Single-step Methods for Calculating Activation Parameters from Raw Kinetic Data

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A general procedure is described for calculating activation parameters from raw kinetic data in one step. The method is applicable to any kinetic order of reaction, and to kinetic experiments carried out either at constant temperature (the conventional method) or under conditions where the temperature varies during the course of each kinetic run. The principle of the new method is to substitute the Arrhenius dependence of the rate constant into the integrated form of a kinetic rate equation. This gives an expression for the concentration of a reactant as a function of time, temperature, initial concentration, activation energy, and pre-exponential factor. Using experimental values of the time, temperature, and initial substrate concentration, the amounts of reactant left unreacted under different conditions may be fitted iteratively to obtain the best values of the activation parameters. These agree closely with those calculated by traditional methods, but the new method has the advantage that the calculated uncertainties in the activation parameters reflect directly the scatter in the experimental observables.

The calculation of activation parameters from raw kinetic data traditionally involves two steps: determination of rate constants for a series of experiments each carried out at a constant temperature; and an Arrhenius (or Eyring) plot of the logarithms of the rate constants against the reciprocals of the temperatures. Considering the case of a first-order reaction as an example, two graphical plots (or two linear regressions) corresponding to equations (1) and (2) are needed.†

$$\ln[\mathrm{X}] - \ln[\mathrm{X}]_o = -kt \qquad (1)$$

$$\ln k = \ln A - E_a/RT \qquad (2)$$

Using the two-step method, it is very difficult to make a proper assessment of the uncertainties in the activation parameters. First, there is the issue of transforming the uncertainties in the values of [X] and k into the uncertainties in their logarithms. Secondly, it is not straightforward to incorporate the uncertainties in the rate constants into the uncertainties in the activation energy. Most often, reported uncertainties in activation energies reflect only the deviations of the individual ln$k$ points from the line of best fit to equation (2); they do not reflect the scatter in the originally observed quantities, namely time, temperature, and reactant concentration. An objective of this work was to develop a mathematical protocol that would allow the uncertainties in the activation parameters to reflect directly the scatter in the experimental observables.

In this paper, we report a method whereby the above objective has been reached. Our method is applicable to reactions of any kinetic order, and can be used not only with conventional kinetic experiments, in which each run is carried out at constant temperature, but also with kinetic experiments where the temperature varies during the course of the run.[1–3] We have compared the traditional two-step and the new one-step procedures for calculating activation parameters both with kinetic data obtained in our own laboratory and with kinetic data from a number of cases obtained from the literature.

Development of the Mathematical Protocol

Constant-temperature Experiments.—If we eliminate k from equations (1) and (2), and write the result in exponential form, we obtain equation (3). If experimental data are available at

$$[\mathrm{X}] = [\mathrm{X}]_o e^{-Ate^{-E_a/RT}} \qquad (3)$$

several temperatures, it is possible to fit [X] to the known values of $[\mathrm{X}]_o$, t, and T in order to choose the parameters A and E_a which provide the best fit. The important distinction between this procedure and the conventional two-step method is that the data for all the different temperatures are fitted simultaneously. We used an iterative non-linear least-squares fit based on a local linear approximation using a standard multiple linear regression package. In practice, we made the following amendments to the procedure: (i) instead of fitting to A (which involves the long extrapolation to $T = \infty$) we fitted a parameter k_{ref} which was defined at a convenient temperature T_{ref} within the temperature interval of the experiment. The pre-exponential factor was then calculated at the very end of the fitting procedure by making use of equation (4), which defines k_{ref}. This

$$k_{ref} = Ae^{-E_a/RT_{ref}} \qquad (4)$$

amendent greatly reduces the statistical correlation between the fitted values of A and E_a. (ii) The second amendment, used only for first-order data, was to treat $[\mathrm{X}]_o$ as well as k_{ref} and E_a as a parameter to be determined in the least-squares fit. This is especially advantageous if early points in the run are in error owing to thermal equilibration not being complete.

The previous paragraph illustrated the procedure for the case of the first-order reaction. We will now generalize. For most simple kinetic models, it is possible to write a function describing the dependence of [X] (as the dependent variable) upon the time t, the initial concentration(s), the temperature T,

$$[\mathrm{X}] = f(t; [\mathrm{X}]_o, T, E_a, k_{ref}) \qquad (5)$$

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† Throughout this paper, the symbols have the following meanings: [X] = concentration; $[\mathrm{X}]_o$ = initial concentration; k = rate constant; t = time; T = temperature; E_a = Arrhenius activation energy; A = pre-exponential factor. All integrations are assumed to be taken over the time limits $0 \longrightarrow t$.

and the fitted parameters E_a and k_{ref}. For kinetic orders higher than first, $[X]_o$ must be measured experimentally.

The fit of [X], t, and T to E_a and k_{ref} is achieved using a group of FORTRAN subroutines called MLREGR.* A driver program is necessary to convert the experimentally determined parameters ([X], t, and T) into the form that is needed for the multiple linear regression performed by MLREGR and to supply the partial derivatives $\partial[X]/\partial E_a$ and $\partial[X]/\partial k_{ref}$; the multiple regression procedure optimizes the values of E_a and k_{ref} so as to minimize the values of the residuals (the differences between the calculated and observed values of [X]) using these partial derivatives. In this paper we have investigated three common kinetic models: first order, second order $X + Y \longrightarrow$ products with $[X]_o \neq [Y]_o$, and second order for the cases $2X \longrightarrow$ products or equivalently $X + Y \longrightarrow$ products with $[X]_o = [Y]_o$. Chart 1 gives the relevant equations† analogous to equation (5), for the different kinetic models, together with the partial derivatives mentioned previously.

For complicated reactions, it is not always possible to write an expression for [X] as a function of time in closed form. However, the kinetic equation may always be written in the form $d[X]/dt = g([X], t; [X]_o, T, E_a, k_{ref})$. This equation can be solved numerically to obtain $[X](t)$ for given values of $[X]_o$, T, E_a, and k_{ref}, using standard numerical methods such as the modified Euler algorithm.[4] The partial derivatives required for least-squares fitting may be evaluated numerically by finite differences, allowing the methods of the present paper to be used for reactions of any complexity.

First order ($X \longrightarrow$ products)

$$[X] = [X]_o \exp[-Lk_{ref}t] \text{ where } L = \exp\left[-\frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right]$$

$$\frac{\partial[X]}{\partial k_{ref}} = -[X]Lt$$

$$\frac{\partial[X]}{\partial E_a} = \frac{[X]Ltk_{ref}}{R}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)$$

Second order ($X + nY \longrightarrow$ products)

$$[X] = \frac{a[X]_o}{n[X]_o - M[Y]_o}$$
$$\text{where } M = \exp(-aLk_{ref}t) \text{ and } a = n[X]_o - [Y]_o$$

$$\frac{\partial[X]}{\partial k_{ref}} = -\frac{a[X][Y]_oMLt}{(n[X]_o - M[Y]_o)}$$

$$\frac{\partial[X]}{\partial E_a} = \frac{a[X][Y]_oMLk_{ref}t}{R(n[X]_o - M[Y]_o)}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)$$

Dimer-type ($2X \longrightarrow$ products or $X + Y \longrightarrow$ products and $[X]_o = [Y]_o$)

$$[X] = \frac{[X]_o}{[X]_oLk_{ref}t + 1}$$

$$\frac{\partial[X]}{\partial k_{ref}} = -\frac{[X][X]_oLt}{[X]_oLk_{ref}t + 1}$$

$$\frac{\partial[X]}{\partial E_a} = \frac{[X][X]_oLk_{ref}t}{R([X]_oLk_{ref}t + 1)}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)$$

Chart 1. Equations for constant-temperature kinetics

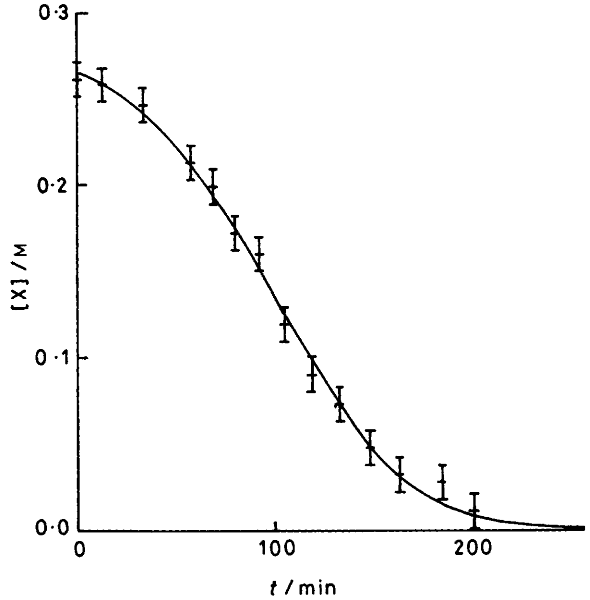

Figure. Variable-temperature [X]–t plot

Variable-temperature Experiments.—A variable-temperature experiment is done by starting the kinetic run at a low temperature where the rate is very slow, and gradually increasing the temperature until the reaction is complete. This creates a plot of [X] *versus* t that has a characteristic sigmoid shape (see Figure). The plot is flat at the beginning of the run where the reaction is slow, curves downwards as the reaction speeds up, and flattens out again as the reaction approaches completion.

The conventional, two-step method of data analysis[1] depends on the fact that the rate constant can be obtained from the slope of the curve. For the case of first order, equation (6)

$$k = \frac{d[X]}{dt} \Big/ [X] \qquad (6)$$

applies. Knowing both the rate constant at various times, and the relationship between time and temperature, a traditional Arrhenius plot can be made, and the activation parameters can be obtained from a single kinetic run. However, the same problems relating to error analysis pertain as in constant-temperature kinetics.

The one-step method of calculation (still for the example of a first-order reaction) was developed by taking equation (6), rearranging, and integrating to give equation (7). Notice that in

$$\int \frac{d[X]}{[X]} = -\int k\,dt \qquad (7)$$

this case $\int k\,dt \neq kt$ because k is not constant in a variable-temperature experiment; it depends on T and hence on t. To integrate, some expression for T in terms of t must be substituted into equation (7). If this expression is more complicated than linear, then the right-hand side of equation (7) cannot be integrated analytically, and numerical integration (quadrature) must be used. For the present the equations will be given with $\int k\,dt$ unintegrated. The equations listed in Chart 1 for the different kinetic orders of reaction are modified as shown in Chart 2.

With the use of numerical quadrature for the right-hand side of equation (7), variable-temperature data may be fitted directly using MLREGR in exactly the same way as for constant-temperature data.

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* MLREGR is a set of FORTRAN subroutines written by R. A. Le Budde and modified by R. J. LeRoy and J. E. Grabenstetter.

† SUP 56705 outlines the derivation of these equations.

First order (X ⟶ products)

$$[\mathrm{X}] = [\mathrm{X}]_o \exp[-k_{\mathrm{ref}}\textstyle\int L\,\mathrm{d}t] \text{ where } L = \exp\left[-\frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_{\mathrm{ref}}}\right)\right]$$

$$\frac{\partial[\mathrm{X}]}{\partial k_{\mathrm{ref}}} = -[\mathrm{X}]\textstyle\int L\,\mathrm{d}t$$

$$\frac{\partial[\mathrm{X}]}{\partial E_a} = \frac{[\mathrm{X}]k_{\mathrm{ref}}}{R}\int L\left(\frac{1}{T} - \frac{1}{T_{\mathrm{ref}}}\right)\mathrm{d}t$$

Second order (X + *n*Y ⟶ products)

$$[\mathrm{X}] = \frac{a[\mathrm{X}]_o}{n[\mathrm{X}]_o - M[\mathrm{Y}]_o}$$

$$\text{where } M = \exp(-ak_{\mathrm{ref}}\textstyle\int L\,\mathrm{d}t) \text{ and } a = n[\mathrm{X}]_o - [\mathrm{Y}]_o$$

$$\frac{\partial[\mathrm{X}]}{\partial k_{\mathrm{ref}}} = \frac{-\mathrm{a}[\mathrm{X}][\mathrm{Y}]_o M}{(n[\mathrm{X}]_o - M[\mathrm{Y}]_o)}\int L\,\mathrm{d}t$$

$$\frac{\partial[\mathrm{X}]}{\partial E_a} = \frac{a[\mathrm{X}][\mathrm{Y}]_o M k_{\mathrm{ref}}}{R(n[\mathrm{X}]_o - M[\mathrm{Y}]_o)}\int L\left(\frac{1}{T} - \frac{1}{T_{\mathrm{ref}}}\right)\mathrm{d}t$$

Dimer-type (2X ⟶ products or X + Y ⟶ products and $[\mathrm{X}]_o = [\mathrm{Y}]_o$)

$$[\mathrm{X}] = \frac{[\mathrm{X}]_o}{[\mathrm{X}]_o k_{\mathrm{ref}}(\int L\,\mathrm{d}t) + 1}$$

$$\frac{\partial[\mathrm{X}]}{\partial k_{\mathrm{ref}}} = \frac{-[\mathrm{X}][\mathrm{X}]_o}{\{[\mathrm{X}]_o k_{\mathrm{ref}}(\int L\,\mathrm{d}t) + 1\}}\int L\,\mathrm{d}t$$

$$\frac{\partial[\mathrm{X}]}{\partial E_s} = \frac{[\mathrm{X}][\mathrm{X}]_o k_{\mathrm{ref}}}{R\{[\mathrm{X}]_o k_{\mathrm{ref}}(\int L\,\mathrm{d}t) + 1\}}\int L\left(\frac{1}{T} - \frac{1}{T_{\mathrm{ref}}}\right)\mathrm{d}t$$

Chart 2. Equations for variable-temperature kinetics

Results

Constant-temperature Experiments.—The results include both first- and second-order reactions. The first-order reactions are the *cis–trans* isomerization of azobenzene studied in our laboratory and, from the literature, the hydrolysis of t-butyl bromide[5] and the decomposition of benzenediazonium chloride.[6] The second-order reactions are the basic hydrolysis of ethyl acetate, carried out in our laboratory, the benzylation of aniline,[7] and the basis hydrolysis of several aliphatic amides.[8] Finally, the first-order decomposition of N_2O_5[9] will be presented in detail as a more complicated example of the application of the one-step method. Complete data, consisting of times and the corresponding concentrations (or values from which the concentrations could be derived) for at least two different temperatures, were given in the original papers. In each case (except that of N_2O_5 which is explained in detail later), the original data were manipulated as little as possible to produce values of [X], or in the cases of azobenzene and benzenediazonium chloride values proportional to [X].

The results are summarized in Table 1. If a value for the activation energy was given in the original paper, it is reported as well. Uncertainties are not given for these reported values, as they were not given in the original papers, and have not been recalculated. In the cases of azobenzene and ethyl acetate, the 'One Step Calc.' value is the one obtained using data obtained in our laboratory. In every case the results of the one-step method agree closely with that of the traditional two-step method (Table 1). In Table 1 and throughout this paper, the quoted uncertainties are given as 95% confidence intervals and not as standard deviations. We re-emphasize that in the one-step approach these uncertainties reflect the fit of the original data ([X], $[\mathrm{X}]_o$, *t*, and *T*) to the kinetic model and not simply the scatter in an Arrhenius plot.

Table 1. Comparison of constant-temperature results for several reactions

Reaction	Total no. data points	Two-step calc. E_a/kJ mol^{-1}	One-step calc. E_a/kJ mol^{-1}	log *A*	Ref.
Azobenzene isomerization	50	87.0[a]	88.8 ± 3.9	10.0	
Bu^{t}Br Hydrolysis	20	86.2	87.1 ± 2.0	10.4	5
$C_6H_5N_2Cl$ Decomposition	129	113.1	113.1 ± 0.2	15.5	6
Ethyl acetate hydrolysis	29	47.2[b]	44.1 ± 2.2	6.8	
$C_6H_5NH_2$ Benzylation	14	56.3	58.5 ± 5.3	5.7	7
Acetamide hydrolysis	27		61.1 ± 4.9	6.3	8
Propionamide hydrolysis	27		61.8 ± 0.4	6.4	8
Butyramide hydrolysis	27		66.6 ± 0.3	6.7	8
Isobutyramide hydrolysis	27		67.7 ± 0.7	6.9	8
N_2O_5 Decomposition	204	103.3	103.3 ± 1.3	13.6	9

[a] Lit.[10] 91—99 kJ mol^{-1}. [b] Lit.[11] 48.1 kJ mol^{-1}.

The first-order thermal isomerization of *cis*-azobenzene was monitored spectrophotometrically, and since the absorbance was proportional to the concentration Abs and Abs_o were used in equation (3) in place of [X] and $[\mathrm{X}]_o$. The data comprised one run with 8 observations at 55.8, two runs with 10 each at 65.6, and two runs with 11 each at 75.5 °C.

The first-order hydrolysis of t-butyl bromide was conducted by Bateman *et al.*[5] in 90% acetone, with determination of acidity (*i.e.* formation of HBr) used to measure the progress of the reaction. The original paper gave the results as %BuOH formed. We used the data in the form [Bu^{t}Br] as calculated by Latham.[12] The data comprised ten observations each at 25 and 50 °C.

The first-order decomposition of benzenediazonium chloride was studied by Moelwyn-Hughes *et al.*[6] in aqueous solution by monitoring the pressure of the nitrogen gas as the reaction proceeded. In this case, *P* and P_o were used as proxies for [X] and $[\mathrm{X}]_o$. The data comprised 33 observations at 60, 67 at 40, and 28 at 15 °C.

The basic hydrolysis of ethyl acetate was carried out in our laboratory, under 'true' second-order conditions, *i.e.* $[\mathrm{EtOAc}]_o \neq [\mathrm{OH}^-]_o$, using the method of Levitt.[13] The progress of the reaction was followed by pipetting aliquots of the aqueous ethyl acetate–NaOH solution into dilute HCl and back-titrating with barium hydroxide. The ionic strength was not kept constant, but the effects of ionic strength on activation energy have been shown to be small.[11] The data comprised 6 observations at −0.2, 8 at 35.0, 6 at 36.7, and 9 at 36.9 °C.

The reaction of aniline and benzyl chloride was studied by Peacock[7] in 99.6% ethanol under true second-order conditions, with the ratio of reactants being *ca.* 4:1. The progress of the reaction was monitored by following the production of chloride ion argentimetrically. The calculated concentrations of aniline and benzyl chloride from the original paper were used in the calculations. The data comprised 6 observations at 35 and 8 at 45 °C.

The basic hydrolyses of several amides were carried out by Crocker *et al.*[8] under pseudo-dimer conditions, using conductivity measurements to follow the reactions. The data comprised 9 observations each at 40.06, 63.2, and 95.9 °C. In Table 1 we show the results for CH_3CONH_2, $C_2H_5CONH_2$, $CH_3[CH_2]_2CONH_2$, and $(CH_3)_2CHCONH_2$. Activation energies were not reported in the original paper.

The thermal decomposition of gaseous dinitrogen pentaoxide, studied by Daniels *et al.*,[9] provides an example which illustrates the versatility of the one-step method. The reaction, equation (8), is complicated by the rapidly established equilibrium between N_2O_4 and NO_2 [equation (9)].

$$N_2O_{5(g)} \xrightarrow{k} N_2O_{4(g)} + \tfrac{1}{2}O_{2(g)} \qquad (8)$$

$$N_2O_{4(g)} \xrightleftharpoons{K} 2NO_{2(g)} \qquad (9)$$

The parameter actually used to monitor the decomposition was the total pressure, P_{tot}. $P_{tot} = P(N_2O_5) + P(O_2) + P(N_2O_4) + P(NO_2)$. Daniels *et al.* calculated the pressure of N_2O_5 remaining at each time and temperature in order to calculate the activation parameters in the conventional way. Since this effectively makes the conventional procedure into a three-step calculation we wished to fit the activation parameters to the observed values of to P_{tot} if possible. This involved finding an algebraic form for equation (10).

$$P_{tot} = f(t;\, P_o,\, T,\, E_a,\, k_{ref},\, K) \qquad (10)$$

The relationship between K and T was already known,[14] and P_o was fitted to the original data using multiple linear regression. The derivation given in Supplementary Publication No SUP 56705 (19 pp)* afforded equation (11) as an intermediate step. Substitution of the Arrhenius equation for k in equation (11) gave the final equation to be fitted by the multiple linear regression program. The success of this approach (calculated E_a essentially identical to the reported value) gives us confidence that the one-step methodology described here can be applied not only to reactions of any kinetic order, but also to the use of any directly observable parameter in the fitting procedure.

$$P_{tot} = \frac{1}{2}P_o(3 - e^{-kt}) + \frac{1}{8K}\left[\sqrt{1 + 16KP_o(1 - e^{-kt})} - 1\right] \qquad (11)$$

Variable-temperature Experiments.—In this section several methods of analysing data from variable-temperature kinetic runs will be detailed and compared. Data will be presented from the thermal *cis* ⟶ *trans* isomerization of azobenzene, a first-order reaction.

As mentioned above, variable-temperature data can be analysed by obtaining instantaneous rate constants from the concentration–time curve (Figure) and then applying the Arrhenius equation. Alternatively, numerical integration can be used to calculate the concentration–time curve, and then the data can be fitted iteratively to trial values of the activation energy and Arrhenius constant. The first approach is the two-step calculation as applied to variable-temperature kinetics, the second is the one-step method. Because variable-temperature kinetic experiments are encountered less commonly than constant-temperature ones, we will now describe both the two-step and the one-step calculations in some detail.

The simplest possible way to treat the experimental data is to calculate 'instantaneous' rate constants by evaluating $\Delta[X]/\Delta t$ in equation (6) by the method of finite differences between neighbouring data points, and then to use these rates in the logarithmic form of the Arrhenius equation. However, this method is unreliable because of the way in which experimental scatter is magnified in the rates, with the result that the final activation energies have very large uncertainties. Consequently this method was not pursued.

Table 2. Activation energies of the *cis* ⟶ *trans* isomerization of azobenzene as calculated by Methods A—C

Run	Total points[a]	Method A	Method B	Method C
1	14 × 1	86.6 ± 11.1	91.5 ± 2.0	93.7 ± 16.4
2	9 × 2	78.1 ± 6.5	75.5 ± 2.3	77.2 ± 15.7
3	11 × 3	97.6 ± 4.5	92.7 ± 2.7	105.4 ± 13.8
4	18 × 2			78.0 ± 20.6
5	15 × 2			84.0 ± 20.0
All	67			90.1 ± 4.9

[a] *E.g.* 9 × 2 means 9 duplicated readings.

The simplest useful method of data analysis (Method A) is to construct the concentration–time and temperature–time curves by hand. The instantaneous rate constants are obtained either by taking the slopes of tangents drawn on the concentration–time curve at known time values, or by calculating derivatives by the method of finite differences. The corresponding temperatures may be read directly from the temperature–time curve. The activation energy is then obtained by a simple least-squares fit of the rate constants and temperatures to the Arrhenius equation.

There are three major problems with this method of data analysis, mainly arising from its subjectivity. First, unless the measured points are very closely spaced, it is difficult to draw a sigmoid curve through them in an unbiased manner; the experimenter tends to impose his own expectations on the curve. Secondly, the process of drawing tangents on the graph can introduce substantial errors. Thirdly, and perhaps most important, it is very difficult to obtain a reasonable estimate of the uncertainty in the final value of the activation energy. In order to demonstrate this last point, it is useful to consider the application of the variable-temperature method to data where the experimental uncertainties are substantial.

Method A was applied to the data obtained from several runs of the azobenzene isomerization (Table 2). The activation energies and uncertainties (as 95% confidence intervals) obtained from these runs are listed in Column A of Table 2. The quoted uncertainties reflect only the scatter in the Arrhenius plot: they contain no contribution from the scatter of the original data points, or from errors arising from the subjective nature of the manually drawn curves. As may be seen from Column A, the error limits derived in this way are over-optimistic, since the results from different runs do not lie within one another's uncertainty limits. However, there is no simple way of obtaining more realistic error limits from this method.

The obvious alternative to drawing the concentration–time and temperature–time curves by hand is to fit an appropriate function to the data points using a least-squares method (Method B). This eliminates errors due to taking points from a hand-drawn curve, and those due to taking slopes of hand-drawn tangents to the curve. We fitted the concentrations–time and temperature–time data using polynomials of the forms (12) and (13). Instantaneous rate constants were then obtained by

$$[X](t) = a + bt + ct^2 + dt^3 + \ldots \qquad (12)$$

$$T(t) = a' + b't + c't^2 + d't^3 + \ldots \qquad (13)$$

differentiation of (12) at various values of t, and the corresponding temperatures were calculated from the temperature–time polynomial. The resulting temperature-dependent rate constants were then fitted to the Arrhenius equation as before.

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* For details of Supplementary Publications see Instructions for Authors, in *J. Chem. Soc., Perkin Trans. 2*, 1988, Issue 1.

The results obtained from the azobenzene data using Method B are shown in Column B of Table 2. Once again, the uncertainties given are 95% confidence intervals based only on the scatter in the Arrhenius plot, and once again they can be seen to be overoptimistic, as the results from the different runs do not lie within one another's uncertainty limits.

Quite apart from the problem of obtaining realistic error limits, there are other difficulties with the polynomial fitting approach. First, no polynomial can reproduce the sigmoid shape of the experimental concentration–time curve, since it necessarily becomes constant at times of positive and negative infinity, whereas polynomials become very fast varying and oscillatory beyond the points fitted. Secondly, there is the problem of choosing an appropriate order of polynomial to fit the concentration–time curve. High-order polynomials are notoriously unstable fitting functions, and can develop artificial oscillations between and beyond the data points. The method must therefore be taken in two steps, with the plot of the concentration–time curve examined for each order of polynomial. An element of subjectivity therefore enters this method in that the equation of the most physically reasonable curve is used to obtain the derivatives.

The one-step calculation requires the numerical evaluation of the definite integral on the right-hand side of equation (7) (or its higher-order analogues, see Chart 2) for each experimental data point. In the present work, these integrals were evaluated using the Gauss–Legendre quadrature formula (14) where relationship (15) holds. The appropriate points x_i and weights w_i have been tabulated;[15] in the present work, 8-point quadratures were found to give converged results.

$$\int_a^b f(y)\mathrm{d}y \simeq \frac{b-a}{2}\sum_{i=1}^{n} w_i f(y_i) \qquad (14)$$

$$y_i = \left(\frac{b-a}{2}\right)x_i + \left(\frac{b+a}{2}\right) \qquad (15)$$

The results for the azobenzene isomerization using numerical integration are given in Column C of Table 2. The uncertainties are larger than in the previous cases but they are now realistic; the E_a values and their uncertainties overlap the mean value of 92 kJ mol^{-1}. This is not true of any of the methods described previously. The numerical integration procedure is free from bias, because it fits the values of E_a and A directly to the data in a single step, rather than fitting the data to some functional form and then obtaining E_a and A separately. In addition it takes into account the scatter in the original data, which is inherently not possible using a two-step procedure. Thus, this method gives a reliable estimate for the energy of activation and the most realistic estimate of the uncertainties involved.

Combination of Data Sets.—The one-step computer program consists of two major parts, a driver and MLREGR. There are three types of kinetic rate laws currently included in the program (first order, second order, and dimer), the treatment of constant- and variable-temperature data being identical, with one minor exception noted in SUP 56705. The use of the multiple linear regression package MLREGR is common to all types of data, the purpose of the driver program being to provide MLREGR with the values of the partial derivatives and residuals. Details of the data input are given in SUP 56705.

This procedure allows conventional, constant-temperature kinetic data to be combined with variable-temperature data. For the azobenzene isomerization, studied in our laboratory, a combination of the data leading to the results of Table 1 with those of Table 2 afforded E_a 91.8 ± 3.0 kJ mol^{-1} and log A 10.47. The basic hydrolysis of ethyl acetate provided the first reported example of a second-order reaction studied using variable-temperature kinetics. A combination of 4 runs with 50 data points gave an activation energy of 43.0 ± 9.8 kJ mol^{-1} and log A 6.47. These data combined with the data leading to the results of Table 1 gave E_a 43.4 ± 1.5 kJ mol^{-1} and log A 6.64.

Conclusions.—One-step methods of data analysis allow activation parameters to be calculated directly from experimental observables. The results are in good agreement with those of traditional methods, but have the advantage that the uncertainty in the final result reflects directly the goodness of fit of the experimentally observed quantities to the kinetic model chosen for the reaction. Consequently, no complicated analysis of error propagation is required.

Our experience with the variable-temperature method of kinetics allows us to pass the following comments on the method. As has been recognized[2] this technique, in principle, permits activation parameters to be obtained from a single kinetic experiment. In practice, there are several points to consider.

(1) It appears that the total amount of work involved is unlikely to be less than that required for the conventional experiments. We calculated activation parameters from all 31 possible combinations of the five data sets relating to Table 2, as described in SUP 56705. To achieve comparable levels of precision in variable-temperature kinetics required approximately the same number of data points to be used as in constant-temperature kinetics.*

(2) Some prior knowledge of the reaction rate profile with temperature must be available before the starting temperature and temperature interval can be chosen. The initial temperature should be lower than that used in constant-temperature experiments, as the reaction rate has to be slow enough that $\mathrm{d[X]}/\mathrm{d}t \simeq 0$ at the beginning of the run. Our experiments seem to indicate (although we have not investigated this systematically) that the other extreme should be similar to that chosen for the highest temperature in constant-temperature kinetics, and the heating rate should be chosen such that the variable-temperature experiment is carried out in a time comparable with a typical constant-temperature run at an intermediate temperature; the actual time is of course dependent on the method chosen to follow the reaction.

(3) Most analyses of variable-temperature reactions will require corrections to be made for the variation of the observed parameter (*e.g.* conductivity[16,17]) with temperature or for expansion of the solvent when using titrimetry or spectrophotometry. This complicates the experimental procedure.

(4) A varying temperature cannot be recorded as precisely as the constant temperature obtainable with a thermoregulated bath.

(5) Our experience with the ethyl acetate hydrolysis carried out under true second-order conditions suggests that it may be difficult to achieve satisfactory precision with variable-temperature kinetics for other than first-order reactions. Our value for the activation energy, 43 kJ mol^{-1} ± 25%, obtained with 50 data points in all, carries an unacceptably large uncertainty compared with the uncertainty obtainable in the variable-temperature, first-order isomerization of azobenzene with a comparable number of data points (*ca.* 5%). We have not investigated this matter systematically because it is hard to separate this point from the inherently greater difficulty of studying kinetics of reactions that are other than first order.

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* It should be noted that although Ahlberg[2] used a polynomial fitting method to analyse his data, he used between 100 and 300 data points per variable-temperature run. This meant that his curves were extremely well defined, and thus the errors in using polynomials for obtaining the derivatives were small.

Experimental

cis–trans *Isomerization of Azobenzene.*—Complete experimental procedures are given in ref. 18.

Ethyl Acetate Hydrolysis.[13]—(A) *Constant temperature.* A stock solution of carbonate-free NaOH was made up by dissolving NaOH (10.06 g) in water (*ca.* 10 ml) and filtering. This solution was then made up to 1.00 l using boiled and cooled water. It was stored in a sealed bottle with a soda lime trap and standardized with potassium hydrogen phthalate (KHP) using phenolphthalein as the indicator. A baryta solution was made using boiled water and $Ba(OH)_2$ (*ca.* 3 g). This solution was filtered and stored in stoppered bottle. It was standardized before each use with KHP. A solution of HCl was made up by diluting concentrated HCl and standardized with the NaOH solution.

The quantities below refer to a kinetic run at 35.0 °C. The experiment was carried out by pouring a solution of 0.013 329M-NaOH (*ca.* 300 ml) into an Erlenmeyer flask of known mass with a ground-glass stopper. The mass of the NaOH solution was determined by difference to be 303.2 g. At 20 °C, the density of this solution (assumed to be equal to that of water within the uncertainties of the experiment) was 0.998 23 g ml^{-1}, giving a volume of 303.7 ml. This flask was placed in a thermostatted bath and brought to a constant temperature. A thin-walled glass ampoule of mass 0.4211 g containing ethyl acetate (0.1943 g) was placed into the NaOH solution and held beneath the surface with a copper wire. The ampoule was broken with a glass rod and this time noted. The solution was mixed well and portions (20.00 ml) were removed at various time intervals using a pipette and noting the time when half the solution had run out of the pipette into a flask containing 0.072 510M-HCl solution (5.00 ml). This solution was then titrated with the 0.011 313N-$Ba(OH)_2$ solution and the concentration of NaOH calculated. The temperature of the thermostatted bath was measured using an electronic (thermistor) digital thermometer.

(B) *Variable temperature.* The solutions were prepared as described above. The ethyl acetate solution was prepared by pipetting ethyl acetate (1.00 ml) into boiled water (*ca.* 400 ml) and making up to 1.00 l. The solution was standardized by mixing a portion with a known excess of the NaOH solution and leaving the mixture for several hours at room temperature. A portion of this solution was removed, added to a portion of the HCl solution, and titrated with $Ba(OH)_2$ to determine the amount of NaOH that reacted with ethyl acetate.

The experiments were performed by pipetting portions of the NaOH solution and the ethyl acetate solution each into Erlenmeyer flasks with ground-glass stoppers, and where necessary adding pipetted portions of recently boiled water to either solution. These flasks were placed in ice-baths and cooled below 5 °C. The solutions were then mixed and poured back and forth between the two flasks to ensure adequate mixing. The time of first mixing and the temperature of the mixed solution were noted. The flask containing the reaction mixture was placed inside a large beaker filled with enough water to cover the liquid level inside the Erlenmeyer flask completely, and placed on a heater–stirrer. Magnetic stir bars were placed in both the beaker and the flask, and were both stirred by the magnetic stirrer. The heater was turned on to just above the lowest setting, and the temperature monitored with an electronic (thermistor) digital thermometer placed in the reaction solution, and well sealed about the mouth of the flask. Portions were removed at frequent time intervals, pipetted into portions of the HCl solution, noting the temperature when the pipette was full and the time when the pipette was half-emptied into the acid solution. This solution was titrated with baryta to determine the amount of NaOH left in the mixture at the time of removal of the portion. The mass of each portion of mixture was determined by weighing each flask before and after the addition of the portion. The density of the mixture was determined to be extremely close to that of water at the corresponding temperature, so tables of water density were used to calculate the volume of each portion.

Computational Results.—These were included with SUP 56705.

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