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Nonisothermal kinetics — comparison of two methods of data treatment

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Summary

A kinetic study of the acid-catalyzed hydrolysis of *p*-nitrophenyl acetate was carried out by subjecting the reaction mixture to a linear increase in temperature. Two commonly used methods of data treatment were compared to determine the precision and limitations of each. In the first method, the concentration data were transformed by a function dependent on reaction order. The resulting function was fitted to a power series with time. The derivative of this equation provided a rate constant at each temperature. A subsequent Arrhenius plot gave an estimation of the pseudo first-order rate constant at 25°C. After a correction was made for the rate of uncatalyzed hydrolysis, the second-order rate constant for acid-catalyzed reaction was determined. The values of E (activation energy) and Z (pre-exponential factor) determined by this method were dependent on the number of terms used in the polynomial fit (see Table 1). In a second data treatment, the temperature values were fitted to a polynomial with respect to time. Using initial estimates of E and Z, predicted concentrations were evaluated by numerical integration of the rate expression. A sequential simplex algorithm (Deming and Parker, 1978) located values for E and Z that satisfied the least-squares criterion. The integration method generated approximations of E, Z, and the second-order rate constant, k_H, which to 3 significant figures did not vary with the number of polynomial terms. The latter method did, however, require an extensive amount of computer time, depending on the initial estimates used in the algorithm. Both techniques yielded similar rate

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parameter estimates which agreed favorably with literature values (Tucker and Owen, 1982; Eriksen and Stelmach, 1965; Connors, 1963; Bruice and Schmir, 1957).

Introduction

Accelerated rate studies on drug decomposition have been conducted by varying the reaction temperature within a single experiment. In some instances, this method enables estimation of the shelf-life of a pharmaceutical product without resorting to a time-consuming kinetic analysis at several different temperatures (isothermal approach), as is traditionally done. Several time–temperature programs have been used effectively for nonisothermal rate studies. Logarithmic (Rogers, 1963) and reciprocal (Eriksen and Stelmach, 1965) heating schemes enable a simplified mathematical treatment of the data. Limitations and caveats to these methods have been published elsewhere (Cole and Leadbeater, 1966; Carstensen et al., 1968). In more recent studies, computation procedures using a digital computer have alleviated the need for a fixed time-temperature profile. In studies by Zoglio et al. (Zoglio et al., 1968, 1975; Maulding and Zoglio, 1970), computer-generated curves based on a rate model were compared to a plot of the experimental data (concentration versus time). Other investigators (Waltersson and Lundgren, 1982; Hempenstall et al., 1983) fitted concentration and time data to a polynomial based on the integrated rate model. The first derivative of this function gives a rate constant at each temperature (derivative approach). Another method (Madsen et al., 1974) relies on a more direct fit of the data to the integrated rate expression (integration approach). In this report, the latter two methods of data analysis are compared to determine precision and accuracy of each. In previous reports describing the derivative method (Waltersson and Lundgren, 1982; Hempenstall et al., 1983), the basis for determining the number of polynomial terms used in the regression was not clearly defined. In this paper, it will be demonstrated that the Arrhenius parameters obtained using this method are dependent on the number of polynomial terms chosen. A criterion for choosing the number of terms is established that provides the best consistency between the results obtained using both methods.

Theoretical

Derivative method

In pharmaceutical formulations in which the drug is in dilute solution, and in which decomposition is irreversible, the decomposition rate is commonly regarded as a pseudo rate-order phenomenon, expressed by:

$$d[D]/dt = -k[D]^n \tag{1}$$

where [D] is the residual drug concentration, k is the observed rate constant, and n is the reaction order. Assuming the applicability of the Arrhenius law, Eqn. 1 can be expressed as:

$$d[D]/[D]^n = -Z\, e^{-E/RT}dt \qquad (2)$$

where E is the observed Arrhenius activation energy, Z is the pre-exponential factor, R is the ideal gas constant, and T is the reaction temperature. If the temperature is linearly increased, Eqn. 2 can no longer be integrated exactly. The integrated expression is thus rewritten as:

$$\int_{D(0)}^{D(t)} d[D]/[D]^n = -Z\int_0^t e^{-E/RT(t)}dt = -ZI_t \qquad (3)$$

where I_t is the integral of the exponential function. For a first-order reaction, Eqn. 3 becomes:

$$\ln[D] = \ln[D]_0 - ZI_t \qquad (4)$$

A solution to Eqn. 4 in terms of E and Z can be approximated by expanding the exponential function, $f(t) = \exp(-E/RT)$, as a Taylor series about $t = 0$:

$$f(t) = f(0) + \sum_{k=1}^{n} f^k(0)(t^k/k!) + R_n(t) \qquad (5)$$

where $f^k(t)$ is the kth order derivative of f(t). $R_n(t)$ is the remainder between the series limit (at $n = \infty$) and the truncated series (for n terms):

$$R_n(t) = f_{n+1}(w)[t^{n+1}/(n+1)!] \qquad (6)$$

The function f(w) is an unknown quantity for which $0 < w < t$. At $t = 0$, f(0) and all derivatives of order k are constants. The expansion is therefore a power series with respect to time. Integration produces another power series, which when substituted into Eqn. 4 gives:

$$f(D) = \ln[D] = \sum_{i=0}^{n+1} b_i t^i + g(w)[t^{n+2}/(n+2)!] \qquad (7)$$

where the b_i are series coefficients, $b_0 = \ln[D]_0$, and g(w) is a function with respect to w. For a first-order reaction, Eqn. 1 can be expressed in the alternative form:

$$d\ln[D]/dt = -k \qquad (8)$$

Taking the derivative of Eqn. 7 leads, therefore, to another polynomial expression relating k to time:

$$d\ln[D]/dt = \sum_{i=0}^{n} (i+1)b_{i+1}t^i + h(w)[t^{n+1}/(n+1)!] = -k. \qquad (9)$$

where h(w) is a function of w. Carrying out the integration on the left side of Eqn. 3 with n = 0 (zero order) and n = 2 (second order) results in the following functions, f(D):

$$f(D) = D \text{ (zero order)} \tag{10}$$

$$f(D) = -1/D \text{ (second order, } D + D \rightarrow \text{product)} \tag{11}$$

$$f(D) = [1/(C_0 - D_0)]\ln[(C_0 - D_0 + D)D_0/DC_0] \quad \text{(second order, } C + D \rightarrow \text{product)} \tag{12}$$

C_0 and D_0 are the initial concentrations of the two reactant species, and C_0 is the concentration of the reactant that is in excess. In the derivative approach, enough polynomial terms are chosen to closely approximate the relationship between f(D) and time. By the ratio test (Schwartz, 1967) $R_n(t)$ can be shown to approach zero as n becomes large. Deviations between the truncated Taylor series and f(t) become greater as t becomes much greater than zero.

The polynomial expression therefore leads to the largest truncation error in k at large values of time. One objective in choosing a polynomial is to choose enough terms such that the truncation error, $R_n(t)$, is within the expected random error. It is also important, however, to choose a polynomial whose derivative has as narrow an error distribution as possible.

Integration method

The other method utilized in this study involves direct evaluation of the integral expression on the right side of Eqn. 3. If T(t) is approximated as a power series, the resulting polynomial enables an iterative evaluation of the integral, I_t, given an initial estimate of E. With initial estimates of E and Z, a least-squares optimization can be used to find the best estimates for these parameters. That is, the problem is to minimize S:

$$S = \sum \{[D]_{\text{observed}} - [D]_{\text{predicted}}\}^2,$$

$$\text{where } [D]_{\text{predicted}} = [D]_0 \exp(-ZI_t) \tag{13}$$

If the temperature–time profile is simple (linear, for example) the problem of divergence of the polynomial at large values of t associated with higher-order terms is minimized.

Programming

Two programs were written in Fortran 77 to carry out the computations summarized in the last section (both programs can be provided upon request).

Program NISO. The derivative method is used to estimate rate constants. A linear least-squares fit of ln k versus 1/T generates values for E, Z, and k at 25°C, as well as all associated standard deviations.

Program NISO3. The integration method is used to obtain E and Z. The integrals, I_t, are evaluated using Simpson's method. An iterative least-squares optimization using a sequential simplex algorithm is employed.

A flow chart for program NISO is shown in Table 1. All real variables are 64-bit precision, and only double precision functions are used. Data (concentration, time and temperature) are read from a user-defined data file stored under the variable name FTITLE. Temperature is expressed in degrees Celsius, and time is entered in minutes.

The number of data is entered from the keyboard, and a summary of the input is printed out. The temperature is converted to kelvins, and time is changed to hours to prevent overflow errors. Additional input data (reaction order and the number of polynomial terms to be used in the fit) are entered interactively via the console. If a reaction order of two is entered, additional input (initial concentration of major reactant and minor reactant) is required. The concentration data are transformed by the appropriate concentration function, f(D), depending upon the reaction order chosen. Once the proper transformed data set is established, a least squares polynomial regression is carried out.

Subroutines SUMPO, SIMEQ3, AND SWAP (Table 1) are used in the polynomial fit, which can generate polynomials up to 14th order. Subroutine SUMPO calculates the sums $\Sigma\, t_i^{2k}$, and $\Sigma\, t_i^k f(D)_i$, for values of k from zero to m, where m is the order of the polynomial. These sums are used to generate the normal simultaneous equations needed to determine the polynomial coefficients. Subroutine SIMEQ3 solves these simultaneous equations by the Gauss-elimination procedure (Daniel, 1981). Subroutine SWAP exchanges rows of the coefficient matrix, to make the largest column element the pivot element. The calculated polynomial coefficients are then returned to the main program. A standard error of the fit is determined, and expected and observed values of $f(D)_i$ are printed.

Rate constants are determined by taking the negative value of the derivative at each time t (Eqn. 8). Subroutine LINFIT determines the two-parameter least-squares fit of ln k vs 1/T. Errors in the fit (estimate, slope, and intercept) are also determined by LINFIT. After returning to the main program, the activation energy (E), pre-exponential factor (Z), and rate constant (k) at 25°C are calculated. Associated errors are also listed. All deviations of the transformed data ($f(D)_i$ and t) from the polynomial regression are checked for unusually large values. If a residual greater than 3 standard deviations is detected, an asterisk is printed beside that value.

A flow chart for program NISO3 is shown in Table 2. Data are entered from a user-defined file, as in program NISO. After entering the number of data points and polynomial terms from the keyboard, a summary of the input data is printed out. The temperature data are converted to kelvins, and the time to hours to prevent overflow error. The time and temperature data are then subjected to a least-squares polynomial fit (up to 14th order).

Program NISO3 utilizes Simpson's method without end corrections to find I_t for

TABLE 1

PROGRAM NISO (FLOW CHART)

Main program	Subroutine	Files
(1) Input (file name, data from file, number of data, number of polynomial terms, and reaction order).	----› ‹----	User-defined data file (stored under FTITLE) (residual drug concentration, time, temperature).
(2) Output (print out input data).		
(3) Convert temperature in degrees Celsius to kelvins, and change time in minutes to hours.		
(4) Determine $f(D)_i$ (dependent on order).		
(5) Polynomial fit of $f(D)_i$ versus time.		
(a) Calculate Σt_i^k and $\Sigma\ t_i^k f(D)_i$	⇄ SUMPO	
(b) Set up coefficient matrix.		
(c) Solve simultaneous equations.	⇄ SIMEQ3 ⇄ SWAP	
(6) Determine $d[f(D)]/dt$ and determine rate constants.		
(7) Do Arrhenius plot using linear least-squares regression, and determine errors associated with fit.	⇄ LINFIT	
(8) Determine Arrhenius parameters from slope and intercept of regression line.		
(9) Output:		
(a) E, Z, and k at 25°C.		
(b) Errors		
1. Standard deviation of the estimate		
2. Standard deviation of the intercept		
3. Standard deviation of the slope		
4. Standard deviation of ln k at 25°C		
5. Correlation coefficient		
6. χ^2 statistic		

each value t. Subroutines SIMI and SUMI serve this purpose. SIMI obtains an integral over each time interval, $(t_{i+1} - t_i)$, where t_{i+1} and t_i are experimental values. Each interval is iteratively split into subintervals by successive halving. After each iteration, the integral is re-evaluated and tested to determine convergence:

$$|I_{k+1} - I_k| < \lambda I_{k+1} \qquad (14)$$

TABLE 2

PROGRAM NISO3 (FLOW CHART)

Main program	Subroutines	Files
(1) Input (file name, data from file, number of data, number of polynomial terms, reaction order).	– – – → ← – – –	User-defined data file (stored under FTITLE) (Stores residual drug concentration, time, and temperature).
(2) Output (print out summary of input data).		
(3) Convert time to hours, and temperature to kelvins.		
(4) Set up normal equations used in polynomial fit of temperature versus time.	⇄ SUMPO	
(5) Solve for normal equations to obtain polynomial coefficients.	⇄ SIMEQ ⇄ SWAP	
(6) Calculate predicted temperature values for each time t, and print observed and predicted temperatures.		
(7) Input reaction order, scaling factors for generation of initial simplex, initial estimates of E and Z, and the maximum number of iterations to be used in the simplex algorithm.		
(8) Generate initial simplex basis.		
(9) Test for convergence (if convergence condition is met, go to step no. 17).		
(10) Find worst point.	⇄ SORT	
(11) Generate new basis by inversion.	⇄ REFLECT	
(12) Calculate sum of residuals squared.		⇄ SIMI
	⇄ SUMI ⇄ SUMRES	
(13) Compare new response to basis response.		
(14) Generate new basis set (using new inversion rule).	⇄ REFLECT	
(15) Determine sum of residuals squared.		⇄ SIMI
	⇄ SUMI ⇄ SUMRES	
(16) Go to step no. 9.		
(17) Calculate standard deviation of the estimate.		
(18) Determine residuals, write tables for predicted and observed data, E, and Z values.		

where I_k and I_{k+1} are successive approximations of the integral I_t over the interval t_i to t_{i+1}. The factor λ is a tolerance factor which is set up in a DATA statement. Different values of λ were used, and the resulting sets of rate parameters were compared. No differences in the first 5 significant figures were observed when λ was less than 10^{-3}.

Choosing smaller tolerance limits resulted in excessive computational time. Because the relative standard error of measurement was about 2%, a tolerance factor of 0.001 yielded integrals with truncation errors less than the expected measurement error. Subroutine SUMI sums the integrals between zero time and any given time, t. With values of I_t obtained from a starting estimate of E, an estimate of Z was used to determine predicted concentrations (Eqn. 13) and the sum of the squared residuals, S.

Program NISO3 uses a variable-size simplex routine (Deming and Parker, 1978) which ensures that the simplex will automatically contract as it approaches the optimum solution, $(\hat{E}, \hat{Z})$. The reader is referred to this paper for a summary of the contraction and expansion rules. Subroutine REFLECT carries out the vertex inversions. Subroutine SUMRES calculates S, the sum of the squared residuals, for each new point, (E_k, Z_k). SUMRES uses values of I(t) calculated by the integration routines SUMI and SIMI. The vertices of each simplex reside in a stack containing the 3 E parameters, E(1) through E(3), the 3 Z parameters, Z(1) through Z(3), and the 3 corresponding responses, S(1) through S(3).

Subroutine SORT ranks the subscripted E and Z values from the worst response, S(1), associated with point (E_1, Z_1), to the best response, S(3), associated with point (E_3, Z_3). After an inversion is made, the inversion rule is modified according to the response at the new point, and point (E_1, Z_1) is again inverted to point (E_{k+1}, Z_{k+1}), using the modified inversion rule. If (E_{k+1}, Z_{k+1}) gives a lower response than (E_k, Z_k), then the previous worst point, (E_1, Z_1), is replaced with (E_{k+1}, Z_{k+1}), S(1) is replaced with S_{k+1}, and subroutine SORT is reintroduced using the new variables in the stack. If (E_k, Z_k) gives a better response than (E_{k+1}, Z_{k+1}), then point (E_1, Z_1) is replaced with (E_k, Z_k), and S(1) is replaced with S_k. Additional rules ensure contraction of the simplex if S_k is greater than S(2), the next-to-worst response. This process is continued until the convergence criterion is met:

$$|S_k - \mathrm{SLOW}| < (\mathrm{TOL} \times S_k), \text{ and } S_k < \mathrm{SLOW} \tag{15}$$

where S_k is the most recent response, SLOW is the lowest previous response, and TOL is a tolerance factor.

When convergence is achieved, control is transferred out of the iterative loop and the lowest values of E and Z are printed, as is a table comprised of calculated and observed concentration values, their associated residuals, and a standard deviation of the fit. An asterisk is typed beside each residual that falls more than 3 standard deviations from the regression curve.

Materials and Methods

The HPLC system used in this study consisted of an Altex Model 110A pump, Rheodyne injector, Kratos Spectroflow 757 UV detector, and an Alltech C-18 column (10 μm, 4.6 mm i.d.). Methanol/water (1 : 1) was used as the solvent. The detector monochrometer was set at 318 nm, and the flow rate was adjusted to 2.0 ml/min. A series of *p*-nitrophenyl acetate standards (2–50 mg/l) were prepared. The detector response was linear in this region ($r = 0.9998$). Repeated 20 μl injections (20 mg/l) resulted in a relative standard deviation of 1.5%.

Experiments 1 and 2 were conducted as follows. A 2-liter flask was charged with 800 ml of standardized 0.25 N hydrochloric acid, and was set up in the heating bath as shown in Fig. 1. The flask was immersed in the bath up to the bottom of its middle neck. The temperature programmer (Honeywell Model 770111 digital control programmer) was set to hold the bath temperature at 35°C for 1 h. An argon atmosphere was established within the reaction vessel. After the hour had elapsed, the temperature was increased at an average rate of 4°C/h. Two minutes after the

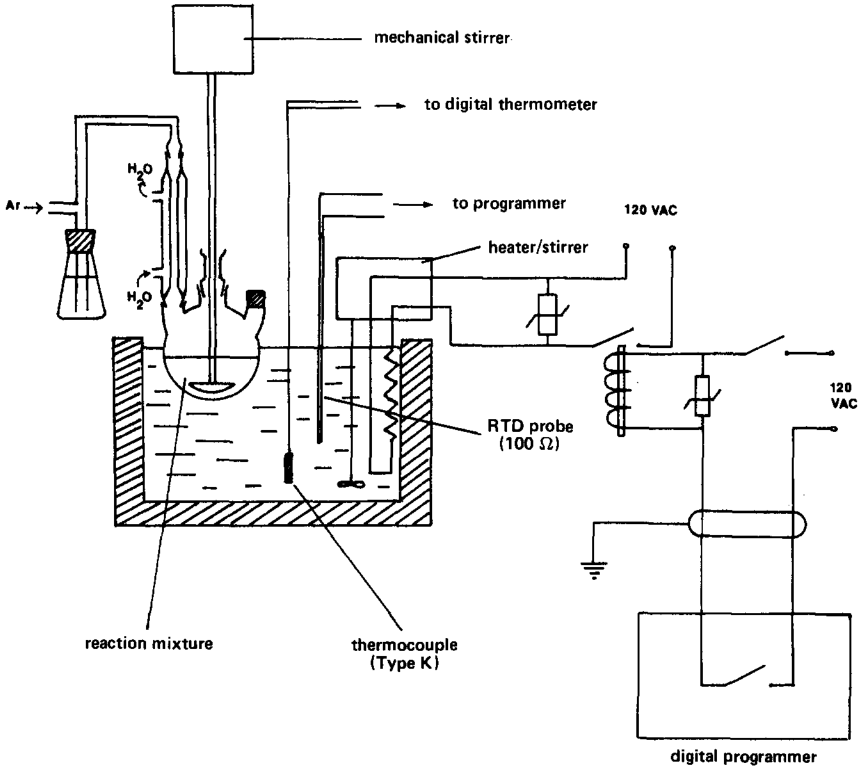

Fig. 1. Heating apparatus.

temperature program started, a solution of 100 mg of *p*-nitrophenyl acetate (Aldrich, purified by recrystallization from ethanol) in 10 ml of anhydrous ethanol was quickly added to the stirred acid solution. After another minute, a 0.2 ml sample of the reaction mixture was transferred by pipette to a small vial and the bath temperature was read from the digital thermometer. A 100 μl syringe was rinsed with an 80 μl portion of the aliquot, and a second portion (80 μl) was loaded onto the sample loop (20 μl). An injection was made and the A/D converter accepting the detector signal was actuated manually. Two peaks eluted from the column, with retention times of about 4.5 and 6.0 min. These corresponded to *p*-nitrophenol and *p*-nitrophenyl acetate, respectively. Accumulation of digital data was complete after about 7 min. Injections were made periodically until the temperature of the bath reached 65°C. At this point over 95% decomposition had occurred.

In experiments no. 2 and no. 3 (Table 4) the bath temperature was monitored throughout the experiment. In experiment no. 1, another thermocouple (type I, Sensortek BAT-12 digital thermometer) was used to measure the temperature within the vessel. The difference between the two temperatures over the course of an experiment was no greater than the limit of precision of both thermometers (±0.1°C). The temperatures measured within the reaction vessel were used in the determination of rate parameters for experiment no. 1.

The concentration of ester in each run was expressed as a fraction of the initial concentration, and the injection times were expressed in decimal minutes. Transformed concentration, time, and temperature (°C) data were transferred to a properly formatted data file for access by the data analysis programs. The input file for experiment no. 3 is shown in Table 3.

Results and Discussion

The hydrolysis of *p*-nitrophenyl acetate has been described by the following rate equation:

$$\text{rate} = \{k_H[H^+] + k_S[H_2O] + k_{OH}[OH^-]\}[\text{ester}] \tag{16}$$

where k_H, k_S, and k_{OH} are second-order rate constants for acid-catalyzed, uncatalyzed, and hydroxide-ion catalyzed hydrolysis, respectively. The Arrhenius parameters defining k_{obs}, the observed rate constant, are a function of those in 3 component rate terms:

$$k_{obs} = Z_{obs} \exp(-E_{obs}/RT) \tag{17}$$

$$= Z_H[H^+] \exp(-E_H/RT) + Z_S[H_2O] \exp(-E_S/RT)$$

$$+ Z_{OH}[OH^-] \exp(-E_{OH}/RT) \tag{18}$$

TABLE 3

INPUT FILE FOR EXPERIMENT No. 3

Concentration (C/C_0)	Time (min)	Temp (°C)
1.00000	0.00	35.9
0.99005	10.00	35.9
0.96720	20.63	37.1
0.95606	31.97	38.0
0.93092	42.15	38.8
0.86849	62.35	40.0
0.79390	91.40	42.1
0.76468	101.17	42.9
0.73930	111.95	43.4
0.70668	123.02	44.0
0.67800	135.28	45.1
0.64663	145.40	45.9
0.61139	155.75	46.5
0.57702	167.40	46.9
0.52852	184.37	48.5
0.49036	196.02	49.0
0.46635	205.58	50.0
0.39549	227.43	51.3
0.36028	239.75	51.9
0.33663	249.50	53.0
0.31164	259.00	53.7
0.26377	277.23	55.0
0.22621	292.07	55.9
0.18650	309.87	57.0
0.14274	332.23	58.8
0.12472	342.70	59.2
0.10759	352.60	60.1
0.09306	362.47	60.9
0.07462	377.07	61.9
0.05749	391.42	62.9
0.03914	410.85	64.1

At low pH in dilute acid the activity of water is approximately unity. Therefore:

$$k_H \approx (k_{obs} - k_S)/[H^+] \tag{19}$$

The parameters k_S and E_S have been determined (Tucker and Owen, 1982) at 65°C for the acid hydrolysis of *p*-nitrophenyl acetate ($k_S = 1.096 \times 10^{-5}$ s^{-1}, and $E_S =$ 14.29 kcal mol^{-1}). Using these values, k_S at 25°C is calculated to be 6.319×10^{-7} s^{-1}.

Table 4 is a summary of the experimental results at one acid concentration, and Table 5 compares the derived k_H and E values with those in the literature. Table 4 compares the results obtained by the derivative and integration methods using different numbers of terms in the polynomial fit. When the number of terms used in the derivative approach was changed, a noticeable effect on the values of E and k_H

TABLE 4

EXPERIMENTAL DATA SUBJECTED TO DERIVATIVE AND INTEGRATION METHODS OF DATA TREATMENT

Experiment	$[H^+]$ (m/l)	No. of data	No. of terms	E (deriv.) [a]	E (int.) [a]	10^5 k_H (deriv.) [b]	$10^5 k_H$ (int.) [b]
1	0.243	17	3	20.6 ± 4.0	17.9	2.7 ± 8.9	4.1
			4	16.7 ± 0.3	17.9	4.7 ± 1.2	4.1
			5	17.9 ± 1.1	17.9	4.1 ± 5.2	4.1
			6	18.3 ± 1.7	17.9	3.9 ± 8.3	4.1
			7	18.6 ± 2.3		3.7 ± 11.0	
			8	21.5 ± 7.5		2.5 ± 35.9	
			10 [d]	19.2 ± 3.3		3.4 ± 15.8	
			12	18.7 ± 8.6		4.2 ± 40.8	
2	0.243	20	4	16.7 ± 1.1		4.8 ± 7.8	
			5	19.5 ± 1.0	17.0	3.0 ± 7.0	4.5
			6	16.2 ± 2.2	17.0	5.2 ± 15.4	4.5
			7	15.9 ± 2.6	17.0	5.6 ± 18.3	4.5
			8 [d]	15.4 ± 4.1		6.0 ± 28.6	
			9	15.5 ± 4.0		6.0 ± 27.7	
3	0.243	31	4	15.6 ± 0.7		5.7 ± 5.4	
			5	17.7 ± 0.5	17.4	4.1 ± 3.9	4.5
			6	17.2 ± 0.2	17.4	4.4 ± 1.8	4.5
			7	18.6 ± 1.3	17.4	3.6 ± 9.7	4.5
			8	19.3 ± 2.1		3.2 ± 15.4	
			10	19.5 ± 2.1		3.1 ± 15.7	
			11 [d]	18.2 ± 1.0		3.8 ± 7.0	
			12	18.1 ± 1.0		3.8 ± 7.3	
			13	17.8 ± 1.3		4.0 ± 9.6	
			15	17.9 ± 1.2		4.0 ± 9.0	

[a] kcal/mol.

[b] Second-order rate constants in $l \cdot mol^{-1} \cdot s^{-1}$ at 25°C, corrected for uncatalyzed hydrolysis.

[c] 95% confidence interval.

[d] Lowest variance in polynomial regression.

was observed. Generally, as the number of higher order polynomial terms was increased beyond a critical value, the error (95% confidence interval) in the Arrhenius plot increased (Table 4). This is explained as resulting from the greater curvilinearity introduced by these terms.

This effect illustrates that although the least-squares polynomial may adquately fit the collected data, there is no guarantee that the first derivative of that function will best satisfy the least-squares criterion, as the error distributions of the two functions are different. This is obvious from the greater radii of curvature in the derivative function.

To show this mathematically, it is assumed that differences between the values predicted from the regression and the transformed concentration data follow a Gaussian distribution. That is:

$$L = b \exp\left[-(P(t) - y_i)^2 / 2\sigma^2 \right], \tag{20}$$

TABLE 5

COMPARISON OF EXPERIMENTAL RESULTS AND LITERATURE VALUES OF E AND k_H

Average values (from integration method):

$\bar{E}_{obs} = 17.4 \pm 0.5$ [a] $\text{kcal} \cdot \text{mol}^{-1}$

$\bar{k}_H = (4.4 \pm 0.1) \times 10^{-5}\ \text{l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ at 25°C

Average values [b] (from derivative method):

$\bar{E}_{obs} = 17.8 \pm 5.7\ \text{kcal} \cdot \text{mol}^{-1}$

$\bar{k}_H = (4.1 \pm 2.1) \times 10^{-5}\ \text{l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ at 25°C

Literature values:

Reference	$E_{obs}(\text{kcal} \cdot \text{mol}^{-1})$	$10^5\ k_H(\text{l} \cdot \text{mol}^{-1}\ \text{s}^{-1})$
Tucker and Owen, 1982	17.1 [c]	4.75 [c]
Connors, 1963		5.3
Eriksen and Stelmach, 1965	18 [d]	
Eriksen and Stelmach, 1965	21 ± 2 [e]	5 ± 1 [e]

[a] 95% confidence interval. Weighted averages are listed (see text).

[b] The values used in determining the average were those obtained from polynomials having the number of terms which gave the best correlations (*r* values) in the Arrhenius plot.

[c] Average of nonisothermal and isothermal data.

[d] Isothermal value (in 0.982 N HCl).

[e] Nonisothermal value (in 0.982 N HCl).

where L is the error probability, P(t) and y_i are the predicted and actual values of the concentration function, and σ is the standard deviation of the data. The value b is a normalizing coefficient equal to $1/\sigma(2\pi)^{1/2}$. It is readily seen that:

$$dL/dt = -(bz/\sigma)[dP(t)/dt]\exp(-z^2/2) \tag{21}$$

where $z = (P(t) - y_i)/\sigma$.

If, for example, a fourth-order polynomial is chosen, then

$$P(t) = a_0 + a_1 t + a_2 t^2 + a_3 t^3 + a_4 t^4 \tag{22}$$

and:

$$dP(t)/dt = a_1 + 2a_2 t + 3a_3 t^2 + 4a_4 t^3 \tag{23}$$

Higher-order terms should approach zero, and $a_0 \simeq 0$ for a first-order process ($C/C_0 = 1.0$). Therefore, $dP(t)/dt > P(t)$ and thus $|dL/dt| > L$. It can also be shown that the truncation error of the derivative is also generally larger than that in the starting polynomial (Pizer, 1975).

In this study, a criterion was therefore established for choosing the correct number of terms. According to the data, the temperature of the bath was constantly increasing. The relationship between the concentration function and time must accordingly exhibit a monotonically decreasing slope (corresponding to a continually increasing rate constant). Therefore, functions that resulted in any negative rate constants were immediately rejected. Finally, the derivative functions which produced the best linear fit (highest negative correlation) in the Arrhenius relationship were chosen. This was in accord with minimization of the error distribution in the derivative.

To test the validity of the above criteria, the results of both methods (integration and derivative) were compared for consistency. The linearity of the temperature-time program allowed a fit with few polynomial terms, and therefore less truncation error was introduced. Numerical integration also averaged out any fluctuation caused by changing the number of terms. This was proven by the fact that the resulting determination of E and k_H was not affected (to 3 significant figures) by varying the number of terms from 3 to 7 in any given experiment. Choosing greater than 5 terms merely resulted in excessive computation time.

The rate parameter estimates obtained in all 3 experiments (derivative approach), which produced the lowest error in the Arrhenius plot, were averaged. Each experimental value was weighted according to the number of data. The weighted means and associated variances were close to those determined from the integration method (see Table 5). This was not the case when rate parameters were determined from polynomials which provided the lowest variance in the concentration–time relationship. This is seen in Table 4, experiment no. 1. Although the lowest variance in the polynomial occurred at $n = 10$ terms, the corresponding derivative produced a much larger error in E and k_H than did the derivative function for $n = 4$.

The first-order rate model produced the highest negative correlation in the Arrhenius plot when the derivative program, NISO, was executed using data from experiment no. 2. Correlation coefficients for each rate model and the corresponding

TABLE 6

EFFECT OF RATE MODEL ON CORRELATION IN THE ARRHENIUS PLOT (DATA FROM EXPERIMENT No. 2)

Reaction order	No. of polynomial terms	Correlation (r)	E (kcal/mol)
0	4	0.508	−4.9
	5	0.477	−4.6
	6	0.472	−4.3
	7	0.329	−2.8
1	4	−0.992	15.6
	5	−0.997	17.7
	6	−0.999	17.2
	7	−0.983	18.6
2	4 [a]	−0.409	14.3
	5 [a]	−0.664	33.1
	6 [a]	−0.951	28.5
	7 [a]	+0.222	40.5
	8 [a]	−0.098	− 0.0

[a] Negative rate constants, which were obtained from the derivative of the polynomial, were ignored.

number of terms used in the polynomial fit are tabulated in Table 6. Negative activation energies were consistently found for the zero-order model using either program NISO or NISO3. Widely varying values for the activation energy (see Table 6) were obtained when a second-order model was employed. Use of the integration method in predicting the best rate model proved to be a very tedious endeavor and was abandoned because of the amount of computer time required.

Conclusions

The hydrolysis of *p*-nitrophenyl acetate was utilized as a model reaction enabling comparison of two methods of data treatment frequently used in nonisothermal rate studies, a derivative and an integral approach. The integral method required much computer time, but was less prone to error transformations caused by differentiation of a 'wavy' polynomial. It was found that the polynomial order which produced the best fit by the least-squares criterion, did not necessarily produce a derivative function having the narrowest error distribution. This resulted in a poor fit in the subsequent Arrhenius plot. Variation in the derivative polynomial occasionally resulted in negative rate constants. Two criteria for choosing the number of terms were therefore adopted: (1) the chosen derivative must decrease monotonically over the time-frame of an experiment; (2) the polynomial resulting in the lowest error in the final least-squares fit should be used in estimating rate parameters.

The average values for E and Z obtained using the above considerations agreed more closely with values obtained from the integration procedure than those determined using the polynomial showing the lowest variance. Both sets of results were in accordance with literature data (Table 5).

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