Kinetics of Hydrolytic Degradation in Unbuffered Solutions

Theoretical Analysis of Autocatalytic Processes Controlled Primarily by Specific Acid Catalysis

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The kinetics of degradation of neutral and acidic molecules which form acidic products in unbuffered solutions has been considered. The validity of the analytic solutions for autocatalytic cases involving specific acid catalysis in competition with specific base catalysis or spontaneous degradation has been verified through analog simulation of the reactions. Since the time required for 10 per cent degradation of a drug is of pharmaceutical interest, the effect on this parameter of variation in initial concentration of drug, rate constants, and dissociation constants of reactants and products was investigated. The equations presented may be applied to the estimation of drug stability under the conditions described, if the relevant kinetic parameters are known.

THE PROBLEMS involved in treating stability in pharmaceutical systems in which the products influence the course of degradation have not been considered in detail. In his comprehensive review of pharmaceutical stability, Garrett (1) suggests that "... autocatalytic degradation may need special treatment..." to apply the principles of stability prediction which have been elaborated. Kinetic mechanisms involving autocatalysis have been described for certain autoxidations (2), biochemical processes (3), and thermal degradations (4, 5). The degradation of amyl nitrite (6) has been shown to be autocatalytic. It is also well known that the "spontaneous" hydrolysis of esters in aqueous solution is autocatalytic, the catalyst being the acid formed upon hydrolysis. In this respect, Zawidzki (7) has reported studies of the autocatalytic hydrolysis of alkyl sulfates and Dawson and Lowson (8, 9) that of ethyl acetate. General theoretical treatments of autocatalytic kinetics have been presented by Zawidzki (10) and Reed and Berkson (11). The latter have discussed the application of the "logistic" function to autocatalytic processes.

This study considers the kinetics of homogeneous degradation of drugs in unbuffered systems which are subject to specific acid and/or base catalysis and form acids and/or bases as products. Sound kinetic technique dictates that stability analysis of such drugs be carried out in buffered solutions to simplify interpretation of experimental data and to extract the maximum information from the study concerning mechanism of reaction and pH of optimum stability.

However, there are instances where it may prove undesirable to prepare buffered pharmaceutical systems containing these drugs. General acid and/or base catalysis may prove sufficiently severe so that buffering actually results in decreased stability when compared to the unbuffered system. Buffers may be incompatible with the drug or with other components of the preparation. In other instances, the pH of maximum stability may be too high (>10) or too low (<2) to permit effective buffering for optimum stability. Drugs of a high order of stability are often formulated in unbuffered systems. Drugs of a low order of stability may be used in unbuffered solution forms which are prepared prior to use and may often have been stored for periods of several weeks. It would seem desirable to have a valid means for predicting the possible extent of degradation in such instances as well as for kinetically analyzing data obtained in the absence of pH control. Although Zawidzki and Dawson have developed theoretical treatments for some specific cases of the type under consideration, no prior *systematic* quantitative treatment of cases of this sort has otherwise been reported.

The specific cases dealt with in this report concern the hydrolytic degradation of neutral and acidic molecules which form acidic products. Examples of the model reactions included in this report are listed in Table I. Although the theory has been developed assuming only hydrolytic degradation, the proposed models may apply to other kinds of degradative processes as well.

Differential equations descriptive of the models have been derived and solved analytically. The complexity of some of the solutions obtained prohibit their ready application to practical

TABLE I.—MODEL REACTIONS TREATED

Case	Reactant	pH-Determining Product	Examples	Ref.
I	Neutral[a] molecule $N \rightarrow H^+ + A^-$	Strong acid	Ethyl trifluoroacetate	(12)
II	Neutral[a] molecule	Weak acid	Choline esters	(13)
	$N \rightarrow HA_2 \rightleftharpoons H^+ + A_2^-$			(14)
			Alkyl sulfates	(15)
III	Weak acid $HA_1 \rightarrow$ $H^+ + A_1^-$	Weak acid HA_2 $H^+ + A_2^-$	Acylsalicylates Alkyl-*dl*-α-(2-piperidyl)- phenylacetates	(16) (17) (18)

[a] Neutral in the sense of acidity, not charge.

problems, necessitating some degree of approximation. An analog computer was used to simulate the models and thus generate the experimental data required to test the validity and useful range of the computational techniques developed which may have specific application to stability prediction in pharmaceutical systems.

THEORY

A generalized differential equation describing the rate of irreversible hydrolytic reactions in unbuffered solutions in the absence of general acid and base catalysis may be written (1)

$$- \frac{d[X]}{dt} = k_H[H^+][X] + k_0[X] + k_{OH}[OH^-][X] \quad \text{(Eq. 1a)}$$

where k_H is the bimolecular rate constant characterizing the specific acid-catalyzed degradation, k_{OH} is the bimolecular rate constant characterizing the specific base-catalyzed degradation, and k_0 is a first-order rate constant which may characterize the spontaneous reaction of a drug with the solvent or an intramolecular catalysis. $[X]$ may be considered to be a neutral, acidic, or basic species of reacting drug. It will prove more convenient to write this rate expression in the form

$$- \frac{d[X]}{dt} = k_H[H^+][X] + ak_H[X] + \frac{bk_H[X]}{[H^+]}$$
$$\text{(Eq. 1b)}$$

where $a = k_0/k_H$ and $b = k_{OH}Kw/k_H$.

The problem reduces to defining hydrogen ion concentration $[H^+]$ in terms of reactant concentrations and appropriate constants to arrive at differential equations which are amenable to integration and computer simulation. Degradations of the type discussed in this report may be followed in practice by measuring changes in pH or reactant concentration. Equations describing the degradation rate may be written as functions of either or both these parameters. In general, equations will be expressed here in terms of concentration of undegraded drug.

The development which follows is based on the premise that the bulk of the observed degradation in the systems studied will be the result of specific acid catalysis, at least in systems which are initially neutral or weakly acidic. The existence of acids initially in the system, specific base catalysis, and/or

first-order degradative processes in this view serve primarily to initiate degradation and thus determine the length of the induction period observed before degradation significantly begins to accelerate. Systems which are perturbed by the presence of bases are not specifically considered in this report. In these instances, specific base catalysis and first-order processes may account for significant degradation.

Case I. Homogeneous Degradation of Neutral Molecules Which Form Strong Acids.—In this case[1] the hydrogen ion formed in the degradation will be reduced by the hydroxyl ion present in solution. In pure water

$$[H^+] = [N_0] - [N] + [OH^-] =$$
$$[N_0] - [N] + \frac{Kw}{[H^+]}$$

or

$$[H^+]^2 - \{[N_0] - [N]\}[H^+] - Kw = 0 \quad \text{(Eq. 2a)}$$

where $[N]$ is the concentration of undegraded drug at any time t and $[N_0]$ its concentration at $t = 0$. The positive root of Eq. 2a is

$$[H^+] = \frac{[N_0] - [N]}{2} + \frac{1}{2}\sqrt{\{[N_0] - [N]\}^2 + 4Kw} \quad \text{(Eq. 2b)}$$

Since it will prove generally true that $[N_0] \gg Kw$,

$$[H^+] \sim [N_0] - [N] \quad \text{(Eq. 2c)}$$

during the bulk of the degradation; at $t = 0$

$$[H^+] = [H_0] = Kw^{1/2} \quad \text{(Eq. 2d)}$$

in pure aqueous solution. Equation 2c is substituted in Eq. 1b which is then integrated[2] to give

$$\ln \frac{\sqrt{\{[N_0] - [N]\}^2 + a\{[N_0] - [N]\} + b}}{[N]} -$$
$$\left(\frac{b}{[N_0]} + \frac{a}{2}\right) \int$$
$$\frac{d\{[N_0] - [N]\}}{\{[N_0] - [N]\}^2 + a\{[N_0] - [N]\} + b} =$$
$$\{[N_0]^2 + a[N_0] + b\}k_H t + \text{constant} \quad \text{(Eq. 3a)}$$

TABLE II.—PARTICULAR SOLUTIONS OF EQ. 1b (HOMOGENEOUS DEGRADATION OF NEUTRAL MOLECULES WHICH FORM STRONG ACIDS)

$$\ln X - Y = \ln Z + C\,k_{H}t$$

Condition	X	Y	Z	C	Equation
$a = b = 0$	$\dfrac{[N_0] - [N]}{[N]}$	0	$\dfrac{[H_0]}{[N_0]}$	$[N_0]$	4[a]
$b = 0$	$\dfrac{[N_0] - [N] + a}{[N]}$	0	$\dfrac{[H_0] + a}{[N_0]}$	$[N_0] + a$	5
$a = 0$	$\dfrac{\sqrt{([N_0] - [N])^2 + b}}{[N]}$	$\dfrac{\sqrt{b}}{[N_0]}\left\{\tan^{-1}\dfrac{[N_0] - [N]}{\sqrt{b}} - \tan^{-1}\dfrac{[H_0]}{\sqrt{b}}\right\}$	$\dfrac{\sqrt{[H_0]^2 + b}}{[N_0]}$	$\dfrac{[N_0] + b}{[N_0]}$	6

[a] Equation characteristic of second-order autocatalytic processes (11, 19).

TABLE III.—PARTICULAR SOLUTIONS OF EQ. 1b (HOMOGENEOUS DEGRADATION OF NEUTRAL MOLECULES WHICH FORM WEAK ACIDS)

$$A \ln \frac{\sqrt{\beta} + \sqrt{\beta - [N]}}{\sqrt{\beta} + \sqrt{\beta - [N_0]}} - B \ln \frac{\sqrt{\beta} - \sqrt{\beta - [N]}}{\sqrt{\beta} - \sqrt{\beta - [N_0]}} + (B - A)\ln Y + Z = Ka_2^{1/2}k_{H}t$$

Condition	A	B	Y	Z	Equation
$a = b = 0$	$\dfrac{1}{\sqrt{\beta} + \dfrac{Ka_2^{1/2}}{2}}$	$\dfrac{1}{\sqrt{\beta} - \dfrac{Ka_2^{1/2}}{2}}$	$\dfrac{[H^+]a}{[H_0]b}$	0	13[c]
$b = 0$	$\dfrac{1}{\sqrt{\beta} + \dfrac{Ka_2^{1/2}}{2} - \dfrac{a}{Ka_1^{1/2}}}$	$\dfrac{1}{\sqrt{\beta} - \dfrac{Ka_2^{1/2}}{2} + \dfrac{a}{Ka_2^{1/2}}}$	$\dfrac{[H^+] + a}{[H_0] + a}$	0	14
$a = 0$	$\dfrac{\sqrt{\beta} + \dfrac{Ka_2^{1/2}}{2}}{\left(\sqrt{\beta} + \dfrac{Ka_2^{1/2}}{2}\right)^2 + \dfrac{b}{Ka_1}}$	$\dfrac{\sqrt{\beta} - \dfrac{Ka_2^{1/2}}{2}}{\left(\sqrt{\beta} - \dfrac{Ka_2^{1/2}}{2}\right)^2 + \dfrac{b}{Ka_1}}$	$\sqrt{\dfrac{[H^+]^2 + b}{[H_0]^2 + b}}$	$D^d\left\{\tan^{-1}\dfrac{[H^+]}{\sqrt{b}} - \tan^{-1}\dfrac{[H_0]}{\sqrt{b}}\right\}$	15

[a] Given by Eq. 10a.   [b] Given by Eq. 11 or 2d.   [c] Dawson and Lowson (9) had derived Eq. 13 expressed in terms of product rather than reactant concentrations.   [d] $D = (A - B) - (A + B)\left\{\left(\dfrac{(Ka_2/4 + (b/Ka_2)}{\sqrt{\beta}}\right)\right\}\dfrac{Ka_2^{1/2}}{\sqrt{b}}$.

If $a^2 > 4b$ the integral will have the value

$$-\frac{2}{\sqrt{a^2 - 4b}}\tanh^{-1}\frac{2\{[N_0] - [N]\} + a}{\sqrt{a^2 - 4b}} \quad \text{(Eq. 3b)}$$

If $4b > a^2$ the integral will be

$$\frac{2}{\sqrt{4b - a^2}}\tan^{-1}\frac{2\{[N_0] - [N]\} + a}{\sqrt{4b - a^2}} \quad \text{(Eq. 3c)}$$

Particular solutions of Eq. 3a that apply to situations in which only specific acid catalysis, specific acid catalysis and first-order degradation, or specific acid and specific base catalysis are involved result when $a = b = 0$, $b = 0$, or $a = 0$, respectively. These are listed in Table II.

In systems free of acid prior to degradation $[H_0]$ is given by Eq. 2d. If strong acid is initially present, $[H_0]$ becomes equal to its concentration, and $[N_0]$ is increased by the amount of acid present. On the other hand, if a weak acid HA_0 with a dissociation constant[3] Ka_0 is present in solution at a fixed concentration C_0, then $[H^+] = [OH^-] + [A_0^-] + [N_0] - [N]$. Therefore

$$[H^+] = \frac{[N_0] - [N]}{2} +$$
$$\frac{1}{2}\sqrt{\{[N_0] - [N]\}^2 + 4\{Ka_0 C_0 + Kw\}} \quad \text{(Eq. 7a)}$$

assuming $C_0 \sim [HA_0]$. At $t = 0$,

$$[H^+] = [H_0] = \sqrt{Ka_0 C_0 + Kw} \quad \text{(Eq. 7b)}$$

The contribution of the weak acid to the rate of degradation will be significant only during the early stages of the reaction if $[H_0] \ll N_0$; otherwise $[H_0]$ must be added to $[N_0]$ wherever it appears in Eqs. 4–6.[4]

When only specific base-catalyzed degradation is considered, Eq. 1a reduces to $-(dN/dt) = k_{OH}Kw[N]/\{[N_0] - [N]\}$ integration of which leads to

$$\ln\frac{[N_0]}{[N]} - \left(1 - \frac{[N]}{[N_0]}\right) = \frac{k_{OH}Kw}{[N_0]}\,t \quad \text{(Eq. 8)}$$

This equation may be modified in the manner discussed when applied to systems containing acid prior to the initiation of degradation.

Case II. Homogeneous Degradation of Neutral Molecules Which Form Weak Acids.—Assuming that a weak acid HA_0 other than the product HA_2 of

Fig. 1.—Computer simulated degradation (according to Eq. 4) of a neutral compound subject only to specific acid catalysis in unbuffered solution. Degradation product is a strong acid; $[N_0] = 0.01$ M. Fraction of undegraded reactant (curve A), $[N]/[N_0]$, and rate of degradation (curve B), $d(N)/d\tau$, are shown as a function of the time parameter $\tau = k_H t$. Inset shows pH variation with τ for this system.
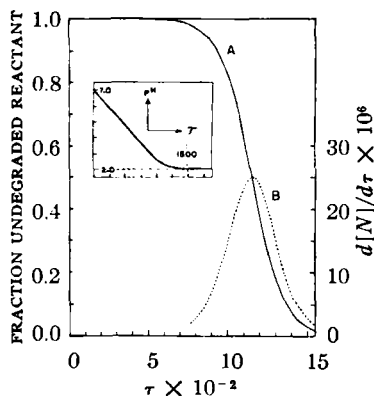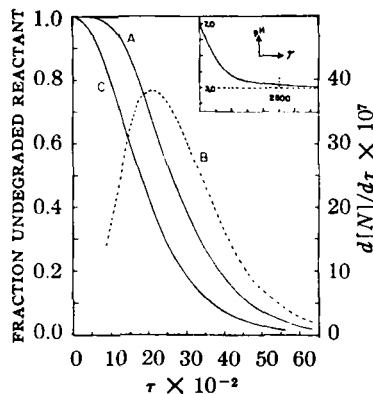

Fig. 2.—Computer simulated degradation (according to Eq. 13) of a neutral compound subject only to specific acid catalysis in unbuffered solution. Degradation product is a weak acid, $pKa_2 = 4.0$; $[N_0] = 0.01$ M. Fraction of undegraded reactant (curve A), $[N]/[N_0]$, and rate of degradation (curve B), $d[N]/d\tau$, are shown as a function of the time parameter $k_H t$. Curve C represents the theoretical course of degradation according to Eq. 16. Inset shows pH variation with τ for this system.

the degradation is also present in solution at a fixed concentration $C_0 = [HA_0] + [A_0{}^-]$, the $[H^+]$ function characteristic of this system may be derived in the following manner. Since $[H^+] = [A_2{}^-] + [A_0{}^-] + [OH^-]$ or

$$[H^+] = \frac{Ka_2[HA_2]}{[H^+]} + \frac{Ka_0[HA_0]}{[H^+]} + \frac{Kw}{[H^+]} \quad (Eq. 9a)$$

and $[N_0] - [N] = [HA_1] + [A_1{}^-]$ therefore,

$$[H^+]^2 - Ka_2 \{[N_0] - [N] - [A_2{}^-]\} - Ka_0 \{C_0 - [A_0{}^-]\} - Kw = 0 \quad (Eq. 9b)$$

where $[N_0]$ is the initial concentration of reactant, and Ka_2 and Ka_0 are the dissociation constants of the product and other acid present in the system. It may be further assumed that during the course of the degradation $[A_2{}^-] > 20 [A_0{}^-]$ and $[A_2{}^-] \gg [OH^-]$, so that $[A_2{}^-] \sim [H^+]$. The resulting quadratic expression can then be solved for $[H^+]$, the positive root of which is

$$[H^+] = Ka_2{}^{1/2} \{\sqrt{\beta - [N]} - Ka_2{}^{1/2}/2\} \quad (Eq. 10a)$$

where $\beta = \{(Ka_2/4) + (Kw/Ka_2) + (Ka_0/Ka_2) \times C_0 + [N_0]\}$. If $Ka_2 \ll [N_0]$, then

$$[H^+] = Ka_2{}^{1/2} \sqrt{\beta - [N]} \quad (Eq. 10b)$$

At $t = 0$

$$[H^+] = [H_0] = \sqrt{\frac{Ka_0{}^2}{4} + Ka_0C_0 + Kw} - \frac{Ka_0}{2} \quad (Eq. 11)$$

in the presence of weak acid, or $[H^+]$ is defined by Eq. 2d in its absence.

Substitution of Eq. 10a in Eq. 1b results in a differential equation which adequately represents all significant features of the model. Its solution[5] takes the form
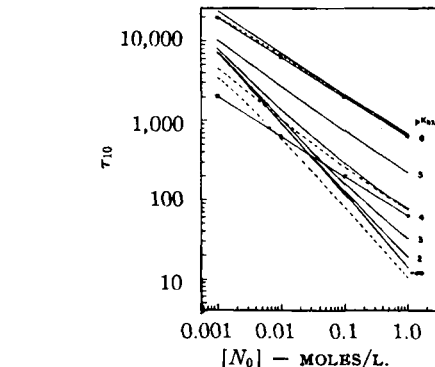

Fig. 3.—Dependence of the time required for 10% degradation of neutral compounds in unbuffered solution on the initial reactant concentration ($[N_0]$) and product acidity (pKa_2). Key: ———, τ_{10}-values computed from Eqs. 4 ($pKa_2 - \infty$) and 13 (pKa_2 2–6) assuming $[H_0] = 10^{-4} M$; ----, τ_{10}-values computed from Eqs. 4 ($pKa_2 - \infty$) and 13 (pKa_2 4 and 6) assuming $[H_0] = 10^{-5.5} M$; and -●—●-, τ_{10}-values computed from Eq. 16 (pKa_2, 4 and 6) assuming $[H_0] = 10^{-7} M$.

$$A \ln (\sqrt{\beta} + \sqrt{\beta - [N]}) -$$
$$B \ln (\sqrt{\beta} - \sqrt{\beta - [N]}) +$$
$$(B - A) \ln \sqrt{\{\beta - [N]\} + \lambda \sqrt{\beta - [N]} + \gamma} +$$
$$\left\{ A\left(1 - \frac{\gamma}{\sqrt{\beta}}\right) - B\left(1 + \frac{\gamma}{\sqrt{\beta}}\right) \right\}$$
$$\int \frac{d(\sqrt{\beta - [N]})}{\{\beta - [N]\} + \lambda \sqrt{\beta - [N]} + \gamma} =$$
$$Ka_2{}^{1/2}k_H t + constant \quad (Eq. 12)$$

where the constants A, B, λ, and γ are complex functions of Ka_2, β, a, and b. Table III lists particular solutions of Eq. 12 for cases where $a = b = 0$, $b = 0$, and $a = 0$, Eqs. 13–15, respectively.

The differential equation[6] which results when Eq.

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[5] Equation 12 was derived by the method of partial fractions and subsequent application of integral No. 29 and 93 (see *Footnote 2*).

[6] This equation is basically the one reported by Zawidzki (7) to characterize the rate of hydrolysis of potassium methane sulfate.

TABLE IV.—EXAMPLES OF KINETIC PARAMETERS RELEVANT TO AUTOCATALYTIC HYDROLYSIS OF SOME COMPOUNDS

Reactant	Ethyl Acetate (9)	Acetyl β-Methyl Choline (14)	Sodium Ethyl Sulfate (15)	Acetylsalicylic Acid (16)	Methyl DL-α-Phenyl-2-piperidyl Acetate HCl (17)	Phosphoramidic Acid (20)
Temp., °C.	25	25	90	25	25	36.8
pKa_1		60		3.69	8.8	3.0[b]
pH-Determining product	Acetic acid	Acetic acid	Sodium bisulfate	Salicylic acid	DL-α-Phenyl-2-piperidyl acetic acid HCl	Ammonium biphosphate
pKa_2	4.75	4.8	2.9	2.97	[a]	7.2[b]
e	1.0	1.0	1.0	0.81	(1.0)[c]	1.0
f	[f]	[f]	1.0	(0.91)[d]	(1.0)[c]	0.555
$k_H^{\bullet}$	6.50×10^{-8}	3.59×10^{-3}	3.30×10^{-2}	1.50×10^{-5}	2.87×10^{-3}	
$k_0^{\bullet}$	[f]	[f]	7.92×10^{-6}	[g]	[f]	7.17×10^{-3}
$k_{OH}^{\bullet}$	6.5	66.7	385.2		1.48×10^{4}	
a			2.4×10^{-3}		1.33×10^{-6}	1.29×10^{-2}
b	1.0×10^{-11}	1.85×10^{-11}	1.93×10^{-9}	2.86[h]		2.57[h]
pH_0	7.0	7.0	6.23		5.4[h]	
$t_{10\%}$ (min.)[h],[i] — Pseudo-1st order	1.6×10^{5}	1.56×10^{4}	1.31×10^{4}	5.02×10^{4}	5.46×10^{4}	4.1
$t_{10\%}$ (min.)[h],[i] — Autocatalytic	3.59×10^{5}	6.32×10^{5}	5.66×10^{2}	5.0×10^{4}	(1.95×10^{5})[j]	11.9

[a] Values not available. [b] Values listed are for 25°, not the temperature specified. [c] Estimated values. [d] Value for the second degradation product, acetic acid, indicates that it is not a pH-determining product. [e] L. mole⁻¹ sec.⁻¹ [f] Values are too small to have a significant effect or be measurable. [g] Values are not relevant to autocatalytic degradation. [h] Computed assuming that initial reactant concentration was 0.01 M. [i] Computed neglecting ionic strength effects. [j] Computed assuming that $pKa_2 = 3.0$.

10b is substituted in Eq. 1b leads to a solution of the same form as Eq. 12, but with less complex coefficients. For the particular case where $a = b = 0$, the solution may be written as

$$\tanh^{-1}\sqrt{\frac{\beta - [N]}{\beta}} = \tanh^{-1}\sqrt{\frac{\beta - [N_0]}{\beta}} + \frac{k_H \beta^{1/2} Ka_2^{1/2}}{2}\, t \quad (Eq.\ 16)$$

If only specific base catalyzed-degradation is considered, i.e., $k_H = k_0 = 0$, then integration of the reduced form of Eq. 1a substituted by Eq. 10a results in

$$\tanh^{-1}\sqrt{\frac{\beta - [N]}{\beta}} - \sqrt{\frac{\beta - [N]}{\beta}} + \frac{Ka_2^{1/2}}{4\beta^{1/2}}\ln\frac{[N]}{[N_0]} = \tanh^{-1}\sqrt{\frac{\beta - [N_0]}{\beta}} - \sqrt{\frac{\beta - [N_0]}{\beta}} + \frac{k_{OH} Kw}{2\beta^{1/2} Ka_2^{1/2}}\, t \quad (Eq.\ 17)$$

Equation 17 can be reduced to a first-order expression, if $\beta \sim [N_0]$, which applies during the very early stages of degradation, since $\tanh^{-1}\sqrt{x} \sim \sqrt{x}$ when $x < 0.07$.

Case III. Homogeneous Degradation of Weak Acids Which Form Weak Acids.—The pH of a solution of a weak acid HA_1 with dissociation constant Ka_1 prior to degradation and in the absence of other acids of comparable or greater strength will be determined by the concentration of that acid. If upon degradation another weak acid HA_2 with dissociation constant Ka_2 is formed, the pH of the system will shift in proportion to the relative values of the respective dissociation constants as well as to the extent of degradation. Let $[A_1] = [HA_1] + [A_1^-]$ be the concentration of reactant and $[A_2] = [HA_2] + [A_2^-]$ the concentration of product at any time t. During the course of degradation, the $[H^+]$ function may be represented by $[H^+] = [A_1^-] + [A_2^-]$. Therefore

$$[H^+]^2 - Ka_1[HA_1] - Ka_2[HA_2] = 0 \quad (Eq.\ 18a)$$

Since $[A_0] - [A_1] = [HA_2] + [A_2^-]$ where $[A_0]$ is the reactant concentration at $t = 0$

$$[H^+]^2 - Ka_1\{[A_1] - [A_1^-]\} - Ka_2\{[A_0] - [A_1] - (A_2^-)\} = 0 \quad (Eq.\ 18b)$$

To simplify Eq. 18b one of two limiting assumptions may be made. If we assume that $Ka_2 > Ka_1$, the pH of the system will be determined largely by the dissociation of the product, except during the early stages of degradation. Furthermore, since $[HA_1] \gg [A_1^-]$, except during the latter stages of degradation, Eq. 18b can be revised to

$$[H^+]^2 + Ka_2[H^+] - Ka_1[A_1] - Ka_2\{[A_0] - [A_1]\} = 0 \quad (Eq.\ 18c)$$

whose root is

$$[H^+] = \frac{1}{2}\sqrt{Ka_2^2 + 4Ka_2[A_0] - 4(Ka_2 - Ka_1)[A_1]} - Ka_2/2 \quad (Eq.\ 19a)$$

or

$$[H^+] = Ka_2^{1/2}\{\sqrt{\beta - e[A_1]} - Ka_2^{1/2}/2\} \quad (Eq.\ 19b)$$

where $\beta = \{Ka_2/4 + [A_0]\}$ and $e = 1 - Ka_1/Ka_2$.

The properties of Eqs. 19a and 19b can readily be ascertained by considering two limiting conditions. If $Ka_1 = Ka_2$, then $e = 0$ and Eq. 19a reduces to

$$[H^+] = [H_0] = \frac{1}{2}\sqrt{Ka_1{}^2 + 4Ka_1[A_0]} - Ka_1/2 \quad \text{(Eq. 20a)}$$

which gives the $[H^+]$ of a solution of reactant prior to degradation. The pH of the solution will be constant and the degradation will be first order. On the other hand, if $Ka_2 \gg 100Ka_1$, then $e \sim 1$ and Eq. 19b reduces to

$$[H^+] = Ka_2{}^{1/2}\{\sqrt{\beta - [A_1]} - Ka_2{}^{1/2}/2\} \quad \text{(Eq. 20b)}$$

which is of the same form as Eq. 10a. Comparison of Eqs. 19b and 10a indicates that Eqs. 13–15 also apply to the degradation of weak acids in homogeneous systems when appropriate changes in symbols are made, e.g., $e \cdot [A_1]$ replaces $[N]$, etc.

If the degradation product were a weaker acid than the reactant, i.e., $Ka_1 > Ka_2$, the pH of the system would be largely determined by the reactant concentration, except during the latter stages of degradation. It follows from Eq. 18b that in this instance

$$[H^+] = Ka_1{}^{1/2}\{\sqrt{\beta + f[A_1]} - Ka_1{}^{1/2}/2\} \quad \text{(Eq. 21a)}$$

where $\beta = \{Ka_1/4 + [A_0]Ka_2/Ka_1\}$ and $f = 1 - Ka_2/Ka_1$. If $Ka_1 \gg 100Ka_2$, then $f \sim 1$ and

$$[H^+] = Ka_1{}^{1/2}\{\sqrt{\beta + [A_1]} - Ka_1{}^{1/2}/2\} \quad \text{(Eq. 21b)}$$

Solutions of Eq. 1b substituted by Eq. 21a similar in form to Eqs. 13–15 may be derived.

More than one weak acid may be formed in a degradation. The pH of the system will be controlled by the strongest acid present as long as sufficient differences in dissociation constants exist. If HA_1 on degradation forms HA_2 and HA_3, assuming that $Ka_2 > Ka_3$ and Ka_1, a $[H^+]$ function can be derived so that

$$[H^+] = Ka_2{}^{1/2}\{\sqrt{Ka_2/4 + (1 + Ka_3/Ka_2)[A_0]} - (1 + Ka_3/Ka_2 - Ka_1/Ka_2)[A_1] - Ka_2{}^{1/2}/2\} \quad \text{(Eq. 22)}$$

This function should adequately describe the pH shift in homogeneous systems, except during the early stages of degradation. It reduces to Eq. 19b if $Ka_2 \gg 100\ Ka_3$.

EXPERIMENTAL

Equation 1b with appropriate $[H^+]$ functions substituted was programmed and solved on an analog computer. Programs were designed so that changes in reactant concentration, hydrogen-ion concentration, or overall rate of degradation could be followed with respect to time. The effect of variation in the following parameters on the kinetics of degradation was investigated: (a) dissociation constants of reactants and products, (b) initial concentration of reactants, (c) spontaneous or hydroxyl ion–catalyzed reactions in parallel with hydrogen ion–catalyzed degradation, and (d) concentration of weak acid other than reactant or product. Computer solutions and results computed from the analytical solutions generally agreed to within better than ±2% (the range of error anticipated with the particular computer and components employed) when crosschecked, thus supporting their validity.

RESULTS AND DISCUSSION

Solvolysis Rates, Acidity, and Concentration.— The essential features of the specific acid-catalyzed hydrolysis of a neutral molecule in solution uncomplicated by the existence of competitive spontaneous or specific base-catalyzed reactions are expressed by Eq. 4 if the degradation product is a strong acid and Eq. 13 if a weak acid.[7] Figures 1 and 2 show the S-shaped curves characteristic of autocatalytic processes as they would be observed in reactions of the type described in the absence of acid other than that derived from the degradation. In these instances the reaction is initiated by $[H^+]$ resulting from the dissociation of water. These curves may be viewed as limiting cases indicative of the slowest
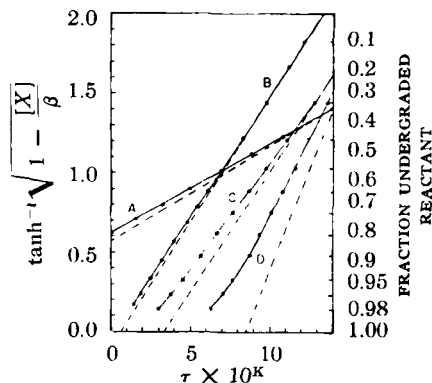

Fig. 4.—Analysis, using Eq. 16, of computer simulated degradation of neutral compounds which form weak acids as products and are subject only to specific acid catalysis in unbuffered solution: curve A, $pKa_2 = pKa_0 = 4.0$, $[N_0] = 0.01\ M$, $C_0 = 0.0044\ M$, $\beta = 0.0144\ M$, $K = -2.0$; curve B, $pKa_2 = 4.0$, $\beta = [N_0] = 0.1 \cdot M$, $K = -2.0$; curve C, $pKa_2 = 4.0$, $\beta = [N_0] = 0.01\ M$, $K = -2.477$; curve D, $pKa_2 = 2.0$, $\beta = [N_0] = 0.1\ M$, $K = -1.204$. Key: O represent values computed from Eq. 16; dashed lines represent the theoretical slope for each case $= \sqrt{\beta K a_2}/2$.

degradation rate observable for the particular conditions they represent. Data are plotted as a function of a time parameter $\tau = k_H t$. The time scale is defined so that it is independent of the actual value of the rate constant k_H.

The most important feature of an autocatalytic process is its induction period. Reactions characterized by Eqs. 4 and 13 significantly begin to accelerate only when the hydrogen-ion concentration becomes a significant fraction (ca. 1%) of the reactant concentration. As shown by the insets in Figs. 1 and 2, the bulk of the observed pH shift takes place during the induction period. For cases represented by Eq. 4, the time course of degradation is symmetrical, the rate of degradation being a maximum at $[N] = {}^1/_2[N_0]$ (curve B, Fig. 1). Degradations better represented by Eq. 13 are unsymmetrical, the rate being a maximum at $[N] = {}^2/_3[N_0]$ (curve B, Fig. 2).[8]

[7] Dawson and Lowson have established the validity of Eq. 13 by application to the autocatalyzed hydrolysis of ethyl acetate (9).

[8] One can readily demonstrate that $d[N]/dt$ will be a maximum at $[N] \sim {}^2/_3\beta$ by differentiation of the equation $-(d[N]/dt) = k_H[H^+][N]$, where $[H^+]$ is given by Eq. 10b. In the example described by Fig. 2, $\beta = [N_0]$.

A convenient measure of the induction period which is also a pharmaceutically significant parameter is the time required for 10% degradation, *i.e.*, τ_{10} in terms of the time parameter. Data comparing the magnitude of decreases in τ_{10} produced by increases in product acidity and reactant concentration are shown in Fig. 3. If $[N_0] - [N] < 10\ Ka_2$, Eqs. 13 and 4 give substantially the same result. The acid can be considered to be effectively 100% dissociated, thus behaving as a strong acid.

If acid other than that owing to the degradation is initially present in the system, it can be seen from the definition of β (Eq. 10a) that its effect would be to increase $[N_0]$ by the amount Ka_0C_0/Ka_2 as well as decrease the initial pH (Eq. 11), thus acting to reduce the induction period. The weak acid normally present in aqueous solution will be carbonic acid (pK_1 6.35 at 25°) which results from solution of atmospheric carbon dioxide. A good grade of distilled water in equilibrium with a normal atmosphere has a pH ~ 5.5. For this system the product Ka_0C_0 will be $\sim 10^{-11}$, a value too small to change β, yet significant enough to reduce τ_{10} because of its effect on the initial pH of the system. The extent of reduction in τ_{10} produced by carbonic acid contaminated water compared to carbon dioxide–free water is also shown in Fig. 3. The magnitude of this effect is an inverse function of $[N_0]$ and a direct function of Ka_2.

When a weak acid decomposes to form another stronger weak acid, the pH of the solution is initially fixed at a value determined by the concentration and acidity of the reactant (Eq. 20a). τ_{10} will be shortened in proportion to the relative values of the two dissociation constants involved. No actual induction period will exist if the initial pH of the system is low (<4) or if $Ka_1/Ka_2 > 0.01$ ($e < 1$). Equation 19b was derived assuming that the dissociation of reactant was negligible. This assumption fails if the reactant concentration is small ($\sim 0.01\ M$). Equation 19b predicts that the $[H^+]$ during the early stages of degradation can be smaller than the $[H_0]$ calculated for the system (Eq. 20a), particularly if $e < 1$. The initial small increase in pH which should be observed is indicative of the shifting in control of acidity of the system from reactant to product. A good example is acetylsalicylic acid which is cited in Table IV. This table lists relevant kinetic parameters for several compounds of the types considered in this report and compares predicted $t_{10\%}$-values for autocatalytic and pseudo-first-order (at constant $[H^+] = [H_0]$) processes. If 10% degradation has taken place in an 0.01 M solution of aspirin, the calculated $[H^+]$ of the system is $1.25 \times 10^{-3}\ M$, whereas $[H_0]$ is $1.37 \times 10^{-3}\ M$. The effect is small enough so that pseudo-first order degradation can be assumed for purposes of analysis. If 50% degradation has taken place, $[H^+]$ is $2.05 \times 10^{-3}\ M$, indicating that the reaction rate is now controlled by the acidity of the salicylic acid. An equation of the form of Eq. 13 then more accurately describes the process.

If the functional group being hydrolyzed is not acidic, one would generally expect that at least one of the degradation products of a weak acid would be stronger acid or one comparable in strength to the reactant. If an acidic group is degraded, acids weaker than the reactant may only be formed. One example of this type is phosphoramidic acid (see Table IV) which would exhibit a negative autocatalytic effect upon degradation in unbuffered solution since the $[H^+]$ continually decreases in proportion to the degree of reaction.

Equation 13 is cumbersome; computations made with it are involved. Unfortunately, the less complex Eq. 16 will not give a valid prediction of τ_{10}, since the assumption upon which it is based (in effect that the dissociation of the product is negligible[9]) fails in the early stages of degradation. The degree of error observed in calculating τ_{10} using Eq. 16 is shown in Fig. 3; it decreases in proportion to product pKa and reactant concentration. A comparison of the form of solutions obtained for Eqs. 13 and 16 is shown in Fig. 2 (curves *A* and *C*, respectively). These curves illustrate the failure of Eq. 16 to account for the induction period accurately, because it makes no provision for the initial state of the system. However, Eq. 16 may have application to the analysis of stability data obtained in the absence of pH control when autocatalytic processes of the type described are involved. It predicts that a straight line with slope equal to $k_H\beta^{\frac{1}{2}}Ka_2^{\frac{1}{2}}/2$ will be obtained if $\tanh^{-1}\{1 - [X]/\beta\}$ is plotted as a function of time. Plots of this type are shown in Fig. 4 which illustrates the limitation of the technique: reactant concentration must be large ($1 - 0.1\ M$), and only data corresponding to the latter stages of degradation should be weighted. These limitations may be overcome in part if the acid degradation product is initially added to the system so that $\beta = [X_0] + C_0$ (the concentration of added acid). Dawson and Lowson (8) have derived an equivalent form of Eq. 16 which they applied to a study of the acetic acid catalyzed hydrolysis of ethyl acetate.

Competitive First-Order and Hydroxyl Ion–Catalyzed Processes.—Specific base-catalyzed or spontaneous degradation also result in reduction of the autocatalytic induction period. Figure 5 shows the course of degradation if it is only specific base-catalyzed. These curves are characterized by a rapid initial rate of degradation which decreases in proportion to the acidity of the product. When
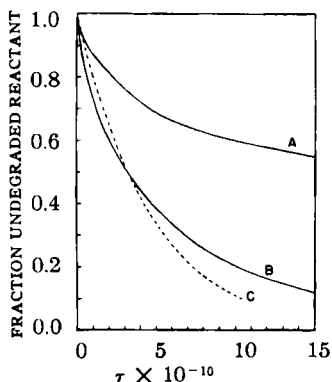

Fig. 5.—Computer simulated degradation of a neutral compound subject only to specific base catalysis in unbuffered solution: curve *A*, degradation product is a strong acid (defined by Eq. 8), $[N_0] = 0.01\ M$; curve *B*, degradation product is a weak acid $pKa_2 = 4.0$ (defined by Eq. 17), $[N_0] = 0.01\ M$. Curve *C* represents a first-order degradation shown for purposes of comparison.

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[9] This assumption is implicit in the derivation of equations generally used for estimating pH (21).

both specific base-catalyzed and acid-catalyzed processes are in competition, the rate of degradation passes through a minimum (Fig. 6) which corresponds to that point in time where the reaction changes from one controlled by the pOH of the system to one controlled by the pH. At this point $[H^+] = \sqrt{b}$ (the catenary of the pH-rate profile), since the rates of specific acid and base catalysis are equal. The $\tan^{-1}$ terms which appear in Eqs. 6 and 15 significantly influence computations only in the vicinity of the minimum.[10]

The relative importance of specific base catalysis in influencing the overall degradative rate is measured by the b-value, a few examples of which are listed in Table IV to show the range in values which may be observed. Figure 7 shows the variation in τ_{10} as a function of b at different levels of product acidity and reactant concentration. Comparison is made with τ_{10}-values computed assuming pseudo-first order kinetics at constant $[H^+] = [H_0]$. If b has a relatively large value, the system will be more stable in unbuffered solution than when maintained at constant pH_0; if it has a small value, the system will be less stable in unbuffered solution.

Where spontaneous hydrolysis is important in initiating degradation, the initial rate will be first
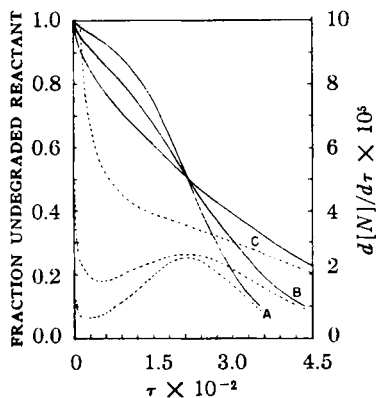

Fig. 6.—Computer simulated degradation (according to Eq. 6) of neutral compounds ($[N_0] = 0.01\ M$) which form strong acids as products and are subject to both specific acid and base catalysis: curve A, $b = 10^{-7}$; curve B, $b = 10^{-6}$; and curve C, $b = 10^{-5}$. For purposes of comparison, k_H was adjusted so that τ_{50}-values were equal. Key: ———, represents plots of fraction of undegraded reactant as a function of τ; – – – –, represents plots of rate of degradation, $d[N]/d\tau$, as a function of τ.

order. Its relative importance in the overall degradation is measured by the a-value (see Table IV). Figure 8 shows the variation in τ_{10} as a function of a at different levels of reactant concentration and product acidity. It gives an indication of the effective range of application of Eqs. 5 and 14. It should be noted that phosphoramidic acid would show transition from autocatalytic to first-order control as its degradation proceeded, in contrast to the data presented in Fig. 8.

[10] Dawson and Lowson (9) divided their analysis of the autocatalytic degradation of ethyl acetate into two stages. In the first stage they evaluated the combined catalytic action of hydrogen-ion and hydroxyl-ion by numerical solution of the differential equation. They employed a form of Eq. 13 in their analysis of the second stage which dealt with only hydrogen-ion catalysis.

Temperature and Solvent Effects.—The effect of temperature on the autocatalytic rate process will depend upon the degree of thermal variation of the dissociation constants of all acid species present (including the solvent) and on the energies of activation of the reactions involved. The dissociation constant may increase or decrease with temperature depending upon the nature of the acid and the temperature range (22). However, the effect is sufficiently small in the case of carboxylic acids to be neglected. The significant increase in acidity of water observed at elevated temperatures will be reflected as an increase in value of b (Table IV). The relative dependency of autocatalytic degradation on hydroxyl-ion catalysis is thereby increased.

The solvent effects which can be analyzed are those owing to moderate changes in dielectric constant and ionic strength. Their influence on the rate constant has been detailed by Garrett (1). It
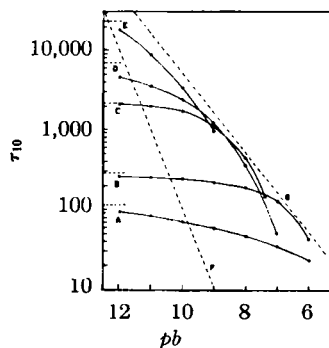

Fig. 7.—Computed τ_{10}-values shown as a function of $b = k_{OH}k_w/k_H$: curves A ($[N_0] = 0.1\ M$) and D ($[N_0] = 0.001\ M$), degradation product is a strong acid, defined by Eq. 6; curve B ($[N_0] = 0.1\ M$), degradation product is a weak acid ($pKa_2 = 4.0$), defined by Eq. 15; curves C ($[N_0] = 0.1\ M$) and E ($[N_0] = 0.001\ M$), degradation product is a weak acid ($pKa_2 = 6.0$), defined by Eq. 15. Curve F represents τ_{10}-values computed assuming pseudo-first order degradation at constant $pH = pH_0 = 7.0$. Curve G represents values computed assuming pseudo-first order degradation at constant $pH = p\sqrt{b}$.

should be noted that increases in ionic strength tend to increase the apparent dissociation constants of weak acids; decreases in dielectric constant tend to decrease them (22). Since the present theory has been developed in terms of the classical dissociation constant, the exact analysis of these effects requires a knowledge of f_H and f_{OH} for the specific system being studied (see *Footnote 3*). In most practical work activity coefficients can be assumed to be unity. The effect of changing ionic strength as a consequence of degradation cannot readily be quantified. Observed deviations from results predicted for autocatalysis, owing to changes in ionic strength, will be especially significant if the degradation product is a strong acid and the reactant concentration is large.

CONCLUSIONS

The validity of the equations which have been presented to describe autocatalytic degradation in systems of the type considered in this report depend on the validity assigned to the $[H^+]$ functions derived. For purposes of estimating stability (as

measured by $t_{10\%}$) in unbuffered aqueous pharmaceutical systems, the exact expressions (*e.g.*, Eqs. 13–15) must be employed. The examples of computed $t_{10\%}$-values shown in Table IV indicate that significant errors can be made in estimates of stability if pseudo-first order degradation is assumed.

The models discussed fail to take into account general acid and base catalysis or reversible reactions such as those which might be observed in simple ester hydrolysis. However, these effects certainly can be neglected for estimation of $t_{10\%}$.
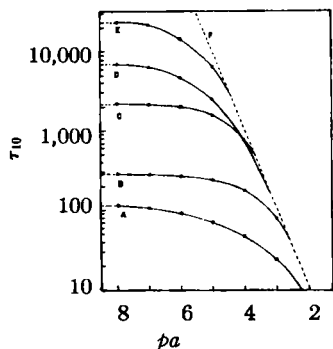

Fig. 8.—Computed τ_{10}-values shown as a function of $a = k_0/k_H$: curves A ($[N_0] = 0.1\ M$) and D ($[N_0] = 0.001\ M$), degradation product is a strong acid, defined by Eq. 5; curve B ($[N_0] = 0.1\ M$), degradation product is a weak acid (pKa$_2$ = 4.0), defined by Eq. 14; curves C ($[N_0] = 0.1\ M$) and E ($[N_0] = 0.001\ M$), degradation product is a weak acid (pKa$_2$ = 6.0), defined by Eq. 14. Curve F represents τ_{10}-values computed assuming pseudo-first order degradation at constant pH = pH$_0$ = 7.0.

Other cases can be considered, such as degradation of neutral molecules or weak bases which form weak bases as products and are subject primarily to specific base catalysis in unbuffered solution. Treatment

of these cases leads to solutions of the same form as those described for *Cases II* and *III*.

The power of the analog computer as a tool in analyzing cases of this sort can readily be ascertained by noting the complexity of the solutions obtained to the differential equations. The computer will prove especially useful in analyzing systems where analytical solutions cannot readily be arrived at—for example, cases complicated by reversible reactions.

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Effect of Antiemetics and Other Compounds on Protoveratrine Induced Emesis in Dogs

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Several known antiemetics and other compounds were evaluated for their ability to prevent protoveratrine induced emesis in dogs and found to be ineffective.

PROTOVERATRINE produces a potent reflex vasodepressor effect in dogs and humans (1).

However, the range between the therapeutic and the toxic dose is quite narrow (2), and it is often difficult to obtain good clinical results without some side effects; the major side effects are nausea and vomiting. Alterations in the protoveratrine molecule to increase the margin between effectiveness and nausea have been attempted (3). A second approach has been directed at the prevention of nausea and vomiting by the administration of antiemetic agents.