Hydrolysis of Amides. Electronic Effects on Kinetics and Mechanism of the Basic Hydrolysis of N-Substituted Benzoylpyrroles

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The hydroxide ion catalyzed hydrolysis of a series of N-substituted benzoylpyrroles has been studied in water at 25°. Hammett treatment of data shows that substituents affect in a very similar way the rate of formation and of decomposition of the tetrahedral intermediate.

The mechanism of the basic hydrolysis of a variety of amides has been examined and it is usually represented by the following scheme of reaction (1) (1).
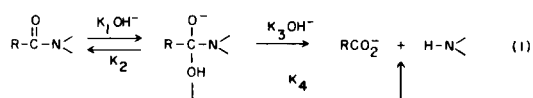
According to the structure of the amide and the pH of the medium, the rate determining step of the reaction is a) the attack of the OH^- on the amide (k_1); b) the decomposition of the tetrahedral intermediate to product either uncatalyzed (k_4) or catalyzed by OH^- (k_3). Equation (2) represents the rate law for the mechanistic scheme

$$K_{obsd} = \frac{K_1 K_4 [OH^-] + K_1 K_3 [OH^-]^2}{K_2 + K_4 + K_3 [OH^-]} \quad (2)$$

From the literature (2) it is known that the basic hydrolysis of N-benzoylpyrrole is second order in hydroxide ion at low concentration of base, while it is first order at high concentration of base; on the other hand, the hydrolysis of N-p-nitrobenzoylpyrrole is first order in hydroxide ion.

We wish now to report a detailed study of the substituent effect in the N-benzoyl group on the various steps of the reaction.

Results and Discussion.

pH-Rate Profiles.

Plots of $k_{obsd}/[OH^-]$ vs. $[OH^-]$ are typically curved for all the substrates examined showing that at low base concentration the hydrolysis is mainly second order in $[OH^-]$, while at high base concentration is largely first order in $[OH^-]$.

The mechanism of the reaction described by eq. 1 can be suggested as the more probable and eq. 2 represents the rate law for this mechanism.

The rate constants for the single steps calculated according to the method of Kershner and Schowen (3) (see Experimental) are reported in Table 1. The statistical treatment shows that k_4 (the rate constant for the water-catalyzed decomposition of the intermediate) is negligible for all the substrates. From the collected data we can observe that k_1 is increased by electron-withdrawing substituents and decreased by electron-releasing substituents.

The similarity of k_3/k_2 values that partitioning of the tetrahedral intermediate to product is essentially affected by the basicity of the leaving group (i.e. the pyrrole anion) rather than by the substituent on the benzene ring.

Furthermore the constancy of k_3 / k_2 suggests that the substituent effect on the breakdown of the intermediate should be essentially governed by its effect on k_1, the rate of formation of the intermediate. The consistency of this

Table I.

Rate Constants for the Hydroxide-Catalyzed Hydrolysis of N-Substituted Benzoylpyrroles
in Water at 25.0 ± 0.1° (μ = 0.2 Added Sodium Chloride) (a,b)

R	k_1 (M^{-1} sec^{-1})	$\frac{k_1}{k_2} k_3$ (M^{-2} sec^{-1})	$\frac{k_3}{k_2}$ (M^{-1})
m-NO$_2$	28.0 ± 0.3	22150 ± 350	791.1
p-CN	25.8 ± 0.2	14720 ± 319	570.5
p-Cl	5.50 ± 0.05	4902 ± 85	891.4
H	2.65 ± 0.04	2039 ± 15	769.3
p-CH$_3$	1.53 ± 0.02	1113 ± 12	727.2
p-t-Bu	1.12 ± 0.02	633.9 ± 8.1	565.9
p-OCH$_3$	1.10 ± 0.01	747.5 ± 7.6	679.6

(a) Error limits are standard deviations. (b) Rate constants were determined from 280 kinetic runs under first-order condition.

Table II

Analytical and Spectral Data N-Benzoylpyrroles

R	M.p. °C	Formula	C		H		N		Pmr	δ,	ppm
m-NO₂ (B)	67-68	$C_{11}H_8N_2O_3$	61.18	(61.10)	3.71	(3.74)	13.08	(12.96)	(Deuteriochloroform): 6.35 (2H, t, β-H-pyrrole), 7.20 (2H, t, α-H-pyrrole), 7.50-8.60 (4H, m, ArH)		
p-CN (C)	85-87	$C_{12}H_8N_2O$	73.70	(73.45)	4.08	(4.12)	14.38	(14.28)	(DMSO): 6.37 (2H, t, β-H-pyrrole), 7.22 (2H, t, α-H-pyrrole), 7.82 (2H, d, ArH), 8.02 (2H, d, ArH)		
p-Cl (D)	68-70	$C_{11}H_8ClNO$	64.65	(64.55)	3.89	(3.94)	6.90	(6.84)	(DMSO): 6.35 (2H, t, β-H-pyrrole), 7.22 (2H, t, α-H-pyrrole)		
p-Me (E)	30-32	$C_{12}H_{11}NO$	77.98	(77.80)	5.94	(5.99)	7.63	(7.56)	(Deuteriochloroform): 2.42 (3H, s, ArCh₃), 6.25 (2H, t, β-H-pyrrole), 7.15 (2H, t, α-H-pyrrole), 7.20 (2H, d, 2,6 ArH), 7.60 (2H, d, 3,5 ArH).		
p-t-Bu (F)	74-75	$C_{15}H_{17}NO$	79.34	(79.25)	7.47	(7.55)	6.26	(6.16)	(Carbon tetrachloride): 1.35 (9H, s, C-Me₃), 6.15 (2H, t, β-H-pyrrole), 7.15 (2H, t, α-H-pyrrole), 7.35 (2H, d, 2,6 ArH), 7.60 (2H, d, 3,5 ArH)		
p-OMe (G)	34-36	$C_{12}H_{11}NO_2$	71.75	(71.61)	5.50	(5.52)	7.02	(6.96)	(Deuteriochloroform): 3.65 (3H, s, OMe), 6.15 (2H, t, β-H-pyrrole), 6.80 (2H, d, 2,6 ArH), 7.15 (2H, t, α-H-pyrrole), 7.55 (2H, d, 3,5 ArH).		

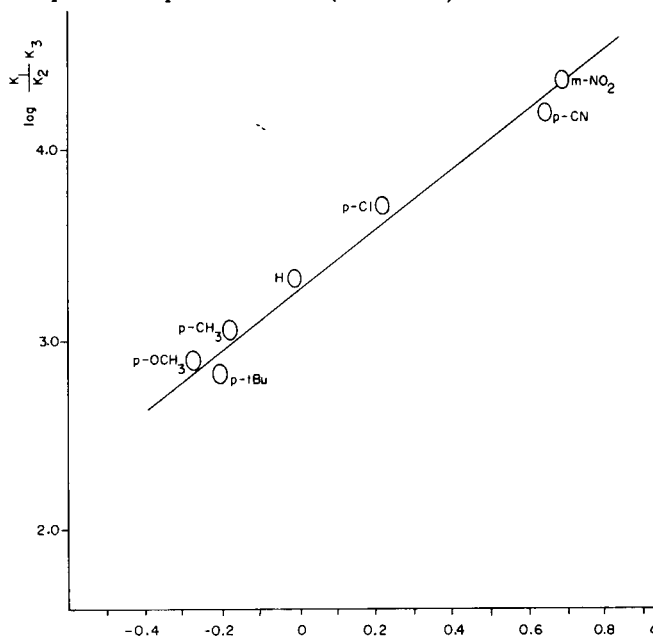(a) Values in parentheses refer to the calculated percentages.
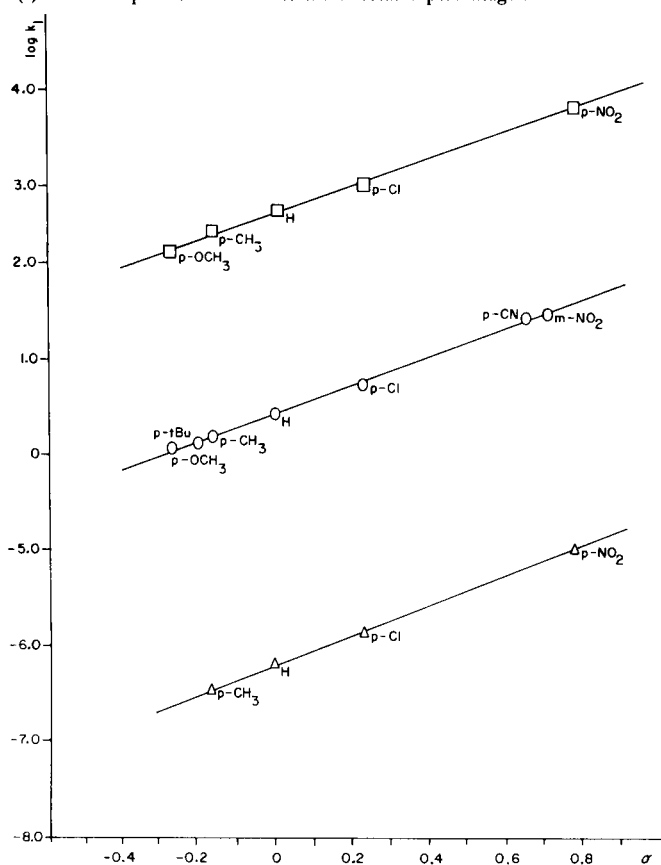
Plots of log k_1 vs σ constants for the hydrolysis of a series of substituted N-benzoylimidazoles (□), substituted N-benzoylpyrroles (o) and p-substituted benzamides. (△)

hypothesis is clearly demonstrated by values of $(k_1 / k_2)k_3$ reported in Table I.

Hammett Treatment.

In Figure 1 the logarithms of k_1 for hydrolysis of the series of substituted N-benzoylpyrroles are plotted vs σ, the Hammett substituent constant. (4) The value of ϱ obtained for the slope of this plot is + 1.48 (r = 0.999).

Plot of log $(k_1 / k_2)k_3$ vs σ constants for the hydrolysis of a series of substituted N-benzoylpyrroles.

This value is close to that obtained for the hydrolysis of p-substituted benzamides, i.e. $\varrho = 1.52$ ($r = 0.990$) using literature data (5) extrapolated at 25° from higher temperature (6) (Fig. 1)

Similar treatment for a series of N-benzoylimidazoles substituted in the benzene ring (Fig. 1) gave a value of $\varrho = 1.39$ ($r = 0.999$) (7).

The similarity of the values, even considering the strong difference in the reactivity of substances ($k_{N-COC_6H_5}$ pyrrole/$k_{benzamide} \cong 1.10^6$ at 25°), indicates that the bond-making process is an important feature of the reaction of all these substrates.

Finally the results obtained by the Hammett treatment on the $\log(k_1 / k_2)k_3$ values ($\varrho = 1.50$), ($r = 0.999$) shows that the electronic demand of the substituents affects in a very similar way both the formation and the decomposition of the intermediate (Fig. 2).

EXPERIMENTAL

Materials.

The series of substituted N-benzoylpyrroles was prepared by reacting the potassium salt of pyrrole with the suitable acid chloride. The acid chloride was a commercial sample or was prepared according to the usual method by treatment with thionyl chloride of the commercially available substituted benzoic acid. A typical procedure is described.

N-Benzoylpyrrole (A).

Potassium (3.36 g., 0.087 mole) was added slowly to a solution of freshly distilled pyrrole (5.82 g., 0.087 mole) in 50 ml. of anhydrous tetrahydrofuran under nitrogen. The mixture was boiled under reflux for 3 hours, cooled, added with 100 ml. of anhydrous toluene, stirred, added with a solution of benzoyl chloride (12.07 g., 0.087 mole) in 50 ml. of anhydrous toluene.

The mixture refluxed for 2 hours, cooled, poured into ice, the organic layer separated and the aqueous layer extracted with ether. Removal of solvents from the organic extract dried under anhydrous sodium sulphate gave a brown oil, which was purified by vacuum distillation, b.p. 90° (0.7 mm) (lit. b.p. 125° at 1.8 mm) (2); δ (deuteriochloroform): 6.35 (2H, t, β-H-pyrrole), 7.25 (2H, t, α-H-pyrrole), 7.28-7.70 (5H, m, ArH).

Physical constants and nmr data for the series are as follows:

N-m-Nitrobenzoylpyrrole (B).

This compound had m.p. 67-68°; δ (deuteriochloroform): 6.35 (2H, t, β-H-pyrrole), 7.20 (2H, t, α-H-pyrrole), 7.50-8.60 (4H, m, ArH).

N-p-Cyanobenzoylpyrrole (C).

This compound had m.p. 85-87°; δ (DMSO): 6.37 (2H, t, β-H-pyrrole), 7.22 (2H, t, α-H-pyrrole), 7.82 (2H, d, ArH), 8.02 (2H, d, ArH).

N-p-Chlorobenzoylpyrrole (D).

This compound had m.p. 68-70°; δ (DMSO): 6.35 (2H, t, β-H-pyrrole), 7.22 (2H, t, α-H-pyrrole), 7.55 (2H, d, ArH), 7.75 (2H, d, ArH).

N-p-Methylbenzoylpyrrole (E).

This compound had m.p. 30-32°; δ (deuteriochloroform): 2.42 (3H, s, ArCH₃), 6.25 (2H, t, β-H-pyrrole), 7.15 (2H, t, α-H-pyrrole), 7.20 (2H, d, 2,6 ArH), 7.60 (2H, d, 3,5 ArH).

N-p-t-Butylbenzoylpyrrole (F).

This compound had m.p. 74-75°; δ (carbon tetrachloride): 1.35 (9H, s, C-(CH₃)₃), 6.15 (2H, t, β-H-pyrrole), 7.15 (2H, t, α-H-pyrrole), 7.35 (2H, d, 2,6 ArH), 7.60 (2H, d, 3,5 ArH).

N-p-Methoxybenzoylpyrrole (G).

This compound had m.p. 34-36°; δ (deuteriochloroform): 3.65 (3H, s, OCH₃), 6.15 (2H, t, β-H-pyrrole) 6.80 (2H, d, 2,6 ArH), 7.15 (2H, t, α-H-pyrrole), 7.55 (2H, d, 3,5 ArH).

All compounds gave parent peak in the mass spectra at 70 eV.

Kinetics and Product Analysis.

First-order constants for hydrolysis of the N-benzoylpyrroles were calculated from absorbance vs time data using a Beckman DB-GT recording spectrophotometer. A stoppered cuvette containing 2 or 3 ml. of an aqueous sodium hydroxide solution was thermostated at 25.0 ± 0.1° for 30 minutes within the cell compartment. The reaction was initiated by adding 10-20 μl of substrate dissolved in acetonitrile. Final concentrations of substances were from 10^{-4} to $10^{-5}M$; the ionic strength ($\mu = 0.2$) was maintained constant by adding sodium chloride, monitoring wavelengths expressed in nm were the following: A (258), B (254), C (256), D (260), E (258), F (262) and G (276). Psuedo-first-order rate constants were calculated using LSQ treatment by means of a Hewlett-Packard 9285 desk calculator fitted out with a HP plotter.

The products of hydrolysis were examined by comparing the final spectra with those obtained from solutions of pyrrole and carboxylic acid under conditions identical to those of the kinetic experiments.

Data Treatment.

The rate of constants for individual steps in the hydrolysis reaction were evaluated according to the method of Kershner and Schowen (3).

Acknowledgements.

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