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Expanding the role of reaction calorimetry[1]

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Abstract

Reaction calorimetry, a scientific tool designed to measure the rate of heat evolution occurring during a reaction or other process, has been employed in various capacities over the last 30 years. Recently, it has expanded to find a variety of uses in process development, process safety and basic research. This review acquaints the reader with the theoretical principles, measurements that can be made and surrounding issues of reaction calorimetry, and then methodically presents the different types of investigations which have been and are being performed in various laboratories around the world. This review also considers aspects of the equipment and how these features play a role in the quality and type of data obtained. The mathematical solution(s) to the energy balance in a variety of cases is presented along with examples of their use in the literature

Keywords: Reaction calorimetry, Review, Heat flow, Automated reactor

Symbols

Symbol	Units	Description
q_r	W	Heat flow due to reaction.
U	$W/m^2 K$	Overall heat transfer coefficient.
A	m^2	Wetted heat transfer area.
T_r	°C	Temperature of reactor contents.
T_j	°C	Temperature of jacket contents.
m	kg	Mass of reactor contents.
C_p	j/Kg K	Heat capacity of reactor contents.

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dT_r/dt	°C/s	Temperature rise rate of reactor contents.
dm_d/dt	kg/s	Mass addition rate of feed stream.
C_{p_d}	J/kg K	Heat capacity of feed stream.
T_d	°C	Temperature of feed stream.
dm_c/dt	kg/s	Mass flow rate of condenser coolant.
C_{p_c}	J/kg K	Heat capacity of condenser coolant.
$T_{c_{out}}$	°C	Temperature of condenser coolant outlet.
$T_{c_{in}}$	°C	Temperature of condenser coolant inlet.
k_{loss}	W/K	Overall heat loss coefficient.
T_{amb}	°C	Ambient temperature.
ΔT_j	°C	Temperature difference between jacket inlet and outlet.
$T_{j_{lm}}$	°C	Log-mean temperature difference of the jacket.
$T_{j_{in}}$	°C	Inlet value of the jacket temperature.
$T_{j_{out}}$	°C	Outlet value of the jacket temperature.
dm_j/dt	kg/s	Mass flow rate of jacket fluid.
C_{p_j}	J/kg K	Heat capacity of jacket fluid.
r_R	moles/L/s	Reaction rate of component R.
R	-	Reactant molecule.
P		Product molecule.
C_R	moles/L	Reactant concentration.
dC_R/dt	moles/L/s	Reaction rate of component R.
k	/s	Rate constant.
ΔH_{rxn}	J/mole	Heat of reaction.
V_{rxn}	L	Volume of reaction mass.
q_{r_o}	W	Heat flow at $t = 0$.
C_{R_o}	moles/L	Concentration of reactant at $t = 0$.
ΔH_{net}	J	Total energy released.
ΔT_{ad}	°C	Adiabatic temperature rise.
T_{onset}	°C	Temperature at which undesired chemistry becomes significant.
$T_{desired}$	°C	Temperature at which desired reaction is carried out.
$(\partial S/\partial T)_P$	$\mathrm{J/kg\ K^2}$	Partial derivative of entropy with respect to temperature.
ΔS_{rxn}	J/kg K	Entropy change of reaction.
ΔG_{rxn}	J/mole	Gibbs free energy change of reaction.
$\Delta C_{p_{rxn}}$	J/kg K	Heat capacity change of reaction mixture.
$FTIR$	-	Fourier transform infrared.
$CSTR$	-	Continuously stirred tank reactor.
$GABA$	-	γ-aminobutyric acid.
MSA	-	Methane sulfonic acid.
H_3PO_3	-	Phosphorous acid.
PCl_3	-	Phosphorous trichloride.
ρ_{PCl_3}	g/ml	Density of PCl_3.
$\rho_{GABA\,feed}$	g/ml	Density of GABA feed.
t	min	Time.
$m_{off-gas}$	g	Mass of off-gas leaving reactor.
m_{GABA}	g	Mass of GABA entering reactor.

$m_{\mathrm{PCl_3}}$	g	Mass of PCl_3 entering reactor.
$m_{effluent}$	g	Mass of Effluent leaving reactor.
Q_{jacket}	kcal/l/hr	Heat load placed upon jacket.
$Q_{GABA\,feed}$	kcal/l/hr	Sensible heat load due to GABA feed.
q_{probe}	W	Heat flow due to calibration probe.
ΔT_{ss}	°C	$T_r - T_j$ at steady state.
ΔT_{probe}	°C	$T_r - T_j$ at while calibration probe is actuated.

1. Introduction

Calorimetry is perhaps one of the older technologies known to science, with published examples dating back to the 18th century [1]. The broad applicability of calorimetry stems primarily from one central theme: virtually every process liberates or consumes some finite amount of energy. That is, if we are clever enough, we can measure the rate and extent of any event using the principles of calorimetry.

Implicit to the concept of calorimetry (measurement of heat flow) is that both kinetics and thermodynamics contribute to the observed measurement. Kinetics emerge as *rates* of heat evolution or absorption, and thermodynamics as the integrated heats(enthalpies) of reactions/phase changes. In this review, numerous investigators demonstrate the utility of this dual kinetic/thermodynamic information.

Over the years, several evolving trends within the overall theme of calorimetry have emerged [2–8] including DSC (differential scanning calorimetry), DTA (differential thermal analysis), Bomb Calorimetry, Solution Calorimetry, Reaction Calorimetry, ARC (accelerating rate calorimetry), and several others. This review restricts itself to the applications of what is now called reaction calorimetry.

Reaction calorimetry is defined herein as the measurement of energy consumption or evolution attendant to a reacting (including phase changes) system under conditions which permit all pertinent rate processes (e.g., heat and mass transfer) to be measured and therefore studied. The preceding qualifier is an important distinction, and is easy to recognize if one considers mixing and mass transfer issues where low volume systems (DSC, DTA) are inadequate.

Perhaps one of the greatest attributes of reaction calorimetry is its relative simplicity. In theory, measurement of temperatures at specific locations is all that is required (for batch reactions). The non-invasive nature of this technology therefore makes it quite attractive to a variety of investigators. Semi-batch and continuous calorimetric investigations require knowledge of the flow rates of certain streams to complete the energy balance. Nonetheless, a large proportion of the systems studied are at least some form of semi-batch operation, and these investigations still benefit greatly from the relative ease with which the required information is obtained during an experiment.

The applications of reaction calorimetry have been explored in recent years by both industrial and academic scientists covering the areas of process safety, process development, and basic research. Figure 1 indicates the frequency of yearly publications for reaction calorimetry for the period 1966-1996. This data was obtained by searching the *CAplus* (*Chemical Abstracts Services*), COMPENDEX PLUS (*Engineering Information, Inc.*), JICST-EPLUS (*Japan Information Center of Science and Technology*),

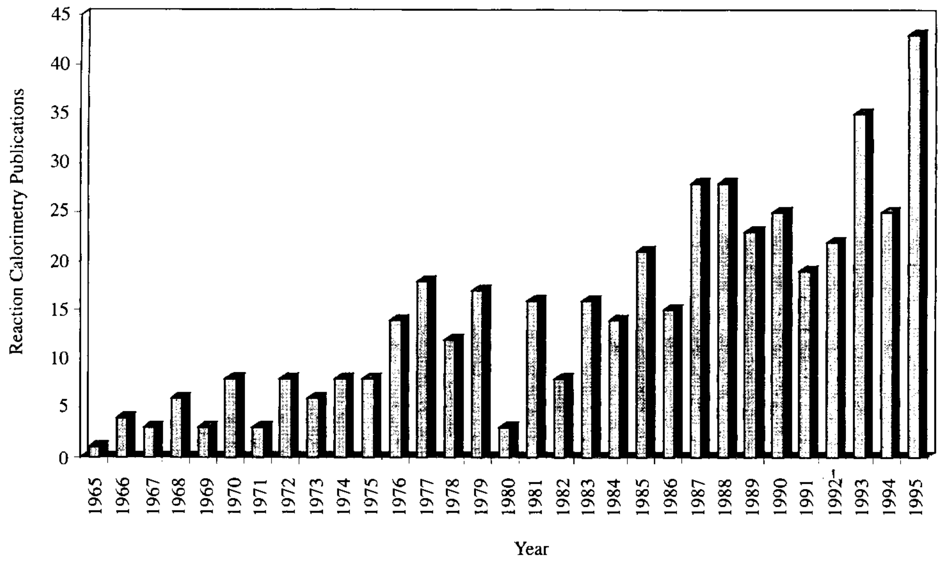

Figure 1. Yearly publications in the field of reaction calorimetry from 1965 through 1995. "Reaction calorimetry" appears either in the title or the keyword list.

CSNB (*Royal Society of Chemistry*), CEABA (*DECHEMA, Deutsche Gesellschaft fuer Chemisches Apparatewessen*), and INSPEC (*Institution of Electrical Engineers*) databases for "reaction calorimetry" in either the title, or the keywords of the publication (it is therefore assumed that reaction calorimetry is the focus of the work).

The half-life of this data is about 10 years, that is, every ten years the number of publications per year doubles. Further analysis of the locations from which the research emanated reveals that the countries of Europe are contributing the greatest (especially if population base is considered) as shown in Figure 2.

The literature may be analyzed with respect to the applications on which these investigations focused. Figure 3 shows the distribution of effort in the various areas. Note that the sum of papers here exceeds the sum of the search because some papers covered multiple topics.

Additionally, the focused nature of some papers on simply measuring and reporting the enthalpy of formation was used as a basic for differentiating them from the broader thermodynamics papers. It is interesting to note the large number of papers which address various aspects of calorimeter design and operation.

The variety of topics shown in Figure 3 are an indicator of the versatility of this technology. The advantages to process safety are readily apparent and several outstanding examples are referenced or discussed herein. Less apparent, but generally of equal impact, are the benefits this technology can provide to those interested in process development. Lastly, and very likely, the area of highest importance is the potential impact of reaction calorimetry on basic research efforts.

This review will address the equipment typically employed, followed by an overview of two common analysis methods (which also affect the instrument design strategy).

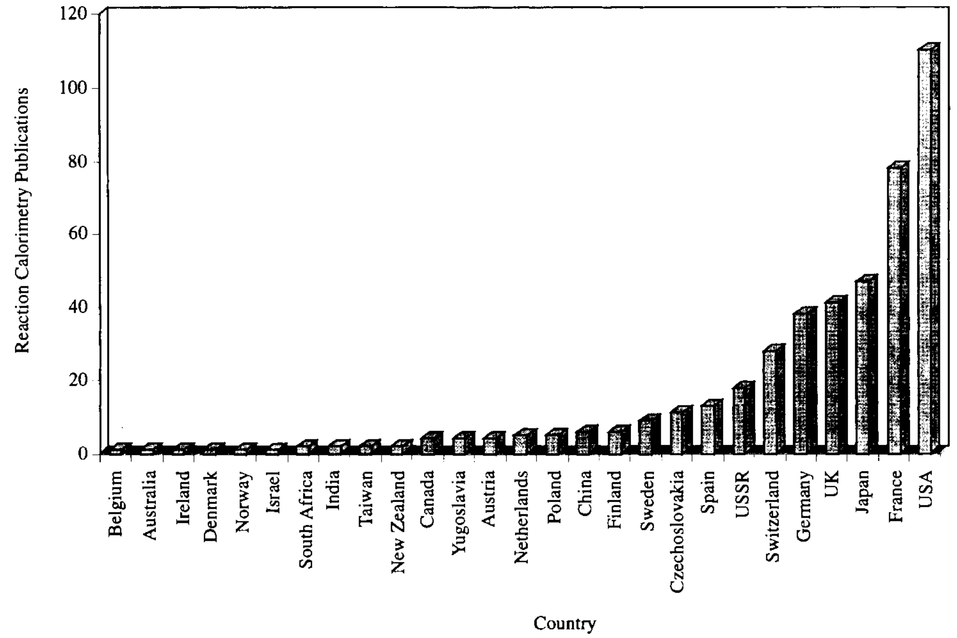

Figure 2. Publications in the field of reaction calorimetry from 1965 through 1995 by country. "Reaction calorimetry" appears either in the title or the keyword list.

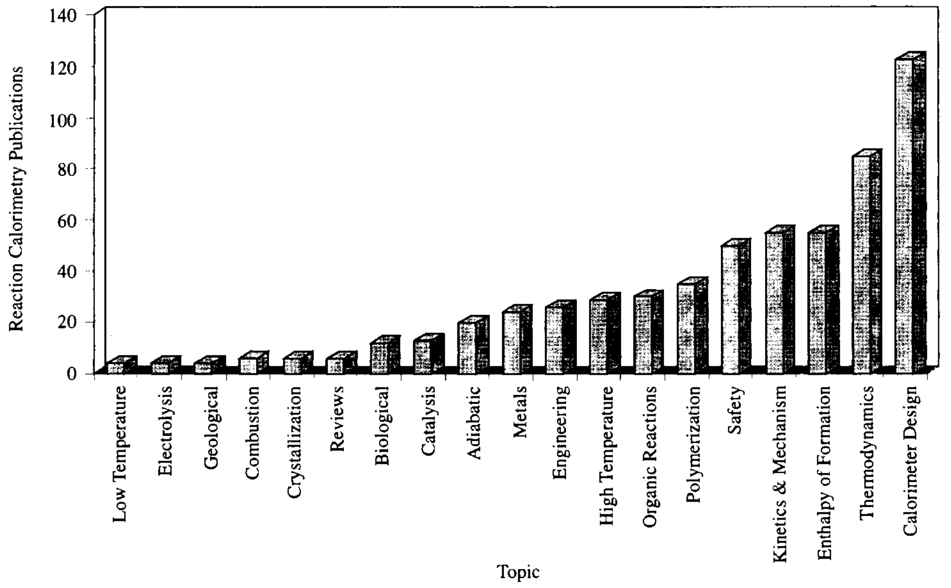

Figure 3. Total publications by topic in the field of reaction calorimetry from 1965 through 1995. "Reaction calorimetry" appears either in the title or the keyword list.

A brief development of the theoretical relationships between heat flow and various physical phenomena will be discussed, and then, finally, a broad view of many of the applications for which reaction calorimetry has been successful will be presented.

Apparatus

General

Typical reaction calorimetry systems consist of a jacketed reaction vessel (reaction volumes ranging from about 0.1L to 10L), a liquid feed system (generally a pump and balance, although sometimes a pneumatic valve and balance are employed), occasionally a solids feed system (hopper mounted on a balance), gas feed system (gas reservoir and regulator, or other equivalent device), and often, a distillation reflux system. Many variations within this basic theme have been reported [9–16].

When consideration is given to the functions described above, and also to the issue of agitation, it is clear that volumes below 0.1L become impractical because of the poor access a small vessel would afford (consider a 10 ml reactor with agitation, feed tubes, sample port, etc.). As vessel volumes increase, there is an accompanying increase in the sensitivity. However, there is also an ever increasing time constant and heat loss factor with which to contend. The time constant refers, in a simple sense, to the time it takes to equilibrate various portions of the reaction vessel following a temperature change (e.g., on a large vessel, the riser to a condenser may take an hour or more to equilibrate). Therefore, it has been found that the volume range described above (0.1L-10L) represents a reasonable compromise.

The quality of data obtained can be greatly enhanced through computer control and the quantity increased through electronic data acquisition. Generally, at a minimum, the reactor temperature and/or jacket temperature must be controlled by computer. Ideally, all controllable parameters should be managed by computer as well as stored electronically. Karlsen and co-workers [17] have discussed the importance of data acquisition in relation to calorimeter-specific parameters, reaction-specific parameters, and other variables which may or may not vary with the extent of reaction. Generally, the use of computer control significantly enhances the reproducibility of certain operations, in particular, additions of feed streams and temperature control [18–19].

Temperature control

A subtle, however significant design feature of the apparatus relates to its method of temperature control. In fact, the excellent temperature control exhibited by many of the available reaction calorimetry units is perhaps the key feature which has allowed this technology to be applied to so many areas. Essentially, the design must be able to accommodate the rapid responses often necessary during exothermic or endothermic reactions processes, assuming isothermal conditions are desired. In many cases, isothermal operation provides additional insight over non-isothermal operating conditions, and is therefore the favored experimental approach.

Most current reaction calorimeters achieve this level of control through a two-reservoir system. The reaction calorimeter maintains one reservoir at a fairly high temperature and the other at a very low temperature (limited by a cooling source, typically an external cooling bath). The computer then operates a control valve which determines the proportion of each stream (hot & cold) which enter the jacket. Upon returning from the jacket, the stream is appropriately split so that each reservoir maintains the proper degree of fill. This allows, through a simple change in the position of the mixing valve, for a rapid change in the jacket temperature. This way, in the event that an exotherm is detected by the reaction calorimeter (usually observed as a temperature rise of the contents), the instrument quickly lowers the jacket temperature so that the reaction mass remains essentially isothermal. Several variations of this general approach exist [20–23], however, they all rely on two-sided control whether it be through reservoirs, or other manipulation techniques.

Heat losses

Heat losses as mentioned above are a problem with which to contend, especially in larger reactors. This seems, at first, inconsistent with the experiences many have observed when up-scaling reactions. Since the surface area to volume ratio decreases with volume, it can be argued that heat losses are minimized in larger reactors. This turns out to be true only under steady state conditions. Consider a large semi-batch reactor. If a set point change is made in the contents temperature, or a temperature ramp executed, while the contents may achieve the new set point relatively quickly, the temperature of the reactor components generally take much longer to equilibrate (consider initiating a reaction at reflux). Therefore, the thermal mass of the reactor itself acts to disguise the true heat flow, since the reactor itself is absorbing or releasing sensible heat to or from the reaction mass [24]. These heat losses are the culprit in larger systems.

When consideration is given to the small lab-scale systems as described earlier, heat losses driven by the difference between the environment and the reactor vessel temperatures dominate. Again, it is the non-steady state period which will have the greatest error associated with it. This shortcoming has been recognized for years, and in an effort to overcome this, elaborate techniques resulting in nearly adiabatic surfaces have emerged [25–27]. These include thermostated head plates with computer controlled algorithms to ensure that the head plate and other non-jacketed surfaces temperature equals the batch temperature (and therefore no heat loss occurs).

Analysis methods

Heat flow vs. Heat balance

Reaction calorimetry may be reduced to mathematical form by applying an energy balance to the reacting system. Consider a semi-batch system as shown in Figure 4. The general energy balance would include terms for the heat evolution rate of the process being carried out, the heat flow through the wall, the heat accumulation of the reactor contents, the sensible heat effect of the feed, the latent heat of vaporization (usually

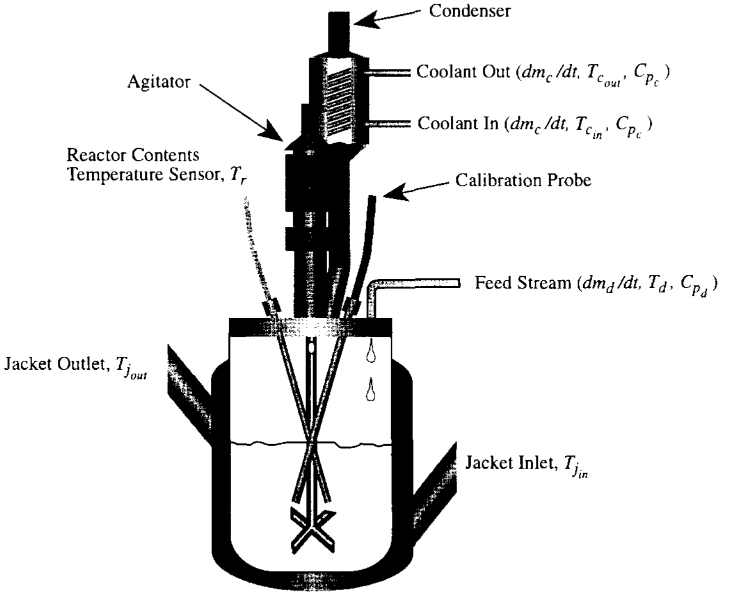

Figure 4. Schematic drawing of a typical reaction calorimeter. The critical variables required to calculate heat flow under batch and semibatch (feed stream) are shown.

captured as a sensible heat gain by a cooling stream, e.g., a condenser), and possibly a rate of heat loss term. Equation (1) shows these terms for a heat flow calorimeter [28–32]:

$$q_r = UA(T_r - T_j) + mC_p(dT_r/dt) + (dm_d/dt)C_{p_d}(T_r - T_d)$$
$$+ (dm_c/dt)C_{p_c}(T_{c_{out}} - T_{c_{in}}) + k_{loss}(T_r - T_{amb}). \qquad (1)$$

In general, there may be more than one feed term, and in theory, the heat loss term can be eliminated through appropriate insulation measures. Equation (1) also employs a single value of T_j. There are some considerations which must be given to the value of T_j used, depending on the design features of the reaction calorimeter. It the flow rate of jacket fluid is high, the inlet and outlet values will not differ much, and an average value of T_j (or possibly just the inlet or outlet value) may be utilized without incurring significant error. It is not necessarily the residence time of the jacket fluid which is critical, since a large jacket volume combined with a relatively long residence time would still yield a small change in the inlet and outlet jacket temperatures. Of importance is the capacity of the jacket fluid during one residence time to absorb or release energy. Equation (1) (specifically the first term) works best in systems where ther is a small ΔT_j. In systems where the inlet and outlet temperatures vary significantly, two approaches may be employed. Equation (1) may be used with the log-mean value of T_j as shown in Equation (2):

$$T_{j_{lm}} = (T_{j_{out}} - T_{j_{in}})/\ln(T_{j_{out}}/T_{j_{in}}). \qquad (2)$$

This approach loses accuracy as ΔT_j increases because the log-mean temperature calculated assumes a specific profile (in this case, between T_r and T_j), derived for a linear system (e.g., a tube or a flat surface). In a jacketed reactor, the log-mean approach is merely an approximation for what is actually a complex variation of surface temperatures. These are influenced not only by the local flow rate of the jacket fluid, but also by the local flow rate of the reaction medium on the other side of the reactor vessel wall. Another approach, one which is the basis for designing purposefully high ΔT_js, is what is referred to as the heat balance technique [33–34]. Lahti [35] recently presented a detailed account of the design, construction, and modeling of a heat balance calorimeter which was applied to a metallocene catalyzed ethylene slurry polymerization. In this method, Equation (1) becomes

$$\begin{aligned} q_r = {} & (dm_j/dt)C_{p_j}(T_{j_{out}} - T_{j_{in}}) + mC_p(dT_r/dt) + (dm_d/dt)C_{p_d}(T_r - T_d) \\ & + (dm_c/dt)C_{p_c}(T_{c_{out}} - T_{c_{in}}) + k_{loss}(T_r - T_{amb}) \end{aligned} \quad (3)$$

Notice that only the first term has changed. Instead of measuring the heat flowing through the wall (the $UA(T_r - T_j)$ term), in Equation (3), a heat balance is performed on the jacket fluid itself (the $(dm_j/dt)C_{p_j}(T_{j_{out}} - T_{j_{in}})$ term), and hence the two names heat flow and heat balance. Each method has its benefits and drawbacks. Table 1compares the two techniques.

Clearly, depending on the goals of the research being conducted, one type of reaction calorimeter may be better suited than the other. The remainder of this section will focus on the theoretical relationships between the heat flow measured by either Equation (1) or Equation (3) and defined physical phenomena.

Reaction calorimeter calibrations

Considering a heat flow calorimetry, the automated laboratory calorimeter may be calibrated by imposing knownq_r values on the system to solve for the unknown

Table 1
Comparison of heat flow to heat balance reaction calorimeters

Issue	Heat flow	Heat balance
Properties of jacket Cooling medium	Independent	Knowledge of C_{p_j}(T) and dm_j/dt required.
Heat transfer characteristics of reaction vessel	Knowledge of U and A required.	Independent
Cooling capability	Rapid response and high rate possible due to high Jacket flow rates.	Slower response and lower rate due to lower jacket flow rates.
Calibration	Required to obtain U and C_p.	Required to obtain C_p, and to account for heat losses.
Operational safety	High cooling capacity equates to increased safety.	Lower cooling capacity equates to reduce safety.

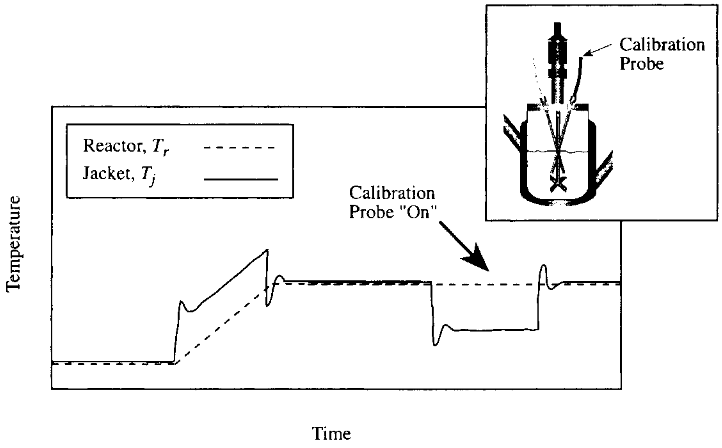

Figure 5. Typical reactor and jacket temperature profiles during a calibration experiment. The right hand side yields U, and the left hand side, C_p.

quantities U and C_p [36–40]. Figure 5 shows the temperature profiles for the jacket and reactor contents during a typical calibration experiment.

There are two distinct parts to the calibration because Equation (1) has two unknowns (a similar approach would be employed to solve for the unknowns of Equation (3)). The first part of the experiment involves a short temperature ramp effected by ramping the jacket temperature. During this period, q_r is equal to 0 since there is no heat generation or consumption. The second portion of the calibration involves the action of a precision heating probe. The calorimeter is instructed to maintain the desired isothermal temperature (using the jacket to remove the heat flow), thus dT_r/dt is equal to 0, and q_r equals the calibration heat flow emitted by the probe. Hence, from these two experiments, the heat transfer coefficient and the heat capacity may be determined. Normally, this procedure is carried out before initiating reactions and after reaction is complete to account for changes in these properties with extent of reaction. Using these two calibration endpoints, C_p and UA initial and final, the data may be analyzed by several methods of varying (linearly, proportional to heat flow, and others) these properties over the course of the experiment. This is necessary since they generally change during reactions, and Equation (1) works best when the most accurate values for U and C_p are employed. Fiaty and co-workers [41] developed a detailed approach to determine inside and outside film heat transfer coefficients in a reaction calorimeter, including a heat loss coefficient.

Relating heat flow to kinetics

A review on reaction calorimetry would not be complete without some mention of the relationship between reaction rate and observed heat flow. While it is not the intention herein to derive all of the possibilities, it is however important to reveal the methods used. Consider a first order irreversible reaction traditionally given as

$$R \rightarrow P \tag{4}$$

The rate of this reaction, r_R, is directly proportional to the rate of heat evolution, q_r. Equation (5) shows the relationship:

$$q_r = r_R \Delta H_{rxn} V_{rxn} \tag{5}$$

From Equation (5), it is clear that the measured heat flow equals the reaction rate (within a factor, $\Delta H_{rxn} V_{rxn}$). The rate expression, assuming mass action kinetics, is given by Equation (6) (for a simple first order reaction):

$$r_R = dC_R/dt = -kC_R \tag{6}$$

Substituting into Equation (5), Equation (7) is obtained:

$$q_r = -kC_R \Delta H_{rxn} V_{rxn} \tag{7}$$

Initially, the heat flow is given as:

$$q_{r_0} = -kC_{R_0} \Delta H_{rxn} V_{rxn} \tag{8}$$

Dividing Equation (7) by Equation (8) yields:

$$q_r/q_{r_0} = C_R/C_{R_0} \tag{9}$$

The result shown in Equation (9), for simple first order reactions shows directly how closely the heat flow is related to the kinetics. Integration of Equation (6) followed by combination with Equation (9) gives:

$$C_R/C_{R_0} = e^{-kt} = q_r/q_{r_0} \tag{10}$$

This approach can be applied to any kinetic model, however, it sometimes does not yield an analytical result, and must be numerically evaluated to extract kinetic parameters from the heat flow data. Nevertheless, Equation (10) is mathematical proof of the elegant, non-invasive (temperature measurements only) nature of reaction calorimetry as a tool for monitoring reactions. The use and extension of this concept has been demonstrated extensively [42–53].

Phase changes and heat flow

Another area of interest for reaction calorimetry is in its ability to monitor phase changes. In these cases, the models appear differently, but the approach is similar. Again, the premise is that the heat flow is measuring the rate of the event, off by a constant, the heat of the phase change.

Studying reactions under reflux or distillative conditions can present difficulties because the heat transfer coefficient is affected by the condenser heat load [54]. Even greater difficulty arises when moving from non-volatile conditions to conditions approaching the boiling point, since large changes in the heat transfer coefficient are possible. Nomen has shown that heat losses near the boiling point can be correlated to vapor pressure [55], and has also described a useful technique for obtaining the required heat transfer coefficient under reflux conditions [56].

Thermodynamics

The information obtained from a reaction calorimeter is closely tied to all of the thermodynamic quantities. For example, the calibration requires determination of C_p. Operation of the calibration probe (in a non-reacting system, and in the adiabatic mode) and monitoring of the resulting adiabatic temperature rise allows the investigator to construct an expression relating enthalpy to temperature. This expression may be differentiated to obtain C_p as a function of temperature. This in turn can be used to derive an expression for entropy as a function of temperature since $(\partial S/\partial T)_P = C_p(T)/T$. With expressions for both enthalpy and entropy as a function of temperature, the Gibbs free energy may be determined. Under reaction conditions, the same principles may be applied to yield quantities such as ΔH_{rxn}, ΔS_{rxn}, ΔG_{rxn}, *and* $\Delta C_{p_{rxn}}$. A large number of papers have been written describing the application of reaction calorimetry to the calculation of the aforementioned thermodynamic quantities [57–67].

Other applications within thermodynamics include construction of enthalpy concentration diagrams for non-ideal systems, obtained by simply measuring the attendant heat flow occurring during the addition of one component into another [68]. VLE measurements may be made, including estimation of activity coefficients, excess properties, and model parameters [69] using a reaction calorimeter.

Applications

Process safety

One of the recent uses (the last 15–20 years) of reaction calorimetry relates to its application to the solution of process safety objectives. In numerous industrial settings, the basic questions surrounding exothermic potential must be answered. Primarily, it must be determined whether the intended reaction could lead, under certain conditions, to a runaway reaction. In the context of process safety, a runaway reaction is defined as a condition under which the desired reaction is not controlled (e.g., in a system which is intended to run isothermally, control of the reaction is achieved through the $UA(T_r - T_j)$ term, but during a runaway reaction, the $mC_p(dT_r/dt)$ term is not zero), and whose final destination (temperature, pressure) may lead to decomposition and other undesired events including elevated pressures and possibly emissions and vessel failure.

Employing a reaction calorimeter, the desired reaction can be carried out, and Equation (11) applied to the data to yield the net heat evolved, ΔH_{net},

$$d(\Delta H_{net})/dt = q_r \qquad (11)$$

The theoretical adiabatic temperature rise, the temperature increase expected in the absence of cooling to the reactor, may be approximated as,

$$\Delta T_{ad} = \Delta H_{net}/mC_p \tag{12}$$

The results of Equation (12) allow for a check of the intrinsic safety of the process by evaluating the following inequality:

$$T_{onset} > T_{desired} + \Delta T_{ad} \tag{13}$$

where T_{onset} is the temperature at which undesired activity is known to initiate, and $T_{desired}$ is the temperature at which the desired chemistry is normally carried out. If the inequality in Equation (13) is true, then the process is said to be intrinsically safe. Most of the advanced techniques found in practice throughout a large majority of industry use this as the starting point of their analysis. A detailed account of several of the methodical approaches (employing reaction calorimetry as a portion of the analysis) to ensuring the intrinsic safety of a factory-scale reactors is given in the literature [70–87].

Stoessel [88] has described a useful analytic method for understanding and controlling the exothermicity in semi-batch reactions. Wiss [89] has addressed low temperature (− 90°C) reaction calorimetry in the synthesis of lithium diisopropylamide and in the preparation of metallated 2,1,3-benzoxadiazole. Other recent work in the area of safety [90–91] has focused on developing specialty techniques for certain types of chemistry (e.g., polymerizations) and on extending the methodology for assessing the safety of a certain process.

Process Development

Relatively few papers utilize reaction calorimetry to carry out process development as shown in Figure 3 (see 'Engineering'). It is likely that a large proportion of the industrial literature, while not explicitly "for process development," is somehow related to process development efforts. That is, a paper which describes mechanism elucidation utilizing reaction calorimetry may very well be a critical contribution to the process development effort at the time it was performed. Therefore, the value and "activity in the area" should not be underestimated. Several notable examples of the use of reaction calorimetry in support of process development effort may be found in the literature [92–99]. The use of reaction calorimeters and calorimetry for process scale-up in combination with reaction simulation tools continues to grow with several recent publications [100–101].

Basic research

The applications defined as basic research include activity in the non-traditional areas when considering reaction calorimetry as well as novel extensions of established areas. For example, studying catalytic, enantioselective reactions [102–103] have recently been investigated. Other recent advances in calorimetric catalysis include the measurement of heats of adsorption, where Wartnaby and co-workers [104], reported heats of adsorption as a function of deposition thickness. Fisher and co-workers [105] have interpreted protein-ligand interactions in enzymatic systems using various types of calorimetry including reaction calorimetry.

Recently, an increasing amount of effort has been placed into studying various aspects of polymerizations with reaction calorimetry. Reaction calorimetry has been used by Saenz De Buruaga and co-workers [106] to perform online control of emulsion polymerizations. Varela De La Rosa and co-workers [107] combined reaction calorimetry with off-line particle size measurements to determine critical kinetic parameters during an emulsion polymerization. Other areas of focus include styrene emulsion polymerization, adiabatic free radical polymerizations, and investigating the particle size distribution during miniemulsion polymerizations [108–117].

Efforts in the area of thermodynamics (as described above) have continued. Thermodynamic parameters have been studied in the complexation of ferrocene derivatives [118]. Additionally, effort is on-going in the measurement of standard enthalpies (some at elevated temperatures), and in the study of surfactants and their interactions [119–125].

An area of recent activity which has great potential relates to the coupling of reaction calorimetry with other online analytical tools. A combination of reaction calorimetry and potentiometry has recently been used to study the peroxidation of a graphite bisulfate [126]. Lambert [127] combined gas evolution measurements with reaction calorimetry to study reactions which led to ketones, aromatic bromides and bromoketo aromatic compounds (and their associated off gases). McKenna and co-workers [128] have combined densimetry, gravimetry and reaction calorimetry to study control issues in multi-component polymerizations, and specifically, the on-line use of these techniques to address control challenges. Clearly, the combination of calorimetric data (global information) with species-specific information will be a continuing area of growth.

Example

An illustration of the capabilities provided by coupled systems is given in the following example: “In-Situ FTIR and Calorimetric Studies of the Preparation of a Pharmaceutical Intermediate” [99]. In this work, in-situ Fourier transform infrared (FTIR) spectroscopy was coupled with an automated laboratory reaction calorimeter to investigate a complex and potentially energetic reaction in a continuously stirred tank reactor (CSTR) system. The FTIR data led to mechanistic insight and the development of a rapid compositional monitor. The reaction calorimeter provided the components required to elucidate a material *and* energy balance for all streams, thus contributing to the reaction system design for factory-scale operation.

In this study [99], a continuous process (4 streams) was investigated utilizing an automated reaction calorimeter coupled with in-situ FTIR monitoring. Figure 6 shows the reaction studied, the bisphosphonation of γ-aminobutyric acid (GABA) to alendronic acid.

Safety testing on the bisphosphonation reaction revealed that significant exothermic activity existed close to the desired operating conditions. Due to this activity, a continuous reactor design (CSTR) was desired for factory operations

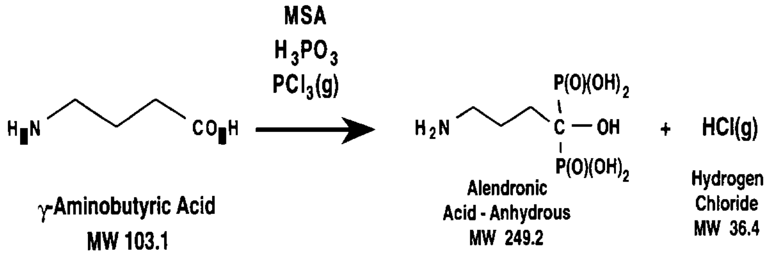

Figure 6. Overall reaction involving γ-amino butyric acid, phosphoric acid and PCl_3 to form the analogous bisphosphonate. The solvent used was methane sulfonic acid (MSA).

thus minimizing the active batch volume, and thereby enhancing the inherent safety of the process.

The equipment utilized in this study was Mettler's RC1 Reaction Calorimeter coupled with Applied Systems' ReactIR Reaction Analysis System. The automated reaction calorimeter was set up in the continuous (CSTR) mode as shown in Figure 7.

Initially, GABA feed was charged to the reactor at 25°C. The reactor contents were then heated to the desired reaction temperature, 90°C. Initial calibrations were performed at this point. The bottom outlet valve was then opened to initiate the flow of reactor contents to the FTIR flow cell, and eventually a tared receiving vessel. Immediately thereafter, the GABA feed pump was started at the desired flow rate, corresponding to a residence time of 1.86 hours. After reaching equilibrium (constant jacket temperature and FTIR profiles), the PCl_3 feed was initiated at a rate correspond-

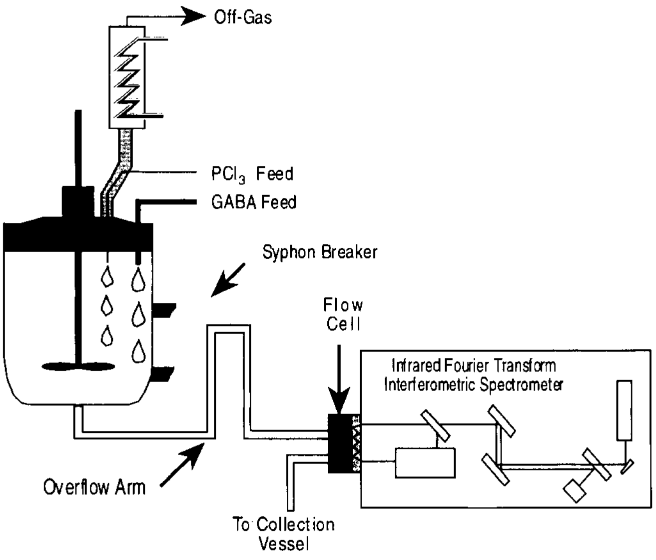

Figure 7. Schematic of the continuous reactor experimental set-up used to study the bisphosphonation of g-amino butyric acid. The effluent from the reactor passed through an FTIR analyzer.

ing to 3 volumes of GABA per volume of PCl_3. The additions were continued until the FTIR, condenser temperature and jacket temperature equilibrated (approximately 3 residence time).

To arrive at a successful scale-up, a complete material and energy balance was required. Table 2 summarizes the overall material balance for the CSTR. The masses were recorded by the reaction calorimeter for each of the streams. The derivatives of these data were taken to yield the average flow rates. Negative mass flow rates indicate that material was removed from the reactor. The mass of off-gas material was obtained by performing a material balance as shown in Eq. (14),

$$m_{off\_gas} = m_{GABA} + m_{PCl_3} - m_{effl} \tag{14}$$

where $m_{off-gas}$ is the mass of material leaving in the off-gas stream, m_{GABA} is the mass of material added through the GABA feed, m_{PCl_3} is the mass of material added through the PCl_3 feed, m_{effl} is the mass of material leaving in the effluent stream.

During the start-up, the GABA feed was brought up to temperature (batch mode) and an overall heat transfer coefficient coefficient, UA, of 9.94 W/K was determined for GABA feed in the reactor vessel at 90°C with a modification of Eq. (1):

$$q_r = q_{probe} = 23.5\,W = UA(T_r - T_j) + mC_p/(dT_r/dt) \tag{15}$$

The GABA feed was then initiated, and once a thermal steady state was attained, the temperature driving force for heat transfer from the reactor, $(T_r - T_j)$, was noted to be -4.0°C. From this value, the sensible heat load due to the GABA feed was determined by Eq. (16):

$$\begin{aligned} Q_{GABA\,feed} &= U(A/V)(T_r - T_j) \\ &= (9.94\ W/K)(-4°K)/1.53\ \text{liters} \\ &= -22.4\ \text{kcal/l/hr} \end{aligned} \tag{16}$$

Once a thermal steady state was attained and a steady baseline observed in the FTIR scans, the PCl_3 feed was initiated. The reactor was operated in this mode continuously for the next 8 hours. A critical measurement for the system is the determination of the overall heat transfer coefficient, U, *during* the reaction at steady state. At conditions near steady state, the calibration probe was actuated. Since all other heat loads in the system are not affected by the addition of heat by the probe (reaction temperature is maintained constant, thus kinetics and physical transport phenomena are not affected),

Table 2
Average Flow Rates for CSTR

Stream	Flow Rate (kg/min)
GABA	0.0201
PCl_3	0.0066
Off-Gas	−0.0043
Effluent	−0.0224

the decrease in the temperature driving force for jacket heat transfer must be proportional (constant of proportionality = UA) to the additional amount of heat introduced by the probe, q_{probe}, as shown in Eq. (17):

$$q_{probe} = UA(\Delta T_{ss} - \Delta T_{probe}) \tag{17}$$

where ΔT_{ss} is the temperature difference between the reactor and jacket at steady state, and ΔT_{Probe} is the temperature difference between the reactor and jacket while the calibration probe delivers heat. Rearrangement of Eq. (17) to solve for UA gives $UA = q_{probe}/(\Delta T_{ss} - \Delta T_{probe})$. Substitution of the steady state values yields the results given in Eq. (18):

$$\begin{aligned} UA &= -23.5W/([90.04^\circ C - 103.03^\circ C] - [90.30^\circ C - 100.45^\circ C]) \\ &= 7.14\,\text{kcal}/^\circ\text{C/hr} \end{aligned} \tag{18}$$

The volumetric expression of the heat transfer coefficient may be used to estimate the heat supplied by the jacket by multiplying by the appropriate temperature driving force. The steady state heat input by the jacket is given in Eq. (19).

$$\begin{aligned} Q_{jacket} &= U(A/V)\Delta T_{ss} \\ &= 4.675\ \text{kcal}/^\circ\text{C/l/hr}\,[90.04^\circ C - 103.03^\circ C \\ &= -60.72\,\text{kcal/l/hr} \end{aligned} \tag{19}$$

Although the jacket heat input may vary depending on the actual conditions employed (flow rates of feed streams, reaction temperatures etc.), the concept of providing a known heat input as a measure of reactor/jacket wall fouling is worth mention. Essentially, on a regular basis in a factory reactor, the overall heat transfer coefficient, U, could be determined in very much the same way as was done herein. The value obtained may slowly decrease over time, thus indicating that the reactor or jacket wall requires cleaning to provide adequate heat transfer rates.

The implications of the calculated required jacket heat input may be considered under conditions which resemble those of the factory reactor. Eq. (19), which related the rate of heat transfer of the jacket to the batch, may be utilized to attain an estimate of the required diameter of the factory reactor. Assuming the reactor to be cylindrical, and that no heat transfer occurs at the ends [(A/V) = (4/D)], Eq. (20) relates the reactor diameter to the jacket heat load, the temperature driving force, and the overall heat transfer coefficient.

$$D = 4U(T_r - T_j)/Q_{jacket} \tag{20}$$

assuming U to be 65 BTU/ft^2/hr/°F (an estimate of the overall heat transfer coefficient for the factor vessel), $(T_r - T_j)$ to be -20°F (this modest value has been assumed due to the safety concerns discussed earlier, and Q_{jacket} to be -60.72 kcal/l/hr, the diameter becomes $D = 0.77$ ft. This diameter has significant implications, since its value does *not* change with volume. Therefore, for a 25 gallon reactor (the estimated volume to be used in the factory), the L/D value would be 9.5. Clearly, this will not be acceptable due to the poor mixing dynamics which would result. Under the conditions presented during this experiment, the factory reactor would require additional heat input through either internal coils, or relaxation of the temperature driving force constraints, or pre-heating various incoming/returning streams, or a combination of all the above. Although internal heating coils could theoretically achieve the desired results, they pose other concerns and therefore will not be considered herein. The other options are discussed below.

The jacket heat load may be reduced by heating the PCl_3 feed and condensate return to 70°C. A 13% reduction in the jacket heat load is possible employing this strategy. This change would bring the L/D value down to 6.3. GABA feed may also be preheated to the reactor temperature (90°C) to reduce the jacket heat load, and this represents a 37% reduction in the jacket heat load. Thus, through preheating of the GABA feed and of the PCl_3 feed and reflux, the jacket heat load can be reduced by nearly 50% to -30.3 kcal/l/hr. Both of these changes would bring the L/D value down to 1.2, a value which would allow for acceptable mixing dynamics.

Simultaneous to the collection of calorimetric data was the acquisition of the infrared absorbance of the CSTR effluent. Figure 8 illustrates the spectrophotometric data collected during the CSTR experiment. The absorbances occurring at 1698.4 cm^{-1}, 1613.5 cm^{-1}, and 1416.6 cm^{-1} are due to the GABA feed, and in particular to the GABA. Previous experiments had suggested the possible presence of an intermediate, however, none of the analytical techniques utilized were able to detect it. The absorbance at 1791 cm^{-1} is clearly an intermediate species. The absorbance occurring at 125.4 cm^{-1} is due to either the alendronic acid intermediate, or the desired product, pyrophosphonate.

Clearly, from the data shown in Figure 8, on-line FTIR allows for in-situ, near-real time compositional analysis of the reaction. This ability would enhance the intrinsic safety of the process by providing information rapidly in the event of a process upset.

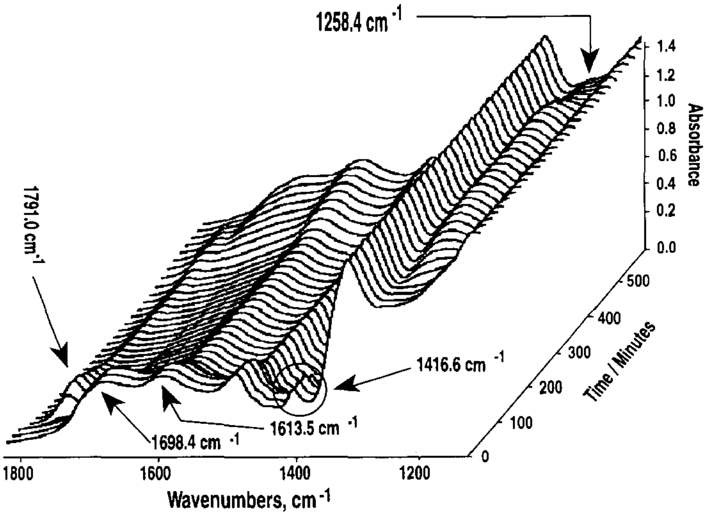

Figure 8. Infrared data collected during the start-up and steady-state periods of the bisphosphonation reaction. Reaction was carried out at 90°C.

The infrared spectra displayed in Figure 8 can be viewed kinetically by plotting the absorbance of a particular wavelength as a function of time. The spectra absorbing at 1698.4 cm^{-1} (GABA-related), 1791.0 cm^{-1} (intermediate-related), and 1258.4 cm^{-1} (product-related) were chosen and appear normalized in Figure 9.

Calibration of the FTIR allows for conversion of the absorbance data into concentration profiles. These data can then be used for traditional kinetics analyses.

In conclusion, for this example [99], the coupling of reaction calorimetry with in-situ FTIR led to a complete material and energy balance for a continuous reaction system.

There are some other interesting applications of reaction calorimetry worth mention. Castanet [129] covers applications in metallic systems, reporting on enthalpies of formation of In-Te melts, Pd-Pt-Ge alloys, and heats of dissolution of solid Cu-Ni alloys. Richardson and co-workers [130] designed a calorimeter, with a sensitivity of 1.3×10^6 n/s, which allows for the measurement of neutron flux when captured via the $^6Li(n,^3H)^4He$ reaction. Mathematical techniques have been applied by Carloff and co-workers [131] which imposed sinusoidal temperature oscillations to decouple chemical reaction heat flow from variations in the overall heat transfer coefficient. Linear sweep-current polarization electrode reactions were monitored by Zhang and co-workers [132] with reaction calorimetry. The technique allows for rapid determination of enthalpy changes of an electrode reaction. Menoud and co-workers [133] developed a method for detecting variations in the baseline heat flow through torque measurements, thus allowing heat flow measurements to be used as an online control tool.

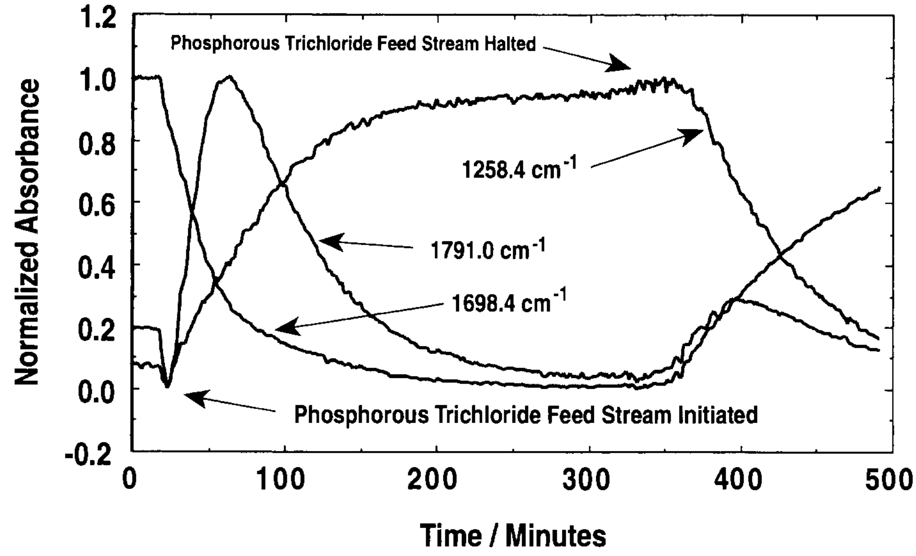

Figure 9. Normalized absorbance data for spectra collected at 1258.4 cm^{-1}, 1791.0 cm^{-1}, and 1698.4 cm^{-1}.

Future challenges and directions

Reaction calorimetry is still evolving as shown in Figure 1. We will likely see another doubling of the activity (as measured by publications) over the next 10 years. In theory, the hardware and software, which constitute a state-of-the-art system today, must improve for this trend to continue. Some of the added activity will be due to extensions of concepts already in place, and the rest from new applications of reaction calorimetry. The new areas may or may not be accessible with the current technology (i.e., the current instruments may have the required precision, or they may not). Improvements in the performance of current technology will likely be the key to opening opportunities for new areas of application.

Several areas require attention today if we are to have a better reaction calorimeter tomorrow. Specifically, heat losses, calibration methods, mixing issues, precision of measured variables, and software control/analysis algorithms are critical areas of concern. Naturally, the extent to which each one of these issues is deficient will depend on the system under consideration. Generally, however, all of the currently available systems fall short somewhat in each of the aforementioned areas. Obviously, heat losses can dampen any improvements made in other areas, therefore, this should be considered first. Any surface which is not included in the calibrated energy balance (i.e., having a heat loss term with a lumped heat loss coefficient does not quality as calibrated) should be critically evaluated for potential improvements relative to heat losses.

The methods used for calibration (whether flow, balance or other type of calorimetry) generally provide 2 undesired features: (1) they are time consuming because they can't be done during reaction, and (2) they only give global parameters (e.g., U). A hint of what is possible was given by Carloff [131], and an extension of that concept would imply that calibrations for the heat transfer coefficient and the heat capacity will be accommodated by the controller algorithm. Providing only a global calibration could be improved by combining computational fluid dynamics (CFD) with vessel geometry and an energy balance which is assessed as a function of position. This would divide the heat transfer surface into many smaller surfaces for which better estimates of the actual heat flow could be made. For this, mixing issues become critical, however, CFD should be able to overcome this. For a heat balance calorimeter, the equivalent challenge would be shifted to the jacket side where intimate knowledge of the jacket fluid is required for high precision.

Obviously, these efforts toward continued improvement have hardware and software implications. Ultimately, enhanced control/measurement of system variables, combined with advanced mathematical treatment of the raw information, will lead to higher precision and accuracy. This in turn will allow processes, which are presently difficult to monitor (e.g., many biological events), to be observed.

The future of reaction calorimetry will expand to fill several important needs. Heat flow as an on-line reaction monitor has yet to be fully exploited at large scale, however, it appears to be a strong possibility [134–135]. The area of greatest opportunity seems to be with coupled technologies. In-situ compositional monitoring, when combined with reaction calorimetry, has yielded several impressive results. This is because the investigator has at their disposal the complete energy and material (species) balance. In a sense, there is nothing more which can be measured. There is a synergy created when this occurs, i.e., either one alone has value, but together they yield more than the individual information sums to. Therefore, this would seem an area of high potential for growth.

Another area which is not as obvious, but which has great possibility, is what is referred to as a use test in the pharmaceuticals and fine chemicals industries. Often, and in an increasing manner due to ever-tightening regulatory constraints, certain lots of raw ingredients are run at lab scale prior to being used in the manufacturing plant. In some cases, every lot which is to be used for production must be 'use tested'. These use tests also require tedious analytical methods to ensure that the product obtained meets required specifications. Reaction calorimetry could be used to provide a fingerprint in-situ, as the use test proceeds, thus obviating most of the time consuming analytical efforts.

Conclusions

Reaction calorimetry is a growing and diversified discipline, having research activities on-going in support of process safety, process development, and basic research objectives. The combination of thermodynamic and kinetic information obtained make it unique among most analytical tools available to the research scientist. It is therefore applied to a vast number of problems for which we seek solutions. As the precision of these instruments improves, the number and types of problems it can engage in will surely increase.

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