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AN ASSESSMENT OF A LOGARITHMIC NONISOTHERMAL STORAGE TEST

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ABSTRACT

The expected biases in kinetic parameter estimates from a logarithmic nonisothermal storage test have been determined by simulation. The magnitude of the biases depends on heating rate, activation energy (E), and rate constant (k_o). Typical errors are -10 to -15% in k_o and +0.5 to +1.0kcal per mole in E. An iterative linear solution is proposed to eliminate these errors.

A nonisothermal storage test enables the activation energy and frequency factor of a reaction to be obtained from a single experiment. Several methods have been described which differ in their time-temperature relationships or in the numerical methods used for parameter estimation[1-8] Within the pharmaceutical area the first of these methods was devised by Rogers (1963)[1].

In the Rogers' method the temperature is programmed so that the reciprocal of the absolute temperature varies logarithmically with time:

$$1/T = 1/T_o - b.\log(1+t) \qquad (1)$$

where b is a convenient heating rate constant, and t the time for the absolute temperature to rise from T_o to T.

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Substituting this into the Arrhenius and first-order equations and integrating yields:

$$\log[\ln(C_o/C)] = \log k_o - \log(1+E.b/R) + (1+E.b/R).\log(1+t) + \log[1-(k_o/k)^{1+R/(E.b)}] \quad (2)$$

where C_o equals the initial concentration of reactant, C the concentration at time t, k_o the rate constant at T_o, E the activation energy, and R the Gas constant.

Rogers has suggested that the last term on the right hand side becomes negligible as the temperature increases (i.e. k greatly exceeds k_o) so a plot of $\log[\ln(C_o/C)]$ versus $\log(1+t)$ will be linear provided initial data are omitted. Hence E and k_o can be evaluated.

The method has been assessed experimentally by Cole & Leadbeater (1966)[9] who suggested that it yields accurate and reliable results. However an examination of their aqueous kinetic results indicates that parameter estimates may be biased; therefore the method has been re-assessed. This has been done using synthetic data so eliminating random variation which may obscure biases in individual experimental tests. Thus expected or long term average biases have been estimated.

METHOD

Synthetic data were generated for a number of activation energies, rate constants and heating rates, for the first-order nonisothermal model. Thirty data pairs were produced at equispaced log(1+t) values as recommended by Rogers. The maximum time was that required for 90% decomposition except in a few cases, where this led to unreasonably high maximum temperatures, the maximum time was that required to reach 95°C.

The activation energy and rate constant for each data set were estimated by regressing $\log[\ln(C_o/C)]$ on $\log(1+t)$. Twenty four regressions were performed on each set, the first using the entire data set (30 pairs) and each subsequent operation having

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the previous first datum deleted; thus the final regression was carried out on six data.

RESULTS AND DISCUSSION

Errors in the calculated activation energies are shown as kilocalories per mole since, for example, an error of 1kcal when E=10kcal per mole will cause the same percentage error in a predicted half-life as 1kcal error when E=20; thus $\Delta E = E_{calc} - E_{true}$. For the same reason, errors in calculated rate constants are shown as percentages: $\Delta k = 100.(k_{calc} - k_o)/k_o$.

Figure 1 shows a typical data set. For curve (a), the points after log(1+t) equals 0.2 appear to lie on a straight line. This abscissa value corresponds to a temperature 18°C above the starting temperature T_o. Curve (b) shows errors in the predicted activation energy as initial data are deleted. For example, when the first used datum is at abscissa value 0.18, the error in E is about 0.5kcal per mole. Figure 2 demonstrates similar curves for different parameter values. In this case curve (a) has no apparently linear section and the error in E is 1.2kcal per mole at the abscissa value which corresponds to a temperature 25° above T_o. By this time 70% decomposition has occurred.

These results were obtained using unweighted linear regression. This assumes homogeneity of variance. If this condition does not hold, each value of the dependent variable must be weighted inversely as its variance. In general, the unweighted regression coefficients will still be unbiased but less accurately determined than the weighted coefficients. However, in the present case, any weighting factor which decreases the weights of early data relative to later data, will produce weighted regression coefficients closer to the true values. This is because the linear model becomes approximately true only when later data are used and early data, when included, bias the coefficients.

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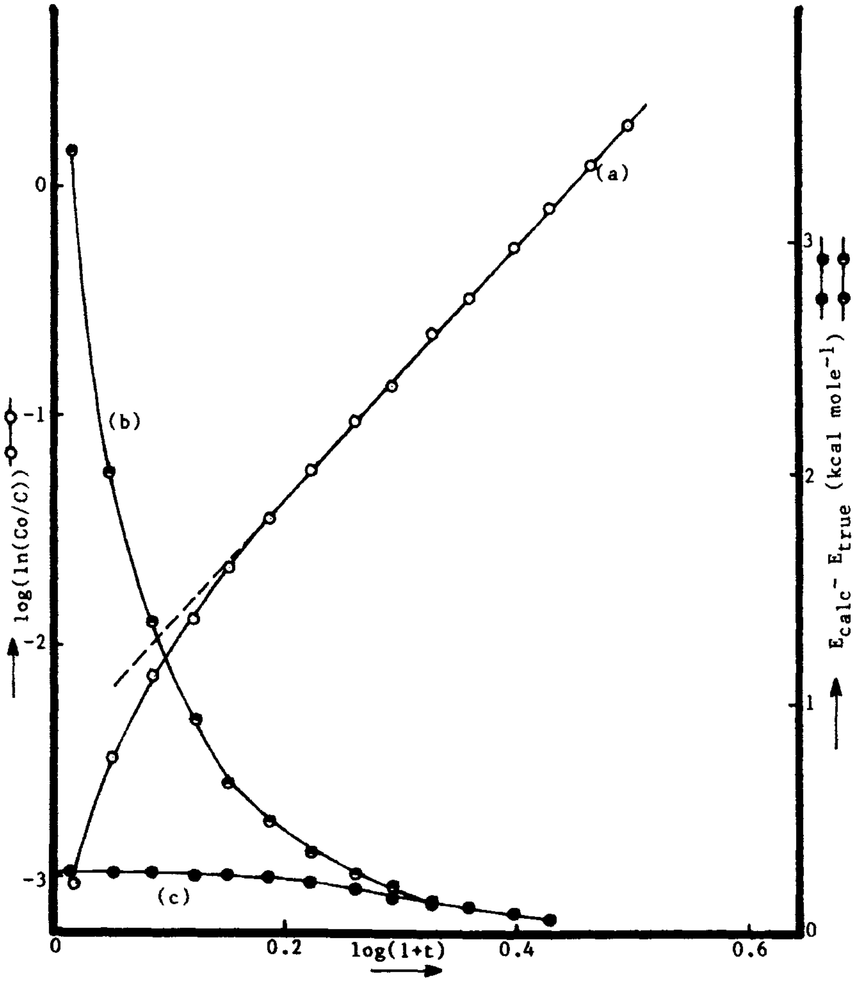

FIGURE 1
Rogers' first-order kinetics plot and corresponding errors in predicted E values as data are sequentially deleted.
(a) first-order plot
(b) E errors - unweighted regression
(c) E errors - weighted regression
k_o=0.02hr^{-1}, E=20kcal mole^{-1}, b=0.001deg^{-1}, T_o=288.15K

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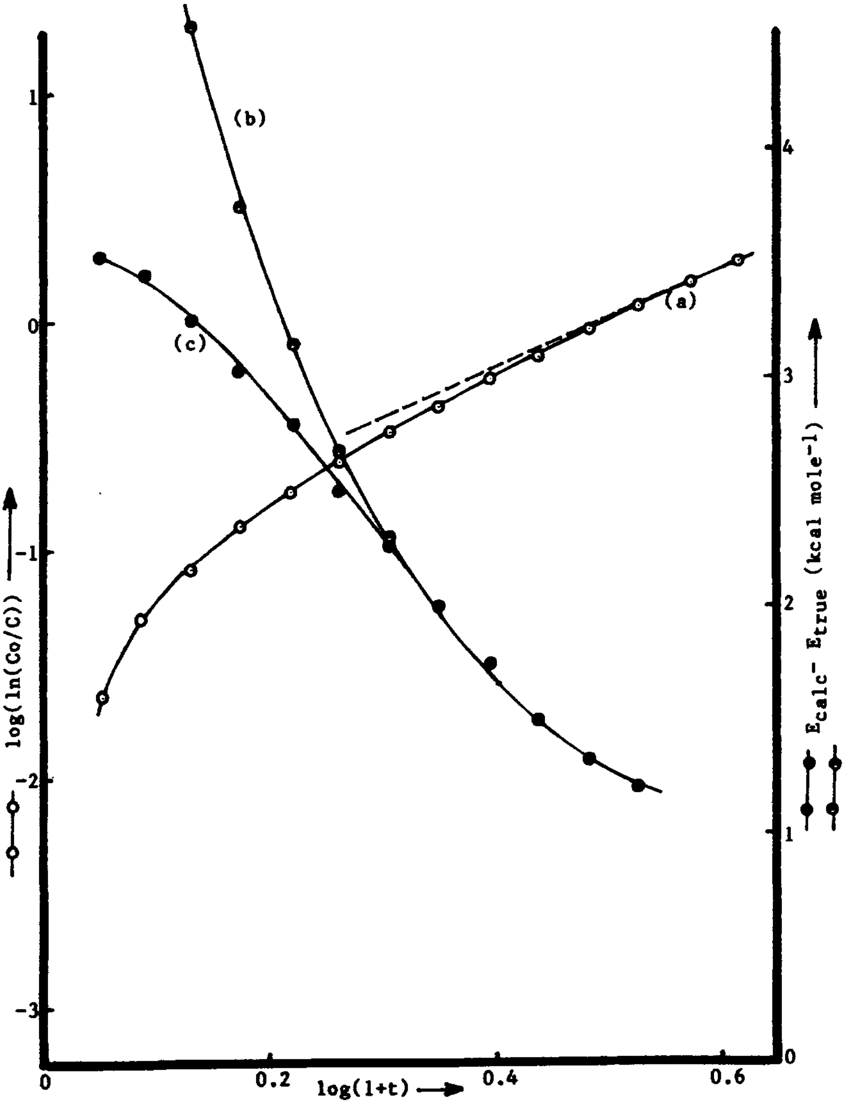

FIGURE 2

Rogers' first-order kinetics plot and corresponding errors in predicted E values as data are sequentially deleted.

(a) first-order plot
(b) E errors - unweighted regression
(c) E errors - weighted regression

k_0=0.2hr^{-1}, E=10kcal mole^{-1}, b=0.0005deg^{-1}, T_0=288.15K

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If Y = f(x) then the variance of Y (V(Y)) is:

$$V(Y) = (dY/dx)^2 . V(x)$$

$$+ \text{ terms involving higher differentials}^{10}$$

Assuming the variance in C of Equation 2 to be constant (V(C)) then:

$$Y = \log[\ln(C_o/C)]$$

$$V(Y) = (dY/dC)^2 . V(C) + \text{higher terms}$$

Therefore the weighting factor 1/V(Y) is approximately:

$$W \simeq [C.\ln(C_o/C)]^2/V(C)$$

This weighting factor places lower weight on early data (for $C=C_o$ $W=0$).

Regressions using this weighting were performed and the errors in predicted values are shown as curve (c) in Figures 1 and 2. The errors are reduced as expected. All subsequent regressions were performed with W=1 (i.e. unweighted regressions), since in all cases where Rogers' method has been used, eye-lines were drawn. Eye-lines probably approximate unweighted regressions more closely than weighted regressions.

The effect of activation energy upon the calculated activation energy is shown in Figure 3(A) and upon calculated rate constant in Figure 3(B). Decreasing E values are seen to cause increasing errors in predicted E and k_o values. Figures 4(A) and 4(B) show the errors in E and k_o for various heating rates. They indicate that the errors are only marginally affected by heating rate changes. The rate constant magnitude has the reverse effect to that of the activation energy (Figures 5(A) and 5(B)); increasing values lead to greater errors in predicted E and k_o values.

The results of the foregoing figures are summarized in Table 1. Values shown are ΔE and Δk values when the first datum used in the regression is 10°C above the initial temperature. The errors for various activation energies are shown in subset (a) for various heating rates in (b) and rate constants in (c).

For slower reactions (e.g. $k_o=2\text{x}10^{-5}$ hr^{-1}) a compromise has

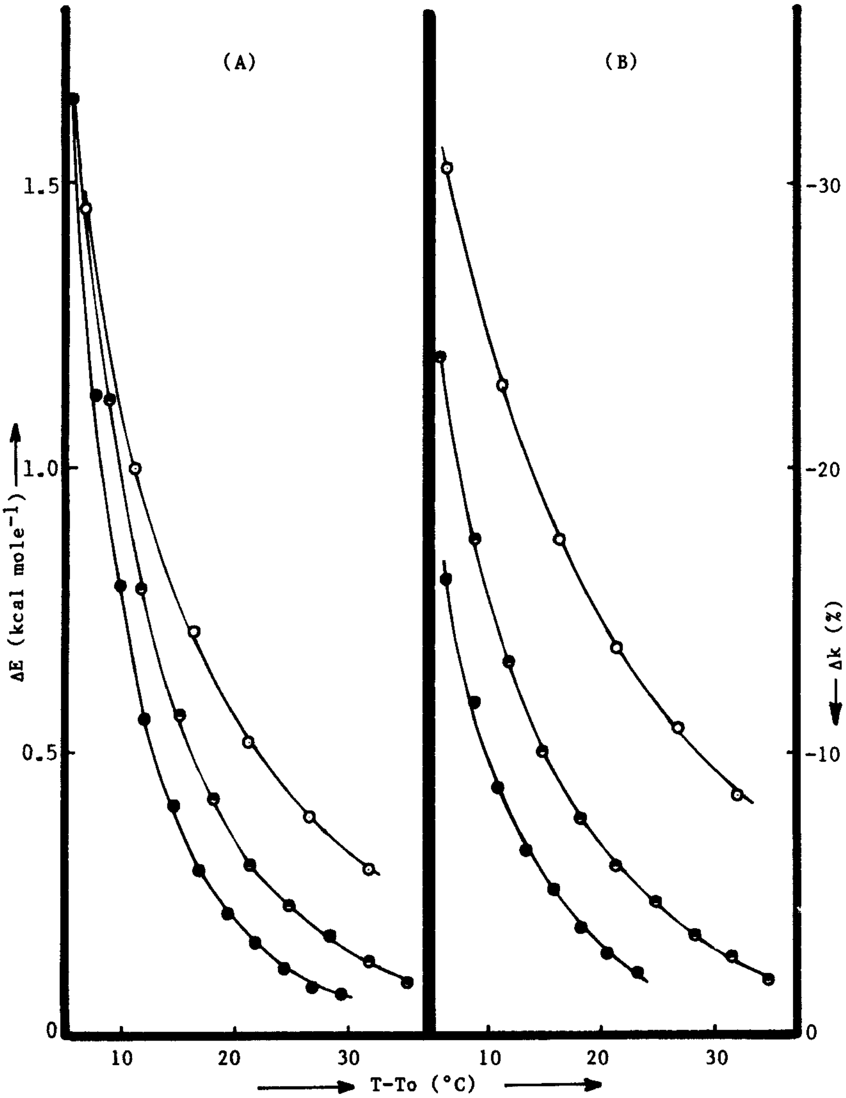

FIGURE 3
Errors in predicted E (A) and k_0 (B) values for various E values versus the temperature of the first datum used in the regression. $k_0=0.02hr^{-1}$, $b=0.001deg^{-1}$, $T_0=288.15K$

○——○ E=10kcal mole^{-1}
◐——◐ E=20 "
●——● E=30 "

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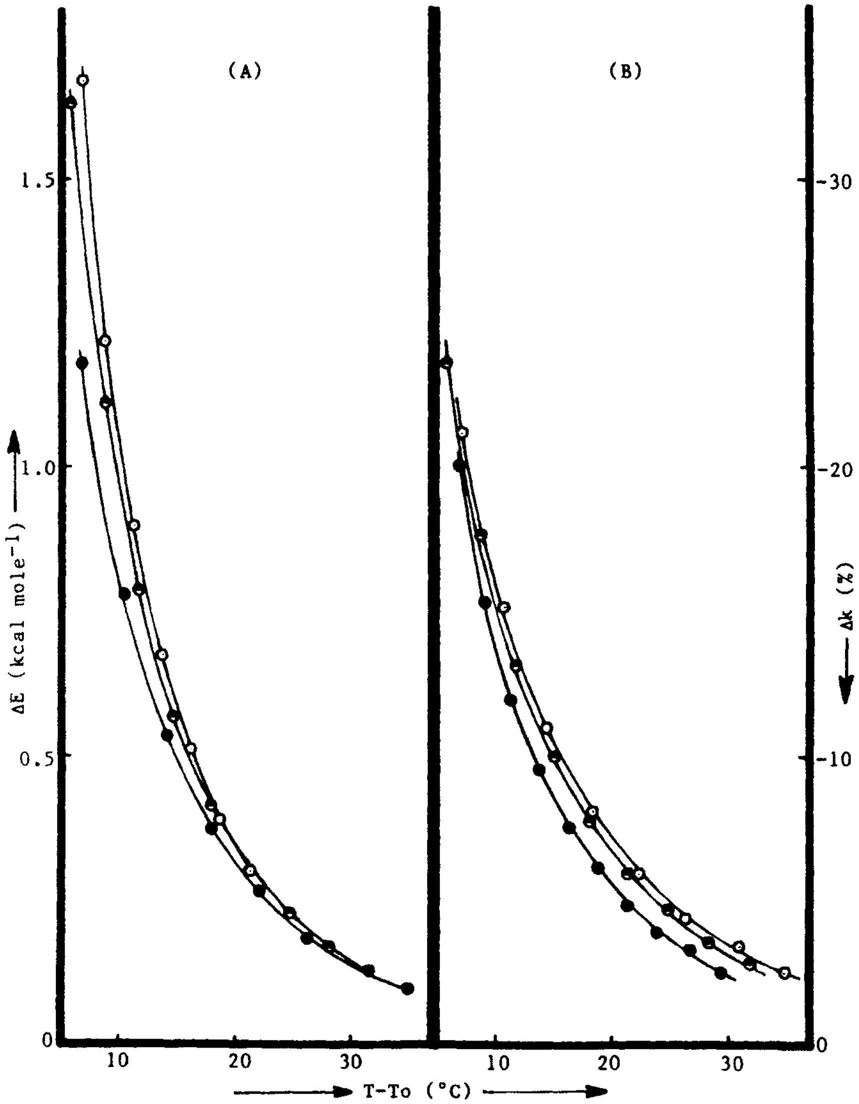

FIGURE 4

Errors in predicted E (A) and k_0 (B) values for various b values versus the temperature of the first datum used in the regression. $k_0=0.02hr^{-1}$, $E=20kcal\ mole^{-1}$, $T_0=288.15K$

○ b=0.0005deg^{-1}
◐ b=0.001 "
● b=0.002 "

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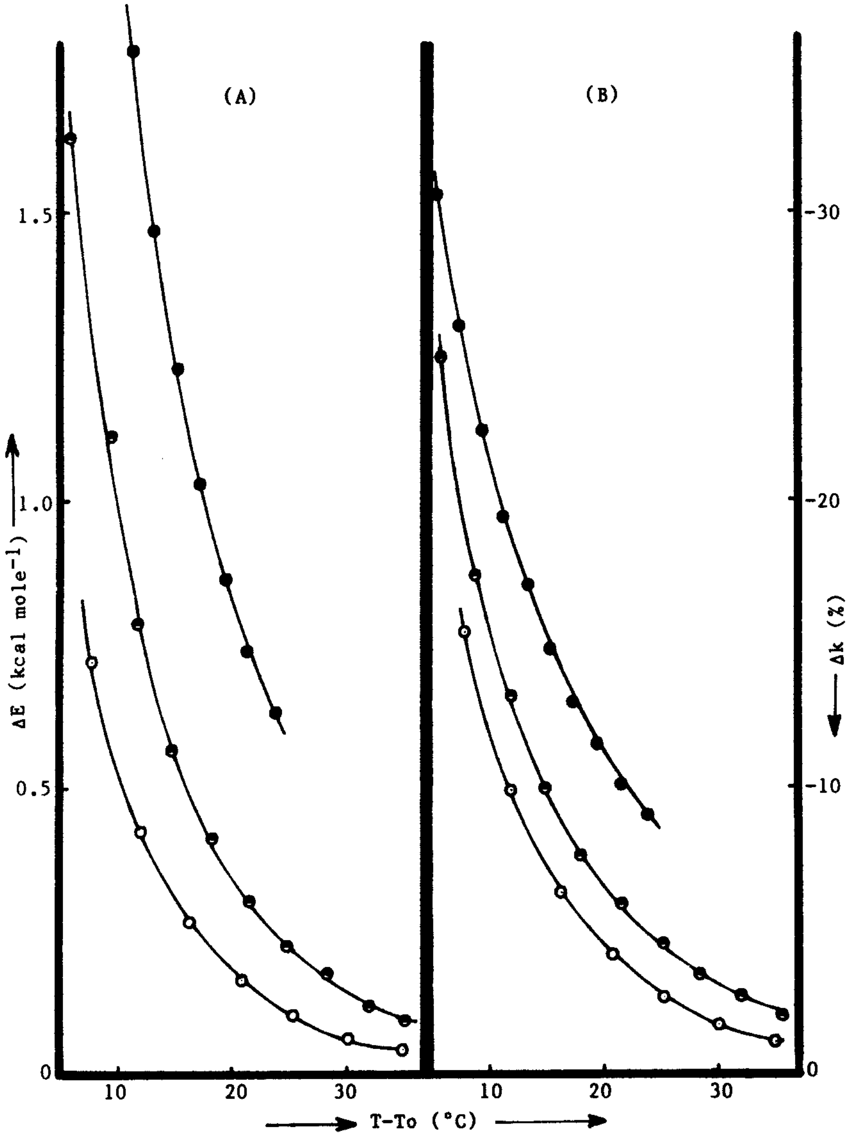

FIGURE 5
Errors in predicted E (A) and k_0 (B) values for various k_0 values versus the temperature of the first datum used in the regression. E=20kcal mole^{-1}, b=0.001deg^{-1}, T_0=288.15K

○ k_0=0.002hr^{-1}
◐ k_0=0.02 "
● k_0=0.2 "

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TABLE 1

Errors in calculated E and k_o values when data 10°C above the starting temperature (T_o) are used.

	E (cal $mole^{-1}$)	b (deg^{-1})	ko (hr^{-1})	ΔE(cal $mole^{-1}$)	Δk(%)
(a)	10000	0.001	0.020	1140	-25.0
	20000	"	"	1010	-15.8
	30000	"	"	780	-10.5
(b)	20000	0.0005	0.020	1100	-16.3
	"	0.001	"	1010	-15.8
	"	0.002	"	840	-14.3
(c)	20000	0.001	0.002	570	-12.3
	"	"	0.020	1010	-15.8
	"	"	0.200	2080	-21.6

to be reached between a low heating rate, which will lead to an excessively long experiment, and a high rate which will lead to the maximum temperature feasible for aqueous solutions, (i.e. about 90-95°C) being attained when only a small fraction of reactant has decomposed. Table 2 shows the effect of activation energy and heating rate upon fraction remaining, ΔE and Δk values, for such a slow reaction. In all cases except b=0.0005 E=30000, the maximum allowable temperature of 95°C was reached before 90% decomposition had occurred. In these cases the theoretical experimental times were 4.7hrs and 31hrs for b=0.001 and 0.0005 respectively.

Tables 1 and 2 cover the range of activation energies and rate constants which are likely to occur in drug stability testing. The heating rates used are also those which would most likely be used in practice and indeed, are those used by Rogers (1963)[1] and Cole & Leadbeater (1966)[9]. It is clear from these

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TABLE 2

Errors in calculated E and k_o values for slower reactions (k_o=2x10^{-5} hr^{-1}) when data 10°C above the starting temperature are used.

b (deg^{-1})	E (cal mole^{-1})	C/Co	ΔE (cal mole^{-1})	Δk (%)
0.001	30000	0.27	200	- 5.5
"	20000	0.96	500	-12.
"	10000	0.998	1200	-26.
0.0005	30000	0.10	182	- 4.0
"	20000	0.67	350	- 8.5
"	10000	0.99	800	-19.

tables that Rogers' method will on average produce E values which are higher than the true values and rate constants which are lower. These biases are greatest for fast reactions and low activation energies but typical errors are 0.5 to 1kcal per mole in E and -10 to -15% in k_o.

Cole & Leadbeater's estimates for aqueous decompositions show similar biases. For sucrose hydrolysis, their average nonisothermal k_o value is 34% lower and E estimate 1.4kcal per mole higher than their isothermal values, while estimates for pralidoxime methanesulphonate are 21% lower and 0.64kcal per mole higher, despite claims of good agreement between methods. However, their nonaqueous reactions do not follow this trend and this may be due to other effects caused by dielectric strength changes with temperature[11].

It might appear from Table 1(b) that the errors could be decreased to acceptable limits by the use of higher heating rates; however, this is not feasible for two reasons. Firstly, the theoretical time for the reaction using parameter values in the

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third row of Table 1(c) is about 1 hour. If the heating rate is increased to 0.01 where ΔE is still 1000cal per mole and Δk=-20%, the time for 90% decomposition falls to 9 minutes and an equivalent linear heating rate of over 400°C per hour is required. This presents severe sampling and heating problems. Secondly, Table 2 shows that, for slower reactions, increasing heating rate increases the errors. Obviously a prior knowledge of the rate constant is required if the heating rate is to be varied to decrease the biases in the results.

For a given set of parameters, the size of the biases depends on how much the temperature corresponding to the first used datum is above the starting temperature (T_o). Cole & Leadbeater have suggested that for reactions with activation energies greater than 20kcal per mole, a 10°C differential would be suitable, and that a slighly higher value would be required for lower activation energies. They found that at 25°C when $b=0.001deg^{-1}$, $k_o=1x10^{-4}hr^{-1}$, $T_o=15°C$, and $E=20kcal\ mole^{-1}$, the final term on the right hand side of Equation 2 was 2% of the left hand side; hence, they concluded a 10°C differential was adequate. For their parameter values, at 25°C, the calculated activation energy has an error of 0.5kcal per mole and the rate constant -12%. Using even higher initial temperatures will reduce the biases further but never eliminate them altogether (Figures 3-5).

The use of data at higher starting temperatures suffers from a further disadvantage. The kinetic parameters will be estimated from data collected over a limited temperature range and fraction decomposition; therefore, the estimates will have wider confidence intervals.

As shown in Table 2, the errors in calculated activation energies and rate constants are relatively small for reactions with low rate constants. However, for such reactions, especially if they also have low activation energies, the fraction decomposition by 95°C is unreasonably small. Cole & Leadbeater have shown that at least 20% decomposition is required to

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establish the order of the reaction by Rogers' method. Decreasing the heating rate would ensure that a greater fraction decomposition had occurred when the reaction reached 95°C but this would lead to impractically long experiments. For example, $b=0.00025$ would require 370hrs for 90% decomposition for the slow reaction in question, and this negates the advantage of rapidity of Rogers' method. This information also negates another claimed advantage of Rogers' method: "it is not necessary for approximate values of k_o and E to be known in advance. The starting and stopping temperatures of the programme can be chosen according to experimental convenience, and the programme constant b can be selected according to the time available for the experiment" (Rogers, 1961)[1]. If such were the case, a choice of 15°C, 95°C for starting and final temperatures and $b=0.001$ so the maximum time period was 4.7 hours could lead to error in excess of 2kcal per mole in E and -20% in k_o for faster reactions or unreasonably small amounts of decomposition in slower reactions especially with low E values. It follows that some prior knowledge of the kinetic parameters is necessary in order to conduct an appropriate experiment.

IMPROVED NUMERICAL SOLUTIONS

The numerical solution of the data for a logarithmic temperature programme can be improved in at least two alternative ways.

Nonlinear Solution - Equation 2 can be expressed in the form:

$$C = C_o.\exp[-k_o.(1+t)^{1+E.b/R}.(1-(k_o/k)^{1+R/(E.b)})/(1+E.b/R)] \quad (3)$$

Equation (3) can be solved by nonlinear minimization techniques regressing C on t with k_o, E, and C_o as parameters. This iterative procedure would require the use of a digital computer.

Iterative Linear Solution - Using the entire data set, $\log[\ln(C_o/C)]$ can be regressed on $\log(1 + t)$ in the usual way. Using the estimate of E from this regression the process is

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repeated this time regressing $\log[\ln(C_o/C)]-\log[1-(1+t)^{-(E.b/R+1)}]$ versus $\log(1+t)$ equivalent to $\log[\ln(C_o/C)]-\log[1-(k_o/k)^{1+R/(E.b)}]$ on $\log(1+t)$. The process is again repeated using the latest estimate of E and so on until no significant change occurs in calculated E and k_o values. If some prior knowledge of the E value is available, the first regression could be performed using it, thereby saving at least one iteration. Results for a typical solution are shown in Table 3 and those for the worst case in Table 4.

From the tables it is clear that three and five iterations for Table 3 and 4 respectively, would have been adequate. If initial estimates for E of 21 and 11kcal per mole had been used in the first iteration, the iterations required could have been reduced to 2 (possibly 1) and two respectively. Unlike the non-linear method, C_o cannot be estimated from the data simultaneously with k_o and E.

TABLE 3

Errors in the predicted E and k_o values versus iteration number for a typical data set: k_o=0.02hr^{-1}, E=20kcal mole^{-1}, b=0.001deg^{-1}, T_o=288.15K.

Iteration Number	ΔE (cal mole^{-1})	Δk (%)
1	3416.	-41.
2	389.	-6.4
3	48.	-0.8
4	6.	-0.1
5	0.7	-0.01

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TABLE 4

Errors in predicted E and k_o values versus iteration number for a worst-case data set: k_o=0.2hr^{-1}, E=10kcal mole^{-1}, b=0.0005deg^{-1}, T_o=288.15K.

Iteration Number	ΔE (cal mole^{-1})	Δk (%)
1	8943.	-56.
2	1956.	-20.
3	487.	-5.7
4	124.	-1.5
5	32.	-0.4
6	8.3	-0.1
7	2.1	-0.03

CONCLUSIONS

The expected values for activation energies produced by Rogers' method are higher than the true values; calculated rate constants are lower. The biases depend on the true activation energy and rate constant as well as heating rate, with typical errors of 0.5-1.0kcal per mole and -10 to -15% in E and k_o respectively. Some knowledge of kinetic parameters is required prior to experimentation by Rogers' method.

The iterative linear solution method enables E and k_o to be estimated to any desired accuracy using the entire data set. It is a feasible operation using a calculator.

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