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Review Article

Prediction of Stability of Drugs and Pharmaceutical Preparations

By EDWARD R. GARRETT

TO PREDICT is "to tell or declare beforehand, foretell or prophesy" (190). In the realms of science, prediction is based on a knowledge of the relations among experimental values under observed experimental conditions. Prediction of the stability of drugs and pharmaceutical preparations depends on quantitative mathematical expressions that permit the calculation of rates of degradation by the substitution of the appropriate values for temperature, concentrations, pressure, time, pH, oxygen content, centrifugal or gravitational stress, light intensities and wavelengths, etc.

These quantitative relations can be obtained from the classical literature of chemistry and physics (83, 169). Judicious experimental design can permit the evaluation of the vital parameters with the minimum expenditure of time and labor. Thus, stability can be predicted for practical circumstances where study, *per se*, is experimentally or economically impractical or unsuitable.

The literature contains many articles on drug incompatibilities or instabilities for which references are cited (18, 134, 158, 192).

However, kinetic and predictive studies of drugs in the pharmaceutical literature are of relatively recent vintage. In fact, *ca.* 1950 can be considered the start of the modern era in the quantitative comprehension and prediction of drug stability.

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This review will be concerned with those studies on drugs and pharmaceutical formulations where quantitative expressions were obtained to permit prediction of stability. It will consider the basic concepts and the rationales which can be applied to permit prognosis. This review will be practically limited to studies conducted in liquid media involving solvolytic processes and leave the aerobic, bacterial, enzymic, or photolytic degradations to another time or another reviewer. The prediction of stability of the complex systems characterized by colloidal suspensions, emulsions, ointments, and solid formulations will, in general, also be ignored.

The basic concepts of kinetics and their applications to the understanding of the mechanisms of reactions of many simple systems and reactive groups are given in many fine books on these subjects (2, 9, 14, 29, 43, 71, 72, 86, 103, 104, 123, 138). Their reading is recommended.

Predictive Use of the Apparent First-Order Rate Constant. The chemical action of a solvent and other solutes on the drug in solution is of prime importance. A systematic approach to its understanding and quantification is to consider the rate of degradation of such a drug as proportional to the concentrations of the reactants in the rate-determining step, or proportional to the concentrations of the reactants in the equilibria which precede such a rate-determining step. The rate of drug transformation is given in concentration, c, change per unit of time; (time-unit^{-1}).

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In most solvolytic reactions with constant conditions of temperature, pH, buffer kind and concentration, and ionic strength, the rate of change per unit of time is proportional to the first power of the concentration of the drug being transformed

$$dc/dt(M/\text{L./sec.}) = kc^1(\text{sec.}^{-1} \times \text{moles/L.}) \quad \text{(Eq. 1)}$$

The rate is considered as apparent first order since it varies as the first power of the concentration, c, of the substrate. On integration of Eq. 1, the logarithm of the concentration, c, when plotted against time is a straight line of slope $k/2.303$

$$\log c = -kt/2.303 + \log c_0 \quad \text{(Eq. 2)}$$

or the logarithm of the fraction of substrate untransformed when plotted against time is a straight line of the same slope

$$\log c/c_0 = -kt/2.303 \quad \text{(Eq. 3)}$$

where c_0 is the original concentration and k is in reciprocal time units (29, 71). It has been recommended that all rate constants be given in units of seconds for ease of literature comparison (161). Some typical semilogarithmic plots for the degradation of thiamine hydrochloride (47) are given in Fig. 1.

The rate constants, k, are frequently used to compare and estimate rates. An alternative constant to use is the half-life, $t_{1/2}$; the time when a concentration is reduced by half its initial value. For all apparent first-order reactions the $t_{1/2}$ is independent of the magnitude of the initial concentration of the substrate and is related to the first-order rate constant, k, by

$$t_{1/2}(\text{sec.}) = -2.303 \log 0.5/k = 0.693/k \quad \text{(Eq. 4)}$$

from the rearrangement of Eq. 3 where $c/c_0 = 1/2$, $t = t_{1/2}$ and k is in sec.$^{-1}$.

Variations on this theme can be chosen to calculate the time of 5 or 10% loss of substrate, *i.e.*, $t_{0.95}$ or $t_{0.90}$, respectively (117). The half-life is only independent of initial substrate concentrations for first-order reactions. It has been used frequently to describe the stability of a drug and the rate dependencies (35, 95, 98, 130, 132, 193, 198). Nelson (143) provides a convenient table to determine the fractional loss of substrate for n half-lives. However for the purpose of a systematic presentation, the concept of the rate constant will be used in this paper as descriptive of the fraction of substrate remaining on exponential decay

$$c/c_0 = e^{-kt} \quad \text{(Eq. 5)}$$

It is apparent that if the apparent first-order rate constant, k, can be determined as a function

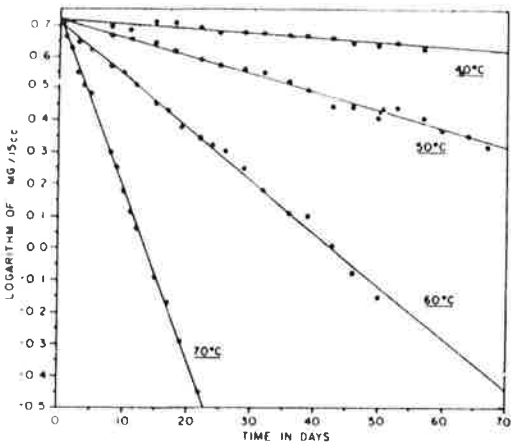

Fig. 1.—First-order plots of the thermal degradation of thiamine hydrochloride in a liquid multivitamin; logarithms of concentration (mg./15 ml.) against time in days. [Figure 1 of Garrett, E. R., THIS JOURNAL, **45**, 470(1956) (47).]

of the physical conditions of the solution, the rate of degradation at a given concentration can be determined by substitution of that concentration, c, into Eq. 1; that the half-life under those conditions can be determined by substitution into Eq. 4; that the fraction of substrate remaining at any time, t, can be determined by use of Eq. 5.

To transform the half-life or first-order rate constants into other time units such as hours, days, years, etc., the conversions are

$$t_{1/2}(\text{time units}) = t_{1/2}(\text{in sec.})/(\text{seconds/time unit}) \quad \text{(Eq. 6)}$$

$$k(\text{time unit})^{-1} = k(\text{sec.}^{-1}) \times \text{sec./time unit} \quad \text{(Eq. 7)}$$

An appropriate procedure for studies that may be ambiguous is to verify the fact experimentally that the apparent first-order rate constant, k, is independent of substrate concentration. This has been done in many such cases (52, 55, 57, 66, 91, 114, 140, 154, 165, 193). Alternative methods of estimating apparent first-order rate constants are from the slopes of plots of concentration changes against time at the initial concentrations of substrate or by the Guggenheim method (81). Such procedures have been used with steroid hemiester hydrolysis and compared to the k values derived from classical plots (59, 61, 68).

Specific Acid-Base Catalyzed Solvolysis.—The simplest catalysts for solvolysis are hydrogen ions and hydroxyl ions so that the apparent first-order reaction rate constant k would be determined by

$$k = k_1[H^+] + k_6[OH^-] \quad \text{(Eq. 8)}$$

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**Definition of Hydr
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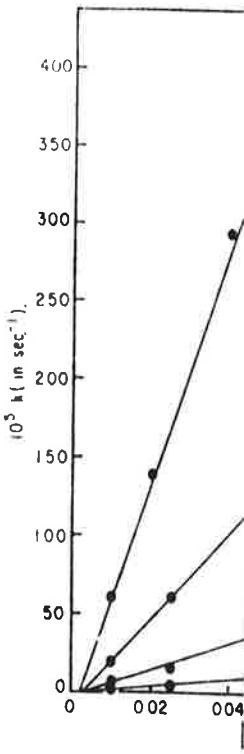

Fig. 2.—Rate constant
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[Figure 3 of Garrett, E.
827(1960)(56).]

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where catalysis by $[H^+]$ and $[OH^-]$ and the respective specific rate constants k_1 and k_6(L./*M*/sec.) are considered specific acid-base catalysis. In general, hydroxyl ion catalysis is negligible when a hydrogen ion catalyzed transformation is operative, and vice versa, so that one method of determining k_1 is to plot the observed rate constant, k, obtained from the slope of the plot of data according to Eq. 2, against the maintained hydrogen ion concentration.

As per Eq. 8 where the contribution of $k_6[OH^-]$ is negligible, the slope of such a plot estimates k_1 in L./*M*/sec. Obviously, k_6 may be similarly obtained by plotting k against $[OH^-]$ when the contribution of k_1 $[H^+]$ is negligible and k_6 in L./*M*/sec. can be estimated. A typical plot in this manner is given in Fig. 2 for the acid hydrolysis of psicofuranine (56). The negative intercept of the plot is due to the fact that the true molarity of hydrochloric acid is the apparent molarity lessened by the amount necessary to neutralize the psicofuranine.

Definition of Hydrogen and Hydroxyl Ion Concentrations and Activities.—The specific bimolecular rate constants are defined in terms of the ratio of the apparent first-order rate constant and the concentration or activity of the catalytic species. The specific rate constants of Eq. 8

$$k_1 = k/[H^+] \text{ when } k_6[OH^-] \sim 0 \quad \text{(Eq. 8a)}$$

or

$$k_6 = k/[OH^-] \text{ when } k_1[H^+] \sim 0 \quad \text{(Eq. 8b)}$$

can be defined in terms of the stoichiometric strong acid or strong alkali concentration, *e.g.*, $[H^+] = [HCl]$ or $[OH^-] = [NaOH]$ on the postulate that the hydrogen or hydroxyl ion catalytic contributions are equivalent to the molarity of the strong acid or base. This is not necessarily true, however, as the effective hydrogen (or hydroxyl) ion concentration (activity) of a strong acid (or base) decreases from expectation with increased concentrations of the acid (or base) (89). The high activity of perchloric acid makes it one of the most ideal acids for the study of specific hydrogen ion catalysis (97, 98, 130–132). Ester hydrolysis is most generally catalyzed only by hydrogen and hydroxyl ions (specific acid-base catalysis) (9, 123) but consumes hydroxyl ions, so that if $k_6 = k/[OH^-]$ is to be determined, then the molar concentration of strong alkali should exceed the concentration substrate by at least tenfold, *e.g.*, $[OH^-] > 10c$ when $[OH^-]$ is taken as equivalent to [NaOH]. A specific example is the determination of $k/[OH^-]$ in the hydrolysis of acetylsalicylates (50). When the molar concentration of strong alkali approaches that of the substrate, bimolecular rate expressions must be used to calculate k_6 (9, 43, 104, 123). It is a similar situation for amides when hydrogen ions are taken up by the liberated amines the concentration of strong acid must greatly exceed the substrate concentration for pseudo first-order techniques to be used in the calculation of the apparent bimolecular rate constant k_1 (70).

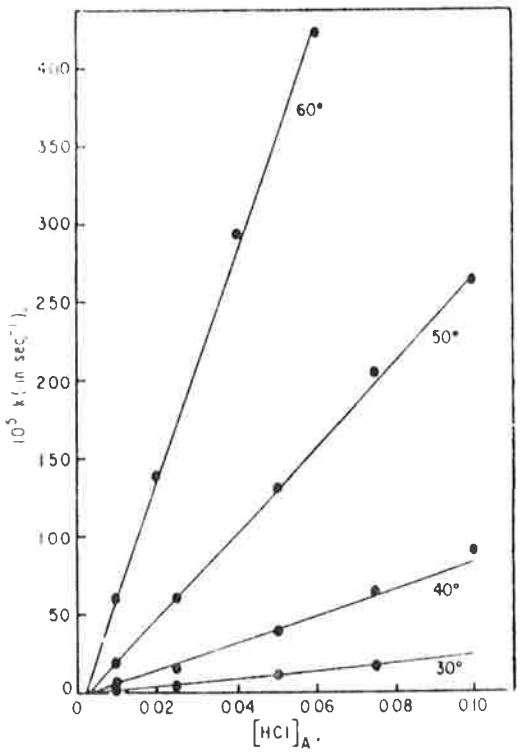

Fig. 2.—Rate constants, k in sec.$^{-1}$, for the apparent first-order degradation of psicofuranine as a function of apparent hydrochloric acid molarity [Figure 3 of Garrett, E. R., *J. Am. Chem. Soc.*, **82**, 827(1960)(56).]

An alternative method is frequently used to calculate k_1 and k_6 where these values are defined in terms of the activities of hydrogen ions and hydroxyl ions, respectively.

The pH can be experimentally determined and, when $k_6[OH] \sim 0$, the logarithmic transformation of Eq. 8 yields

$$\log k = \log k_1' - \text{pH} \quad \text{(Eq. 9)}$$

so that the slope of the logarithm of the apparent first-order rate constant against the experimentally determined pH is negative and equal to unity, and the antilog of the intercept yields the bimolecular rate constant k_1'. This k_1' value is related to the specific bimolecular rate constant k_1 by

$$k_1' = f_H \cdot k_1 \quad \text{(Eq. 10)}$$

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where f_{H^+} is the activity coefficient (2, 89, 149) for the hydrogen ion and

$$k = k_1' \ 10^{-pH} \text{ when } k_6[OH^-] \sim 0 \quad \text{(Eq. 11)}$$

where the pH is the experimentally determined ($-\log a_{H^+}$), where a_{H^+} is the hydrogen ion activity.

A similar development for k_6' yields

$$\log k = \log k_6' - pOH = \log k_6 - pKw + pH \quad \text{(Eq. 12)}$$

The pK_w for a given temperature and solvent can be obtained from the literature (89, 149) so that k_6 can be calculated from the intercept of the plot of the logarithm of the apparent first-order rate constant against the experimentally determined pH. Thus, Eq. 8 is redefined in terms of pH as

$$k = k_1' \ 10^{-pH} + k_6' \ 10^{-(pKw - pH)} \quad \text{(Eq. 13)}$$

where the k_1' and k_6' values of Eq. 12 will frequently differ slightly from the k_1 and k_6 of Eq. 8 and yet be the desired values for prediction of solvolysis rates in intermediate pH ranges where pH is experimentally determined.

Comparisons of k_1 determined from stoichiometric catalytic concentrations and from pH measurements (*i.e.*, k_1') have been made in the cases of the solvolysis of the antibiotic streptovaricin (53) and the solvolysis of the antibiotic psicofuranine (56). An interesting comparison of measured pH and the pH calculated from kinetic rate constants is given for the solvolysis of acetylsalicylates (50).

It is frequently difficult to determine pH experimentally at high concentrations of hydrogen or hydroxyl ions so as to deduce the bimolecular rate constants k_1 and k_6 as from plots of Eqs. 9 and 12. However, stoichiometric acid concentrations can be converted to pH values corresponding to hydrogen ion and hydroxyl ion activities from the data on electrolytes in the literature (2, 89, 149).

For example, in concentrated hydrochloric acid solutions

$$pH = -\log f_{HCl}[HCl] \quad \text{(Eq. 14)}$$

where the mean activity coefficient of hydrochloric acid, f_{HCl}, is given at various temperatures, solvent mixtures, and HCl concentrations (89, 149). This definition of pH has been used in the study of the acid catalyzed solvolysis of hydrocortisone hemiester in alcohol-water mixtures (59) and of N-acetyl-*p*-aminophenol (114).

In the study of the acid catalyzed solvolysis of the antibiotic streptozotocin (57), the pH calculated from the activity coefficients (89) and the hydrochloric acid concentrations can be compared to the observed pH values of the solutions. Reasonable agreement is obtained above a pH of 1.2 and within 0.15 pH units below that value.

Similarly

$$pH = pKw - pOH = pKw + \log f_{NaOH}[NaOH] \quad \text{(Eq. 15)}$$

where f_{NaOH}, the mean activity coefficient of sodium hydroxide, and pKw are given in the literature for many solvent mixtures, temperatures, and solutes (89, 149). This definition of pOH has been used in the study of the alkaline hydrolysis of the antibiotics psicofuranine (56) and actinospectacin (69), where the k_6 values determined from the calculated hydroxyl ion activities and the stoichiometric [NaOH] have been compared.

Frequently, data exist in the literature to permit prediction of pH of buffer solutions under the conditions of preparation. An example of this procedure is in the study of barbital degradation in an ammonia buffer system (80) where the dissociation constants for the ammonia buffer system (8) and barbital (128) are given in the literature as a function of temperature. By the use of available activity coefficients (89, 115) and discreet approximations (7), the pH at various temperatures was calculated from the equation for the thermodynamic equilibrium constant for the buffer used. It is interesting to compare this approach (80) in the determination of the pH for the dependency of barbital kinetics to that of phenobarbital kinetics where the pH was determined experimentally (88).

Another method of characterizing hydrogen or hydroxyl ion concentrations is by the spectrophotometric determination of the degree of dissociation of a weakly acidic or basic indicator of known pKa where the spectrophotometric absorptivities of the charged and uncharged forms differ (73). The [OH⁻] calculated thusly has been used to determine the kinetic dependencies of the solvolysis of homatropine and atropine methyl-bromides (151).

Specific methods of calculating hydrogen and hydroxyl ion concentrations or activities for the prediction of the apparent first-order rate constants for the degradation of various pharmaceuticals are indicated in Table I. Methyl *dl*-α-phenyl-2-piperidylacetate (170) has exhibited specific acid-base catalyzed solvolysis where the log *k vs.* pH profile is given in Fig. 3 and the pH of minimum degradation is *ca.* 3. Specific acid-base catalyzed solvolysis has also been exhibited by the alkyl *dl*-α-(2-piperidyl)-phenyl-

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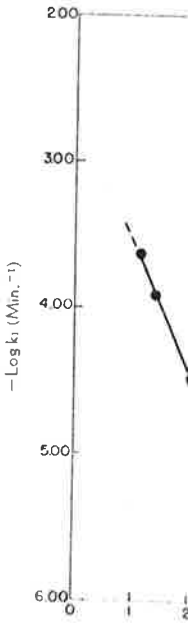

Fig. 3.—pH Dep
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TABLE

Compoun

Psicofuranine

Actinospectacin

Streptozotocin

Streptovaricin
Chloramphenicol

Acetylsalicylic acid
β-Cyclopentylpropion
acid
Trimethylacetylsalicy
Diethylacetylsalicylic

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acetates with pH *ca.* 3 of maximum stability (155) and N-acetyl-*p*-aminophenol with a pH 5–6 of maximum stability. The minimum of the catenary as exemplified in Fig. 3 and the pH of minimum overall rate at the isocatalytic point can be calculated from the specific acid-base catalytic constants as demonstrated in the literature

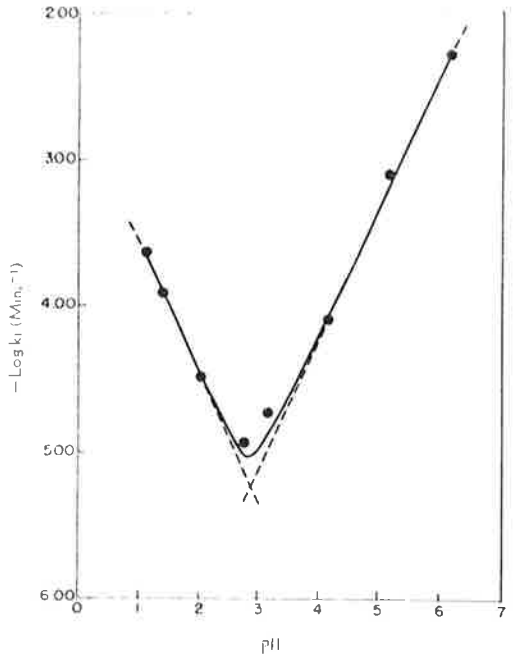

Fig. 3.—pH Dependency of the hydrolysis of methyl DL-α-phenyl-2-piperidylacetate at 80° [Figure 5 of Siegel, S., Lachman, L., and Malspeis, L., This Journal, **49**, 431(1959) (170).]

(35, 113, 170). Many other examples of such catenaries are given in books on kinetics and mechanisms of reactions (2, 9, 43, 104, 123).

Catalysis by Solvent.—If the apparent first-order rate constants calculated from Eqs. 8 or 13 do not agree with the observed values for intermediate pH ranges, then catalysis by solvent or solutes, intramolecular catalysis, or ionic strength must be considered as contributing to the overall rate.

The simplest modification of Eq. 8 is

$$k = k_1[H^+] + k_6[OH^-] + k_2 \quad \text{(Eq. 16)}$$

When the k plotted against $[H^+]$ has an intercept which cannot be attributed to hydroxyl ion attack, a solvent catalytic effect k_2 is implicated. This is further confirmed when k plotted against $[OH^-]$ has the same intercept or when

$$k = k_2, k_1[H^+] \sim 0 \sim k_6[OH^-] \quad \text{(Eq. 17)}$$

Such solvent attack on a degradable species is frequently apparent from the log k-pH profiles as with thiamine (193), pyridine-2-aldoxime methiodide (35), methyl pyrrolidylacetylsalicylate hydrochloride (51), and streptovaricin (53), which is given in Fig. 4.

General Acid-Base Catalysis.—Not only may hydrogen and hydroxyl ions and solvent alone catalyze the decomposition of drugs in solution, but charged species contributed from excipients or buffers may do so also. A general rule is that if solvent does catalyze, other catalytic species exist which can act as acids or bases with catalytic activity, and

Table I.—Predictive Equations for Kinetics of Solvolysis of Drugs

Compound	Dependency of Apparent First-Order Rate Constant, k, in pH Region Studied[a]	Remarks	References
	Antibiotics		
Psicofuranine	$k_1 10^{-pH} f_{SH^+} + (k_4 10^{-pH} + k_6 10^{-pOH}) f_S + k_9 10^{-pOH} f_{S^-}$	*b, d, g, h, i, j, k, l, q, s*	(56, 66)
Actinospectacin	$k_3 10^{-(pKw - pH)} f_{HS} + k_6 10^{-pOH} f_{S^-} + \Sigma_i k_i A_i^-$	*b, d, i, j, k*	(69)
Streptozotocin	$k_1 10^{-pH} f_{SH^+} + (k_4 10^{-pH} + k_5 + k_6 10^{-(pKw - pH)}) f_S$	*b, d, g, h, i, l, m, s*	(57)
Streptovaricin	$k_1[H^+]$ (or $k_1 10^{-pH}$) $+ k_2$	*e, e, g, h, i, l, m, n*	(53)
Chloramphenicol	$k_2 + k_3 10^{-(pKw - pH)}$ (chloride solvolysis)	*b, d, i, s*	(91)
	$k_1[H^+]' + k_2 + k_3 10^{-(pKw - pH)} + \Sigma_i k_i \times HA_i + \Sigma_i B_i$ (amide solvolysis)	*b, d, g, h, i*	(97, 98)
	$k_1[H^+]' + k_2$ where $k_1 = k_1' 10^{m/D}[H_2O]$	*b, e, g* / *t*	(132)
	Salicylates		
Acetylsalicylic acid	$k_1 10^{-pH} f_{HS} + (k_4 10^{-pH} + k_5 + k_6[OH^-]) f_{S^-}$	*d, e, f, g, h, i, j, k, l, m, q, t*	(34, 50, 58)
β-Cyclopentylpropionylsalicylic acid			
Trimethylacetylsalicylic acid	where $k_5 = k_5' + k_5''[C_2H_5OH]/[HOH]$	*t*	(50, 58)
Diethylacetylsalicylic acid			

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