 50 °C (μ = 0.5 maintained with KCl). The profile for the methyl ester is linear with slope of 1.0 at pH values above 8.0. The second-order rate constant for hydroxide ion catalysis (k_{OH}) is 0.70 M^{-1} s^{-1}. At lower pH there is a plateau in the profile which is considerably less in D_2O than in H_2O (k_{H_2O}/k_{D_2O} = 3.6). The data give a good fit to

$$k_{obsd} = [k_{gb} + k_{OH}(OH^-)][K_1/(K_1 + a_H)] \qquad (3)$$

where k_{gb} is the rate constant for intramolecular general base catalysis by the neighboring imidazoyl group ($k_{gb} = 8.5 \times 10^{-6}$ s^{-1}) and K_1 is the dissociation constant of the conjugate acid of the imidazoyl group (pK_1 = 6.1). Buffer catalysis was not observed in half-neutralized methoxyethylamine buffers (0.1–1.0 M) at pH 8.93 or in half-neutralized imidazole buffers (0.1–1.0 M) at pH 6.67. The pH–log rate constant profile for the trifluoroethyl ester is linear with slope of 1.0 in the pH range 4–12 ($k_{OH} = 5.7 \times 10^3$ M^{-1} s^{-1}) even though the pK_1 of the neighboring imidazoyl group is 6.3. General base catalysis by buffer bases was not observed in morpholine buffers at pH 8.29 with total buffer concentrations in the range 0.05–1.0 M or in cacodylate buffers at pH 5.59 with total buffer concentrations in the range 0.02–0.50 M. The value of k_{obsd} is increased 12% in 1.0 M total imidazole buffer at pH

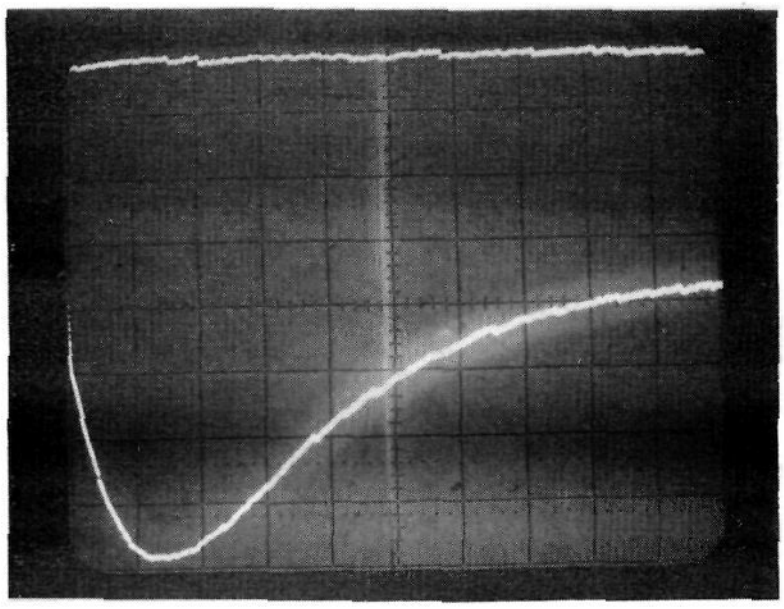


Figure 2. Oscilloscope trace at 270 nm for hydrolysis of phenyl *o*-(2-imidazoyl)benzoate in 0.5 M Tris buffer at 30 °C, pH 8.04, and $\mu = 0.5$. The time scale is 2 s/division.

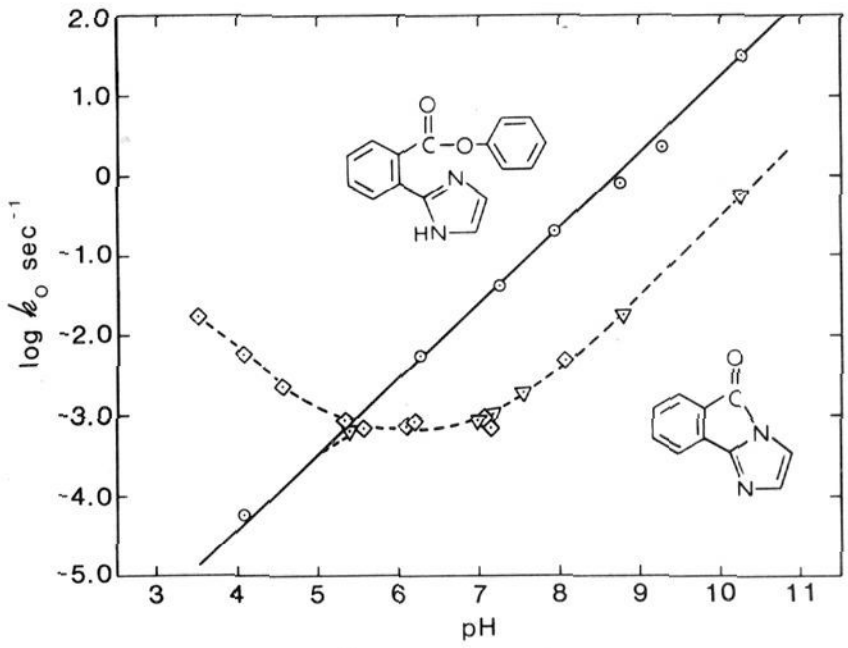


Figure 3. Plots of log k_0 vs. pH for hydrolysis of phenyl *o*-(2-imidazoyl)-benzoate, first step (⊙) and second step (▽), and acylimidazole (IV) (◈) at 30 °C and $\mu = 0.5$. Rate constants were obtained by extrapolation to zero buffer concentration.

Table I. Rate Constants for Hydrolysis of Esters of *o*-(2-Imidazoyl)benzoic Acid and IV at 30 and 50 °C ($\mu = 0.5$ with KCl)

Compd	T, °C	k_{OH}, M^{-1} s^{-1}	$k_{H_2O} \times 10^4$ s^{-1}	k_H, M^{-1} s^{-1}
I	50	0.70	0.085	
	30	0.152		
II	50	5.74×10^3		
	50 (D_2O)	6.31×10^3		
	30	1.92×10^3		
III	30	1.2×10^5 [a]		
	30	2.1×10^3 [b]		
IV	30	2.15×10^3	7.08	56.3

[a] First step (cyclization). [b] Second step (intermediate hydrolysis).

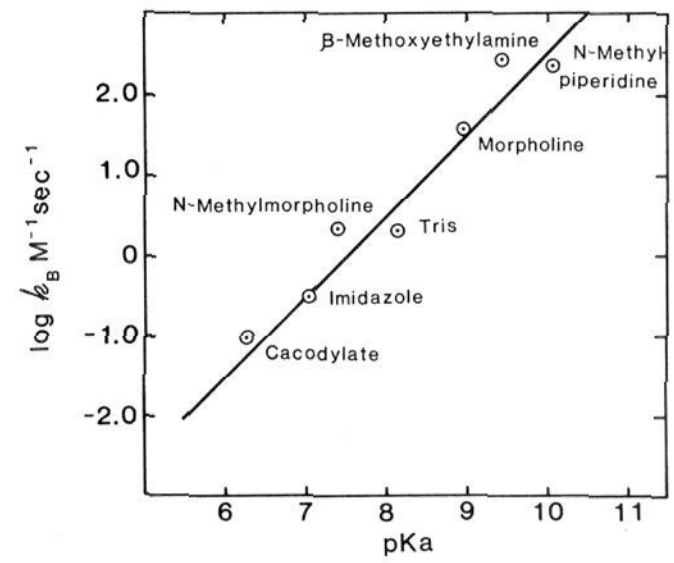


Figure 4. A Brønsted plot of log k_B for general base catalyzed cyclization of phenyl *o*-(2-imidazoyl)benzoate to IV vs. the pK_a of the conjugate acid of the base catalyst at 30 °C and $\mu = 0.5$. Statistical corrections do not make a significant difference in the slope (1.0).

7.27 in comparison with 0.10 M buffer and 5% in 0.5 M total *n*-butylamine buffer at pH 10.00 in comparison with 0.05 M total buffer.

Two discrete steps are observed in the hydrolysis of the phenyl ester III at 30 °C. In Figure 2 an oscilloscope trace is shown from a stopped-flow determination illustrating these steps. The pH–rate constant profiles for both steps are presented in Figure 3. Rate constants were obtained by extrapolation to zero buffer concentration. Also shown in Figure 3 is the pH–rate constant profile for hydrolysis of the acylimidazole intermediate (IV) in the reaction, which hydrolyzes with hydroxide ion, hydronium ion, water, and buffer catalysis as do other acylimidazoles.[14] Rate constants are given in Table I. The spectral characteristics of the observed intermediate are identical with those of IV (λ_{max} 240 nm). The pH–rate constant profile for the first step in the hydrolysis of III (cyclization to IV) is linear with slope of 1.0 in the pH range 5.5–10. The value of k_{OH} at 30 °C is 1.2×10^5 M^{-1} s^{-1}. The second step in the reaction has rate constants that are essentially identical with those obtained for hydrolysis of IV. At pH values <5.5 only one step can be observed in hydrolysis of III. From Figure 3 it is apparent that at low pH cyclization must be rate determining.

Buffer catalysis was observed in the cyclization of III. Plots (not shown) of k_{obsd} vs. total buffer concentration at three pH values for reactions carried out in *N*-methylmorpholine buffers showed that the base species of the buffer is catalytically active. Rate constants for these reactions (k_B) are given in Table II. Also given are the range of buffer concentrations employed and the percent increase in k_{obsd} at the highest buffer concentration compared with the value of k_{obsd} at zero buffer concentration. In calculating second-order rate constants, the average pH of each series of buffers was employed since the difference in pH within each series of buffers (0.02–0.04 pH units) is within the error of the pH meter readings (±0.02 pH units). Correction of individual rate constants for this pH difference did not yield significantly different results. A Brønsted plot of log k_B vs. the pK_a of the conjugate acid of the base is presented in Figure 4. The slope β is 1.0 ($r = 0.97$). In cacodylate and acetate buffers, general acid catalysis of the reaction of the neutral species, or the kinetically equivalent general base catalysis of the reaction of the protonated species, can also be detected. Rate constants k_{BH} are given in Table II.

The experimentally determined pseudo-first-order rate constants for II and the first step in hydrolysis of III (rate constants obtained by extrapolation to zero buffer) fit the theoretical linear plots of slope 1.0 expected from

$$k_0 = k_{OH}(K_w/a_H) \quad (4)$$

In order that the reaction at high pH involve nucleophilic attack by the neighboring group (shown in the case of III by observation of IV as an intermediate) and the kinetics follow eq 4, either the imidazole anion must be the nucleophile or a kinetically equivalent reaction must occur (neutral species +

Table II. Rate Constants for General Base Catalyzed Hydrolysis of Phenyl *o*-(2-Imidazoyl)benzoate and IV at 30 °C (μ = 0.5 M with KCl)

Compd	Base	pK_a[a]	Buffer concn, range of M	% catalysis[b]	k_B, M^{-1} s^{-1}	k_{BH}, M^{-1} s^{-1}
III[c]	*N*-Methylpiperidine	10.10	0.025–0.125	42	229.6	
	β-Methoxyethylamine	9.45	0.01–0.10	643	300.2	
	Morpholine	8.60	0.0125–0.125	424	41.6	
	Tris	8.15	0.025–0.50	171	2.03	
	N-Methylmorpholine	7.41	0.02–0.125	39[d]	1.62	
	Imidazole	7.05	0.01–0.10	43	0.32	
	Cacodylate	6.28	0.025–0.25	98[e]	0.10	1.10[f]
	Acetate	4.60				0.0007[f]
III[g]	*N*-Methylmorpholine	7.41			0.061	
	Imidazole	7.05			0.02	
	N-Methylimidazole	7.00			0.019	
	Cacodylate	6.28			0.034	0.09[h]
IV	Imidazole	7.05			0.021	
	N-Methylimidazole	7.00			0.019	
	Cacodylate	6.28			0.027	0.14[h]

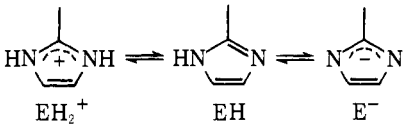
[a] Determined at the same temperature and ionic strength as the rate measurements. [b] [(k_{obsd} (at highest buffer concn) $-k_0$)/k_0] × 100. [c] First step (cyclization). [d] At ph 7.93. [e] At pH 7.25. [f] Calculated as general base catalysis of the reaction of the protonated species. [g] Second step (intermediate hydrolysis). [h] General acid catalysis.

$^-$OH). The reactions should then follow

$$k_0 = k_A[K_2K_1/(K_2K_1 + K_1a_H + a_H^2)] \quad (5)$$

where

$$K_1 = (EH)a_H/(EH_2^+) \text{ and } K_2 = (E^-)a_H/(EH)$$



EH_2^+ EH E^-

Equation 5 reduces to

$$k_0 = k_A[K_2K_1/(K_1a_H + a_H^2)] \quad (6)$$

in the neutral pH range since K_1 for II is 5×10^{-7} and K_2 is $\sim 10^{-13}$.[15] Equation 6 may be rearranged to

$$k_0 = (k_AK_2/a_H)[K_1/(K_1 + a_H)] \quad (7)$$

Since K_2 for the imidazole ring should be comparable with K_w for water,[15] the kinetics at pH values above pK_1 should follow eq 4. However, at $a_H > K_1$ eq 7 simplifies to

$$k_0 = k_AK_2K_1/a_H^2 \quad (8)$$

and the plot of log k_0 vs. pH will be linear with a slope of 2.0. Consequently, to account for the observed pH–rate constant profiles, there must be another term in the expression for k_0 which is important at pH values below pK_1 and which will allow the profile to be linear with slope of 1.0. A reaction of that type would be a nucleophilic reaction of the neutral species (EH), for which

$$k_0 = k_{Im}[K_1/(K_1 + a_H)] \quad (9)$$

would be applicable. Thus the equation for the nucleophilic reaction would then be

$$k_0 = [k_{Im} + (k_AK_2/a_H)][K_1/(K_1 + a_H)] \quad (10)$$

The equation for k_0 at all pH values is

$$k_0 = (k_{Im}K_1a_H + k_AK_1K_2)/(a_H^2 + K_1a_H + K_1K_2) \quad (11)$$

Inclusion of a term in eq 10 for the observed general base catalysis in cyclization of III gives the equation for k_{obsd},

$$k_{obsd} = [k_{Im} + (k_AK_2/a_H) + k_B(B)][K_1/(K_1 + a_H)] \quad (12)$$

From eq 10, for the pH–rate constant profile to be linear at pH values near neutrality,

$$k_{Im} = k_AK_2/a_H \quad (13)$$

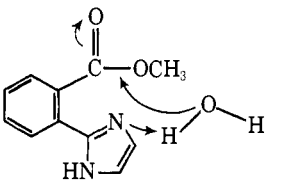
must hold at pK_1. Thus k_{Im} is 6.3×10^{-4} s^{-1} for the trifluoroethyl ester II at 50 °C.

A plot of log k_{obsd} vs. pH for hydrolysis of trifluoroethyl benzoate at 50 °C was linear with slope of 1.0 in the pH range 8–11. The value of k_{OH} is 6.56 M^{-1} s^{-1}. Buffer catalysis was not observed in the hydrolysis of this ester in piperidine (0.05–1.0 M total buffer) or *N*-methylmorpholine (0.05–0.50 M total buffer).

In calculating the second-order rate constants k_{OH}, 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.[16] At 50 °C these constants have the value 5.50×10^{-14} and 7.94×10^{-15}.[16]

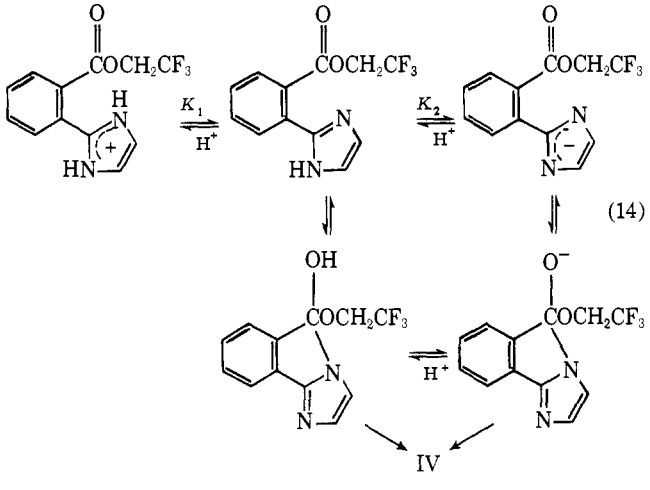
Discussion

The second-order rate constant k_{OH} for hydrolysis of methyl *o*-(2-imidazoyl)benzoate at 30 °C (0.152 M^{-1} s^{-1}) is approximately the same as that for hydrolysis of methyl benzoate (0.125 M^{-1} s^{-1}),[17] showing that the neighboring group is not participating in the reaction at high pH. The pK_a of the imidazoyl group is only ~2 pK_a units less than that of the amino group of methyl 2-aminomethylbenzoate, in which case the neighboring amino group acts as an intramolecular nucleophile in a hydroxide ion and general base catalyzed reaction.[9] Thus, on the basis of nucleophile basicity, the lack of participation by the imidazoyl group of I is somewhat surprising. Part of the lack of reactivity may reside in the steric situation resulting from the cyclic structure of the neighboring group. Nucleophilic attack would result in a tricyclic transition state which might be expected to be relatively unfavorable. In the neutral pH region (pH 6–8) there is a plateau in the pH–rate constant profile which in view of the large D_2O solvent isotope effect (k_{H_2O}/k_{D_2O} = 3.6) may indicate a general base mechanism in which a proton is transferred from a H_2O molecule in the transition state V. A kinetically equivalent possibility is attack of hydroxide ion on the protonated species.



V

The pH-log rate constant profile for hydrolysis of the trifluoro ester (II) is linear with slope of 1.0 in the pH range 4–12 even though the pK_a of the imidazoyl group is 6.3. The value of k_{OH} is 10^3 larger than k_{OH} for hydrolysis of trifluoroethyl benzoate, which is beyond what would be expected from a difference in electronic effects considering that I and methyl benzoate hydrolyze with nearly identical rates. Therefore, the imidazole group must be participating in the reaction. The k_{OH} value is slightly larger in D_2O than in H_2O ($k_{OH}/k_{OD} = 0.9$). This fact, plus the shape of the pH-rate constant profile, makes it unlikely that the neighboring group is acting as a classical general base. The D_2O solvent isotope effect is similar to that observed previously in hydroxide ion catalyzed nucleophilic reactions of 2-substituted benzoate esters,[8,9] but is considerably greater than in hydroxide ion catalyzed ester hydrolysis reactions.[18] The rate enhancement associated with the neighboring group must be due to a nucleophilic reaction. A hydroxide ion catalyzed nucleophilic reaction of the neutral species or the kinetically equivalent reaction of the imidazole anion would be in accord with the experimental data at high pH. However, at pH values below pK_1 such reactions would give rise to a pH-log rate constant profile of slope 2.0 as observed in the cyclization of methyl 2-aminomethylbenzoate.[9] Since a hydroxide ion catalyzed reaction of the protonated compound is unlikely, a slope of 1.0 in the pH-log rate constant profile at low pH is only in accord with an uncatalyzed or water catalyzed reaction of the neutral species. Thus the pathway must be changing with pH (eq 14) as the concentration of the



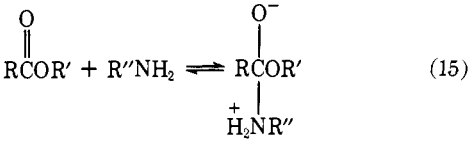
(14)

anion (or OH^-) becomes relatively less important. However, this change does not produce an inflection in the pH-rate constant profile, indicating that the products of the rate and equilibrium constants through the two pathways are nearly identical at pK_1. From eq 13, at pK_1, $k_{Im} = k_A$ (10^{-7}). A 10^7 difference in magnitude of the rate constants for the anionic and neutral species is in accord with a Brønsted β of 1.0 for the intramolecular nucleophilic reaction,[19] indicating that the critical transition states resemble products. The pH-log rate constant profile for cyclization (first step) of the analogous *n*-propylthiol ester[20] also has a slope of 1.0 at all pH values (5–11). Bimolecular reaction of the anionic species of substituted imidazoles with *p*-nitrophenyl acetate has been observed previously,[21] and, at high pH values, phenyl acetate, *p*-nitrophenyl toluate, acetoxime acetate, and trifluoroethyl acetate are subject to nucleophilic attack by imidazole anion (or the equivalent neutral species + ^-OH).[22] In those bimolecular reactions where rate constants for attack by both the anionic and neutral species were determined, reaction of the neutral species is of greatest significance near pH 7,[23] in marked contrast to the intramolecular reaction of II where, at pH 7, 83% of the reaction is through the anionic species.

The second-order rate constant for hydroxide ion catalyzed cyclization of II at 30 °C (Table I) is similar to that for hydrolysis of the acylimidazole IV, which explains why IV is not detected spectrophotometrically in the cyclization reaction. However, the hydrolysis of II must proceed with rate-limiting formation of the intermediate IV since buffer catalysis is not observed even though IV hydrolyzes with strong general base catalysis. This pronounced buffer catalysis leads to observed rate constants for hydrolysis of IV that are greater than for hydrolysis of II. At pH <6.5, IV hydrolyzes much faster than II even with a 20° difference in temperature (Figures 1 and 3). The 2-substituted benzoate esters with aliphatic alcohol leaving groups that have previously been studied[8-10] all have second-order rate constants for hydroxide ion catalysis of the cyclization reaction, k_{OH}, of 10^4 M^{-1} s^{-1} at 30 °C. However, k_{OH} for hydrolysis of II is only 10^3 M^{-1} s^{-1} at 30 °C in spite of a leaving group of much lower pK_a (12.4).[24] This again reflects the relative difficulty of intramolecular nucleophilic attack by an imidazole group.

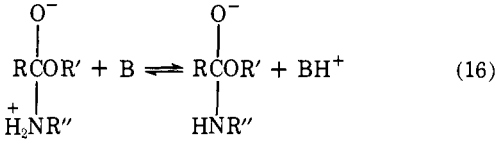
Two discrete steps can be observed in the hydrolysis of the phenyl ester (III) at pH values >5.5, which correspond with cyclization (phenol release) to the cyclic intermediate (IV) and slower hydrolysis of the intermediate. The close similarity of the rate constants for breakdown of the observed intermediate and IV and the identity of their spectral characteristics clearly establish that IV is the intermediate. At pH values <5.5 only one step can be observed in the reaction, which must be rate-determining formation of IV. The pH-log rate constant profile for the formation of the intermediate again follows eq 4. As in the case of the trifluoroethyl ester the profile is linear at all pH values with slope of 1.0, and the reaction scheme can be considered to be the same, i.e., nucleophilic attack by the neutral imidazole ring, and the imidazole anion or the kinetically equivalent attack of the neutral species catalyzed by hydroxide ion. The profile again indicates that the product of the rate and equilibrium constants for the two processes are identical at pK_1. Bimolecular general base catalysis occurs in both steps in the hydrolysis of III. The Brønsted plot of Figure 4 for general base catalysis in the cyclization step has a slope β of 1.0, indicating that a proton-transfer step in the thermodynamically unfavorable direction is rate determining.[25] This was also the case in intramolecular aminolysis of methyl 2-aminomethylbenzoate.[9]

Satterthwait and Jencks[26] have suggested that in the bimolecular aminolysis of aliphatic esters nucleophilic attack is by the neutral amine to give a zwitterion intermediate (eq 15). The rate-determining step at high pH is abstraction of a



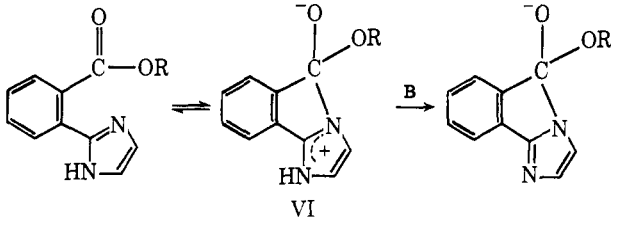
(15)

proton from the zwitterion by a general base catalyst (eq 16),



(16)

a proton transfer through water (alkyl esters), or direct breakdown of the intermediate to products (phenyl esters). A proton transfer analogous to eq 16 cannot be rate limiting in the intramolecular aminolysis of methyl 2-aminomethylbenzoate.[9,27] The rate-determining step in the intramolecular reaction is most likely proton transfer to or from a tetrahedral intermediate. With imidazole as an intramolecular nucleophile, proton transfer from a zwitterion cannot be rate determining (eq 17) as in bimolecular aminolysis reactions; the intermediate

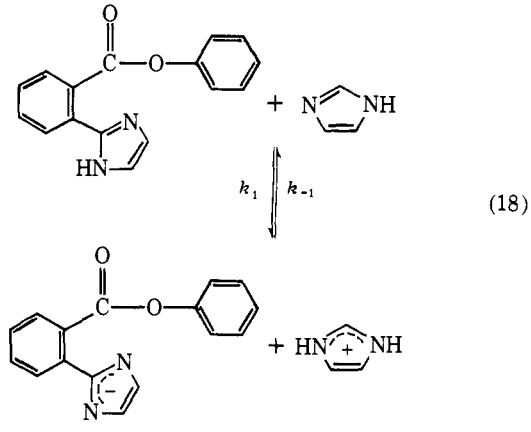


VI

$$+ BH^+ \longrightarrow \text{products} \quad (17)$$

VI should have a relatively low pK_a so that rate-determining proton transfer from it should give rise to curvature in the Brønsted plot ($\beta = 0$ with bases of high pK_a).

In the imidazole catalyzed hydrolysis of *p*-cresol acetate, a second-order dependence on imidazole concentration has been observed[2,28] which was considered to be general base catalysis by imidazole of the nucleophilic attack of a second imidazole. The rate-limiting proton-transfer step in the general base catalyzed cyclization of III cannot be proton abstraction by base from the imidazoyl group to give the imidazole anion as in eq 18. The rate constant for this reaction is given in eq 19



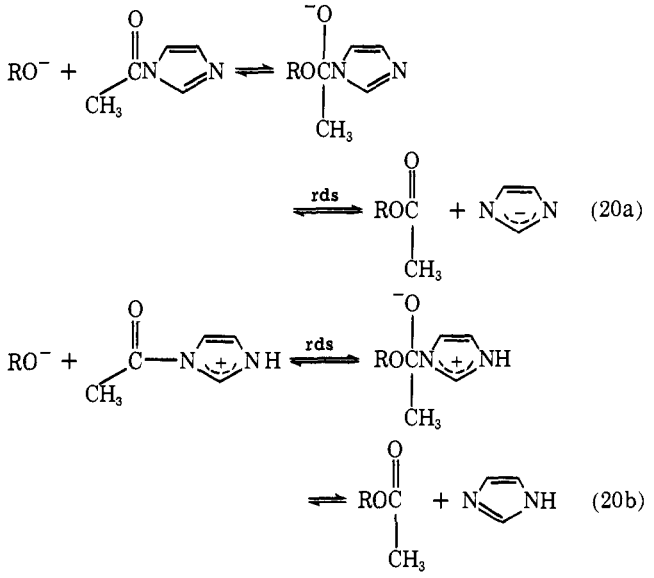
(18)

where K_a is the dissociation constant of imidazolium ion. Assuming K_2 and K_a to have the values 10^{-13} and 10^{-7}, respectively, and k_{-1} to be the rate constant for a diffusion controlled reaction (10^{10} M^{-1} s^{-1}), k_1 has the value 10^4 M^{-1} s^{-1} which is larger than the experimentally determined second-order rate constant for imidazole catalysis by a factor of 10^4. A similar calculation permitted ruling out rate-determining proton abstraction from the hydroxyl group of ethyl 2-hydroxymethyl-4-nitrobenzoate in cyclization of that compound to 5-nitrophthalide.[8]

$$k_1 = k_{-1}(K_2/K_a) \quad (19)$$

Oakenfull and Jencks[29] have made a thorough study of the reactions of oxide ions with *N*-acetylimidazole. The Brønsted coefficient β for nucleophilic attack is 1.3 for reaction of these ions with *N*-acetylimidazole, indicating a transition state resembling products with expulsion of imidazole anion. Trifluoroethoxide is 10^5 more reactive in this reaction than phenolate ion. There is little sensitivity to base strength of the nucleophile in reactions of strongly basic nucleophiles with *N*-acetylimidazolium ion ($\beta = 0$). Phenolate and trifluoroethoxide have almost identical rates indicating little bond formation in the transition state (rate-determining attack if there is a tetrahedral intermediate). It was concluded[29] that either reactions of strong bases with the neutral and protonated species proceed by a concerted pathway in one or both cases or there is a tetrahedral addition intermediate whose lifetime is too short for it to reach equilibrium with respect to proton transfer (eq 20).

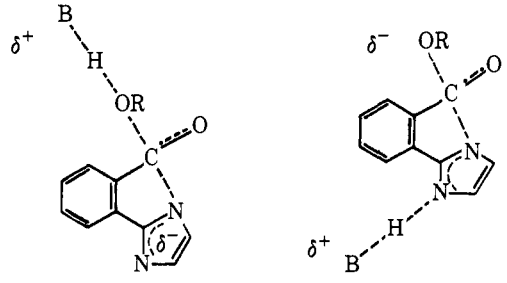
Considering that aminolysis of an ester is the microscopic reverse of alcoholysis of an amide, a scheme similar to eq 20 in the intramolecular reactions of II and III would demand



(20a)

(20b)

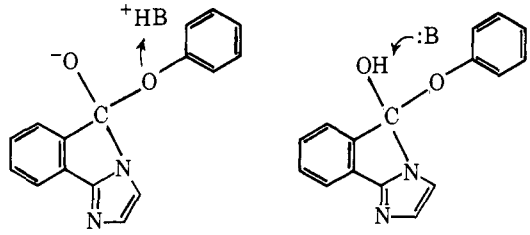
different rate-determining steps in the anionic and neutral species reactions. However, the β of 1.0 for the nucleophile in intramolecular neutral and anionic species reactions and the same large influence of the leaving group in the two reactions (200-fold comparing trifluoroethoxide and phenolate) both point to transition states resembling products. Concerted reactions, without a tetrahedral intermediate, would necessitate that the buffer catalyzed reaction of III involve general acid catalysis of the attack of the imidazole anion (VII), or general base catalyzed attack of neutral species (VIII). In reactions



VII VIII

of *N*-acetylimidazole with alcohol nucleophiles the preferred mechanism for imidazole catalysis is proton donation to the leaving imidazole, with nucleophilic attack by alkoxide ion.[30] However, concerted proton transfer and bond making and breaking are not consistent with $\beta = 1.0$ in the general base catalyzed reaction of III. Thus it is likely that, in the intramolecular reactions, a tetrahedral intermediate is being formed whose breakdown is rate limiting in both the anionic and neutral species reaction. In bimolecular reactions of imidazole with esters, imidazole catalysis would involve removal of a proton from the attacking amine. The general base catalyzed intramolecular reaction of III is therefore taking place through a different mechanistic pathway than that of the corresponding intermolecular reaction.

Since proton abstraction from the nucleophile by a general base cannot be rate determining in the buffer catalyzed cyclization reaction of III, then buffer catalysis of the nucleophilic reaction may involve general acid catalysis of the breakdown of an anionic tetrahedral intermediate (IX), or the kinetically equivalent general base catalyzed decomposition of a neutral tetrahedral intermediate (X). General acid catalysis of the breakdown of a tetrahedral intermediate at high pH (IX) is, however, difficult to rationalize in view of the absence of buffer catalysis in the cyclization of II where the leaving group is poorer. General acid catalysis might reasonably be expected to be more advantageous as the leaving group is made worse. Also, a zwitterion intermediate in which a



IX X

proton is completely transferred to the leaving group would be highly reactive, and, if the rate constant for its decomposition is $>10^{13}$ s^{-1}, proton transfer and C-O bond breaking would necessarily be concerted.[31] The general base catalyzed cyclization of 2-aminomethylbenzamide at high pH must involve general acid catalyzed breakdown of an anionic tetrahedral intermediate, and proton transfer to the leaving group is concerted with C-N bond breaking as shown by $\beta = 0.4$ ($\alpha = 0.6$).[32] Thus, mechanism X, supported by $\beta = 1.0$, is most likely in cyclization of III.

Mechanism X requires that the carbonyl oxygen be protonated in formation of a stable tetrahedral intermediate. This might occur to prevent rapid reversion of a zwitterionic tetrahedral intermediate to the reactant state. Such a proton transfer could be mediated by water in a concerted or stepwise manner as has been suggested in the bimolecular aminolysis of aliphatic esters.[26] A totally concerted preequilibrium formation of a neutral tetrahedral intermediate would avoid the unstable zwitterion VI as an intermediate.

At pK_1 intramolecular nucleophilic reaction of the anionic species confers no kinetic advantage over the neutral species since the contributions of the two reactions to k_{obsd} are identical. The equilibrium concentration of the tetrahedral intermediate in each case must then be independent of whether the attacking species is the neutral species or the anion, i.e., formation of a tetrahedral intermediate is at complete equilibrium with respect to the reactant state. Thus ease of proton transfer and ease of nucleophilic attack must exactly compensate in their effects on the equilibrium concentration of the tetrahedral intermediate. The closely similar rate constants for hydroxide ion catalyzed cyclization of aliphatic esters of 2-substituted benzoic acid, regardless of whether the nucleophile is hydroxymethyl,[8] aminomethyl,[9] or mercaptomethyl,[10] must also be due to compensating effects of proton transfer and nucleophile ability in formation of a tetrahedral intermediate since the rate constants for breakdown of the tetrahedral intermediates to products should be closely similar (the leaving groups are aliphatic alcohols of similar basicity).

Conclusions

A sufficient number of intramolecular nucleophiles have now been studied in the 2-substituted benzoate system that generalizations are possible for reactions of esters with poor leaving groups ($pK_a = 10$–16). (1) When the pK_a of the neutral nucleophile is high (>13), as with an aminomethyl group, nucleophilic attack on aliphatic esters probably occurs through the neutral species, and both hydroxide ion and external general base catalysis are observed. The rate-determining step in the general base catalyzed reaction is a proton transfer which is very likely proton transfer to or from a tetrahedral intermediate. The Brønsted coefficient β for general base catalyzed cyclization of methyl 2-aminomethylbenzoate[9] and ethyl 2-hydroxymethyl-4-nitrobenzoate[8] is 1.0. (2) When the neutral nucleophile has a reasonably low pK_a, as in the case of mercaptomethyl (11.1), so that an appreciable concentration of anion exists in solution, then hydroxide ion catalysis is observed in nucleophilic reactions of aliphatic esters at pH values below the pK_a, but buffer catalysis is not significant.[10] Nucleophilic attack in that case is probably by the anionic species at high pH. (3) When the leaving group is sufficiently good ($pK_a <$ 12.5), the two pK_a values of a neighboring imidazole group (6.3 and 13) are such that nucleophilic reactions of both the neutral and anionic species can be observed. The neighboring imidazoyl group in the 2-substituted benzoate ester system differs from the hydroxymethyl,[8] aminomethyl,[9] and mercaptomethyl[10] nucleophiles that have been previously studied in that cyclization does not occur in reactions of the methyl ester. The relatively unfavorable nucleophilic ability must result from a smaller equilibrium concentration of tetrahedral intermediate. However, when the pK_a of the leaving group is lowered to 12.4 with the trifluoroethyl ester[24] and 10 with the phenyl ester,[33] then nucleophilic reactions occur respectively through specific and general base pathways similar to those encountered with the other nucleophilic groups.

The intramolecular reactions of II and III are strikingly different from corresponding bimolecular reactions, as was also found to be the case in intramolecular aminolysis of aliphatic esters.[9] There appears to be no a priori reason why the mechanisms should be the same for intramolecular and bimolecular reactions. In view of the close similarity of an enzyme reaction, proceeding through an enzyme substrate complex, and a chemical intramolecular reaction, it is therefore clear that only intramolecular catalysis should be employed as a model to gain insight into analogous enzymatic reactions.

In reactions of α-chymotrypsin with aliphatic ester substrates, intracomplex nucleophilic attack by serine-195 at pH 7 may occur in large part through the neutral species since the pK_a of the serine hydroxyl group is high[34] and general base catalysis by histidine-57 takes place. Catalysis by histidine-57 very likely involves proton transfer to or from a tetrahedral intermediate analogous to catalysis by imidazole in cyclization of ethyl 2-hydroxymethyl-4-nitrobenzoate.[8] A neutral alcoholic hydroxyl group would be a poor nucleophile toward an ester carbonyl even in an intracomplex reaction, i.e., a zwitterion tetrahedral intermediate would decompose rapidly to starting material. However, such an intermediate would also be stabilized rapidly by proton transfer, which in view of the expected low pK_a of the addition intermediate would occur at a diffusion controlled rate with all bases including H_2O. The generally accepted mechanism for acylation of α-chymotrypsin[2,3] involves partial proton abstraction from serine-195 by histidine-57, but whether the hydroxyl proton is partially removed to assist nucleophilic attack or in a subsequent step to stabilize the tetrahedral intermediate is immaterial since this step should not be rate limiting when the leaving group is poor. Formation of a tetrahedral intermediate may then be an equilibrium process.

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Antiaromatic Interaction in the 9-Methoxybicyclo[4.2.1]nona-2,4,7-trien-9-yl Cation. Evidence of Orbital Symmetry Control over 4π-Electron Interactions

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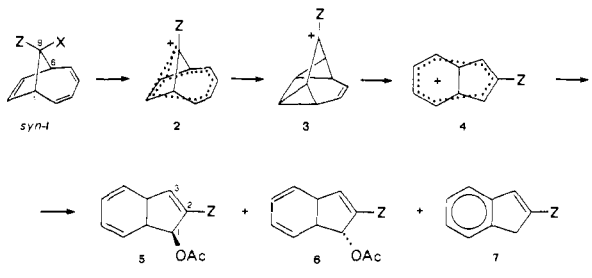
Abstract: Ionization reactions of *anti*-9-chloro-9-methoxybicyclo[4.2.1]nona-2,4,7-triene (**8**) proceed without skeletal rearrangements under conditions of short life. Rate constants were measured for the reaction of **8** and its more saturated analogues with pyridine. From the relatively low reaction rate of triene **8** it is concluded that the [4.2.1] cation is destabilized consequent to the homoantiaromatic interaction between the cationic center and the butadiene moiety. In addition to the kinetic results, the presence of this type of interaction is revealed by a NMR study of the 9-methoxybicyclo[4.2.1]nona-2,4-dien-9-yl cation (**21**) and the 11-methoxybicyclo[4.4.1]undeca-2,4,8-trien-11-yl cation (**25**) under conditions of long life, i.e., superacid media. The ^1H and ^{13}C NMR data point to an interaction of the cationic center with one of the double bonds of the butadiene moiety. Obviously the mode of homoconjugative interaction is controlled by orbital symmetry.

The theoretical analysis of bicycloaromatic stabilization in π-bridged ions by Goldstein and Hoffmann[1,2] has led to considerable effort directed toward experimental tests of their theory. In particular the bicyclo[4.2.1]nona-2,4,7-trien-9-yl cation has evoked interest because of its stability which is expected on the basis of homoaromatic and longicyclic stabilization. Yet, the solvolysis of *syn*-bicyclo[4.2.1]nona-2,4,7-trien-9-yl *p*-toluenesulfonate (*syn*-**1a**) afforded the rearranged products *cis-exo*-dihydroindenyl acetate (**5a**) and indene (**7a**)



only.[3-5] The deuterated analogue (**1b**) produced **5b** and **7b** with the deuterium exclusively at C_2.[4,5] Interaction of the monoene and diene units of the cation, visualized by structures **2** and **3**, has been suggested to account for the observed path of rearrangement. The introduction of electron-releasing groups at C_9 (**1d,e**) did not affect the path of rearrangement.[6] However, in these cases not only the *cis-exo*-dihydroindenyl derivatives (**5d,e**) were formed, but also the cis-endo compounds (**6d,e**). The intermediacy of a bicycloaromatic ion **2** has also been proposed to explain the enhanced reactivity of *syn*-**1a** with respect to the more hydrogenated analogues.[5,6] Subsequently this interpretation was dismissed by Kirmse[7] on the basis of the observation that both *syn*- and *anti*-**1a** have identical rates and product mixtures. Therefore, the nature of the intermediate species remains unclear.[8]

In this paper we describe the results of a study on the ionization of the 9-methoxy derivative of **1** (**8**) and the more hydrogenated analogues (**9** and **10**) under conditions of short life, which proceeds without skeletal rearrangements. Furthermore, the 9-methoxybicyclo[4.2.1]nona-2,4-dien-9-yl cation (**21**) and the 11-methoxybicyclo[4.4.1]undeca-2,4,8-trien-11-yl cation (**25**) could be generated under conditions of long life. The NMR data reveal an unusual type of homoconjugation which is extensively discussed.

Results

Experiments under Conditions of Short Life. The α-chloro ethers **8**, **9**, and **10** were prepared by treatment of the corresponding dimethyl ketals with PCl_5 in ether. In contrast with the earlier reported 7-chloro-7-methoxynorbornene[9] which

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