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Phenoxybenzamine stability in aqueous ethanolic solutions. II. Solvent effects upon kinetics

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Summary

Determination of phenoxybenzamine (I) cyclization kinetics utilizing the pH stat method required that studies be conducted at apparent pH values below the apparent pK_a values of the drug. This condition confers the benefit of improved I solubility and enables the cyclization rate constant ($k_{1,app}$) to be measured in solvent mixtures from 7 : 3 ethanol : water up to and including water.

I conjugate acid apparent pK_a values were determined in solvents up to 4 : 6 ethanol : water and allowed specific rate constants for cyclization (k_1) to be determined over the 7 : 3 to 4 : 6 ethanol : water range. A semilogarithmic plot of k_1 versus solvent ionizing power was linear and enabled values over the 3 : 7 to 0 : 10 ethanol : water range to be obtained by extrapolation. The apparent pK_a of I conjugate acid in water was calculated from experimental $k_{1,app}$ and extrapolated k_1 values in water.

The ethylenimonium ion [N-benzyl-N-(1-phenoxy-2-propyl)ethylenimonium ion, II] solvolysis rate constants (k_2, the sum of the individual rate constants k_w and k_{alc} for reaction of II with water and ethanol, respectively) were obtained over the 1 : 1 to 3 : 7 ethanol : water range. The pH stat method required that this process be measured at apparent pH values above the apparent pK_a, where drug solubility is low. k_2 in water was thus estimated by extrapolation of a log k_2 versus dielectric constant reciprocal plot. The rate constant for reformation of I (k_{-1}) was negligible over the 3 : 7 to 0 : 10 ethanol : water range.

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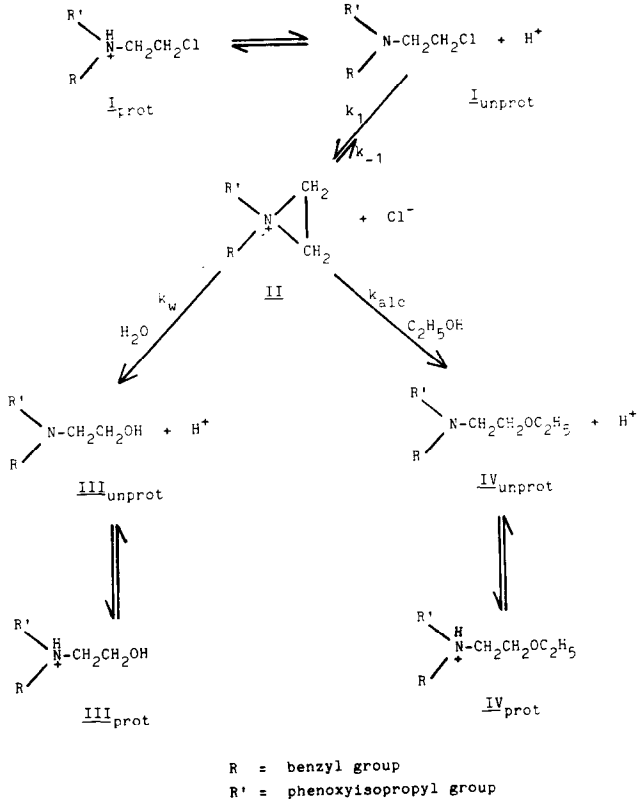
The influence of solvent upon changes in k_1, k_{-1} and k_2 and upon the basicity of I and its two solvolysis products, 2-(N-benzyl-2-hydroxyethylamino)-1-phenoxypropane (III) and 2-(N-benzyl-2-ethoxyethylamino)-1-phenoxypropane (IV), was in agreement with theory. Concentration–time profiles of I, II and total solvolysis product(s) in 1 : 1 and 0 : 10 ethanol : water were plotted using these rate constants.

Introduction

Prior to parenteral use, acidified non-aqueous solutions of phenoxybenzamine (I)-HCl are diluted with aqueous solutions. These solutions are infused slowly, commonly over a period of at least 1 h (Martindale: The Extra Pharmacopoeia, 1977). The drug has also been prepared in buffered pH 7.0 perfusion solutions, which are allowed to stand 24 h before use (Collins et al., 1969). Estimation of the extent of drug degradation in such solutions requires data obtained in solutions



Scheme 1.

more aqueous than the 1 : 1 ethanol : water solutions previously described (Adams and Kostenbauder, 1985).

The purpose of the present study was to extend potentiometric pH stat analysis to the kinetics of phenoxybenzamine decomposition (Scheme 1) in solutions of varying proportions of aqueous ethanol, including entirely aqueous solutions at pH values where drug solubility is adequate.

Materials and Methods

Materials and instrumentation

All materials, methods of solvent treatment and storage, and analytical instrumentation have been described in the previous paper.

Kinetic procedures

Rate of hydrogen ion formation. The operation of the pH stat and the preliminary addition of titrant for initial pH adjustment are the same as previously described. In contrast to the previous study, the total fraction of hydrogen ion titrated during the reaction was not determined. Since evaluation of $k_{1,app}$ requires only initial rates, the reactions were not necessarily followed to completion. In all solvent mixes within the pH 4.00 to 5.00 range, the reaction was followed for a minimum of 2.4 cyclization half-lives. Over the pH 6.50 to 7.50 range, the reaction was followed for a total time of not less than 1.9 solvolysis half-lives. As solvents of increasing proportions of ethanol were used, the reaction was followed through more solvolysis half-lives.

The concentrations of I-HCl and sodium hydroxide titrant were approximately $4.3–4.8 \times 10^{-4}$ M and 8.9×10^{-2} M, respectively, for studies in 4 : 6–7 : 3 ethanol : water. In 3 : 7 ethanol : water the values were 4.7×10^{-5} M and 1.1×10^{-2} M, respectively, and in the more aqueous solvents the values were 2.5×10^{-5} M and 5×10^{-3} M, respectively. A drug concentration of 5×10^{-4} M is claimed to be the lower limit for potentiometric titration (Newton et al., 1982). The poor I-HCl solubility in 3 : 7 ethanol : water and more aqueous solvents required drug concentrations lower than this limit. The validity of these studies in the 10^{-5} M range is indicated by the internal consistency of the $k_{1,app}$ values in water, i.e. a 10-fold increase in rate constant for a one unit pH increase.

pK_a determinations

Mixed solvent apparent acid dissociation constant ($p_sK'_a$) values at 30 ± 0.02°C were determined by half-neutralization. Concentrations of each compound, meter standardization against aqueous buffers, and the absence of necessity to correct for significant concentrations of hydrogen ion or hydroxyl ion were the same as in the previous report.

TABLE 1

EXPERIMENTAL FIRST-ORDER APPARENT CYCLIZATION RATE CONSTANTS [a] AND CALCULATED SPECIFIC CYCLIZATION RATE CONSTANTS IN ABSOLUTE ETHANOL:WATER MIXTURES

Solvent (ethanol:water) [c]	Y [b]	k_{app} (min^{-1})					k_1 (min^{-1})
		pH 3.50	pH 4.00	pH 4.25	pH 4.50	pH 5.00	
0:10	3.493	– [d]	0.0114 ± 0.0001	0.0196 ± 0.0007	0.0358 ± 0.0007	0.112 ± 0.002	1.14 [e]
1:9	3.312	–	–	–	0.0449 ± 0.0009	–	1.00 [e]
2:8	3.051	–	0.0165 ± 0.0008	–	0.0520 ± 0.0030	–	0.830 [e]
3:7	2.721	–	–	–	0.0704 ± 0.0015	–	0.655 [e]
4:6	2.196	–	–	–	0.0763 ± 0.0038	–	0.459 [f]
1:1	1.655	0.00877 ± 0.00000	–	–	0.0694 ± 0.0040	–	0.293 [f]
6:4	1.124	–	0.0247 ± 0.001	–	0.0689 ± 0.010	–	0.211 [f]
7:3	0.595	–	0.0224 ± 0.0000	–	–	–	0.143 [f]

[a] Results expressed as mean ± S.D. ($n = 3$ at pH 4.50 and 0:10, 1:9, 2:8, 4:6 and 6:4 ethanol:water; $n = 2$ for all other values).

[b] Y values at 25.0°C are from Fainberg, A.H. and Winstein, S., Correlation of solvolysis rates. III. *t*-Butyl chloride in a wide range of solvent mixtures. J. Am. Chem. Soc., 78 (1956) 2770–2777.

[c] x volumes of absolute ethanol plus $10 - x$ volumes of water, each at ambient temperature before mixing.

[d] Not determined.

[e] Obtained from a plot of log k_1 versus Y (Fig. 1).

[f] Calculated from $k_1 = k_{1,app}[{}_sK'_{a1} + (H^+)]/{}_sK'_{a1}$; an average value is reported when $k_{1,app}$ was determined at more than one pH value.

Results and Discussion

Effect of solvent on cyclization rate

Apparent first-order cyclization rate constants ($k_{1,app}$) were determined at one or more pH values in solvents ranging from 7:3 ethanol:water to entirely aqueous solutions (Table 1). Potentiometric pH stat analysis does not allow direct determination of the specific cyclization rate constant k_1. Apparent pK_a values ($p_sK'_{aI}$) were determined in solvents up to 4:6 ethanol:water (Table 2), thus k_1 values were calculated from $k_{1,app}$ and $p_sK'_{aI}$ values over the 7:3 to 4:6 ethanol:water range (Table 1).

The Winstein-Grunwald equation (Reichardt, 1965) for the correlation of solvolysis rates (Eqn. 1) predicts that a plot of log k versus Y will be a straight line.

$$\log \frac{k}{k_0} = mY \tag{1}$$

where k = the rate constant for solvolysis in a given solvent; k_0 = the rate constant for the same compound in the standard solvent (80% ethanol); m = the sensitivity of the compound to changes in the ionizing power of the solvent; Y = the ionizing power of the solvent. In agreement with Eqn. 1, a straight line relationship between log k_1 and solvent ionizing power was observed over the 7:3 to 4:6 ethanol:water solvent range (Fig. 1). Extrapolation of the plot allowed estimation of k_1 in water. The estimated value of k_1 in water is 1.14 min^{-1} ($t_{1/2}$ = 0.608 min). Henkel et al.

TABLE 2

APPARENT pK_a VALUES OF THE CONJUGATE ACIDS OF PHENOXYBENZAMINE (I) [a] AND SOLVOLYSIS PRODUCTS (III AND IV) [b] IN ABSOLUTE ETHANOL:WATER MIXTURES

Solvent			$p_sK'_a$		
ethanol:water	water concentration [c] (M)	dielectric constant [d]	I	III	IV
0:10	55.27	78.54	–	–	–
2:8	44.95	69.0	–	7.40	–
3:7	39.66	63.8	–	7.18	–
4:6	34.18	58.3	5.20	6.92	6.98
1:1	28.53	52.6	5.01	6.67	6.70
6:4	22.12	46.6	4.85	6.56	6.59
7:3	17.05	40.7	4.73	6.41	6.44
8:2	11.30	34.9	4.61	6.29	6.29

[a] The average of either 4 or 5 determinations, S.D. ≤ 0.0503.

[b] The average of two determinations, differing by not more than 0.03 pH units in all cases.

[c] At 30°C, based upon densities at 30°C, from Handbook of Chemistry, 10th Edn., Lange, N.A. (Ed.), McGraw-Hill, New York, NY, 1961, pp. 1178–1180.

[d] At 25°C, from Harned, H.S. and Owen, B.B., The Physical Chemistry of Electrolytic Solutions, 2nd edn., Reinhold, New York, NY, 1950, p. 118.

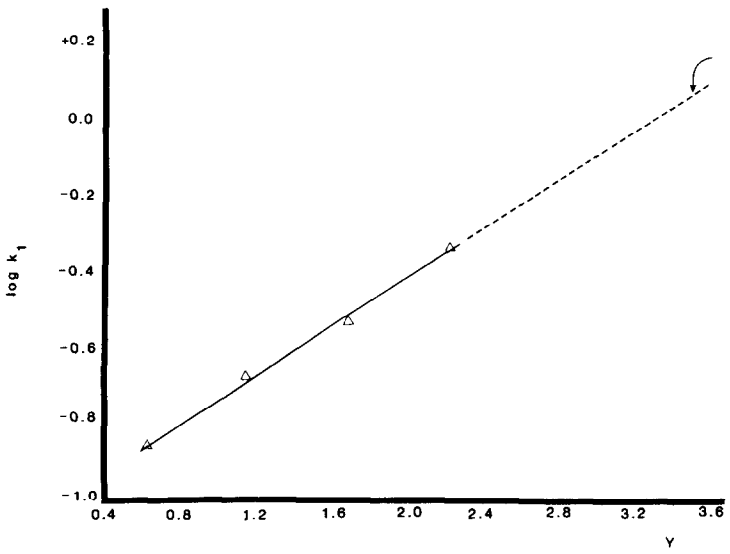


Fig. 1. Plot of log k_1 versus Y ($r = 0.999$) extrapolated to water (indicated by arrow).

(1976) examined the rate of I cyclization in an alkaline solution of 2 : 8 acetone : water at 37°C. Extrapolation of their k_1 to water by use of the m value obtained in the present study yields a k_1 of 0.453 min^{-1} ($t_{1/2} = 1.53$ min). Assuming a positive activation energy for the cyclization of 2-chloroethylamines (Cohen et al., 1948), consistency with the present study would require a k_1 for their study somewhat greater than 1.14 min^{-1}.

It should be emphasized that for a particular compound Eqn. 1 assumes solvent effects on the rate constant are related entirely to changes in the ionizing power of the solvent. However, solvent changes are altering $f_{1,unprot}$, the fraction of I unprotonated, at a particular apparent pH (such as pH 4.50) through an effect on $p_sK'_{a1}$. The result is an effect on $k_{1,app}$ different from the solvent effect on k_1. Thus, $k_{1,app}$ values cannot be fitted to Eqn. 1.

The value of m in Eqn. 1 distinguishes between an S_N1 and S_N2 mechanism. An S_N1 reaction involves a transition state in which the charge is localized, while the S_N2 transition state involves a dispersed charge. Consequently the S_N2 reaction is generally much less susceptible to changes in solvent ionizing power than is the S_N1 reaction. Values of m are thus close to unity for S_N1 reactions and in the 0.25–0.35 range for S_N2 reactions (Wiberg, 1964). Cyclization of a 2-chloroethylamine involves a neighboring-group mechanism in which the nitrogen atom functions as a nucleophile and pushes out the leaving chlorine atom. Chapman and James (1954) have referred to this process as an 'internal S_N2' mechanism. Consistent with expectations, a value of m of 0.312 was observed, indicating relatively low susceptibility of the reaction to changes in solvent ionizing power.

Qualitatively, the observed change in k_1 is consistent with the theory of Hughes and Ingold (Ingold, 1969). The transition state is more polar than intact I, thus the

TABLE 3

ESTIMATED APPARENT pK_a VALUES OF THE CONJUGATE ACIDS OF I AND III IN WATER

Compound	$p_wK'_a$
I	5.99 ($\pm$0.0216) [a]
III	7.70 [b]

[a] The mean value ($\pm$S.D.) calculated from each of the 4 values of $k_{1,app}$ in water in the pH range of 4.00 to 5.00 and the value of k_1 extrapolated to water.

[b] Extrapolated from Fig. 2.

reaction rate is favored by increasingly polar solvent mixes. It should be noted that a comparison of the solvent effect based upon apparent cyclization rate constants would be misleading. Thus, $k_{1,app}$ at pH 4.50 falsely appears to indicate a decrease in reaction rate as solvent polarity increases. This effect is solely a result of the increase in $p_sK'_{aI}$ with solvent polarity, as mentioned earlier. Apparent pK_a values of weak acid and weak base drugs frequently change with changes in the composition of a solvent mixture (King, 1963). Therefore, it is important that observations concerning solvent effects on reaction rate be based upon the specific rate constant for degradation rather than upon an apparent rate constant which, under conditions of changing pK_a, represents a progressively changing fraction of the specific constant.

Effect of solvent on apparent pK_a values of I, III and IV conjugate acids

$p_sK'_{aI}$, $p_sK'_{aIII}$ and $p_sK'_{aIV}$ values were determined over a range of solvent compositions (Table 2). Due to limited solubility, values for I and IV could be determined in solutions no more aqueous than 4:6 ethanol:water. The greater solubility of III allowed additional values to be determined in the 3:7 and 2:8 ethanol:water mixtures.

The general influence of increasing the solvent dielectric constant in ethanol:water mixtures is a relatively small increase in the pK_a of ammonium type acids (King, 1963; Brown et al., 1955). Thus, as the proportion of water in the solvent increases, an increase in basicity of I, III and IV occurs.

The value of $p_wK'_{aI}$, the apparent pK_a of the conjugate acid of I in water (5.99, Table 3) [1], was calculated from experimentally obtained values of $k_{1,app}$ in water and the value of the specific rate constant k_1 extrapolated to water. The apparent pK_a values determined in the present study were not thermodynamic constants (Benet and Goyan, 1967), nor were they referred to the standard state in each solvent mixture (Cookson, 1974). Nevertheless, a plot of $p_sK'_{aIII} + \log[H_2O]$ versus dielectric constant reciprocal ($1/\epsilon$), according to Yasuda (1959) and Shedlovsky (1962), as recommended by Benet and Goyan (1967), was linear in the three most aqueous solvents in which $p_sK'_{aIII}$ was determined (Fig. 2). Linearity is frequently observed

[1] This value has previously been reported as 4.4 (American Hospital Formulary Service, 1978). In view of the similarity of $p_sK'_{aI}$ values in 1:1 ethanol:water and 1:1 methanol:water observed between the present study and that of Beddoe and Smith (1971), along with the anticipated increase in pK_a as the solvent water proportion increases, this previous value appears erroneous.

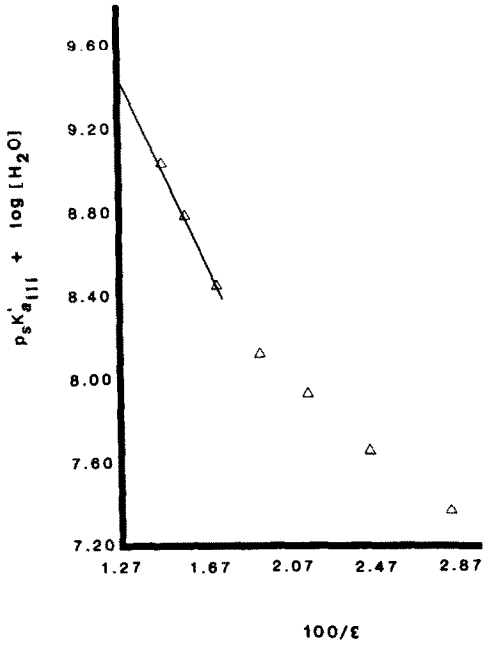


Fig. 2. Plot of $p_sK'_{aIII} + \log[H_2O]$ versus dielectric constant reciprocal extrapolated to water ($r = -1.00$ for $100/\epsilon \leqq 1.72$).

for $1/\epsilon$ values of less than 0.02; in the present study excellent linearity was observed starting with the 4 : 6 ethanol : water solvent ($1/\epsilon = 0.0172$). Linearity was not found for 1 : 1 ethanol : water ($1/\epsilon = 0.0191$). Extrapolation of the plot to water ($1/\epsilon = 0.0127$) yields a $p_wK'_{aIII}$ of 7.70.

Intuitively, the close structural relationship between I and III might be anticipated to result in a similar pK_a sensitivity of each compound to change in solvent. Indeed, although $p_wK'_a$ values for each compound were estimated by different methods, the increases in apparent pK_a, 0.98 and 1.03 units, respectively, are very close from 1 : 1 ethanol : water to water.

Inductive (March, 1968) and hydrogen bonding (King, 1963) effects are expected to result in greater base strength for hydroxy compound III than for ethoxy compound IV. Lack of apparent $p_sK'_{aIV}$ values in the higher dielectric constant range prevented extrapolation to water. However, the trend in Table 2 suggests a slightly higher $p_wK'_{aIV}$ than $p_wK'_{aIII}$, indicating that IV may be a slightly stronger base than III, contrary to expectations.

Effect of solvent on reverse reaction rate

The value of the second-order rate constant k_{-1} decreased with increasing water concentration (Table 4). Semilogarithmic plots of pH 4.50 pH stat data, representing loss of total I, were linear through at least 4–7 half-lives over the 3 : 7 to 0 : 10 ethanol : water range. This linearity indicated that k_{-1} is negligible relative to $k_{1,app}$ and k_2 in the more aqueous solvents and within the pH range of this investigation.

TABLE 4

REVERSE AND SOLVOLYSIS RATE CONSTANTS IN ABSOLUTE ETHANOL:WATER MIXTURES

Solvent (ethanol:water)	k_{-1} ($mM \cdot min^{-1}$)	k_2^a (min^{-1})	pH
0:10	– [b]	– [c]	
1:9	– [b]	– [c]	
2:8	– [b]	– [c]	
3:7	– [b]	$0.0137 \pm 0.0006(3)$	6.50
		0.0132 [d]	7.00
4:6	0.002 [e]	$0.0207 \pm 0.0006(3)$	6.50
		$0.0191 \pm 0.0002(2)$	7.50
1:1	0.004 [f]	$0.0289 \pm 0.0008(8)$ [f]	6.50–9.50

[a] Results expressed as mean ± S.D. (n in parentheses).
[b] Negligible.
[c] Not reported (see text).
[d] Based upon only one study.
[e] Based upon analog computer analysis of one pH 4.50 study.
[f] Reported in the previous paper.

Analog computer fitting of the pH 4.50 data in 3 : 7 ethanol : water corroborated this observation. The lower drug concentrations used in the 0 : 10 to 3 : 7 ethanol : water studies, however, tend to decrease the importance of this second-order process. Very high chloride ion concentrations could influence the rate of this process, as described later. The effect of increased solvent polarity upon k_{-1} is consistent with Hughes and Ingold theory. The transition state is less polar than II, thus the reaction rate is decreased by increasingly polar solvent mixes.

Effect of solvent on II solvolysis rate

First-order solvolysis rate constants were determined at two or more pH values in 1 : 1, 4 : 6 and 3 : 7 ethanol : water (Table 4). As predicted by Hughes and Ingold theory, the value of k_2 decreased as solvent polarity increased. Thus, the effect of increased solvent polarity on the value of k_2 is diametrically opposed to its effect on k_1. This qualitative difference has the interesting result that changes in solvent polarity that increase the decomposition rate of I serve to stabilize II. This effect is discussed further in the next section.

Although studies were performed in less aqueous solvents, a decrease in the k_1/k_2 ratio and an increase in k_{-1} prevented application of the equation described previously (Adams and Kostenbauder, 1985) to obtain k_2. Low drug solubility in the range of pH 6.50 and above complicated determination of k_2 in solvents more aqueous than 3 : 7 ethanol : water. The low titrant concentration necessitated by low drug solubility was very sensitive to slight carbon dioxide dissolution, leading to baseline drift. Consequently, values of k_2 are not reported for these solvents.

A plot of average log k_2 in each solvent versus dielectric constant reciprocal is linear over the range of 1 : 1 to 3 : 7 ethanol : water ($r = 0.996$). Extrapolation of this

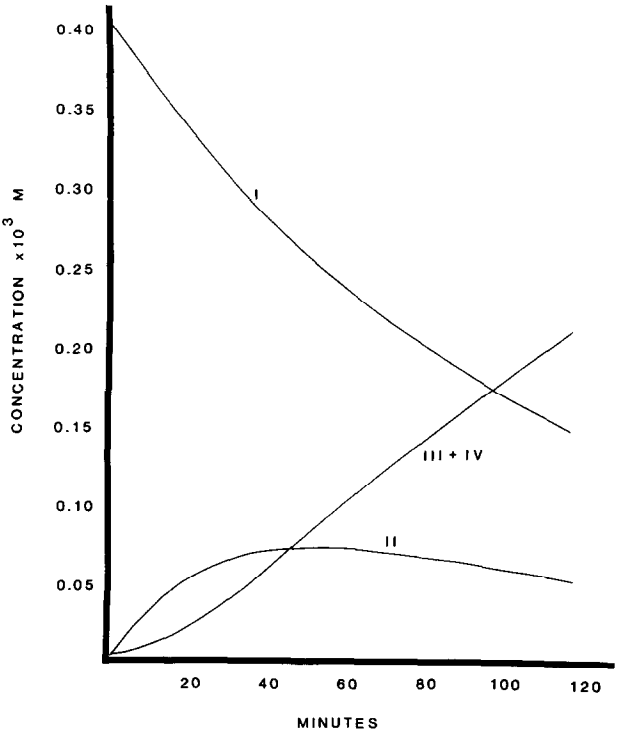


Fig. 3. Analog computer-generated plots of I, II and III + IV versus time at pH 3.50 in 1 : 1 ethanol : water. Initial conditions for I and chloride ion are 4.00×10^{-4} M; $k_{1,app}$ equals 0.009 min^{-1}, k_{-1} equals 4×10^{-6} M·min^{-1} and k_2 equals 0.029 min^{-1}.

plot yields an estimate of k_2 in water of 7.04×10^{-3} min^{-1} ($t_{1/2} = 98.4$ min) [2]. Henkel et al. (1976) examined the rate of hydrolysis of II in a 14 : 86 acetone : modified Kreb's/sodium bicarbonate buffer solution at 37°C. A k_2 of 0.0362 min^{-1} ($t_{1/2} = 19.1$ min) was obtained. An approximate comparison with results of the present study may be made by: (1) extrapolation of k_2 (Table 4) to 14 : 86 ethanol : water using a log k_2 versus dielectric constant reciprocal plot; and (2) temperature correction employing an activation energy estimated from a series of tertiary aliphatic 2-chloroethylamine ethylenimonium ions (Cohen et al., 1952) as 18.0 kcal/mol. These corrections yield an approximate k_2 of 0.0179 min^{-1} ($t_{1/2} =$ 38.8 min), about 50% of the previously reported value. The dielectric constants of the two solvent mixtures are almost equal and cannot explain the observed differences. A significant difference between studies is the use of a buffer solution in the

[2] An additional study (Rosen and Ehrenpreis, 1974) has reported a mechanism for II hydrolysis, a value of k_2 and its activation energy, based on NMR spectroscopy. The authors added I-HCl to deuterated water, followed by neutralization. The relatively high concentration of sparingly water-soluble I-HCl required for this analytical method would appear to yield a suspension rather than a solution, thereby invalidating the authors' results.

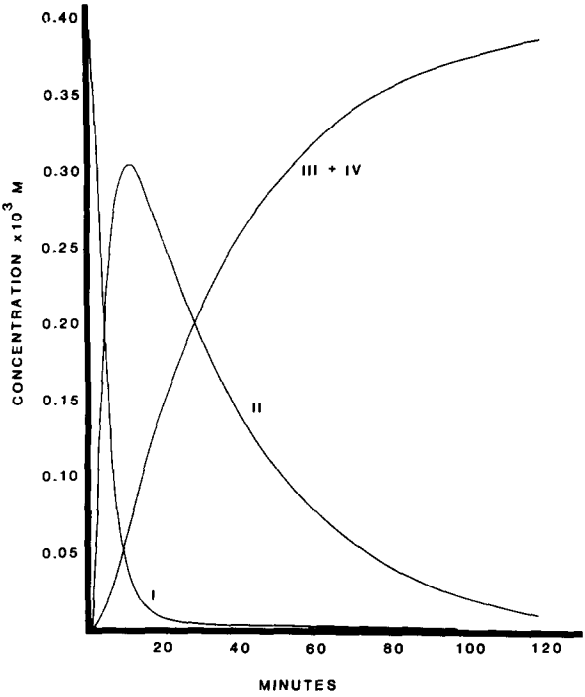


Fig. 4. Analog computer-generated plots of I, II and III + IV versus time at pH 6.50 in 1 : 1 ethanol : water. All conditions are identical to those of Fig. 3 except that $k_{1,app}$ equals 0.284 min^{-1}.

previous study. Catalysis of II hydrolysis by buffer anions could readily explain the observed difference.

Hydrolysis of an ethylenimonium ion derived from an aliphatic 2-chloroethylamine may proceed via an S_N1 or an S_N2 mechanism (Ross, 1953). The solvolysis of II is pH-independent (Table 4). Although the data do not permit distinguishing between these two mechanisms, it is apparent that S_N2 displacement by hydroxide ion is not involved over the pH 6.50 to 9.50 range. This finding is consistent with the pH-independency observed in the hydrolysis of aqueous solutions of N-methyl-N-(2-chloroethyl)ethylenimonium ion over the pH 3.6 to 8.5 range (Cohen et al., 1952). Hydroxide ion is known to catalyze the hydrolysis of certain ethylenimonium ions, however, as found for N-methyl-N-(2-hydroxyethyl)ethylenimonium ion hydrolysis over the pH 4.0 to 9.2 range (Cohen et al., 1952).

Concentration–time profiles

Analog computer-generated plots of I (protonated plus unprotonated), II, and the sum of III and IV (protonated plus unprotonated) in 1 : 1 ethanol : water indicate the sensitivity of drug decomposition to pH changes over the pH 3.50 to 6.50 range (Figs. 3 and 4). Plots over the same apparent pH range in water (Figs. 5 and 6) may be obtained using the extrapolated values of k_1 and k_2. The absence of the second-order process k_{-1} in water allows use of the integrated rate equations for a

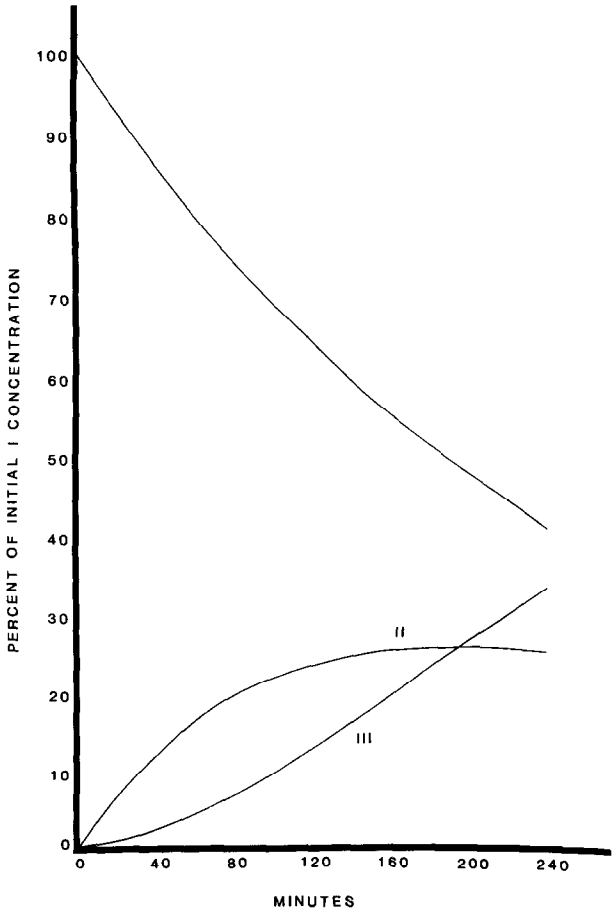


Fig. 5. Calculated plots of I, II and III versus time at pH 3.50 in water. Values of $k_{1,app}$ and k_2 are 3.68×10^{-3} min^{-1} and 7.04×10^{-3} min^{-1}, respectively.

series A to B to C reaction (Moore and Pearson, 1981) and expression of concentrations in percentage rather than molar terms. In both solvents, plots at pH 7.50 and 8.50 are essentially identical to the pH 6.50 plots. At pH 3.50 in 1 : 1 ethanol : water, I concentration requires 78.9 min to decrease to half; II remains below 20% of initial I concentration. At this pH in water, I concentration requires 189 min to decrease to half; the maximum II concentration is about 26% of initial I concentration. At pH 6.50 in 1 : 1 ethanol : water, I concentration decreases to half in 2.44 min and II increases to almost 80% of initial drug concentration. At this pH in water, the corresponding values are 0.796 min and 96.1%. At pH 7.40 in 1 : 1 ethanol : water, the half-life of cyclization (2.37 min) is so short and the reversible process so small that less than 10% of intact drug remains 8.0 min after the solution is prepared. At this pH in water, the decomposition is even greater (cyclization $t_{1/2} = 0.632$ min); only 10% of intact drug remains at 2.1 min. Examination of Figs. 3–6 indicates that

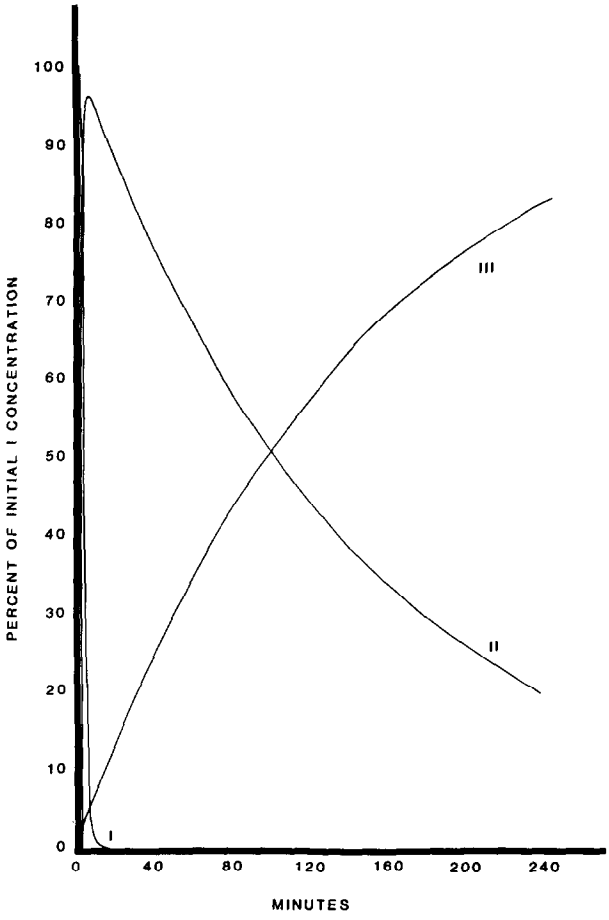


Fig. 6. Calculated plots of I, II and III versus time at pH 6.50 in water. Values of $k_{1,app}$ and k_2 are 0.871 min^{-1} and 7.04×10^{-3} min^{-1}, respectively.

peak II concentration is higher at each pH in water than at the corresponding pH in 1 : 1 ethanol : water.

Since II is the pharmacologically active species (Henkel et al., 1976), the conversion of I to II is obviously desirable at the alpha-receptor. However, optimum drug delivery to receptors separated from the general circulation by lipoidal membranes requires that the drug exist predominantly in the more lipid form I than in the ionic form II (Johansson et al., 1973; Ross et al., 1973). The relative proportions of I and II can be controlled by pH adjustment of the intravenous fluid into which the drug is dissolved and the storage time of this solution once prepared. For instance, an acidified non-aqueous solution of I-HCl may be diluted immediately before use with Sodium Chloride Injection or Dextrose Injection (Martindale: The Extra Pharmacopoeia, 1977), both of which are acidic. The present study examined the stability of 2.5×10^{-5} M aqueous solutions of I-HCl. The effect of the very high chloride ion

concentration (0.15 M) present in an isotonic sodium chloride solution, for instance, was not studied but could result in an observable rate for the k_{-1} process. However, assuming no significant effect of sodium chloride or dextrose upon the kinetics and based solely upon pH considerations, then at pH 3.00 and 30°C the cyclization half-life of I should be about 10 h. At pH 7.40, within 10 min the solution would consist almost entirely of the less diffusible II species.

In addition to the importance of the relative proportions of I and II to drug activity, the rate of product formation must be considered, since III and IV are pharmacologically inactive (Nickerson and Gump, 1949; McLean et al., 1957). In 1 : 1 ethanol : water at pH 3.50, 25% of the drug will be converted to products in 62 min, compared to only 13 min at pH 6.50. In water, the length of time required to form 25% of product(s) is longer at each pH than at the corresponding pH in 1 : 1 ethanol : water. Thus, 25% of III is formed in 192 min and 42 min at pH 3.50 and 6.50, respectively.

It should be emphasized that the kinetics observed under the in vitro conditions of this study are not applicable in vivo. The presence of additional biological nucleophiles (Harvey and Nickerson, 1954), the high serum chloride ion concentration, the potential for protein binding (Ross, 1975) and temperature are among the factors that can influence the stability of the drug upon injection.

References

Adams, W.P. and Kostenbauder, H.B., Phenoxybenzamine stability in aqueous ethanolic solutions. I. Application of potentiometric pH stat analysis to determine kinetics. Int. J. Pharm., 25 (1985) 293–312.

American Hospital Formulary Service, Phenoxybenzamine Hydrochloride, American Society of Hospital Pharmacists, Bethesda, MD, January, 1978, Section 12:16

Beddoe, F. and Smith, H.J., Inhibition of acetylcholinesterase by dibenamine and dibenzyline. J. Pharm. Pharmacol., 23 (1971) 37–49.

Benet, L.Z. and Goyan, J.E., Potentiometric determination of dissociation constants. J. Pharm. Sci., 56 (1967) 665–680.

Brown, H.C., McDaniel, D.H. and Hafliger, O., Dissociation constants. In Braude, E.A. and Nachod, F.C. (Eds.), Determination of Organic Structures by Physical Methods, Vol. 1, Academic, New York, NY, 1955, p. 619.

Chapman, N.B. and James, J.W., N-Ethyl(or -methyl or -phenyl)-N-2-halogenoethyl-1(or -2)-naphthylmethylamines. Part II. Chemical reactivity and pharmacological activity. J. Chem. Soc., (1954) 2103–2108.

Cohen, B., Van Artsdalen, E.R. and Harris, J., Reaction kinetics of aliphatic tertiary β-chloroethylamines in dilute aqueous solution. I. The cyclization process. J. Am. Chem. Soc., 70 (1948) 281–285.

Cohen, B., Van Artsdalen, E.R. and Harris, J., Reaction kinetics of aliphatic tertiary β-chloroethylamines in dilute aqueous solution. II. Hydrolysis of the ethylenimonium ion. J. Am. Chem. Soc., 74 (1952) 1875–1878.

Collins, G.M., Bravo-Shugarman, M. and Terasaki, P.I., Kidney preservation for transportation: initial perfusion and 30 hours' ice storage. Lancet, 2 (1969) 1219–1222.

Cookson, R.F., The determination of acidity constants. Chem. Rev., 74 (1974) 5–28.

Harvey, S.C. and Nickerson, M., Reactions of Dibenamine and some congeners with substances of biological interest in relation to the mechanism of adrenergic blockade. J. Pharmacol. Exp. Ther., 112 (1954) 274–290.

Henkel, J.G., Portoghese, P.S., Miller, J.W. and Lewis, P., Synthesis and adrenoceptor blocking action of

aziridinium ions derived from phenoxybenzamine and dibenamine. J. Med. Chem., 19 (1976) 6–10.
Ingold, C.K., Structure and Mechanism in Organic Chemistry, 2nd edn., Cornell University Press, Ithaca, NY, 1969, pp. 457–463.
Johansson, J.G., Lindborg, B., Dahlbom, R., Ross, S.B. and Akerman, B., Cyclizing compounds. II. Tertiary N-[2-(2,6-dimethylphenoxy)ethyl]-N-haloalkylamines with local anaesthetic action. Acta Pharm. Suec., 10 (1973) 199–208.
King, J.F., Applications of dissociation constants, optical activity, and other physical measurements. In Bentley, K.W. (Ed.), Technique of Organic Chemistry, Vol XI, Part 1, Interscience, New York, NY, 1963, pp. 323–324, 344–345.
March, J., Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, McGraw-Hill, New York, NY, 1968, p. 228.
Martindale: The Extra Pharmacopoeia, 27th edn., Wade, A. (Ed.), 1977, pp. 1655–1657.
McLean, R.A., Kerwin, J.F. and Fellows, E.J., Reaction rate and oral effectiveness of certain adrenergic blocking compounds. J. Pharmacol. Exp. Ther., 119 (1957) 566–571.
Moore, J.W. and Pearson, R.G., Kinetics and Mechanism, 3rd edn., Wiley, New York, NY, 1981, pp. 290–291.
Newton, D.W., Murray, W.J. and Lovell, M.W., pK_a determination of benzhydrylpiperazine antihistamines in aqueous and aqueous methanol solutions. J. Pharm. Sci., 71 (1982) 1363–1366.
Nickerson, M. and Gump, W.S., The chemical basis for adrenergic blocking activity in compounds related to Dibenamine. J. Pharmacol. Exp. Ther., 97 (1949) 25–47.
Reichardt, C., Empirical parameters of the polarity of solvents. Angew. Chem. Int. Ed. Engl., 4 (1965) 29–40.
Rosen, G.M. and Ehrenpreis, S., In vivo and in vitro potency of dibenamine and phenoxybenzamine: correlation with stability of the aziridinium ring. Arch. Int. Pharmacodyn. Ther., 209 (1974) 86–93.
Ross, S.B., Johansson, J.G., Lindborg, B. and Dahlbom, R., Cyclizing compounds. I. Tertiary N-(2-bromobenzyl)-N-haloalkylamines with adrenergic blocking action. Acta Pharm. Suec., 10 (1973) 29–42.
Ross, S.B., Pharmacokinetics of haloalkylamines: cyclization and distribution in blood in vitro and in vivo. J. Pharm. Pharmacol., 27 (1975) 322–328.
Ross, W.C.J., The chemistry of cytotoxic alkylating agents. In Greenstein, J.P. and Haddow, A. (Eds.), Advances in Cancer Research, Vol. 1, Academic, New York, NY, 1953, p. 412.
Shedlovsky, T., The behavior of carboxylic acids in mixed solvents. In Pesce, B. (Ed.), Electrolytes, Proc. Int. Symp., Trieste, Yugoslavia, 1959, Pergamon, New York, NY, 1962, pp. 146–151.
Wiberg, K.B., Physical Organic Chemistry, Wiley, New York, NY, 1964, p. 419.
Yasuda, M., Dissociation constants of some carboxylic acids in mixed aqueous solvents. Bull. Chem. Soc. Jpn., 32 (1959) 429–432.