Hydrolysis of Amides. Kinetics and Mechanism of the Basic Hydrolysis of *N*-Acylpyrroles, *N*-Acylindoles and *N*-Acylcarbazoles

P. Linda* and A. Stener

Istituto di Chimica, Università di Trieste, Trieste, Italy

A. Cipiciani and G. Savelli*

Dipartimento di Chimica, Università di Perugia, Perugia, Italy

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The hydroxide ion catalyzed hydrolysis of *N*-formyl, *N*-acetyl and *N*-benzoylpyrroles, -indoles and -carbazoles has been studied in water at 25.0°. The rate constants of formation of the tetrahedral intermediate are strongly increased by releasing steric hindrance in the acyl portion as shown by the higher reactivity of *N*-formyl derivatives in comparison with *N*-acetyl and *N*-benzoyl derivatives.

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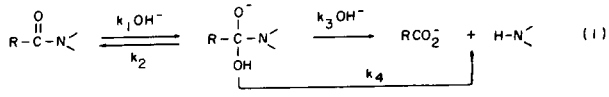
Recently we established that the mechanism of the basic hydrolysis of *N*-(substituted)benzoylpyrroles (1) and of some *N*-acylcarbazoles (2) closely follows the usual pattern of the hydroxide-catalyzed hydrolysis of a variety of activated amides (3-8). According to the structure of the

Scheme I

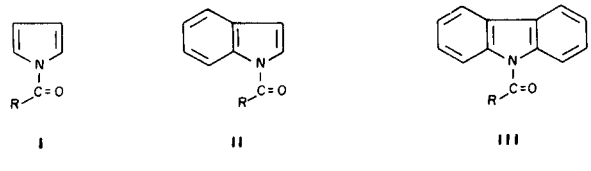


amide and the *p*H of the medium the rate determining step of the reaction is either the attack of the OH^- on the amide or the decomposition of the tetrahedral intermediate to products. Equation (2) represents the rate law for the mechanistic scheme:

$$k_{obs} = \frac{k_1k_4\,[OH^-] + k_1k_3\,[OH^-]^2}{k_2 + k_4 + k_3\,[OH^-]}$$

We wish now to report a detailed study of the substituent effect in the acylgroup and the annelation effect on the various steps of the basic hydrolysis of *N*-acylpyrroles (I) -indoles (II) and -carbazoles (III).

Figure



R = H, Me, Ph

Results and Discussion.

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

Analogous plots for all the *N*-formyl derivatives did not show curvature at any OH^- concentration at which rates were measurable, due to their high reactivities. The plots log k_{obsd} *vs* *p*H were straight lines of slope between 1.5-2.0 showing the occurence of first and second order terms in OH^-. The mechanism of the reaction described in Scheme 1 can be suggested as the more probable and equation 2 represents the rate law for this mechanism.

The rate constants for the single steps, collected in Table 1, have been calculated according to the method of Kershner and Schowen (3) for the *N*-acetyl and *N*-benzoyl derivatives and through a non linear regression analysis by using an iterative Gauss-Newton method (9) for the *N*-formyl derivatives. The results showed that k_4 (the rate constant for the water catalyzed decomposition of the intermediate) is negligible for all the substrates.

Table 1

Rate Constant for the Hydroxide-Catalyzed Hydrolysis of *N*-Acylpyrroles, -indoles and -carbazoles in water at 25.0 ±0.1° (μ = 0.2, Added Sodium Chloride)

Compound	$k_1(M^{-1}sec^{-1})$	$\frac{k_1}{k_2}k_3(M^{-2}sec^{-1})$	$\frac{k_3}{k_2}(M^{-1})$
N-Formylpyrrole	405	8100	20
N-Formylindole	300	5340	8.7
N-Formylcarbazole	180	1570	8.7
N-Acetylpyrrole	8.5	148	17.4
N-Acetylindole	1.0	143.1	143.1
N-Acetylcarbazole	0.75	256.4	341.9
N-Benzoylpyrrole	3.1	2380	767.0
N-Benzoylindole	1.3	182.7	140.5
N-Benzoylcarbazole	1.1	148	132.1

(a) Rate constants were determined from 240 kinetic runs under first order conditions.

From the data of Table 1 we can observe that *N*-formyl derivatives are very much more reactive than *N*-acetyl and

N-benzoyl derivatives, which reactivities are substantially similar. The relative rates of formation of the tetrahedral intermediate (k_H/k_{Me} and k_{Me}/k_{Ph}) are reported in Table II.

Table II

Effect of Substitutions in the Acylmoiety on k_1

	R-(CO)-N-Pyrryl	R-(CO)-N-Indolyl	R-(CO)-N-Carbazolyl
k_H/k_{Me}	50	500	240
k_{Me}/k_{Ph}	2.7	0.8	0.7

The substitution of a methyl group by a hydrogen atom enhances the reactivity of the substrate much more in pyrrole than in the other heterocyclics and this fact can be ascribed to a greater relief of steric hindrance in the over crowded transition states for *N*-acetylcarbazole and -indole than in *N*-acetylpyrrole.

Relative relief of steric inhibition can also explain the similarity of k_1 for indole and carbazole derivatives in the *N*-acetyl and *N*-benzoyl series (Table 1), where the stronger inhibitory effects appear to be due to the annelation of a first benzene ring (indole), while successive annelation (carbazole) appears to be less important. This effect is smoothed down in the formyl series, probably because of a less overcrowded starting situation.

On the other hand electronic effects appear to be more important on the k_{Me}/k_{Ph} ratios, in fact we can observe that *N*-acetyl- and *N*-benzoylazoles have comparable reactivities. These data can be rationalized with the fact that carbon-nitrogen conjugation is considerably reduced in *N*-acylazoles as compared with a simple amide.

For example the carbonyl stretching frequencies are 1719, 1720 and 1695 cm^{-1} for *N*-acetylpyrrole, -indole and -carbazole, respectively, as compared with 1600 cm^{-1} for aliphatic amides (5), and the barriers for rotation about the amide bonds are much lower than for simple amides, *e.g.*, *N,N*-dimethylacetamide (10). The reduced carbon-nitrogen conjugation allows a greater extent of conjugation of the phenylgroup with the carbonyl and therefore the electronic situation of the carbon atom of the carbonyl group is substantially different in *N*-benzoylazoles in respect of that of *N*-acetylazoles.

EXPERIMENTAL

Materials

N-Acetylpyrrole (A), *N*-acetylindole (B), *N*-acetylcarbazole (C), *N*-benzoylpyrrole (D), *N*-benzoylindole (E), *N*-benzoylcarbazole (F), *N*-formylcarbazole (G) were available from previous studies. *N*-Formylpyrrole (H) bp 79-82° (60 mm) (lit bp 80° at 60 mm) (11); ir: ν CO 1700 cm^{-1}; nmr (deuteriochloroform): δ 6.35 (2H, m, β-H), 7.25 (2H, m, α-H), 8.90 (1H, s, N-CHO); *N*-formylindole (I) bp, 136-137° (15 mm) (lit bp 137-138° at 15 mm) (12) ir: ν CO 1700 cm^{-1}; nmr (carbon tetrachloride): δ 6.30-6.60 (1H, d, 3-H), 6.90-7.70 (4H, m, ArH + 2-H), 8.00-8.50 (H, m, 7-H), 8.70-9.20 (1H, s, N-CHO) were prepared from the appropriate Grignard reagent and ethyl formate according to the literature methods.

Kinetics and Product Analysis.

First order constant for hydrolysis of the *N*-acylpyrroles, indoles and carbazoles 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 concentration of substances were from 10^{-4} to 10^{-5} *M*; the ionic strenght (μ = 0.2) was maintained constant by adding sodium chloride, monitoring wavelenghts expressed in nm were the following A (238), B (236), C (270), D (255), E (248), F (270), G (272), H (248) and I (239). Pseudo-first-order rate constant were calculated using LSQ treatment by means of a Hewlett-Packard 9825 desk calculator fitted out with a HP 9872A plotter and using an iterative Gauss-Newton method by means of a IBM 370/158 calculator. The products of hydrolysis were examined by comparing the final spectra with those obtained from solutions of the appropriate heterocyclic and carbocyclic acid under conditions identical to those of the kinetic experiments.

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REFERENCES AND NOTES

(1) A. Cipiciani, P. Linda and G. Savelli, *J. Heterocyclic Chem.*, **16**, 673 (1979).

(2) A. Cipiciani, P, Linda and G. Savelli, *ibid.*, **16**, 677 (1979).

(3) L. D. Kershner and R. L. Schowen, *J. Am. Chem. Soc.*, **43**, 2014 (1971).

(4) R. H. de Wolfe and R. C. Newcomb, *J. Org. Chem.*, **36**, 3870 (1971).

(5) F. M. Menger and J. A. Donohue, *J. Am. Chem. Soc.*, **95**, 432 (1973).

(6) J. Kavalek and V. Sterba, *Collect. Czech. Chem. Communn.*, **40**, 1176 (1974).

(7) V. Gani and P. Viout, *Tetrahedron*, **32**, 1669 (1976).

(8) V. Gani and P. Viout, *ibid.*, **32**, 2883 (1976).

(9) Statistical Package for the Social Sciences (SPSSH), University of California, Los Angeles 1979.

(10) K. Dahlquist and S. Forsen, *J. Phys. Chem.*, **73**, 4124 (1969).

(11) L. Alessandri, *Atti Accad. Lincei*, **24**, 194 (1915).

(12) N. Potokhin, *J. Russ. Phys. Chem. Soc.*, **59**, 761 (1927); *Chem. Abstr.*, **22** 3409 (1928).