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Kinetics of hydrolysis of diltiazem

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Summary

The kinetics of the hydrolysis of diltiazem in aqueous solution was studied. An HPLC assay was used to monitor the hydrolysis of diltiazem to desacetyldiltiazem. Log k-pH profiles were constructed for 50, 60, 70, and 80 °C from the first-order rate constants and pH values ranging from 1 to 8. The log k decreases with increasing pH up to pH 4 and increases with increasing pH above pH 4. Slopes of -1 and $+1$ were obtained for the acid and alkaline branches of the log k-pH profiles and were consistent with specific hydronium and hydroxyl ion catalyses. Significant buffer catalysis was observed with acetate and phosphate buffers in the hydrolysis. A positive primary salt effect was observed within the hydronium-ion-catalyzed hydrolysis and a negative effect in the hydroxyl-ion-catalyzed reaction. The activation energy for the hydronium-ion-catalyzed hydrolysis (15 kcal) is slightly higher than that for the hydroxyl-ion-catalyzed hydrolysis (13 kcal). The hydronium-ion-catalyzed reaction involving two ions of the same positive charge exhibits a greater decrease in entropy of activation (-30 cal K^{-1}) than the hydroxyl-ion-catalyzed reaction (-17 cal K^{-1}).

Introduction

Diltiazem is a calcium channel blocker (Barnhart, 1989) that has been used widely in the treatment of various cardiovascular disorders for many years. Despite the importance of this drug as a coronary vasodilator, there were relatively few studies which were concerned with the stability of diltiazem in aqueous solutions. Stability studies of diltiazem in aqueous sugar solutions (Suleiman et al., 1988) and under ultraviolet irradiation (Suleiman et al., 1989) were reported. Some data regarding the effect of pH on the stability of diltiazem in aqueous solution were reported by Davis et al. (1986) and Caille et al. (1989). Diltiazem hydrolyzes to desacetyldiltiazem and demonstrates significant instability at alkaline pH.

Since the stability studies appearing in the literature were of a preliminary nature pertaining to different aspects of the study, this experiment was undertaken to investigate the effects of pH, temperature, ionic strength, and buffer concen-

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tration on the kinetics of the hydrolysis of diltiazem to provide fundamental information for the stabilization of the drug.

Materials and Methods

Materials

Diltiazem hydrochloride was obtained from Profarmaco (Milan, Italy). The purity of the drug substance was greater than 99% as determined by HPLC analysis. The water used for investigation of the kinetics was deionized and distilled. Acetonitrile was HPLC grade. All chemicals were ACS reagent grade and were used as received.

HPLC analysis

The chromatography system consisted of a pump (Perkin Elmer 410), an automatic injector (Perkin Elmer ISS 100), a diode array detector (Perkin Elmer 480), and a networking computer system (Waters 860). The HPLC method employed a 250 mm × 4.6 mm i.d., 5 μm particle size, cyano-bonded silica column (Zorbax CN) and a mobile phase consisting of 0.036 M NaH_2PO_4 : acetonitrile (55 : 45 v/v). The flow rate was 1.5 ml/min and the detector wavelength for ultraviolet absorbance detection was 240 nm. The detector linearity for diltiazem hydrochloride over the concentration range 1–10 μg/ml gave excellent linear response (correlation coefficient > 0.999). The reproducibility at 5 μg/ml was shown to be less than 1% RSD ($n = 10$). The initial concentration of each drug solution was designated 100%; all subsequent concentrations were expressed as a percentage of the initial concentration. Duplicate injections were made for each sample.

Kinetic method

Stock solutions of diltiazem hydrochloride (100 μg/ml) and buffers (0.2 M) were prepared in water. In a typical experiment, 5 ml of the diltiazem stock solution, an appropriate amount of hydrochloric acid (pH 0.8–2.3), acetate (pH 3.8–5.0), phosphate (pH 6.0–7.3), or borate (pH 8.1) buffer stock solution and an appropriate amount of 1 M NaCl to maintain an ionic strength of 0.2 were transferred to a 100 ml volumetric flask and filled to volume with water. The reaction flask was kept in a constant temperature water bath at 50.0, 60.0, 70.0, or 80.0 °C (±0.5°C). Aliquots were sampled at appropriate time intervals and quenched to 4°C in a refrigerator. The samples were allowed to warm to room temperature before assaying by HPLC. An average of eight samples was withdrawn from each flask to generate a first-order plot. The pH values of the buffer solutions were measured at the respective study temperatures. The pH values of the highly acidic solutions were calculated from the published activity coefficients (Harned and Owen, 1958).

Results and Discussion

Rate constants

Using the HPLC procedure, diltiazem can be separated from desacetyldiltiazem. At constant pH, diltiazem degrades by an apparent first-order process. The apparent first-order rate constants (k) were obtained (Tables 1 and 2) from the slopes in accordance with

$$\log A_t = -kt/2.303 + \log A_0 \qquad (1)$$

where A_t and A_0 are the peak areas at time t and zero, respectively.

Ionic strength effect

The effect of ionic strength on the rate of hydrolysis of diltiazem at pH 2.34 and 6.06 was studied. The ionic strength effect should conform to the expression (Bronsted-Bjerrum equation) applied to reactions between ionic species:

$$\log k = \log k_0 + 1.02 z_A z_B (\mu)^{1/2} \qquad (2)$$

where k_0 is the rate constant at infinite dilution, z_A and z_B represent the charges of the reactants A and B, and μ is the ionic strength of the solution. The rate of reaction between ions of the same sign increases with increasing ionic strength, whereas that between ions of opposite sign decreases with increasing ionic strength. This expression is applicable to dilute solutions only.

Marked deviations from the relationship have been observed with increasing ionic strength. The maximum ionic strength for this study was 0.53. Fig. 1 shows plots of log k as a function of square root of the ionic strength and illustrates the positive primary salt effect observed in the hydronium-ion-catalyzed reaction at pH 2.34 and the negative effect in the hydroxyl-ion-catalyzed reaction at pH 6.06. The positive primary salt effect is expected for the reaction of the positively charged diltiazem with positively charged hydronium ion at pH below 4. When the positively charged diltiazem is reacted with negatively charged hydroxyl ion at pH above 4, the salt effect is expected to be negative.

General acid-base catalysis

The rate constants were independent of buffer concentration at constant pH and ionic strength for borate buffer and gave no evidence of general acid-base catalysis. However, significant buffer catalysis was observed with acetate and phosphate buffers in the hydrolysis of diltiazem. The rate constants for the hydrolysis studied in different buffer concentrations are given in Table 2.

The possible catalytic contributions to the apparent first-order rate constant in the acetate buffer region may be expressed by

$$k = k_{OH}[OH^-] + k_{HAc}[CH_3COOH] + k_{Ac}[CH_3COO^-] \quad (3)$$

where k_{OH}, k_{HAc}, and k_{Ac} are the respective second-order rate constants. Since, when K_a is the dissociation constant of CH_3COOH,

$$[CH_3COOH]/[CH_3COO^-] = [H^+]/K_a \quad (4)$$

$$k = k_{OH}[OH^-] + (k_{HAc}[H^+]/K_a + k_{Ac}) \times [CH_3COO^-] \quad (5)$$

or

$$k = k_{OH}[OH^-] + (k_{HAc} + k_{Ac}K_a/[H^+]) \times [CH_3COOH] \quad (6)$$

the plots of k against $[CH_3COOH]$ or $[CH_3COO^-]$ at constant $[H^+]$ should be linear and of positive slopes with intercept values of $k_{OH}[OH^-]$. When slopes (S_1) of Eqn 5,

$$S_1 = k_{HAc}[H^+]/K_a + k_{Ac} \quad (7)$$

are plotted against the hydronium ion activity, the resultant slope is k_{HAc}/K_a, and the resultant intercept is k_{Ac}. Similarly, from the slopes (S_2) of Eqn 6 against $1/[H^+]$,

$$S_2 = k_{HAc} + k_{Ac}K_a/[H^+] \quad (8)$$

k_{Hac} and k_{Ac} can be evaluated separately from the resultant intercept and the slope when K_a is known.

TABLE 1

Apparent first-order rate constants, k (in s^{-1}), for the hydrolysis of diltiazem in hydrochloric acid

HCl (N)	pH [a]	k ($\times 10^6$)			
		80.0 °C	70.0 °C	60.0 °C	50.0 °C
0.20	0.82	212	119	57.0	33.8
0.16	0.91	180	95.0	45.5	25.1
0.12	1.03	148	77.1	38.0	18.8
0.08	1.19	103	51.2	27.2	13.4
0.04	1.48	49.4			
0.03	1.60	35.7	20.2	8.53	3.97
0.02	1.76	24.2	12.6	6.89	2.78
0.01	2.05	12.2	5.06	3.54	1.92
0.005	2.34	6.15			

[a] Calculated values. The effect of temperature on pH is negligible (Harned and Owen, 1958).

TABLE 2

Apparent first-order rate constants, k (in s^{-1}), for the hydrolysis of diltiazem in buffer solutions

Buffer	Total buffer concentration (M)	80.0 °C		70.0 °C		60.0 °C		50.0 °C	
		pH	k ($\times 10^6$)	pH	k ($\times 10^6$)	pH	k ($\times 10^6$)	pH	k ($\times 10^6$)
Acetate	0.02	3.83	0.497	3.81	0.216	3.85	0.0863		
	0.04		0.512		0.216		0.0985		
	0.06		0.520		0.210		0.110		
	0.08		0.549		0.233		0.117		
	Intercept [a]		0.482		0.210		0.0780		
	0.02	4.23	0.475	4.20	0.210				
	0.04		0.570		0.260				
	0.06		0.616		0.300				
	0.08		0.738		0.300				
	Intercept [a]		0.410		0.192				
	0.02	4.54	0.792	4.60	0.255	4.58	0.0876		
	0.04		0.792		0.355		0.0988		
	0.06		0.966		0.422		0.109		
	0.08		1.00		0.478		0.130		
	Intercept [a]		0.655		0.204		0.0760		
	0.02	4.95	1.49	5.00	0.450	5.05	0.173		
	0.04		1.54		0.585		0.188		
	0.06		1.78		0.647		0.245		
	0.08		1.86		0.715		0.277		
	Intercept [a]		1.28		0.400		0.123		
Phosphate	0.02	6.06	14.8						
	0.04		15.7						
	0.06		16.4						
	0.08		18.7						
	Intercept [a]		13.6						
	0.02	6.48	36.8						
	0.04		39.0						
	0.06		40.7						
	0.08		41.6						
	Intercept [a]		35.6						
	0.02	6.85	69.8	6.90	22.8	6.83	9.44	6.87	4.00
	0.04		71.7		26.9		10.2		4.00
	0.06		82.2		24.4		10.4		4.53
	0.08		89.8		29.9		10.5		5.09
	Intercept [a]		59.0		22.2		9.00		3.50
	0.02	7.28	148	7.35	55.0	7.30	20.1	7.27	8.38
	0.04		160		55.8		20.2		8.38
	0.06		175		60.0		20.9		8.37
	0.08		181		66.8		24.3		9.91
	Intercept [a]		136		49.5		19.0		7.85
Borate	0.02					8.05	110	8.10	45.7
	0.04						108		45.0
	0.06						113		46.0
	0.08						110		45.5
	Intercept [a]						110 [b]		45.5 [b]

[a] Obtained from plots of k vs total buffer concentration.

[b] Average of the k values listed.

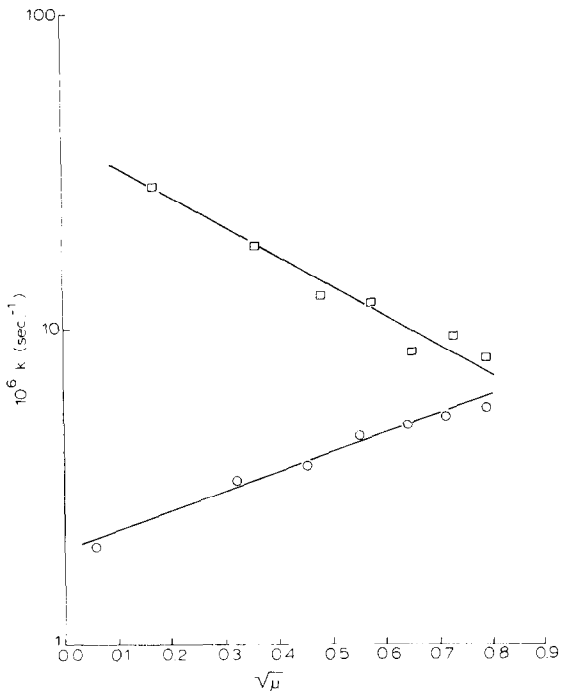

Fig. 1. Semilogarithmic plots of the first-order rate constants as a function of square root of ionic strength (μ) at pH 2.34 (○) and at pH 6.06 (□) in the hydrolysis of diltiazem at 80.0°C.

The apparent first-order rate constant (k) is plotted against [CH_3COO^-] (Fig. 2) and [CH_3COOH] (Fig. 3) for various pH values. The fact that the slopes (S_1) in Fig. 2 are independent of pH within experimental error indicates the non-variance of ($k_{HAc}[H^+]/K_a + k_{Ac}$) with [$H^+$] and, thus, the lack of a catalytic rate constant, k_{HAc}, in acetate buffer catalyzed hydrolysis of diltiazem. The catalytic rate constant, k_{Ac}, is equal to the slope (S_1) of the lines in Fig. 2 and was estimated to be 9×10^{-6} s^{-1} M^{-1} at 80°C. The identical value of k_{Ac} can be obtained from the slope of plots of the slopes (S_2) of Fig. 3 against $1/[H^+]$ in accordance with Eqn 6. The intercepts of the plots in Figs 2 and 3 vary and are consistent with hydroxyl ion catalysis, i.e., the intercepts ($k_{OH}[OH^-]$) against [OH^-] give a linear plot with a slope of k_{OH}. The $k_{OH}[OH^-]$ value was obtained from the extrapolated intercept of the plot of rate constant against buffer concentration at constant pH and the determined $k_{OH}[OH^-]$ values were used in the log k-pH profiles.

When the apparent first-order rate constant (k) is plotted against [HPO_4^{2-}] and [$H_2PO_4^-$] for the hydrolysis in phosphate buffer, similar figures were obtained to those in the case of acetate buffer. The fact that the slopes of k against [HPO_4^{2-}] do not significantly change with pH and that slopes of k against [$H_2PO_4^-$] do increase with increasing pH indicates that the catalytic species is HPO_4^{2-} and not $H_2PO_4^-$. The catalytic rate constant ($k_{HPO_4^{2-}}$) was estimated to be 7×10^{-4} s^{-1} M^{-1} at 80°C.

In the buffer catalysis, the catalytic species are the conjugate bases of the buffers. Although diltiazem may require both an acid and a base to assist its transformation to desacetyldiltiazem, it does not necessarily follow that both must enter the reaction at the rate-limiting step. It seems that only conjugate bases of the buffers partici-

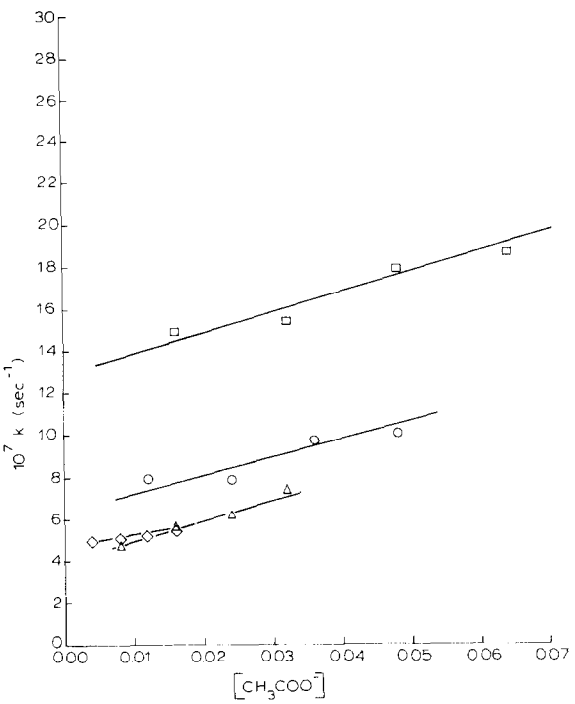

Fig. 2. First-order rate constants in the hydrolysis of diltiazem in acetate buffer at 80.0°C as a function of pH and the concentration of buffer anion, [CH_3COO^-]. pH 3.83 (◇), pH 4.23 (△), pH 4.54 (○), pH 4.95 (□).

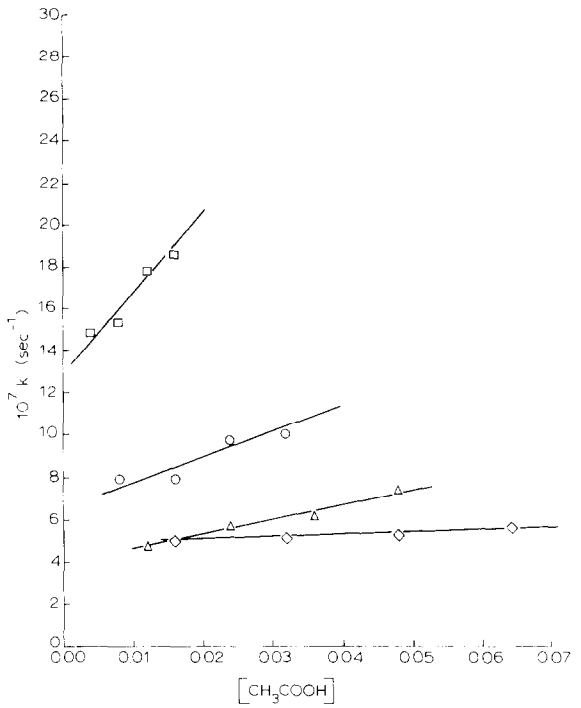

Fig. 3. First-order rate constants in the hydrolysis of diltiazem in acetate buffer at 80.0°C as a function of pH and the concentration of buffer acid, [CH_3COOH]. pH 3.83 (◇), pH 4.23 (△), pH 4.54 (○), pH 4.95 (□).

pate in the rate-limiting step and that the other enters only into a subsequent rapid step.

Log k-pH profile

The log k-pH profiles were constructed from the first-order rate constants (Tables 1 and 2) and pH values at 50.0, 60.0, 70.0, and 80.0 °C (Fig. 4). The log k decreases with increasing pH up to 4 and increases with increasing pH above 4 in accordance with

$$k = k_H[H^+] + k_{OH}[OH^-] \quad (9)$$

since $[H^+][OH^-] = K_w$,

$$k = k_H[H^+] + k_{OH}K_w/[H^+] \quad (10)$$

The log k-pH profile in conformity with Eqn 9 or Eqn 10 clearly shows that the protonated diltiazem is hydrolyzed by hydrogen and hydroxyl ion catalysis, with maximum stability at pH 4. The pH of maximum stability agrees with the previous data reported by Davis et al. (1986). Slopes of approx. −1 and +1 were obtained for the acid and alkaline branches of the log k-pH curves. A break in the base catalysis region of the profile was not detected because the hydrolysis reaction was not studied at higher pH values closer to the pK_a of the tertiary amine (expected $pK_a \approx 10$). The reaction at pH 9 or 10 proceeded too rapidly to be monitored by HPLC. The catalytic rate constants (Table 3) were determined from the intercepts of the linear segments in accordance with

$$\log k = \log k_H - pH \quad (11)$$

for the acid branch characterizing the hydrogen ion attack on the protonated diltiazem, or in accordance with

$$\log k = \log k_{OH} - pK_w + pH \quad (12)$$

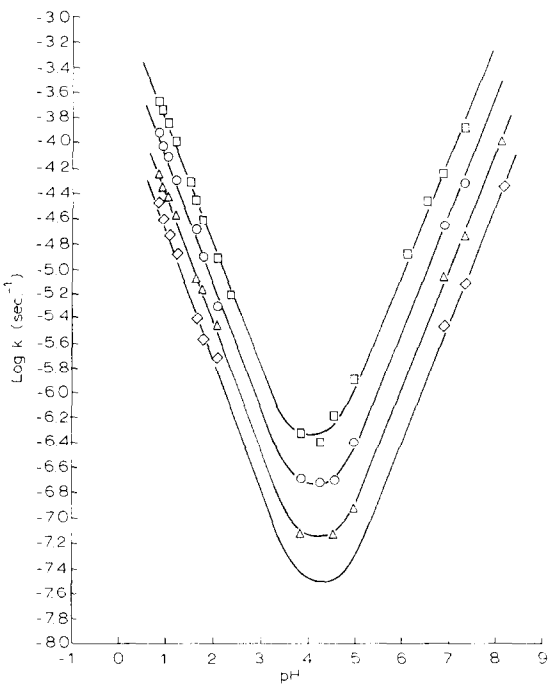

Fig. 4. Log k-pH profiles for the hydrolysis of diltiazem at 50.0°C (◇), 60.0 °C (△), 70.0°C (○) and 80.0 °C (□).

for the alkaline branch characterizing the hydroxyl ion attack on the protonated diltiazem.

Isocatalytic point

Between the branches of acid and alkaline catalysis of the log k-pH curves (Fig. 4), the rate constant passes through a minimum. The hydrogen ion activity ($[H^+]_{min}$) where the rate constant minimum occurs can be found by differentiating k with respect to $[H^+]$ in Eqn 10 and equating to zero. Then

$$[H^+]_{min} = (k_{OH}K_w/k_H)^{1/2} \quad (13)$$

or

$$[pH]_{min} = (pK_w + \log k_H - \log k_{OH})/2 \quad (14)$$

The isocatalytic points are included in Table 3. The dominant feature of the log k-pH profiles is that the isocatalytic point is shifted to lower pH because of a large k_{OH}/k_H.

The difference between the experimentally determined rate constant (Table 2 and Fig. 4) at the isocatalytic point and that calculated from Eqn 9 or 10 may be attributed to water-catalyzed reaction (spontaneous reaction). The estimated water-catalyzed reaction rate constants (k_{H_2O}) are included in Table 3.

Rate dependence on temperature

The dependence of the catalytic rate constants on temperature is given by the Arrhenius equation

$$\log k = -E_a/2.303RT + \log A \quad (15)$$

where E_a is the activation energy, and A is the frequency factor. The Arrhenius parameters calculated in accordance with Eqn 15 are included in Table 3. The Arrhenius parameters show a higher activation energy for the hydrogen ion attack on the protonated diltiazem than for the hydroxyl ion attack. The greater resistance of the protonated diltiazem to the hydrogen attack is manifested by the higher activation energy. The entropy also provides a major contribution to the difference in the hydrolysis rate. The hydronium-ion-catalyzed reaction involving two ions of the same positive charge exhibits a greater decrease in entropy in the transition state, as the transition state has a charge greater than either of the reactants.

Pharmaceutical significance

The hydrolytic instability of diltiazem, even in mildly alkaline solutions, requires great care in

TABLE 3

Catalytic rate constants [a], Arrhenius parameters [b], and entropies of activation for the hydrolysis of diltiazem

Temperature (°C)	k_H ($\times 10^4$) (s^{-1} M^{-1})	k_{OH} (s^{-1} M^{-1})	k_{H_2O} ($\times 10^7$) (s^{-1})	$[pH]_{min}$
80.0	14.3	34.1	2.4	4.1
70.0	7.40	19.8	1.0	4.2
60.0	3.50	10.9	0.39	4.2
50.0	1.90	6.40		4.3
37.5 [c]	0.693	2.72		4.5
25.0 [c]	0.243	1.13		4.6
Log A	6.69	9.54		
E_a (kcal)	15.4 ± 1.5	12.9 ± 1.1		
$\Delta S^{\ddagger}$ (cal K^{-1})	−29.9 ± 5.3	−16.9 ± 3.2		

[a] Where $k = k_H[H^+] + k_{OH}[OH^-]$.
[b] Where $\log k = -E_a/2.303RT + \log A$.
[c] Extrapolated from E_a and $\log A$.

the formulation of liquid and solid dosage forms so that the microscopic environment is acidic (pH 4.0–4.5) if possible. Alkaline lubricants and excipients should not be used and granulations should be kept as free of water as possible. When a diltiazem aqueous solution has to be buffered with acetate or phosphate buffer, buffer concentrations as low as possible should be used. Higher concentrations of neutral salt will aid in the stabilization of diltiazem in the buffer solutions of pH above 4.

Acknowledgments

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