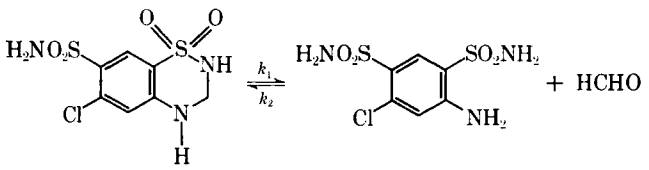
# Hydrolysis of Hydrochlorothiazide

**Keyphrases** □ Hydrochlorothiazide hydrolysis—kinetics pH profile—hydrochlorothiazide Hydrolysis rates—hydrochlorothiazide

*Sir:*

Since the earlier report of Rehm and Smith (1) that the hydrolysis of hydrochlorothiazide proceeds to an equilibrium, no studies investigating this reaction in detail have been reported. Yamana *et al.* (2) have investigated the hydrolysis in 1 *N* NaOH solution. Under these conditions the base-catalyzed disproportionation of formaldehyde into methanol and formic acid becomes significant.

In this paper, we report on the reaction over the pH range from 1 to 13. Reversible kinetics were observed for the reaction (Scheme I) over the pH range from 1 to 9.




*Scheme I*

We have evaluated the rate of the forward reaction, $k_1$; the rate of the reverse reaction, $k_2$; and the extent of reaction as a function of pH. In Table I are data obtained at several pH values and concentrations.

Figure 1 shows a plot of log $k_1$ *versus* pH. The pseudo first-order rate constants were obtained by taking the initial slopes of plots of log $(a-x)$ *versus* time where $a$ is the initial concentration of hydrochlorothiazide and $x$ is the concentration of disulfonamide produced, and/or from plots of

$$\log \frac{1-(1-X_e)(1-X)}{(1-X)-(1-X_e)} \textit{ versus } \text{time}$$

where $X$ is the fraction reacted at time, $t$, and $X_e$ is the fraction reacted at equilibrium. There was agreement to within 2% between rate constants obtained by each method. In alkaline solution, $k_1$ was evaluated by determining the initial rates of formation of disulfonamide produced over the first few percents of reaction. The value obtained in this study for the hydrolysis in 1 *N* NaOH solution, 60°, was $2.24 \times 10^{-2}$ hr.$^{-1}$ which is in excellent agreement with the value of $1.8 \times 10^{-2}$ hr.$^{-1}$ which can be extrapolated from the data in Yamana's paper (2).

**Table I**—Extent of Reaction and Equilibrium Constant as a Function of pH and Concentration

| pH | $C_0$ ( $\times 10^4$ *M*)[a] | $X_e$[b] | $K$ ( $\times 10^4$ *M*)[c] |
|---|---|---|---|
| 1.50 | 6.74 | 0.410 | 1.9 |
| 4.61 | 6.65 | 0.407 | 1.9 |
| 4.62 | 16.8 | 0.283 | 1.9 |
| 4.60 | 67.2 | 0.164 | 2.2 |
| 7.41 | 6.72 | 0.398 | 1.8 |
| 8.18 | 67.2 | 0.158 | 2.0 |
| 4.38[d] | 6.78 | 0.419 | 2.1 |

[a] Initial concentration of hydrochlorothiazide. [b] $X_e$ = Fraction reacted: $1 - C_{eq}/C_0$. [c] $K$ = [HCHO] [disulfonamide] / [hydrochlorothiazide]. [d] Formation of hydrochlorothiazide from equimolar ($6.78 \times 10^{-4}$) concentrations of disulfonamide and formaldehyde.

The pH rate profile in Fig. 1 is relatively complex and not amenable to simple interpretation. The inflection point at pH = 4.6 does not agree with either of the two pK values of hydrochlorothiazide (8.6 and 9.9). A pH rate curve such as this which cannot be explained by the ionization of the reactants usually indicates a change in rate-determining step. A change in rate-determining step will not occur unless there are at least two steps and an intermediate in a reaction. The explanation which is most tenable at this time is that an imine intermediate is formed. That this type of scheme, where one of the inflection points is not due to an ionizable group in the compound, leads to a bell-shaped curve has been recognized in the hydrolysis of *o*-carboxyphthalimide (3), Schiff base formation and hydrolysis (4, 5), reactions of amines with imido esters (6), and thiazoline hydrolysis (7, 8).

Several factors which make the formation of an imine seem particularly reasonable are: the observed log $k$-pH profile for hydrochlorothiazide is similar to that observed for a Schiff base hydrolysis (4); formamide intermediates have been reported in the hydrolysis of

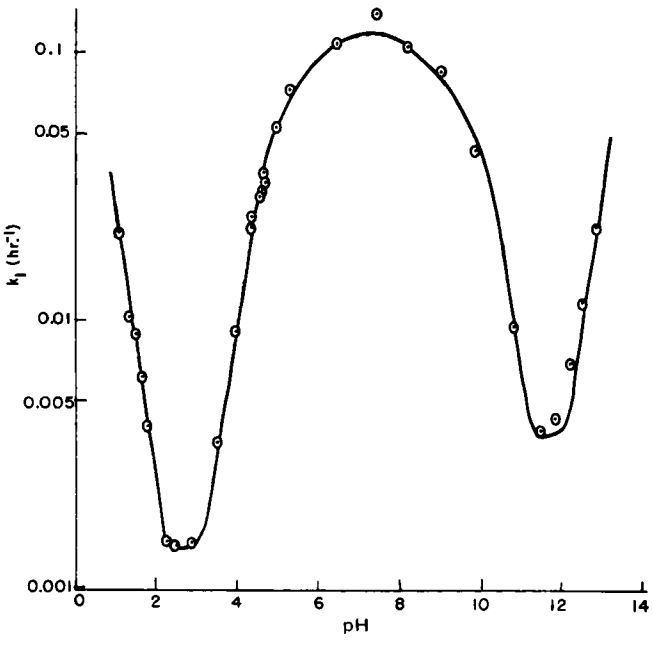
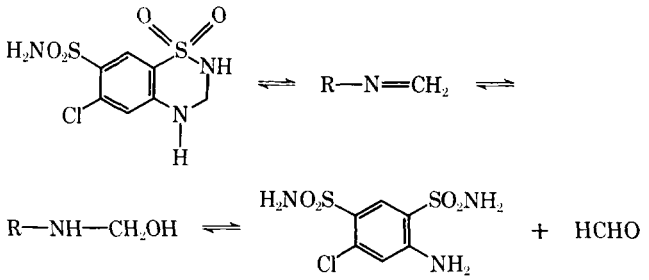



**Figure 1**—*pH-Rate profile of the hydrolysis of hydrochlorothiazide at 60°C.*

chlorothiazide (9); and analogous compounds have been reported from the reaction of *o*-aminosulfonamides with various aldehydes, formic acid, and orthoesters (10–12).

The hydrolytic reaction therefore most likely proceeds with ring opening to form an imine which undergoes attack by water or hydroxide ion to yield a carbinolamine (13); decomposition of this aminoalcohol then yields formaldehyde and 4-amino-6-chloro-*m*-benzene disulfonamide (Scheme II).



*Scheme II*

Other mechanisms could be postulated. We are presently extending this study to consider the susceptibility to general acid-base catalysis and to consider the effects of substituents in the 2, 3, and 4 positions on the hydrolytic reaction.

(1) C. R. Rehm and J. B. Smith, *J. Pharm. Sci.*, **49**, 386(1960).

(2) T. Yamana and Y. Mizukami, *Yakugaku Zasshi*, **85**, 1057 (1965).

(3) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, **83**, 2267 (1961).

(4) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832(1962).

(5) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193(1956).

(6) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962).

(7) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsolb, *ibid.*, **81**, 5089(1959).

(8) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830(1961).

(9) T. Yamana, H. Koike, Y. Mizukami, T. Motoya, and Y. Insemi, *Yakugaku Zasshi*, **84**, 971(1964); T. Yamana and Y. Mizukami, *ibid.*, **87**, 1304(1967); T. Yamana, Y. Mizukami, M. Nishida, M. Izak, N. Kitade, and K. Shinai, *ibid.*, **87**, 1447(1967).

(10) J. H., Freeman, and E. C., Wagner, *J. Org. Chem.* **16**, 815(1951).

(11) F. C. Novello, S. C. Bell, E. L. A. Abrams, E. Ziegler, and J. M. Sprague, *ibid.*, **25**, 970(1960).

(12) J. G. Topliss, M. H. Sherlock, F. H. Clarke, M. C. Daly, B. W. Pettersen, J. Lipski, and N. Sperber, *ibid.*, **26**, 3842(1961).

(13) W. P. Jencks, in "*Progress in Physical Organic Chemistry*," **vol. 2**. S. G. Cohen, A. Streitwieser, and R. W. Taft, Eds., Interscience, New York, N. Y., 1964, pp. 63–128.

J. A. MOLLICA
C. R. REHM
J. B. SMITH
Ciba Pharmaceutical Co.
Development and Control Department
Summit, NJ 07901

Received December 12, 1968.
Accepted for publication January 24, 1969.

# Lidocaine—An Unusual Incidence of an Acyclic *Cis* Amide Configuration

**Keyphrases** ☐ Lidocaine configuration—acyclic *cis* amide ☐ IR spectrophotometry—structure ☐ PMR spectroscopy—structure

*Sir:*

Very little spectroscopic data [infrared (IR) or proton magnetic resonance (PMR)] have been published for lidocaine (2-diethylamino-2′,6′-acetoxylidide) or for molecules closely related to lidocaine. By analogy with various ring-substituted anilides, lidocaine might be expected to have the *trans* amide configuration (1, 2). We have found, surprisingly, that the IR spectra of the free base in the solid state (flurolube/mineral oil) and in solution ($CCl_4$) indicated the existence of the *cis* amide configuration, in contrast to salts of the base where the *trans* configuration has been deduced (3).

The following evidence supports our assignment of the *cis* structure (Fig. 1). In the solid state the IR spectrum of lidocaine showed only one symmetrical broad band at 3,235 cm.$^{-1}$ due to the NH stretching vibration, a strong amide I band at 1,662 cm.$^{-1}$ (with a weak shoulder at 1,685 cm.$^{-1}$), and a strong amide II band at 1,490 cm.$^{-1}$. On deuterium substitution these bands were replaced by bands at 2,385, 1,655, and 1,407 cm.$^{-1}$, respectively. The IR spectrum of a $CCl_4$ solution (0.26 *M*) of lidocaine gave only one symmetrical band at 3,312 cm.$^{-1}$ attributed to NH stretching, and strong bands at 1,690 and 1,494 cm.$^{-1}$ for the amide I and II bands, respectively. On deuteration these bands were shifted to 2,460, and 1,694 and 1,393 cm.$^{-1}$, respectively. Since the amide II frequency [a mixed vibration involving NH in-plane bending and C-N stretching (4)] is quite characteristic of *trans* amides at ~1,550 cm.$^{-1}$, and of *cis* amides at ~1,485 cm.$^{-1}$, it is inferred that the free base has the *cis* amide configuration. Moreover, the fact that the amide NH stretching band at 3,312 cm.$^{-1}$ in $CCl_4$ shows no shift on dilution to 0.003 moles/l. confirms the absence of polymeric *trans* forms and supports the existence of dimeric *cis* amide forms (4).

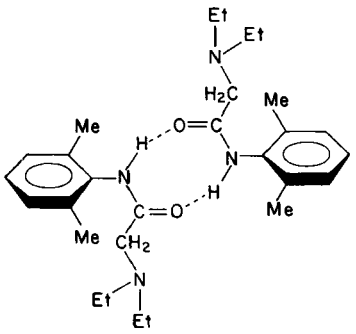


**Figure 1**—*Lidocaine in the* cis *amide configuration.*