

Parenteral Formulation VI: Hydrolytic Degradation of Esters in Parenteral Solutions*

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ABSTRACT: Many widely used drugs are esters of carboxylic acids. The factors which govern rates and mechanisms of ester hydrolysis are briefly discussed and pH rate profiles of various esters are presented. The reaction rates are often dramatically affected by solvents. Ionic strength plays a role in reactions involving two ionic species. Acid or base catalysis by ingredients commonly used in parenteral solutions is discussed. These factors which affect the hydrolytic degradation are illustrated with examples of drugs commonly used in injectable products. Procaine is a classical example of ester-linkage hydrolysis. Using kinetics of procaine as reference point, the relative solvolytic rate of other structurally-related local anesthetics is discussed and predicted. Steric hindrance and electronic effects are important in predicting the relative stability of the procaine-related drugs. The effects of ionic strength, temperature and pH on the hydrolysis of meperidine, a substituted ethyl acetate, are discussed. From these parameters, the optimum conditions for stable meperidine solutions could be predicted. Both hy-

droxyl-ion and hydrogen ion catalysis account for the instability of atropine solutions which are hydrolyzed outside the range of pH 3 to 5. Homatropine and scopolamine solutions also hydrolyze with increasing pH.

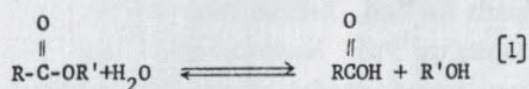
I. Introduction and Theory

Many of our most important and widely used drugs are derivatives of carboxylic acids. This classification would include esters, lactones, amides, and lactams. Drugs included in this category would be penicillin, aspirin, procaine, atropine, ascorbic acid, meperidine, and numerous others. In this paper, we will consider the factors which govern rates and mechanisms of ester hydrolysis. We will start with a brief theoretical outline and illustrate this with examples of esters which are commonly available as parenteral products. (Lactones, amides, lactams, etc. will be treated in future publications.) Several reviews and publications have concerned themselves with the rates and mechanisms of hydrolysis of carboxylic acid esters (1,2). Also, general textbooks on kinetics cover factors which govern all reactions in solution (3,4).

The overall reaction rate for ester

*Presented at the Annual Meeting of the Parenteral Drug Association in Las Vegas, Nevada on November 11, 1971.

hydrolysis can be expressed as follows:



A general classification of mechanisms for ester hydrolysis has been given by Ingold (3). There are eight possible mechanisms which can be postulated.

$A_{AC} 1$
 $A_{AC} 2$ [most common]
 $A_{AL} 1$
 $A_{AL} 2$ [has not been observed]

These would involve combinations of the following three pairs: alkyl-oxygen (AL), or acyl-oxygen (AC) cleavage; acid (A) or base (B) catalyzed hydrolysis; and a rate determining step which is a unimolecular (1) or a bimolecular process (2). The eight combinations are usually expressed as follows:

$B_{AC} 1$ [has not been observed]
 $B_{AC} 2$ [most common]
 $B_{AL} 1$
 $B_{AL} 2$

pH Profile

One of the most valuable pieces of information and one of the most common methods employed in studying a reaction is to measure the hydrolytic

rate as a function of the hydrogen ion concentration. A plot of the rate constant as a function of pH yields what is commonly known as a pH rate profile. The overall rate of hydrolysis for an ester can be expressed as follows:

$$-\frac{dE}{dt} = \left[K_H + K_H + [H^+] + K_{OH} - [OH^-] + K_N [N] + K_{GB} [GB] + K_{GA} [GA] \right] [E] \quad [2]$$

K_U = rate constant for uncatalyzed or water catalyzed reaction.

K_{H+} = rate constant for the acid catalyzed hydrolysis.

K_{OH} = rate constant for the hydroxide ion catalyzed hydrolysis.

K_N = rate constant for nucleophilic catalysis.

K_{GB} = rate constant for general base catalysis.

K_{GA} = rate constant for general acid catalysis.

A particular compound may be subject to some or all of these terms and at any particular pH value only one or two terms are significant. The simplest profile observed is usually a catenary in which the compound is subject only to hydrogen ion catalysis and hydroxide ion catalysis. Deviations from this type of profile indicate that the reaction is more complex and subject

to other types of catalysis. These are illustrated in the examples which are given below. The effects of other nucleophiles or of general acids or general bases are usually studied by varying their concentration while maintaining constant pH. One plots the rate constant as a function of the species in question at constant pH and extrapolates to "zero buffer concentration" to

obtain the rate constant for the specific acid ($K_H +$) or specific base (K_{OH-}) catalysis. The pH of the solution can be considered to have the greatest effect on the rate of hydrolysis. A one-fold change in pH amounts to a ten-fold change in the rates of hydroxide ion or hydrogen ion concentration, and as can be seen in the above equation, the rate is generally proportional to the hydrogen ion concentration.

Solvent

Solvents can have a dramatic effect on reaction rate. We will present here merely a simplified treatment — by summarizing the equations which consider the effect of solvent. The treatment usually considers reaction between two ions or between an ion and a neutral molecule. Where both reactants are ions in a solvent medium which is a continuous dielectric, the absolute rate theory gives us the following equation:

$$\ln k = \ln k_0 - \frac{N}{RT} \cdot \frac{Z_A Z_B e^2}{\epsilon \gamma^\ddagger} \quad [3]$$

$\ln k$ = rate constant at dielectric constant, ϵ .

$\ln k_0$ = rate constant in medium of infinite dielectric constant.

N = Avogadro's number

Z_A = charge on ion A; Z_B = charge on ion B.

e = electronic charge

T = absolute temperature

R = gas constant

ϵ = dielectric constant

$\gamma^\ddagger$ = proportional to the inter-atomic distance in the activated complex.

The equation predicts a linear relationship in a plot of $\ln k$ versus $1/\epsilon$ with a positive slope if the charges are of opposite sign and a negative slope if the charges are of the same sign. The above equation would predict no effect of dielectric constant if one of the

molecules were neutral (either Z_A or Z_B would be 0.) However, there is an effect of dielectric constant on the rate of reaction between an ion and a neutral molecule. This is generally expressed as follows:

$$\ln k = \ln k_0 + \frac{NZ_A^2 e^2}{2\epsilon RT} \left[\frac{1}{r} - \frac{1}{\gamma^\ddagger} \right] \quad [4]$$

where k = rate constant at dielectric constant, ϵ .

k_0 = rate constant in a medium of infinite dielectric constant.

r = radius for the reactant ion and the other symbols are as defined above.

This equation also predicts that the logarithm of the rate constant will vary linearly with the reciprocal of the dielectric constant.

For a reaction between two dipolar molecules with no net charge, an expression relating the rate constant to the dipole moment can also be generated. These equations not only predict a linear relationship between the rate constant and the reciprocal of the dielectric constant, but also include in the slope a contribution due to the dipole moments.

Ionic Strength

For reactions involving two ionic species, the rate constant is dependent on the ionic strength which is defined as follows.

$$\mu = \frac{1}{2} \sum_i c_i z_i^2 \quad [5]$$

μ = ionic strength

c_i = concentration of the ion

z_i = valence of the ion

For aqueous solutions at room temperature, one can write the following equation for the variation of rate constant with ionic strength. (The constant 1.02 is valid for aqueous solutions at 25°C.)

$$\log k = \log k_0 + 1.02 Z_A Z_B \sqrt{\mu} \quad [6]$$

One normally plots $\log k/K_0$ vs. $\sqrt{\mu}$ and obtains a straight line with a slope equal to $Z_A Z_B$. Therefore, this equation predicts that for a simple neutral ester, there should be no ionic strength effect because the product $Z_A Z_B = 0$. This is essentially true in dilute solution. However, although the above equation predicts that ionic strength will have

no effect when one of the reactants is a neutral molecule, there is an effect due to ionic strength at higher concentrations. The activity coefficient of neutral molecules will be effected by ionic strength and one can have an expression which gives a linear relationship with the logarithms of the rate constant and ionic strength, b is an empirical constant.

$$\ln k = \ln k_0 + b\mu \quad [7]$$

These above two effects of salts are commonly called the primary salt effect. There is also a secondary salt effect which is the effect of ionic strength on the dissociation constants of buffer species which can catalyze a reaction. From a practical point of view, the addition of an inert salt such as sodium chloride to adjust isotonicity could effect the rate of reaction as a primary salt effect. Buffers which may be added to adjust pH also are ionic species and, hence, can exert a primary salt effect as they control their own ionic environment; in addition, they can exert a secondary salt effect and it is possible that they can act as catalysts.

Catalysis

Many esters are subject to general acid, general base, or nucleophilic catalysis in addition to hydrogen ion or hydroxide ion catalysis which are considered to be specific acid and specific base catalysis, respectively. Many other acidic or basic species such as acetic acid, acetate, citric acid, citrate, phosphoric acid, phosphate, etc. which are commonly used as buffering agents in parenteral solutions are examples of

general acids and general bases. Several linear free-energy relationships quantitate the catalytic constant with a property of the species and relate the

rate constants for a series of reactions. For acid-base catalysis, this free energy relationship is the Bronsted Catalysis Law. This can be expressed as follows:

$$\begin{aligned} k_{GA} &= G_A K_A^{\alpha} \\ \text{and} \quad k_{GB} &= G_B K_B^{\beta} \end{aligned} \quad [8]$$

Where: k_{GA} = specific rate constant for general acid catalysis.

k_{GB} = specific rate constant for general based catalysis.

K_A = acid dissociation constant.

K_B = basic dissociation constant.

$\left. \begin{array}{l} G_A \\ G_B \\ \alpha \\ \beta \end{array} \right\}$ constants characteristic of the solvent, temperature, and reaction.

α, β - positive, and vary from 0 to 1.

The effect of buffers on rate can be predicted and estimated through employment of the above equations. Another type of catalysis which esters are subject to is nucleophilic catalysis. An example of a nucleophile could be an amine or one of the above-mentioned basic buffer species. They could react with an ester to form the respective acyl derivative which itself may be a product or this acyl intermediate could be very unstable and break down to generate an acid and alcohol and regenerate the nucleophile to yield a net catalytic effect. General base catalysis, on the other hand, does not form any reactive intermediate but accelerates the reaction by promoting proton transfer. It is sometimes difficult to differentiate between general base catalysis and nucleophilic catalysis. A practical result of adding a buffering agent

or an amine to control pH or solubility, may be that these compounds accelerate decomposition of the active ingredient.

All the above-mentioned effects can be caused by those agents which are commonly considered to be inert ingredients. But as we have attempted to point out, these "inerts" can exert profound effects on the rate of reaction. For example, the sodium chloride which is added to adjust isotonicity will also have an effect on ionic strength. The bisulfite which is added as an anti-oxidant also affects ionic strength and can also exert its own catalytic effect, as a general base or nucleophile. The common acetate or phosphate buffers can act as general or nucleophilic catalysts in addition to exerting an effect on ionic strength. Alcohol or other organic solvents which may be added

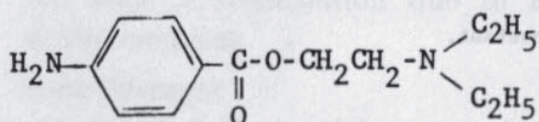
to aid solubility will also affect the dielectric constant of the medium.

The above parameters will now be illustrated with examples from the literature regarding drugs widely used in parenterals.

II. Procaine and Structurally Related Local Anesthetics

1. Procaine

Procaine, a well-known local anesthetic, has the chemical structure



Aside from oxidative breakdown, instability of procaine in solution is due mainly to the hydrolysis of the ester linkage (6) with the formation of p-

aminobenzoic acid and diethylamino-ethanol. Since procaine in solution can exist in three different forms (the free base, P, the singly charged ion, PH^+ ; and doubly charged ion, PH_2^{++}), the total drug concentration in solution is then given by $P_T = P + \text{PH}^+ + \text{PH}_2^{++}$. The concentration of each form is interrelated by the acid dissociation constants. The rate of hydrolysis of the doubly charged form which exists below pH 2.3 was shown to be very slow and, for all practical purposes, the acid-catalyzed hydrolysis is negligible in the deterioration of procaine. Thus, the hydroxyl ion catalyzed reaction will be the most important hydrolysis mechanism and can be expressed by the following overall equation:

$$\frac{d \ln P_T}{dt} = \left[K_1 [\text{OH}^-] + K_2 K_b \right] \frac{[\text{OH}^-]}{K_b + [\text{OH}^-]} \quad [9]$$

$$P_T = P + \text{PH}^+$$

K_b = Dissociation constant

k_1 = Specific rate constant for hydroxide ion catalysis of Pr

k_2 = Specific rate constant for hydroxide ion catalysis of PrH^+

This equation is valid for all procaine molecules.

As observed, the degradation rate of procaine at any given temperature and pH is first order in nature with respect to the ester concentration. The dependency of the rate of hydrolysis on the hydroxyl ion activity is shown in Figure 1. The hydrolytic rate was obtained at 40°C and expressed in terms of the half-life of the drug.

The authors concluded that procaine was subject only to specific acid and specific base catalysis (the acid catalysis was also very small). The deviation from the simple catenary described earlier is due to ionization of the procaine and the inflection point in the pH profile agrees with the dissociation constant.

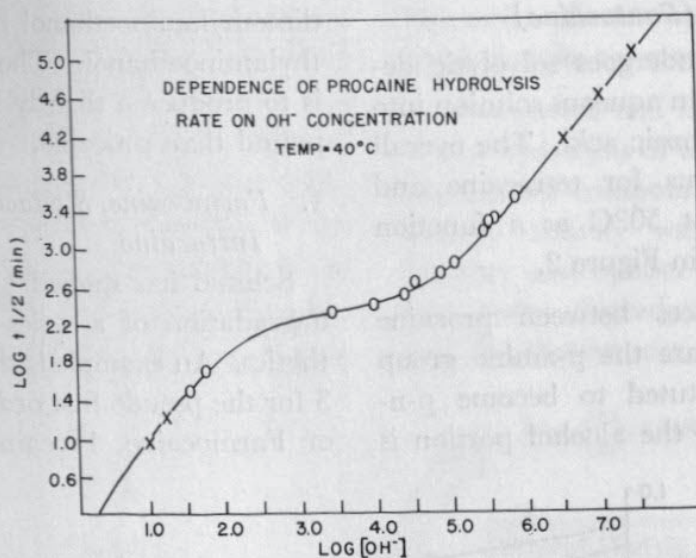


FIG.1.

FIG. 1 Half-life of procaine with the hydroxyl ion content of the reaction mixture. Circles, experimental points at 40° C.; crosses, experimental points other than 40° C., corrected to 40° C.
(Reproduced with permission from *J. Amer. Pharm. Assoc., Sci. Ed.*, 39, 405 (1950).

Thus, the kinetics of the solvolysis of procaine are relatively straight forward. From the above data, one can extrapolate other experimental conditions and the kinetics of the degradation of other structurally related local anesthetics.

2. Chloroprocaine

What effect does the substitution of a chlorine atom in the benzene ring have on the hydrolytic rate of the procaine molecule? Since the substitution of chlorine could exert an electron-withdrawing effect (permanent polarization effect), it is anticipated that procaine will be more stable than chloroprocaine. The electronegative chlorine will attract electrons, hence rendering the carboxyl carbon more positive and hence more susceptible to hydroxyl ion attack. This is supported by the work of Boltze and Katzmann (7) and Aven and Foldes (8) who report that chloro-

procaine is hydrolyzed about two or three times faster than procaine in alkaline media.

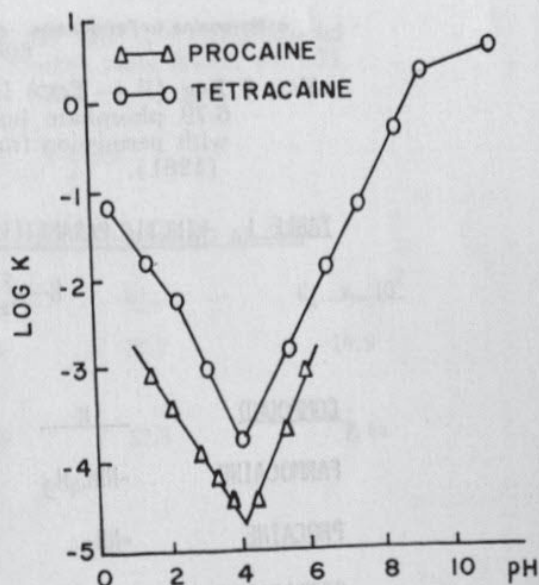


FIG. 2.

FIG. 2 Overall velocity constant for procaine (lower curve) and for tetracaine (upper curve) at 50° C. as a function of pH.

3. Tetracaine (Pontocaine)

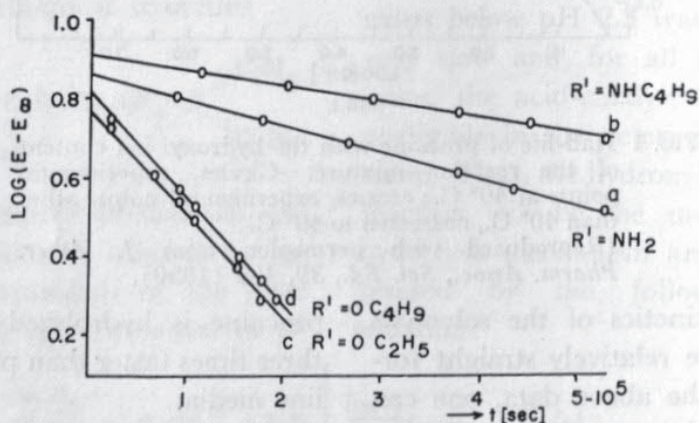
Tetracaine undergoes solvolytic decomposition in an aqueous solution into p-butylaminobenzoic acid. The overall velocity constants for tetracaine and procaine (9) at 50°C as a function of pH is shown in Figure 2.

The differences between procaine and tetracaine are the p-amino group which is substituted to become p-n-butylamino and the alcohol portion is

dimethylaminoethanol rather than diethylaminoethanol. The overall effect is to produce a slightly less stable compound than procaine.

4. Farmocaine, Stadacaine and Intracaine

Schmid has studied (10) the rate of degradation of a series of local anesthetics. An example is shown in Figure 3 for the pseudo first order degradation of Farmocaine, Procaine, Stadacaine,



a=Novocaine b=Farmocaine c=Intracaine d=Stadacaine
FIG. 3

FIG. 3 Log $(E - E_{\infty})$ in relation to time (sec) in pH 6.79 phosphate buffer at 49.8°C. (Reproduced with permission from *Pharm. Acta Helv.*, 38, 423 (1961).

TABLE I. KINETIC PARAMETERS OF SOME LOCAL ANESTHETICS

COMPOUND	R	TIME FOR 10% DEGRADATION AT 20°C (DAYS)	
		PH = 5 PH = 7	
FARMOCAINE	-NHC ₄ H ₉	4900	49
PROCAINE	-NH ₂	2800	28
STADACAINE	-OC ₄ H ₉	725	7
INTRACAINE	-OC ₂ H ₅	725	7

FROM H. W. SCHMID, *PHARM. ACTA HELV.*, 36, 423 (1961).
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and Intracaine in phosphate buffer at pH of 6.79 ionic strength of 0.16, and at 49.8°C. The attached Table I was constructed from the various tables of Schmid's work. As shown in the table, the difference in the stability of the local anesthetics is due primarily to an electronic effect which alters the electronic density at the reaction center.

The steric effect is only of little significance in these compounds.

5. Panthesine and Larocaine

The hydrolysis of a series of structurally related compounds with local anesthetic activity was investigated by Mueller and Speiser (11,12). Pseudo-first order degradation of Larocaine and Panthesine was observed and the

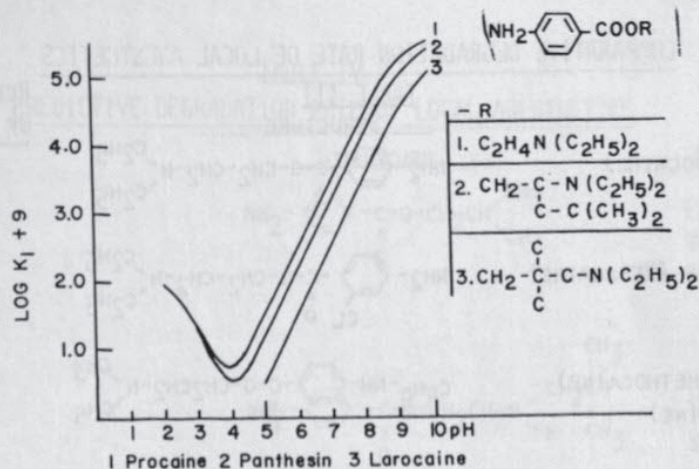


FIG. 4

FIG. 4 Log K dependence on pH (20° C.) (Reproduced with permission from *Pharm. Acta Helv.*, 40, 671 (1965).

TABLE II

		SECOND ORDER RATE CONSTANT AT 20°C		
COMPOUND	R	$\frac{k_H}{k_1} \times 10^5$	k_2	$k_1 \times 10^2$
PROCAINE	$-C-C-N \begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}$	2.46	25.7	14.9
PANTHESINE	$-C-C-N \begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}$ $C-C \begin{matrix} CH_3 \\ CH_3 \end{matrix}$	2.23	12.5	7.44
LAROCAINE	$-C-C-C-N \begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}$ C	-	3.18	5.37

F. MILLER AND P. SPEISER, *PHARM. ACTA HELV.*, 40, 620 (1965).
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dependency of log K on pH for Procaine, Panthesine and Larocaine at 20°C is shown in Figure 4. The relative stability toward hydrolysis is in the order of Procaine > Panthesine > Larocaine.

As shown in Table II, with the intermediate chain increasing in length, the stability of the esters is increased

slightly. The lengthening of the chains has a negative effect on the activation entropy which caused the greater stability of the diethylaminobutyl ester. This steric effect is particularly marked in the compounds with ramified intermediate chains, in which the entropy is rendered negative by the steric inhibition of the free mobility in one

COMPARATIVE DEGRADATION RATE OF LOCAL ANESTHETICS

COMPOUND	TABLE III STRUCTURE	RELATIVE RATE OF DEGRADATION
PROCAINE (NOVOCAINE)	<chem>NC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem>	1
CHLOROPROCAINE (NESACAINE)	<chem>NC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem> CL	2-3 (A)
TETRACAINE (AMETHOCAINE) (PONTOCAINE)	<chem>CCCCNC(=O)c1ccc(cc1)C(=O)OCCN(C)CC</chem>	1-2 (B)
PANTHESINE	<chem>NC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem> CH ₂ -CH-CH ₃ CH ₃	0.5 (c)
LAROCAINE	<chem>NC(=O)c1ccc(cc1)C(=O)OCC(C)CCN(CC)CC</chem> CH ₃	0.12 (c)
INTRACAINE	<chem>CCOC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem>	4 (D)
STADACAINE	<chem>CCCCOC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem>	4 (D)
FARMOCAINE	<chem>CCCCNC(=O)c1ccc(cc1)C(=O)OCCN(CC)CC</chem>	0.6 (D)

transition state, so that the stability is enhanced.

The relative rates of degradation of these local anesthetics are summarized in Table III, using the hydrolytic rate of procaine as reference.

6. Prediction to Other Local Anesthetics

From the above, the relative rate

of the degradation of related local anesthetics may be predicted based on their chemical structure as illustrated in Table IV.

7. Change of Solvent for Procaine

The comparative hydrolytic rate of procaine in protium oxide (water) and deuterium oxide at 100°C and pH = 8.0 is illustrated in Figure 5 (13).

TABLE IV
PREDICTIVE DEGRADATION RATE OF LOCAL ANESTHETICS

COMPOUND	STRUCTURE	COMMENTS
ISOBUCAINE		LESS STABLE THAN PROCAINE
BUTETHAMINE		STABILITY IS SIMILAR TO PROCAINE.
METHBUTETHAMINE		MORE STABLE THAN PROCAINE
PROPOXYCAINE		MORE STABLE THAN CHLORO-PROCAINE

(A) FROM REF. 12 AND 13

(B) FROM REF. 14

(C) FROM REF. 17 AND 18, K_2 AT 20°C

(D) FROM REF. 16, K_2 AT 20°C

Procaine is shown to be twice as stable in D_2O as in H_2O . This indicates that OD^- is not as potent as OH^- as a catalyst.

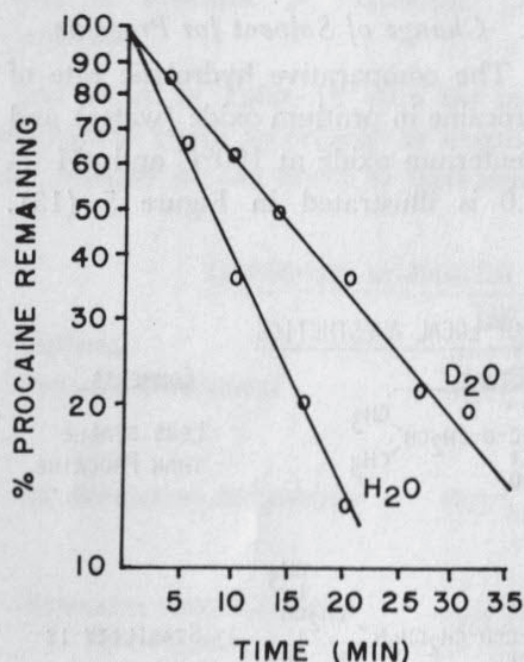


FIG. 5

FIG. 5 Rate of hydrolysis of procaine in protium oxide and deuterium oxide at pH and at "apparent" pH 8.0 ($100^\circ C.$). (Reproduced with permission from *J. Pharm. Sci.*, 53, 978 (1964).

8. Effect of Ionic Strength on Reaction Rate of Pontocaine at $70^\circ C$

As discussed in the introduction, the addition of salt to the formulation does alter the rate constant due to the effect of ionic strength. As shown in Table V, the observed effect is real but not large.

III. Meperidine and Related Compounds

1. Meperidine

Meperidine hydrochloride (Ethyl 1-Methyl-4-phenylisonipecotat Hydrochloride) is an analgesic, spasmolytic and sedative drug, available in various pharmaceutical dosage forms, alone and in combinations with other drugs as tablets, injections, and syrups.

Meperidine is a substituted ethyl acetate or an ester of amino butyric acid. The acid and base catalyzed hydrolysis of phenyl substituted aliphatic esters was studied by Smith and Levenson (14,15) who found that the introduction of a phenyl substituent in

TABLE V

EFFECT OF IONIC STRENGTH ON REACTION RATE OF PANTOCAINE AT $70^\circ C.$

REACTION TYPE	M	K (SEC ⁻¹) X 10 ⁵
B + OH ⁻	0.010	8.32
	0.160	8.32
BH ⁺ + OH ⁻	0.106	1.27
	0.130	1.17
	0.160	1.04
BH ⁺ + H ⁺	0.100	0.093
	0.130	0.098
	0.160	0.105

FROM H. W. SCHMID, *PHARM. ACTA HELV.*, 36, 423 (1961).

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an alpha position of the ester slows down the rate. Alkaline hydrolysis rate is increased while the rate of acid hydrolysis is decreased at the same time

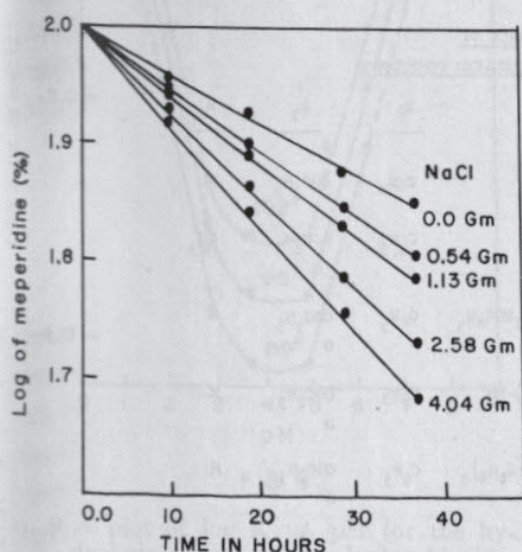


FIG. 6

FIG. 6 Effect of increasing concentration of NaCl on the rates of hydrolysis of meperidine in 0.1123 N HCl at 70° C. (Reproduced with permission from Patel, R. M., "A Kinetic Study of the Hydrolysis of Meperidine HCl," Dissertation, Univ. of Iowa, August, 1965.)

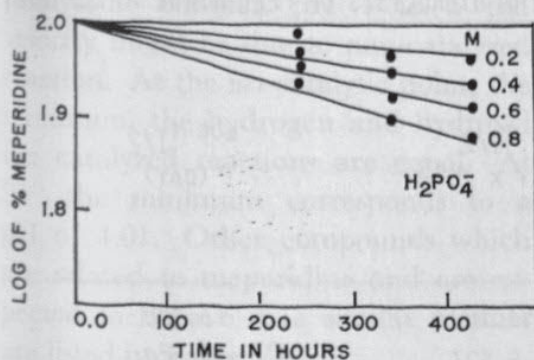


FIG. 7

FIG. 7 Pseudo first-order character of the hydrolysis of meperidine at different concentrations of dihydrogen phosphate ion at pH 4.01 and ionic strength of 0.80. (Reproduced with permission from Patel, R. M., "A Kinetic Study of the Hydrolysis of Meperidine HCl," Dissertation, Univ. of Iowa, August, 1965.)

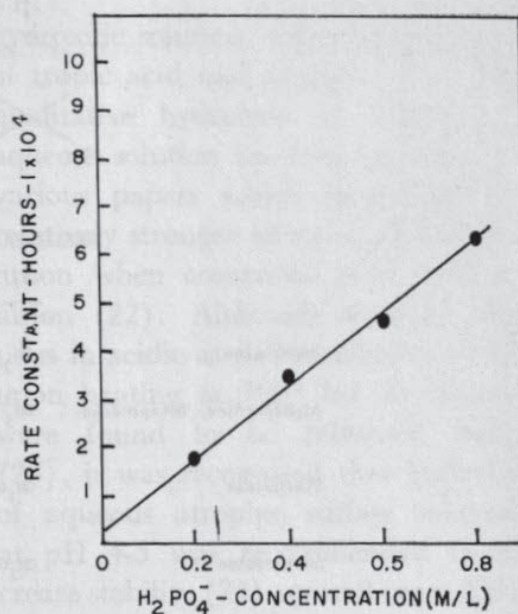


FIG. 8

FIG. 8 Effect of dihydrogen phosphate concentration on the pseudo first-order rate constant of meperidine hydrolysis at 94.7° C. and constant ionic strength of 0.8 and pH 4.01. (Reproduced with permission from Patel, R. M., "A Kinetic Study of the Hydrolysis of Meperidine HCl," Dissertation, Univ. of Iowa, August, 1965.)

in compounds containing quaternary ammonium ion (16).

In the study of the kinetics of meperidine degradation in aqueous solution the effect of temperature, ionic strength and pH were investigated (20). The sodium chloride concentration was varied in order to study the effect of ionic strength by observing the hydrolytic rate at 70°C (Figure 6). The catalytic effect of H_2PO_4^- ion on the rates of meperidine hydrochloride at constant ionic strength and pH was investigated (Figures 7 and 8). Hydrolysis of meperidine was found to be a specific hydronium ion catalyzed reaction in dilute hydrochloric acid solutions. The hydrolysis of the protonated form of meperidine is first

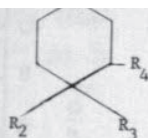


TABLE VI
MEPERIDINE AND RELATED COMPOUNDS

	R ₁	R ₂	R ₃	R ₄
			O	
Meperidine	CH ₃	C ₆ H ₅	COC ₂ H ₅	H
Alphaprodine, Betaprodine	CH ₃	C ₆ H ₅	OCC ₂ H ₅ O	CH ₃
Piminodine	CH ₂ CH ₂ CH ₂ NHC ₆ H ₅	C ₆ H ₅	COC ₂ H ₅ O	H
Anileridine	CH ₂ CH ₂  NH ₂	C ₆ H ₅	COC ₂ H ₅ O	H
Diphenoxylate	CH ₂ CH ₂ C [C ₆ H ₅] ₂ CN	C ₆ H ₅	COC ₂ H ₅ O	H

order over a wide pH range 1 to 7. Dihydrogen phosphate ion has a small catalytic effect. At pH 4.01 maximum stability was observed. Aqueous solutions should be buffered between pH 3.5 and 4.0 for maximum shelf life.

The half-life periods, $t_{1/2}$ calculated from K at 25°, for each pH value, are listed in Table VII and a plot of log K vs. pH expressed in days is shown in Figure 9. In this pH rate profile there are three regions: one in which an

TABLE VII, HALF-LIFE, $t_{1/2}$, CALCULATED FOR THE HYDROLYSIS OF MEPERIDINE AT 25°C.

PH	LOG K* (HR ⁻¹)	$t_{1/2}$	LOG $t_{1/2}$
		DAY X 10 ⁻³	(DAY)
2.057	-4.75	1.380	3.140
2.860	-5.35	6.523	3.750
3.680	-6.70	125.9	5.100
4.885	-6.70	125.9	5.100
6.171	-5.60	10.02	4.011
6.762	-5.24	4.365	3.640

K* = EXTRAPOLATED FROM THE ARRHENIUS PLOT

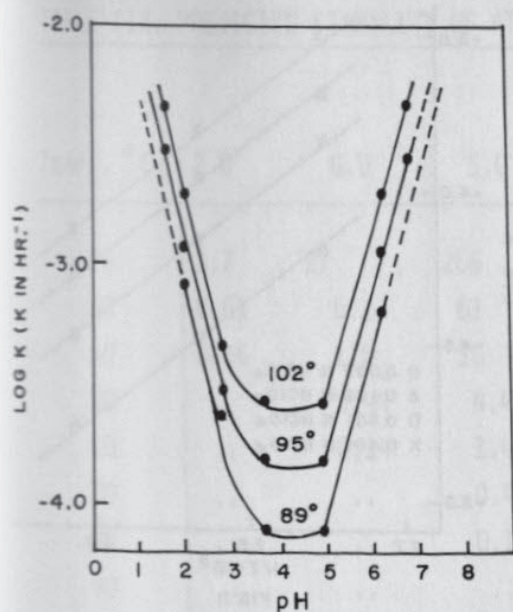


FIG. 9

Fig. 9 A plot of log K vs. pH for the hydrolysis of meperidine hydrochloride. (Reproduced with permission from Patel, R. M., "A Kinetic Study of the Hydrolysis of Meperidine HCl," Dissertation, Univ. of Iowa, August, 1965.)

acid-catalyzed reaction takes place, a pH-independent region, and a region in which the reaction is hydroxyl ion catalyzed. Between pH 4 to 5 the velocity might be due to non-catalyzed reaction. At the iso-catalytic point, the minimum, the hydrogen and hydroxyl ion catalyzed reactions are equal. At 95° the minimum corresponds to a pH of 4.01. Other compounds which are related to meperidine and are expected to behave in a similar manner are listed in Table VI.

2. Atropine and Analogs

Atropine is defined by the *International Pharmacopeia* as DL-tropanyl-2-hydroxyl-1-phenyl-propionate. As was demonstrated by Kraut in 1864, atropine undergoes hydrolysis on heating either with hydrochloric acid or barium

hydroxide solution, with the formation of tropic acid and tropine (21). The qualitative hydrolysis of atropine in aqueous solution has been described in various papers which recognized the relatively stronger effect of alkaline solution when compared with acid solution (22). Although atropine solutions in acidic as well as alkaline media upon heating at 100° for 30 minutes were found to be relatively stable (23), it was recognized that buffering of aqueous atropine sulfate solutions at pH 4-5 was recommended to increase stability (24) up to 2 years (25). Atropine sulfate was found to be less stable than the nitrate or phosphate (26). In another study (27), the optimum pH for atropine sulfate was 3.2-3.6. The improved stability at lower pH could be demonstrated after sterili-

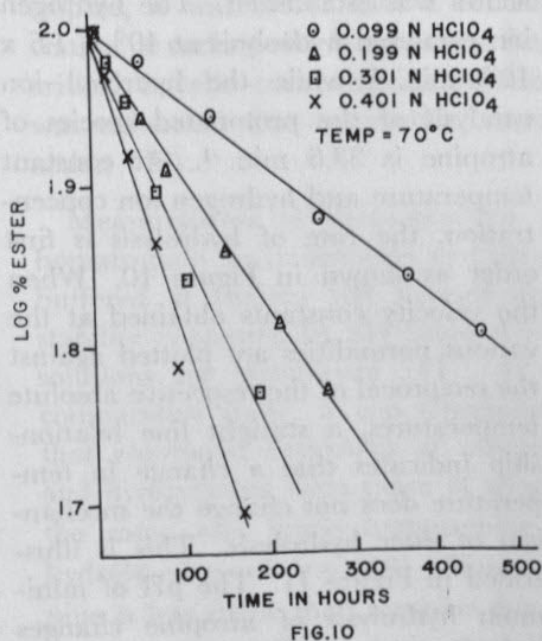


FIG. 10 Hydrolysis of atropine in dilute perchloric acid solutions at 80° C. (Reproduced with permission from *J. Am. Pharm. Assoc., Sci. Ed.*, 46, 531 (1957).)

zation of solutions at various pH values (28-31). A mechanism involving intramolecular hydrogen-bonding between the ester carbonyl and protonated amine was postulated in a kinetic study of atropine (30). During slow alkaline hydrolysis of atropine solutions, the intermediate apoatropine was detected with tropic and atropic acids as end products (32). A 44% loss was found in an isotonic atropine-borax-boric acid solution after storage at room temperature for only one month (33). The container alkalinity has also been implicated in the instability of atropine solutions (34). Atropine solutions are also hydrolyzed to tropine by fungus contamination (33) and by bacteria within a short period of time (36-38).

In a kinetic study of the proton catalyzed hydrolysis of atropine (39) the temperature dependency of this reaction was established. The hydrogen ion catalyzed hydrolysis at 40° is $1.6 \times 10^{-5} \text{ min.}^{-1}$ while the hydroxyl ion catalysis of the protonated species of atropine is 33.6 min.^{-1} . At constant temperature and hydrogen ion concentration, the rate of hydrolysis is first order as shown in Figure 10. When the velocity constants obtained at the various normalities are plotted against the reciprocal of the respective absolute temperatures, a straight line relationship indicates that a change in temperature does not change the mechanism of ester hydrolysis. This is illustrated in Figure 11. The pH of minimum hydrolysis of atropine changes inversely with increase in temperature, the values decreasing from 4.11 at 0° to 3.24 at 100°. Stability of atropine at various pH and temperatures

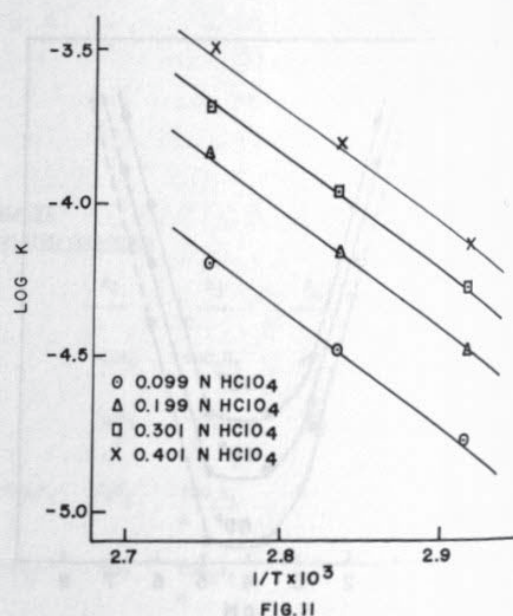


FIG. 11 Temperature dependency of the hydrolytic reaction of atropine catalyzed by hydrogen ions. (Reproduced with permission from *J. Am. Pharm. Assoc., Sci. Ed.* 46, 531 (1957).

is shown in Table VIII. Both hydroxyl-ion and hydrogenion catalysis account for the instability of atropine solutions, the former for instability above pH 5 and the latter for that below pH 3.

3. Homatropine

Similar to atropine, solutions of homatropine are also very stable at low pH even when autoclaved (40-43). However, with increase of temperature and at higher pH, decomposition takes place. Second order alkaline hydrolysis of aliphatic carboxylic esters and the retarding effect of a negative ionic charge were demonstrated by Ingold (3). The alkaline hydrolysis of highly substituted esters (i.e., homatropine, scopolamine) was also reported (17-19) as being generally facilitated by the positive charge on the quaternary

TABLE IIX. PREDICTED STABILITY OF ATROPINE IN AQUEOUS SOLUTIONS, $\tau_{1/2}$ IN YEARS

TEMP., °C.	pH						
	7.0	6.0	5.0	4.5	4.0	3.0	2.0
20	2.7	27	266	811	1800	548	56
30	0.61	6.1	61	194	473	203	21
40	0.16	1.6	16	49	135	80.7	8.5
50	..	0.44	4.4	13.8	39.2	33.3	3.6
60	..	0.14	1.4	4.3	12.9	14.4	1.6
70	..	..	0.46	1.39	4.34	6.52	0.76
80	..	..	0.17	0.5	1.63	3.04	0.37
90	..	..	..	0.21	0.65	1.48	0.19
100	..	..	..	0.1	0.31	0.76	0.10

salt. An investigation of the chemical kinetics of the hydroxyl ion catalyzed hydrolysis of homatropine (44) has shown that the deterioration consists of two reactions. The heat of activation for the two reactions involving the free and acid form of the base as calculated from Arrhenius plots are 12.3 and 11.4 kilocalories, respectively. Homatropine free base degrades at a rate approximately five times that of atropine base, and the salt form of homatropine degrades at a rate approximately eight times that of the salt form of atropine.

The effect of nonionic surfactants on the chemical stability of homatropine in the presence of various concentrations of polyoxyethylene lauryl ether and polysorbate 80 at increasing temperatures was studied (45). Hydrolysis of these solubilized systems is pseudo first-order degradation with the logarithm of the rate constant being linearly dependent on the concentration of the surfactant. The rate of

hydrolysis was increased with increased temperature. In another investigation of the effect of the surface active agents on the hydrolysis of solubilized homatropine, it was found that a concentration of surface-active agent less than critical micelle concentration stability was enhanced due to micellar interaction (46).

Measurements of decomposition of homatropine hydrobromide eye drops buffered at various pH showed that stability is assured by pH below 4.5 if solutions are autoclaved (47). In a comparative study, it was determined that enzymatic hydrolysis of atropine and hyoscyamine takes place at almost the same rate while homatropine is hydrolyzed much less (48). Homatropine is less stable than atropine due to the inductive effect of the hydroxyl group, thus enhancing the positive character of the carbonyl group and accelerating nucleophilic attack.

4. Scopolamine

Scopolamine or hyoscyne hydrolyzes in a manner similar to atropine. If scopolamine is boiled with dilute alkali, tropic acid and the alkaloids scopine or scopoline, both optically active compounds, are formed.

Straub stated that stable solutions of scopolamine are possible by using a vehicle of 10% mannitol (49), but pH in a range of 3.2-3.6 of a scopolamine hydrobromide produced the best stability even at sterilization temperatures (26). In another study, 1% solutions of the alkaloid were stable for 2 years if the pH was kept below 4.5 and bacterial contamination prevented (27). The stability of scopolamine hydrobromide injectable solutions was found to be affected by light, heat and pH (50). Alkaline hydrolysis at pH 8-8.5 resulted in scopine, at pH 9-10 in both scopine and scopoline. In simulated intestinal fluid lipase hydrolyzed the emulsified ester. The enzymatic degradation of scopolamine hydrobromide solutions with tissue homogenates (51), and with serum from certain species (52) was also described.

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