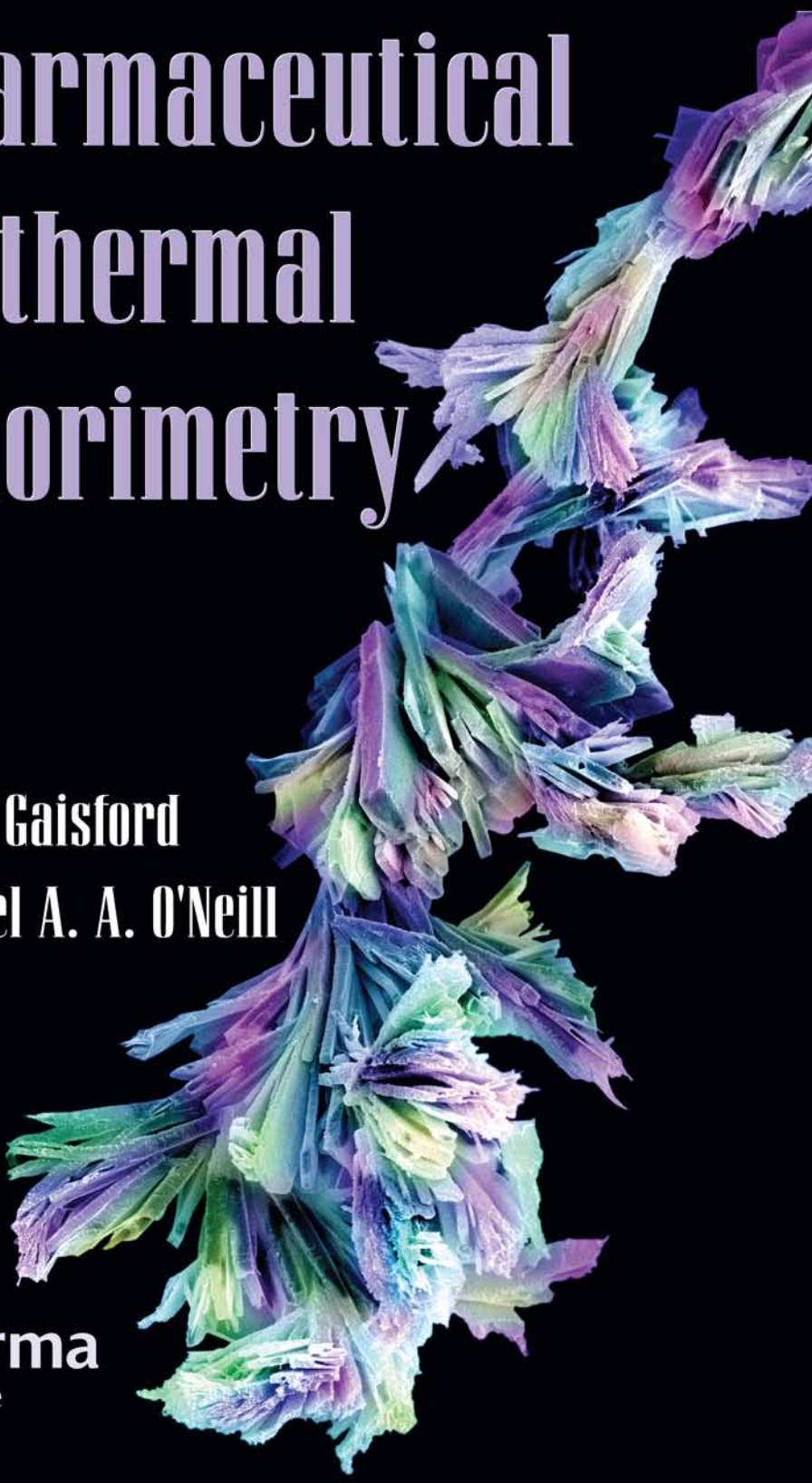
Pharmaceutical Isothermal Calorimetry



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Dedication

This text is dedicated to the memory of two men who played important roles in instilling the virtues of calorimetry into the authors.

First to Richard Lipscombe, who worked tirelessly in Professor Beezer's laboratory ensuring the calorimeters (and students) were working at maximum efficiency; Richard's legacy, as any student who worked with him will testify, was to inculcate the values of experiment design, instrumental set-up and sample handling into all those around him. The advice he gave us is as relevant today as it was then and underpins Chapter 2.

Secondly, to Tom Hofelich who spent many happy years working for Dow Chemicals. Although the authors only met Tom on a few occasions, mostly at international conferences, his infectious humour and good nature shone through. One memory that stands out is his response to the question that was asked of him, "Why did you present your data in Calories when the SI unit for heat is Joules?" when presenting at a conference in London. Tom replied, "When they rename the Calorimetry Conference the Joulerimetry Conference I will present my data in Joules!" A priceless comment from a priceless man who will be sadly missed, not just by the authors but by all those in the field of calorimetry.

S. Gaisford and MAA O'Neill
May 2006

Preface

Almost all reactions take place with a change in heat content or enthalpy and the quantitative study of such heat changes in chemical reactions has been pursued for many years. For years thermochemical studies were concentrated in University research departments. Now, however, these studies have increasingly been seen by industry, particularly the pharmaceutical industry, as having importance in the discovery, development and characterization of their products. This stems from the universality of the application of the microcalorimetric technique: it is nondestructive, noninvasive and invariant to the physical form of the sample. Until recently the utility of this method was limited by a need to have relatively rapid (minutes rather than hours or days) reactions for study—industry, for example, is concerned with recording product stability data that are valid for years. New data analysis techniques allow for the determination of both thermodynamic and kinetic parameters that has opened these new areas for study.

Commercial calorimeters have been available for some years and by now most major pharmaceutical companies have purchased instruments. There has not been a concomitant increase in the number of trained calorimetrists. An earlier book (Thermometric Titrimetry by Tyrrell and Beezer) noted that "Widespread acceptance of any instrumental technique of analysis is always delayed until a rapid, reliable instrument is commercially available . . ." Thus it is not the instruments that present the problem but rather the absence of a handbook on the principles of the method, the data analysis methods that have been developed, and a guide and review of the procedures that have been proposed to exploit such instruments. This book, therefore, fills a significant void—it offers the possibility of learning of the practice of calorimetry (both instrument and experimental design and data analysis methods) through a carefully developed text. Indeed, given the increasing industrial use of calorimetry it is important that the topic is treated in a text designed carefully to guide both

experienced and potential (undergraduates and postgraduates) practitioners through modern applications. This is particularly aimed at preformulation and formulation issues and issues encountered during the design and development of novel drugs and delivery systems.

The authors are experts in the subject matter and deal with its complexities with a thoughtful and considered development. Their experience and sensitivity is shown in the style and manner with which they discuss practical problems; choice of instrument, experimental design and the appropriate data analysis method. It is apparent from the material presented that their own experiences of learning about the practice of calorimetry has informed their text and this ensures that any good scientist, whether experienced or not, will be able to use this book as a source for advice and guidance.

A.E. Beezer
April 2006

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1

Principles of Calorimetry

INTRODUCTION

It is an inevitable consequence of the laws of nature that if a material can change from its current state to a more stable state, then it will do so. This may involve an individual material changing its physical or chemical form, or it may be the result of an interaction between two or more materials. Diamond, for example, is the metastable form of carbon and over time it will convert to graphite. The only consideration to be taken into account in determining if such change is of importance is the length of time over which it will occur. In the case of the transition of diamond to graphite the process occurs over millions of years and it may hence be ignored. For other materials, the rate of change may be more of an issue and chemical or compositional alterations may be needed to ensure stability over an acceptable period.

For manufactured materials, it is generally the case that the initial state is the one with the desired properties, and over time changes in the material will lead to deterioration in its properties and hence, by definition, a loss of quality. The measurement and, consequently, quantification of change is therefore of critical importance if use-by dates are to be specified. Using the product before the stated use-by date ensures that its performance will be within the manufacturer's limits. Of course, use-by dates are more important for some products than others; knowing the lifetime of a pacemaker battery is likely to be more important than knowing that of a radio battery, for instance. Similarly, an emulsion paint that has phase separated can be reconstituted by mixing, but it is unlikely that a patient would do the same with a pharmaceutical cream.

As intimated earlier, knowledge of change (or stability) is especially important for pharmaceuticals. Two principal reasons for this are that (*i*) it is often the case that the bioavailability of a drug depends to a large degree on

its physical form (whether it is formulated as a particular polymorph or in an amorphous form, for instance), and (*ii*) a drug may degrade to an inactive or, worse, toxic compound. The manufacturing specifications for pharmaceuticals are thus tight, but most products require a use-by date that is sufficient to cover the time taken for manufacture, distribution, and storage. Typically, a pharmaceutical may be expected to degrade by less than 2% over a two-year period.

The analytical challenge, therefore, is to be able to measure change in a given product (and from an industrial view, to measure change as rapidly and cheaply as possible, using a minimum of sample and operator time), using a *stability assay*. In the specific case of pharmaceuticals, it is desirable to be able to measure small changes (both chemical and physical) over a short experimental time in order to predict long-term stability. There are many analytical tools available to meet this challenge (such as spectroscopy and chromatography, for instance), but most of these require that the sample being studied possess a particular feature to enable successful analysis. In a spectroscopic analysis, the study molecule must possess a suitable chromophore and, in a chromatographic analysis, the study molecule (or the other components) must interact to some extent with the column material. In the best case, this results in a specific assay being developed for any particular sample and, in the worst case, renders some samples unsuitable for analysis. Nevertheless, it is the case that the vast majority of pharmaceutical stability assays are conducted using high-performance liquid chromatography (HPLC).

A further problem with conventional stability assays is that most products are formulated to be stable and hence will not degrade to any considerable extent during the measurement period. In other words, if an assay cannot detect any change in a product, a decision must be made as to whether that is because the product has not actually changed or because any change was below the detection limit of the measuring technique. To ameliorate this problem, stability assays are often conducted under stress conditions. Usually this would involve an increase in both temperature and/or relative humidity (RH). The resulting increase in degradation rate allows a rate constant (k) to be determined at each temperature, although study periods may still extend for weeks or months. The data are then plotted in accordance with the Arrhenius relationship ($\ln k$ vs. $1/T$) and the predicted rate constant under storage conditions is obtained.

Necessarily, it is assumed that the analysis results in a linear relationship and that any reaction processes occurring under stress conditions are the same as those that would occur under storage conditions. There are many reasons why this may not be so: different reaction pathways may predominate at higher temperatures, the sample may change its crystal state or go through a glass transition, or water may be involved in degradation. If there is any doubt about the extrapolation, then long-term storage studies (holding the sample directly under expected storage conditions) are conducted to confirm the findings.

HPLC analysis of an active pharmaceutical ingredient (API) cannot, of course, detect if a solid drug has changed polymorph, because dissolution of the sample before analysis removes any solid-state history, nor will it be of use if it is a change in the properties of an excipient, or an interaction between excipients, that causes the product to fail to meet its specification.

Calorimetry, the measurement of heat, offers an alternative approach for the measurement of change. It is an extremely useful technique, because when change occurs, it invariably occurs with a change in heat content. In other words, *heat is a universal accompaniment to chemical and physical change.* The result is that calorimetry can detect, and potentially quantify, the changes in a wide range of materials. The only properties required of the sample are that the process being followed results in a detectable quantity of heat and that the sample (or at least a representative part of it) fits within the calorimetric vessel. Isothermal calorimetry (IC), the measurement of heat as a function of time, in particular, is suited to the measurement of pharmaceutical samples, because it is sensitive enough to allow the analysis of samples non-destructively (i.e., it does not cause any extra degradation other than that which would have occurred upon storage), directly under storage conditions. This means that there is no need for elevated temperature stability studies (and hence no requirement for extrapolation of data) and samples can be recovered and used in other studies (particularly important in the early stages of the drug discovery process, when samples may exist only in milligram quantities). Calorimetry is also invariant to the physical form of a sample, meaning that complex heterogeneous systems are open to investigation. Furthermore, because both physical and chemical processes occur with a change in heat content, the technique is not limited in its detection ability to chemical degradation, in the way HPLC is. This unique combination of qualities makes IC ideally suited to the characterization of pharmaceutical materials.

Careful experimental design allows the investigation of virtually any system, and recent advances in data analysis and interpretation methodologies have resulted in the increasing application of the technique to stability testing of pharmaceuticals. Indeed, careful data analysis can result in a description of the reaction process in terms of both thermodynamics and kinetics, the only technique for which such a complete analysis is possible. It is the purpose of this book to explain, in the context of pharmaceutical development and formulation, the basic principles of IC and good experimental practice, to review the latest developments in experimental techniques and data interpretation and to explore some of the future challenges and applications of the technique. The first half of the book (Chaps. 1–3) deals with the fundamentals of calorimeter operation, good experimental design and data analysis, while the remainder of the text focuses on applications to specific areas; these chapters progress from issues in preformulation, through formulation, to final product characterization and quality assurance, and have been organized to match the development process of a pharmaceutical.

BRIEF HISTORY OF CALORIMETRY

Calorimetry [from calor (Latin), heat; metry (Greek), measurement] can trace its origins back to Black's ice calorimeter, although the first practical calorimeter design is usually regarded to be that of Lavoisier and Laplace in 1780 (1). In these simple designs, a heat-radiating body is surrounded by ice. The heat released causes some of the surrounding ice to melt, whereupon the water is routed out of the calorimeter into a collecting vessel. By knowing the quantity of the water produced and the latent enthalpy of fusion of water, the total heat output for the process, Q, can be determined (kJ kg^{-1}). This is a thermodynamic term, although it is not a very useful measure of the energy of a reaction. This is because the change in enthalpy determined cannot be compared directly with the change in enthalpy for a different reaction, unless the molecular weights of the reagents in both reactions are the same. It is more useful to determine the change in enthalpy in units of kJ mol^{-1}, although this requires that the number of moles of material available for reaction is known.

In one of their first experiments, Lavoisier and Laplace (1) measured the heat of combustion of carbon, finding that "one ounce of carbon in burning melts six pounds and two ounces of ice." This allowed a value for the heat of combustion of -413.6 kJ mol^{-1} to be calculated. When compared with the most accurate current value of -393.5 kJ mol^{-1}, it can be seen that the ice calorimeter was remarkably accurate. In a later experiment, a guinea pig was placed in the sample cell. By comparing the heat evolved from the guinea pig with the amount of oxygen consumed, they concluded (1)

> . . . respiration is thus a combustion, to be sure very slow, but otherwise perfectly similar to that of carbon; it takes place in the interior of the lungs, without emitting visible light, because the matter of the fire on becoming free is soon adsorbed by the humidity of these organs. The heat developed in the combustion is transferred to the blood which traverses the lungs, and from this is spread throughout all the animal system.

This conclusion is remarkably astute, given the limited number of data on which it is based, and shows the power of the calorimetric technique. It is also somewhat ironic that the heat-flow recorded from the guinea pig experiment reflects the most complex case that could be encountered, arising from the heat-flows of many thousands of simultaneous metabolic reactions. More than 200 years later, it is the lack of a general method capable of analyzing data derived from such complex reactions that is limiting the widespread use of IC.

It is also possible to gain kinetic information about the sample if the number of water drops falling per unit time is measured. This is because the rate of droplet production is quantitatively proportional to the power output of the sample. Thus, even from this simple experiment, it should be clear that

calorimetric measurements allow both thermodynamic and kinetic analysis of a sample.

Modern calorimeters do not differ greatly in principle from these early designs; they simply measure power directly with greater accuracy and are capable of measuring endothermic as well as exothermic events (an ice calorimeter can only measure exothermic events). Measurement of the heat output from a reaction (q) gives thermodynamic information, whereas measurement of heat output as a function of time (power, $\mathrm{d}q/\mathrm{d}t$) conveys kinetic information.

Until about the late 1950s, most researchers had no option but to use homemade instruments; even so, careful design and construction resulted in instruments that were capable of recording data very accurately. In a review of the development of calorimeters and calorimetrists over the latter half of the 20th century, Wadsö (2) notes the following opening paragraph from Chapter 9 of the second volume of IUPAC's (International Union of Pure and Applied Chemistry) monograph, *Experimental Thermochemistry* (3):

> The design and construction of a suitable calorimeter is one of the first problems facing the experimental thermochemist planning to measure directly the heat of a chemical reaction. During the past 30 years [i.e. between ~1930–1960] over 300 papers on reaction calorimetry have been published, and more than 200 different reaction calorimeters have been described. This evident need for variety in calorimeter design reflects the very variegated nature of the chemical reactions that have been thermochemically studied.

Thus, the expectation of any user of calorimetry during that period was that the first task to be accomplished when undertaking research was the construction of a bespoke calorimeter. However, advances in data acquisition hardware and electronics led to the first commercially-available instruments becoming available in the 1960s and today there are a number of manufacturers that produce highly sensitive and well-developed calorimeters that allow the investigation of a wide range of samples. (The properties of a range of these instruments are to be found later in this chapter, and a list of manufacturers is provided at the end.) Indeed, the availability and ease of use of these instruments have led to the widespread use of calorimetry for the routine characterization of the physical and chemical properties of many industrial materials.

Wadsö (2), in the same review, also notes that the introduction of commercial microcalorimeters during the 1960s marked a paradigm shift in the use and applications of the technique, with an increasing number of (predominantly) biologists using the instruments as "process monitors" (in a similar manner to that of Lavoisier and Laplace); in other words, the focus of calorimetry moved away from classically designed quantitative thermodynamic measurements on pure materials toward qualitative measurements of complex systems. It is still the case that many isothermal calorimeters are used as process monitors, but new methods are being developed that allow quantitative data analysis rather

than qualitative analysis. A discussion of the application of these methods is a central theme of this text.

All calorimeters measure the heat changes that occur in a sample over time and can be classified into two main types, depending upon the temperature control they maintain over the course of an experiment. In differential scanning calorimetry (DSC), the sample is subjected to a preprogrammed temperature change over time (this can be linear or modulated by some mathematical function; see section "Differential Scanning Calorimetry"), whereas in IC the sample is held at a constant temperature. In practice, this means that DSC is limited to studying thermally driven events, usually phase transitions such as melting or recrystallization, whereas IC is used to monitor longer-term events, such as chemical degradation, aging, recrystallization, or the formation of hydrates/solvates. Wadsö (4) has reviewed some of the applications of IC at near ambient temperatures.

Even though it might be expected from the above discussion that IC would be more suited to the study of pharmaceuticals, it is the case that DSC is much more commonly used in the pharmaceutical arena; indeed, the point has been reached where DSC is regarded as a standard analytical tool, in the way HPLC is, and is treated as a "black-box," simply requiring an operator (not necessarily a calorimetrist) who knows how to load samples. IC, conversely, is perceived to be a research tool that requires careful sample preparation, which produces difficult-to-interpret data and that requires the services of an experienced operator. In part, this is correct; proper use of IC does require a knowledgeable and careful operator, but this is also true for DSC. Additionally, recent developments in data analysis routines are making IC much more accessible to nonspecialists; it should also be remembered that the operating principles of IC are much simpler than those of DSC.

The focus of this book is on the potential applications and benefits of using IC in pharmaceutical development, and the reader is referred to other texts for detailed discussions of the application and use of DSC (a list of information sources is appended at the end of this chapter). However, this chapter discusses the principles of both IC and (briefly) DSC, so the reader can draw a comparison, and recognize the important differences between the techniques, and visualize the types of applications for each. It is appropriate first to discuss the thermodynamic basis for both instruments, and explain the benefits of using heat as a marker for change, so that these sections can be fully appreciated.

HEAT AS AN INDICATOR OF CHANGE

All analytical instruments measure the change in some property of the sample under investigation. As stated earlier, the property change being measured in calorimetry is heat (q, given the SI unit of Joules, J). (Note that the use of calories, Cal, is still prevalent but that all heat data in this text conform to SI nomenclature; to convert from J to Cal multiply by 4.184.) As, necessarily, calorimetric

measurements must be made as a function of time, calorimeters record an output of power (dq/dt, given the SI unit of Watts, W; note that 1 W is equivalent to 1 Js^{-1}). Thus, the raw output from a calorimetric experiment is a plot of power versus time (often called a thermogram). Integration of the data results in the total quantity of heat released (Q).

The primary reason that calorimetry has so many potential applications is that, as noted earlier, *heat is a universal indicator of chemical or physical change*. This means that potentially all processes are open to calorimetric investigation, because there are very few events that occur without a change in heat content.[a] This is a unique advantage of calorimetry compared with other analytical techniques. There is no need for a sample to possess a specific functional group, as there is in a spectroscopic or chromatographic analysis, for example, and nor is there a need to design a specific assay for a particular compound. A sample can simply be placed in a calorimetric ampoule and be monitored (indeed, the only requirement of sample is that it, or at least a representative fraction of it, will fit into an ampoule).

Moreover, in IC, the sample is studied nondestructively (i.e., the calorimeter does not cause any additional degradation to that which would have occurred upon storage during the same time period). This is a massive advantage for the study of pharmaceutical samples, where only a few milligrams of material may be available or the material may be very expensive. In a DSC experiment, the sample is often destroyed or is returned in a different physical state (a different polymorph for instance, reflecting the different cooling rates exerted upon the sample in the calorimeter compared with during its manufacture).

A further benefit of using changes in heat to monitor samples is that both chemical and physical processes can be observed; this is in contrast to other analytical tools, such as HPLC or UV spectroscopy, where solid samples need to be dissolved prior to analysis. As well as potentially increasing the rate of degradation prior to quantification through hydrolysis, dissolving samples clearly removes the solid-state history of the sample, and information on the number of polymorphs or percent amorphous content will be lost.

However, the universal nature of heat (as eloquently phrased, heat does not come in different colors) is also the technique's biggest drawback. It is often the case that calorimetric data are complex in form and derive from several simultaneous (including both physical and chemical) processes. Furthermore, calorimetric data are extremely (and perhaps uniquely) susceptible to systematic errors introduced by the accidental measurement of one or more of a range of

[a]Some reactions may occur at constant enthalpy. For example, in the Joule–Thomson experiment, a gas is allowed to flow from a region of high pressure to a region of low pressure through a porous plug. The expansion of the gas can be shown to occur at constant enthalpy (5). The Joule–Thomson coefficient is defined as the change of temperature with pressure at constant enthalpy. As a gas undergoes a pressure change through the plug, it changes temperature. Most gases, at room temperature, are cooled by the Joule–Thomson effect.

processes (such as solvent evaporation and/or condensation, erosion, side reactions, and so on) that may occur concurrently with the study process(es). Care must therefore be taken to ensure that erroneous or unexpected powers have not been accidentally introduced as a corollary of poor experimental design or execution. This is the main reason why calorimetric data need to be analyzed assiduously, often in combination with other complementary data.

Some of these issues are discussed in Chapter 3, which describes methods by which calorimetric data may be analyzed and interpreted; however, as heat is a thermodynamic term, a brief description of thermodynamics is given below to aid the reader through the later chapters.

INTRODUCTION TO THERMODYNAMICS

Thermodynamics is a general term, which means the study and quantification of transformations of energy. The part of the universe being studied is referred to as the *system*, around which are its *surroundings*, where experimental measurements are made. The system and the surroundings are separated by a *boundary*; it is the description of the boundary that characterizes the system and the surroundings. If matter and/or energy can be transferred through the boundary, the system is described as *open*. If matter cannot be transferred through the boundary but energy can, the system is *closed*. If neither matter nor energy can be transferred through the boundary, the system is *isolated*.

Work, energy, and heat are the basic concepts of thermodynamics. Energy is defined as the capacity of a system to do work. (Usually, work has been done *by* a system if a weight has been raised in the surroundings, and work has been done *on* the system if a weight has been lowered in the surroundings.) When the energy of a system changes as a result of a temperature difference between it and its surroundings, the energy change occurs by a transfer of heat. If a system loses heat, it is said to have undergone an *exothermic* process (and, hence, the change in heat is given a negative sign), and if the system gains heat it is said to have undergone an *endothermic* process.

The total energy content of a system is known as its internal energy (U). It is impossible to quantify in absolute terms the internal energy of a system, so thermodynamics deals only with changes in internal energy (ΔU). Hence, for a given process:

$$\Delta U = U_f - U_i \tag{1}$$

where U_f and U_i are the internal energies of the system in its final and initial states, respectively.

At this point it is important to note that internal energy is both a state property and an extensive property. A state property is one that depends only on the current state of a system, not on how the system arrived at that state (other state properties including, for instance, temperature, pressure, and density). Thus, a 1-L sample of water at 80°C and atmospheric pressure has the same internal energy regardless of whether it was heated to 80°C from room temperature or

cooled from boiling. An extensive property is one that is dependent upon the size (extent) of the system (and includes properties such as mass and volume). Considering water (at 80°C and atmospheric pressure) again, a 2-L sample will contain twice the internal energy as a 1-L sample. Temperature, by contrast, is an *intensive* property (i.e., it is not dependent on the extent of the system), so while the internal energies of the 1-L and 2-L water samples differ, they are at the same temperature. Other intensive properties include density, pressure, and all normalized quantities (such as molar terms). Energy, heat, and work are all measured in Joules (J; 1 J = 1 kg m^2 s^{-2}).

There are two further properties of internal energy that are of importance; the first is that heat and work are equivalent ways of changing the internal energy of a system. The second is that the internal energy of an isolated system is constant. Together, these properties form the basis for the first law of thermodynamics.

First Law of Thermodynamics

One way of stating the first law is "the internal energy of a system is constant unless it is altered by doing work or by heating." Mathematically, this is formulated as:

$$\Delta U = q + w \tag{2}$$

where q represents the transfer of heat to or from, and w represents the work done on or by the system. Conventionally, both heat loss and work done by the system are given negative signs, because the first law is usually written from the perspective of the system under study, not the surroundings.

It is possible to conduct a more powerful analysis of thermodynamic changes if infinitesimally small changes of state are considered (represented by prefix d). Hence:

$$\mathrm{d}U = \mathrm{d}q + \mathrm{d}w \tag{3}$$

In practice, work can take forms other than lifting a weight (such as the electrical work of driving a current through a circuit, for example) so can be defined as work of expansion (w_{exp}) and additional work (w_a). As such, Equation (3) can be reformulated as:

$$\mathrm{d}U = \mathrm{d}q + \mathrm{d}w_{exp} + \mathrm{d}w_a \tag{4}$$

If a system is kept at a constant volume, then no work can be done on the surroundings ($w_{exp} = 0$). If it is assumed that no additional work can be performed ($w_a = 0$), then the heat added or removed from a system is equal to the change in its internal energy:

$$\mathrm{d}U = \mathrm{d}q_V \tag{5}$$

where q_V represents the change in heat for a system at constant volume.

If a system is free to change volume against a constant external pressure, then the change in internal energy is not equal to the heat supplied or

removed, because the system must convert some of the heat to work against its surroundings. In this case, $dU < dq$. However, it can be shown that (6), at constant pressure, the heat supplied or removed is equal to the change in enthalpy (ΔH) of the system (enthalpy, like internal energy, is a state property and an extensive property):

$$dH = dq_p \tag{6}$$

where q_p represents the change in heat for a system at constant pressure.

Enthalpy and internal energy are related through:

$$H = U + pV \tag{7}$$

where p is the pressure and V is the volume of the system. Note that as in nearly all cases, unless the experiment is specifically designed otherwise, measurements are performed at constant (atmospheric) pressure, calorimeters measure heat as a change in enthalpy, not a change in internal energy.

Heat Capacities

Both the internal energy and enthalpy of a system change as a function of temperature, a dependence that can be formulated in terms of the heat capacity (C) of the system.

For a system at constant volume, the heat required to bring about a change in temperature (dT) is given by:

$$dq_V = C_V\, dT \tag{8}$$

where C_V is defined as the heat capacity at a constant volume. Since, as noted above, $dU = dq_v$ then:

$$dU = C_V\, dT \tag{9}$$

If one of the variables is held constant during a change of another, the derivative is known as a partial derivative. The prefix d is replaced by ∂, and the variables held constant are represented by a subscript. Hence:

$$C_V = \left(\frac{\partial U}{\partial T}\right)_V \tag{10}$$

A similar consideration of the change in enthalpy for a system at constant pressure results in the following definition:

$$C_P = \left(\frac{\partial H}{\partial T}\right)_P \tag{11}$$

Second Law of Thermodynamics

The second law deals with the direction of spontaneous change. It is evident in everyday life that some processes occur spontaneously and some do not.

A glass knocked from a table will smash upon contact with the floor, but the glass fragments do not spontaneously reassemble back into the glass. Similarly, hot objects and their surroundings spontaneously equalize to the same temperature, but an object does not spontaneously rise above or below the temperature of its surroundings. Clearly, there is some property of a system that characterizes whether change will occur spontaneously or not; this is termed entropy (S). Entropy relates to the degree of disorder of a system. The more disorder is present, the higher the entropy. In simplistic terms, enthalpy and internal energy show which changes are permissible (i.e., those changes where energy is conserved), whereas entropy shows which changes are spontaneous. The second law of thermodynamics can be described as, "the entropy of an isolated system must increase during the process of spontaneous change." Mathematically,

$$\Delta S_{\text{tot}} > 0$$

where ΔS_{tot} is the total entropy of all parts of an isolated system.

For a system in mechanical and thermal contact with its surroundings, any change in state is accompanied by a change in entropy of the system (ΔS) and the surroundings ($\Delta S'$). For an irreversible change, the change in entropy must be greater than zero:

$$\mathrm{d}S = \mathrm{d}S' \geq 0 \quad \text{or} \quad \mathrm{d}S \geq -\mathrm{d}S'$$

As $\mathrm{d}S' = -\mathrm{d}q/T$, it follows that for any change:

$$\mathrm{d}S \geq \frac{\mathrm{d}q}{T}$$

This is known as the Clausius inequality and is important in the derivation of two more fundamental terms, the Helmholtz and the Gibbs functions (see section "Helmholtz and Gibbs Functions").

Third Law of Thermodynamics

The third law states that "if the entropy of every element in its stable state at $T = 0$ is zero, then every substance has a positive entropy which may become zero at $T = 0$ and does become zero for crystalline substances." In other words, the entropy of a perfect crystal becomes zero at absolute zero.

Helmholtz and Gibbs Functions

For a system at a given volume, $\mathrm{d}q_{\text{v}} = \mathrm{d}U$; the Clausius inequality thus becomes:

$$\mathrm{d}S - \frac{\mathrm{d}U}{T} \geq 0$$

or

$$T\,\mathrm{d}S \geq \mathrm{d}U$$

If either the internal energy or entropy is constant then:

$$dU_{S,V} \geq 0 \quad \text{or} \quad dS_{U,V} \geq 0$$

These two terms effectively define the conditions that must be met for change to occur spontaneously; either the entropy must increase or the internal energy must decrease. (This means energy must transfer to the surroundings, thus increasing the entropy of the surroundings.)

Similarly for a system at constant pressure, $dq_p = dH$ and:

$$dS - \frac{dH}{T} \geq 0$$

or

$$T\,dS \geq dH$$

If either the enthalpy or entropy is constant then:

$$dH_{S,P} \geq 0 \quad \text{or} \quad dS_{H,P} \geq 0$$

As before, these two terms define the conditions that must be met for change to occur spontaneously; either the entropy must increase or the enthalpy must decrease (again causing an increase in entropy of the surroundings).

These conclusions are usually expressed more simply by the introduction of two more thermodynamic terms: the Helmholtz function (A) and the Gibbs function (G). Hence:

$$A = U - TS \tag{12}$$

$$G = H - TS \tag{13}$$

and as it is more common to consider changes in the Helmholtz and Gibbs functions at constant temperature:

$$dA = dU - T dS \tag{14}$$

$$dG = dH - T dS \tag{15}$$

These equations can be written with Δ prefixes rather than d prefixes when the change involved is measurable rather than infinitesimal.

$$\Delta A = \Delta U - T\Delta S \tag{16}$$

$$\Delta G = \Delta H - T\Delta S \tag{17}$$

The Gibbs function and the Helmholtz function simply summarize the changes in entropy and energy that are required if a system is to undergo a spontaneous change. Evidently, from the preceding discussion, if spontaneous change

is to occur, then the value of ΔA or ΔG will be negative. As ΔS must be positive, attainment of a negative ΔA or ΔG is most readily achieved if a process involves a decrease in ΔH or ΔU. In this case, the process is said to be enthalpically driven. A positive value of ΔH or ΔU can also lead to spontaneous change, but only with a significant contribution from ΔS. In this case, change is said to be entropically driven. As most experimental measurements are conducted at constant pressure, the Gibbs function is usually used as the determinant of change.

CLASSIFICATION OF CALORIMETERS

Nomenclature

There is a wide range of instruments commercially available; they are based on a number of different operating principles and use a variety of nomenclatures. Unfortunately, there is no common agreement on the naming of instruments and this often leads to confusion (7). Two notable examples are micro- (or nano-) calorimetry and isothermal DSC. In the former case, it is unclear as to whether the instrument is measuring heat on a micro- (or nano-) Watt scale, or if the sample size required for measurement is on the order of micro- (or nano-) grams. The latter case refers to a DSC temperature program that includes isothermal steps, but the name literally means isothermal temperature scanning calorimetry! Of course, such terms are often introduced by instrument manufacturers eager to promote the benefits of a new design (surely a nanoWatt instrument would be better than a microWatt instrument). An instrument may also be named after a designer or an operating characteristic (Black's ice calorimeter, Parr's oxygen bomb calorimeter, gas perfusion calorimetry, and so on), which again reveals no details of its operating principles.

An excellent example of the spread of names used by authors to describe their calorimeters is provided by Hansen (7), who noted that the following techniques were described in a Special Issue of Thermochimica Acta on developments in calorimetry; levitation melting calorimetry, IC, flow calorimetry, water-absorbed dose calorimetry, microcalorimetry, DSC analysis, temperature-modulated DSC (TMDSC), high-temperature calorimetry, and nanocalorimetry. Clearly, unless one is familiar with all the above instruments, these names will cause confusion, not least because it is unclear in most of the cases as to how the actual measurement is made. It has been suggested that, as in the way common names for chemicals have been replaced with IUPAC-sanctioned nomenclature, names for calorimeters and calorimetric procedures must be replaced or supplemented with a systematic nomenclature that gives a clear indication of the method and mode of operation of the calorimeter used (7), although this is some way away, and common or trade names will probably never disappear.

The problems caused as a result of the lack of a common standard nomenclature have been discussed elsewhere (7–10) and shall not be further discussed

here. It is, however, important to know the basic designs and operating principles underpinning all modern calorimeters in order to understand the origin of calorimetric signals and to draw comparison between them.

Measuring Principles

There are only three methods by which heat can be experimentally measured:

1. Measurement of the power required to maintain isothermal conditions in a calorimeter, the power being supplied by an electronic temperature controller in direct contact with the calorimeter (power compensation calorimetry).
2. Measurement of a temperature change in a system which is then multiplied by an experimentally determined cell constant (adiabatic calorimetry).
3. Measurement of a temperature difference across a path of fixed thermal conductivity which is then multiplied by an experimentally determined cell constant (heat conduction calorimetry).

Note that all calorimetric measurements therefore require a minimum of two experiments (one for measurement and one for calibration), although further measurements may be needed for blank corrections (such as the determination of a baseline or the correction for dilution enthalpies in a titration experiment). A discussion of the need for, and methods of, calibration (including chemical test reactions) is the basis of Chapter 2.

Power Compensation Calorimeters

In power compensation calorimetry, an electrical element is used either to add heat or remove heat from the calorimetric vessel as the sample reacts, maintaining the sample and vessel at a given temperature. The power output from the sample is thus the inverse of the power supplied by the element. In order to be able to heat and cool, the element is usually based on the Peltier principle. A typical application of this type of calorimetry is power compensation DSC.

Adiabatic Calorimetry

In an ideal adiabatic calorimeter, there is no heat exchange between the calorimetric vessel and its surroundings. This is usually attained by placing an adiabatic shield around the vessel. Thus, any change in the heat content of a sample as it reacts causes either a temperature rise (exothermic processes) or fall (endothermic processes) in the vessel. The change in heat is then equal to the product of the temperature change and an experimentally determined proportionality constant (or calibration constant, ε, which is the effective heat capacity of the system). The proportionality constant is usually determined by electrical calibration.

In practice, true adiabatic conditions are difficult to achieve, and there is usually some heat-leak to the surroundings. If this heat-leak is designed into the calorimeter, the system operates under semi-adiabatic (or isoperibol) conditions and corrections must be made in order to return accurate data. These corrections are usually based on Newton's law of cooling (the most common being the method of Regnault–Pfaundler). These principles are discussed more fully, in the context of solution calorimeters, in the section "Semi-Adiabatic Solution Calorimeters".

Heat Conduction Calorimeters

A heat conduction calorimeter is surrounded by a heat-sink, which acts to maintain the system at a constant temperature. Between the vessel and the heat-sink is a thermopile wall. Any heat released or absorbed upon reaction is quantitatively exchanged with the heat-sink. The thermopiles generate a voltage signal that is proportional to the heat flowing across them; this signal is amplified, multiplied by the cell constant (determined through electrical calibration), and recorded as power versus time. An isothermal system is not limited to reaction processes that reach completion within a short time, as semi-adiabatic instruments are, because it is always (essentially) in equilibrium with its surrounding heat-sink. Furthermore, the greater measuring sensitivity of the thermopiles (as opposed to the thermisters used in semi-adiabatic instruments) means that smaller sample masses can be used.

Single and Twin Calorimeters

In addition to the three types of calorimetry mentioned earlier, which deal with the method by which heat is measured, it is also important to consider the merits of single and twin calorimeters. A single calorimeter has, as its name suggests, only one calorimetric vessel, meaning that a blank experiment is a necessary precursor for any sample experiment in order to subtract out the heat change inherent in simply conducting an experiment. Adiabatic calorimeters are usually single vessels (such as the solution calorimeter discussed in the section "Semi-Adiabatic Solution Calorimeters"). Twin calorimeters have two calorimetric vessels, usually machined to be as closely matched as possible, connected in the opposition (i.e., an exothermic process will produce a positive signal on one side and a negative signal on the other). Such a design automatically corrects for any environmental factors that may affect the data and, if a suitable reference is available, also allows subtraction of the blank signal during an experimental measurement. Usually, twin calorimeters are used for extremely sensitive measurements as they produce considerably less baseline noise than single instruments.

Calorimeter Selection for Pharmaceutical Studies

There is clearly a wide range of calorimetric instrumentation available and it is important to understand the types of sample which each is most suited to study

in order that calorimetric measurements are made efficiently and, more importantly, accurately. The ubiquitous nature of heat means that calorimetric measurements are more prone to systematic and operator-induced error than most other analytical techniques; these errors become proportionately more significant as the heat output from the study sample decreases. Moreover, the design of many instruments is a compromise between factors desirable for good calorimetric measurement and factors necessary to ensure a certain measurement function (11), meaning that careful experimental design and suitable calibration (preferentially using chemical test reactions) are essential precursors to accurate sample measurement.

Adiabatic (temperature change) calorimeters are really suited only to the study of events that go to completion within one to two hours because of the inherent difficulties in making the necessary heat-loss corrections over longer time periods (12). This effectively means that this type of calorimeter is not suited to pharmaceutical stability assays, where a rate of degradation of just 1% to 2% per year or less may reasonably be expected. However, adiabatic calorimeters have found widespread application in pharmaceutical preformulation, because they allow the physical characterization of APIs and excipients, and the number of applications of the technique is growing. Examples from the recent literature include its use to detect polymorphs (13), to rank the stability of polymorphs (14), to investigate interactions between species (15–17), to quantify small amorphous contents (18–19), and to study the formation of liposomes (20). In these types of experiment, reaction is initiated by breaking an ampoule, containing (usually) a solid sample, into a reservoir of liquid; they are therefore often referred to as solution calorimeters, and this term will be adopted throughout the rest of the text.

Both power compensation and heat conduction calorimeters are suitable for studying long-term processes. Power compensation instruments have a poorer detection limit but a better capacity to cope with high powers and are therefore usually used to study energetic reactions with large heat rates (21). The power compensation principle also underpins many DSC designs. Heat conduction calorimeters, because they can measure micro- and even nanoWatts are most suited, and most commonly used, for the study of long-term, low-energy reactions, typified by the degradation mechanisms often followed by pharmaceuticals.

OPERATING PRINCIPLES

From the above discussion, it can be seen that there is a great range of calorimetric techniques and that some instruments are more suited to the study of pharmaceutical materials than others. In this section, the operating principles of the most commonly encountered forms of calorimetry in pharmaceutics are explained and it is shown how data are generated and manipulated. Knowledge of how calorimetric data are derived is essential to ensure proper reporting and interpretation of results.

Heat Conduction Calorimetry

In heat conduction IC, a sample and a reference (of similar heat capacity and in equal quantity to the sample) are maintained at a constant temperature in the calorimeter vessel; any heat released (or absorbed) by reaction is quantitatively exchanged with a surrounding heat-sink via an array of thermocouples (a thermopile). The thermopile generates an electrical potential (U; note that this term is distinct from internal energy) that is proportional to the heat flowing across it; this is multiplied by an experimentally determined proportionality constant (ε) to give the raw power signal (P_R), which is plotted as a function of time:

$$P_R = \frac{dq}{dt} = \varepsilon U \tag{18}$$

The value of ε is determined by an electrical calibration (see section "Electrical Calibration"). The total heat quantity released (Q) is given by the product of the electrical potential time integral and the proportionality constant:

$$Q = \varepsilon \int U \, dt \tag{19}$$

A typical calorimetric arrangement of this type is shown in Figure 1. Note that both the sample and the reference cells will generate an electrical potential; the reference cell is therefore connected in opposition to the sample (i.e., events, which generate a positive potential on the sample side, will generate a negative potential on the reference side and vice versa), because this automatically corrects for environmental temperature fluctuations and instrumental noise. Note also that exothermic reactions cause heat to flow toward the heat-sink, whereas endothermic reactions cause heat to flow from the heat-sink. Data can be plotted with exothermic events as either a positive or negative value (depending upon whether the calorimeter records data from the point of view of the instrument or the sample), and it is important to define which convention is being used when reporting data. If, as is often the case, exothermic events are recorded as positive signals, then, in order to comply with scientific convention, it is necessary to invert the sign of any thermodynamic data produced.

Although this simple description of a twin cell isothermal calorimeter allows a basic understanding of power–time data, a mathematical description of the instrument is preferable. Such a description starts with the principles of the thermocouples that make up the thermopiles. A thermocouple consists of two strips of dissimilar metals that are coupled at one end. When there is a temperature difference between the coupled and uncoupled ends, the thermocouple generates a small electrical potential (known as the Seebeck effect). The output from a thermocouple array (or thermopile) is thus the sum of the electrical potentials produced by the individual thermocouples (U), which is directly

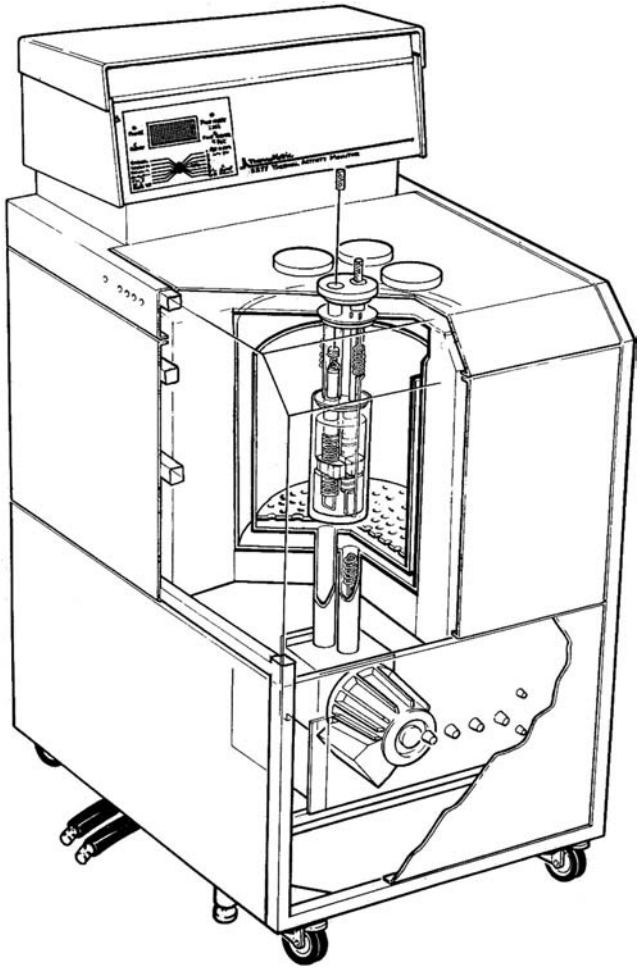

Figure 1 A schematic representation of a Thermal Activity Monitor (TAM). *Source*: Courtesy of Thermometric AB.

proportional to the temperature difference (ΔT) caused by reaction:

$$U = g\Delta T = g(T - T_o) \tag{20}$$

where g is the Seebeck coefficient (V K^{-1}); T_o, the equilibrium temperature of the vessel; and T, the temperature rise (or fall) caused by reaction. The value of g is characteristic for a given type of thermopile; the larger its value the more sensitive the thermopile. From this:

$$T = \frac{U}{g} + T_o \tag{21}$$

And hence the time derivative of dT is given by:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \frac{1}{g}\frac{\mathrm{d}U}{\mathrm{d}t} \tag{22}$$

If ideal conditions are assumed, then there is no time delay between heat being released (or absorbed) and heat being measured. In that case, the measured electrical potential, multiplied by the proportionality constant, gives power directly, as stated earlier. However, the real case is not usually that simple, and there is a delay between heat change in the sample and heat measurement (known as the dynamic response of the instrument). In order to quantify the dynamic response, it is necessary to have some appreciation of the steps that occur between heat being released (or absorbed) by a sample and that heat causing an electrical potential to be generated by the thermopiles.

For an exothermic process, as reaction occurs, heat is released, which initially accumulates in the sample vessel. This must cause the temperature in the vessel to rise (although this rise is usually regarded to be negligible, because otherwise the experiment would not be conducted under isothermal conditions), the magnitude of the temperature rise being dependent upon the heat capacity of the vessel (C; note here that this heat capacity term is sample-dependent, because the vessel is assumed to mean the calorimetric ampoule and its contents). For simplicity, it is necessary to assume that the heat generated by, and hence the temperature rise of, the sample is uniform. As the temperature of the sample rises, a temperature gradient is formed between the vessel and the heat-sink. Heat must necessarily flow towards the heat-sink in order to restore thermal equilibrium; the rate of heat transfer is dependent on the heat transfer coefficient (k in W K^{-1}) of the thermopiles. As the heat transfers, the thermopiles generate the electrical potential from which the raw data derive. The principle is the same for endothermic processes but will involve a temperature fall and subsequent heat-flow into the vessel. The measured thermal power therefore derives from two events (heat accumulation and heat transfer), and can be represented by a heat balance equation:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = \Phi + C\frac{\mathrm{d}T}{\mathrm{d}t} \tag{23}$$

where the term $C\,\mathrm{d}T/\mathrm{d}t$ represents the temperature change (heat accumulation) in the vessel caused by reaction, and Φ represents the heat flow in or out of the vessel across the thermopiles. (Note that it is assumed that all the heat released or absorbed traverses the thermopiles, which is unlikely. However, this discrepancy is accounted for by the electrical calibration, discussed subsequently.) According to Newton's law of cooling, the rate of heat transfer is proportional to the temperature difference between the vessel (T) and the heat-sink (T_o):

$$\Phi = k\Delta T = k(T - T_\mathrm{o}) \tag{24}$$

where k is the heat transfer coefficient.

It follows that where k is the heat transfer coefficient:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = k(T - T_\mathrm{o}) + C\frac{\mathrm{d}T}{\mathrm{d}t} \tag{25}$$

This is the general heat balance equation for a single calorimeter and shows why single calorimeters are greatly affected by small temperature fluctuations in the heat-sink (because of the term $T - T_\mathrm{o}$).

For a twin calorimeter, a heat balance equation can be written for both the sample and the reference sides (denoted by the subscripts S and R respectively):

$$\frac{\mathrm{d}q_\mathrm{S}}{\mathrm{d}t} = k_\mathrm{S}(T_\mathrm{S} - T_\mathrm{o}) + C_\mathrm{S}\frac{\mathrm{d}T_\mathrm{S}}{\mathrm{d}t} \tag{26}$$

$$\frac{\mathrm{d}q_\mathrm{R}}{\mathrm{d}t} = k_\mathrm{R}(T_\mathrm{R} - T_\mathrm{o}) + C_\mathrm{R}\frac{\mathrm{d}T_\mathrm{R}}{\mathrm{d}t} \tag{27}$$

As stated above, the output from a twin calorimeter is the difference between the sample and reference sides then:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = \frac{\mathrm{d}q_\mathrm{S}}{\mathrm{d}t} - \frac{\mathrm{d}q_\mathrm{R}}{\mathrm{d}t} = k_\mathrm{S}(T_\mathrm{S} - T_\mathrm{o}) + C_\mathrm{S}\frac{\mathrm{d}T_\mathrm{S}}{\mathrm{d}t} - k_\mathrm{R}(T_\mathrm{R} - T_\mathrm{o}) - C_\mathrm{R}\frac{\mathrm{d}T_\mathrm{R}}{\mathrm{d}t} \tag{28}$$

Assuming a precision instrument and careful selection of an inert reference with a heat capacity matching the reference then:

$$k = k_\mathrm{S} = k_\mathrm{R} \tag{29}$$

$$C = C_\mathrm{S} = C_\mathrm{R} \tag{30}$$

$$T_\mathrm{R} = T_\mathrm{o} \tag{31}$$

$$\frac{\mathrm{d}q_\mathrm{R}}{\mathrm{d}t} = 0 \tag{32}$$

And hence it can be written that:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = \frac{\mathrm{d}q_\mathrm{s}}{\mathrm{d}t} = k(T_\mathrm{S} - T_\mathrm{R}) + C\,\frac{\mathrm{d}T_\mathrm{S}}{\mathrm{d}t} \tag{33}$$

The reason that twin calorimeters are unaffected by external temperature fluctuations is now clear; the heat flow from the sample can be determined by the measurement of the temperature difference between the sample and reference sides and does not require knowledge of T_o.

Tian Equation

The Tian equation is perhaps the most well-known mathematical description of heat conduction calorimeters and relates the heat balance equations derived earlier to the electrical potential produced by the thermopiles. From the earlier

discussion it can be seen that:

$$(T - T_o) = \frac{U}{g} \tag{34}$$

which allows the following equation to be constructed:

$$\frac{dq}{dt} = \frac{k}{g} U + \frac{C}{g} \frac{dU}{dt} \tag{35}$$

Rearrangement gives:

$$\frac{dq}{dt} = \frac{k}{g} \left(U + \frac{C}{k} \frac{dU}{dt} \right) \tag{36}$$

If the following definitions are made:

$$\varepsilon = \frac{k}{g} \tag{37}$$

$$\tau = \frac{C}{k} \tag{38}$$

where ε is the proportionality constant referred to earlier and τ is the time constant of the instrument, then the Tian equation is obtained:

$$\frac{dq}{dt} = \varepsilon \left(U + \tau \frac{dU}{dt} \right) \tag{39}$$

The Tian equation as written above applies to a single vessel, but exactly the same derivation applies to a twin vessel, although in this case k and τ will represent the differential proportionality constant and the differential time constant respectively. The proportionality constant has units of $W\,V^{-1}$ and typically ranges between 2 and 6 $W\,V^{-1}$ for a modern instrument. The time constant has units of s^{-1} and reflects the dynamic response of the instrument. The time constant increases if the heat capacity of the vessel increases or the heat transfer coefficient decreases. The time constant of a commercial instrument with a 5 mL volume is around 100 seconds and with a 20 mL volume is around 500 seconds. If the study reaction occurs over a long time period (hours or days), then the output signal recorded by the instrument approximates to a real-time measurement and the raw data can be used directly to determine the kinetic parameters. For short-term reactions (on the order of minutes), the delay in measurement response can become significant and dynamic correction is needed in order to reconstruct the true power–time profile. Dynamic correction is discussed in detail in the section "Dynamic Data Correction."

Sensitivity

The sensitivity (S; note that this term is distinct from entropy) of a calorimeter is given by the magnitude of the output signal generated for a given amount of heat produced, in this case:

$$S = \frac{\Delta U}{\Delta q} \tag{40}$$

The sensitivity is also affected by the heat capacity of the calorimetric vessel, because the magnitude of U is dependent upon the temperature difference across the thermopile. It follows that the smaller the heat capacity, the larger the value of ΔT (for a given quantity of heat) and hence ΔU and S. However, calorimeters with small heat capacities are more prone to environmental temperature fluctuations than calorimeters with large heat capacities; therefore, a compromise in design is required between calorimetric sensitivity and long-term stability. Many current designs utilize an aluminium heat-sink around the thermopiles with the whole apparatus contained within an air box or water bath.

Dynamic Data Correction

From the preceding discussion, it can (hopefully) be appreciated that, in the ideal case, the raw power (P_R) output from a calorimeter would reflect the true rate of heat generation in the sample, but in the real case, there is a dynamic delay in measurement, which is approximated by the Tian equation and, as such P_R is actually directly proportional to the measured electrical potential. It is thus possible to use the Tian equation to remove the dynamic delay from the raw power signal, resulting in the corrected power (P_C), if the time constant of the instrument is known. This is called dynamic correction and is usually achieved automatically by dedicated instrument software (methods to determine the time constant of instruments are detailed in the section "Determination of Time Constants").

Dynamic correction of calorimetric data becomes important for short-term processes where the kinetic response of the sample is significantly affected by the delay in the measurement response of the instrument because of its time constant. It is also often used in titration experiments (see section "Titration Calorimetry"), where the true rate of heat generation caused by interactions in the sample drops to zero well before the measured response, allowing experiments to be conducted much more quickly.

It is important to note, however, that a number of assumptions are made in order to derive the Tian equation (the major assumption being that there are no temperature gradients within the sample) and that it only approximates the true dynamic delay inherent to the instrument. The corrected data so produced, while much more closely resembling the true response of the sample, often contain artifacts, such as "overshoots," where both endothermic and exothermic events are indicated, even though it may be known that only one event is occurring in the sample. In principle, these artifacts could be removed by manually altering

the values of the time constant(s), but this would be time consuming in practice. It is therefore easier to use corrected data to determine reaction enthalpies and reduce the time taken to perform certain experiments, and to note that the use of such data to elucidate kinetic information must be undertaken with caution.

The following section describes briefly the processes involved in dynamic correction so that a user fully appreciates the nature of the data so produced. A fuller account of the steps discussed subsequently can be found in the superb review by Randzio and Suurkuusk (22). It should also be noted that the discussion that follows is only one way of reconstructing calorimetric data and that other methods have been discussed in the literature (23,24).

Starting with the premise (introduced earlier) that:

$$P_R = \varepsilon U \tag{18}$$

then

$$\frac{dP_R}{dt} = \varepsilon \frac{dU}{dt} \tag{41}$$

and the Tian equation can be written as:

$$P_C = P_R + \tau \frac{dP_R}{dt} \tag{42}$$

or

$$P_C - P_R = \tau \frac{dP_R}{dt} \tag{43}$$

The left-hand side represents the difference between the true rate of heat production from the sample and the rate actually measured by the instrument (the degree of correction); as this term approaches the detection limit of the instrument, it becomes impossible to differentiate between the true and the measured response, and dynamic correction is not possible. The right-hand side essentially represents the gradient of the power–time curve. Therefore, if the detection limit and time constant of an instrument are known, it is possible to calculate the magnitude of the slope above which a Tian correction should be applied if the kinetic response of the sample is important.

The Tian equation as written above is predicated on several assumptions that, while making its derivation relatively straightforward and its application easy to follow, in practice means that it is not the most accurate method for data correction. The major assumption in the derivation of the Tian equation is that the calorimetric cell and its contents are at the same temperature. Consideration of how experiments are actually performed (the sample is loaded into an ampoule which is then sealed and placed in the calorimeter) suggests that, initially at least, the temperature of the sample (T_s) and the cell (T_c) will not be the same. Given that the temperature gradient giving rise to the measured signal is external to the calorimetric cell, it is clear that some temperature

difference between the sample and the cell will affect the measuring response of the calorimeter. The degree to which the measurement is affected will be governed by the rate of heat transfer between the sample and the cell (k_{sc}) and between the cell and the heat-sink (k_{co}). As before, both of the heat exchange coefficients have units of W K^{-1}. In the same manner as described earlier, the heat balance equations for both the sample and the cell can then be written:

$$\frac{dq}{dt} = k_{sc}(T_s - T_c) + C_s \frac{dT_s}{dt} \tag{44}$$

$$k_{co}(T_c - T_o) + C_c \frac{dT_c}{dt} = k_{sc}(T_s - T_c) \tag{45}$$

where C_c and C_s are the heat capacities of the cell and the sample, respectively. (Note that earlier the heat capacity was defined as that of both the cell and its contents.) The right-hand side of Equation (45) represents the power exchanged between the sample and the cell; this term also appears in Equation (44). In order to remove T_s (which is not directly measured in an experiment), it is necessary to differentiate Equation (45) and then substitute both Equation (45) and its derivative into Equation (44), resulting in:

$$\tau_s \tau_c \frac{d^2T_c}{dt^2} + (\tau_s + \tau_c)\frac{dT_c}{dt} + \frac{k_{co}}{k_{sc} + k_{co}} T_c = \frac{1}{k_{co} + k_{sc}} \frac{dq}{dt} + \frac{k_{co}}{k_{sc} + k_{co}} \left(T_o + \tau_s \frac{dT_o}{dt} \right) \tag{46}$$

where τ_s and τ_c are defined as:

$$\tau_s = \frac{C_s}{k_{sc}} \tag{47}$$

$$\tau_c = \frac{C_o}{k_{sc} + k_{co}} \tag{48}$$

A similar equation can be written for a reference material, prepared under the same conditions as the sample (the subscript r denoting a property of the reference material):

$$\tau_r \tau_c \frac{d^2T_c}{dt^2} + (\tau_r + \tau_c)\frac{dT_c}{dt} + \frac{k_{co}}{k_{rc} + k_{co}} T_c = \frac{1}{k_{co} + k_{rc}} \frac{dq}{dt} + \frac{k_{co}}{k_{rc} + k_{co}} \left(T_o + \tau_r \frac{dT_o}{dt} \right) \tag{49}$$

Subtracting the sample and reference equations (which is valid only assuming the reference material has the same heat capacity and heat transfer coefficient to the

cell as the sample) yields:

$$\frac{\mathrm{d}q}{\mathrm{d}t}=k_{\mathrm{co}}(T_{\mathrm{c}}-T_{\mathrm{r}})+(k_{\mathrm{co}}+k_{\mathrm{sc}})\left[(\tau_{\mathrm{s}}+\tau_{\mathrm{c}})\frac{\mathrm{d}(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t}+\tau_{\mathrm{s}}\tau_{\mathrm{c}}\frac{\mathrm{d}^2(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t^2}\right] \tag{50}$$

Note here that T_{c} appears in Equation (50), whereas in the earlier derivations T_{s} was used; this simply reflects the fact that in the earlier cases T_{s} and T_{c} were assumed to be equal and here the actual measured temperature (T_{c}) is used.

If the rate of heat exchange between the sample and the cell is much smaller than the rate of heat exchange between the cell and the heat-sink (in other words, the calorimeter behaves ideally and the rate-limiting step is heat transfer from the sample to the calorimeter), then k_{sc} is much smaller than k_{co} and:

$$\frac{\mathrm{d}q}{\mathrm{d}t}=k_{\mathrm{co}}\left[(T_{\mathrm{c}}-T_{\mathrm{r}})+(\tau_{\mathrm{s}}+\tau_{\mathrm{c}})\frac{\mathrm{d}(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t}+\tau_{\mathrm{s}}\tau_{\mathrm{c}}\frac{\mathrm{d}^2(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t^2}\right] \tag{51}$$

It can be seen that Equation (51) has a form similar to that of the Tian equation but that there appears a second-order time derivative of the temperature difference and the coefficient of the first-order derivative has altered. In practice, it is difficult to know the value of k_{sc}. However, if the following definitions are made:

$$\tau_1+\tau_2=\left|\frac{k_{\mathrm{co}}+k_{\mathrm{sc}}}{k_{\mathrm{co}}}\right|(\tau_{\mathrm{s}}+\tau_{\mathrm{c}}) \tag{52}$$

$$\tau_1\tau_2=\frac{k_{\mathrm{co}}+k_{\mathrm{sc}}}{k_{\mathrm{co}}}(\tau_{\mathrm{s}}\tau_{\mathrm{c}}) \tag{53}$$

Then Equation (51) can be rewritten as:

$$\frac{\mathrm{d}q}{\mathrm{d}t}=k_{\mathrm{co}}\left[(T_c-T_r)+(\tau_1+\tau_2)\frac{\mathrm{d}(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t}+\tau_1\tau_2\frac{\mathrm{d}^2(T_{\mathrm{c}}-T_{\mathrm{r}})}{\mathrm{d}t^2}\right] \tag{54}$$

The values of τ_1 and τ_2 differ from the values of τ_{s} and τ_{c} and are known as the first and second time constants of the calorimeter, respectively. Using the same definitions of P_{R} and P_{C} as described earlier, Equation (54) can be rewritten in the form:

$$P_{\mathrm{C}}=P_{\mathrm{R}}+(\tau_1+\tau_2)\frac{\mathrm{d}P_{\mathrm{R}}}{\mathrm{d}t}+\tau_1\tau_2\frac{\mathrm{d}^2P_{\mathrm{R}}}{\mathrm{d}t^2} \tag{55}$$

Equation (55) can be used to reconstruct corrected power data from the raw power signal and is indeed used in some commercial software (for instance, in Digitam, Thermometric AB). In order to apply this correction, the proportionality constant (ε) must be known (as this is required to determine P_{R}) as must the two time constants. The value of the proportionality constant is determined by electrical