

AN ACCELERATED STORAGE TEST WITH PROGRAMMED TEMPERATURE RISE

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Received April 30, 1963

The rate constant of a reaction at room temperature and the activation energy can be calculated from values of the concentration of the reactant as a function of time. Measurements are made while the temperature of the reacting system is raised in accordance with a pre-determined programme. The method makes use of the Arrhenius equation, but it does not suffer from the disadvantages of the usual method in which several experiments are done at fixed elevated temperatures.

THE stability of a preparation at room temperature can be predicted by measuring the rate of decomposition at two or more higher temperatures, and the method has found important applications in pharmacy (Garrett, 1962).

It is assumed that the relation between rate constant k and temperature T ($^{\circ}$ K.) can be described by the Arrhenius equation,

$$\frac{d \log k}{d (1/T)} = - \frac{E}{2.303 R}$$

where E is the activation energy for the reaction, R is the molar gas constant, and logarithms are taken to the base 10. The activation energy can be calculated if the rate constant is known at two temperatures; alternatively, from a knowledge of the rate constant at one temperature and the activation energy, the rate constant at some other temperature can be calculated. This is conveniently done by a graphical plot of $\log k$ as a function of $1/T$, although Tootill (1961) has pointed out the advantages of a statistical approach.

If moderately high temperatures, such as 60° or 80° , are chosen for the experiment, the rate of reaction may be increased by a factor of ten or more over that at room temperature, and so the "shelf life" at room temperature, which may be years for some pharmaceutical preparations, can be predicted from the results of a few weeks' work. The method suffers from the disadvantage that the rate of decomposition should be known at least approximately in advance, so that suitable elevated temperatures can be chosen, and there is a risk that at the higher temperatures used, the reaction mechanism may alter. A method is now proposed that largely avoids these difficulties.

A single experiment is done, replicated if thought desirable, in which the temperature of the preparation is steadily raised in accordance with a predetermined programme, and samples are withdrawn at intervals and analysed in the usual way. This provides the information necessary to calculate the activation energy of the reaction and the rate constant at any temperature.

Let t represent the time and c the concentration of the reactant; T_0 and T_t are the temperatures ($^{\circ}$ K.) at the start and at time t , and k_0 and k_t are the corresponding rate constants. The rise of temperature is programmed so that the reciprocal of the temperature varies logarithmically with time

$$1/T_0 - 1/T_t = 2.303 b \log (1 + t)$$

where b is a constant of proportionality which can be chosen as desired.

Since $d(\log k)/d(1/T) = -E/2.303R$, then

$$\begin{aligned} \log k_t &= \log k_0 + (E/2.303R)(1/T_0 - 1/T_t) \\ &= \log k_0 + (Eb/R) \log (1 + t) \\ \therefore k_t &= k_0(1 + t)^{Eb/R} \end{aligned}$$

If first-order kinetics are assumed, $-dc/dt = k.c$, and

$$\begin{aligned} - \int_{c_0}^{c_t} \frac{dc}{c} &= \int_0^t k \cdot dt \\ \therefore 2.303 \log (c_0/c_t) &= k_0 \int_0^t (1 + t)^{Eb/R} \cdot dt \\ &= \frac{k_0 \cdot [(1 + t)^{1 + Eb/R} - 1]}{1 + Eb/R} \\ &= \frac{k_0(1 + t)^{1 + Eb/R} \cdot [1 - (k_0/k_t)^{1 + R/Eb}]}{1 + Eb/R} \\ \therefore \log [2.303 \log (c_0/c_t)] &= \log k_0 - \log (1 + Eb/R) \\ &\quad + (1 + Eb/R) \log (1 + t) \\ &\quad + \log [1 - (k_0/k_t)^{1 + R/Eb}] \end{aligned}$$

If other orders of reaction are assumed, similar equations are obtained. In general,

$$\log f = \log k_0 - \log (1 + Eb/R) + (1 + Eb/R) \log (1 + t) + \log [1 - (k_0/k_t)^{1 + R/Eb}]$$

where f is $(c_0 - c_t)$ for zero order, $[2.303 \log (c_0/c_t)]$ for first order, $(1/c_t - 1/c_0)$ for second order, etc.

The final term on the right-hand side of the equation varies with time. Just after the start of the experiment, it is large and negative, but it rapidly tends to zero as the reaction proceeds, and it becomes negligible as k_t becomes substantially greater than k_0 .

A graph of $\log f$ as a function of $\log (1 + t)$ will therefore be a straight line from that time after which k_0 is negligible in comparison with k_t . The slope of the straight line is equal to $(1 + Eb/R)$. Since b , the programme constant, and R are known, the activation energy E can be calculated. If the graph is not a straight line after the initial period during which k_t is only slightly greater than k_0 , this may be because the

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wrong order of reaction has been assumed, or because the mechanism changes as the temperature is raised. The intercept at $\log(1+t) = 0$ is equal to $\log k_0 - \log(1 + Eb/R)$, and so if the slope and the intercept are measured, the rate constant k_0 at temperature T_0 can be calculated. From k_0 and E , the rate constant at any other temperature can be calculated.

It is thus possible from a single experiment to estimate the activation energy for the reaction and the rate constant at any temperature. The straight-line plot provides a built-in check that the correct order of reaction has been assumed, and that this and the activation energy are independent of temperature over the range studied. If the $\log f$ vs. $\log(1+t)$ graph is initially straight and then curls over, this may indicate a change of mechanism at the higher temperature, and the slope and intercept of the line through the points at the lower temperatures should be used for the calculations.

It is not necessary for approximate values of k_0 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.

If desired, the experiment can be stopped as soon as the requisite number of points have been plotted to enable the slope and the intercept to be measured with sufficient accuracy, and so high temperatures with their attendant difficulties may be avoided.

EXPERIMENTAL

The method has been tested by experiments on the first-order decomposition of riboflavine and of sucrose in aqueous solution.

Riboflavine. A $10^{-4}M$ solution of riboflavine in $0.05N$ sodium hydroxide was used. A value of $0.0005/2.303 = 2.171 \times 10^{-4}/\text{deg.}$ was selected for b , with $1/T_0 = 0.00350/\text{deg.}$, so that the temperature was programmed to rise from 12.5° to 55° in 7 hr. (Fig. 1). The riboflavine solution was distributed in 10 ml. portions into 25 ml. flasks in a water-bath, and the temperature was raised during the day by manual adjustment of the bath thermostat. Initially, the temperature rise was about 0.25° per min., and adjustment was needed every 1 or 2 min.; later, the rate fell to about 0.05° per min., and adjustment was made only every 5 or 10 min. A thermometer in one of the flasks was used to monitor the temperature.

For analysis, the method of Guttman (1962) was used. A 10 ml. aliquot was cooled under the tap and diluted to 25 ml. with N acetic acid, and the extinction was measured at $445 m\mu$ in 1 cm. cells in a Hilger and Watts "Uvispek" spectrophotometer. The concentration c is directly proportional to the extinction or absorbance A . The experiment, including the analyses, was done in subdued light.

The graph of $\log [2.303 \log (A_0/A_t)] = \log [2.303 \log (c_0/c_t)]$ as a function of $\log(1+t)$ is shown in Fig. 2. The times of removal of samples for analysis are spaced logarithmically, so that the points are spread uniformly across the graph. The slope is 2.95 and the intercept at \log

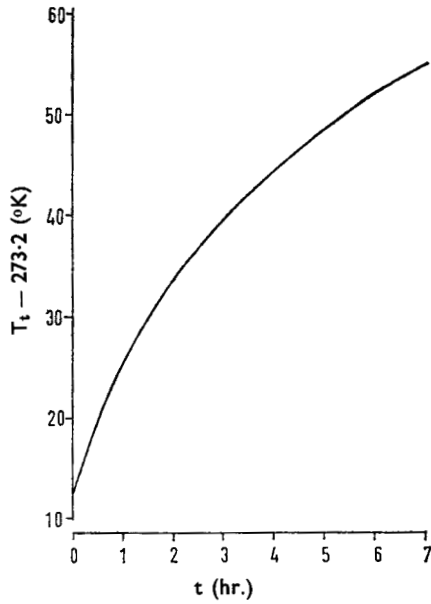


FIG. 1. Temperature rise according to the programme $(0.00350 - 1/T_t) = 0.0005 \log(1 + t)$, with T_t in °K, and t in hr.

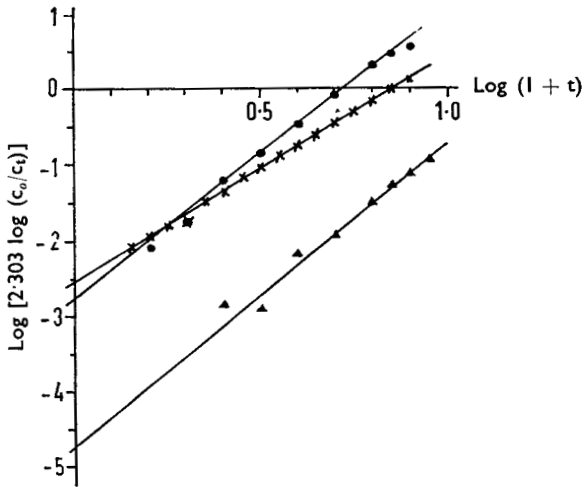


FIG. 2. Decomposition during temperature rise according to the programme $(0.00350 - 1/T_t) = 0.0005 \log(1 + t)$, with T_t in °K and t in hr.

- × — × riboflavin in N/20 sodium hydroxide.
- — ● sucrose in N/6 hydrochloric acid.
- ▲ — ▲ sucrose in N/600 hydrochloric acid.

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$(1 + t) = 0$ is -2.55 . Therefore the activation energy $E = 1.987 \times 10^{-3} \times (2.95 - 1)/(2.171 \times 10^{-4}) = 17.85$ kcal./mole; $\log k_0 = -2.55 + \log 2.95 = -2.08$ and so $k_0 = 0.0083$ /hr. The rate constant at 20° calculated from E and k_0 is 0.018 /hr. The rate constant was also measured directly in a separate experiment by determination of $d(\log c)/dt$ at a constant temperature of 20° and was found to be 0.019 /hr. A value of 0.016 /hr. at 20° can be interpolated from the results for the decomposition of similar riboflavine solutions reported by Guttman (1962); his value for the activation energy was about 19.2 kcal./mole.

Sucrose (i). A 40 per cent w/v solution of sucrose in 0.0002 per cent w/v phenylmercuric nitrate solution was prepared and 20 ml. portions were distributed into flasks. To each was added 10 ml. of 0.5N hydrochloric acid, and the programmed temperature rise was started, with $1/T_0 = 0.00350$ /deg. and $b = 2.171 \times 10^{-4}$ /deg.

For analysis, a flask was removed from the bath and cooled under the tap, and the solution was diluted to 50 ml. with 0.26N sodium hydroxide. The optical rotation α was measured at $546.1 \text{ m}\mu$ in a 20 cm. tube in a Hilger and Watts photoelectric polarimeter. The concentration c_t is directly proportional to $(\alpha_t - \alpha_\infty)$, where α_∞ is the rotation when hydrolysis

is complete and is approximately $-0.32 \alpha_0$, and so $\log \left[2.303 \log \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty} \right]$
 $= \log [2.303 \log (c_0/c_t)]$ was plotted as a function of $\log (1 + t)$.

The slope of the graph (see Fig. 2) is 3.82 and the intercept at $\log (1 + t) = 0$ is -2.75 . Therefore the activation energy is 25.8 kcal./mole, and the rate constant at 20° is predicted to be 0.021 /hr. The rate constant at 20° measured directly was found to be 0.024 /hr. A value of 0.020 /hr. can be interpolated from the results for the decomposition of similar alkaline sucrose solutions reported by Jackson and Gillis (1920); their value for the activation energy was about 25.5 kcal./mole.

Sucrose (ii). Another sucrose decomposition experiment was done, but with a concentration of hydrochloric acid only about one-hundredth of that in experiment (i). The slope of the graph (see Fig. 2) is 4.02 and the intercept at $\log (1 + t) = 0$ is -4.74 . Therefore the activation energy is 27.6 kcal./mole, and the rate constant at 20° is predicted to be 0.00022 /hr. The rate constant at 20° measured directly was found to be 0.00023 /hr.

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The paper was presented by the AUTHOR.