Kinetics and Mechanism of the Basic Hydrolysis of Indomethacin and Related Compounds: A Reevaluation

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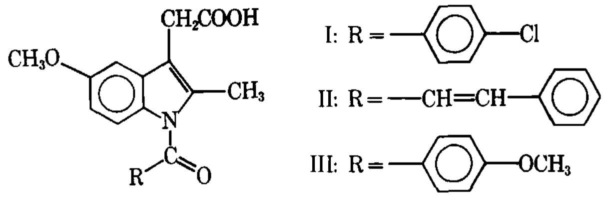
Abstract ☐ The kinetics of the hydrolysis of indomethacin and related compounds were studied in an alkaline medium at 25°. The pseudo-first-order rate constants were evaluated from log absorbance *versus* time plots in the ultraviolet. These compounds showed a second-order rate constant at low concentrations of hydroxide ion and a first-order rate constant at higher concentrations of hydroxide ion.

Keyphrases ☐ Indomethacin—kinetics of the hydrolysis in alkaline medium ☐ Kinetics—hydrolysis of indomethacin

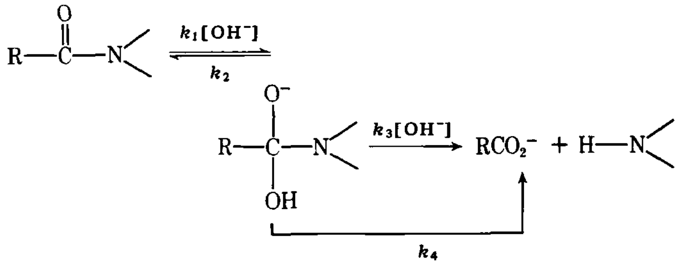
The kinetics of the alkaline hydrolysis of indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid (I)] have been investigated in several studies.



Hajratwala and Dawson (1) measured the apparent first-order rate constants in the pH 11–12 range at different temperatures, and suggested that the experimental data were in agreement with a mechanism involving the reaction of the monodissociated species of indomethacin with the hydroxide ion and postulated a rate law of the type: $k_{obs} = k_1[OH^-]$. Krasowska (2) described a linear relationship between log k_{obs} *versus* pH in the range of pH 7–10 at 50, 60, and 70°, but no conclusions were drawn on the mechanism of the hydrolysis of I.

The aim of this study was to reinvestigate the mechanism of the basic hydrolysis of I and to compare its behavior with that of simpler models in view of our previous results on related compounds (3–5).

A variety of amides undergo basic hydrolysis, as is shown in Scheme I.



Scheme I

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 hydroxide ion on the amide (k_1) and (*b*) the decomposition of the tetrahedral intermediate to products either uncatalyzed (k_4) or catalyzed by hydroxide ion (k_3). Equation 1 represents the rate law for the mechanistic Scheme I.

$$k_{obs} = \frac{k_1k_4[OH^-] + k_1k_3[OH^-]^2}{k_2 + k_4 + k_3[OH^-]} \qquad \text{(Eq. 1)}$$

Many *N*-acyl derivatives of pyrroles, indoles, and carbazoles show a second-order rate constant at low concentrations of hydroxide ion, and a first-order rate constant at higher concentrations of base (3–5). Only the hydrolysis of *N*-(4-nitrobenzoyl)pyrrole was found to be first-order in hydroxide ion at all base concentrations (6). This behavior was ascribed to the electronic polarization by the nitro group destabilizing the carbonyl of the substrate, reducing k_2 and increasing k_1. These electronic effects enlarge the ratio k_3/k_2 and the formation of the tetrahedral intermediate becomes the rate-determining step.

EXPERIMENTAL

Materials—All materials were analytical grade; water double-distilled in glass was used throughout. Indomethacin[1], cinmetacin[2] (II), and 1-(4-methoxybenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid (III)[3] were used without further purification.

1-(4-Chlorobenzoyl)indole (IV)—A solution of 1.2 g (10 mmoles) of indole and 34 mg (0.1 mmole) of tetrabutylammonium hydrogen sulfate in 30 ml of dichloromethane was stirred at room temperature while 1 g of finely powdered sodium hydroxide was added, followed by a solution of 2.6 g (15 mmoles) of 4-chlorobenzoyl chloride in 10 ml of dichloromethane over a 15-min period. The mixture was cooled in a water bath, stirred for 20 min, and the product was removed by filtration. This material was recrystallized from *n*-hexane to give IV as white crystals, mp 114–115° [lit. 114.5–115.5° (7, 8)] IR (mineral oil): 1680 cm^{-1} (C=O); NMR (deuterochloroform): 6.6 (d, *J* = 4 Hz, 1, indole-3 proton), 7.2–7.9 (m, 8, aromatic protons), 8.3–8.5 ppm (m, 1, indole-7 proton)[4].

Kinetic Studies—A stoppered quartz cell containing an aqueous sodium hydroxide solution (3 ml) was thermostated at 25 ± 0.1° for 20 min within the cell compartment. The reaction was initiated by adding 10–20 μl of the substance dissolved in acetonitrile. The initial concentration of the substrates in the reaction cell was in the order of 10^{-4}–10^{-5} *M*. An ionic strength of 0.2 was maintained constant by adding sodium chloride.

Absorbance (against an appropriate blank) was recorded as a function of time at 325 nm for I, 320 nm for II, 315 nm for III, and 305 nm for IV[5]. Pseudo-first-order rate constants (k_{obs}) were calculated using regression analysis. The correlation coefficients were between 0.993–0.999.

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

Data Treatment—The rate constants for individual steps in the hydrolysis reaction were evaluated according to the method of Kershner and Schowen (9)[6].

RESULTS AND DISCUSSION

The effects of hydroxide ion concentration on the apparent first-order rate constant, k_{obs}, for the indole derivatives are shown in Table I.

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[2] Chiesi Farmaceutici, Parma, Italy.
[3] Compagnia di Ricerca Chimica, San Giovanni al Natisone, Italy.
[4] IR spectra were recorded on a Perkin-Elmer model 399 spectrophotometer; NMR spectra were registered on a JEOL 60 MHz spectrometer.
[5] Perkin-Elmer model 552 spectrophotometer.
[6] Hewlett-Packard model 9825A Computer.

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Table I—Effect of the Hydroxide Ion Concentration on the Pseudo-First-Order Rate Constant at 25.0 ± 0.1°

$[OH^-]$ 10^3 M	k_{obs} 10^4, sec^{-1} [a]			
	I	II	III	IV
1.0	2.21	0.471	0.269	15.1
1.5		0.906		
2.0	4.05	1.23	0.633	
2.5		1.63		40.9
3.0	6.49		0.978	
4.0	8.75	2.69	1.42	
5.0	13.2		1.81	96.3
6.0		4.31		
7.0	17.5			
7.5		5.51	2.74	151
10.0	27.4	7.58	3.98	209
12.4		10.0		
15.0	42.6		3.85	322
17.3		14.4		
20.0	60.3		8.51	427
21.8		18.2		
25.0	77.1	21.4	10.7	
30.0	89.6		12.8	633
31.7		27.8		
34.6			15.6	
40.0	128	35.6	17.5	
44.5		39.8	20.3	
50.0	162	45.1	22.9	1057

[a] Average of two or three runs.

Plots of rate constant–hydroxide ion concentration *versus* hydroxide ion concentration are shown in Fig. 1. The mechanism of hydrolysis shown in Scheme I is the most probable. Equation 1 represents the rate law for this mechanism. The rate constants for the single steps are reported in Table II together with relevant data presented in our previous papers [*i.e.*, 1-(4-chlorobenzoyl)pyrrole (V) and 1-(4-methoxybenzoyl)pyrrole (VI)] (3). The statistical treatment showed that k_4 (the rate constant for the water-catalyzed decomposition of the tetrahedral intermediate) is negligible.

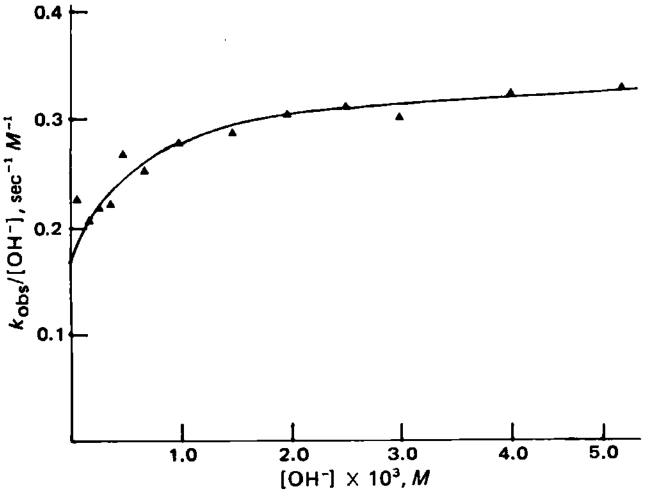

Figure 1—*Effect of concentration of hydroxide ion on the hydrolysis of indomethacin at 25.0 ± 0.1° and ionic strength 0.2.*

Table II—Rate Constants for the Hydroxide Ion-Catalyzed Hydrolysis in Water at 25.0 ± 0.1°

	k_1, M^{-1} sec^{-1}	$k_1k_3k_2$, M^{-2} sec^{-1}	k_3k_2, M^{-1}
I	0.34	120	350
II	0.09	54	600
III	0.05	35	700
IV	2.20	2200	1000
V[a]	5.50	4900	900
VI[a]	1.10	800	700

[a] Data from Ref. (3).

From the data one can observe that 1-(4-chlorobenzoyl)indole (IV) shows a value of k_1 (the rate constant of formation of the tetrahedral intermediate) about 7 times higher than I, and this can be ascribed to steric inhibition by the methyl group in the 2-position of I to the attack of the hydroxide ion, since this reaction appears to be more sensitive to steric effects than to electronic effects (3–5). Similarly steric effects affect the k_3/k_2 ratio favoring the decomposition of the intermediate rather than the return to the reactants. Furthermore, electronic effects resulting from substitution in the benzoyl ring of the indomethacin series closely parallel those in the pyrrole series, as shown by the fact that the k_1 relative ratio of I–III is ~7 and is quite similar to that of V–VI (~5). Finally, the fact that the k_3/k_2 values are of the same order of magnitude shows that partitioning of the tetrahedral intermediate to products is the result of a subtle balance among steric, electronic, and leaving-group effects.

In conclusion, the kinetics of hydrolysis of indomethacin and cinmetacin, are similar to that of analogous models used in this study. A knowledge of the mechanism of hydrolysis of simple molecules is important to rationalize the behavior of more complex compounds.

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