Computerized Extrapolation of Hydrolysis Rate Data

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The program RATE was developed to aid in the extrapolation and interpretation of hydrolysis rate data to a format that is useful for environmental risk assessment. Hydrolysis data typically are reported in the literature as pseudo-first-order rate constants at the temperature and pH of the reaction medium used to obtain the kinetic information. The utility of RATE lies in its ability to estimate first-order rate constants at other values of temperature and pH and to convert pseudo-first-order rate constants to second-order rate constants. RATE will also calculate the half-life for the overall reaction, including neutral-, base-, and acid-mediated hydrolysis, at any selected temperature and pH. RATE, programed in FORTRAN, is used to systematically analyze data for entry in FATE, a comprehensive environmental fate constants information system database.

INTRODUCTION

Estimates of the rates of transport and transformation of chemicals are important to scientists, engineers, and others involved with managing the production and disposal of chemicals relative to environmental risk minimization. For many chemicals, hydrolysis is an important transformation process. Hydrolysis is a reaction of a chemical with water in which a new carbon–oxygen bond is formed in place of a carbon–X bond. The result of this reaction is one or more new chemicals that may or may not react further with water. Comprehensive discussions of hydrolysis mechanisms are available in the literature.[1–4]

The increased necessity for assessing the potential risk posed by chemicals to human health and to ecosystems has resulted in the development of mathematical models and other procedures that estimate the transport and transformation of chemicals in aqueous environments. Two models currently in use that exemplify the need for fate data are EXAMS[5,6] and WASP.[7] These models require the input of the following hydrolysis parameters for each chemical: second-order acid and base rate constant and a first-order neutral rate constant at 25 °C; activation energies of the acid, base, and neutral hydrolysis processes; the half-life of the reaction at pH 7; and the corresponding preexponential factor A from the Arrhenius equation[8]

$$k = Ae^{-E/RT} \tag{1}$$

where k is the reaction rate constant, A is the preexponential factor that represents the rate of reaction in the absence of a temperature constraint (i.e., $k = A$ when $T = \infty$), E is the Arrhenius activation energy, R is the gas constant, and T is the reaction temperature in Kelvin.

Hydrolysis rate constants are determined experimentally by monitoring the disappearance of a chemical over time in a buffered medium at a constant temperature and are commonly reported in the literature as pseudo-first-order rate constants at the pH and temperature of the reaction medium. Frequently, data are taken under extreme conditions of temperature and/or pH to accelerate for measurement purposes the transformation of chemicals that have long half-lives. That is, half-lives of months or years are reduced to hours or days.

A number of kinetic runs, preferably from several temperature and pH values, provide the experimental data necessary to quantify the effects of temperature and pH on the rate of reaction of a chemical. Data are measured over a range of pH values to determine whether the chemical is susceptible to acid- and/or base-mediated hydrolysis, or whether hydrolysis is independent of pH. Measurements at two or more temperatures within each pH range are used to determine the acid, base, and neutral activation energies that contribute to the overall reaction. Analysis of the reaction products may be useful for confirming that the observed reaction between the chemical and water is hydrolysis and to assess the environmental impact of the chemical reaction.

The need for hydrolysis data at environmentally relevant conditions of temperature and pH led to the development of the RATE program. The utility of RATE lies in its ability to estimate first-order rate constants at temperature and pH values other than those at which the measurements were made in the laboratory and to convert pseudo-first-order rate constants to second-order rate constants when the rate of reaction is sensitive to acid- and/or base-mediated hydrolysis. RATE also calculates an activation energy from a linear regression when the data array contains hydrolysis rate constants that have been measured at two or more temperatures. Additionally, use of RATE leads to consistency in the analysis of laboratory data, reduces the chance for error involved in the repetition of manual calculations, and allows the standardization of chemical hydrolysis rate data.

RATE PROGRAM

The menu-driven FORTRAN program RATE transforms pseudo-first-order hydrolysis rate constant data determined at a known pH and temperature to equivalent second-order acid and base rate constants and a first-order neutral rate constant at a selected temperature. The formula for the overall hydrolysis rate constant is

$$k_{\mathrm{h}} = k_{\mathrm{a}}[\mathrm{H^+}] + k_{\mathrm{n}} + k_{\mathrm{b}}[\mathrm{OH^-}] + \sum_i k_{\mathrm{HA}}[\mathrm{HA}] + \sum_j k_{\mathrm{B}}[\mathrm{B}] \tag{2}$$

where k_{h} is the observed or estimated rate constant for hydrolysis at a specific and constant pH and temperature, usually pH 7 and 25 °C, k_{a} and k_{b} are second-order rate constants for specific acid- and base-mediated hydrolysis, respectively, k_{n} is the neutral rate constant, k_{HA} and k_{B} are rate constants

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for general acid- and base-mediated hydrolysis, respectively, $[H^+]$ is the hydrogen ion concentration, $[OH^-]$ is the hydroxide ion concentration, $[HA]$ is the ith general acid concentration, and $[B]$ is the jth general base concentration. When hydrolysis is not sensitive to pH, the rate constant k_h is equal to k_n.

The rate of a hydrolysis reaction can be altered by the ionic strength of the buffered medium or the presence of organic solvents or metal ions. Generally, however, chemical additions to the hydrolysis reaction medium are kept as low as possible while still achieving the buffering or extraction requirements of the chemical being analyzed. The concentrations of buffer or solvent can be varied experimentally to test for the effects of buffer or solvent catalysis. RATE does not account for the concentrations of buffers or metal ions or the presence of solvents in the overall rate equation. Rather, the assumption is made that these concentrations are low enough to be included within the overall rate constant k_h. Therefore, the equation for k_h used in RATE becomes

$$k_h = k_a[H^+] + k_n + k_b[OH^-] \qquad (3)$$

Parameter Initialization. RATE allows values used for the input parameters to be established before data are entered for analysis. These include the gas constant R, the Arrhenius activation energy, the input and output time units, and the output temperature for the rate constants.

A default value of 20 kcal mol^{-1} for the activation energy is used in RATE when no measured value is available. This value was chosen because reactions of organic chemicals generally have an activation energy in the range of 10–35 kcal mol^{-1}.[9]

Hydrolysis data that have been measured at two or more temperatures for each pH range may be analyzed by RATE by fitting the data to a linear regression of the Arrhenius equation (eq 1) to determine an experimental value for the activation energy. The rate of hydrolysis of organic chemicals increases with temperature by a factor of approximately 2 for each 10 °C rise in temperature. A plot of the data as log k_h versus $1/T$ produces a straight line, where the intercept equals log A and the slope equals $-E/(2.303R)$. The constant 2.303 converts natural logarithms to common logarithms.

Changes in temperature of a buffered reaction medium affect the hydrolysis rate of reaction by altering the hydrogen and hydroxide ion concentrations and, therefore, the effective pH of the medium. The equilibrium constant for pure water, K_w, changes as a function of temperature. These changes must be accounted for when extrapolating hydrolysis data from one temperature to another. RATE uses the equation developed by Harned and Owen[10]

$$\log K_w = (-6013.79/T) - 23.652 \log T + 64.7013 \quad (4)$$

to account for the increased dissociation of water.

Time units must be specified for the first-order rate constants input for analysis by RATE. The output may be reported in one or several reciprocal time units.

The input temperature consists of the temperature of the reaction medium that was used to measure each rate constant. If an output temperature other than the default value of 25 °C is required, it must be initialized.

Plot of Standardized log k_h versus pH. The input data array for RATE includes three values for each rate constant: the observed pseudo-first-order hydrolysis rate constant, the temperature, and the pH of the reaction medium. RATE uses the Arrhenius equation (eq 1), a temperature of 25 °C, and an activation energy of 20 kcal mol^{-1} to transform the data

into a plot of log k_h versus pH at 25 °C. Data points that fall parallel to a line defined by the equation

$$\log k_h = \log k_a - pH \qquad (5)$$

where the slope is -1 represent the acid portion of the overall hydrolysis rate constant. Data points that fall parallel to a line defined by the equation

$$\log k_h = \log k_b K_w + pH \qquad (6)$$

where the slope is $+1$ represent the base portion of the overall hydrolysis rate constant. Data points that fall along a horizontal line defined by the equation

$$\log k_h = \log k_n \qquad (7)$$

where the slope is 0 are insensitive to pH and represent nucleophilic attack by water or neutral hydrolysis. The plot of log k_h versus pH generated by RATE may be used to determine visually the transition points between acid- and/or base-mediated hydrolysis or neutral hydrolysis.

Data that do not fall parallel to one or more of the three lines defined by eqs 5, 6, or 7 in relation to the rest of the data represent a lack of sufficient data points to determine a linear regression or indicate that the reaction mechanism is more complex than traditional first-order hydrolysis. Complex reactions may include the acid/base dissociation of organic chemicals, parallel reactions, consecutive reactions, competitive reactions, two parallel reactions with a common product, reactions involving two or more discrete steps with the formation of an intermediate product, etc.

Extrapolation of Rate Constant Data. RATE converts pseudo-first-order rate constants determined at fixed values of temperature and pH that have been entered in the data array to second-order rate constants. The second-order rate constants, together with the activation energy, may be used to calculate the overall hydrolysis rate constant at other values of temperature and pH.

Extrapolation of hydrolysis data with RATE first requires a subset of data to be analyzed as acid, base, or neutral hydrolysis, depending on the standardized plot of log k_h versus pH. Next, one determines how the activation energy will be calculated by RATE by choosing one of the three options:

(a) For a single data point, or several data points at the same temperature, the activation energy is set to the default value of 20 kcal mol^{-1} or 83.72 kJ mol^{-1}.

(b) A value for the activation energy can be supplied by the user.

(c) A data set that consists of several data points obtained at different temperatures can be analyzed by linear regression of the Arrhenius equation, providing the temperature differential of the data points is at least 10 °C, and providing there are sufficient data points to generate a linear regression.

Extrapolation of Acid Constants. RATE calculates second-order acid rate constants by dividing the pseudo-first-order rate constant by the hydrogen ion concentration $[H^+]$ at the experimental temperature, using the equation

$$pH = -\log [H^+] \qquad (8)$$

The program computes and reports the second-order acid rate constant at the selected temperature using one of the three options with the activation energy described previously.

Extrapolation of Base Constants. RATE calculates second-order base rate constants by dividing the pseudo-first-order

Table I. First-Order Hydrolysis Rate Constants for 1,1,2,2-Tetrachloroethane Measured in 0.100 M Phosphate Buffered Water from Cooper et al.[11]

pH	k_{obs}, h^{-1}	temp, °C	pH	k_{obs}, h^{-1}	temp, °C
4.97	0.146	95	6.88	0.0259	55
5.00	0.153	95	6.85	0.0123	50
5.01	0.132	95	6.88	0.0162	50
4.95	0.0587	88	6.88	0.0141	50
5.01	0.0705	88	8.84	0.612	45
5.01	0.0617	88	8.85	0.917	45
4.97	0.0230	80	8.86	0.948	45
5.00	0.0219	80	8.97	0.960	45
5.00	0.0212	80	8.82	0.294	40
5.00	0.0052	70	8.87	0.465	40
5.03	0.0055	70	8.92	0.392	40
5.03	0.0055	70	8.86	0.192	35
6.82	0.378	70	8.87	0.184	35
6.87	0.347	70	8.87	0.174	35
6.90	0.358	70	8.88	0.0760	30
6.85	0.0828	60	8.90	0.0777	30
6.86	0.0787	60	8.91	0.0789	30
6.91	0.0915	60	8.91	0.0604	30
6.85	0.0274	55	8.91	0.0894	30
6.88	0.0260	55	8.95	0.0591	30

rate constant by the hydroxide ion concentration [OH$^-$] at the experimental temperature, using the equilibrium expression

$$[OH^-] = K_w/[H^+] \qquad (9)$$

The program calculates a value for K_w at the temperature of the reaction medium with the Harned–Owen equation (eq 4). RATE computes and reports the second-order base rate constant at the selected temperature using one of the three options with the activation energy discussed previously.

Extrapolation of Neutral Constants. First-order neutral rate constants are not affected by the pH of the reaction medium and, therefore, are not adjusted for [H$^+$] or [OH$^-$] in the reaction medium. RATE computes and reports the first-order neutral rate constant at the selected temperature using one of the three options with the activation energy discussed previously.

Calculation of the Half-Life of the Reaction. The half-life of the hydrolysis reaction provides an indication of the overall persistence of the chemical in the environment. The half-life is calculated by RATE from the overall rate constant k_h (eq 3) that includes the appropriate contributions of acid-, base-, and neutral-mediated hydrolysis. The equation for the half-life is

$$t_{1/2} = \ln 2/k_h = 0.693/k_h \qquad (10)$$

SAMPLE ANALYSIS OF HYDROLYSIS WITH RATE

Hydrolysis rate constant data for the chemical 1,1,2,2-tetrachloroethane from Cooper et al.[11] have been analyzed with RATE. Forty first-order rate constants were measured over the pH range 5–9 in 0.100 M phosphate-buffered water at 11 temperatures ranging from 30 to 95 °C (Table I) and were reported as k_{obs} (h^{-1}). The data were extrapolated to first- and second-order rate constants at 25 °C with RATE and have been compared to the results given by Cooper et al.[11] (Table II).

The standardized plot of the data generated by RATE for visual inspection is shown in Figure 1. Cooper et al.[11] found that the reaction for tetrachloroethane was a single base-mediated reaction for the pH range 5–9, with no evidence for the occurrence of neutral- or acid-mediated processes.

Table II. Summary of Data Analyzed by Cooper et al.[11] for the Chemical 1,1,2,2-Tetrachloroethane Compared with an Extrapolation of the Data with RATE

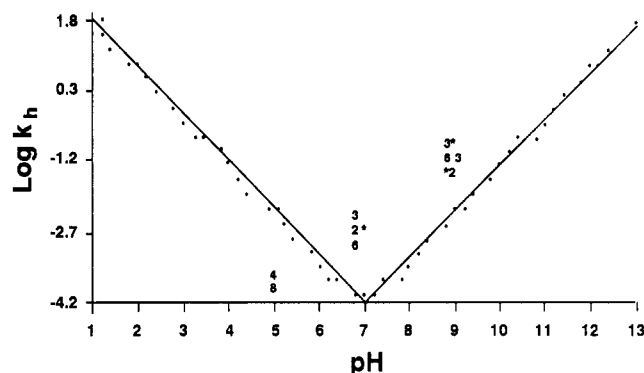|	RATE	Cooper et al.[11]
k_a, 25 °C	0.0/M·yr	0.0/M·yr
k_b, 25 °C	2.6×10^7/M·yr	2.5×10^7/M·yr
k_n, 25 °C	0.0/yr	0.0/yr
k_h, pH 7, 25 °C	2.6/yr	2.5/yr
$t_{1/2}$, pH 7, 25 °C	98 days	102 days
$\log A$	19.04 M^{-1} s^{-1}	$15.87 + 0.54$ M^{-1} s^{-1}
E	88.9 kJ mol^{-1}	$91.1 + 3.4$ kJ mol^{-1}

Figure 1. Plot of the 40 rate constants generated by Cooper et al.[11] that have been standardized with RATE. The log of the first-order rate constants have been calculated with the default values of E, R, and T. Individual data points have been represented by an asterisk, and multiple data points have been represented by the appropriate numerical digit. The two dotted lines represent acid- and base-mediated hydrolysis, where the slopes of the lines equal -1 or $+1$, respectively. Neutral hydrolysis would be represented by data with a slope of zero.

First-order data analyzed with RATE resulted in an overall hydrolysis rate constant at pH 7 for 1,1,2,2-tetrachloroethane of

$$k_h = 0.0 \underset{\text{(acid)}}{M^{-1} \text{ yr}^{-1}} + 2.6 \times 10^7 \underset{\text{(base)}}{M^{-1} \text{ yr}^{-1}} + 0.0 \underset{\text{(neutral)}}{\text{yr}^{-1}} \qquad (11)$$

with a half-life of 98 days, a log A equal to 19.04 and an estimated activation energy for the base rate constant of 88.9 kJ mol^{-1} or 21 kcal mol^{-1} (Table II). Cooper et al.[11] reported comparable values of log A equal to 15.87 and an activation energy for the base rate constant of 91.1 kJ mol^{-1}. In addition, they monitored and identified the products of the reaction as 1,1,2-trichloroethene and HCl.

Technically, hydrolysis is defined as a substitution reaction. However, for certain polyhalogenated aliphatic chemicals, including 1,1,2,2-tetrachloroethane, base-mediated elimination reactions can compete with nucleophilic substitution, accounting for the products that were observed.

The data array reported by Cooper et al.[11] was exceptional in that it contained 40 observed rates of reaction measured at 11 temperatures spanning a 65 °C differential. This allowed the investigators to develop an Arrhenius equation to estimate a reliable activation energy for the hydrolysis reaction.

DISCUSSION

The RATE program was developed to improve the extrapolation and interpretation of hydrolysis rate constant data reported in the literature. Measured pseudo-first-order rate constants are transformed by RATE into a format of second-order acid and base rate constants, a first-order neutral rate constant, and an overall half-life of the reaction at 25 °C or any other selected temperature. There has been an increased demand for hydrolysis data in a format useful for environ-

mental risk assessment in order to compare the expected hydrolysis rates of reaction of diverse classes of chemicals under various environmental conditions and to streamline the extrapolation of laboratory rate constant data to other values of pH or temperature of interest.

Whenever an attempt is made to extrapolate and interpret data from one form to another, problems may arise with the subset of available data. The use of statistical methods, such as linear regression, to obtain a best value for a rate constant are based on the assumption that a great number of measurements are represented in the data array. Unfortunately, this assumption is rarely met in chemical kinetic studies because of the time and expense involved. Therefore, it is important to remember that these treatments of data provide only *estimates* of selected parameters.

Using Cooper's data, we have demonstrated that an analysis of first-order hydrolysis data with RATE corresponds very closely with an independent statistical analysis of the data provided by the authors. A comparison of the results is presented in Table II.

The RATE program is currently used with FATE, an environmental fate constants information system database[12] that contains data for 12 environmental rate and equilibrium constants. Hydrolysis data measured at different values of temperature and pH are extrapolated to standard conditions that are applicable to the processes of environmental risk assessment.

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