Calorimetric Measurement of the Kinetics of Slow Reactions

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A brief review of the application of calorimetry to measurement of the kinetics of slow processes is presented. Processes degrading or otherwise changing the properties of materials often occur too slowly to be readily measured by conventional chemical analyses but can be measured in a relatively short period of time by heat conduction calorimetry. Instrument selection and derivation of rate laws from calorimetric data are discussed, and illustrative examples are presented.

Introduction

Calorimetry is unique among the methods used to determine the kinetics of chemical reactions. Other methods measure some property of the system as a function of time, and the time derivative must be taken to determine the rate of the reaction. Calorimetry directly measures the rate of heat generation which is proportional to the rate of the process. Because nearly all processes generate heat, calorimetry is a very general method. This generality is both a strength and a weakness, however. Because the calorimeter measures all processes occurring simultaneously, significant processes are unlikely to be missed, but the desired signal may be lost in a background of processes of no interest.

Temperature-change calorimetry can be used to determine the kinetics of reactions with time constants on the order of seconds. Temperature-change calorimeters with time constants of less than 1 s and with heat leak constants small enough to make them suitable for reactions that go to completion in an hour or two have been commercially available for many years. Although temperature-change calorimeters are useful for the study of reaction kinetics in this range of rates, there are many other methods that can readily be applied to reactions with this range of rates. In some circumstances, calorimetry has some advantages over other methods for studying the kinetics of moderately fast reactions,1-3 but this application will not be discussed further in this paper.

Reactions that take more than about 1 h and up to a few millenia to go to completion are conveniently studied by either power compensation or heat conduction calorimetry. Because these types of calorimeters measure the rate of a process directly, there is no need to wait for the products or the decrease in reactants to reach a measurable amount. Calorimetry is thus capable of determining the kinetics of very slow processes in a very short time compared to the time for a significant amount of reaction to occur. Because power compensation calorimetry has a higher detection limit for heat rates, which limits its application to less slow processes, this paper focuses mostly on heat conduction calorimetry and applications to very slow reactions.

Design and Selection of the Calorimeter

The principles involved in designing isothermal calorimeters for the study of slow phenomena were developed in the early part of the 1900s4 and have been incorporated into commercial calorimeters for many years. Because these principles are well-known, the details of instrument design are not discussed here. What is of interest here is a means for comparison of different instruments for a particular application.5

The minimum detectable reaction rate \( R_{\text{md}} \) of the calorimetric method is

\[
R_{\text{md}} = \frac{\phi_{\text{md}}}{\Delta H}
\]

where \( \phi_{\text{md}} \) is the minimum detectable heat rate of the calorimeter and \( \Delta H \) is the enthalpy change for the reaction. On a practical basis, \( \phi_{\text{md}} \) can be taken as the sum of the uncertainty in the baseline of the calorimeter with an unreactive blank and the uncertainty in the heat rate measurement with the sample in place. In eq 1, \( R_{\text{md}} \) is in units of moles per time. Reaction rates on the order of a few micromoles per year are easily measured in a few hours with any of several brands of commercially available heat conduction calorimeters.

A more useful measure of the detection limit for comparison of calorimeters is given by

\[
R_{\text{md}} = \frac{\phi_{\text{md}}M}{\Delta H m}
\]

where \( M \) is the molecular mass of the reactants and \( m \) is the sample mass. In eq 2, \( R_{\text{md}} \) has units of reciprocal time. Equation 2 provides a means for comparing the detection limits of calorimeters with different sizes of reaction vessels. The ratio of \( \phi_{\text{md}} \) to the useable volume of the calorimeter vessel is thus a useful index of the detection limit of a given calorimeter. The combinations of \( \phi_{\text{md}} \) and reaction vessel volumes for some representative heat conduction calorimeters are listed in Table 1 together with the resultant detection index. Note that

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If $x = 1$ and $y = 0$, a first-order rate law

$$\phi_t = -\Delta H \beta m (1 - \alpha_t) = Be^{-kt} \quad (6)$$

is obtained. The time function is obtained from the $x$ function by separating the variables in eq 4, integrating, and solving for the appropriate $x$ function to be substituted. A linear plot of $\ln \phi_t$ against $t$ is proof of this rate law as shown in eq 7. Values for $k$ and the constant $B$

$$\ln \phi_t = \ln B - kt \quad (7)$$

may be obtained from the slope and intercept of the plot. If $y = 1$ and $x = 1$, then the heat rate will be described by a power function of $t$ as shown in eq 8. Proof of the

$$\phi_t = -\Delta H \beta m k a_t^{1-x} = -\Delta H \beta m (xkt)^{1-x}/x = B t^{1-x}/x \quad (8)$$

applicability of this rate law is obtained from the linearity of a plot of $\ln \phi_t$ against $\ln t$ as shown in eq 9.

$$\ln \phi_t = \ln B + [(1 - x)/x] \ln t \quad (9)$$

Values of $B$ and $x$ can be obtained from the intercept and slope of the plot. Note that this equation can describe heat rates that increase with time as well as rates that decrease with time.

If $x$ and $y$ are both between 0 and 1, an equation describing an autocatalytic process is obtained.

$$\phi_t = -\Delta H \beta mk a_0^{1-x} (1 - \alpha_t)^{1-y} \quad (10)$$

There is no general solution for eq 10 in the time domain. Data must be fitted to an empirical function of $t$ unless $x$ and $y$ have values for which there is an exact mathematical solution for the integral of eq 10.

Methods for simultaneous determination of the $\Delta H$ value and the order of a reaction in the reactant domain solely from data collected during an experiment have been demonstrated. In the reactant domain, the rate law is

$$\phi_t = k \Delta H (n_0 - Q_t/\Delta H)^m \quad (11)$$

where $n_0$ is the number of moles of reactant initially present. $Q_t$ is the total amount of heat liberated by the reaction to time $t$, and $m$ is the order of the reaction with respect to the reactant. If $m = 1$,

$$\phi_t = k(\Delta H n_0 - Q_t) \quad (12)$$

and a plot of $\phi_t$ against $Q_t$ will be linear with slope $-k$ and intercept $k \Delta H n_0$. If $m = 2$,

$$\phi_t = k \Delta H n_0^2 - 2kQ_t - kQ_t^2/\Delta H \quad (13)$$

and a plot of $d\phi_t/dQ_t$ against $Q_t$ will have an intercept $-2k$ and slope $-2k/\Delta H$. Other cases where $m$ is an integer can be dealt with similarly in that some function of $\phi_t$ plotted against some function of $Q_t$ will result in a determination of $k$ and $\Delta H$ for the reaction. In general, because $\phi_t$ can always be expressed as $f(t)$ as shown above and $Q_t$ is then equal to $\int f(t)$, in principle there should always be a way to obtain the constants $k$ and $\Delta H$ from $\phi_t$ data taken as a function of time. Thus,
calorimetry provides a unique means for simultaneously obtaining kinetic and thermodynamic data on very slow reactions.

Many systems of interest are kinetically too complex to apply any of the above treatments directly to obtain numerical values for $k$ and $\Delta H$. For example, $\beta$ and $\Delta H$ are not separable (see eq 3), and there is no prior way of knowing $\beta$ for a given lot of material unless $\beta = 1$, e.g., reaction of a limiting reagent in solution. Complex materials often degrade by more than one path, and the measured heat rate must be assumed to be a sum of rate laws. Furthermore, the mechanisms of many reactions change as the reaction progresses and the concentrations of products build up. If the products of the initial reaction undergo further degradation, the heat from these further reactions add to, and thus complicate theoretical analysis of, the calorimetric data. In these cases, a qualitative understanding of the relation between rate laws and the calorimetric signal may be all that is possible. Practically, for many applications, such a qualitative understanding may be all that is necessary.

Even the nature of the reaction is often not known at the beginning of a study, and identification of the reaction becomes an important part of the planning for the calorimetric measurements. In this case, determination of which environmental variables affect the rate is necessary. A related calorimetric method is to measure the temperature at which the onset of the main reaction becomes detectable by temperature scanning calorimetry. Temperature scanning calorimetry provides a unique means for rapid, routine qualification tests much nearer the actual use temperature for individual lots of materials that degrade by autocatalytic mechanisms. Integration of eq 4 gives

$$\alpha = k t$$

and when $\alpha = 1$, i.e., at the end of the induction period,

$$k = 1/t_i$$

where $k$ is a lot-dependent constant and $t_i$ is the length of the induction period. Substitution of eq 5 to eliminate $k$ gives

$$t_i = -\Delta H/\beta m/\phi_t$$

which shows that the induction time is inversely proportional to the heat rate per mass of sample. The heat rate is thus a direct measure of the relative induction times of different lots of a material. If $\Delta H$ and $\beta$ can be estimated, an absolute estimate of $t_i$ is possible. Experience shows that $t_{\text{max}}$, the time to the peak of the autocatalytic reaction, can often be used in place of $t_i$ for relative predictions of use life.

**Temperature Dependence of the Rate Law**

The temperature dependence of the rate law may be described by substitution of the Arrhenius equation (17) for $k$ in the above equations. The value of $E$ for a zero-order process, eq 5, may be obtained from the slope of a plot of $\ln(\phi/t)$ against $T^{-1}$ as shown by eq 18 assuming

$$\ln(\phi/t) = \ln(-\Delta H/\beta A) - E/RT$$

$\Delta H$ and $\beta$ are independent of temperature. The exponential rate law, eq 6, leads to a value of $k$ at each temperature; so, $E$ may be evaluated from the slope of a plot of $\ln k$ against $T^{-1}$. When the rate law is a power function of $T$ (eq 8), assuming $\Delta H$, $\beta$, and $\gamma$ are independent of temperature, the slope of a plot of $\ln[\phi(t/m^{(1-x)/x})^{-1}]$ against $T^{-1}$ is $-E/RT$ as shown in eq 19. Because $\alpha_{\text{max}}$, the fraction reacted at the maximum

$$\ln[\phi(t/m^{(1-x)/x})^{-1}] = \ln(-\Delta H/\beta x^{(1-x)/x} A^{1/x}) - E/RT$$

rate, is independent of temperature, $E$ for an autocatalytic reaction can be obtained from $\phi_{\text{max}}$ values obtained as a function of temperature. A plot of $\ln \phi_{\text{max}}$ against $T^{-1}$ should be linear and have a slope equal to $-E/RT$ if $\Delta H$ and $\beta$ are constant. A more exhaustive treatment of the problem of determining Arrhenius parameters from isothermal rate–time curves is given in Brown and Galwey. Determination of $\phi_t$ as a function of time at several temperatures is usually required for obtaining the temperature dependence of the rate law. Isothermal calorimetry has been shown to be a faster and more
accurate method for obtaining activation energies than methods involving analysis of the sample as a function of time.\textsuperscript{25}

Much effort has been expended to develop methods for the simultaneous determination of the rate law and its temperature dependence by temperature scanning calorimetry. Such an approach has both theoretical and experimental difficulties.\textsuperscript{25–31} Resolution of many of these difficulties has occurred only recently.\textsuperscript{32–35} Thus, rate laws derived from temperature scanning methods must be regarded with skepticism, particularly from older literature. Further discussion of this topic is beyond the scope of this review.

In the context of this paper, temperature scanning calorimetry, particularly of the heat conduction type with approximately a 1 mL sample capacity, is very useful for quickly establishing the temperature range of applicability of isothermal methods. Because the activation energies of very slow reactions tend to be very large and because changing the operating temperature of an isothermal calorimeter may take a day or more, determination of the appropriate temperature range for a study can be a slow process by isothermal calorimetry. Slow scans of different size samples in a large-volume (\approx 1 mL) DSC allow rapid determination of the range of temperatures over which the reaction will produce a measurable heat rate and not be too fast to study by isothermal calorimetry.\textsuperscript{13,14,20}

**Sample Preparation**

Typically, samples are simply sealed in a container and placed in the measuring chamber of the calorimeter. However, if meaningful results are to be obtained, several precautions must be followed. The history of the sample must be known, i.e., the time at which \( t = 0 \) is required. Calorimetric measurements can rarely be started at \( t = 0 \), but the time of the measurement on this time scale must be known. Measurements need not be continuous, but the sample must be held at the measurement temperature between measurements. Because very small heat rates are often measured, care must be taken to ensure that the measured heat comes from the sample and not from the container or contaminants. The sample container must not react with the sample and must not produce heat itself. Loss or gain of volatiles from labels, solvents, fingerprints, etc., on the container must be avoided. Actinically glass and plastic containers are usually problematic because of slow and variable reactions in these materials. Freshly machined, swaged, or cleaned metal containers often produce heat for some time and should be aged and tested before use. The heat rate produced by an empty container should always be measured before use. If reaction of the sample with the container is a possibility, containers of different materials can be used to determine if the container material has an effect on the results. Elastomeric seals can be a problem because of energy release from relaxation, loss of volatiles such as plasticizers, and transport of gases. For example, most fluorocarbon polymers are quite permeable to water, oxygen, nitrogen, and other low molecular weight gases. One of the most reliable and simple sample containers is a flame-sealed glass ampule. Copper wire and Magic Transparent Scotch tape have been found to be unreactive near room temperature and are sometimes useful for labeling and supporting sample containers.

Many of the slow reactions of interest involve a gas as one of the reactants, e.g., oxidation by oxygen, reaction with water vapor, and reactions with acidic or basic gases such as \( \text{CO}_2 \) or \( \text{NH}_3 \). If a sealed sample container is used, care must be taken either to buffer the concentration of the gas in the container or to see that the reactant is not depleted during the time of the experiment. Some gases can be buffered in a sealed container by adding an open vial of a material with a fixed vapor pressure to the sample container. For example, water vapor pressure over the sample can be fixed with saturated salt solutions.\textsuperscript{37,38} and carbon dioxide can be buffered with a bicarbonate solution.\textsuperscript{39} Alternatively, the headspace over the sample may be perfused with a gas stream of known temperature, composition, and constant flow rate.\textsuperscript{40} Perfusion usually leads to greater baseline uncertainty and the possibility of unwanted reactions, however.

The concentration of gases in the headspace can be changed by changing the gas composition or by changing the pressure. Flexible glass capillary tubing such as that used for gas chromatography columns is a convenient material to use for connection of the sample container to a high-pressure gas source.\textsuperscript{13}

**Illustrative Examples of Applications**

References to early uses of calorimetry to study slow processes can be found in Calvet\textsuperscript{4} and Calvet and Prat.\textsuperscript{41} More recent literature is too extensive for a full review here, so only key, particularly illustrative, examples of particular interest to the author are discussed.

**Kinetics of Reactions in Solution: Tests of Methodology.** Numerous studies of reactions in solution have been done to verify the applicability of isothermal calorimetric techniques for determination of kinetics of reactions in solution. Acetylsalicylic acid (aspirin) hydrolysis as a function of pH and temperature is a commonly used test reaction. The results are typically in good agreement with results from other methods.\textsuperscript{42,43} In 1982 the hydrolysis reaction of triacetin in imidazole/acetic acid buffer was proposed as a means for testing the calibration of calorimeters for heat rate measurements.\textsuperscript{44} Details of the kinetics of triacetin hydrolysis have recently been published.\textsuperscript{45}

**Lovastatin: Autocatalytic Oxidation of a Pure Material.** Hansen et al.\textsuperscript{8} explored the theory and methodology for applying isothermal heat conduction calorimetry to degradation reactions of pure, solid materials, with primary emphasis on decomposition of drugs. The autocatalytic oxidation of Lovastatin (Mevacor), a cholesterol-lowering drug, was the focus of the experimental studies reported in the paper. Figures 2 and 3 illustrate the data collected. A following paper\textsuperscript{23} described the use of heat rate measurements made near the beginning of the induction period to predict the shelf life of different lots of Lovastatin. Figure 4 summarizes the conclusions of that paper. Angberg et al.\textsuperscript{42,43,46–50} Buckton and Beexer,\textsuperscript{51} Buckton et al.\textsuperscript{52} Pikal,\textsuperscript{53} Pikal and Dellerman,\textsuperscript{54} and Koenigbauer\textsuperscript{25} have reviewed the applications of calorimetry to pharmaceutics.

**Pineapple Juice Concentrate: A Complex Food Product.** The purpose of this study\textsuperscript{44} was to optimize the process by which pineapple juice is concentrated. If the juice is heated at too high a temperature or for too long a time, it turns brown and develops a bitter taste. Samples of concentrate prepared on a laboratory scale
by a low-temperature vacuum method were used in the study. A DSC method was first used to identify the temperature range to be studied (see Figure 5), and then isothermal heat conduction calorimetry was used to determine the rate laws and identify the reactions occurring in the concentrate (see Figure 6). Two reactions were identified. A reaction first order in time and independent of O₂ concentration was shown to be sucrose hydrolysis, and the other reaction zero order in time and dependent on O₂ concentration was shown to lead to the formation of colored and bitter products from oxidation of glucose and other components of the juice. Reactions were identified by the addition of known components followed by determination of the effects of the addition on the kinetics of the two reactions. Potential catalysts and inhibitors of the reactions were studied in the same way. A contour map of juice quality versus time and temperature was the final result of the study.

Polymers and Oils: Oxidation. Isothermal calorimetry has primarily been used only to determine the induction time for onset of autocatalytic oxidation, although it is clear from some data that measurement of heat rates during the induction time could be used to predict shelf life, i.e., the time to onset of rapid oxidation. Budrugeac and Segal have partially reviewed some of the applications of calorimetry to relative prediction of the organic polymer lifetime. No review has been published on the calorimetric determination of the stabilities of oils, both edible and technical, but calorimetric methods have frequently been used for this purpose. A primary interest in connection with both polymers and oils has been in assessing the effects of molecular structure and the efficacy of different antioxidants on oxidation rates. No use has been made of the heat rate during the induction periods to predict lifetimes of these materials.

Crystallization: Change in Physical Properties. Isothermal calorimetry can be used to measure the rate
of crystallization of materials as exemplified by the data in Figure 7. Besides polymers, crystallization rates have also been measured, for example, on mullite, caffeine, and aluminum alloys. Methods for deriving the rate laws for phase transformations directly from the calorimetric data have been developed. The degree of disorder within partially crystalline materials can also be measured by calorimetry, either from measured enthalpy changes on dissolution of the sample or from measurement of the heat rate produced during crystallization of the amorphous part of the sample. Measurement of the degree of disorder in semicrystalline materials can often be done by measuring the heat rate after the sample is placed in a sealed container together with a small vial or test tube containing a liquid solvent. The vapor from the solvent catalyzes crystallization of the amorphous fraction of the sample, typically in an autocatalytic fashion. The amount of amorphous material is thus obtained from integration of the peak in the heat rate curve that occurs during crystallization. Figure 8 shows the data obtained with a purely amorphous drug in the presence of 30 μL of water in a 1 mL ampule. Reprinted with permission from ref 61.

Figure 7. Heat rate from crystallization of amorphous polypropylene containing various antioxidants at 70 °C.

Figure 8. Heat rate from 25.8 mg of a pure, 100% amorphous drug in the presence of 30 μL of water in a 1 mL ampule. Reprinted with permission from ref 61.

Polymerizations, Adhesives, and Cements: Slow Reactions of Sample Components. Isothermal calorimetry has been used to study the processes involved in curing, setting, aging, and polymerization of polymers, adhesives, and cements.

Sorption of Water: Thermodynamic Information from Kinetic Data. A rapid calorimetric method for determining the equilibrium water vapor pressure over a hydrate or saturated solution has been developed. The vapor space over the sample in an isothermal calorimeter is titrated with water vapor generated by continuously scanning the temperature of a container of water outside the calorimeter or by mixing dry and saturated gas streams. The rate of heat production in the sample, which is proportional to the rate of water sorption by the sample, remains very small until the equilibrium water vapor pressure of the phase being formed is reached. The heat rate increases linearly with water vapor pressure above the equilibrium water vapor pressure. The change in $d\phi/dp_{H_2O}$ signals the appearance of a new phase. In the regions of the titration curve before and after a phase change, the value of $d\phi/dp_{H_2O}$ is proportional to the rate for water sorption.

Batteries: Corrosion, Electrochemistry, and Electrolysis. A battery on the open circuit may be considered as simply a package of energy. The rate of loss of that energy, and hence the lifetime of the battery, may be determined by simply inserting the battery into an isothermal calorimeter. This principle is the basis for calorimetric quality control tests now routinely done on batteries to be used in critical applications such as heart pacemakers and satellites. Corrosion of battery materials under both open- and closed-circuit conditions can also be studied by isothermal calorimetry.

Explosives: Decomposition of High-Energy Materials. High-energy materials usually have decomposi-
tion rates readily measurable at low temperature by isothermal calorimetry.²⁰,²¹

Compatibility of Materials: Hazard Analysis and Excipient Reactions in Pharmaceuticals. Because heat is probably the most general indicator of the occurrence of chemical and physical reactions, the presence or absence of a heat effect can be used as an indicator of the presence or absence of any reaction. This principle has been used in hazard analysis to determine whether mixing of materials such as chemical wastes together or storage of high-energy compounds will create a potentially hazardous situation.²¹,²² Materials can be mixed in very small quantities, and the heat rate can be measured within a few minutes with quite simple calorimetric equipment in this application.²³ The question of how various components of a drug formulation affect the long-term stability can be answered quite rapidly by measuring the heat rate from various formulations under various conditions.²⁵,²⁴,²⁵

Metabolic Rate: Growth Rate, Toxicity, Stress, Biochemistry. The same calorimetric methods used for measurement of slow processes can be used to measure the metabolic rate of organisms, tissues, and cell cultures. Measurements of the metabolic rate can among other things be used to determine the growth rate.²⁴,²⁵,²⁶ Toxicity,²⁷ response to environmental stress,²⁸,²⁹,³⁰ and relative activities of biochemical pathways.²⁹,³⁰

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