# Kinetics of Acid-Catalyzed Hydrolysis of Dexoxadrol

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**Abstract** ☐ The kinetics of the hydronium-ion-catalyzed hydrolysis of the ketal group in dexoxadrol hydrochloride [$d(+)$-2,2-diphenyl-4-(2'-piperidyl)-1,3-dioxolane hydrochloride], an orally active analgesic agent, were determined as functions of acid concentration, ionic strength ($\mu$), and temperature. Pseudo-first-order kinetics were observed. Specific reaction rate constants increased with increasing $\mu$; log $k'/$[H$^+$] was linearly related to $\sqrt{\mu}$ at $\mu \leq 0.03$. The energy ($\Delta E_a$), enthalpy ($\Delta H\ddagger$), and entropy ($\Delta S\ddagger$) of activation were 16.8 kcal./mole, 16.2 kcal./mole, and $-18.8$ e.u., respectively. The rate of dexoxadrol hydrolysis was about 2% of that reported in the literature for 2,2-diphenyl-1,3-dioxolane, indicating a marked retardation due to the protonated piperidyl moiety. For a 60-min. residence time at pH 2.0 in the stomach, it was estimated that more than 91% of orally ingested dexoxadrol would remain intact.

**Keyphrases** ☐ Dexoxadrol—kinetics of acid-catalyzed hydrolysis ☐ Hydrolysis, acid catalyzed—dexoxadrol, kinetics ☐ Kinetics of hydrolysis—dexoxadrol, acid catalyzed

Dexoxadrol hydrochloride [$d(+)$-2,2-diphenyl-4-(2'-piperidyl)-1,3-dioxolane hydrochloride, I][1] is a potent, orally active analgesic agent in man (1–4). The synthesis (5), physicochemical properties (6), and pharmacology (7–9) of I were reported previously. The known instability of ketals in acid solution made it important to determine the extent of possible degradation of orally administered I in the stomach. Therefore, the kinetics of the acid-catalyzed hydrolysis of I were determined and are the subject of this report.

## EXPERIMENTAL

Acid hydrolysis of I yields $l$-2-(2-piperidyl)-1,2-ethanediol (II) (10) and benzophenone (III). Production of III was confirmed in the present study by: (*a*) the UV spectra of reaction mixtures at completion of hydrolysis which were identical to the spectrum of III, and (*b*) TLC of a chloroform extract of the reaction mixture which showed only one UV-absorbing product, identical to III [TLC used silica gel G and the plates were developed with isooctane–chloroform (80:35), $R_f \sim 0.3$].

In the kinetic studies, aqueous solutions of I and of hydrochloric acid were preequilibrated to the desired temperature and rapidly mixed to yield the final concentrations shown in Table I. Each reaction mixture was placed in a UV spectrophotometer equipped with a constant-temperature cell compartment. Absorbances ($A_t$) were determined at appropriate times at 247 nm., the absorption maximum of III ($\epsilon = 11,570$), until no further absorbance increases occurred ($A_\infty$). Pseudo-first-order reaction rate constants, $k'$, were
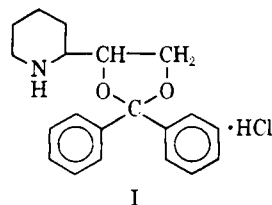
CH—CH₂ structure I (figure)

I

obtained from the slopes of plots of log ($A_\infty - A_t$) versus time. The analytical wavelength chosen was highly sensitive to the production of III, since neither I ($\lambda_{318}$, $\epsilon = 10,700$; $\lambda_{247}$, $\epsilon < 300$) nor II absorbs significantly at 247 nm. Based on observed $A_\infty$ values and the molar absorptivity of III, determined under the same conditions, hydrolysis of I was complete (mean yield of III in all studies at 37° was 102.7%).

## RESULTS AND DISCUSSION

The generally accepted mechanism for the acid-catalyzed hydrolysis of acetals and ketals involves a rapid protonation of the substrate molecule followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion (11, 12, and references cited therein). Thus, the reaction should show first-order dependence on the acetal or ketal and hydronium ion.

In the present study, plots of log ($A_\infty - A_t$) versus time were strictly linear, confirming first-order dependence on I (Fig. 1). Pseudo-first-order reaction rate constants, $k'$, obtained from the slopes of these plots are shown in Table I along with the resulting values of $k'/$[H$^+$]. Hydronium-ion concentrations were converted to activities by interpolation of the data of Harned and Owen (13) and were used to calculate the specific reaction rate constants, $k_H$- (Table I).

Inspection of the data shows that $k'/$[H$^+$] and $k_H$ $^+$ increased with acid concentration and, therefore, with ionic strength ($\mu$), since the latter was permitted to vary with the acid concentration. For hydrolysis of a neutral species, $k_H$ $^+$ should be essentially independent of $\mu$. However, the pKa of I is approximately 8.9 (6). As a consequence, I was completely in the cationic form in the systems studied, and the hydronium-ion-catalyzed hydrolysis involved a reaction between like-charged ions. In such a case, an increase in the rate constant with increasing $\mu$ would be predicted, with log $k'/$[H$^+$] linearly related to $\sqrt{\mu}$ at low values for $\mu$ (14). To test this relationship for the present system, linear least-squares regression of log $k'/$[H$^+$] versus $\sqrt{\mu}$ (for $\mu \leq 0.03$) was conducted with predetermined theoretical slopes of 1.00, 0.97, and 0.93 at 30, 37, and 44°, respectively (14). The resulting curves (Fig. 2) provided convincing evidence for the predicted effects of $\mu$ on the rate constants. Accord-
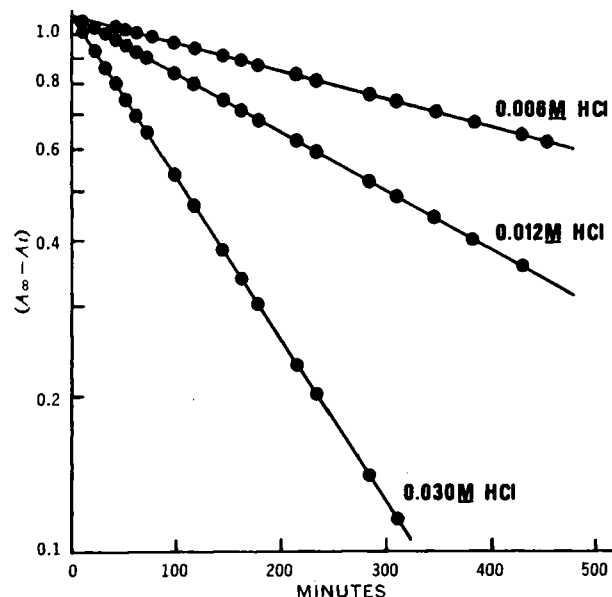


**Figure 1**—*Pseudo-first-order reaction rate curves for dexoxadrol hydrolysis at 44°.*

Table I—Reaction Conditions and Kinetic Constants for Dexoxadrol Hydrolysis

| Temperature | Dexoxadrol, $M \times 10^5$ | Hydrochloric Acid, $M \times 10^2$ | $k'$, sec.$^{-1}$ | $k'/[H^+]$, $M^{-1}$ sec.$^{-1} \times 10^3$ | $k_H^{+a}$, $M^{-1}$ sec.$^{-1} \times 10^3$ | $k_0^b$, $M^{-1}$ sec.$^{-1} \times 10^3$ |
|---|---|---|---|---|---|---|
| 30° | 8.67 | 0.60 | $5.90 \times 10^{-6}$ | 0.983 | 1.07 | 0.818 |
| 30° | 8.67 | 1.20 | $1.28 \times 10^{-5}$ | 1.07 | 1.19 | |
| 30° | 8.67 | 3.00 | $3.68 \times 10^{-5}$ | 1.20 | 1.41 | |
| 37° | 8.67 | 0.15 | $2.38 \times 10^{-6}$ | 1.59 | 1.70 | 1.59 |
| 37° | 8.67 | 0.60 | $1.17 \times 10^{-5}$ | 1.95 | 2.13 | |
| 37° | 9.26 | 0.60 | $1.14 \times 10^{-5}$ | 1.90 | 2.07 | |
| 37° | 8.67 | 1.20 | $2.58 \times 10^{-5}$ | 2.15 | 2.41 | |
| 37° | 9.26 | 1.20 | $2.45 \times 10^{-5}$ | 2.04 | 2.29 | |
| 37° | 9.26 | 3.00 | $6.80 \times 10^{-5}$ | 2.27 | 2.66 | |
| 37° | 14.46 | 3.00 | $6.77 \times 10^{-5}$ | 2.26 | 2.64 | |
| 37° | 14.46 | 3.00 | $6.70 \times 10^{-6}$ | 2.23 | 2.62 | |
| 37° | 8.67 | 3.00 | $7.37 \times 10^{-5}$ | 2.46 | 2.88 | |
| 37° | 8.67 | 4.80 | $1.17 \times 10^{-4}$ | 2.44 | 2.94 | |
| 37° | 8.67 | 4.80 | $1.15 \times 10^{-4}$ | 2.40 | 2.89 | |
| 37° | 8.67 | 7.20 | $1.80 \times 10^{-4}$ | 2.50 | 3.09 | |
| 37° | 8.67 | 7.20 | $1.87 \times 10^{-4}$ | 2.60 | 3.21 | |
| 37° | 8.67 | 9.60 | $2.65 \times 10^{-4}$ | 2.76 | 3.48 | |
| 37° | 8.67 | 9.60 | $2.60 \times 10^{-4}$ | 2.71 | 3.41 | |
| 44° | 8.86 | 0.60 | $2.07 \times 10^{-5}$ | 3.45 | 3.76 | 2.80 |
| 44° | 8.86 | 1.20 | $4.26 \times 10^{-5}$ | 3.55 | 3.98 | |
| 44° | 8.86 | 3.00 | $1.10 \times 10^{-4}$ | 3.97 | 4.67 | |

$^a$ $k_H^+ = k'/a_{H^+}$. $^b$ Intercept from log $k'/[H^+]$ versus $\sqrt{\mu}$ for $\mu \leq 0.03$ (Fig. 2).

ingly, $k_0$ (specific reaction rate constant at infinite dilution) was obtained from the intercept of each curve in Fig. 2 and is shown in Table I.

Parameters of activation for the hydrolysis of I were determined from $k_0$ at 30, 37, and 44° and appropriate linear regressions (Fig. 3). Similar determinations were made utilizing $k_H$ - values obtained at the three temperatures in 0.006, 0.012, and 0.030 $M$ HCl solutions. From the summary in Table II, it may be seen that the classical Arrhenius activation energy ($\Delta E_a$) is in good agreement with the

value of 17.2 kcal./mole reported by Ceder (15) for the hydrolysis of 2,2-diphenyl-1,3-dioxolane under similar conditions. The enthalpy of activation ($\Delta H\ddagger$) is somewhat larger than that reported by De Wolfe et al. (16) for the hydrolysis of 2,2-diphenyl-1,3-dioxolane in 30% dioxane ($\Delta H\ddagger = 14.6$ kcal./mole). Fife and Hagopian (12) suggested that steric inhibition of resonance in the incipient carbonium ion should make $\Delta H\ddagger$ more positive. The differences in $\Delta H\ddagger$ may, therefore, reflect such an inhibition by the piperidyl moiety present in I. The entropy of activation ($\Delta S\ddagger$) is considerably more negative than values reported for the hydrolysis of 2,2-diphenyl-1,3-dioxolane in 30% dioxane ($\Delta S\ddagger = -8.3$ e.u.) (16) and for a series of 2-phenyl-2-alkyl-1,3-dioxolanes in 50% dioxane ($\Delta S\ddagger = -8.6$ to $-8.9$ e.u.) (12). Although the magnitude of $\Delta S\ddagger$ is typical of those observed for bimolecular reactions (17), there is no reason to conclude that the mechanism of reaction for I differs
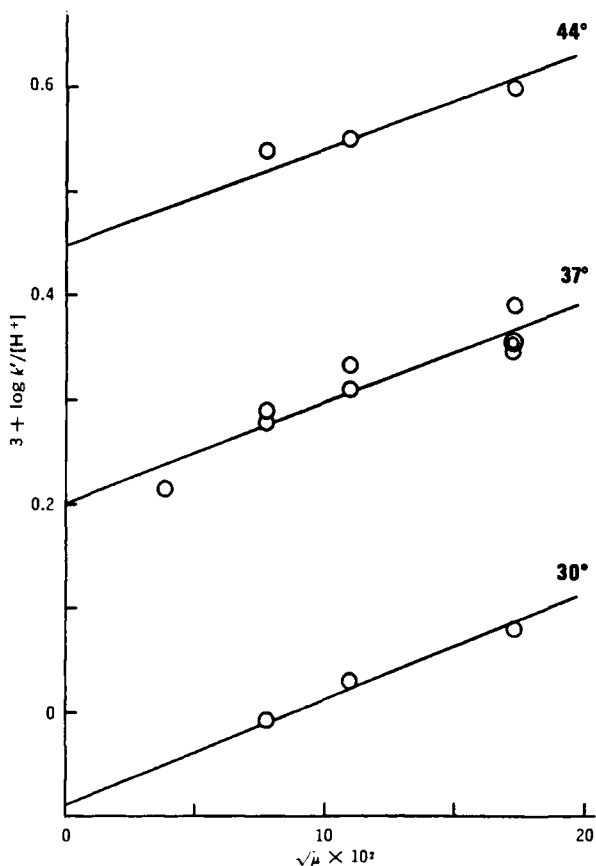


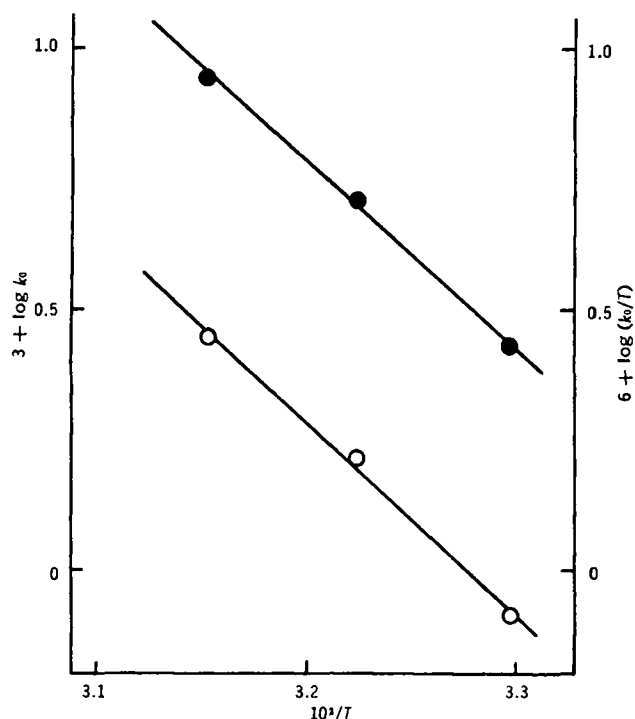Figure 2—Linear least-squares regression of log k'/[H$^+$] versus $\sqrt{\mu}$ with predetermined theoretical slopes.



Figure 3—Linear least-squares regression of log $k_0$ versus $1/T$ (O) and log $(k_0/T)$ versus $1/T$ (●).

**Table II—Activation Parameters for Dexoxadrol Hydrolysis**

| Basis for Calculation | $\Delta E_a$, kcal./mole | $\Delta H\ddagger$, kcal./mole | $\Delta S\ddagger$, e.u. |
|---|---|---|---|
| $k_0$ | $16.9 \pm 0.6$ | $16.3 \pm 0.6$ | $-19.1 \pm 1.9$ |
| $k_{H^+}$, 0.006 $M$ HCl | $17.2 \pm 0.5$ | $16.6 \pm 0.5$ | $-17.3 \pm 1.7$ |
| $k_{H^+}$, 0.012 $M$ HCl | $16.6 \pm 1.0$ | $15.9 \pm 1.0$ | $-19.3 \pm 3.2$ |
| $k_{H^+}$, 0.030 $M$ HCl | $16.4 \pm 0.8$ | $15.8 \pm 0.8$ | $-19.4 \pm 2.7$ |
| Mean | $16.8 \pm 0.8$ | $16.2 \pm 0.8$ | $-18.8 \pm 2.5$ |

from that generally accepted for ketal hydrolysis. Rather, it appears that I represents a case where steric hindrance in the transition state produces an increase in $\Delta H\ddagger$ and a decrease in $\Delta S\ddagger$ (17).

The data of De Wolfe et al. (16) allow a comparison of the hydrolysis rates for I and 2,2-diphenyl-1,3-dioxolane. These investigators found $k_{H^+} = 7.50 \times 10^{-2}$ $M^{-1}$ sec.$^{-1}$ for the latter compound at 30° (0.0197 $M$ HCl in 1.3% dioxane–98.7% water). Interpolation of the data for I from Fig. 2 gave $k_{H^+} = 1.29 \times 10^{-3}$ $M^{-1}$ sec.$^{-1}$ at 30° (0.0197 $M$ HCl in water). Presence of the protonated piperidyl group in I, therefore, produced a greater than 98% reduction in hydrolysis rate, reflecting the less favorable entropy of activation.

De Wolfe et al. (16) found that hydrolysis of a number of benzophenone ketals was susceptible to general acid catalysis. The catalytic constants for acids other than the hydronium ion were small but significant. For example, dichloroacetic acid (HA) catalyzed the hydrolysis of 2,2-diphenyl-1,3-dioxolane (30°, 20% dioxane) such that $k_{H^+}/k_{HA} = 40$. No attempt was made in the present studies to determine the role of general acid catalysis in the hydrolysis of I. However, it may be concluded from the data in Table I (37°, 0.03 $M$ HCl) that the protonated substrate (a Bronsted acid) did not make a significant catalytic contribution to its own hydrolysis, since observed rate constants were independent of initial I concentration.

Oral doses of I in man have ranged from 10 to a maximum of 150 mg. (1–4). Since the solubility of I is high (11.66 mg./ml. at 23°) (6), rapid and complete dissolution should occur in the stomach. Gastric pH and emptying times vary widely. To provide a reasonable estimate of the stability of I during its transit through the stomach, a pH of 2.0 (corresponding to the data for 0.012 $M$ HCl in Table I) and a residence time of 60 min. (approximately three half-lives for the stomach emptying process) (18) were assumed. Under those conditions, more than 91% of orally ingested I would survive hydrolysis. This estimate is consistent with the high order of oral activity observed in clinical studies.

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