

Programmed kinetic studies

SIR,—Recently Cole & Leadbeater (1966) described a detailed evaluation of the “non-isothermal kinetics” test proposed by Rogers (1963) and Eriksen & Stelmach (1965). This test allows calculation of the complete rate equation (i.e., $\log k = f(1/T)$, k being the rate constant of a homogeneous degradation, T being the absolute temperature) in a single experiment. The single-step equation for first order cases, using the nomenclature of Cole and Leadbeater is

$$\log \left(\ln \frac{C_o}{C_t} \right) = \log k_o - \log \left(1 + \frac{EB}{R} \right) + \left(1 + \frac{EB}{R} \right) \log (1 + t) \\ + \log \left(1 - \left[\frac{k_o}{k_t} \right]^{1 + \frac{R}{EB}} \right) \quad \dots \quad 1$$

and is derived from the relation

$$\frac{d(\log k)}{d(1/T)} = - \frac{E}{2.3 R} \quad \dots \quad 2$$

and the programming function

$$\frac{1}{T_o} - \frac{1}{T_t} = B \ln (1 + t) \quad \dots \quad 3$$

The authors point out precautions to be taken, suggest preliminary experiments where needed (order of reaction) and call attention to the assumptions made by the originators of the test.

A few further comments may be added for the benefit of those who plan on using “non-isothermal kinetics” as tool for stability predictions.

The case sometimes occurs where distinct, non-zero equilibria eventually are reached, and in these situations, the theory underlying the linear programming leads to equations which cannot be made linear. The simplest example (Carstensen, 1968) of equilibrium which may be visualized is $A \rightleftharpoons B$, where A is the parent compound and B the degradation product. If A_o is the initial concentration, x the fraction decomposed, and k_+ and k_- the forward and reverse rate constants, then the rate equation

$$\frac{dx}{dt} = k_+ (1 - x) - k_- x \quad \dots \quad 4$$

after rearrangement and invokement of initial conditions integrates to

$$x = x_e (1 - e^{-(k_+ + k_-)t}) \quad \dots \quad 5$$

where the equilibrium fraction is $x_e = \frac{k_+}{k_+ + k_-}$; although this may be made

linear in isothermal experiments, e.g. by following $\log \frac{A_o (1 - x)}{A_o (1 - x_e)}$ (i.e. the

logarithm of the amount of drug remaining, divided by the amount at “infinite time”) as a function of time, the equilibrium concentration $A_o (1 - x_e)$ changes with temperature by a van't Hoff relationship. Where equation 5 applies, equation 2 (at constant pressure) would take the forms:

$$\frac{d(\log k_+)}{d(1/T)} = -\frac{E_a}{2.3 R} \quad \dots \dots \dots 6$$

and

$$\frac{d(\log k_-)}{d(1/T)} = -\frac{E_a + H}{2.3 R} \quad \dots \dots \dots 7$$

where H is the heat of reaction. The only measurable parameter would be $(k_+ + k_-)$, and there is no way of expressing $d(\log(k_+ + k_-))/d(1/T)$ in manageable analytical form. The actual effect is that α_∞ in the original paper of Rogers (1963), apart from not representing zero concentration, is not time-independent (temperature-independent). Similar arguments hold for the slightly different

programming $\left(\frac{1}{T_0} - \frac{1}{T_t} = a t\right)$ employed by Eriksen & Stelmach (1965).

Apart from this limitation, it should be borne in mind that whenever a kinetic salt effect exists (see e.g. Garrett, 1958), linearity might be lost. If the experiment is conducted at a particular ionic strength (by using buffers) which is usually the case, then the kinetic salt effect will change with temperature, since the factor to $2 z_+ z_- \sqrt{\mu}$ is

$$1.825 \cdot 10^6 \left[\frac{\rho}{\epsilon^3 T^3} \right]^{\frac{1}{2}}$$

where ρ denotes density, ϵ dielectric constant, T absolute temperature, z charge, and μ ionic strength. For example, the value of this coefficient for water is 0.509 at 25° and 0.468 at 60° (Harned & Owen, 1954). It should be noted that the factor does not vary proportionally to T^{-1} but to $T^{-3/2}$. The temperature dependency of the dielectric constant further complicates the behaviour as the temperature is increased. Since the factor difference at two temperatures equals the logarithm of the ratio of rate constants (over and above the inverse temperature effect) the contribution can be sizable. It is even more pronounced in systems which are not completely aqueous (e.g. 50:50 acetone water), and have smaller and more temperature sensitive dielectric constants. Therefore, it would be advisable always to check for kinetic salt effect before conducting single-step stability studies.

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