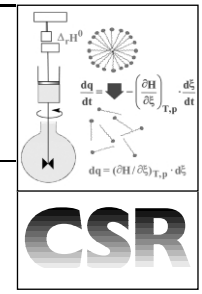
Three important calorimetric applications of a classic thermodynamic equation



Michael J. Blandamer,*[a] Paul M. Cullis[a] and Peter T. Gleeson[b]

[a] *Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH. E-mail: mjb@le.ac.uk; pmc@le.ac.uk*
[b] *19 Deans Street, Oakham, Rutland UK LE15 6AF. E-mail: peter@gleeson.evesham.net*

Received 12th March 2003
First published as an Advance Article on the web 1st July 2003

The thermodynamic background to three calorimetric techniques is discussed; (i) titration microcalorimetry, (ii) adiabatic calorimetry, and (iii) heat conduction calorimetry. Relevant equations for each technique are derived from a common equation for the enthalpy *H* of a closed system. General patterns which emerge in the measured parameters are presented for adiabatic and heat conduction calorimeters linked to applications of these techniques.

1 Introduction

Classic thermodynamics[1] leads to the conclusion that for closed systems at fixed temperature and fixed pressure, all spontaneous chemical reactions drive a given system to a minimum in Gibbs energy, *G*. Moreover for a given closed system, the minimum in Gibbs energy is unique.[2] Enthusiasm for this conclusion is tempered by the realisation that the Gibbs energy *G* of a system cannot be measured. However the isothermal dependence of Gibbs energy on pressure equals the volume of the system[1] which clearly can be measured leading to estimates of partial molar volumes and related compressibility and expansibility parameters[3] although problems are encountered when isentropic compressions are involved.[4,5]

The corresponding isobaric derivative of Gibbs energy with respect to temperature using the Gibbs–Helmholtz equation (1) yields the enthalpy *H*. Thus,

$$H = G - T \cdot (\partial G/\partial T)_p \quad (1)$$

Again unfortunately the enthalpy of a given closed system cannot be measured. Nevertheless thermodynamics shows that differences in enthalpies at constant pressure for a given system as a function of both composition and temperature can be measured calorimetrically.

The independent variable, enthalpy *H*, is defined[1] by the three independent variables, *T*, *p* and ξ, the latter describing the composition – molecular organisation of a given closed system; equation (2).

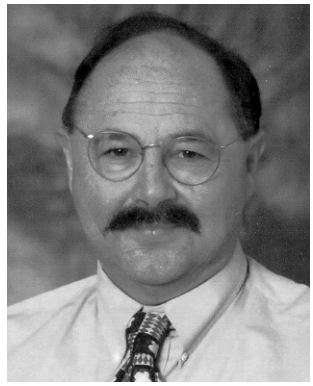
$$H = H[T,p,\xi] \quad (2)$$

Mike J. Blandamer is an Emeritus Professor at the University of Leicester, having retired in September 1999. Mike graduated from the University of Southampton with BSc and PhD degrees in 1961. Following postdoctoral research at NRC in Ottawa (Canada) with Ross E. Robertson, he joined the staff at the University of Leicester. Currently Mike is Vice-President of Oakham Bowling Club and writes reports of club matches in a weekly column for the 'Rutland Times'.

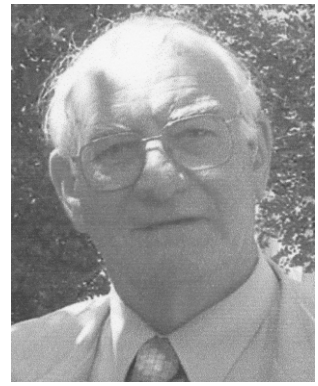
Paul M. Cullis is Professor of Organic Chemistry at the University of Leicester. Paul graduated in Chemistry from the University of Exeter and gained his DPhil. at the University of Oxford. Following a post-doctoral fellowship at The University of North Carolina, Chapel Hill, USA, Paul returned as a post-doctoral fellow at the University of Oxford. Paul was appointed to a lectureship at the University of Leicester in 1981 and then to the chair of Organic Chemistry in 1990. Paul is an avid supporter of the 'Tigers', Leicester City Rugby Football Club.

Peter E. Gleeson retired from the University of Natal, having previously been for 25 years at Middlesex Polytechnic (now Middlesex University). He was educated at various primary schools in India and at St Anselm's College in Birkenhead. He graduated in physics at the University of Liverpool and subsequently qualified as a Chartered Electrical Engineer at Imperial College, gaining a PhD of the University of London in 1980 for studies in vibration at the Department of Mechanical Engineering. Peter is an EBA qualified bowling coach and a leading member of Oakham Bowling Club in Rutland. He plays his viola in the Stamford Chamber Orchestra and the Leicester Symphony Orchestra.

Mike J. Blandamer



Paul M. Cullis



Peter E. Gleeson

 DOI: 10.1039/b207308k

Equation (3) is the general differential[1] of equation (2).

$$dH = \left(\frac{\partial H}{\partial p}\right)_{T,\xi} \cdot dp + \left(\frac{\partial H}{\partial T}\right)_{p,\xi} \cdot dT + \left(\frac{\partial H}{\partial \xi}\right)_{t,p} \cdot d\xi \quad (3)$$

At this stage the signs of dp, dT and dξ are not defined. For isobaric changes, the change in enthalpy is given by the heat dq recorded by, for example, a calorimeter. Then

$$dq = \left(\frac{\partial H}{\partial T}\right)_{p,\xi} \cdot dT + \left(\frac{\partial H}{\partial \xi}\right)_{t,p} \cdot d\xi \quad (4)$$

Here $(\partial H/\partial T)_{p,\xi}$ is the differential dependence of enthalpy H on temperature at constant pressure and composition whereas $(\partial H/\partial \xi)_{T,p}$ is the differential dependence of enthalpy H on composition at fixed temperature and pressure. Equation (4) is the key equation for three calorimetric techniques reviewed here; (i) titration micrcrocalorimetry,[6–11] (ii) adiabatic calorimetry[12–14] and (iii) heat conduction calorimetry.[12–14] We concentrate attention on the latter two techniques, nevertheless describing the general form of the thermodynamic analysis for the three techniques. We show how key equations emerge from simple reorganisation of equation (4).

Actually 'adiabatic calorimetry' is a slight misnomer. The thermodynamic changes accompanying, for example, mixing of two liquids are monitored by recording the change in temperature of samples held within a thermally insulated reaction vessel. Nevertheless these vessels are rarely perfectly thermally insulated so that rather than adiabatic, the process is monitored by an isoperibol calorimeter where the flow of heat to the surroundings is not zero, although minimised as far as possible.

2 Titration microcalorimetry

We comment briefly on Titration Microcalorimetry[6–11] because this technique illustrates the way in which equation (4) forms the basis of practical calorimetry. In this technique small aliquots of a solution (*e.g.* 10^{-5} dm^3) containing for example a known amount of chemical substance j, dn_j are injected into a small sample cell (*e.g.* 1.5 cm^3) containing an enzyme. The calorimeter records the accompanying heat dq, leading to the ratio, (dq/dn_j). Then from equation (4) at constant temperature,

$$\left(\frac{dq}{dn_j}\right) = \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \left(\frac{d\xi}{dn_j}\right) \quad (5)$$

Experiment yields the ratio (dq/dn_j) over a series of injected aliquots. Interpretation of the results is complicated by the fact that according to equation (5), (dq/dn_j) is given by the product of two terms which are unknown *a priori*. Progress is made by formulating models for chemical reactions taking place in the sample cell; *e.g.* substrate binding to an enzyme,[8–11] micelle deaggregation,[6] formation of inclusion complexes[15] and adsorption of small molecules by a soluble polymer.[16] Then having set down a model, and this is the challenge, for the chemical reaction in the sample cell and hence the quantity $(d\xi/dn_j)$, analysis of the experimental results yields the enthalpy of reaction, $(\partial H/\partial \xi)_{T,p}$.

3 Law of Mass Action

In the two calorimetric techniques discussed below, Adiabatic Calorimetry and Heat Conduction Calorimetry, a key consideration is the dependence on time of the chemical composition, ξ of a sample cell; *i.e.* the derivative dξ/dt where dξ describes the extent of chemical reaction.[1,17]

We illustrate the point by reference to a first order unimolecular chemical reaction in which chemical substance X forms chemical substance, product P.

Thus	X	→	P
Amounts at 't = 0'	n_X^0		0 mol
Amounts at time t	$n_X^0 - \xi$		ξ mol
For reaction in volume V			
Concentration at time t	$(n_X^0 - \xi)/V$		(ξ/V) mol m^{-3}

According to the Law of Mass Action, at fixed T and p

Rate of Reaction,

$$\frac{d(\xi/V)}{dt} = k \times [n_x^0 - \xi]/V \quad (6)$$

The amounts of chemical substances are volume-normalised assuming that volume V is independent of time.

$$\frac{d\xi}{dt} = k \cdot V \cdot [c_x^0 - (c_p/c_x^0)] \quad (7)$$

In other words, ξ, dξ/dt and c_p are time dependent. Classic analysis of the kinetics of chemical reaction[18] yields an equation for c_p at time t. Thus

$$c_p = c_X^0 \cdot [1 - \exp(-k \cdot t)[\quad (8)$$

Hence

$$d\xi/dt = k \cdot V \cdot c_X^0 \cdot \exp(-k \cdot t) \quad (9)$$

Two important limits are noted. At $'t = 0'$, (dξ/dt) equals $k \cdot V \cdot c_X^0$; at $'t = \infty'$, $c_p = c_X^0$ and (dξ/dt) is zero. The above analysis is readily extended to second and higher order chemical reactions and to more complicated reaction schemes.[17]

4 Thermal imaging calorimetry

Here the starting point is again equation (4) which is used to describe the changes taking place between time t and time (t + dt) where by definition dt is positive. The rate of transfer of heat at constant pressure from the surroundings to the system (using the acquisitive convention) dq/dt is related to the rate of change of temperature (dT/dt) and rate of reaction (dξ/dt). As noted above, calorimeters are rarely completely thermally insulated. Thus for isoperibol calorimeters monitoring an exothermic reaction, heat flows spontaneously from the sample cell to the surroundings. We examine this aspect below. Thus,

$$\left(\frac{dq}{dt}\right) = \left(\frac{\partial H}{\partial T}\right)_{p,\xi} \cdot \frac{dT}{dt} + \left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \frac{d\xi}{dt} \quad (10)$$

In a perfectly insulated system, (dq/dt) is zero and therefore an exothermic chemical reaction in the sample cell produces an increase in temperature.

Equation (10) is rearranged as an equation for the rate of change of temperature, dT/dt. Thus,

$$\frac{dT}{dt} = \frac{1}{(\partial H/\partial T)_{p,\xi}} \cdot \frac{dq}{dt} - \frac{(\partial H/\partial \xi)_{T,p}}{(\partial H/\partial T)_{p,\xi}} \cdot \frac{d\xi}{dt} \quad (11)$$

An indication of the patterns[19] which can emerge is obtained if we assume that the sample cell is perfectly thermally insulated; *i.e.* dq/dt) is zero. Further if the sample cell contains a dilute solution in n_1 moles of solvent, $(\partial H/\partial T)_{p,\xi}$ is effectively the isobaric heat capacity of the solution in the sample cell given by $[n_1 \cdot C^*_{p1}(\lambda)]$ where $C^*_{p1}(\lambda)$ is the molar isobaric heat capacity of the solvent. Then,

$$\frac{dT}{dt} = -\frac{(\partial H/\partial \xi)_{T,p}}{n_1 \cdot C^*_{p1}(\lambda)} \cdot \frac{d\xi}{dt} \quad (12)$$

In effect equation (12) links the rate of change of temperature of a solution in the sample cell to the rate of chemical reaction. Further if the solution is dilute $(\partial H/\partial \xi)_{T,p}$ equals the standard enthalpy of reaction $\Delta_r H^0$, assuming that ambient pressure is close to the standard pressure. Hence,

$$\frac{dT}{dt} = -\frac{\Delta_r H^0}{n_1 \cdot C^*_{p1}(\lambda)} \cdot \frac{d\xi}{dt} \quad (13)$$

In the case of an exothermic reaction, equation (13) requires that with $(d\xi/dt) > 0$, the temperature of the solution in the sample cell increases with time.

5 Adiabatic calorimetry; model system

A general pattern for this calorimetric technique[19] emerges after combining equation (13) for a perfectly thermally insulated sample cell with equation (9) for the dependence of composition on time for a first order reaction. Then

$$\frac{dT}{dt} = -\frac{\Delta_r H^0}{n_1 \cdot C^*_{p1}(\lambda)} \cdot k \cdot V \cdot c^0_X \cdot \exp(-k \cdot t) \quad (14)$$

All terms on the r.h.s. of equation (14) are positive with the exception of $\Delta_r H^0$, which can be either positive or negative. In the event that the chemical reaction is exothermic, then dT/dt is positive, the temperature increasing with time for which (dT/dt) is time dependent. Thus the temperature increases rapidly after the reaction is initiated but the rate decreases to zero as the concentration of reactant decreases. The fact that the temperature of the sample cell changes with time means that the rate constant is time dependent. If the temperature of the sample cell is T_0 at $'t = 0'$ and T at time t, $k(t)$ is simply related to $k(T_0)$ using the Arrhenius equation. Equation (15) is the general equation for the temperature dependence of the solution in the sample cell.[19]

$$T(t) = T(t = 0) - \frac{\Delta_r H^0}{n_1 \cdot C^*_{p1}(\lambda)} \cdot V \cdot c^0_X \cdot \int_{t=0}^{t} k \cdot \exp(-k \cdot t) \cdot dt \quad (15)$$

A typical pattern[19] for the dependence of $T(t)$ on time is shown

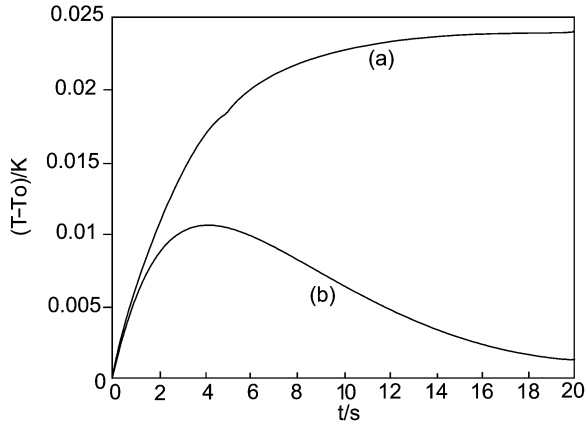


Fig. 1 Calculated dependence of temperature on time using equations (15) and (16); $\Delta_r H^0 = -10$ kJ mol^{-1}; $n_1 = 0.277$ mol; $C^*_{p1}(\lambda)$ J K^{-1} mol^{-1}; $V = 5$ cm^3; $c^0_X = 0.1$ mol dm^{-3}; (a) $\alpha = 0$ and (b) $\alpha = 0.2$.

in Figure 1. The temperature rises to a limiting value in the limit $(t \rightarrow \infty)$.

However for real systems, heat flows from the sample cell to the surroundings. The impact of this flow on the recorded temperature is calculated obtained using Newton's Law of cooling written in the following form where α is positive and characteristic of the calorimeter.

$$dT/dt = -\alpha \cdot (T - T_0) \quad (16)$$

Under these circumstances the temperature rises to a maximum which is less than $T(t = \infty)$ predicted by equation (15). The temperature then decreases such that limit$(t \rightarrow \infty)$ $T = T_0$; Figure 1.

Equation (15) signals a way of using the temperature of the solution to monitor the progress of chemical reaction[20] (binding, conformational changes chemical reaction *etc.*) *e.g.* formation of inclusion complexes by cyclodextrins in aqueous solution.[21] A particularly important application concerns the rapid screening of combinatorial libraries of compounds to identify important lead compounds in pharmaceutical research. Rapid developments in the field of combinatorial synthesis have had a major impact on drug discovery programmes. Combinatorial synthesis[22–27] allows the simultaneous syntheses of large 'libraries' of diverse molecules from which potential new drugs (*e.g.* potent enzyme inhibitors) can be identified. Because such parallel synthesis can generate millions of different compounds, the success of this approach depends on establishing high though put, sensitive methods for screening large number of compounds for activity.[24–27] Thermal methods offer a potentially general approach to identifying potent enzyme inhibitors, using heat (rather than spectroscopic changes) to detect tight binding.[28]

6 Heat conduction calorimetry

In this technique the flow of heat from a sample cell in which chemical reaction is taking place to the surroundings in the form of a heat sink formed, for example, by an aluminium block is measured.[12–14] The heat flow is monitored using a thermopile placed between sample cell and the heat sink. A temperature difference between sample cell and heat sink produces an electric potential.

The flow of heat is such that the temperature of the sample cell can be treated as constant. Kinetic and thermodynamic information emerges from the rate of flow of heat. As with the two techniques discussed above, the starting point to the analysis is again equation (4). While the spontaneous chemical reaction is taking place in the sample cell, the system in this application is constrained by isothermal and isobaric conditions. Therefore,

$$dq = (\partial H/\partial \xi)_{T,p} \cdot d\xi \quad (17)$$

Hence in the time period dt, the rate of flow of heat from the sample cell to the heat sink (using the acquisitive convention) is given by equation (18).

$$\frac{dq}{dt} = -\left(\frac{\partial H}{\partial \xi}\right)_{T,p} \cdot \frac{d\xi}{dt} \quad (18)$$

We illustrate the analysis[29] by considering the case where a single chemical reaction in the sample cell involves solutes in dilute solution. Then $(\partial H/\partial \xi)_{T,p}$ is the standard enthalpy of reaction. In the event that the enthalpy of reaction is exothermic, then heat flows from the sample cell to the heat sink. The term, $d\xi/dt$ for a first order unimolecular reactions is given by equation (19); *c.f.* equation (9). Then

$$dq/dt = -\Delta_r H^0 \cdot k \cdot V \cdot c^0_X \cdot \exp(-k \cdot t) \quad (19)$$

The integral of equation (19) yields an equation for the amount of heat flowing from the sample cell to the heat sink over the time interval, $t = 0$ to time t.

$$\int_{t=0}^{t} dq = -\Delta_r H^0 \cdot V \cdot c^0_X \cdot [1 - \exp(-k \cdot t)] \quad (20)$$

Thus in the limit ($t \rightarrow \infty$), the total amount of heat passing to the heat sink by an exothermic reaction is given by $[-\Delta_r H^0 \cdot V \cdot c_X^0]$.

Initially the rate of reaction is fast and so the rate dq/dt is high but as reactants are consumed, dq/dt approaches zero. The total amount of heat flowing from the sample cell decreases with time. reaching for an exothermic reaction a limiting value dependent on $\Delta_r H^0$ and the amount of reactant solute originally

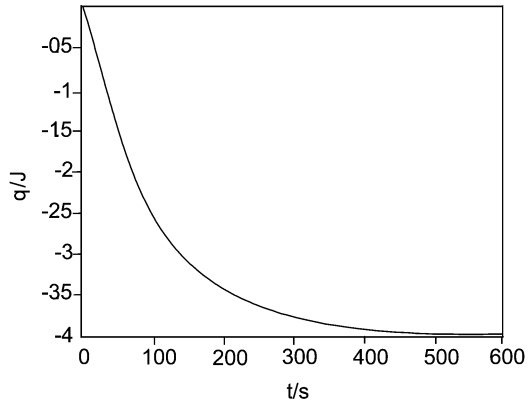


Fig. 2 Dependence of heat q on time calculated for a first order reaction in a reaction vessel, volume 5 cm^3, containing reactant X at a concentration of 0.1 mol dm^{-3}; rate constant, $k = 10^{-2}$ s^{-1}; $\Delta_r H^0 = -8$ kJ mol^{-1}.

placed in the sample cell; Figure 2.

This technique has been extensively developed to characterise complex reactions,[30] probe long term stabilities of, for example, pharmaceutically important compounds,[31] determine orders, rate constants and enthalpies of reaction,[32] screen catalysts[33] and examine mechanisms of organic reactions.[34,35]

7 Summary

The review has drawn together the thermodynamic treatments of three calorimetric techniques. Of course the close links emerge from the first and second laws of thermodynamics coupled with the (extrathermodynamic) law of mass action. The second law is crucial in determining the direction of spontaneous chemical reaction in a given sample cell.[1]

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