(27) All computations were performed on a CDC6600-CYBER172 multi-mainframe computer using the Indiana University Molecular Structure center XTEL interactive program library. The latter is based in part on the Los Alamos code of A. C. Larson and J. Iber's Northwestern University programs. Molecular fitting was by S. C. Nyburg's BMFIT, and drawings were by C. Johnson's ORTEP.
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General-Base-Catalyzed Intramolecular Aminolysis of Thiol Esters. Cyclization of *S*-*n*-Propyl *o*-(2-Imidazolyl)thiolbenzoate. Relationship of the Uncatalyzed and Base-Catalyzed Nucleophilic Reactions

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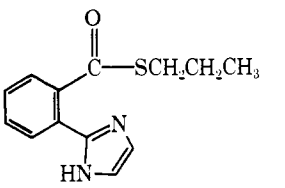
Abstract: Rate constants have been obtained at 30 °C in H_2O for hydrolysis of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate. The reaction involves rapid formation and subsequent breakdown of an acylimidazole intermediate. A plot of log k_0 for cyclization vs. pH is linear with a slope of 1.0 at all pH values. The contributions to k_0 of the uncatalyzed neutral species and apparent hydroxide ion catalyzed reactions are equal at the pK_a of the nucleophile. The kinetic data indicate that cyclization to a tetrahedral intermediate is an equilibrium step, breakdown of the tetrahedral intermediate being rate determining. The value of k_{OH} for cyclization of the thiol ester is 5×10^6 greater than for hydrolysis of *n*-propyl thiolbenzoate. In comparison with bimolecular attack of imidazole on *n*-propyl thiolbenzoate the effective molarity of the neighboring imidazolyl neutral species is 1.6×10^3 M while that of the imidazolyl anion is 7×10^2 M. General base catalysis is observed in the intramolecular nucleophilic reaction. The value of the Brønsted coefficient β is 1.0, indicating that the rate-determining step is a proton transfer in the thermodynamically unfavorable direction. This step may be proton abstraction by the base from a neutral tetrahedral intermediate. This relationship appears to be general for intramolecular aminolysis reactions in the 2-substituted benzoate system.

Both intramolecular and bimolecular aminolyses of esters have been extensively studied.[1-9] Intramolecular aminolysis of 2-substituted benzoate esters having poor leaving groups (pK_a = 10–16) proceeds with striking mechanistic differences in comparison with analogous bimolecular reactions.[8,9] Neighboring aminomethyl and imidazole nucleophiles in the 2-substituted benzoate esters give rise to intramolecular reactions which are characterized by linear plots of the logarithms of the rate constants vs. pH, showing hydroxide ion catalysis of the nucleophilic reaction (or the kinetically equivalent reaction of the anionic species). In the case of neighboring imidazole displacement of trifluoroethanol or phenol leaving groups,[9] an uncatalyzed neutral species reaction also occurs. Brønsted plots for general base catalysis have slopes of 1.0, which indicate that a proton transfer in the thermodynamically unfavorable direction is rate determining.[10] This step is most likely proton transfer to or from the tetrahedral intermediate. A number of extremely important questions have arisen as a result of the studies of intramolecular reactions of the 2-substitued benzoate esters.[8,9,11] Among these are (1) What is the general relationship between the neutral species and OH^--catalyzed nucleophilic reactions and how is it influenced by leaving group? (2) What is the mechanistic significance of the buffer catalysis that has been observed? Why is it found in the 2-substituted benzoate system and apparently not in other intramolecular systems that have previously been studied?[12-14] (3) Is the Brønsted β value of 1.0 a general feature of these reactions?

If the mechanistic differences in the intramolecular aminolysis reactions of 2-substituted benzoate esters in comparison with similar bimolecular aminolysis reactions are due to proximity of the nucleophile and the carbonyl in the intramolecular system, then similar differences might also exist in the reactions of 2-substituted benzoate esters and corresponding *intramolecular* reactions where degrees of freedom exist for rotation of the nucleophile away from the carbonyl. To determine whether this is the case in the intramolecular reactions of thiol esters, we have studied the hydrolysis of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate (I). The intramolecular nucleophilic reaction of *S*-*n*-propyl γ-(4-imidazolyl)-thiolbutyrate,[12] having the same entering and leaving groups as I but in which the nucleophile is not rigidly held adjacent to the carbonyl, occurs through attack by the neutral species without buffer catalysis. In contrast we have found that I cyclizes through attack by both the neutral and anionic species (or a kinetic equivalent) with pronounced general base catalysis.



I

The mechanism of neighboring imidazole participation in the hydrolysis of thiol esters in constrained systems is of great interest in view of the fact that a number of protease enzymes such as papain have both cysteine and histidine in the active site, and histidine may participate in the hydrolysis of the acyl-thiol intermediate.[15]

Experimental Section

***S*-*n*-Propyl *o*-(2-imidazolyl)thiolbenzoate hydrochloride (I)** was prepared by heating at reflux 2 g of *N*,2-(2′-benzoyl)imidazole[9] with a concentrated solution of *n*-propyl mercaptan in tetrahydrofuran for 6 h. The solvent and excess thiol were removed at low pressure and

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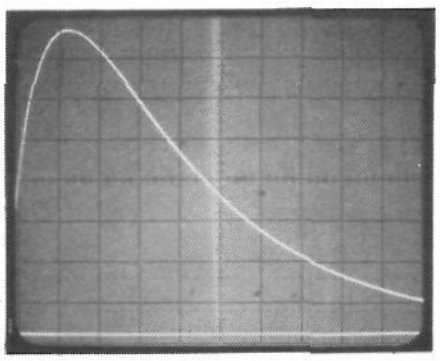


Figure 1. Oscilloscope trace at 245 nm for the hydrolysis of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate in 0.2 M Tris buffer at 30 °C, pH 8.5, μ = 0.5. The time scale is 2.0 s/division.

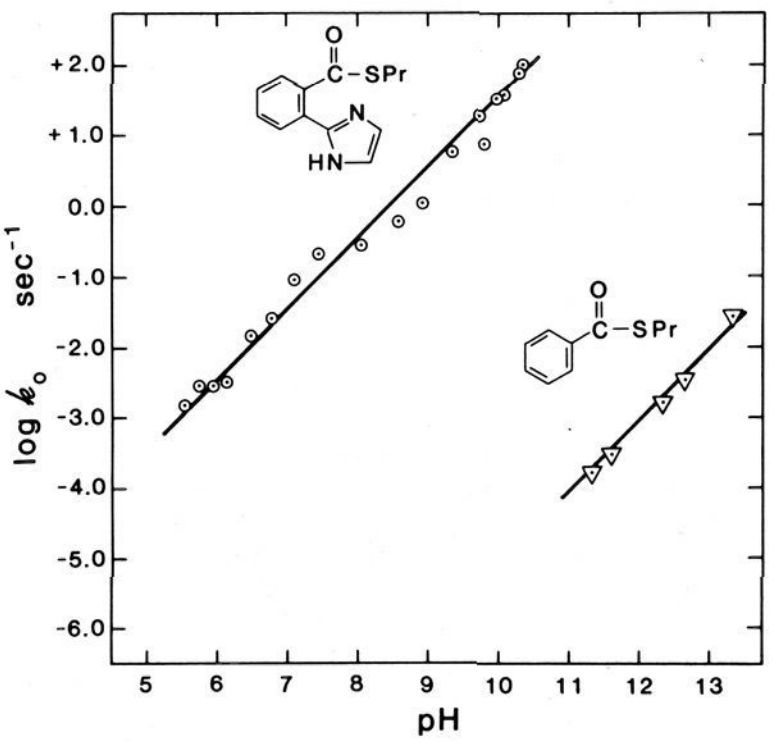


Figure 2. Plots of log k_0 vs. pH for cyclization of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate (I) (○) and hydrolysis of *n*-propyl thiolbenzoate (II) (▽) at 30 °C and μ = 0.5. For I, rates are extrapolated to zero buffer concentration from pH 5.5 to 9.8, while above pH 9.8, rate constants were obtained at low concentrations (0.02 M) of triethylamine or piperidine buffers. Rate constants for hydrolysis of II were obtained in KOH solutions.

the resulting solid was taken up in chloroform. After filtration, HCl gas was bubbled into the filtrate for 5 min, and the chloroform was removed by rotary evaporation. The residue was washed several times with hexane and ether until the washes were colorless. Further purification was effected by taking the solid up in a minimum amount of chloroform, adding the concentrate dropwise to five times its volume of dry ether, and then decanting the solution from the precipitate which formed. The thiol ester hydrochloride was purified by repeatedly washing the precipitate with cold acetonitrile. This treatment yielded a light tan solid, mp 157–159 °C. Anal. Calcd for $C_{13}H_{15}ClN_2OS$: C, 55.21; H, 5.30; N, 9.90. Found: C, 54.93; H, 5.40; N, 9.63.

***S*-*n*-Propyl thiolbenzoate (II)** was prepared as previously described[16] by stirring 0.025 mol of *n*-propyl mercaptan, benzoyl chloride, and pyridine at room temperature in 20 mL of benzene for 30 min. After the pyridine hydrochloride was filtered off, the solvent and unreacted thiol were removed from the filtrate by rotary evaporation. The residue was fractionally distilled yielding a colorless liquid, boiling at 102 °C (2.6 mm) (lit.[16] bp 121–122 °C (7 mm)).

Buffers were prepared from reagent grade materials. Amine buffers were freshly distilled or recrystallized prior to use. Deuterium oxide (99.8 atom % D) was purchased from Bio-Rad Laboratories.

Kinetic Methods. The rates of cyclization of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate were measured employing a Beckman 25 recording spectrophotometer or a Durrum D110 stopped-flow apparatus equipped with a Hewlett-Packard Model 1207B storage oscilloscope. The cyclization reaction was followed by observing an absorbance increase at 245 nm after injecting 20 μL of I (dissolved in Me_2SO) into 3 mL of buffer. The UV spectra of the products of the hydrolysis reactions were identical with those of equal concentrations of *o*-(2-imidazolyl)benzoic acid and *n*-propyl mercaptan. At the higher pH values the stopped-flow apparatus was employed. The substrate in

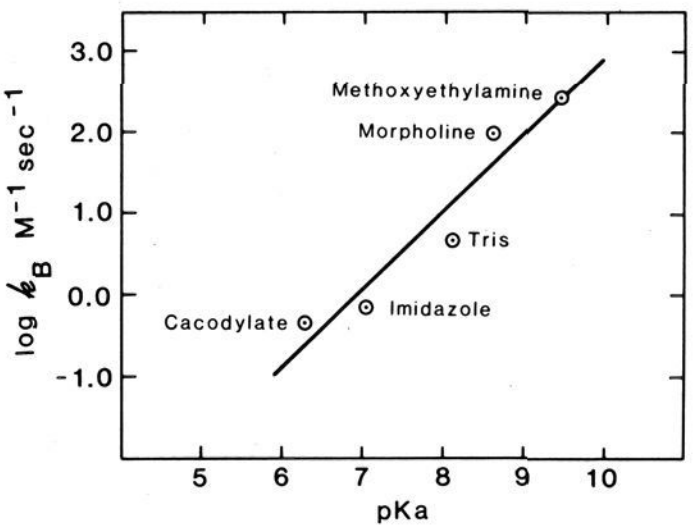


Figure 3. A Brønsted plot of log k_B for general-base-catalyzed cyclization of *S*-*n*-propyl *o*-(2-imidazolyl)thiolbenzoate to III vs. the pK_a of the conjugate acid of the base catalyst at 30 °C and μ = 0.5.

10^{-3} or 10^{-2} M HCl solution was placed in one syringe and the appropriate buffer in the other. The drive syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 30 ± 0.1 °C. With each buffer four to six runs were tabulated. Infinity points were stable. Rate constants for hydrolysis of the intermediate produced in cyclization of I were determined at 30 ± 0.1 °C by following the absorbance decrease at 245 nm or an absorbance increase at 270 nm. An absorbance decrease at 274 nm was employed in determining rate constants for the hydrolysis of II after injecting 20 μL of 2×10^{-2} M solution in acetonitrile into 3 mL of buffer.

Reaction solution pH values were measured with either a Radiometer Model 22 pH meter with a GK 2303 C combination electrode or a Beckman Model 3500 pH meter with a combination electrode standardized against Mallinckrodt standard buffer solutions. The pD was determined by using the glass electrode correction equation of Fife and Bruice.[17] Pseudo-first-order rate constants were calculated with an IBM 370-158 computer using a rigorous least-squares procedure.

Results

Two discrete steps are observed at 30 °C in the hydrolysis of I: cyclization to an acylimidazole intermediate and subsequent hydrolysis of the intermediate to *o*-(2-imidazolyl)benzoic acid. In Figure 1 an oscilloscope trace is shown from a stopped-flow determination illustrating these steps. The pH–log (rate constant) profile for the cyclization step is shown in Figure 2. Values of k_0 (pH 5.5–9.8) were obtained by extrapolation of k_{obsd} to zero buffer concentration. The plot is linear with a slope of 1.0 from pH 5.5 to 10.5. The value of k_{OH} at 30 °C is 2×10^5 M^{-1} s^{-1}. The value of k_{OH} for hydroxide ion catalyzed hydrolysis of the acylimidazole intermediate is 2×10^3 M^{-1} s^{-1}, and k_{H_2O} for water catalysis is 7×10^{-4} s^{-1}.

Strong buffer catalysis is observed in the cyclization of I. The base form of the buffer is catalytically active, and the Brønsted plot of log k_B vs. pK_a of the conjugate acid of the base (Figure 3) has a slope of 0.96 (r = 0.96). If only the amine bases are included the slope is 1.14. Utilizing statistical corrections the slope is then 1.05 (r = 0.95). The second-order rate constant for Tris catalysis is larger in H_2O than D_2O ($k_B(H_2O)/k_B(D_2O)$ = 2.0). In cacodylate and acetate buffers general acid catalysis of the cyclization of the neutral species of I or the equivalent general base catalysis of cyclization of the protonated species is detected. The second-order rate constants for the general-base-catalyzed reactions are given in Table I.

The hydrolysis of *n*-propyl thiolbenzoate at 30 °C was studied at high pH and in the presence of imidazole buffers. From the plot of log k_{obsd} vs. pH at high pH (Figure 2) the value of k_{OH} for hydroxide ion catalysis is 4.3×10^{-2} M^{-1} s^{-1}. Imidazole buffers catalyze the hydrolysis of this ester. A plot of log k_{obsd} vs. the free base form of imidazole is shown in

Table I. Rate Constants for the General-Base-Catalyzed Cyclization of *S*-*n*-Propyl *o*-(2-Imidazolyl)thiolbenzoate (I) to *N*,2-(2′-Benzoyl)imidazole at 30 °C and μ = 0.5 with KCl

base	pK_a[a]	buffer concn range, M	%[b] catalysis	(pH)[c]	k_B, M^{-1} s^{-1}	k_{BH^+}, M^{-1} s^{-1}
β-methoxyethylamine	9.45	0.025-0.10	360	(9.35)	291[d]	
morpholine	8.60	0.025-0.10	570	(8.93)	101[e]	
Tris	8.10	0.05-0.50	524	(8.05)	5.0[d]	
imidazole	7.05	0.05-0.25	130	(6.78)	0.78[f]	
cacodylate	6.28	0.01-0.10	890	(6.15)	0.48[f]	1.15
acetate	4.60	0.02-0.10	89	(5.55)		0.12
Tris (in D_2O)	8.75	0.1-0.5	150	(8.77 (pD))	2.47[d,g]	

[a] Determined at the same temperature and ionic strength as the rate measurements. [b] $[(k_{obsd}$ (at the highest buffer concentration) $- k_0)/k_0] \times 100$. [c] pH at which the percent catalysis was calculated. [d] Determined at two buffer ratios. [e] Determined at one buffer ratio. [f] Determined at three buffer ratios. [g] Determination in D_2O.

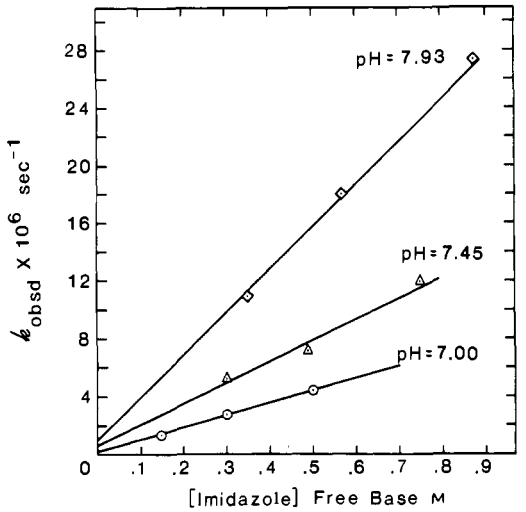


Figure 4. A plot of k_{obsd} vs. the concentration of free base form of imidazole buffer for the hydrolysis of *n*-propyl thiolbenzoate (II) at 30 °C and μ = 0.5 M: pH 7.0 (○), 7.45 (△), and 7.93 (◇).

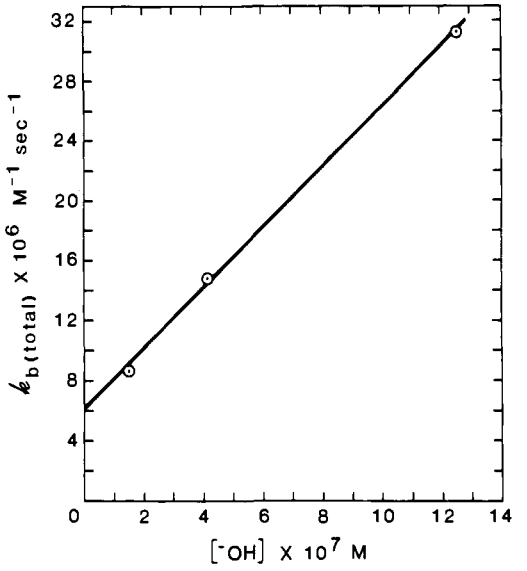


Figure 5. A plot of the slopes of Figure 4 vs. hydroxide ion concentration.

Figure 4. The slopes increase as the pH increases indicating hydroxide ion catalysis of the reaction of the thiol ester with imidazole. A plot of the slopes of Figure 4 vs. hydroxide ion concentration (Figure 5) is linear and extrapolates to an intercept at zero (OH^-). Consequently, there is a term in the rate expression for both uncatalyzed and hydroxide ion catalyzed reaction with imidazole. The expression for the observed pseudo-first-order rate constant is

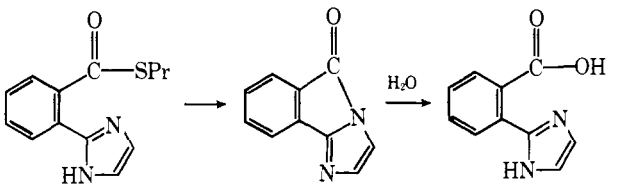
$$k_{obsd} = k_0 + k_{Im}(Im) + k_{Im'}(Im)(OH^-) \qquad (1)$$

where k_0 is the observed rate constant at zero imidazole concentration, k_{Im} is the second-order rate constant for the uncatalyzed reaction with imidazole, and $k_{Im'}$ is the third-order rate constant for hydroxide ion catalyzed reaction of imidazole with the thiol ester. The latter term possibly results from reaction of the anionic species of imidazole. The rate constant for catalysis by that species, k_{Im^-}, is related to $k_{Im'}$ by eq 2, where K_w is the ion product of water at 30 °C (1.47×10^{-14}) and K_a' is the dissociation constant of the neutral imidazole (3.16×10^{-15} M).[18] The value of k_{Im} from the intercept of Figure 5 is 6.12×10^{-6} M^{-1} s^{-1}, while the slope of Figure 5 yields the value for $k_{Im'}$, 20.1 M^{-2} s^{-1}. From eq 2, k_{Im^-} is calculated to be 93.3 M^{-1} s^{-1}.

$$k_{Im^-} = k_{Im'}\left(\frac{K_w}{K_a'}\right) \qquad (2)$$

Discussion

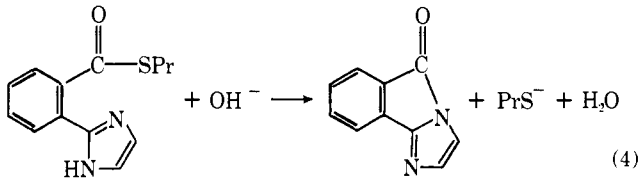
Two discrete steps, cyclization to *N*-2-(2′-benzoyl)imidazole (III) and slower hydrolysis of the intermediate, can be observed in the hydrolysis of the thiol ester I at pH values greater than 5.5 (eq 3). The similarity of the rate constants for breakdown



III
+
n-PrSH (3)

of the observed intermediate and synthetically prepared III and the identity of their spectral characteristics[9] clearly establish that III is the intermediate. At pH values less than 5.5 only one step can be observed in the formation of *o*-(2-imidazolyl)benzoic acid, which indicates that hydrolysis of III is then faster than cyclization. The pH dependence of k_{obsd} in hydrolysis of III is consistent with this interpretation.[9] The pH-log (rate constant) profile for the formation of the intermediate is linear at all pH values with a slope of 1.0. The value of k_{OH} for cyclization of I is 5×10^6 greater than k_{OH} for hydroxide ion catalyzed hydrolysis of *n*-propyl thiolbenzoate. Thus, the neighboring imidazole group is giving rise to an extremely facile nucleophilic reaction.

In the cyclization of I to the acylimidazole intermediate the linear plot of log k_0 vs. pH with slope of 1.0 at high pH indicates hydroxide ion catalysis in the reaction of the neutral species (eq 4) or a kinetic equivalent. However, the plot is also



(4)

still linear at pH values as low as 5.5 and there is no break in the pH region where the pK_a of the imidazole function would occur.[9] Values of log k_0 for the hydrolytic reaction at pH 4.2–4.9, determined at 285 nm, also gave a reasonable fit to a theoretical line of slope 1.0. If the reaction only involved OH^- catalysis of the reaction of the neutral species, then at the pK_1 of the imidazole group the slope would change to 2.0 as observed in cyclization of methyl 2-aminomethylbenzoate.[8] Thus, a reaction must be occurring at low pH that will allow a profile of slope 1.0. Such a reaction would be an uncatalyzed or water-catalyzed reaction of the neutral species. The equation for k_0 would then be eq 5, or the equivalent eq 6 for reaction of the imidazole anion:[9]

$$k_0 = [k_N + k_2(OH^-)]\left[\frac{K_1}{K_1 + a_H}\right] \quad (5)$$

$$k_0 = \left[k_N + \frac{k_A K_2}{a_H}\right]\left[\frac{K_1}{K_1 + a_H}\right] \quad (6)$$

where k_N, k_2, and k_A are rate constants for the neutral species, hydroxide ion catalyzed reaction, and anionic species reaction, respectively, K_1 is the dissociation constant of the conjugate acid of the imidazole group, and K_2 is the dissociation constant of the neutral imidazole. For the pH–rate constant profiles to be linear at all pH values, then at a pH corresponding to pK_1 eq 7 or 8 must hold:

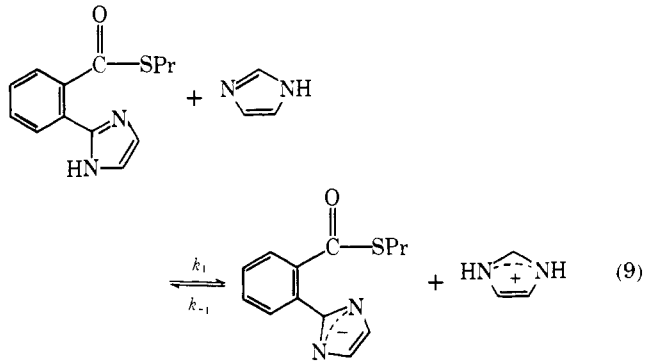
$$k_N = k_2(OH^-) \quad (7)$$

$$k_N = k_A K_2 / a_H \quad (8)$$

i.e., the contributions of the two reactions to k_0 will be a function of pH and will be equal at pK_1. This was also found for neighboring imidazole group participation in the hydrolysis of the trifluoroethyl and phenyl esters of *o*-(2-imidazolyl)-benzoic acid.[9] In cyclization reactions of esters of *o*-(2-imidazolyl)benzoic acid an uncatalyzed neutral species reaction is significant only with the better leaving groups ($pK_a \leq 12.4$).[9] Hydroxide ion catalysis occurs in the intramolecular nucleophilic reactions of aliphatic esters of 2-aminomethyl-,[8] 2-hydroxymethyl-,[11] or 2-mercaptomethylbenzoic acid,[19] but uncatalyzed neutral species reactions were not detected.

Phenyl *o*-(2-imidazolyl)benzoate cyclizes much faster than the corresponding trifluoroethyl ester in both the anionic species and the neutral species reactions.[9] In view of the difference in pK_a of phenol (10)[20] and trifluoroethanol (12.4),[21] the difference in the rate constants implies a large influence of the leaving group in the critical transition states. An ortho aminomethyl group gives rate constants (k_{OH}) that are ~300-fold greater than found with a neighboring imidazole group,[9,22] indicating that β for the nucleophile is also 1.0 or greater. Thus, the kinetic data indicate that breakdown of a tetrahedral intermediate is rate determining in both the hydroxide ion catalyzed and uncatalyzed neutral species reactions with formation of the tetrahedral intermediate through nucleophilic attack by the neighboring group at complete equilibrium with respect to the reactant state. This would explain the completely linear pH–rate constant profiles for esters with leaving groups of $pK_a < 12.4$, including I, and the fact that the contributions of the two reactions to k_0 are a function only of pH, not nucleophilicity. If formation of the tetrahedral intermediate is an equilibrium process, then at pK_1 there will be no kinetic advantage from reaction of the anionic species of the nucleophile rather than the neutral species. Ease of proton transfer and ease of nucleophilic attack must exactly compensate in their effects on the equilibrium concentration of the tetrahedral intermediate.

General base catalysis by various buffer bases is observed in the cyclization of I, and the Brønsted coefficient β is within error 1.0. In classical general-base-catalyzed reactions bases of widely different types have been found to lie on a single line.[23,24] The Brønsted coefficient close to 1.0 indicates that the rate-determining step in the reactions of I must be a proton transfer in the thermodynamically unfavorable direction.[10] Proton removal from the neighboring imidazole group by a general base cannot be rate limiting. In the reaction of eq 9 k_1,

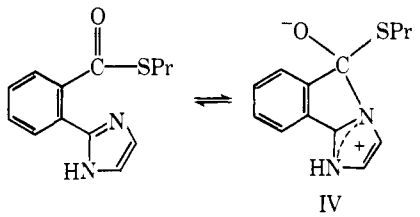


(9)

the rate constant for proton transfer, is given by eq 10 where K_a is the dissociation constant of imidazolium ion (10^{-7} M) and K_2 is the dissociation constant of the imidazole group of the reactant. Assuming that K_2 has a value of 5×10^{-14} M,[18] then, since k_{-1} is the rate constant for a diffusion-controlled reaction (10^{10} M^{-1} s^{-1}), k_1 would be 5000 M^{-1} s^{-1}, which is 10^4-fold larger than the experimentally determined second-order rate constant for imidazole catalysis in the cyclization of I.

$$k_1 = k_{-1}\left(\frac{K_2}{K_a}\right) \quad (10)$$

Nucleophilic attack by the neutral species would lead to a zwitterion intermediate IV. Such an intermediate would be



(11)

IV

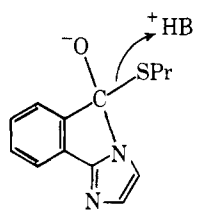
quite unstable, and would revert rapidly to starting material. It must therefore be stabilized by transfer of a proton. Rate-determining proton transfer from an acyl imidazolium intermediate IV to a general base would be thermodynamically favorable with general bases of high pK_a ($\beta = 0$). Likewise, rate-determining proton transfer to IV from general acids would be thermodynamically unfavorable ($\alpha = 1.0$) when the pK_a of the catalyst exceeds that of the intermediate. Curvature would consequently occur in the Brønsted plot near the pK_a of the intermediate, which would be expected to be reasonably low.[25] In the rearrangement of *S*-acetylmercaptoethylamine,[25] where protonation of a zwitterionic intermediate was considered to be rate determining, a Brønsted plot for general acid catalysis had a change in slope from 0 to 1.0 at pH 7.4. Therefore, in view of the completely linear Brønsted plot of Figure 3, proton transfer to or from IV is probably not the rate-limiting step. Such a proton-transfer step was likewise ruled out as rate limiting in cyclization of other 2-substituted benzoate esters including methyl 2-aminomethylbenzoate[8] and phenyl *o*-(2-imidazolyl)benzoate,[9] where Brønsted plots are

Table II. Nucleophilic Reactions of 2-Substituted Benzoate Esters at 30 °C

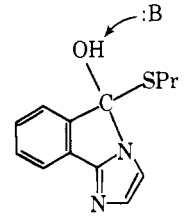
nucleophile	leaving group	k_{OH},[a] $M^{-1}s^{-1}$	general base catalysis	β	ref
$-CH_2OH$	EtOH	10^4	+	1.0	11
$-CH_2SH$	$(CH_3)_3COH$	3×10^3	−		19
$-CH_2NH_2$	CH_3OH	7×10^3	+	1.0	8
	CF_3CH_2OH[b]	2×10^5	+	1.0	22
	phenol[b]	5×10^7	+		22
	CH_3OH[c]		−		9
	CF_3CH_2OH[b]	10^3	−		9
	phenol[b]	1.2×10^5	+	1.0	9
	$CH_3CH_2CH_2SH$[b]	2×10^5	+	1.0	

[a] Second-order rate constant for cyclization. [b] Completely linear pH-rate constant profiles (slope = 1.0). [c] No intramolecular nucleophilic participation.

still linear at $pK_a > 11$. The most likely rate-determining step in the general-base-catalyzed reaction then is proton transfer to an anionic species or from a neutral tetrahedral intermediate (V and VI). Formation of a tetrahedral intermediate has been



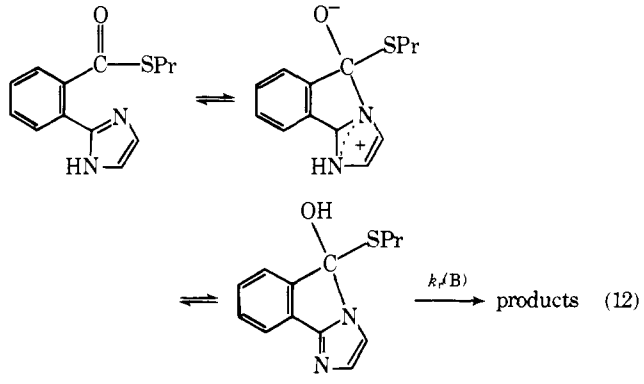
V



VI

conclusively demonstrated in thiol ester hydrolysis[26,27] and aminolysis.[28] The β value of 1.0 in cyclization of I supports VI.

It may be surmised that nucleophilic attack by the neutral nucleophile will necessitate proton transfer steps, one of which will be rate determining in a general-base-catalyzed reaction (eq 12). A species in which the carbonyl oxygen is protonated

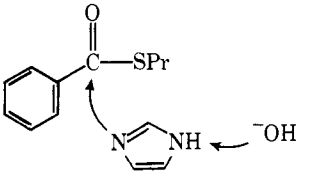


(12)

must then be produced rapidly in order to prevent reversion back to the reactant state. Such a proton transfer could be mediated in a concerted or stepwise manner as suggested in the bimolecular aminolysis of aliphatic esters.[7] A totally concerted preequilibrium formation of a neutral tetrahedral intermediate would avoid the unstable zwitterion IV as an intermediate. This might be especially important with a neighboring imidazole group since the zwitterion IV would be extremely reactive and might not have a sufficient lifetime ($<10^{-13}$ s) to be considered a discrete intermediate. Nucleophilic attack by the anionic species would, of course, generate an anionic tetrahedral intermediate directly.

The data for the various nucleophiles and leaving groups in the 2-substituted benzoate system are collected in Table II. It can be concluded that in the intramolecular aminolysis reactions of 2-substituted benzoate esters with poor leaving groups (pK_a = 10–16) the relationship between the rate constants for the apparent hydroxide ion catalyzed reaction and the uncatalyzed neutral species reaction is not a function of the difference in pK_a between the nucleophile and the leaving group, nor is the magnitude of β (1.0) a function of the leaving group. In all cases the tetrahedral intermediate must be at complete equilibrium with respect to the reactant. Whether an uncatalyzed neutral species reaction will take place does, however, depend on the basicity of the leaving group. For occurrence of an intramolecular nucleophilic reaction when the leaving group is an aliphatic alcohol of $pK_a \sim 16$ the nucleophile must be reasonably basic as with an aminomethyl group.[8] A neighboring imidazole group does not act as an intramolecular nucleophile in the hydrolysis of methyl *o*-(2-imidazolyl)benzoate, presumably because imidazole is expelled preferentially from the tetrahedral intermediate.

Imidazole is a catalyst in the hydrolysis of ethyl thiolacetate[29] and butyl thiolacetate.[30] The reactions of neutral imidazole with these esters at 25 or 30 °C have second-order rate constants up to 100-fold greater than in the imidazole-catalyzed hydrolysis of II. The decreased reactivity of II is very likely due to the relative deactivating effect of the phenyl group. Bimolecular thiol ester aminolysis reactions generally involve rate-determining formation of a tetrahedral intermediate at pH > 4,[2,31-33] although partitioning of the tetrahedral intermediate may be of kinetic significance in some cases.[1,33] General acid–general base catalysis has been detected in the aminolysis reactions.[1] Hydroxide ion catalyzed attack of imidazole was also observed in hydrolysis of II and occurs as in VII or a kinetic equivalent. This type of reaction has been detected in the aminolysis of a variety of thiol esters.[34-36]



VII

Rate-determining breakdown of a tetrahedral intermediate to products in an intramolecular reaction in contrast with rate-determining formation of a tetrahedral intermediate in analogous bimolecular reactions could reflect an increased concentration of the intermediate in the former case. This would result because of the greater ease of formation of the tetrahedral intermediate in the intramolecular reaction due primarily to favorable entropy and proximity effects.[1,37] Translational entropy of the nucleophile is not lost in an intramolecular reaction. In contrast, only low steady state levels of tetrahedral intermediate may be formed in bimolecular reactions with breakdown to products more rapid than reversion to reactants.

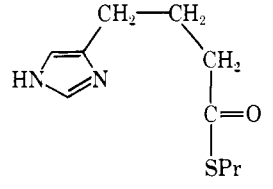
The efficiency of intramolecular imidazole and imidazole anion as nucleophiles in the cyclization of the *S-n*-propyl thiol ester I can be expressed as their respective effective molarities.

The effective molarity is the ratio of the first-order rate constant for maximum participation by the intramolecular nucleophile divided by the second-order rate constant for the exactly analogous bimolecular reaction, in this case imidazole-catalyzed hydrolysis of II. The ratio of rate constants ($s^{-1}/M^{-1}s^{-1}$) has units of molarity and can be considered to be the concentration of imidazole required in the bimolecular reaction to attain a pseudo-first-order rate constant of the magnitude of that in the intramolecular reaction. Reasonable values of pK_1 and pK_2 at 30 °C would be 6.5[9,38] and 13.3, respectively.[38] At pK_1 k_{obsd} is equal to the first-order rate constant for imidazole neutral species attack (10^{-2} s^{-1}).[39] The value of k_A can then be calculated to be 6.3×10^4 s^{-1}. Thus, the effective molarity of the neighboring imidazole neutral species of I is 1.6×10^3 M while that of the imidazole anion is 7×10^2 M. Although these effective molarities are the largest that have been observed in neighboring-group reactions of thiol esters,[40] they are small in comparison with those found[14,41] in the intramolecular nucleophilic reactions of carbamate esters (10^5–10^8 M). The comparative effective molarity of the neighboring group of I could reflect greater difficulty of the intramolecular reaction and/or a greater ease of bimolecular attack on the reference compound II. A difference in rate-determining step with the comparison reaction would reduce greatly the apparent efficiency of the neighboring group of I.

Conclusions

Four intramolecular nucleophilic aminolysis reactions have now been observed with 2-substituted benzoate esters to give completely linear pH–rate constant profiles with slopes of 1.0 at pH values through the pK_a of the nucleophile. In these reactions two different nucleophilic groups have been employed (aminomethyl and imidazole) and three different leaving groups have been utilized. Thus, the linear pH–rate constant profiles are not coincidentally produced by the magnitude of the rate constants for the OH^- catalyzed and uncatalyzed reactions but are a property of the 2-substituted benzoate system.

The mechanism and/or rate-limiting step of bimolecular aminolysis of thiol esters (rate-determining attack of amine at the carbonyl)[1,2,31-33] is different than that of the intramolecular reaction of I. General base catalysis by imidazole does not take place in the bimolecular nucleophilic reaction of II with imidazole. The mechanism of cyclization of I is also different than that of the less sterically constrained *S*-*n*-propyl γ-(4-imidazolyl)thiolbutyrate (VIII), which cyclized only



VIII

through reaction of the neutral species and with no apparent buffer catalysis.[12] The mechanistic differences encountered in the reactions of substituted butyrate esters[12,13,42] cannot be ascribed to the leaving group since the phenol and *n*-propyl thiol leaving groups are in common, but again must be due to the 2-substituted benzoate system. Two readily apparent differences are the more deactivated carbonyl of the benzoate esters and the much greater rigidity of that system; i.e., there are fewer degrees of freedom for rotation of the nucleophile away from the reaction center. In cyclization of the 2-substituted benzoate esters the proximity of the nucleophile to the carbonyl enhances greatly the ease of the attack step (bond making), but a cyclic zwitterionic intermediate would be quite unstable and would revert rapidly to reactant unless it were stabilized by proton transfer. These features could result in equilibrium formation of a neutral tetrahedral intermediate and rate-limiting decomposition of the tetrahedral intermediate to products. Only a low steady-state level of tetrahedral intermediate is formed in the cyclization of S-*n*-propyl γ-(4-imidazolyl)thiolbutyrate,[1,12] although higher concentrations are achieved in the cyclization of phenyl esters of γ-(4-imidazolyl)butyric acid.[1,42] Proton transfer cannot occur in reactions of substituted phenyl *N,N'*-dimethylaminobutyrate and valerate esters,[13] and in those reactions a zwitterionic tetrahedral intermediate may break down directly to products. Sterically constraining a nucleophile close to the carbonyl in the 2-substituted benzoate esters has produced a mechanism involving general base catalysis in which a proton-transfer step is rate determining ($\beta = 1.0$) even when the leaving group is relatively good. Thus, the lack of rotational degrees of freedom of I has led to a mechanism not seen in comparable bimolecular reactions or in intramolecular reactions where degrees of freedom exist. It has long been thought that enzymes owe their efficiency in part to restriction of functional groups in the active site in close proximity to the reaction center. Consequently, it is quite probable that with esteratic enzymes the steric situation resembles that of appropriate 2-substituted benzoate esters with corresponding mechanistic consequences.

It has been suggested that in deacylation of cysteine proteases the imidazole ring of histidine functions as a classical general base catalyst by partially abstracting a proton from a water molecule in the transition state.[15] This mechanistic assignment has been based mainly on large D_2O solvent isotope effects.[43,44] However, general base catalysis by imidazole in the hydrolysis of thiol esters has been infrequently observed in chemical systems. The only examples of such catalysis are in the hydrolysis of ethyl trifluorothiolacetate[26] and in the reaction of δ-thiovalerolactone with hydrazine.[30] It is clear that very large rate enhancements can be obtained in intramolecular nucleophilic reactions of thiol esters, and on that basis a nucleophilic reaction in the enzymatic deacylation reaction might be preferred. General base catalysis in breakdown of a tetrahedral intermediate analogous to that in cyclization of I would also allow the observed solvent isotope effect to be in accord with a nucleophilic mechanism. The principal argument against a nucleophilic mechanism in enzymatic deacylation is that back attack by the thiol leaving group could severely reduce the efficiency of a nucleophilic reaction. However, reversibility effects could be eliminated in the enzyme reaction through conformational changes or by direct participation of other functional groups.[45] Thus, at the present time the enzymatic mechanism must be considered an open question.

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Nucleophilic Substitution Reactions of *trans*-4-(Para-substituted phenoxy)-3-buten-2-ones

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Abstract: Reactions of *trans*-4-(para-substituted phenoxy)-3-buten-2-ones (**1–6**) with primary amines to give 4-alkylamino-3-buten-2-ones in water are characterized by (1) rates which are first order in amine and **1–6**, (2) a Hammett type $\rho^* = 0.11$ for reactions of **1–6** with aminoethanol, (3) $\beta_{nuc} = 0.37$ for reactions of 4-(*p*-anisoxy)-3-buten-2-one (**1**) with ethyl glycinate, trifluoroethylamine, 2-ethoxyethylamine, 2-aminoethanol, and *n*-butylamine, (4) a deuterium solvent kinetic isotope effect $k_2(H_2O)/k_2(D_2O) = 0.98$ for reaction of **1** with 2-aminoethanol, and (5) a Ritchie N^+ coefficient of 1 ± 0.2 for reactions of **1** with imidazole, ethyl glycinate, *n*-butylamine, and hydroxide ion. Reactions of thiols with the title compounds give 4-alkylthio-3-buten-2-ones at low concentrations of thiol and 4,4-dialkylthiobutan-2-ones at high concentrations of thiols. The former reactions are characterized by (1) rates which are first order in thiolate anion and **1–6** and (2) $\rho^* = 0.14$ for reactions of **1**, 4-(*p*-chlorophenoxy)-3-buten-2-one (**4**), and 4-(*p*-nitrophenoxy)-3-buten-2-one (**6**) with *N*-acetylcysteine. These data support an addition–elimination reaction with nucleophilic attack rate determining. The kinetics of the reactions of **1** and **4** with morpholine and *N*-methylaminoethanol appear to provide evidence for the partitioning of the putative **1**- and **4**-amine addend between **1** and **4** and products.

Introduction

For reactions of *trans*-3-methoxy-4′-substituted acrylophenones with primary amines in water to give 3-alkylamino-4′-substituted acrylophenones and methanol, an addition–elimination reaction mechanism previously established[1-11] for aromatic and vinylic nucleophilic substitution reactions was postulated and attack of amines at the 3 carbon to give zwitterionic intermediates was indicated by the data to be the rate-determining step in this complex reaction.[12] The present study describes the kinetics results of some reactions of *trans*-4-(para-substituted phenoxy)-3-buten-2-ones (**1–6**) with amines and thiols (eq 1, X = CH_3O (**1**), CH_3 (**2**), H (**3**), Cl (**4**), CN (**5**), NO_2 (**6**); Y = NH, S).

$$p\text{-X—}C_6H_4OCH{=}CHCOCH_3 + RYH \rightarrow p\text{-X—}C_6H_4OH + RYCH{=}CHCOCH_3 \quad (1)$$

These reactions likely take place via a similar addition–elimination mechanism, and the data suggest that, for reactions of **1–6** with primary amines and with thiols, nucleophilic attack is rate determining. For reactions of **1** and **4** with secondary amines, there is kinetics evidence for the formation of zwitterionic intermediates.

Experimental Section

Apparatus. The apparatus used was previously described.[12]

Reagents and Compounds. 4-(Para-substituted phenoxy)-3-buten-2-ones (**1–6**) were available from a previous study or were prepared as needed by following the published procedure.[13] 3-Butyn-2-one (Pfaltz and Bauer), phenols, amines, and thiols (Aldrich) were purchased and purified as necessary. Certified ACS grade inorganic salts and organic solvents were purchased from Fisher. Deuterium oxide and DCl were purchased from Diaprep, Inc. Tap distilled water was redistilled through a Corning AGla still.

Kinetics. The reactions of **1–6** with amines and thiols were monitored by recording the increase or decrease in absorbance vs. time at the following wavelengths (nm): **1**, 265, 282; **2**, 265, 285; **3**, 260, 285; **4**, 262, 290; **5**, 275; **6**, 250, 410. Reactions were carried out under pseudo-first-order conditions ([**1–6**] = 10^{-4} to 10^{-5} M) at 30 °C, and ionic strength was maintained at 0.1 M by using added KCl. The pH of each solution remained constant throughout runs. Reactions were started by adding **1–6** in methanol or dioxane from a calibrated syringe to 3-mL cuvettes filled with appropriate solution which had been brought to reaction temperature. Pseudo-first-order rate constants were obtained by multiplying the slopes of plots of $\log((A_\infty - A_i)/(A_\infty - A_t))$, for absorbance increase, and $\log((A_i - A_\infty)/(A_t - A_\infty))$ for absorbance decrease vs. time by 2.303. pD was calculated by adding 0.4 to pH meter readings.[14]

Products. *cis*-4-*tert*-Butylamino-3-buten-2-one. A 1.7-g (10 mmol) quantity of **3** was added to 0.8 g (10 mmol) of *tert*-butylamine in 50 mL of water. To this mixture was added 2 drops of concentrated HCl and the mixture was stirred at room temperature until aliquots of the reaction mixture showed no further change in absorbance at 285 nm. The mixture was diluted with 50 mL of water and this was extracted with 100 mL of $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous

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