

## Report

# Stability of Lidocaine in Aqueous Solution: Effect of Temperature, pH, Buffer, and Metal Ions on Amide Hydrolysis

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The degradation of lidocaine in aqueous solution obeys the expression

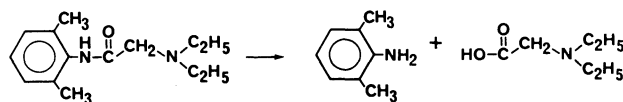
$$k_{\text{obs}} = (k_{\text{H}^+}[\text{H}^+] + k_o) [\text{H}^+]/([\text{H}^+] + K_a) + k'_o K_a/([\text{H}^+] + K_a)$$

where  $k_{\text{H}^+}$  is the rate constant for hydronium ion catalysis, and  $k_o$  and  $k'_o$  are the rate constants for the spontaneous (or water-catalyzed) reactions of protonated and free-base lidocaine. At 80°C, the rate constants for these processes are  $1.31 \times 10^{-7} \text{ M}^{-1} \text{ sec}^{-1}$ ,  $1.37 \times 10^{-9} \text{ sec}^{-1}$ , and  $7.02 \times 10^{-9} \text{ sec}^{-1}$ ; the corresponding activation energies are 30.5, 33.8, and 26.3 kcal mol<sup>-1</sup>, respectively. It was found that the room temperature pH of maximum stability is ~3–6 and that lidocaine is more reactive in the presence of metal ions such as Fe<sup>2+</sup> and Cu<sup>2+</sup>. The dissociation constant,  $K_a$ , for lidocaine at 25–80°C was also measured at 0.1 M ionic strength and a plot of  $pK_a$  versus  $1/T$  gave a slope of  $(1.88 \pm 0.05) \times 10^3 \text{ K}^{-1}$  and intercept  $1.56 \pm 0.16$ .

**KEY WORDS:** kinetics of lidocaine degradation; aqueous stability;  $pK_a$ ; amide hydrolysis.

## INTRODUCTION

Lidocaine exhibits exceptional stability in most parenteral solutions (1–3) and is extremely resistant toward hydrolysis at room temperature, even in strongly acidic or basic media (4–7). At higher temperatures, however, lidocaine degrades slowly, to give primarily 2,6-dimethylaniline and *N,N*-diethylaminoacetic acid, as shown in Scheme I (4).



Scheme I

Despite the importance of this drug as a powerful local anesthetic, little is known about the temperature and pH dependence on lidocaine degradation in aqueous solution. Conflicting accounts regarding the stability of lidocaine have been reported; for example, an early study found only 0.05% drug loss after 3 hr at 116°C (4), whereas another study showed more rapid drug loss (2.5%) after reaction for 12 hr at 96°C (5). Furthermore, the pH of maximum stability for lidocaine has not been accurately determined. Previous reports of lidocaine hydrolysis in aqueous solution (4–7) have not discerned conclusively whether lidocaine exhibits a sharply defined pH of maximum stability, as do formamide (8), acetamide (9), and  $\alpha$ -propylamino-2-methylpropionanilide (10), or whether it shows a broad pH range of maximum stability (characteristic of a predominant spontaneous or

water-catalyzed reaction), as observed for *N*-(1-aminoalkyl)amides (11,12) and certain hydroxy anilides (13). In order to determine the pH of maximum stability for lidocaine, and to delineate the factors that affect the rate of lidocaine degradation, the effect of pH, temperature, buffer, propylene glycol, and added metal ions on the hydrolysis of lidocaine in aqueous solution was investigated.

## EXPERIMENTAL

**Apparatus and Reagents.** Reverse-phase chromatography of lidocaine was carried out using a high-performance liquid chromatography (HPLC) system consisting of a Model 725 Micromeritics autoinjector, a Model 110A Altex pump, a Model 770 Spectra Physics spectrophotometric detector, and an SP 4000 computing integrator. A 250  $\times$  4.6-mm Partisil 5 ODS 3 column (Whatman) was used for analysis. Lidocaine hydrochloride USP was used for all experiments herein. HPLC-grade methanol, tetrahydrofuran (Burdick and Jackson), and distilled, deionized water were used for the preparation of mobile phase. Potassium hydrogen phosphate, sodium hydroxide, hydrochloric acid, iron (II) chloride, copper (II) chloride, heptane sulfonic acid sodium salt, propylene glycol, and 2,6-dimethylaniline were of the highest grade commercially available (Aldrich or Mallinckrodt) and were used without further purification.

**HPLC Conditions.** A linear response ( $\pm 1\%$ ) throughout the range of 0.1–10  $\mu\text{g}$  lidocaine injected and separation of lidocaine from its degradation products, 2,6-dimethylaniline and *N,N*-diethylaminoacetic acid, were achieved using the following conditions: mobile phase, water:methanol:tetrahydrofuran (48.2:48.2:1.6, v/v) containing 0.02 M heptane sulfonic acid sodium salt and 0.02 M KH<sub>2</sub>PO<sub>4</sub>; flow rate,

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1.0 ml/min; detection, 230 nm; injection volume, 10–50  $\mu$ l; and typical retention times, 12–12.5 min for lidocaine and 9.5–10 min for 2,6-dimethylaniline (capacity factors, 5.66 and 4.33, respectively).

**Kinetics.** For all experiments, 0.01 *M* buffer solutions ( $\mu = 0.10$ ) containing lidocaine (35  $\mu$ g/ml) were prepared shortly before use and the pH's were determined at 21, 60, and 80°C; pH's at 100°C were extrapolated from linear plots of pH (at 21–80°C) versus the reciprocal of absolute temperature. A summary of the buffer solutions used and pH's is given in Table I. For strongly acidic or alkaline solutions at 80 and 100°C, the hydronium and hydroxide ion activities were calculated from published activity coefficients (14,15) or  $H_o$  values (16,17). In a typical experiment, 10-ml aliquots of reaction solution containing lidocaine were transferred to pretreated ampoules, flame-sealed, and stored at 80 or 100°C. Several of these samples were also refrigerated immediately after flame-sealing and were later used as controls for the initial time points. At known time intervals, up to ~300 days, ampoules were removed and refrigerated until 6–10 samples for each kinetic run were taken. Upon removal of the last samples, the stored solutions were allowed to warm to room temperature and then all samples were analyzed by HPLC on the same day. Rate measurements were carried out using varying acetate buffer concentrations up to 0.15 *M* in order to determine the effect of buffers on this reaction. Reaction kinetics were also carried out at 100°C with added iron (II) chloride and copper (II) chloride (10 and 50 ppm) at pH 7.6 or with added 20 and 80% (v/v) aqueous propylene glycol. Peak area integration values were used directly in first-order fits of the data and most reactions were followed to less than 90% remaining. Nonlinear least-squares analysis (18) was used to obtain the best-fit rate constants from the log(rate)–pH profiles.

**$pK_a$  Determinations.** The  $pK_a$  of lidocaine at 0.1 *M* ionic strength (NaCl) was determined by preparing a solution of lidocaine (0.0103 *M*) and lidocaine hydrochloride (0.0103 *M*) and measuring the pH's at the temperature of study using a Radiometer PHM 64 pH meter and Model GK2401C combination electrode. Buffer dilutions were not carried out during the pH measurements because the  $pK_a$  of lidocaine is insensitive to ionic strength (19).

Table I. Summary of Rate Constants for the Degradation of Lidocaine in Aqueous Solution<sup>a</sup>

Buffer ( $\mu = 0.1$ )	80°C		100°C	
	pH <sup>a</sup>	$10^9 k$ (sec <sup>-1</sup> )	pH <sup>b</sup>	$10^8 k$ (sec <sup>-1</sup> )
0.1 <i>M</i> HCl	1.0	$15.8 \pm 1.31$	1.0	$15.5 \pm 0.10$
0.005 <i>M</i> HCl	2.3	$1.58 \pm 0.31$	2.3	$2.40 \pm 0.79$
0.01 <i>M</i> phosphate	4.5	$1.32 \pm 0.07$	4.6	$1.60 \pm 0.19$
0.01 <i>M</i> phosphate	5.6	$2.38 \pm 0.15$	5.8	$2.76 \pm 0.10$
0.01 <i>M</i> phosphate	7.2	$4.91 \pm 0.35$	7.2	$6.54 \pm 0.33$
0.01 <i>M</i> phosphate	8.3	$5.97 \pm 0.66$	8.3	$5.76 \pm 0.24$
0.01 <i>M</i> phosphate	8.8	$7.33 \pm 0.42$	8.5	$5.23 \pm 0.37$
0.01 <i>M</i> KOH	10.6	$6.32 \pm 0.17$	10.1	$4.05 \pm 0.06$
0.1 <i>M</i> KOH	11.7	$7.88 \pm 0.18$	11.1	$4.10 \pm 0.08$

<sup>a</sup> pH determined at 80°C.

<sup>b</sup> pH extrapolated from a linear plot of pH (21–80°C) versus the reciprocal of absolute temperature.

## RESULTS AND DISCUSSION

**Effect of pH and Temperature.** For all experiments, apparent first-order kinetics were observed, and the pH dependence on lidocaine degradation is given by the data in Table I. The log (rate)–pH profiles are shown in Fig. 1; the best-fit lines in this figure were generated using Eq. (1).

$$k_{\text{obs}} = (k_{\text{H}^+}[\text{H}^+] + k_o) [\text{H}^+]/([\text{H}^+] + K_a) + k_o'K_a/([\text{H}^+] + K_a) \quad (1)$$

The rate constants of Eq. (1) are for catalysis by hydronium ion ( $k_{\text{H}^+}$ ) and for the spontaneous (or water-catalyzed) reactions of protonated ( $k_o$ ) and free-base forms of lidocaine ( $k_o'$ ). The factors  $[\text{H}^+]/([\text{H}^+] + K_a)$  and  $K_a/([\text{H}^+] + K_a)$  represent the fractions of protonated and unprotonated lidocaine, respectively, and are an integral part of Eq. (1) necessary for fitting the pronounced curved region near pH 7 in the log(rate)–pH profile. The  $K_a$  values used for the fit of Eq. (1) were determined by least-squares analysis of  $pK_a$  versus  $1/T$  (Table II), as shown in Fig. 2. The secondary rate constants derived from the data in Table I are given in Table III; the corresponding activation parameters are summarized in Table IV.

The log (rate)–pH profiles in Fig. 1 show that lidocaine hydrolysis is only weakly catalyzed by hydronium ion and even less so by hydroxide ion; in fact, the hydroxide term  $k_{\text{HO}^-}[\text{HO}^-]$  was not required in Eq. (1) for fitting the data up to pH ~12. Hydroxide ion-catalyzed amide hydrolysis for other amides has been observed in strongly alkaline solutions, although it went undetected for lidocaine, even in 0.1 *M* KOH at 100°C (4,5). In the mid-pH region, the dominant rate constants of Eq. (1) are  $k_o$  and  $k_o'$ , denoting the spontaneous or water-catalyzed reaction of protonated and free-base lidocaine, respectively. At 80°C, the spontaneous reaction for free-base lidocaine was found to be approximately five times faster than for protonated lidocaine. This rate ratio becomes even more pronounced at lower temperatures, and at 25°C,  $k_o'$  is calculated to be approximately 36

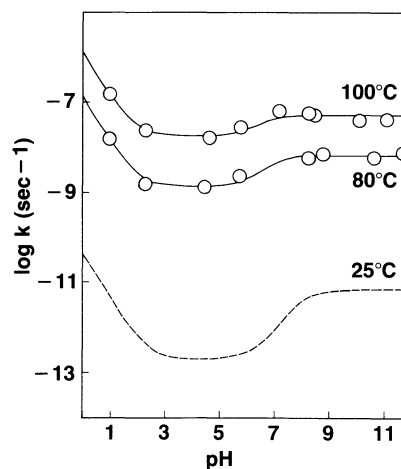


Fig. 1. Log(rate)–pH profile for the degradation of lidocaine in aqueous solution at 80 and 100°C. The dashed line is the calculated log(rate)–pH profile for lidocaine at 25°C and is included to show the pH range of maximum stability (pH 3–6) at room temperature.

Table II. Effect of Temperature on the  $pK_a$  of Lidocaine<sup>a</sup>

Temperature (°C)	$pK_a$	Reference
10	8.24	20
21	7.97	This paper
25	7.92	20
38	7.57	20
50	7.41	This paper
65	7.14	This paper
80	6.91	This paper
100	6.62 <sup>b</sup>	This paper

<sup>a</sup> Ionic strength = 0.1 M.<sup>b</sup> Calculated from the least-squares line of  $pK_a$  versus  $1/T$  having a slope of  $(1.88 \pm 0.05) \times 10^3 \text{ K}^{-1}$  and intercept  $1.56 \pm 0.16$ .

times larger than  $k_o$ . This difference in relative rates is not critical for drug formulation, however, because even the faster reaction ( $k'_o$ ) has a calculated room-temperature shelf life ( $t_{90}$ ) of >400 years. At 25°C, the pH of maximum stability for lidocaine is ~3–6, as shown by the calculated log (rate)–pH profile (dashed line in Fig. 1). At temperatures above 100°C the rate constants  $k_o$  and  $k'_o$  are much closer in magnitude, and at 145°C they are predicted to be equal at  $2.4 \times 10^{-6} \text{ sec}^{-1}$ ; above this temperature  $k_o > k'_o$ . Thus, at 145°C, lidocaine stability is independent of pH from pH 2 to pH 12, where the predicted shelf life is approximately 12 hr.

**Effect of Additives.** A study was carried out to determine if the anomalous rate constants in the literature for lidocaine degradation (4–7) could be caused by buffers, by the adventitious presence of metal ions, or by the addition of added alcohols such as propylene glycol. Inspection of Table V shows that acetate buffer up to 0.15 M did not noticeably accelerate the rate of drug degradation, and little, if any, buffer catalysis is expected in the 0.01 M phosphate solutions used herein. This lack of buffer catalysis for amide hydrolysis has been reported previously for *N*-(1-aminoalkyl)amides (12,13), compounds that show log(rate)–pH

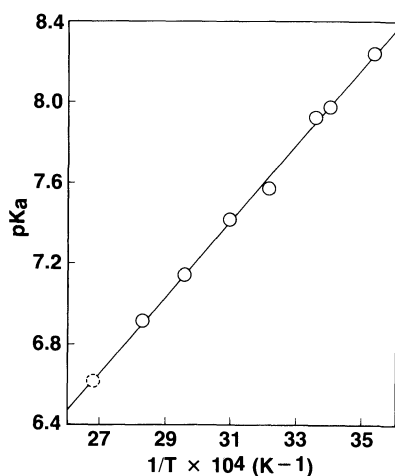


Fig. 2. Relationship between lidocaine  $pK_a$  and the reciprocal of absolute temperature. The dashed circle is the  $pK_a$  (6.62) at 100°C calculated from linear least-squares analysis. The data points at 10, 25, and 38°C are from Ref. 20.

Table III. Summary of Rate Constants for the Degradation of Lidocaine in Aqueous Solution

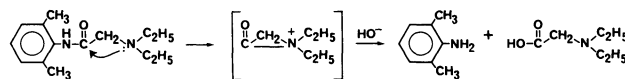
Temperature (°C)	Rate constant <sup>a</sup>		
	$k_{H^+} (M^{-1} \text{ sec}^{-1})$	$k_o (\text{sec}^{-1})$	$k'_o (\text{sec}^{-1})$
100	$1.35 \times 10^{-6}$	$1.82 \times 10^{-8}$	$5.26 \times 10^{-8}$
80	$1.31 \times 10^{-7}$	$1.37 \times 10^{-9}$	$7.02 \times 10^{-9}$
25 <sup>b</sup>	$4.32 \times 10^{-11}$	$1.90 \times 10^{-13}$	$6.86 \times 10^{-12}$

<sup>a</sup> Obtained from a nonlinear least-squares fit (Ref. 18) of the rate data to Eq. (1).<sup>b</sup> Rate constants at 25°C were calculated from  $E_a$  and log  $A$  given in Table IV.

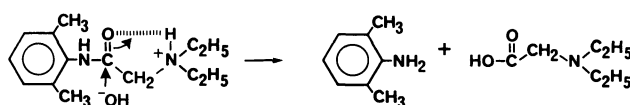
profiles remarkably similar to that of lidocaine. Added propylene glycol increased the rate of lidocaine degradation only slightly; such rate enhancements with added alcohols have been observed previously (21) and may be due to a change in the reaction mechanism from hydrolysis to esterification or, perhaps, to a solvent effect.

The largest increase in the rate of lidocaine degradation was observed when  $\text{FeCl}_2$  and  $\text{CuCl}_2$  were present. Even at 10 ppm each these metal salts provided a 14-fold increase in degradation rate, possibly by increasing the rate of nucleophilic attack on the carbonyl carbon by complexation of the metal with the carbonyl oxygen and amine nitrogen. Other explanations involving breakdown of the tetrahedral intermediate formed in base-catalyzed amide hydrolysis are less satisfactory but may still account for the small rate accelerations observed herein (22). This sensitivity to added metal ions shows that the disparity in reaction rates reported earlier (4–7) could be due to the presence of adventitious metal ions, especially since untreated glass ampoules can leach metal ions or other impurities which may effect the reaction rate (23). Thus, to ensure minimal drug loss upon autoclaving aqueous lidocaine solutions, care should be taken to avoid contamination by metal ions such as  $\text{Fe}^{2+}$  and  $\text{Cu}^{2+}$ .

**Reaction Mechanism.** It is interesting to speculate on the reason(s) why  $k'_o$  is greater than  $k_o$ . The following kinetically indistinguishable mechanisms predict  $k'_o > k_o$ : intramolecular nucleophilic catalysis (Scheme II), intramolecular general-acid-specific-base catalysis (Scheme III), and intramolecular general-base catalysis (Scheme IV).



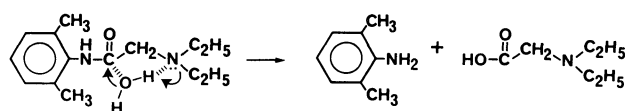
Scheme II



Scheme III

Table IV. Summary of Activation Parameters for the Degradation of Lidocaine in Aqueous Solution

Rate constant	$E_a$ (kcal mol <sup>-1</sup> )	log $A$	$\Delta H^\ddagger$ (kcal mol <sup>-1</sup> )	$\Delta S^\ddagger$ (cal mol <sup>-1</sup> K <sup>-1</sup> )
$k_{H^+}$	30.5	12.0	29.8	-5.96
$k_o$	33.8	12.1	33.1	-5.65
$k'_o$	26.3	8.16	25.6	-23.5



Scheme IV

It has been argued that intramolecular nucleophilic catalysis may be the favored mechanism for the reaction of some amides such as allopurinol derivatives, since the allopurinol moiety is a good leaving group (24,25). This mechanism probably does not occur for lidocaine hydrolysis, however, because the ensuing lactam product would be strongly sterically strained and so its formation would be unlikely. For the mechanism of Scheme III to be kinetically competent, the protonated form of lidocaine must react with hydroxide ion at pH  $\sim 7$ , resulting in an unusually fast reaction between a protonated amide and a hydroxide ion. This is unlikely inasmuch as specific-base catalysis does not readily occur with free-base lidocaine, even in 1 M KOH at 80°C (Fig. 1), and it is improbable that N-protonation of lidocaine should promote the specific-base catalysis reaction by a factor of  $>10^5$ . It is more probable that lidocaine reacts by a mechanism involving general-base catalysis by an intramolecular reaction with the tertiary amine group through a water molecule (Scheme IV). Intramolecular base catalysis by the amine group is plausible because the five-membered cyclic transition state is entropically favored, and because the base strength (and sensibly the nucleophilicity) of lidocaine is relatively high ( $pK_a = 7.92$  at 25°C). In this case the rate enhancement by intramolecular general-base catalysis is expected to be less than an order of magnitude, and this is the type of rate enhancement observed experimentally for lidocaine degradation.

The rate constants in Table III for lidocaine degradation at 80–100°C can be used to estimate lidocaine stability at temperatures used for autoclaving. Stability determinations car-

ried out by others (4–7) showed non-first-order kinetics (where pseudo-first-order kinetics are expected for a simple amide hydrolysis) or were followed for short reaction times, such that reliable rate constants could not be obtained. It is concluded that lidocaine is extremely stable across the entire pH range, however, less so in the presence of metal ions as  $Fe^{2+}$  and  $Cu^{2+}$ .

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Table V. Effect of Additives on the Rate of Lidocaine Degradation at 100°C<sup>a</sup>

Additive	Amount	$k_{obs}$ (sec <sup>-1</sup> )
Acetate buffer ( $\mu = 0.15$ )	0.15 M <sup>b</sup>	$9.85 \times 10^{-9}$
Acetate buffer ( $\mu = 0.15$ )	0.009 M <sup>b</sup>	$1.06 \times 10^{-8}$
Propylene glycol/water	20% (v/v)	$8.67 \times 10^{-8}$
Propylene glycol/water	80% (v/v)	$3.34 \times 10^{-7}$
FeCl <sub>2</sub> /CuCl <sub>2</sub>	10 ppm each	$8.00 \times 10^{-7}$
FeCl <sub>2</sub> /CuCl <sub>2</sub>	50 ppm each	$1.69 \times 10^{-6}$
None	—	$5.65 \times 10^{-8}$

<sup>a</sup> The pH of all solutions (except for acetate buffer, pH 4.2) was determined at room temperature and found to be pH 7.6.

<sup>b</sup> Total buffer concentration.