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Enthalpimetric Analysis

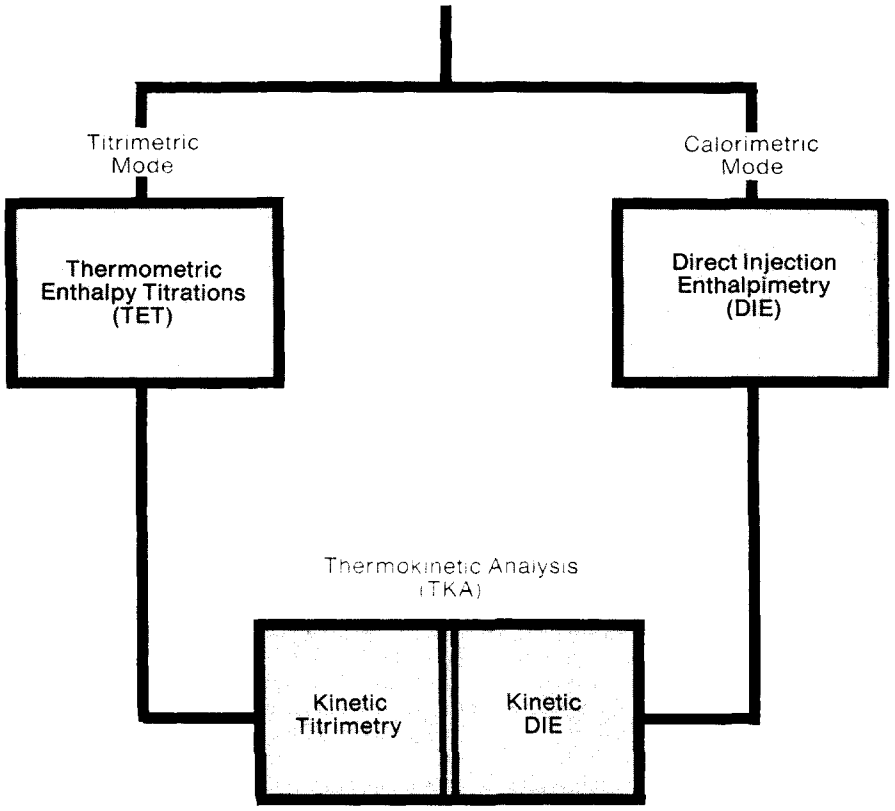

Figure 1. Relevant nomenclature

In view of the multiplicity of terms used to describe this field of analytical chemistry, a brief discussion of the relevant nomenclature is warranted. The terms used in this report are explicated in Figure 1. The two main types of enthalpimetric analysis, thermometric enthalpy titrations (TET) and direct injection enthalpimetry (DIE), can be delineated as titrimetric and calorimetric methods, respectively. In practical terms they can be differentiated by the mode of introduction of the reactants into the adiabatic cell.

TET experiments are characterized by the continuous addition of the titrant to the titrate under effectively adiabatic conditions. The total amount of heat evolved (if the reaction is exothermic) or absorbed (if the reaction is endothermic) is monitored automatically using the unbalance potential of a Wheatstone bridge circuit, incorporating a temperature sensitive semiconductor (thermistor) as one arm of the bridge (vide infra). The virtual cessation of heat evolved (or absorbed) is used to locate the equivalence point of the titration.

DIE, on the other hand, involves the injection of a single "shot" of a reactant into the solution under investigation, the reagent being in stoichiometric excess. The corresponding caloric "pulse", which is directly proportional to the number of moles of analyte reacted, is recorded using identical circuitry to that employed with TET. Although initially the emphasis was on fast processes, both thermometric and direct enthalpimetric procedures can be adapted to study rate-controlled processes. When the latter type of conditions prevails, the designations kinetic titrimetry and kinetic DIE are appropriately used. The kinetic approach to enthalpimetric analysis, in general, can be referred to as thermokinetic analysis (TKA).

In all the above instances the amount of heat evolved (or absorbed), Q, in the reaction may be calculated from Joule heating calibration experiments. The calibration circuitry is described later.

Fundamental Principles

The principles involved in enthalpimetric analysis are based on fundamental correlations inherent in adiabatic calorimetry:

$$Q = -n_p \cdot \Delta H \qquad (1)$$

where Q denotes the total amount of heat evolved (or absorbed), n_p the number of moles of product formed, and ΔH the molar enthalpy of reaction. Furthermore, the temperature change, ΔT, observed in an adiabatic cell can be explicated as in Equation 2:

$$\Delta T = Q/K \qquad (2)$$

where K denotes the effective heat capacity of the system. Combination of Equations 1 and 2 yields

$$\Delta T = \frac{-\Delta H \cdot n_p}{K} \qquad (3)$$

The heat capacity of the system, K, will remain essentially constant if the change in volume of the solution is minimized. Moreover, if it is assumed that ΔT is caused entirely by the reaction and that $\Delta H = \Delta H^\circ$ = constant, the observed temperature change, ΔT, is obviously proportional to the number of moles of product formed, n_p (and hence of reactant consumed):

$$\Delta T = \text{constant} \cdot n_p \qquad (4)$$

A typical TET enthalpogram (a thermometric titration curve) is

shown in Figure 2a. Curvature in the region of the equivalence point may be caused by less than quantitative conversion of reactants to products (equilibrium curvature) or by the slow attainment of titration equilibria (kinetic curvature). In general, prohibitive limitations may arise if the relevant equilibrium constant is unfavorable. Furthermore, conventional thermometric enthalpy titrations are normally restricted to reactions whose effective rate is fast compared to the rate of addition of titrant. An end-point correction procedure for slower rates has been described. Appropriate computations can be used for the thermometric determination of first order rate constants up to a limit of 600,000 M^{-1} s^{-1} (*1*).

In a recent communication (*2*), it has been suggested that the hitherto universally accepted linear relationship between ΔT and the volume of added titrant, Δv, is valid only over a narrow range of volume if one takes into account that some heat transfer actually occurs between the ambient medium and the reaction cell which is necessarily not quite 100% adiabatic. It is recommended that a more practical representation of a thermometric enthalpy titration would be achieved by a plot of $1/\Delta T$ vs. $1/v$.

A typical direct injection enthalpogram is shown in Figure 2b. The technique is based on the measurement of the total heat evolved (or absorbed), Q, rather than of an end point.

The application of TET and DIE enthalpograms to the determination of an analyte is contingent upon the knowledge of certain fundamental quantities—the stoichiometry of the titration reaction with the titrimetric technique and the heat of reaction with the calorimetric approach.

Fundamental thermodynamic information (the heat, ΔH, the equilibrium constant, K, and hence the free energy, ΔG, and entropy, ΔS, of a reaction) can be deduced from thermometric titration curves (*3*).

Practical Aspects

The methodology in its present form has been the subject of several reviews (*3–10*). The salient features of the experimental apparatus are a reagent addition system, an adiabatic cell incorporating a temperature sensor, a calibration heater and a stirring device, and a temperature-measuring circuit and a recorder (Figure 3).

Reagent Addition. *Titrimetric Procedures.* Reproducible, constant titrant addition is generally achieved using either a motor-driven syringe or in some instances a *pulse-free* peristaltic pump. Uniformity of titrant and titrate temperatures is routinely obtained by passing the tubing conveying the titrant to the adiabatic cell through a constant temperature bath. The disadvantages of liquid titrants can be circumvented by the injection of gaseous reagents into liquid titrates (*6, 14*). The heat capacity of a gas is negligible when compared to that of a comparable volume of liquid; therefore, the temperature of gaseous titrants need not be regulated. Furthermore, changes in the heat capacity of the adiabatic cell and its contents will be small, thus minimizing a nonlinearizing effect on the resultant enthalpogram. The idea may be further extended to the thermometric determination of gaseous samples with gaseous titrants (*11*). The titrants, which can be diluted if necessary with an inert gas, are standardized by injection into a liquid absorbate and subsequent titration with an appropriate reagent. The fundamental requirements for a gas-phase titration are identical to those for liquid-phase experiments—a favorable equilibrium constant and relatively fast kinetics.

Calorimetric Methods. For conventional liquid-phase direct injection enthalpimetry, the emphasis is on quasi-instantaneous injection of the reagent. As the injected reagent is usually in excess and the heat capacity of the system is conveniently determined after each injection, precise volume measurements are not a prerequisite of this approach. Accordingly, a manually operated syringe is adequate. For sequential analysis, in which a series of samples is injected into an excess of reagent, gravimetrically calibrated syringes with Chaney adaptors are recommended. The same thermostating considerations as in TET experiments obviously apply. Ingenious immersion pipets (where the titrate solution itself serves as thermostat for the titrant) have been used to obviate any temperature mismatch between reactants. Such a system is indeed the basis of a versatile direct injection enthalpimeter for multicomponent analysis (*4*).

Adiabatic Cell. Successful enthalpimetric determinations are contingent upon the measurement of small temperature changes. Consequently, it is important that extraneous heat effects in the reaction cell be minimized. A conventional silvered Dewar flask has a relatively large heat transfer coefficient. However, special thin-walled Dewar flasks have been de-

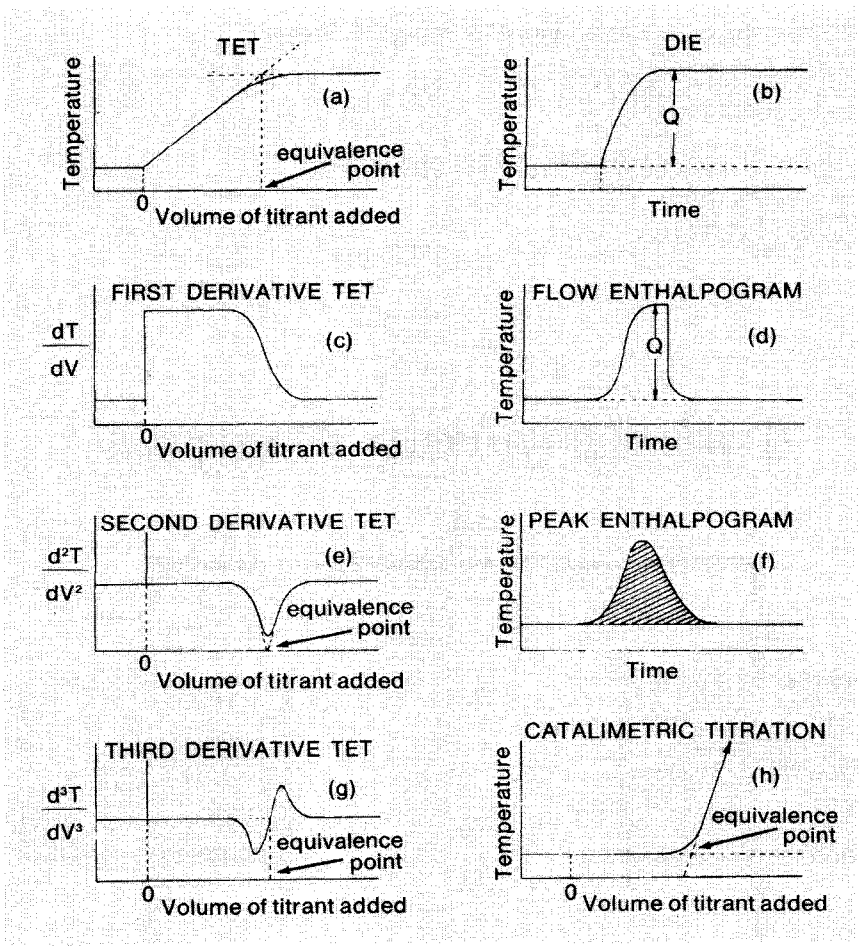

Figure 2. Typical enthalpograms. TET, thermometric enthalpy titration; DIE, direct injection enthalpimetry

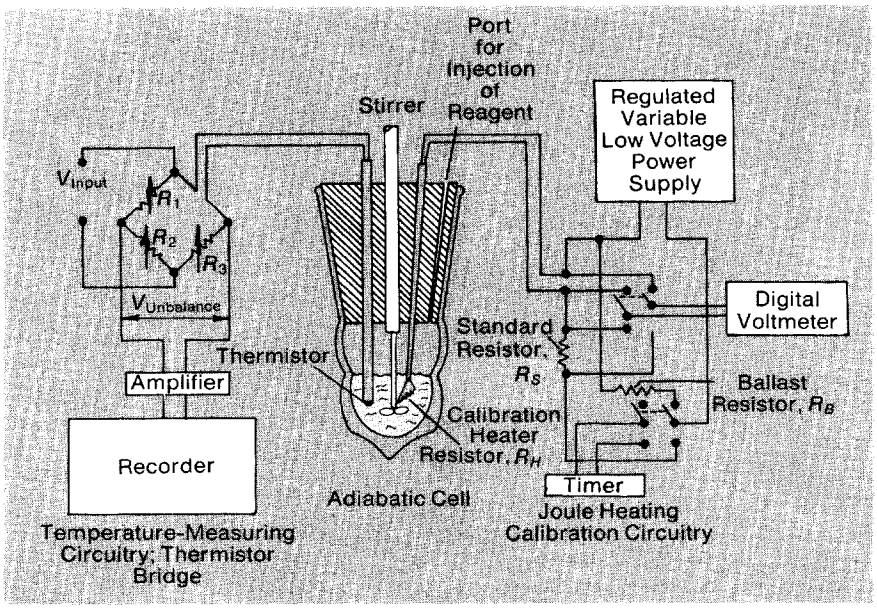

Figure 3. Diagram of apparatus and circuitry used in enthalpimetric analysis

signed (*12, 22*), incorporating an appropriate reaction cell which has a heat transfer modulus of 11×10^{-4} min^{-1} and an equilibration time of only 3 s. This cell now forms the basis of a sophisticated isothermal titration-microcalorimeter (*12*) (v.i.).

Analytical data *can* be obtained by using simple styrofoam insulated reaction cells which maintain pseudo-adiabatic conditions for the short period of a titration. This method is not recommended for fundamental thermochemical investigations.

At the heart of enthalpimetric analysis lies the temperature measurement system. Thermometric titrations were performed as early as 1913 utilizing a conventional mercury thermometer as temperature sensor (*8*). Modern interest in enthalpimetric analysis was engendered by the simple, inexpensive, rapidly responding, automated instrumentation made possible by the use of thermistors as temperature transducers. Thermistors are semiconductor devices which have a large temperature coefficient of resistivity, on the order of −4% per degree. Even though the thermistor resistance, R_T, varies *exponentially* with temperature:

$$R_T = A \exp B/(C + T) \qquad (5)$$

(where A, B, and C are material constants characteristic of a given thermistor), R_T approximates a *linear* function of temperature over a small range ($T \leq 0.1$ °C). The changing resistance is usually monitored with the aid of a Wheatstone bridge circuit, whose unbalance potential is proportional to ΔT (and to Q if K is constant) and plotted automatically on the ordinate scale of a recording dc millivoltmeter. The corresponding chart abscissa is a measure of volume and/or time. To avoid localized temperature and concentration gradients in the adiabatic reaction cell, efficient stirring is imperative.

Calibration Heater. Generally, the caloric axis (ordinate) of enthalpograms is calibrated chemically or electrically, though this is not strictly necessary for a purely end-point determinative titrimetric use. Chemical calibration involves reliance on an accurately known heat of reaction and requires stringent reproducibility of reaction volumes in successive experiments. This limitation is circumvented by electrical calibration with occasional verification against suitable thermochemical standards. The circuitry for electrical calibration by Joule heating appears as part of Figure 3. The calorimeter is calibrated by passing a constant current, i, through a calibration heater, R_H (which is immersed in the solution), and a standard resistor, R_S. The heat dissipated within the calorimeter may then be calculated from Equation 6:

$$Q \text{ (calories)} = \frac{i^2 R_H t}{4.184} = \frac{V_S V_H t}{4.184\ R_S} \qquad (6)$$

where V_S and V_H are potential drops measured across the standard resistor and the calibration heater.

Changes in the heat capacity of the system occur as titrant is added. Accordingly, calibrations are generally performed both before and after the experiment. The desired caloric quantity is the total reaction heat evolved (or absorbed) up to the equivalence point. A weighted average of the pre- and post-titration calibrations is used:

$$C_{ep} = C_0 + a(C_{final} - C_0) \qquad (7)$$

where C_{ep} is the desired calibration factor at the equivalence point, expressed in calories per chart ordinate unit, C_0 the calibration factor effective before the start of the titration (when the volume is v_0), and C_{final} the calibration factor measured after the titration (volume = v_{final}). The fraction of total titrant added required to reach the equivalence point is denoted by a:

$$a \equiv \frac{v_{ep} - v_0}{v_{final} - v_0}$$

In the calorimetric mode of enthalpimetric analysis, $v_{ep} = v_{final}$ and only one calibration is required.

Temperature Measuring Circuits—dc. Conceptually, the simplest method for continuous measurement of the small resistance change of the temperature sensing thermistor is its incorporation as one arm of a dc Wheatstone bridge (Figure 3). In this configuration the bridge unbalance potential, $V_{unbalance}$, may be related by Equation 8 to the resistances of the three unchanging arms, R_1, R_2, R_3, to the variable resistance of the thermistor-containing arm, R_T, and to the applied bridge potential, $V_{applied}$:

$$V_{unbalance} = V_{applied} \times \left(\frac{R_1}{R_1 + R_2} - \frac{R_T}{R_3 + R_T}\right) \qquad (8)$$

The variation of the unbalance potential is, for all purposes herein described, linear over a small temperature range ($\Delta T \leq 0.1$ °C). An unavoidable feature of such bridge circuits is that a finite current must pass through the thermistor which is, as a result, self-heated. The sensed temperature is therefore not strictly that of the solution in which the device is immersed but rather is the temperature of the thermistor itself, the difference between the two being dependent upon the rates of self-heating and of heat dissipation at the stirred solution interface. (Stirring itself imparts heat to the solution.) To minimize this temperature differential, the applied bridge potential is either pulsed (v.i.) or minimized. Methods for bridge potential optimization have been described (*13*). In ultrahigh sensitivity experiments, a linear ramp generator circuit may also be necessary. In these situations the temperature increase due to stirring and thermistor heating may be prohibitively large, resulting in a steeply sloping baseline. This problem can be obviated by the introduction of an equal but opposite electrical signal (*3*). Low bridge voltages require that the entire bridge circuit including the thermistor leads be carefully shielded to avoid noise pickup. The small unbalance potential is amplified by a low noise dc amplifier, the output of which is usually fed into a recording dc millivoltmeter.

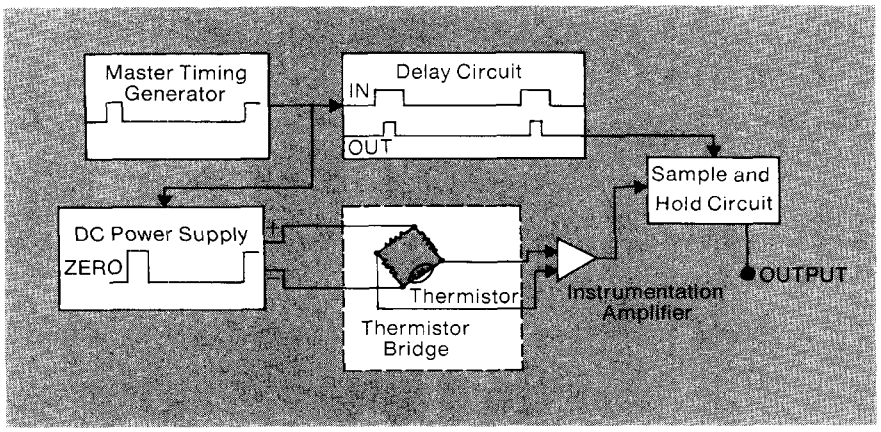

Figure 4. Schematic diagram of pulsed dc (partial duty) Wheatstone bridge circuit

Differential Titrations. There have been numerous modifications of the standard dc amplified bridge circuit. Differential titrations involve a simultaneous blank titration in an identical adiabatic cell, where titrant is added to the pure solvent. The temperature difference between the actual titration and the blank is recorded on the ordinate of corresponding differential enthalpograms. In this way, extraneous heat effects due to undesired simultaneous or sequential reactions, heats of dilution, and temperature mismatch between titrant and titrate may be eliminated (*10*). Differential titrations are implemented by the replacement of bridge resistor R_1 with a thermistor possessing characteristics equivalent to those of R_T, and its placement in the blank titration cell. By an examination of Equation 8, equivalent temperature changes of the two thermistors will cause no change in the bridge unbalance potential.

Derivative Titrations. (Figure 2, curves c, e, g.) In an attempt to improve thermometric end-points, first derivative, second derivative, and even third derivative plots of the bridge output signals have been obtained through the use of differentiating circuits. By the use of such derivative techniques, end-points may yield well-defined nonmonotonic pulses amenable to trigger digital threshold readouts.

Resolution Enhancement. The ultimate resolution of the temperature measurement circuitry is limited by omnipresent noise sources (Johnson and pickup) and dependent upon the temperature coefficient of the thermistor and its heat dissipation. Theoretical treatments of the ultimate resolution of thermistors and thermistor bridges have very recently become available (*13*). The practical resolution is 10 microdegrees.

Investigations have shown that a barium titanate ceramic device, commonly called a positive temperature coefficient (PTC) device, has a temperature coefficient on the order of +16% per degree (*15*). This inherent fourfold sensitivity enhancement over thermistor technology has proved useful in high-sensitivity thermochemical studies.

The problem of thermistor self-heating has been attacked via the development (*27*) of a pulsed (partial duty) dc Wheatstone bridge (Figure 4). The applied bridge potential is greater than that used in conventional dc bridge circuitry (a gain in sensitivity), but the concomitant temperature differential between the thermistor and the measured solution is minimized by pulsation of the bridge power. In practice, the bridge is powered for 10% of the total duty cycle of 50 ms. The basic duty cycle of the bridge is set by a master timing generator, the output of which is a rectangular wave train. This train is used to periodically energize a dc power supply which in turn powers the thermistor bridge. The power dissipated in the thermistor bridge is controlled by the output of the timing generator. After amplification of the bridge unbalance potential, the still pulsatile train is fed to a sample-and-hold circuit which is triggered by the master timing pulse. The triggering is adjusted so that the sampling time occurs in the middle of the duty cycle of the power supply, thus eliminating transients which occur at either end of the master pulse.

Thermistor Bridges—ac. Several ac-powered bridge circuits have been described in the literature during the past several years (*3, 16, 17*). This may be related to the ready availability of highly stable ac amplifiers and to the improvement of signal-to-noise ratios using phase sensitive detectors. A schematic diagram of a typical ac thermistor bridge is illustrated in Figure 5. However, the effectiveness of the ac system is somewhat limited by the introduction of stray capacitance. In our opinion, the advent of stable dc amplifiers and the application of good shielding techniques to dc bridge circuitry minimize the advantages of ac circuits.

Other Thermistor Circuits. Some novel bridge designs have been proposed but remain generally unaccepted. These include linearized Wheatstone bridges and circuits utilizing operational amplifiers (*3*), which exhibit improved linearity and increased sen-

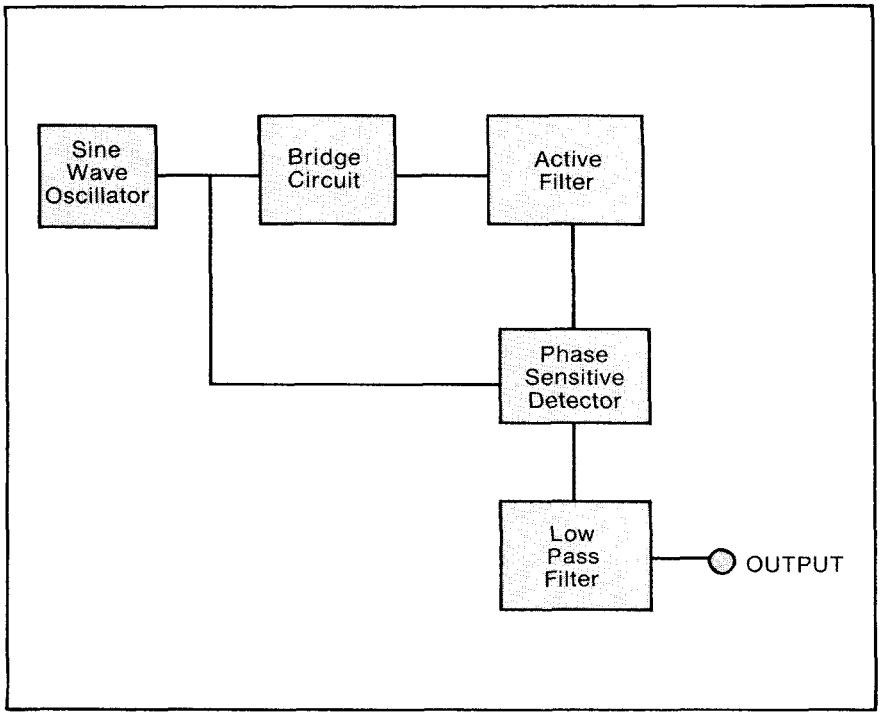

Figure 5. Schematic diagram of ac thermistor bridge

sitivity and ease of grounding. These advantages notwithstanding, the simplicity and general lack of noise of the standard dc bridge circuit have insured its continued use for most enthalpimetric instrumentation.

Quartz Resonator Thermometer. Because of the scarcity of temperature transducers possessing a high sensitivity to very small temperature changes, thermistors have remained the mainstay of enthalpimetric temperature-measuring devices. Recently, the quartz resonator thermometer (QRT) has been proposed as a new instrument for enthalpimetric analysis (*3*). This device consists of a small quartz crystal incorporated as part of an oscillator circuit. The resonant frequency of this circuit (about 28.2 MHz ± 1 kHz per degree) as monitored by a frequency counter, is a linear function of the temperature of the quartz crystal. The degree of resolution is dependent upon the length of the counting period. With highly sophisticated frequency counters, a resolution of a few microdegrees may be obtained with a counting time of 10 s. The merits of this system are twofold: The measurement is highly insensitive to external noise sources, and the output may be directly calibrated in terms of a standard temperature scale. In contradistinction, thermistor bridge circuitry previously discussed is capable only of recording outputs proportional to temperature *change*. The use of the QRT for enthalpimetric analysis is encumbered by several inherent disadvantages. These include extended counting periods necessary for the attainment of adequate resolution, the large physical size of the probe coupled with its considerable thermal mass, and inadequate chemical resistance of the probe enclosure.

Modifications of Enthalpimetric Analysis

Flow Systems. *Continuous Flow Enthalpimetry.* Continuous flow enthalpimetry has proved to be a valuable modification of enthalpimetric analysis, particularly when utilized for the on-line analysis of industrial process streams (*10*). The technique, based on the fundamental principles inherent in flow calorimetry, consists of passing two reactant solutions at a constant rate through a mixing chamber (the reagent being in stoichiometric excess) and continuously monitoring the heat output of the product stream (Figure 6). The temperature of the product stream, T_p, is directly related to the temperatures of the sample and reagent streams, to the molarity of the sample, and to the ratio of the sample and reagent flow rates. Accordingly, any fluctuation of the sample concentration will manifest itself as a change in T_p of the product stream. A process stream can be assayed by monitoring the heat pulse obtained when a sample of reagent is injected into the stream at periodic intervals. The shape of the resultant enthalpogram is dictated by sample size. A typical continuous flow enthalpogram is shown in Figure 2d.

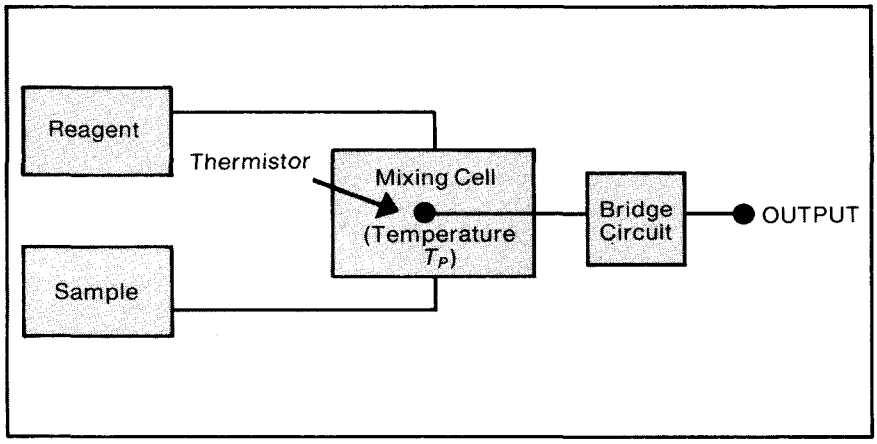

Figure 6. Schematic diagram of flow enthalpimetry

One of the latest and potentially significant advances in the development of enthalpimetric flow systems is the immobilization of a large stoichiometric excess of reagent (in the form of an enzyme) on the walls of the reaction chamber (*18*). As the analyte flows through, it is catalytically converted to products with zero order kinetics prevailing. The corresponding heat change is monitored in the usual manner. The enzyme (reagent), acting as a true catalyst, remains unchanged, thus permitting sequential analyses. In a similar vein, an enzyme thermistor based on the measurement of heat generated in an enzyme-coated PVC coil in intimate contact with a thermistor has recently been described (*19*).

Peak Enthalpimetry. A new method called peak enthalpimetry has been reported (*20*) in the context of contemporary requirements for sequential analysis with particular reference to clinical analysis. A typical peak enthalpimetric apparatus is schematized in Figure 7. A carrier liquid (an inert

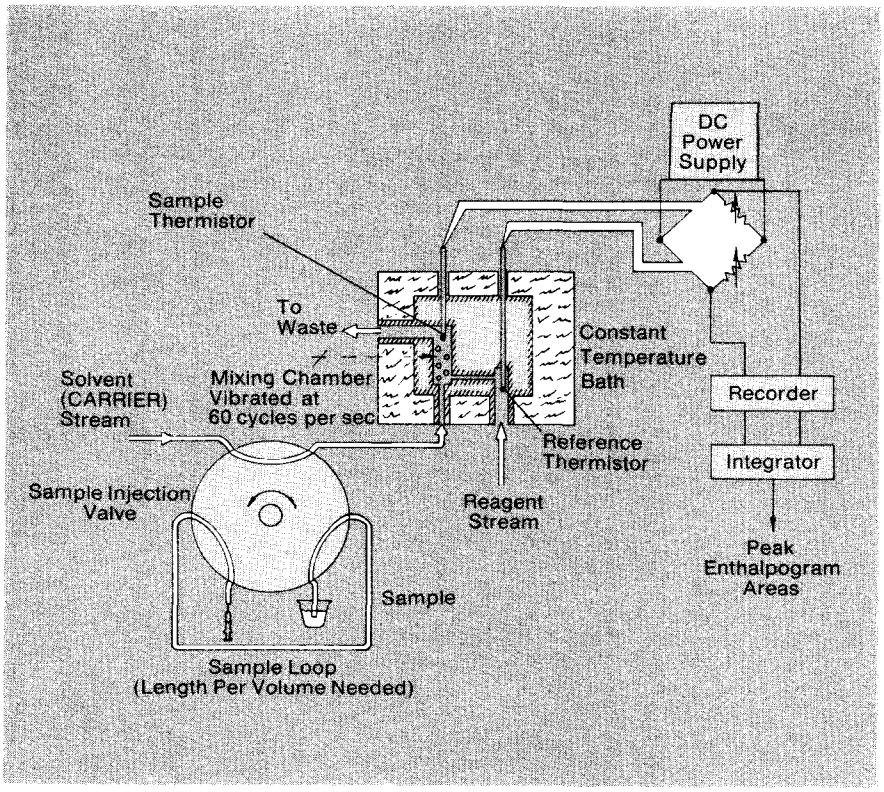

Figure 7. Schematic diagram of peak enthalpimetry apparatus

solvent) and a reagent solution are made to flow into a mixing cell from constant pressure reservoirs. The two separate streams merge and are homogenized by the vibration (60 Hz) of glass beads contained within the mixing cell. A discrete volume of sample is injected into the carrier stream, producing a cylindrical plug of sample solution bounded by the solvent. As the sample is swept toward the mixing chamber, diffusional spreading occurs, resulting in an essentially Gaussian distribution profile as it reaches the reaction cell. The pseudo-Gaussian temperature profile of the product stream, measured in a differential mode, reflects the concentration profile of the analyte entering the reaction cell. Moreover, the output from the thermistor bridge is a measure of the instantaneous concentration of the sample. Thus, an integration of the area bounded by the peak will be a measure of the amount of reactable material in the sample (Figure 2f). With the incorporation of automatic

Table I. Selected Applications of Enthalpimetric Analysis

Type of determination	Analyte(s)	Reagent(s)	Method	Ref
BIOCHEMICAL				
Enzyme assay	Hexokinase	Glucose, ATP	Kinetic DIE	(*25*)
	Lactate dehydrogenase	Sodium pyruvate, NADH	TET or kinetic DIE	(*26*)
Substrate determination using enzyme catalysis	Glucose in serum, plasma, and whole blood	Hexokinase, ATP	Kinetic DIE	(*25*)
	Urea	Urease	Kinetic DIE	(*28*)
Proteins	Total serum protein	Phosphotungstic acid	TET	(*16*)
Immunological	Antibodies (IgG, IgM)	Standard antigens and haptens	TET	(*29*, *30*)
PHARMACEUTICAL				
Alkaloids	Codeine phosphate, morphine sulfate, etc.	Silicotungstic acid	TET	(*31*)
Sulfonamides	Sulfathiazole, sulfisoxazole	KOH in propan-2-ol	TET with catalyzed end-point	(*32*)
INDUSTRIAL				
Petrochemical	Water, oxygen, and low molecular weight alcohols in hydrocarbons	Triethylaluminum	Continuous Flow Enthalpimetry	(*10*)
Polyesters, polyethers	Glycerole–alkylene oxide polyethers, butane-1,4-diol-adipic acid polyesters	Acetic anhydride	DIE	(*33*)
Fertilizers	PO_4^{3-}, K^+, NH_4^-, NO_3^- carbamide	Several sequentially added reagents	DIE	(*34*)
Ceramics	NO_4^{2-} in glass	H_2O_2	DIE	(*35*)
Bayer Process control	$NaOH/Al_2O_3/Na_2CO_3$,	H^+	TET	(*4*)
Nuclear technology	Free acid in nuclear fuels	NaOH	TET	(*36*)
Minerals				
Bauxites	SiO_2, Al_2O_3, Fe_2O_3, TiO_2, and others	Various	DIE	(*37*)
Coal	Phenol	KOH in propan-2-ol	TET with catalyzed end-point	(*6*)
INORGANIC				
Complexometric	Mn(II) in presence of Zn(II)	EDTA	Differential TET	(*38*)
	Mn(II) in presence of Ca(II)			
Anions	I^-, NO_2^-, SO_3^{2-}, and others	Various	Peak enthalpimetry	(*39*)
GASEOUS				
Gas/gas	NH_3, aliphatic amines	HCl(g)	TET	(*11*)
Gas/liquid	CO_2, SO_2	KOH	DIE	(*6*, *14*)
ORGANIC FUNCTIONAL GROUP	For an exhaustive review, see Ref. *10*			

injection and digital printout, the seriatim performance of many analyses is feasible.

Catalimetric Enthalpy Titrations. Standard enthalpimetric analysis has sensitivity limits dictated by the heat liberated (or absorbed) during a reaction. For titrates present at low concentration and those with small heats of reaction, a catalimetric technique has been developed (*4, 10*). This methodology takes advantage of a secondary indicator reaction which occurs only after virtual completion of the analytically interesting primary reaction: The sequence is controlled by selecting an indicator reaction which has an appropriate equilibrium constant. A judiciously chosen catalimetric reagent which reacts with excess titrants is added. If the heat of reaction between the catalimetric reagent and titrant is large, the heat of the analysis reaction becomes unimportant per se, but the correct equivalence point is indicated by the commencement of heat evolution (or absorption) engendered by the secondary reaction. In a recent application an alkali-catalyzed polymerization has been used as the indicator reaction in the determination of acidic functions of sulfanilamide derivatives (and of sulfonamide formulations) by use of catalimetric enthalpy titrations (*21*).

Isothermal Titration Calorimetry. Evident fundamental assumptions underlying the concept of enthalpimetric analysis are that the relevant system is effectively adiabatic and that ΔH is independent of temperature. If an efficient adiabatic cell is used, these approximations hold for most analytical measurements using virtually instantaneous reactions. For precise fundamental measurements and for reactions with slower kinetics, isothermal calorimetry has been utilized. That method is beyond the scope of the present review. However, a technique combining titration calorimetry and isothermal calorimetry has been reported (*4, 12, 22*), a description of which is warranted. The method closely parallels that of thermometric enthalpy titrations, with the exception that the temperature of the adiabatic calorimeter and its contents is held constant throughout the titration. This is achieved via the incorporation of a thermoelectric cooling device and a variable heater (Figure 8). The heat of reaction can be correlated to the power required to maintain isothermal conditions. Both endothermic and exothermic reactions have been studied in this manner at temperatures held constant to ±0.0002 °C and heat effects measured with a precision of ±0.02 calories. The isothermal method, albeit very precise, is time consuming, a restriction that may limit its applicability from an analytical viewpoint.

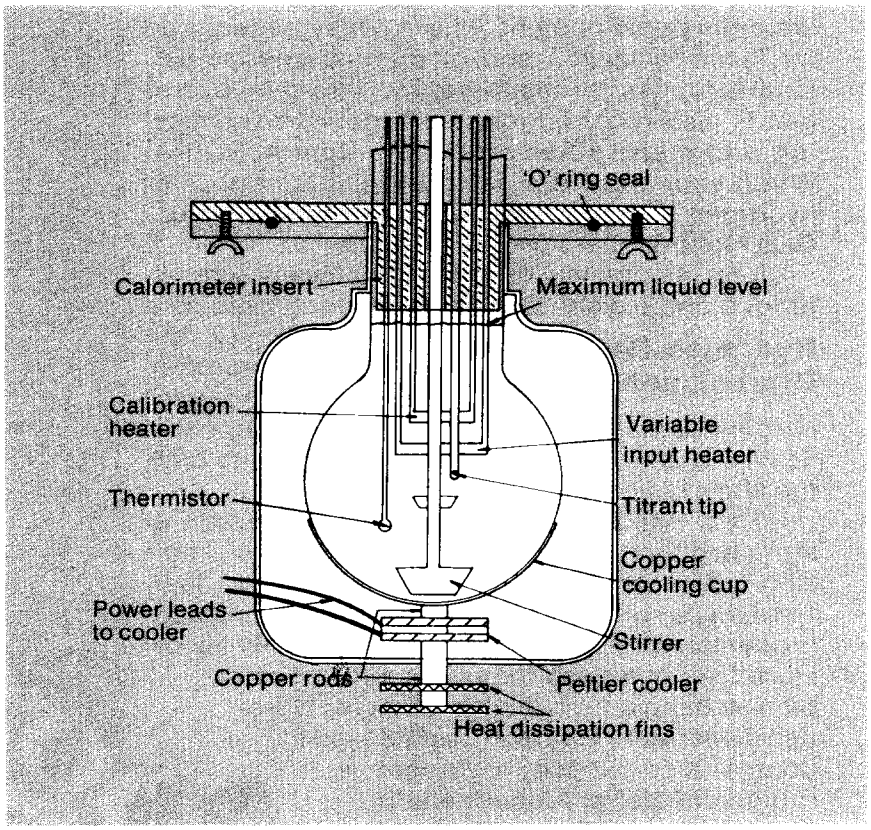

Figure 8. Isothermal titration calorimeter (from ref. *22*)
Courtesy of the American Institute of Physics

Applications

A brief summary of some selected applications is shown in Table I. The survey outlines a few innovative and topical applications of enthalpimetric investigations taken from recent reports. This list should not be regarded as an exhaustive review. More complete surveys of enthalpimetric determinations can be found elsewhere (*6, 10, 23, 24*).

As the varied nature of the survey suggests, enthalpimetric analysis has found acceptance in many fields. The high tolerance level of the technique to nonreactable impurities has resulted in numerous industrial and commercial applications where matrix problems might otherwise be prohibitive. Indeed, enthalpimetric flow methods have been particularly successful in continuous quality control of industrial process streams.

An enthalpimetric approach to clinical analysis has been recently developed (*25*). Its salient feature is reliance on a fundamental thermodynamic property, ΔH, in lieu of empirical standards. Specificity has been achieved by the utilization of the inherent selectivity found in enzyme-catalyzed reactions. Moreover, the possibility exists for serum and, in some cases, whole blood analysis without prior deproteinization (*25*).

Clearly, the volume of reports in the literature suggests that there is growing interest in the utilization of enthalpimetric methods for both analytical and fundamental studies. The versatility and simplicity of the technique, combined with a classic foundation in fundamental thermochemistry, make enthalpimetric analysis an inherently attractive methodological approach.

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