Kinetics of Indomethacin Degradation I: Presence of Alkali

B. R. HAJRATWALA ˣ and J. E. DAWSON

Abstract □ The kinetics of indomethacin degradation were followed in alkaline aqueous solutions at various temperatures between 20.1 and 40.7°. The apparent first-order rate constants were evaluated from log absorbance *versus* time plots at λ_{max} 318 nm. The primary salt effect was positive. The rate constant–hydroxide-ion concentration profile was linear with a positive slope, suggesting the following rate law: $k_{obs} = k_1 [OH^-]$. The experimental data fit the proposed reaction of degradation, $I^- + OH^- \xrightarrow{k_1}$ products, where I^- = monodissociated indomethacin species. Activation energies and other related parameters were calculated from Arrhenius-type plots.

Keyphrases □ Indomethacin—degradation in alkaline aqueous solutions, various temperatures, kinetics, effect of ionic strength □ Degradation—indomethacin in alkaline aqueous solutions, various temperatures, kinetics, effect of ionic strength □ Kinetics—degradation of indomethacin in alkaline aqueous solutions, various temperatures, effect of ionic strength □ Anti-inflammatory agents—indomethacin, degradation in alkaline aqueous solutions, various temperatures, kinetics

Indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, I] is a relatively new (1, 2) anti-inflammatory agent; it is not related to salicylates but is an acid. It is stable in neutral or slightly acidic media but is decomposed by strong alkali (3). Its physical properties, *e.g.*, solubility (4), polymorphism (5), and release rates from suppository bases (6, 7), have been reported, but its degradation kinetics have not.

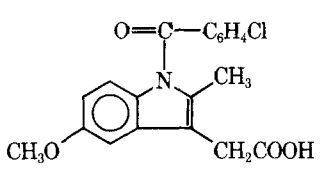
The purposes of this investigation were to study the degradation of indomethacin in alkali, to establish the order of reaction, to study the effect of ionic strength, and to obtain an Arrhenius-type plot.

EXPERIMENTAL

Materials—All materials, including indomethacin[1], sodium hydroxide, and sodium chloride, were analytically pure grade. All-glass double-distilled water was used throughout.

Kinetic Studies—An accurately weighed quantity (~100 mg) of indomethacin was dissolved in 30 ml of 95% ethanol, and the volume was adjusted to 50 ml with water at 25°. The indomethacin solution, 0.1 *N* sodium hydroxide, and water were all kept at the temperature of the study. Mixtures of the indomethacin solution (2 ml), varying quantities of 0.1 *N* sodium hydroxide, and water to a final volume of 100 ml were immediately transferred to a quartz cell kept in a constant-temperature cell holder[2]. The initial concentration of indomethacin in the reaction cell was approximately 1.1×10^{-4} *M*.

Absorbance (against an appropriate blank) was recorded as a function of time at λ_{max} 318 nm. The pH was measured at the beginning and end of each run, and no significant change in pH was found. The absorbance data obtained were used to construct semilogarithmic plots of the function $(A_t - A_\infty)$ *versus* time, where A_t is the observed absorbance at time t, and A_∞ is the observed equilibrium absorbance value. Such plots are illustrated in Fig. 1, where the degradation behavior is observed to follow first-order kinetics. The apparent first-order rate constants, k_{obs} (Table I), were calculated using regression analysis (10 or more points). Correlation coefficients were between −0.993 and −0.999.



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Effect of Ionic Strength—The effect of ionic strength was investigated at 25.8° in 0.005 *M* hydroxide-ion concentration adjusted to the ionic strengths of 0.045, 0.165, 0.505, and 1.00 and in 0.01 *M* hydroxide-ion concentration adjusted to the ionic strengths of 0.05, 0.17, 0.51, and 1.00. The ionic strength was adjusted by addition of sodium chloride (Fig. 2).

Effect of Hydroxide-Ion Concentration and Temperature—The study was carried out in various concentrations of hydroxide ion at 20.1, 25.8, 30.3, 35.1, and 40.7°.

Determination of pKa of Indomethacin—About 100 mg of indomethacin, accurately weighed, was dissolved in ethanol, and the volume was made up to 100 ml with water. The solutions were titrated potentiometrically (8) with 0.1 *M* KOH at 30°. The pKa's were calculated on a specially written Fortran program[3], using both Debye and Guntelberg activity coefficients (9). The difference between the pKa values calculated by the two methods was in all cases less than 0.002 unit. The pKa's reported are an average of 13 data points, with a range of ±0.05 unit.

RESULTS AND DISCUSSION

Figure 2 shows the effect of ionic strength. At both hydroxide-ion concentrations, there was a positive ionic strength effect with the slope of the line less than 1. At 0.005 and 0.01 *M* hydroxide-ion concentrations, the slopes of the line were 0.168 and 0.077, respectively. Since even model pharmaceutical systems by necessity are in concentration ranges above 0.01 ionic strength, it is not unusual to study pharmaceuticals at high ionic strength (10–12). This positive ionic strength effect suggests that the reaction of ions of like sign plays a role in the mechanism of indomethacin degradation (13).

Figure 3 shows the effect of varying hydroxide-ion concentrations on indomethacin degradation at various temperatures. The rate constant–hydroxide-ion concentration profile suggests a simple

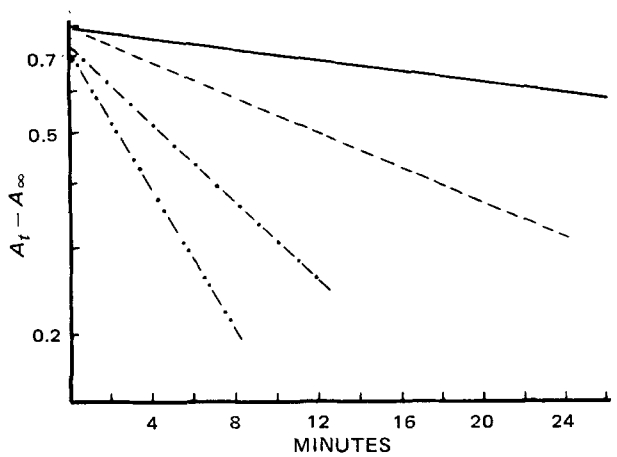

Figure 1—*Plot showing overall first-order character of indomethacin degradation at various hydroxide-ion concentrations* (M) *at 25.8°. Key: —, 0.001; - - -, 0.003; - · -, 0.006; and - · · -, 0.01. (Data were replotted from absorbance* versus *time recorder tracings.)*

[1] Lot L-590,229-00A108, Merck Sharp & Dohme, Rahway, N.J.
[2] Shimadzu spectrophotometer.
[3] Available on request from the authors.

Table I—Effect of Hydroxide-Ion Concentration on the Apparent First-Order Rate Constant, k_{obs}, for Indomethacin Degradation at Various Temperatures

	$k_{obs} \times 10^2$, min^{-1}				
[OH$^-$], M	20.1°	25.8°	30.3°	35.1°	40.7°
0.001	0.95 (0.86)[a]	1.34	1.74	2.16	2.83
0.002	2.15	3.04	3.84	5.32	6.51
0.003	3.26	4.48 (4.64)	5.91	8.05	10.12
0.004	4.45	6.25 (6.15)	8.00	11.03	13.70
0.005	5.78	7.53 (7.81)	9.96	13.66 (13.73)	17.38 (16.99)
0.0055	—	9.11	—	—	—
0.006	6.68	9.90 (9.83)	11.87	16.98	21.40
0.0065	—	10.73	—	18.13	—
0.007	—	10.75	15.20	19.20	—
0.0075	—	11.24	—	20.68	—
0.008	8.95 (9.18)	—	17.91 (17.46)	—	—
0.010	—	17.22 (17.06)	22.12 (21.03)	—	—

[a] Duplicate values are in parentheses.

mechanism. The reaction shown in Scheme I, where I^- is the monodissociated species of indomethacin, would give a rate constant–hydroxide-ion concentration profile that fits the experimental points well.

$$I^- + OH^- \xrightarrow{k_1} \text{products}$$
Scheme I

The overall velocity of the reaction is given by:

$$\frac{d[I]_T}{dt} = k_1[I^-][OH^-] \quad \text{(Eq. 1)}$$

and:

$$[I]_T = [I] + [I^-] \quad \text{(Eq. 2)}$$

where I = undissociated indomethacin species. The brackets signify molar concentrations of the appropriate species. Because of the overall first-order character of the reaction:

$$-\frac{d[I]_T}{dt} = k_{obs}[I]_T \quad \text{(Eq. 3)}$$

and:

$$K_a = \frac{K_w[I^-]}{[I][OH^-]} \quad \text{(Eq. 4)}$$

Combining these equations and substituting in Eq. 1 yield:

$$k_{obs} = \frac{k_1K_a[OH^-]^2}{[OH^-]K_a + K_w} \quad \text{(Eq. 5)}$$

The pKa for indomethacin was 6.02, 5.69, and 5.45 at 30° in 70, 60, and 50% ethanol in water, respectively. It was necessary to determine the pKa of indomethacin in the presence of ethanol because of its low solubility in water. Increasing concentrations of ethanol increase the pKa of weak acids, *e.g.*, sulfathiazole (14, 15), phenobarbital (16), and ascorbic acid (17). For the present study, for a weak acid such as indomethacin, $[OH^-]K_a \gg K_w$, where K_w is the ionic product for water. Thus, Eq. 5 reduces to:

$$k_{obs} = k_1[OH^-] \quad \text{(Eq. 6)}$$

Table II shows the values for k_1 at various temperatures together with standard errors of estimate and correlation coefficients.

The good agreement of the experimental data with Eq. 6 does not prove that Scheme I is correct but justifies its proposal. In considering the effect of hydroxide-ion concentration on the degradation of indomethacin in aqueous solution, Schemes I–VI are possible.

$$I^- + H^+ \xrightarrow{k_2} \text{products}$$
Scheme II

$$I^- \xrightarrow{k_3} \text{products}$$
Scheme III

$$I + OH^- \xrightarrow{k_4} \text{products}$$
Scheme IV

$$I + H^+ \xrightarrow{k_5} \text{products}$$
Scheme V

$$I \xrightarrow{k_6} \text{products}$$
Scheme VI

Schemes II and VI and III and IV are kinetically indistinguishable. On the basis of experimental results, Schemes II and V cannot be considered. If Schemes II (or VI) and V hold, the observed rate con-

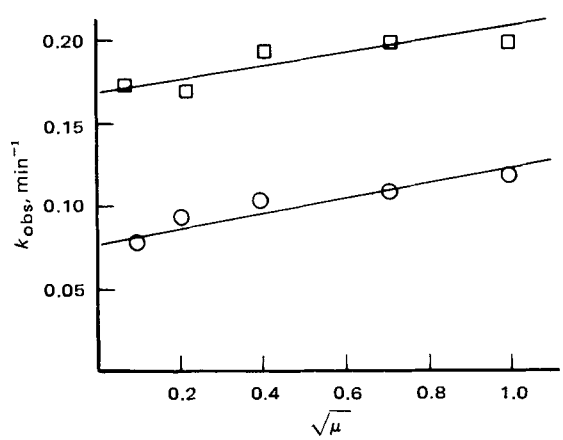

Figure 2—*Effect of ionic strength (μ) on the degradation of indomethacin at 25.8° in 0.005* M (○) *and 0.01* M (□) *hydroxide-ion concentrations.*

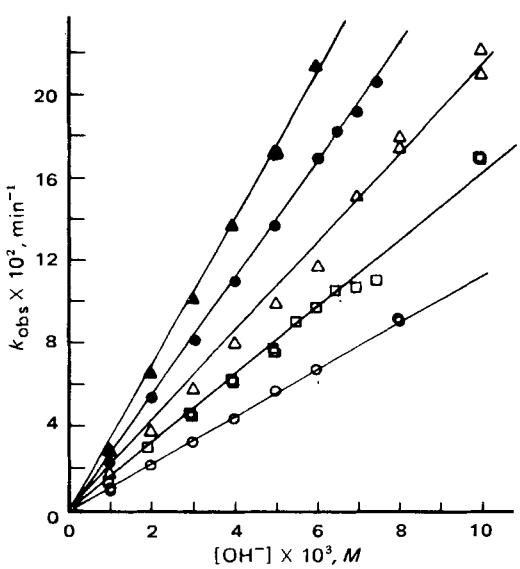

Figure 3—*Effect of varying concentrations of hydroxide ion on indomethacin degradation at various temperatures. Key:* ○, *20.1°;* □, *25.8°;* △, *30.3°;* ●, *35.1°; and* ▲, *40.7°.*

Table II—Second-Order Hydroxide-Ion Catalytic Rate Constant for Indomethacin Degradation at Various Temperatures

	20.1°	25.8°	30.3°	35.1°	40.7°
k_1, liter mole^{-1} min^{-1}	11.26	16.25	21.39	27.60	34.59
SE	0.1441	0.4967	0.5923	0.2655	0.4078
r	0.9995	0.9954	0.9976	0.9995	0.9994
n	9	16	11	10	7

Table III—Activation Energies and Other Parameters for Indomethacin Degradation in Aqueous Solution at 25° Obtained from Arrhenius-Type Plots

Hydroxide-Ion Concentration, *M*	E_a, kcal mole^{-1}	$\Delta H^{\ddagger}$, kcal mole^{-1}	$\Delta S^{\ddagger}$, cal mole^{-1} deg^{-1}	$\Delta F^{\ddagger}$, kcal mole^{-1}	$-r$	*n*
0.001	10.1	9.5	−35.2	20.1	0.995	6
0.002	10.0	9.4	−33.9	19.6	0.997	5
0.003	10.3	9.7	−32.3	19.3	0.998	6
0.004	10.2	9.6	−31.8	19.1	0.998	6
0.005	10.0	9.5	−32.0	19.0	0.996	8
0.006	10.3	9.7	−30.7	18.9	0.996	6
k_1	10.0	9.5	−21.4	15.8	0.997	5

stant would be inversely proportional to the hydroxide-ion concentration. If Scheme III (or IV) holds, the observed rate constant would be independent of the hydroxide-ion concentration. Thus, only Scheme I can be proposed.

The effect of temperature on the reaction rate can be expressed using the Arrhenius equation. As shown in Fig. 4, plots of log *k versus* $1/T$ yield a straight-line relationship at all hydroxide-ion concentrations used. Table III shows the activation energy values and other parameters calculated. The parallel slopes of the Arrhenius-type plots indicate that the mechanism of degradation is identical at all hydroxide-ion concentrations used.

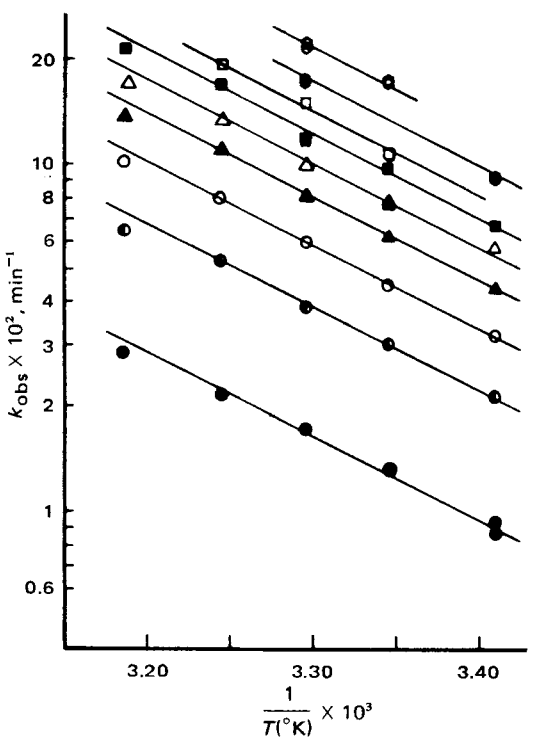

Figure 4—*Arrhenius plots showing temperature dependence of* k_{obs}, *the apparent first-order indomethacin degradation rate constant, at various hydroxide-ion concentrations* (M). *Key:* ○, *0.01;* ●, *0.008;* □, *0.007;* ■, *0.006;* △, *0.005;* ▲, *0.004;* ○, *0.003;* ◐, *0.002; and* ●, *0.001.*

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