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ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY · MAY 1995

Impact Factor: 2.78 · DOI: 10.1021/j100018a051

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Determination of Thermodynamic and Kinetic Parameters from Isothermal Heat Conduction Microcalorimetry: Applications to Long-Term-Reaction Studies

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Received: September 12, 1994; In Final Form: February 22, 1995⊗

The application of heat conduction isothermal microcalorimetry has been proposed for some time as a rapid and general technique for the determination of both thermodynamic and kinetic parameters of chemical reactions. These applications have been suggested as being of particular relevance to solid-state reactions and, industrially important, to the prediction of long-term stability and of compatibility data for pharmaceutical materials. However, there has yet to be the development of a *general* procedure that does not require additional noncalorimetric data and that is free of assumptions, which can be used to determine the thermodynamic and kinetic parameters for a reaction, from calorimetric data. It is the purpose of this paper to describe such a general approach which does not depend upon knowledge of initial concentrations (quantity), enthalpy, or any predetermined reaction order. Equations have been developed which incorporate calorimetrically accessible data (Φ, the power, and q, the heat output) and which also include the rate constant, k, the change in enthalpy of the reaction, ΔH, and the order of reaction. A second procedure is also described which depends *only* on the analysis of the calorimetric signal and which involves no formal chemical kinetic based equations. The methods described allow estimation of, for example, the annual extent of degradation of a solid compound. The methods developed have been tested through examination of both calculated and experimental data. The experimental work examined very slow reactions (lifetime of years) of known order (there are little reliable enthalpy data available for slow reactions) and involved calorimetric observation of these reactions for up to 50 h. In all cases, the method yielded the appropriate, i.e., conforms to literature data, rate constant, reaction order, and, where available, reaction enthalpy. Some situations in which this microcalorimetric approach and subsequent data analysis will be of utility are discussed.

Introduction

All chemical and physical changes are accompanied by changes in heat content or enthalpy. Thus, in principle, all chemical reactions, including solid-state, solution-phase, gas-phase, biological, etc., can be studied in microcalorimeters. Heat conduction, isothermal microcalorimetric output is of power (Φ in watts) vs time and hence is capable of analysis to produce not only thermodynamic data but also the kinetic data. The thermodynamic data are, of course, not strictly capable of molecular interpretation in the absence of other information, e.g., chemical analysis. However, kinetic data are the foundation of mechanistic investigations, and many of the systems of interest (drug stability, compatibility, solid-state reactions, biological processes, etc.) are complex and present considerable difficulties in analysis. Microcalorimetry, being a general reaction investigation method, may, therefore, be of some advantage in the study of complex, heterogeneous reaction systems without the need for additional analytical investigation.

The development of a treatment for flow microcalorimetric investigations was presented some time ago[1] as was the basis of the dynamic correction treatment of microcalorimetric output data.[2] This latter presentation was really concerned with correcting the output data for the thermal lags within the calorimetric system. There has, to date, been no wholly satisfactory data treatment method presented which is of more universal application.

Determination of the kinetics of solid-state reactions and, in particular, of the decomposition of drugs is known to be a particular problem.[3−8] Indeed, the work of Hansen et al.[8] gives a detailed account of the background to the determination of **kinetic** parameters from heat-leak calorimeters. This publication also provides a detailed discussion of the needs of such a method if it is to prove an acceptable alternative to the well-established and almost universally practiced policy of conducting stability-indicating studies at elevated temperatures and extrapolating to the required storage conditions through application of the Arrhenius equation.[5] A recent review[9] has also provided an overview of the applications of microcalorimetry in the field of physical pharmacy. This review describes the problems associated with high-temperature stability-indicating investigations and, in particular, provides a comparison of isothermal and scanning calorimetry with respect to their sensitivities in such studies. It can be shown[9] that a commercial DSC (for example, a Perkin-Elmer DSC 7) is some 10 000-fold less sensitive than a current commercially available heat conduction microcalorimeter (TAM, Thermometric AB, Jarfalla, Sweden). The use of high-temperature studies and the subsequent application of the Arrhenius equation do, however, require the assumption that the observed high-temperature process is the same as that which occurs at the lower temperature of interest. The use of isothermal heat conduction microcalorimeters in estimating long-term stabilities and in the study of long, slow reactions has not increased in relation to this sensitivity gap in part because of the absence of some general method of data management which can yield the desired kinetic data independently of the knowledge of any other data, e.g., enthalpy, chemical analytical result, etc.

The most detailed procedure described so far[8] relies upon the establishment of equations which are of fixed, and in principle only, integral order. An example is presented which,

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⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1995.

0022-3654/95/2099-7108$09.00/0

TABLE 1[a]

reaction	corresponding rate eq	transformed eq that can be applied to calorimetric data
$A \rightarrow B$	$dx/dt = k(A - x)^m$	$dq/dt = \Delta Hk(A - (q/\Delta H))^m$
$A + B \rightarrow C$	$dx/dt = k(A - x)^m(B - x)^n$	$dq/dt = \Delta Hk(A - (q/\Delta H))^m(B - (q/\Delta H))^n$
$A \leftrightarrows C$	$dx/dt = k(A/x_e)(x_e - x)$	$dq/dt = kA(\Delta H - (q/x_e))$
$A + B \rightleftharpoons C$	$dx/dt = k_1(A - x)(B - x)$	$dq/dt = k_1(A\Delta H - q)(B\Delta H - q) - (k_{-1}q)$
Ng equation[b]	$dx/dt = Ak(x/A)^m(1 - (x/A))^n$	$dq/dt = Ak\Delta H(q/A\Delta H))^m(1 - [q/(A\Delta H)])^n$
autocatalytic	$dx/dt = k(A - x)(x_c + x)$	$dq/dt = k(A\Delta H - q)(x_c\Delta H + q)$
coagulation	$dx/dt = k(z - x)^2$	$dq/dt = k\Delta H(z - (q/\Delta H))^2$
Michaelis–Menten[c]	$d[ES]/dt = k(K_c[E][S])$	$dq/dt = k\Delta H(K_c[E][S] - (q/\Delta H))$

[a] x_e = concentration (moles) of material that has reacted before equilibrium is established. x_c = concentration of material that has accumulated prior to the onset of reaction. z = initial number of particles of a specific radius prior to aggregation. K_c = the enzyme–substrate equilibrium constant. [b] This equation is taken from ref 17 and is claimed to permit analysis of thermal decomposition in the solid state. [c] First-order form of the Michaelis–Menten equation.

under certain constraints, can be used to describe nonintegral-order reactions. The discussion does not explore the investigation of such reactions nor indeed propose a *general* treatment for any order of reaction, subject to changing order throughout the reaction lifetime. The purpose of the method developed in this paper is to permit direct analysis of calorimetric data *without* any prior assumptions and is that the outcome of the analysis yield reaction order, rate constant, and enthalpy for the reaction under study. It is also a requirement of a successful treatment method that if the reaction mechanism changes through the observation period, then this should be indicated by the treatment and that the parameters for each contributing reaction process be determinable.

Any developed method should find wide application in many areas—more particularly in the more intractable problems associated with the study of heterogeneous reaction systems. Such systems cover the range of *solid-state degradation reactions*, *compatibility trials*, *polymerization reactions*, *latex coagulation*, *solid-state oxidations*, *multiphase systems*, etc.

Theoretical Approach

This paper details two methods that can be employed for the interpretation of calorimetric data. The first method is a perfectly general method of analysis and can be extended to reactions of integral or nonintegral order and to reactions in any or mixed phases. The method requires neither preconceptions about the nature of the reaction nor additional analytical techniques to supply auxiliary data. In general, the calorimeter produces two types of data: heat flow, dq/dt (Φ in watts), and heat output (q in joules). The analytical method involves a plot of heat flow against heat output. Through use of an iterative procedure, one can then determine the rate constant, order, and change in enthalpy (ΔH) for the reaction. There is a second method of analysis that can be used for the determination of the extent of reaction. This method is independent of any knowledge of concentration terms. It can be applied to complex heterogeneous mixtures where there may be several competing reactions.

Development of the Equations

For the **first** method of analysis, it is necessary to write suitable equations that can be applied to the calorimetric data. Although here the equations have been written for solution-phase reactions for simplicity, these types of equations can be applied to other types of reaction schemes, phases, and stoichiometry, e.g., solid-phase reactions, compatibility studies, etc. (see Table 1).

From a general reaction scheme such as

$$aA + bB \rightarrow cC$$

where a, b, and c are determined by the stoichiometry of the equation, one can write a general kinetic equation to describe the reaction

$$\frac{1}{c}\frac{dC}{dt} = -\frac{1}{a}\frac{dA}{dt} = -\frac{1}{b}\frac{dB}{dt} = k(A - ax)^m(B - bx)^n \quad (1)$$

This general kinetic equation can be applied to calorimetric data by substituting for x (the number of moles of A that have reacted at time t), by the heat output, for the same time period, measured from the calorimeter (q) divided by the change in enthalpy for the reaction. As $q = x\Delta H$, so $x = q/\Delta H$ and hence

$$\frac{dq}{dt} = \Phi = k\Delta H\left(A - \frac{aq}{\Delta H}\right)^m\left(B - \frac{bq}{\Delta H}\right)^n \quad (2)$$

By entering the calorimetric data into a suitable graphics software package (see results and discussion), the heat flow (Φ) can be plotted against the corresponding heat output (q) for any reaction or physical process under study. Applying an appropriate equation, such as eq 2, the constants of the equation (k, ΔH, and order) can be determined by a process of iteration.

An alternative approach is to use an integrated form of the equation; here the stoichiometric coefficient has been omitted for simplicity:

$$q = k\Delta H\left(A - \frac{q}{\Delta H}\right)^m\left(B - \frac{q}{\Delta H}\right)^n t \quad (3)$$

By plotting q vs t, the same procedure of iteration can be used to determine the constants of the equation. This method has the advantage that there is less error associated with the abscissa because q is the cumulative area under the Φ–t curve (cf. eq 2, where the abscissa is determined by the value of Φ). It also permits the calculation of either the thermodynamic or kinetic parameters for zero-order reactions if one or the other parameter can be determined by another procedure/experiment.

$$\Phi = k\Delta H\left(A - \frac{q}{\Delta H}\right)^0 \quad \text{so} \quad q = k\Delta Ht \quad (4)$$

It should be noted that A term in the above equations is not restricted to the number of moles of starting material. A mass term, area, concentration, etc., can be substituted for A (see Table 1).

Entering approximate values (for convenience) of k, ΔH, A, and order into the curve-fitting graphics package (see Results and Discussion) and applying the appropriate equation, the constants of the equation can be determined. The parameters derived from this treatment will remain constant over the time period for which the mechanism of reaction is unchanged. A change of mechanism will result in the derivation of different values of k, ΔH, and order. Thus, in exploiting this treatment, calculation of k, ΔH, and order should be made at time intervals along the Φ vs q plot. Variations in the derived parameters

should be ascribed to changes in the reaction mechanism. For example, a solid-state oxidation rate may be surface area controlled initially but, after formation of an oxide annulus, may become diffusion controlled. By taking sections of data at different time periods along the power−time curve and calculating the kinetic and thermodynamic parameters, progressing along the power−time curve, these values should remain constant as long as the surface oxidation mechanism of the reaction remains constant for the life span of the experimental analysis. If there is a change in reaction mechanism to say diffusion controlled, the point at which the rate constant and/or order changes can be identified.

For reactions that are sufficiently fast and that are first order, a related but simpler method can be used to determine the rate constant for the reaction. As $q = x\Delta H$, so $q_{total} = A\Delta H$, assuming the reaction goes to completion, where q_{total} is the total heat output for the reaction and A is the initial number of moles of starting material.

For a first-order reaction,

$$\frac{dq}{dt} = \Phi = k(A\Delta H - q) \quad \text{so} \quad \Phi = k(q_{total} - q) \tag{5}$$

By taking two time points, t_1 and t_2, along the calorimetric signal, one can determine Φ_1 and Φ_2 and the corresponding q_1 and q_2 values. Writing eq 5 for times t_1 and t_2 produces

$$\Phi_1 = k(q_{total} - q_1) \qquad \Phi_2 = k(q_{total} - q_2) \tag{6}$$

The elimination of q_{total} from the equations yields

$$k = \frac{\Phi_2 - \Phi_1}{q_1 - q_2} \tag{7}$$

By taking pairs of data points Φ_1, Φ_2 and q_1, q_2 progressively along the calorimetric power time curve, the calculated rate constant will remain the same, provided that the mechanism of the reaction does not change. This method can only be applied to relatively fast reactions that have significant changes in Φ_1 and Φ_2 values as a function of time.

The **second** method of analysis is a procedure for the determination of the extent of reaction. It should be noted that no thermodynamic, kinetic (in terms of rate constants), or mechanistic information can be derived from this method; only the extent of reaction at time = t can be found. The value of this method is that it can be applied to a compound or mixed compounds of unknown compositions that possess complex reaction paths (e.g., solid-state reactions) and that cannot be evaluated by other methods of calorimetric data analysis. The only requirement necessary for analysis by this method is that an nth order fitting equation can be found that will describe the power−time signal from the calorimeter for the reaction. In exploiting this method of analysis, only the calorimetric output data are analyzed, and there is no implication of a kinetic order deduced for the process under observation. The method proposed allows identification of percentage reaction of the sample up to a specified time. For simplicity, we have illustrated this method using an equation that will describe an exponential-type power−time signal, (although, as noted above, any equation fitted to the calorimetric output data can form the basis of the analysis.)

$$\Phi = ae^{-kt} \tag{8}$$

where Φ is the heat flow for the reaction, a is the initial heat flow at $t = 0$, and k is a constant of the equation (experimental constant). It should be noted that the signal observed, Φ, at $t = 0$ is directly proportional to the quantity of reacting material present. Also note that the experimental signal decay, used for simplicity, to illustrate this second method of analysis would also conform to the expected signal for a first-order kinetic process.

The procedure, on writing a suitable equation for the observed power−time signal, is to determine the experimental (*not* rate) constant, k. This can be achieved by integrating the equation between $t = 1$ and $t = 2$:

$$q = \int \Phi \, dt = \left(\frac{a}{-k}e^{-kt_2}\right) - \left(\frac{a}{-k}e^{-kt_1}\right) \tag{9}$$

From the **calorimetric data** produced from the reaction under study, the value of q, the associated time period (t_1 and t_2), and a value of a (Φ at $t = 1$) can be inserted into the equation. Then by a process of iteration, k can be determined. The integrated equation can then be rewritten for a time period of say 1 year ($t_1 = 0$ and $t_2 = 1$ year), and inserting the previously calculated value of k, the heat output q_{1year} (the heat output for the reaction for 1 year) can then be calculated. The calculation can also be made for the heat output for the total life span of the reaction ($t_2 \rightarrow \infty$). Thus, the fraction of reaction over the time period studied = q_{1year}/q_{total}.

The procedure for analyzing an unknown compound of an unknown molar quantity placed in the calorimeter is to make calorimetric observations for, say, 50 h (50 h being the time period necessary to produce an *area* (in joules) under the power−time curve that is large enough to differentiate between an exponential experimental constant of 1×10^{-11} and an exponential experimental constant of 2×10^{-11} s^{-1}). Other reaction mechanism may require different time periods to effect the discrimination described here. This illustration is offered to allow some indication of the sensitivity of the calorimeter, operated under optimal conditions and recording a signal of ~0.1 μW.

From the calorimeter, a value of heat output for the 50-h period can be determined (q_{50}); i.e.,

$$q_{50} = \left(\frac{a}{-k}e^{-kt_{50}}\right) - \left(\frac{a}{-k}1\right) \tag{10}$$

By a process of iteration, k, here the ***experimental constant***, can then be determined. (Note, in the case of a *first-order reaction*, that the experimental constant is the same as the reaction first-order rate constant.) The annual degradation rate (%), for example, can then be found by determination of q_{1year} (the heat output for 1 year, etc.) and q_{total} (the total heat output for the reaction), which can be calculated from

$$q_{total} = \frac{a}{k} \tag{11}$$

Thus, $(q_{1year}/q_{total})100$ = % degradation p.a. For example, consider a solid compound of M_{wt} 100, of which a 1 g sample is loaded into the calorimeter. Assuming that the sample exhibits an exponential calorimetric signal upon degradation, with an associated ΔH value of −50 kJ mol^{-1}, the heat output for this 1 g sample over a 50-h period would be 0.018 J or 1.8×10^4 μJ. Assuming a modest, initial heat flow (a) of 0.1 μW, the *experimental constant* can be calculated by **iteration** of the equation

$$q_{50} = 1.8 \times 10^4\ \mu\text{J} = \left(\frac{0.1}{-k}e^{-k(1\text{year})}\right) - \left(\frac{0.1}{-k}\right) \tag{12}$$

The calculation of the experimental constant, in this case, reveals

TABLE 2: Base Hydrolysis of Ethyl Ethanoate in Aqueous Solution (0.01 mol dm^{-3} Ethyl Ethanoate and 1 mol dm^{-3} Sodium Hydroxide)

time, h	calcd rate const, dm^3 mol^{-1} s^{-1}	pub rate const,[12] dm^3 mol^{-1} s^{-1}	ΔH_{cal}, kJ mol^{-1}	order
1–5	$7.9 \times 10^{-2} \pm 3 \times 10^{-3}$	7.25×10^{-2}	29.9 ± 4.3	2
5–6	6.5×10^{-2}		mixed variable ΔH	1.74[b]
6.2–7	$5.3 \times 10^{-4} \pm 5 \times 10^{-6}$		29.0 ± 3.1	1
7–8	$6.0 \times 10^{-4} \pm 7 \times 10^{-6}$		28.5 ± 3.0	1

[a] Variable rate constant. [b] Mixed, variable order.

a value of $k = 2 \times 10^{-10}$ s^{-1}. By reinserting this experimental constant into the equation and integrating between $t = 0$ and $t = 1$ year, q_{1year} can be determined as

$$q_{1year} = \left(\frac{0.1}{-2 \times 10^{-10}} e^{-2\times10^{-10}(1year)}\right) - \left(\frac{0.1}{-2 \times 10^{-10}}\right) \quad (13)$$

$q_{1year} = 3.1$ J, and again, integrating between $t = 0$ and $t =$ infinity yields q_{total}; $q_{total} = 500$ J. The annual degradation rate is thus (3.1 J/500 J)100%, *0.62% pa.*

Results and Discussion

The experimental evaluation of these two methods of analysis is limited by the lack of published kinetic and thermodynamic data characterizing very-long-term reactions. There is extensive tabulation for relatively short-term reactions of the kinetic data (order, rate constants, activation energy, etc.) published, but it is seldom associated with good thermodynamic data. We have, therefore, used as an illustration for the first method of analysis, the base hydrolysis of ethyl ethanoate (ethyl acetate), the oxidation of ascorbic acid, and the imidazole-catalyzed hydrolysis of triacetin. The second method of analysis has necessarily been evaluated using theoretical data since there appears not to be any reliable, easily accessible, extensive, long-term (years) kinetic data published. All experiments were carried out at 298.15 K using the isothermal microcalorimeter (TAM Thermometric, Sweden). The operation of this instrument was as described in the manufacturer's manual.[10] For additional details, see ref 11. Calorimetric data should be, in principle, collected over at least a 50-h time period, using the dedicated Digitam software. This is to ensure the accuracy of the calculation of thermodynamic and kinetic parameters of very slow reactions (50 h being the time required to have a significantly different area under the power–time curves for two first-order reactions of rate constants 1×10^{-11} and 2×10^{-11}). However, the reactions that we report in this paper have involved time periods for the calorimetric analysis that varied from 10 h to 20 days. The 10 h analysis was for reactions that were relatively fast and therefore do not require extended data collection. The calorimetric analysis that was run for 20 days was on a slow reaction and was also carried out to ensure that the isothermal microcalorimeter was consistently stable over very long time periods. This gives us confidence in the sensitivity of the calorimeter over long periods of data collection.

The calorimetric data were analyzed by converting the data to ASCII files and importing them into Origin, a graphic curve-fitting package.

Figure 1 shows the power–time graph for the base hydrolysis of ethyl ethanoate at 298.15 K. This hydrolysis reaction has been shown[12] to have an overall order of 2: first order with respect to ethyl ethanoate and first order with respect to sodium hydroxide. The power–time curve obtained reveals discontinuities that indicate changes in reaction mechanism and/or order throughout the lifetime of the reaction. The analytical methods described in the theoretical section permit the identification, and

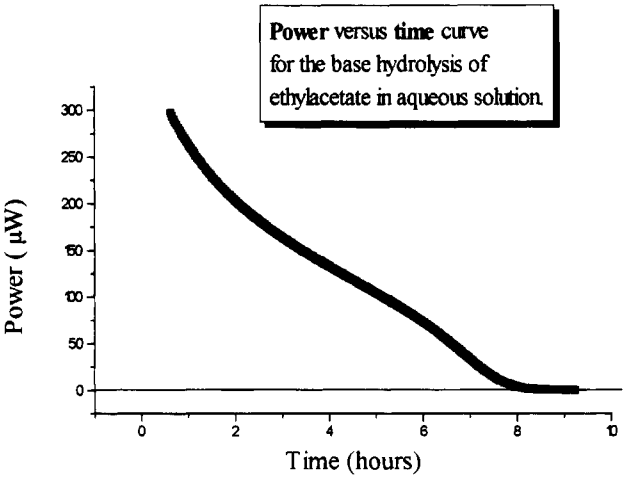

Figure 1. Base hydrolysis of ethyl ethanoate in aqueous solution. A solution of 0.01 mol dm^{-3} ethyl ethanoate and 1 mol dm^{-3} sodium hydroxide was made and equilibrated inside the microcalorimeter for 20 min before data collection commenced. The reaction was carried out, in quadruplet, at 25 °C for a period of 36 h.

the determination, of succeeding order and associated rate constant of the reaction by sequentially analyzing the data using the iterative procedure (see theoretical section). From time $t = 0$ to $t = 5$ h, the reaction, at the selected concentrations, temperature, etc., is second order. The calculated rate constant and the change in enthalpy for the reaction agreed, within experimental error, with literature values (see Table 2). From $t = 5$ h to $t = 6.3$ h, the order of the reaction was mixed and variable, with an overall apparent order of 1.7, and from $t = 6.3$ h to $t = 10$ h, the order of the reaction was 1. We conclude from these results that the concentration of ethyl ethanoate determines these sequential reaction orders. Initially the concentration of ethyl ethanoate is relatively high, and the concentration of base is in excess at all times. As the reaction proceeds, the concentration of ethyl ethanoate becomes limiting, passing through a mixed order period before the reaction becomes pseudo-first-order with respect to ethyl ethanoate. The reaction then goes to completion when the ethyl ethanoate is exhausted.

Figure 2 shows a power–time curve for the oxidation of ascorbic acid in aqueous solution. Previously published data[13] show that this reaction involves two steps: the oxidation of ascorbic acid to dehydroascorbic acid followed by the hydrolysis of dehydroascorbic acid to other products. This reaction has been characterized previously[13] and has been shown to be first order for both the oxidation step and for the hydrolysis step. The calorimetric data were analyzed using the proposed iterative procedure, sequentially, along the power–time curve. From $t = 0$ to $t = 1.8$ h, the reaction that relates to the oxidation step could be identified. The determined rate constant and change in enthalpy are, within experimental error, as previously published (ref 13; see Table 3). Between $t = 1.8$ h and $t = 3$ h, the rate constant for the reaction became mixed (indeterminable). From $t = 3$ h to $t =$ (ca.) 50 h, the reaction was first

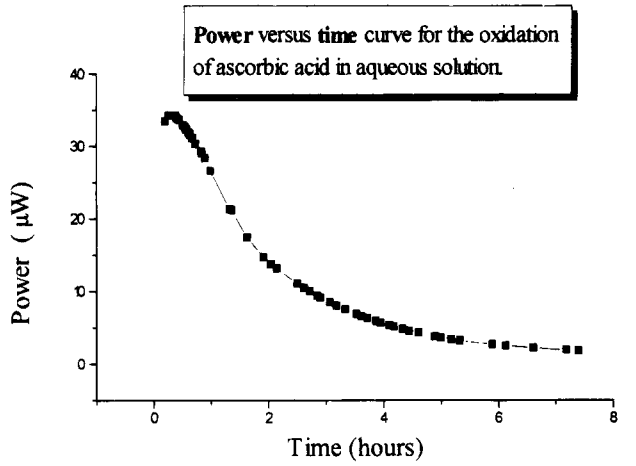

Figure 2. Power–time curve for the oxidation of ascorbic acid in aqueous solution. A 2 mmol dm^{-3} ascorbic acid solution at pH 6 that was completely saturated with oxygen was used. The reaction was studied over a 60-h period at 25 °C.

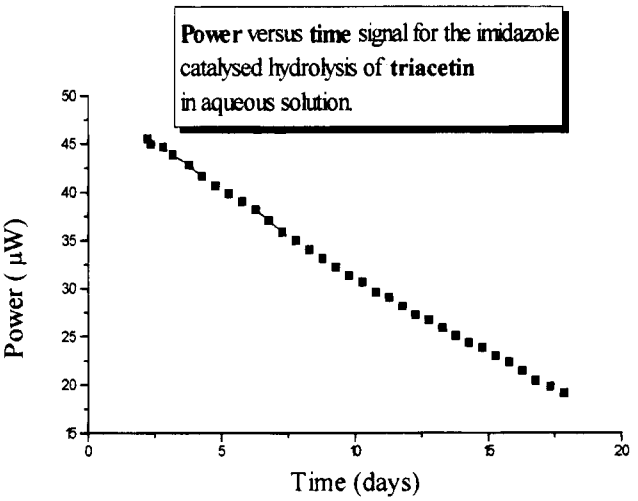

Figure 3. Imidazole-catalyzed hydrolysis of triacetin reaction in aqueous solution. The proportions of triacetin and imidazole buffer were those described by Wadso et al.[14] This reaction has been studied over a period of 20 days at 25 °C.

TABLE 3: Oxidation of Ascorbic Acid in Solution (2 mmol dm^{-3} Ascorbic Acid, pH 6, Solution Saturated with Oxygen[13])

time, h	rate const, s^{-1}	order	ΔH, kJ mol^{-1}
0.33–1.5	$2.8 \times 10^{-4} \pm 6.1 \times 10^{-5}$	1	116.7 ± 16.5
1.5–3	variable		
3–6	$6.35 \pm 7.7 \times 10^{-6}$	1	129.9 ± 12.5

order with an associated rate constant and change in enthalpy consistent[13] with the hydrolysis reaction of dehydroascorbic acid.

Figure 3 shows the power–time curve for the imidazole-catalyzed hydrolysis of triacetin. This reaction has been previously proposed as a method of calibration of an isothermal flow calorimeter[14] by identification of the calorimetric signal as a function of time. The published data were not analyzed for reaction order or for rate constants nor was the reaction characterized thermodynamically. Using the above iterative method of analysis, the order of the reaction was determined as first with an associated rate constant of 1.18×10^{-6} s^{-1} and a change in enthalpy of 34.7 ± 0.3 kJ mol^{-1}. The rate constant determined for this reaction agreed, within experimental error, with literature values. The reaction was carried out over a time period of 20 days. A more detailed study, characterizing this reaction up to 40 days, will be reported in a future publication.[15]

Conclusion

The isothermal calorimeter is a nondestructive, noninvasive analytical tool that is sensitive enough to measure, for example, the reaction rate of a compound that has a first-order rate constant of 1×10^{-11} s^{-1} (the half-life of such a reaction is **2200 years**). On integration of the power–time curve, the heat output for the reaction can be determined. Therefore, as we have shown, the calorimeter is capable of producing two types of data, heat flow (Φ, this may be regarded as a kinetic term) and heat output (q, thermodynamic term). Using the analytical method described above, from a plot of heat flow vs heat output from the calorimetric data, and then through use of an iterative program, one can determine the constants of the kinetic/thermodynamic equation. This new analytical method offers a procedure that can accurately determine rate constants, kinetic order, and change in enthalpy for the reaction under study. The application of this analytical procedure is perfectly general and is independent of the phases or nature of the material being analyzed (solid state and solution, gas, or mixed phases). By analyzing the calorimetric data sequentially over time, information about changes in reaction mechanism can be determined as well as the associated thermodynamic parameters. For example, results for the solid-state oxidation of ascorbic acid[16] have indicated that, initially, oxidation occurs at the surface of the ascorbic acid crystals, and as an annulus of oxidized material is formed, the rate subsequently becomes limited by the rate at which oxygen can diffuse through the annulus to the remaining reactable ascorbic acid surface (a detailed study of the oxidation of ascorbic acid in the solid state will be published at a later date).

The second method of analysis described above in the theoretical section requires *no* prior assumptions about order, rate constants, or enthalpy and hence is, in principle, perfectly general. It is capable, moreover, of identifying reactions of nonintegral order. This method can be applied to complicated, mixed heterogeneous reactions. The extent of degradation can be determined by integration of the power–time curve from the calorimeter. From this, the experimental constant can be calculated, and this leads to the determination of the total heat output for the reaction and hence to the annual heat output. This finally permits calculation of the annual degree of degradation of the compound.

These mathematical methods for the determination of the kinetics of reaction make the assumption that the observed reaction mechanism remains constant throughout the lifetime of the reaction process. A change in reaction mechanism can only be determined by this method of analysis, if the change occurs within the time period of calorimetric observation.

The types of applications for this method of analysis are numerous and varied. Most obviously, the immediate application is in long-term-stability studies, principally in the pharmaceutical research industry. However, the generality of the technique and the indifference of technique to sample presentation give the analytical method very wide ranging applicability. Extending these obvious uses, we can include applications in which the rate and the thermodynamics of the process are vital but difficult to obtain in anything other than estimated terms. For example, amongst many types of industrial, medicinal, pharmaceutical, and agricultural applications, the analytical method above can be applied to the following (the following list is drawn from presentations to the U.S. calorimetry conference in the last 5 years; these presentations did not include kinetic and thermodynamic data; the analysis of data was phenomenological in context): the determination of the shelf life of drugs and formulations produced by the pharmaceutical

industry; the curing of resins and other materials where the time needed to cure is important; the drying of paints, etc.; growth of crystals in a variety of matrices, e.g., solution emulsions; viability of tissue for grafts, transplants, etc.; the bioactivity profile of biopsy material, e.g., from cancerous growths; photochemistry including free-radical degradation, etc.; the degradation of cellulose (paper and telecommunication industry); the viability and quality of germinating seeds and plant material; the rate of corrosion of materials; the stability and safety of pyrotechnic materials; the performance characteristics of electrical circuits and components, particularly batteries, etc.; food quality and decay rate; microbial growth, metabolism, and response toward metabolic modifiers, e.g., drugs; aggregation of latex; determination of binding constants and thermodynamic parameters for enzyme−substrate reactions; determination of binding constants for drugs to proteins. This list is by no means exhaustive; it simply describes some currently proposed applications of microcalorimetry. The capacity for direct and continuous observation of processes occurring in real samples without the need to use inferential or end-point methods is the great advantage. The analytical techniques proposed in this paper will allow a better identification of crucial kinetic and thermodynamic parameters describing these processes through direct observation that is nondestructive or invasive. The analytical applications are very wide ranging, from homogeneous phases to complex heterogeneous systems.

Acknowledgment. R.J.W. is grateful to Pfizer Central Research, Pfizer Ltd., Sandwich, Kent, for financial support: in particular to Dr. T. Dolan and Dr. P. Brewer for helpful discussions. We are all grateful to Mr. R. P. Lipscombe for specialist technical advice on use of the isothermal calorimeter and for keeping it running at its optimal performance level. We are also grateful to Prof. L. D. Hansen (Brigham Young University) and to the referees of this paper for their constructive comments. R.J.W. is also grateful to various members of Prof. Beezer's research group for testing out the mathematical analytical procedure on their calorimetric data.

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JP9424320