tion for the Spirocycles 12, 13, and 14. Using a mixture of 0.1 M aqueous sodium hydroxide containing 63 mol % dimethyl sulfoxide tritium exchange from spirocycles 12, 13, and 14 was studied at 25.07 and 13.11°. The results are displayed in Table IV. Each entry is the average of duplicate runs.

Dependence of the Rate Constant on Mol % Dimethyl Sulfoxide. According to the general procedure, tritium exchange from spiro [2.3]hexadiene 12 and spiro[2.3]hex-4-ene 13 was followed in aqueous solutions of 0.10 M sodium hydroxide containing 46.0, 50.4, 59.0, and 63.0 mol % dimethyl sulfoxide in separate determinations. The second-order rate constants were calculated and are presented in

Table II. Duplicate runs were carried out at each different concentration of dimethyl sulfoxide.

Base-Catalyzed Hydrolysis of N-Acylpyrroles. A Measurable Acidity of a Steady-State Tetrahedral Intermediate

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Abstract: The basic hydrolysis of N-acetylpyrrole is second order in hydroxide ion at low base concentrations while first order in hydroxide ion at high base concentrations. There is an inverse solvent isotope effect and no general base catalysis. On the other hand, the hydrolysis of N-p-nitrobenzoylpyrrole is first-order in hydroxide ion and is subject to general base catalysis. The mechanisms of the two hydrolyses (involving a change in the rate-determining step in the acetyl system) and the source of their differences are analyzed in detail. We also describe a unique sigmoid pH–rate profile for N-salicylylpyrrole. Its flex point lies 1.4 pH units *above* the pK_a of the substrate. Moreover, the rate is independent of the pH for all pH values above 11. These results are interpreted in terms of a kinetically important ionization of a steady-state intermediate, the first example of its kind. Both formation and collapse of the intermediate involve intramolecular participation.

The mechanisms for the base-catalyzed hydrolysis of a variety of acetamides, acetanilides, and acylimidazoles have been explored in detail.[2–4] We report here an investigation of the basic hydrolysis of yet another type of amide, the N-acylpyrrole. Since N-acylpyrroles are interesting from an electronic standpoint,[5] we were curious about their hydrolytic behavior which had previously never been studied. We also had a specific reason for carrying out this work: Pollack and Bender[6] maintained that the basic hydrolysis of p-nitroacetanilide involves an anionic intermediate that collapses *via* a preequilibrium ionization rather than by a general base mechanism. They based their conclusion solely on the presence of an inverse solvent isotope effect, recognizing that this is not always a decisive piece of evidence. We found that N-acetylpyrrole displays kinetics very similar to those of p-nitroacetanilide (including an inverse solvent isotope effect). However, N-acylpyrroles react somewhat faster than anilides, thereby enabling us to operate at a pH range where general base catalysis can be observed. Thus, we could test the validity of the solvent isotope effect as a mechanistic criterion.

Experimental Section

Synthesis. We used two methods to prepare the N-acylpyrroles. The first, direct acylation of pyrrole, was successful only with N-acetylpyrrole. The second method, reaction of an amide with 2,5-dimethoxytetrahydrofuran,[7] provided the other substrates.

N-**Acetylpyrrole.** Triethylamine (30 g, 0.30 mol) was added to a mixture of pyrrole (22 g, 0.33 mol) and acetic anhydride (36 g, 0.35 mol). The solution was boiled under reflux for 16 hr, cooled, diluted with 100 ml of ether, and washed with water and saturated aqueous sodium chloride. A tar-like precipitate formed during the sodium chloride wash. After filtering the ether layer through anhydrous sodium sulfate, we removed the ether with the aid of a rotary evaporator to secure a thick brown oil. The oil was distilled through a 6-in. Vigreux column to give 18 g (50%) of N-acetylpyrrole, bp 178° (lit.[8] 179–181°). After purification of the product by two distillations through a spinning band column, we obtained material which was greater than 99% pure (glc). The ir spectrum (carbonyl at 1719 cm⁻¹) and nmr (AA′BB′ sextet) were consistent with acetylation on the nitrogen.

Anal. Calcd for C_6H_7NO: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.96; H, 6.58; N, 12.71.

N-**Benzoylpyrrole.**[7] 2,5-Dimethoxytetrahydrofuran (8.5 g, 0.064 mol) and benzamide (6.0 g, 0.050 mol) in 50 ml of glacial acetic acid were boiled under reflux for 48 hr. The mixture was cooled, poured onto ice, neutralized with sodium bicarbonate, and extracted with ether. Removal of the solvent from the ether extract left a thick brown oil which was purified first by steam distillation and then by vacuum distillation, bp 125° (1.8 mm). The colorless product (4.0 g, 47%) possessed a carbonyl stretching band at 1698 cm⁻¹ and a characteristic nmr sextet (triplets at δ 6.0 and 7.1). Glc analysis proved that the product was greater than 95% pure.

N-p-**Nitrobenzoylpyrrole.** Equimolar amounts of p-nitrobenzamide (16.6 g) and 2,5-dimethoxytetrahydrofuran (13.2 g) were dissolved in 100 ml of glacial acetic acid, and the mixture was heated

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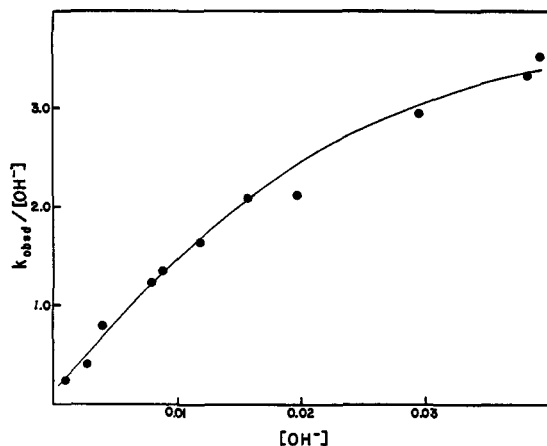(8) P. Linda and G. Marino, *Ric. Sci.*, 37, 424 (1967); *Chem. Abstr.*, 68, 39570q (1968).

Figure 1. Plot of $k_{obsd}/[OH^-]$ vs. $[OH^-]$ for the hydrolysis of N-acetylpyrrole at 25.0°.

Figure 2. Plot of $k_{obsd}/[OH^-]$ vs. $[OH^-]$ for the hydrolysis of N-benzoylpyrrole at 25.0°.

gently for 2 hr. The acetic acid was removed under reduced pressure, leaving a dark granular residue which was extracted with 500 ml of ether in small portions. Since the solid obtained upon removal of the ether could not be purified by crystallization, we chromatographed it on a Silicar CC-7 column using benzene as the eluent. About 3 g of N-p-nitrobenzoylpyrrole was collected. This was sublimed at 120° (0.25 mm) to give yellow crystals, mp 127–128°, in 14% yield.

Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.16; H, 3.73; N, 12.96.

N-Salicylylpyrrole. This compound was prepared in 21% yield from 5.0 g of salicylamide (0.036 mol) and 5.0 g of 2,5-dimethoxy-tetrahydrofuran (0.038 mol) by the same procedure used for N-benzoylpyrrole. After purification of the product by distillation (100°, 0.7 mm), we obtained material which was greater than 95% pure (glc) and which had a strong ir band at 1640 cm⁻¹. Attempts to increase the scale of the preparation failed.

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.66; H, 4.93; N, 7.40.

Reagents. Eastman spectro grade acetonitrile and Columbia 99.8% deuterium oxide were used without modification. Triethyl-enediamine (Dabco) was purified by crystallization from heptane followed by sublimation. Trimethylamine, purified by means of low-temperature distillations over phthalic anhydride, was used immediately to prepare aqueous stock solutions. We determined the amine concentrations in the stock solutions by titrations prior to the kinetic runs. N-Methylpyrrolidine was also distilled over phthalic anhydride to remove primary and secondary amines. Buffers were made from reagent grade materials; their pH values were obtained with a Corning Model 12 pH meter standardized with Harleco pH 10.00 and pH 7.00 buffers.

Kinetics. First-order rate constants for hydrolysis of the N-acyl-pyrroles at constant pH were calculated from absorbance vs. time data obtained with the aid of Cary 14 and Beckman DB-GT recording spectrophotometers. A stoppered cuvette containing 3.00 ml of a buffer or aqueous sodium hydroxide solution was equilibrated at 25.0 ± 0.1° for 20 min within the thermostated cell compartment of one of the spectrophotometers. We initiated the reaction by adding 50 μl of substrate dissolved in acetonitrile. Proper mixing was accomplished by stirring the solution quickly with a rod flattened at one end. The ensuing hydrolysis was followed until no change in absorbance could be detected for at least one half-life. Concentrations of N-acetylpyrrole, N-benzoylpyrrole, and N-p-nitrobenzoylpyrrole within the cuvettes were about 1×10^{-4}, 1×10^{-4}, and 7×10^{-5} M, respectively; monitoring wavelengths were 238, 255, and 245 nm, respectively. Agreement between repeat runs was 3%. When we added 25 μl of substrate solution instead of 50 μl, the rate constants remained unchanged.

Product Analysis. The products of N-acylpyrrole hydrolyses were examined spectrophotometrically as follows. We calculated molar extinction coefficients (from 350 to 220 nm at 5 nm intervals) from spectra traced at the completion of the kinetic runs. We then compared these values with the sum of the coefficients obtained from solutions of purified pyrrole and carboxylic acid under conditions identical to those of the kinetic experiments. Agreement was 10% or better at the several wavelengths. Sharp isosbestic points also indicated that our kinetic systems were well behaved.
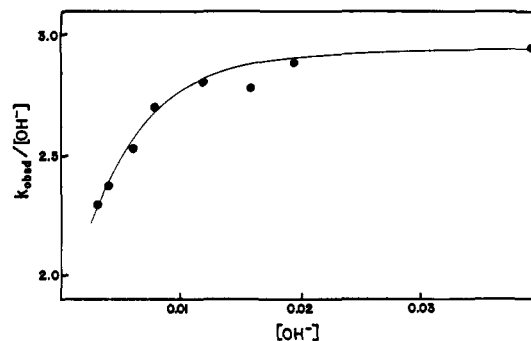
Table I. Observed Rate Constants for the Lyoxide Catalyzed Hydrolysis of N-Acetylpyrrole at 25.0° in Water and Deuterium Oxide[a]

$[OH^-] \times 10^2$, M	$k_{obsd} \times 10^2$, sec⁻¹
Water	
3.94	13.8
3.94	14.1
3.83	12.9
2.96	8.80
1.97	4.22
1.58	3.32
1.18	1.97
0.895	1.21
0.787	1.00
0.394	0.320
0.266	0.115
Deuterium Oxide	
3.78	18.3
3.33	15.0
3.33	14.0
2.83	13.2
1.89	6.80
1.66	6.00
0.850	2.12
0.803	2.02
0.333	0.446
0.160	0.100

[a] 1.6% acetonitrile; no added salt.

pK_a of N-Salicylylpyrrole. The pK_a value was determined spectrophotometrically using imidazole buffers. We avoided phosphate and borate buffers in order to preclude the possibility of complex formation.

Results

The rate constants for the hydrolysis of N-acetylpyrrole in basic water and deuterium oxide are presented in Table I. A plot of $k_{obsd}/[OH^-]$ vs. $[OH^-]$ for the reaction in water (Figure 1) is distinctly curved. If the amide hydrolysis were first order in hydroxide,[9,10] then we would have obtained a horizontal straight line. If the hydrolysis were second order (or mixed first and second order) in hydroxide,[11] then Figure 1 would be a straight line with a positive slope. Clearly, at low $[OH^-]$ the hydrolysis of N-acetylpyrrole is mainly second order in hydroxide,[12] while at high $[OH^-]$ the reaction approaches first-order behavior. The transition is even more striking in the hydrolysis of N-benzoylpyrrole (Table II, Figure 2). A rate expression

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(10) M. L. Bender and R. D. Ginger, *ibid.*, 77, 348 (1955).
(11) S. S. Biechler and R. W. Taft, *ibid.*, 79, 4927 (1957).
(12) The log k vs. log $[OH^-]$ profile at low hydroxide concentrations has a slope of 1.75.

Table II. Observed Rate Constants for the Hydroxide Ion Catalyzed Hydrolysis of N-Benzoylpyrrole at 25.0° [a]

[OH⁻] × 10², M	k_{obsd} × 10², sec⁻¹
3.93	11.6
1.94	5.61
1.57	4.36
1.18	3.34
1.18	3.29
0.785	2.13
0.590	1.54
0.590	1.49
0.590	1.46
0.393	0.934
0.294	0.673
0.294	0.679

[a] 1.6% acetonitrile–water (v/v); no added salt.

which accounts for our data has the form shown in eq 1

$$k_{obsd} = C_1[OH^-]^2/(C_2 + C_3[OH^-]) \quad (1)$$

(where C's are constants). The same type of equation was used in the analysis of the basic hydrolysis of p-nitroacetanilide[6] and trifluoroacetanilides.[13–16] However, while the trifluoroacetanilides display solvent isotope effects substantially greater than unity, *inverse* isotope effects are found for both p-nitroacetanilide (0.61 at [OH⁻] = 4.60 × 10⁻³ M)[6] and N-acetylpyrrole (0.59 at [OH⁻] = 1.60 × 10⁻³ M; see Table I).[17]

On the basis of the inverse solvent isotope effect alone, Pollack and Bender[6] concluded that general base catalysis is unimportant in the hydrolysis of p-nitroacetanilide. If this is correct,[18] then the kinetically similar N-acetylpyrrole hydrolysis should remain unperturbed by general bases. Fortunately, we were able to test for general base catalysis in the classical manner because N-acetylpyrrole (unlike p-nitroacetanilide) reacts at a convenient rate in buffered solutions of low alkalinity. We found that N-acetylpyrrole in buffers of N-methylpyrrolidine (pK_a = 10.46) hydrolyzes with a rate that is independent of the amine concentration up to 0.5 M. Likewise, quinuclidine possesses no general base capabilities at 0.1 N. This tertiary amine (pK_a = 10.58)[19] is unhindered so that its inertness cannot be attributed to a sterically impeded proton transfer.[20] Thus, the hydrolysis of N-acetylpyrrole is a function of pH but not of buffer concentration, and the conclusions of Bender and Pollack are confirmed.

Surprisingly, we found that the hydrolysis of N-p-nitrobenzoylpyrrole differs from that of N-acetylpyrrole in two important ways. (1) The hydrolysis rate of the nitrobenzoyl compound is proportional to the concentration of trimethylamine and triethylenediamine (Dabco) at constant pH (Table III). Dabco catalysis is markedly diminished in deuterium oxide. At pH

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(14) R. L. Schowen, H. Jayaraman, and L. Kershner, *J. Amer. Chem. Soc.*, **88**, 3373 (1966).
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(16) P. M. Mader, *ibid.*, **87**, 3191 (1965).
(17) Solvent isotope effect values are given for low [OH⁻] where both reactions are mainly second order in hydroxide.
(18) Some general base-catalyzed reactions manifest inverse solvent isotope effects. G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).
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(20) F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).

Table III. Rate Constants for Hydrolysis of N-p-Nitrobenzoylpyrrole in Buffered Solutions[a] at 25.0°

Buffer	[Buffer], M	pH	Ionic strength[b]	k_{obsd} × 10³, sec⁻¹
(CH₃)₃N[c]	0.230	9.97	0.5	4.49
	0.149			4.86
	0.118			3.82
	0.053			3.68
	0.000			3.2[d]
	0.230	9.72	0.5	3.05
	0.149			2.60
	0.118			2.32
	0.053			1.94
	0.000			1.5[d]
	0.230	9.46	0.5	1.64
	0.149			1.43
	0.118			0.74
	0.053			1.05
	0.000			0.89
	0.230	9.23	0.5	0.93
	0.149			0.78
	0.118			0.74
	0.053			0.57
	0.000			0.48[d]
Dabco[e]	0.500	9.61	f	2.93
	0.200			2.10
	0.100			1.91
	0.050			1.58
	0.000			1.5[d]
	0.500	9.40	f	2.27
	0.200			1.62
	0.100			1.18
	0.050			0.89
	0.000			0.68[d]
	0.500	9.20	f	1.77
	0.200			1.21
	0.100			0.88
	0.050			0.54
	0.000			0.50[d]
	0.146	9.02	f	0.59
	0.117			0.48
	0.073			0.45
	0.073			0.43
	0.015			0.28
	0.000			0.26[d]
Carbonate	0.250	10.11	1.0	6.95
	0.200			6.51
	0.100			5.94
	0.070			5.50
	0.070			5.28
	0.000			4.9[d]
	0.250	9.40	1.0	1.14
	0.200			1.13
	0.100			1.01
	0.070			0.99
	0.000			0.92[d]

[a] 1.6% acetonitrile–water (v/v). [b] Maintained by addition of KCl. [c] pK_a = 9.76. [d] Estimated with ±10% error by extrapolating to zero buffer concentration. [e] Triethylenediamine, pK_a = 8.6 (J. Hine, J. G. Houston, J. H. Jensen, and J. Moulders, *J. Amer. Chem. Soc.*, **87**, 5050 (1965). [f] No added KCl; ionic strength less than 0.1 in all runs.

9.4, k_{H_2O}/k_{D_2O} = 4.1 (this figure includes a small correction for the difference in free-amine concentration in H₂O and D₂O). We presume that a general base mechanism is operative because of the isotope effect and because the alternative possibility, nucleophilic catalysis, would lead to an extremely hindered tetrahedral intermediate (with the central carbon bearing a benzene ring, a pyrrole ring, a tertiary amine, and an oxygen anion). (2) The rate of hydrolysis of N-p-nitrobenzoyl-pyrrole (extrapolated to zero buffer concentration) is a linear function of the hydroxide ion concentration
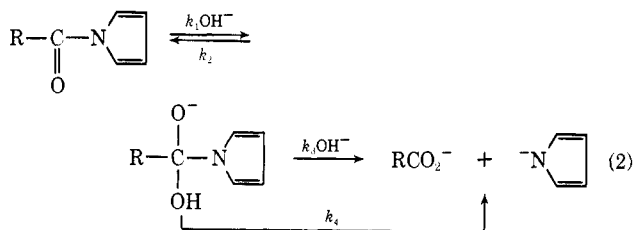
(Figure 3). Such linearity contrasts with the behavior of N-acetylpyrrole shown in Figure 1. Figure 3 has a slope near unity (1.1 ± 0.1), signifying a simple bimolecular amide hydrolysis. N-p-Nitrobenzoylpyrrole has an apparent normal solvent isotope effect of 4.5 (estimated from the rates at pH 9.40 and pD 9.40[21a] at zero buffer concentration). When we correct this value for $K_W(H_2O)/K_W(D_2O) = 6.5$, the true isotope effect is inverse (0.69) which is consistent with that often found for simple hydroxide ion catalyzed hydrolyses.[21b]

Clearly, N-p-nitrobenzoylpyrrole and N-acetylpyrrole react by different mechanisms. The nature of the mechanisms and the reasons for their differences are the subject of the next section. We will also discuss the highly interesting behavior of N-salicylylpyrrole.

Discussion

Acylpyrroles are unusual amides. The unshared pair of electrons are delocalized away from the carbonyl in order to maintain a Hückel number of electrons in the pyrrole system. As a result, the activation energy for rotation about the amide bond of N-acetylpyrrole is about 7 kcal/mol less than that for N,N-dimethylacetamide.[22] The reduced nitrogen–carbonyl conjugation is further manifested in N-acetylpyrrole by a carbonyl stretching frequency of 1719 cm^{-1}, a 124 cm^{-1} increase from that of N-acetylpyrrolidine.[23] The leaving group in our N-acylpyrrole hydrolyses, pyrrole, is an extremely weak base which protonates on an α carbon with a $pK_a = -3.80$.[24] Pyrrole is also a weak acid of $pK_a = 17.51$,[25] comparable to that of p-nitroaniline ($pK_a = 18.37$).[26] The reduced electron density on the N-acylpyrrole carbonyl favors nucleophilic attack; the enhanced electron delocalization in pyrrole favors ejection of the amine. Both factors explain why N-acylpyrroles are roughly 10^4 more reactive than simple aliphatic amides.

The hydrolysis of N-acetylpyrrole and N-benzoylpyrrole passes from largely second order in hydroxide ion at low base concentration to largely first order in hydroxide ion at high base concentration (Figures 1 and 2). This observation demands (1) the presence of an intermediate and (2) hydroxide ion catalyzed destruction of that intermediate.[27] The simplest mechanism that we can envision is shown in eq 2. While one of

$$R-\overset{\underset{\|}{O}}{C}-N\underset{k_2}{\overset{k_1OH^-}{\rightleftharpoons}}$$

$$R-\overset{\underset{|}{OH}}{\underset{|}{C}}-N\overset{k_3OH^-}{\xrightarrow{\hspace{1cm}}} RCO_2^- + {}^-N \quad (2)$$

the hydroxide ions obviously participates as a nucleophile, the role of the second is less evident from the

(21) (a) pD = meter pH + 0.4: P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960). (b) M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963).

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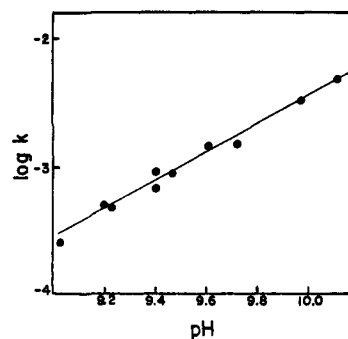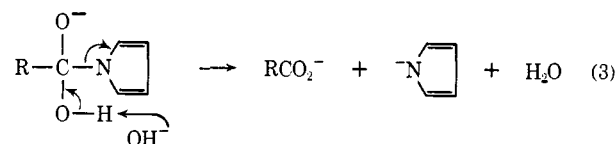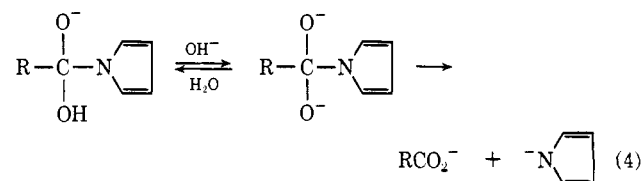
Figure 3. Log k vs. pH profile for the hydrolysis of N-p-nitrobenzoylpyrrole. Rate constants in sec^{-1} at 25.0° were obtained by extrapolating to zero buffer concentration (see Table III).

equation. Conceivably, attack by this hydroxide ion on the intermediate occurs concertedly with ejection of pyrrole anion (eq 3). Alternatively, the tetrahedral

$$R-\overset{\underset{|}{O^-}}{\underset{\underset{OH^-}{|}}{\underset{O-H}{C}}}-N \longrightarrow RCO_2^- + {}^-N + H_2O \quad (3)$$

intermediate ionizes to a dianion prior to its collapse (eq 4). We feel certain that N-acetylpyrrole reacts by

$$R-\overset{\underset{|}{O^-}}{\underset{\underset{OH}{|}}{C}}-N \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} R-\overset{\underset{|}{O^-}}{\underset{\underset{O^-}{|}}{C}}-N \longrightarrow$$

$$RCO_2^- + {}^-N \quad (4)$$

means of eq 4. The absence of general base catalysis and the presence of an inverse solvent isotope effect (see previous section) support this conclusion convincingly.

Equation 5 depicts the rate law for the general

$$k_{obsd} = \frac{k_1k_4[OH^-] + k_1k_3[OH^-]^2}{k_2 + k_4 + k_3[OH^-]} \quad (5)$$

mechanistic scheme in eq 2. We evaluated the three independent parameters of eq 5 with the aid of an iterative nonlinear least-squares program using the Hartley method of steepest decent.[28] Since k_4 (the rate constant for uncatalyzed collapse of intermediate to product) is small for N-acetylpyrrole and negligible for N-benzoylpyrrole, eq 5 simplifies to eq 6.[29] The values

$$k_{obsd} = \frac{k_1k_3'OH^-]^2}{k_2 + k_3[OH^-]} \quad (6)$$

for k_1 and k_3/k_2 for N-acetylpyrrole are 8.5 M^{-1} sec^{-1} and 20 M^{-1}, respectively. This compares with $k_1 = 2.2 \times 10^{-3}$ sec^{-1} and $k_3/k_2 = 17$ M^{-1} for p-nitroacetanilide.[6] We see that partitioning of the tetrahedral intermediate toward product is nearly equal for N-acetylpyrrole and p-nitroacetanilide; this accords with the similar basicity of the pyrrole anion ($pK_a = 17.51$)[25] and the p-nitroaniline anion ($pK_a = 18.37$).[26] On the other hand, N-acetylpyrrole has a k_1 which is 3900 times

(28) We wish to thank Mr. B. A. Blumenstein for use of this program.

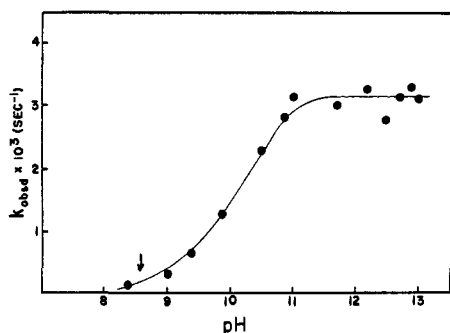(29) In mechanisms obeying eq 4, k_3 represents the product of an equilibrium constant and a rate constant.

Figure 4. pH–rate profile for the hydrolysis of N-salicylylpyrrole at 25.0°, $I = 0.1$. Rate constants have been extrapolated to zero buffer concentration. The arrow indicates the pK_a of the substrate.

Figure 5. Mechanism of hydrolysis of N-salicylylpyrrole.

greater than the k_1 for p-nitroacetanilide. The rate difference reflects the impaired amide resonance stabilization in N-acetylpyrrole. The pyrrole moiety cannot donate its unshared pair of electrons to the carbonyl without suffering loss of aromatic character. pK_a values support this explanation. Pyrrole (pK_a = -3.80)[24] is a far weaker base than p-nitroaniline (pK_a = 1.09).[30] The great susceptibility of the N-acetylpyrrole carbonyl to nucleophilic attack is revealed by another comparison: k_1 for N-acetylpyrrole and for p-nitrophenyl acetate[31] differ by a factor of less than 2.

The rate-limiting step in a mechanism depends solely on the highest point of the energy profile. When $\Delta F^{\ddagger}$ is greater for conversion of a steady-state intermediate into products than into reactants, product formation is rate determining. At low hydroxide concentrations, the rate of formation of product from tetrahedral intermediate ($k_3[\mathrm{OH^-}]$ in eq 2) is small relative to the rate of collapse back to reactants (k_2). Hence, product formation is rate determining. Since two hydroxides are involved in the transition state of this slow step, we observe overall third-order kinetics. When the hydroxide concentration is large, $k_3[\mathrm{OH^-}]$ becomes fast relative to k_2, formation of intermediate is now rate limiting, and we observe overall second-order kinetics. Figures 1 and 2 illustrate this transition.

The kinetic behavior of N-p-nitrobenzoylpyrrole and N-acetylpyrrole differs appreciably. N-p-Nitrobenzoyl-pyrrole hydrolysis is first order in hydroxide ion over the entire pH range that we investigated (Figure 3). The hydrolysis of N-p-nitrobenzoylpyrrole is subject to general base catalysis (Table III). Why are there these differences? Electron withdrawal by the nitrobenzene moiety enhances the acidity of the hydroxy group of the tetrahedral intermediate in eq 2,[32] thereby making the k_3 step more favorable relative to the k_3 of the N-acetyl-pyrrole system. More importantly, electron polarization by the nitrobenzene group destabilizes the carbonyl of the starting material, reducing k_2 (and increasing k_1). These electronic effects enlarge the k_3/k_2 ratio so that formation of a tetrahedral intermediate becomes entirely rate determining. Consequently, the reaction is first-order in hydroxide ion. The susceptibility of N-p-nitrobenzoylpyrrole hydrolysis to general base catalysis

(30) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

(31) F. M. Menger and C. E. Portnoy, J. Amer. Chem. Soc., 90, 1875 (1968).

(32) Compare, for example, the pK_a of CH_3CO_2H (4.76) with the pK_a of $O_2NC_6H_4CO_2H$ (3.44).
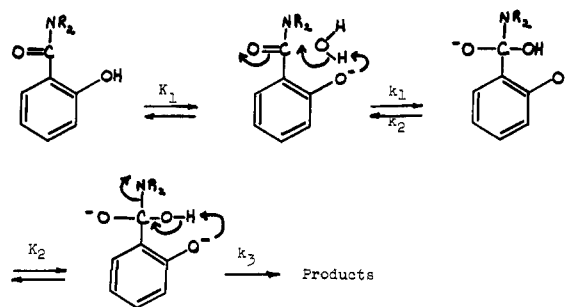
in the k_1 step seems reasonable in light of the fact that ethyl chloroacetate and other acyl-activated carboxylic acid derivatives also respond to general base catalysis.[33] In summary, the mechanisms of the hydrolysis of N-acylpyrroles, including the nature of the rate-determining step, hang in a delicate balance; a relatively small electronic modification in the substrate suffices to perturb the balance and determine the mechanism.

The above results prompted us to investigate N-salicylylpyrrole, a system which could exhibit an intramolecular general base catalysis similar to that found with p-nitrophenyl salicylate.[21b] We did indeed obtain
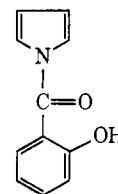
a pH–rate profile consistent with intramolecular participation (Figure 4). At pH 10 the salicylylpyrrole reacts almost three orders of magnitude faster than N-acetyl-pyrrole. But two features of the profile are particularly astounding. (1) The sigmoidal curve has a flex point at pH 10, over 1.4 units above the pK_a of N-salicylyl-pyrrole ($pK_a = 8.59$). (2) The rate is independent of the hydroxide concentration for all pH values above 11. The first observation demands a kinetically important ionization of a phenol, a phenol considerably less acidic than the starting material. The second observation demands a mechanism in which no rate step following ionization of the phenol involves a hydroxide ion. In Figure 5 we present a scheme that incorporates these specifications. N-Salicylylpyrrole ($pK_a = 8.59$) loses a proton, and the resulting anion reacts via an intramolecular general base catalysis to form a tetrahedral intermediate. Alternatively, the intermediate may form via a kinetically equivalent specific base/general acid mechanism. In any event, the phenolic intermediate (with a pK_a near 10) subsequently ionizes to a dianion. In the final step, the dianion collapses to product. The observable ionization of a steady-state intermediate is a highly interesting property of this mechanism. Quite reasonably, the pK_a of the intermediate is displaced upwards relative to that of the N-salicylylpyrrole because proton loss by the intermediate leads to a species bearing two negative charges. Moreover, the anion of N-salicylylpyrrole has the advantage of being resonance stabilized by the ortho carbonyl. Note also that Figure

(33) W. P. Jencks and J. Carriuolo, J. Amer. Chem. Soc., 83, 1743 (1961).

5 explains why hydroxide ion does not participate in the collapse of the intermediate above pH 11 as occurs with N-acetylpyrrole (see eq 4). Such a mechanism would produce an intermediate with a triple negative charge.

The proposed mechanism obeys the steady-state rate law given in eq 7.[34] When $K_1[OH^-] \gg 1$ (above pH

$$k_{obsd} = \frac{k_1 k_3 K_1 K_2 [OH^-]^2}{[k_2(1 + K_2[OH^-]) + \quad k_3 K_2[OH^-]][1 + K_1[OH^-]]} \quad (7)$$

(34) $K_1 = [A^-]/[HA][OH^-]$; $K_2 = [A^{2-}]/[A^-][OH^-]$.

9.6 where greater than 90% of the substrate is anionic), the equation simplifies to eq 8. When $K_2[OH^-] \gg 1$

$$k_{obsd} = \frac{k_1 k_3 K_2 [OH^-]}{k_2(1 + K_2[OH^-]) + k_3 K_2[OH^-]} \quad (8)$$

(above pH 11), the rate expression further simplifies to eq 9. Thus the observed rate constant becomes independent of the pH, in accord with experiment.

$$k_{obsd} = k_1 k_3/(k_2 + k_3) \quad (9)$$

Elimination of Water from Hexanol at 10^{-11} to 10^{-5} Second Following Field Ionization

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Abstract: The elimination of water from hexanol following field ionization (FI) has been studied at times from 10^{-11} to 10^{-5} sec. Investigation of the deuterated species hexanol-3,3-d_2 and hexanol-4,4-d_2 firmly establishes that the elimination of water involves hydrogen from C-3 as well as from C-4. Phenomenological rate constants $\bar{k}(t)$ have been calculated as functions of time from 10^{-11} to 10^{-5} sec for the process involving transfer of hydrogen from C-3 *via* a five-membered cyclic transition state and for that involving transfer from C-4 *via* a six-membered cyclic transition state. Comparison of the kinetics of the two processes suggests that the six-membered transition state is thermodynamically favored over the five membered; for the most energetic ions (produced by FI), however, the reactions *via* the two transition states occur with equal probability. It is opined that the frequency factors for the five- and six-membered transition states are both of the same order of magnitude (10^{10} sec⁻¹). Hydrogen–deuterium randomization is unimportant at times less than 10^{-9} sec following FI and probably at longer times as well. We suggest that the conclusions of the electron impact studies on hexanol have overestimated the importance of transfer of hydrogen from C-4 in the loss of water.

The elimination of water from alcohols to form what is formally an ionized olefin can be observed following both electron impact (EI) and field ionization (FI). EI measurements[2-5] on a variety of deuterium-labeled aliphatic alcohols indicate that the process is not a 1,2 elimination analogous to thermal dehydration.[6] Rather, the loss of water following EI involves the transfer of hydrogen to the hydroxyl group from more remote positions in the alkyl chain.[7] The EI studies suggest that with hexanol 90% of the hydrogen is transferred from C-4, while the remainder *appears* to come from C-3 (ref 5) (and possibly from C-5 as well[4]). It is not, however, possible to conclude from the EI data that hydrogen transfer occurs directly from C-3 to the hydroxyl *via* a five-membered transition state, for

there exists the very real possibility that deuterium incorporated at C-3 migrates to C-4 (*i.e.*, partial H/D randomization) prior to a specific 1,4 elimination. This difficulty in distinguishing between nonspecific hydrogen transfers (*i.e.*, transfer from more than one position in a chain to some active site) and specific hydrogen transfer preceded by partial H/D randomization is a fundamental limitation of the integrated view of events (over ~10^{-6} sec) afforded by EI mass spectra.

We have studied the fragmentation of specifically deuterated hexanols using the unique capabilities of FI mass spectrometry,[8] and have established that the loss of water from hexanol is indeed nonspecific inasmuch as it involves hydrogen transfer from both C-3 and C-4 (and possibly from other sites to a small degree). Our prime objective in undertaking this FI study of hexanol was to measure and compare kinetics of two processes which are apparently similar, in that they eliminate the same neutral molecule, yet actually distinct, in that they involve cyclic transition states of different sizes. Differences in the kinetics of such processes can then be tentatively attributed to the differing cyclic transition

(1) John Simon Guggenheim Memorial Fellow, 1970-1972.

(2) (a) W. H. McFadden, M. Lounsbury, and A. L. Wahrhaftig, *Can. J. Chem.*, **36**, 990 (1958); (b) W. H. McFadden, D. R. Black, and J. W. Corse, *J. Phys. Chem.*, **67**, 1517 (1963).

(3) C. G. MacDonald, J. S. Shannon, and G. Sugdowz, *Tetrahedron Lett.*, 807 (1963).

(4) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964).

(5) S. Meyerson and L. C. Leitch, *ibid.*, **86**, 2555 (1964).

(6) 1,2 elimination is induced by EI of ethanol where there is no long side chain; see J. Momigny, *Bull. Soc. Roy. Sci. Liege*, **24**, 111 (1955).

(7) In the case of a 1,4 elimination there are intriguing analogies with the Barton reaction in the liquid phase; see M. M. Green, J. G. McGraw, II, and M. Moldowan, *J. Amer. Chem. Soc.*, **93**, 6700 (1971).

(8) In sharp contrast to EI mass spectrometry, FI mass spectrometry provides a (time-) resolved view of events at times as short as the order of 10^{-12} sec; the kinetics of a reaction can be measured as a function of time over the interval 10^{-12}–10^{-5} sec.