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A comparison of chemical reference materials for solution calorimeters

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Abstract

Solution calorimeters are based on semi-adiabatic or isothermal heat-conduction principles and differ in the way they record data. They also have different measuring sensitivities and require different quantities of solute and solvent. As such, the choice of chemical test substance is not straightforward. Usually the dilution of KCl is recommended; it is possible to purchase a reference sample of KCl that has a certified enthalpy of solution and this standard material is usually used to test semi-adiabatic instruments. Here, we review the suitability of a range of chemical test substances (KCl, sucrose and Tris) for an isothermal heat-conduction solution calorimeter. It was found that KCl was not the best test material because its relatively high enthalpy of solution ($\Delta_{\text{sol}}H$) necessitated the use of small samples (2 mg), resulting in a relatively large standard deviation (σ_{n-1}) in the values recorded ($\Delta_{\text{sol}}H = 17.14 \pm 0.49\ \text{kJ mol}^{-1}$); furthermore, KCl data must be corrected to account for the effect of dilution, although the correction was found to be small ($0.07\ \text{kJ mol}^{-1}$) under the experimental conditions employed here. Sucrose appears to be a much more robust test material for isothermal heat-conduction instruments because its lower enthalpy of solution allows the use of much larger samples (20 mg), which minimises experimental errors. The $\Delta_{\text{sol}}H$ value returned ($6.14 \pm 0.08\ \text{kJ mol}^{-1}$) is in excellent agreement with the literature. It is also cheap, readily available and requires minimal preparation although its widespread use would require the preparation of a certified reference sample.

Keywords: Solution calorimetry; Calibration; Chemical test material; Potassium chloride; Sucrose; Tris

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1. Introduction

In solution calorimetry, the heat of solution ($\Delta_{\text{sol}}H$) is recorded as a solute (usually a solid) dissolves in a liquid. Such measurements are valuable during pharmaceutical preformulation because they allow the physical

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characterisation of active pharmaceutical ingredients (APIs) and excipients, and the number of applications of the technique is growing. Examples from the recent literature include its use to detect polymorphs (Souillac et al., 2002), to rank the stability of polymorphs (Willson and Sokoloski, 2004), to investigate interactions between species (Arnot et al., 2004; Chadha et al., 2002, 2004), to quantify small amorphous contents (Harjunen et al., 2004; Hogan and Buckton, 2000) and to study the formation of liposomes (Barriocanal et al., 2004).

With this increase in applications comes a need for well-characterised calibration and test procedures. These are vital to ensure that instruments are operated properly and are functioning correctly, that data from different instruments or different laboratories are comparable and that the data obtained are validated and can be incorporated into regulatory documents. There are a number of requirements imposed upon a test reaction; it should be robust, simple to perform, require commonly available materials that require no special preparation prior to use and it should be applicable across a range of instrumentation (Beezer et al., 2001). A number of chemical test reactions for solution calorimeters have been proposed and discussed, including the dissolution of Tris in 0.1 M HCl (Irving and Wadsö, 1964; Hill et al., 1969), the dissolution of KCl or NaCl in water (Kilday, 1980; Uriano, 1981; Archer and Kirklin, 2000) and the dissolution of propan-1-ol in water (Olofsson et al., 2000). The dissolution of sucrose in water can also be used (Gao and Rytting, 1997; Salvetti et al., 1996), although this is not currently recognised by the International Union for Pure and Applied Chemistry (IUPAC) as a test reaction. A recent review by Wadsö and Goldberg (2001) summarises the test reactions for isothermal calorimeters approved by IUPAC.

There are two types of solution calorimeter design commercially available; instruments that operate on a semi-adiabatic principle (i.e. that record a temperature change upon reaction) and instruments that operate on a heat-conduction principle (i.e. that record a power change directly upon reaction). The sensitivities of these instruments, and hence the quantities of solute and solvent required for experiment, vary considerably (typically, semi-adiabatic instruments are less sensitive and require much larger sample volumes). Furthermore, it is possible to use dynamic correction on data from heat-conduction instruments (which removes the effect of the thermal inertia of the system; a further discussion can be found in Section 2.3.2) and hence collect both ‘raw’ and ‘corrected’ data. Raw data reflect the actual measurement response of the instrument, while corrected data reflect the real-time response of the sample (the response shown by corrected data will therefore occur over a shorter time-period than observed for raw data). It is vital that the right instrument and method of data manipulation are selected for particular samples and that appropriate test reactions are recommended in each case.

As mentioned above, one of the defining characteristics of a chemical test reaction is its uniformity of response across a range of instrumentation. In a recent publication, the applicability of some of the chemical test reactions listed above (Tris into 0.1 M HCl and KCl and sucrose into water) to semi-adiabatic solution calorimeters was examined (Yff et al., 2004). The effect of the various ways of treating the data so produced was also discussed. The resulting data suggested that the dissolution of KCl (200 mg) into water (100 mL) was the most accurate and the most precise test reaction. In this work, we report the results of a similar trial of test reactions using an isothermal heat-conduction solution calorimeter. The results are compared with those obtained previously, the specific aim being to recommend the most appropriate test reaction, and hence validation procedure, for each type of instrument. A further aim of this study is to examine the effect of dynamically correcting the raw power–time signal on the standard deviation of the values returned from each of the test reactions and hence to recommend whether this procedure should be adopted in routine use.

2. Materials and methods

2.1. Materials

Potassium chloride was obtained as a Standard Reference Material from the National Institute for Standards and Technology (NIST, formerly the Bureau of Standards, USA, KCl, SRM 1655) and was dried, in accordance with NIST recommendations, at 800 K for 4 h prior to use (it should be noted that a more recent study concluded that heat treatment at this temperature resulted in a higher probability of corrupting the sample than improving the accuracy of the measurement

(Archer, 1999), but this temperature pre-treatment is still indicated by NIST and so was employed here). Sucrose (>99.5% purity) and Tris (trishydroxymethylaminomethane, >99.8% purity) were purchased from Sigma and were used as received. HCl solution (0.1 M) was purchased from VWR. Aqueous solutions were prepared using deionised water (Elga DV25 water purifier).

2.2. Methods

Data were recorded using a 2265 20-mL micro solution ampoule (Thermometric AB, Järfälla, Sweden). The design and operating principles of the instrument have been discussed previously (Bastos et al., 2003). Briefly, it contains three metal cartridges (each comprising three pieces) that can be charged with solid sample (typically up to ∼20 mg, although larger samples can be used depending on the density of the sample); the cartridges are loaded into the underside of the lid of the sample vessel. The lower part of the vessel (glass in these experiments) holds a reservoir of solvent (typically up to 17 mL) into which the cartridges are introduced (by means of rods that are accessible externally to the instrument). Once thermal equilibrium has been attained the cartridges are pushed into the solvent (either sequentially or simultaneously) where they fall apart, dispersing the solid sample which subsequently dissolves into the solvent.

In order to produce consistent data, the cartridges are numbered and they are loaded into the same receptacles in the instrument; in this work, we elected to load sample only into cartridge 2 and use cartridges 1 and 3 as blank references. The sample data (both raw and corrected) were then adjusted to compensate for the heat associated with the dispersion of the cartridge by subtracting the average power associated with dispersing cartridges 1 and 3. Samples were loaded into cartridge 2 and were accurately weighed on a Sartorious microbalance (accurate to ±0.00001 g). The vessel was charged with deionised water (15 mL, KCl and sucrose) or HCl solution (15 mL, Tris). The instrument was maintained at 298 K using a precision water bath (TAM, accurate to ±0.0001 °C). When the system had reached thermal equilibrium (shown by a baseline signal of zero) a dynamic calibration was performed. Following this, the cartridges were dispersed into the solvent in numerical order. The vessel's contents were stirred at 120 rpm using a turbine stirrer. Power data were recorded (every second) using the dedicated software package Digitam 4.1; the amplifier was set to its maximum range (3000 μW) and a 20-mL glass ampoule containing water (KCl and sucrose, 15 mL) or HCl solution (Tris, 15 mL) was used as a reference. Data analysis was performed using Origin (Microcal Software Inc., USA). Experiments were repeated a minimum of four times. Data are quoted throughout with a standard deviation (S.D., σ_{n-1}) which represents a confidence limit of 68%. The cartridges were coated with Repelcote (Sigma) prior to use in order to avoid the possibility of interaction between KCl and steel.

2.3. Solution calorimeters

Semi-adiabatic and heat-conduction instruments operate on different principles, and while these have discussed in detail elsewhere (see for example, Hill et al., 1969; Bastos et al., 2003; Yff et al., 2004) it is worth briefly considering these differences here because they impact upon the subsequent discussion of the data.

2.3.1. Semi-adiabatic solution calorimeters

In an ideal adiabatic calorimeter, there is no heat exchange between the calorimetric vessel and its surroundings and so 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, as is the case with the Thermometric SolCal used in the previous study (Yff et al., 2004), 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).

At the start of an experiment, the SolCal is held above or below the temperature of its thermostatting bath (typically by up to 200 mK). With time the instrument will approach the temperature of the thermostatting bath; data capture is initiated when this approach becomes exponential (this assumption is a necessary precursor to employing the heat-balance equations used to calculate the heat evolved or absorbed by the system contained within the vessel). Thus, the response due to dissolution, and any electrical calibrations (usually two are performed; one before and one after the break to ensure the heat capacity of the system has remained constant), must be performed before the instrument reaches thermal equilibrium with the bath. In practice, this limits the technique to studying events that, ideally, reach completion in less than 30 min. The SolCal typically requires relatively large volumes of sample and solvent (200 mg and 100 mL, respectively) because of its measuring sensitivity although, dependent upon the magnitude of the enthalpy change of the system under investigation, some reactions can be investigated with as little as 20 mg of sample.

2.3.2. 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 power flowing across them; this signal is amplified, multiplied by the cell constant (determined through electrical calibration) and recorded as power versus time. A heat-conduction calorimeter system is not limited to reaction processes that reach completion within 30 min, 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 thermistors often used in semi-adiabatic instruments) means that smaller sample masses can be used. In the case of the Thermometric 20-mL micro solution ampoule used here, sample masses can range up to ∼20 mg but are usually in the range 1–3 mg.

A further consideration of the use of heat-conduction calorimeters concerns dynamic correction of the data. The aim of dynamic correction is to remove the effect of the thermal inertia inherent in any calorimeter (i.e. the delay between heat being released by the sample and that heat causing a measurable voltage to be generated by the thermopiles) and it is principally used for short-term events, typically in titration experiments. However, since one outcome from dynamic correction is an improvement in the signal to noise (S/N) ratio of the data it offers the potential to reduce the standard deviation of dissolution experiments, because peak areas can be determined with greater precision.

In the case of the TAM dynamic correction is achieved by application of a modified form of the Tian equation:

$$P_C = P_R + (\tau_1 + \tau_2)\frac{dP_R}{dt} + \tau_1\tau_2\frac{d^2P_R}{dt^2} \quad (1)$$

where P_R and P_C are the raw and corrected powers, respectively, and τ_1 and τ_2 are termed the first and second time constants of the instrument (for a further discussion of the derivation and use of Equation (1) see, for example, Randzio and Suurkuusk, 1980). The time constants, τ_1 and τ_2, are determined by a least squares analysis of data following an electrical calibration (and are hence not user defined). It is important to note that a number of assumptions are made in order to derive Equation (1) (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, therefore often contain artefacts, such as ‘overshoots’ where both endo- and exothermic events are indicated even though it is known that only one event is occurring in the sample. In principle, these artefacts could be removed by altering the values of τ_1 and τ_2 but this would be difficult in practice because the software does not allow these values to be manually entered. As such, corrected data can be used to determine reaction enthalpies and it is noted that the use of such data to elucidate kinetic information must be undertaken with caution. It can be shown that the total net heat change recorded for both dynamically corrected and raw data, in the ideal case, is the same (Randzio and Suurkuusk, 1980).

3. Results and discussion

3.1. KCl

The dissolution of KCl into water has long been recommended as a test reaction for solution calorime-

Table 1
A summary of the literature values for $\Delta_{\mathrm{sol}}H$ (kJ mol^{-1}) for the three test materials and the values determined using SolCal

Calibrant	$\Delta_{\mathrm{sol}}H$ (kJ mol^{-1})	
	SolCal[a]	Literature
KCl	17.556 ± 0.02	17.584 ± 0.05 (Uriano, 1981)
Sucrose	6.17 ± 0.15	6.17 ± 0.16 (Gao and Rytting, 1997)
Tris	−29.72 ± 0.02	−29.75 ± 0.02 (Hill et al., 1969)

[a] Values determined by Yff et al. (2004).

ters as it is robust, easy to perform and a standard reference material is available; the enthalpy of solution of the NIST certified KCl into water is 17.584 ± 0.017 kJ mol^{-1} (Uriano, 1981), and the system has been well described in the literature (for instance; Kilday, 1980; Uriano, 1981; Archer, 1999). Literature data for KCl dissolution are shown in Table 1. Typical raw power–time data for the dissolution of KCl into water recorded using the 20-mL micro solution ampoule are shown in Fig. 1. The two small exothermic peaks represent the breaking of cartridges 1 and 3 (both empty), while the endothermic peak represents the dissolution of KCl (2 mg) from cartridge 2. The sample mass was chosen to be 2 mg because it was noted that using larger sample masses caused the signal to go off-scale (the instrument was set on its largest amplifier range). The equivalent dynamically corrected (using Equation (1)) data are shown in Fig. 2. It is immediately apparent that the dynamically corrected data show that the dissolution process is completed very quickly (ca. 3 min), while the raw data do not return to the baseline for a considerably longer period (ca. 30 min), which reflects the thermal inertia of the calorimeter. The mean value of $\Delta_{\mathrm{sol}}H$ for KCl was 16.76 ± 0.40 kJ mol^{-1} when using raw data and 17.21 ± 0.49 kJ mol^{-1} when using corrected data (these data are summarised in Table 2. Also shown in Table 2 are the relative standard deviations, R.S.D., for the data; these are discussed in Section 3.4).

Three important observations can be noted. Firstly, the values returned from the raw and dynamically corrected data differ. It was noted above that dynamic correction should not change the total quantity of heat measured for a process. The likely reason for this difference is that the S/N ratio is much greater for the dynamically corrected data (see Figs. 1 and 2) meaning it is much easier to construct a baseline for the corrected data. Secondly, the standard errors in the measurements recorded here are significantly larger than those reported by Uriano (1981) and Yff et al. (2004). Possible reasons for this are discussed later, in the context of the data obtained for all the test reactions, but it should be noted that the manufacturer's stated R.S.D. for the 20-mL solution ampoule is <4%. Thirdly, the value of $\Delta_{\mathrm{sol}}H$ from the raw data is lower than the certified value

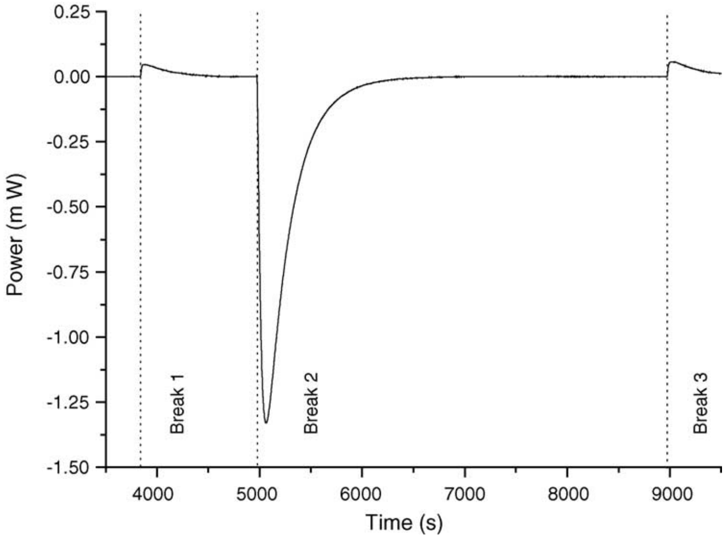

Fig. 1. Typical raw power–time data for the dissolution of KCl (2 mg) into water (15 mL).

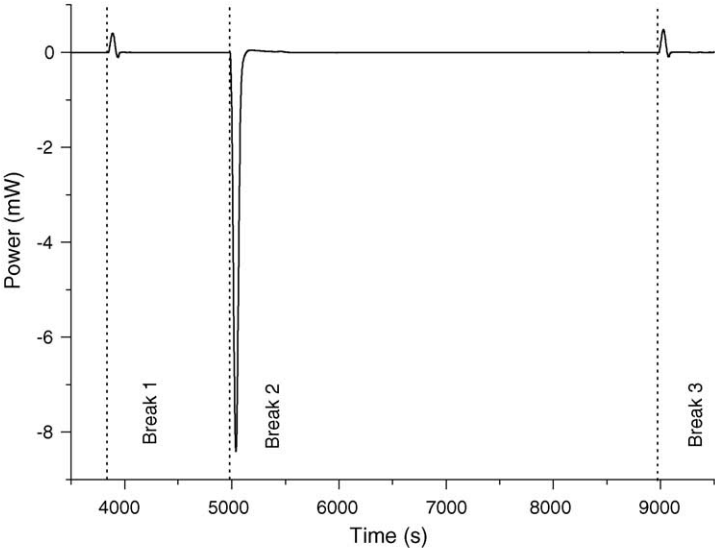

Fig. 2. Typical dynamically corrected power–time data for the dissolution of KCl (2 mg) into water (15 mL).

of 17.584 ± 0.017 kJ mol^{-1}, and the value obtained by Yff et al. (2004) of 17.556 ± 0.019 kJ mol^{-1}, although the value from the dynamically corrected data agrees within the standard deviation.

One of the major drawbacks of using KCl as a reference material is that the value of $\Delta_{sol}H$ varies as a function of the concentration achieved after dissolution, because of the effect of the enthalpy of dilution ($\Delta_{dil}H$); thus, the certified value for the NIST reference material of 17.584 kJ mol^{-1} applies only if a final concentration of 0.111 mol kg^{-1} is attained in the calorimetric vessel. This corresponds to a molar ratio of water to KCl of 500:1 and is often written as $\Delta_{sol}H$ (500 H_2O, 298.15 K). If measurements are performed under different conditions, then the value obtained (nH_2O, 298.15 K) must be corrected to that which would have been recorded at 500 H_2O, in order to draw comparison. These corrections are explained in the certification certificate supplied with the NIST sample (Uriano, 1981), although the data supplied there apply only to experiments performed where n varies from 100 to 1000.

Modern solution calorimeters, such as those discussed here, use milligram samples and are capable of detecting very small powers; one consequence of this is that it is not possible to perform the KCl experiment under the certification conditions in either the SolCal or the 20-mL micro solution ampoule, because the heat generated would be of a magnitude sufficient to saturate the amplifiers.

Table 2
A summary of the values for $\Delta_{sol}H$ (kJ mol^{-1}) obtained using the 20 mL micro reaction calorimeter

Calibrant	$\Delta_{sol}H$ (kJ mol^{-1})					
	Raw data	S.D. (σ_{n-1})	R.S.D.	Corrected data	S.D. (σ_{n-1})	R.S.D.
KCl	16.76 ($n = 4$)	0.40	2.39	17.21	0.49	2.85
Sucrose	5.94[a] ($n = 6$) 6.08[b] ($n = 5$)	0.80[a] 0.09[b]	13.46[a] 1.48[b]	5.97[a] 6.14[b]	0.70[a] 0.08[b]	11.73[a] 1.30[b]
Tris	−30.45 ($n = 4$)	1.02	3.35	−30.48	1.01	3.31

[a] Using a sample mass of 7 mg.
[b] Using a sample mass of 20 mg.

The effects of KCl concentration on $\Delta_{sol}H$ have been studied extensively by Kilday (1980), who corrected the observed enthalpy values over a range of water ratios ($n = 500$–10,000) to account for the enthalpy of dilution (values of $\Delta_{dil}H$ for KCl into water at 25 °C are available from Parker (1965)). This resulted in a value for $\Delta_{sol}H_\infty$, the enthalpy of solution at infinite dilution ($\Delta_{sol}H_\infty = 17.241 \pm 0.018\ \text{kJ mol}^{-1}$).

In the case of the experiments performed using the 20-mL micro solution ampoule, the final concentration attained in the vessel is $0.00179\ \text{mol kg}^{-1}$ (or $n = 31000$). The magnitude of the correction necessary for the enthalpy of dilution at this concentration is very small ($0.07\ \text{kJ mol}^{-1}$) and corrects the measured enthalpy value to $17.14 \pm 0.49\ \text{kJ mol}^{-1}$, a result that is in good agreement with the value of $17.241\ \text{kJ mol}^{-1}$ for $\Delta_{sol}H_\infty$, given the standard deviation of the data. Considering the SolCal data (Yff et al., 2004), the dissolution of KCl (200 mg) into water (100 mL) results in a final concentration of $0.0268\ \text{mol kg}^{-1}$ (or $n = 2100$). This requires a correction of $0.233\ \text{kJ mol}^{-1}$, which corrects the measured enthalpy of solution, $17.556\ \text{kJ mol}^{-1}$, to $17.323 \pm 0.02\ \text{kJ mol}^{-1}$. These corrections were not considered in the previous work because the data were discussed in the context of the certified value.

From the data discussed above, it would appear that, for milligram solution calorimeters at least, it would be better to use the value of $\Delta_{sol}H_\infty$ as the reference enthalpy, rather than $\Delta_{sol}H$ (500 H_2O, 298.15 K), if KCl is to be used as a test substance, because this more closely matches the conditions under which experiments are performed and reduces the complexity of the correction that must be made to the data.

3.2. Sucrose

The dissolution of sucrose into water is not an IUPAC recommended test reaction for solution calorimeters although the dilution of sucrose solutions has been suggested as a test reaction for flow calorimeters (Wadsö and Goldberg, 2001). It does, however, have a number of advantages that make it potentially suitable for the task; it is readily available, easily prepared in a pure form and does not absorb water so it does not need to be dried before use nor stored in a desiccator. Sucrose does not have a certified enthalpy of solution, although some reference data are available from the literature (presented in Table 1).

Fig. 3 shows an average raw power–time trace for the dissolution of sucrose (7 mg) into water. The corresponding dynamically corrected (using Equation (1)) data set is shown on the inset graph in Fig. 3. The cal-

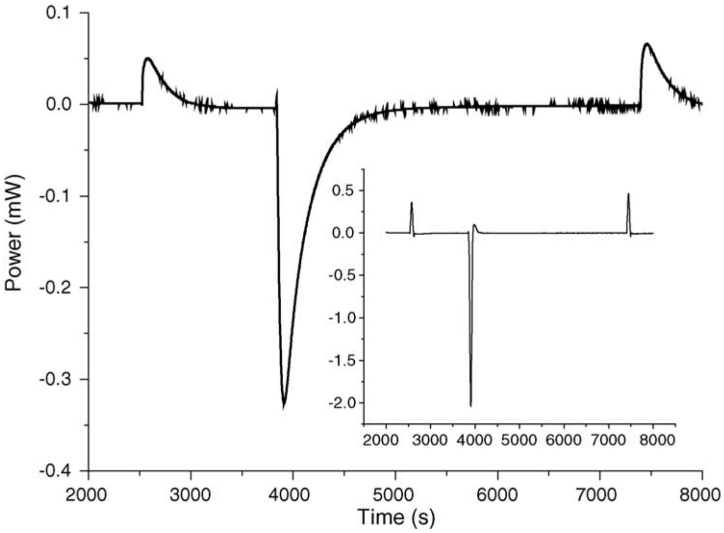

Fig. 3. Typical raw power–time data for the dissolution of sucrose (7 mg) into water (15 mL). The corresponding dynamically corrected data are shown on the inset graph.

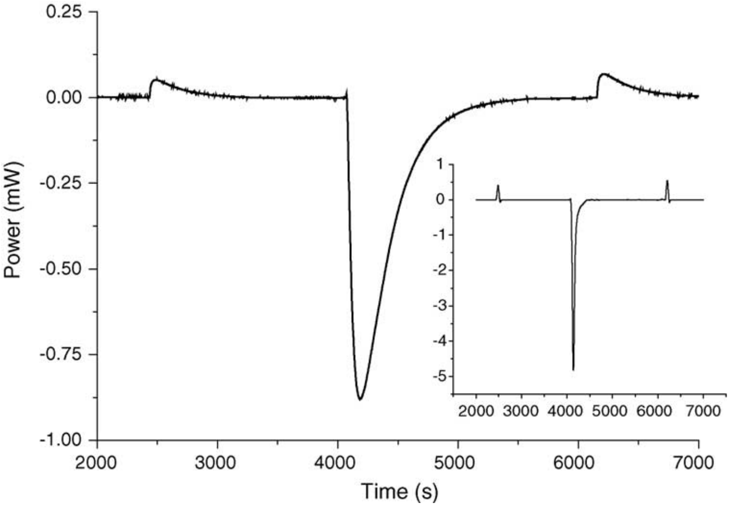

Fig. 4. Typical raw power–time data for the dissolution of sucrose (20 mg) into water (15 mL). The corresponding dynamically corrected data are shown on the inset graph.

culated mean values of $\Delta_{\text{sol}}H$ are $5.94 \pm 0.80\,\text{kJ mol}^{-1}$ and $5.97 \pm 0.70\,\text{kJ mol}^{-1}$, respectively. Both mean values agree with the literature value of $6.17\,\text{kJ mol}^{-1}$ obtained by both Gao and Rytting (1997) and Yff et al. (2004) if the relatively large standard deviations are considered.

The standard deviations were reduced when larger samples of sucrose (20 mg) were used. Fig. 4 shows typical raw and dynamically corrected data for such experiments. The calculated mean values of $\Delta_{\text{sol}}H$ are $6.08 \pm 0.09\,\text{kJ mol}^{-1}$ and $6.14 \pm 0.08\,\text{kJ mol}^{-1}$, respectively, values which are in much better agreement with the literature. In addition, the standard deviations are much smaller than with the 7 mg samples. Again, possible reasons for this are discussed below.

3.3. Tris

The dissolution of Tris in dilute HCl solution was first suggested as a test reaction for solution calorimeters by Irving and Wadsö (1964) and subsequently characterised by Hill et al. (1969). The reaction gives a value of $\Delta_{\text{sol}}H$ of $-29.744 \pm 0.003\,\text{kJ mol}^{-1}$ at 25 °C (Hill et al., 1969) and it is the manufacturer's recommended test reaction for the 20-mL micro solution ampoule. Although it has been widely used as a test reaction, there are potential problems with its use in steel vessels, which are susceptible to acidic attack, and it is recommended that the reaction be carried out, as was the case here, in a glass ampoule.

Fig. 5 shows an average raw power–time trace for the dissolution of Tris (2 mg) into HCl solution. The corresponding dynamically corrected (using Equation (1)) data set is shown in the inset graph in Fig. 5. The calculated mean values of $\Delta_{\text{sol}}H$ are $-30.45 \pm 1.02\,\text{kJ mol}^{-1}$ and $-30.48 \pm 1.01\,\text{kJ mol}^{-1}$ for the raw and corrected data, respectively, which agree with the literature value within the standard deviation. The SolCal gave a value of $-29.72 \pm 0.02\,\text{kJ mol}^{-1}$ (Yff et al., 2004).

3.4. Comparison of test reactions

The first conclusion that can be drawn from the data presented above is that the standard deviations of the 20-mL micro solution ampoule data are greater than those recorded previously using the SolCal (Yff et al., 2004); these errors are also significantly greater than those quoted for the literature reference values (Table 1). In nearly all cases, the standard deviation was reduced slightly when data analysis was performed using dynamically corrected data, but these differences are not significantly different. As mentioned above, the manufacturer's stated R.S.D. in measurements using this equipment is <4%; although the data presented here are mostly within this limit (the exception being

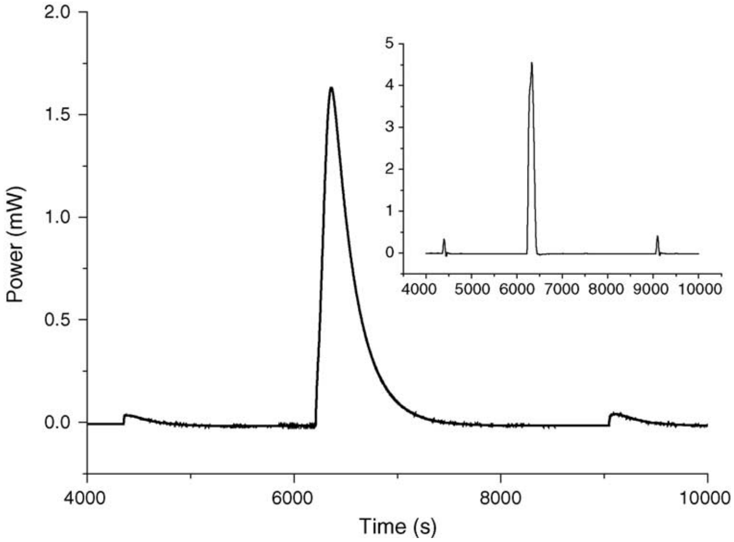

Fig. 5. Typical raw power–time data for the dissolution of Tris (2 mg) into HCl (15 mL). The corresponding dynamically corrected data are shown on the inset graph.

the 7 mg sucrose samples), it is worth considering the reasons for these values because, being the more sensitive instrument, this at first seems counter-intuitive although it is often the case that greater sensitivity reduces the resolution of the data.

For the 20-mL micro solution ampoule, dissolution of greater than 2 mg KCl produced a quantity of heat sufficient to saturate the amplifiers; the SolCal and other semi-adiabatic instruments utilise much larger sample masses. There are always small standard errors in the weighing and these will become more significant as the sample mass decreases. In this work, samples were weighed on a six-figure microbalance, directly into cartridge 2. Analysis of the repeatability of the mass measurements, conducted using a certified 2 mg mass showed a standard deviation of ±0.00001 g (R.S.D. ± 0.5%). There is also an error in the repeatability of the blank responses recorded for cartridges 1 and 3; averaging the data recorded here for both blank cartridges showed a standard deviation ±0.004 J (R.S.D. ± 24.3%). Although this error sounds large, the measured heat upon breaking is small (mean 0.016478 J); furthermore, cartridge breaking is a mechanical event that is inherently irreproducible, because the three pieces of the cartridge must pass over the turbine stirrer before settling on the base of the vessel. In the case of the lowest energy system (7 mg sucrose) this R.S.D. in the blank response translates to a ±3.3% error in $\Delta_{\mathrm{sol}}H$, a value that improves to ±0.9% in the KCl samples. There is also an error in dispensing the solvent into the vessel (measured using a 5-mL Gilson pipette). Analysis of the repeatability of the volume of liquid dispensed showed a standard deviation of ±0.1 mL/5 mL dispensed (R.S.D. ± 2% of the dispensed volume). This error in volume will not affect the measured value of $\Delta_{\mathrm{sol}}H$ but does affect the correction necessary to account for dilution. Finally, there is the possibility that when the rods are depressed to break the cartridges the instrument is rotated in the calorimeter causing a frictional heat; this would manifest itself in the heat of cartridge breaking, as the events occur simultaneously, although care was taken here to ensure this effect was negligible. In combination, it is clear that the magnitudes of the errors discussed above account for the measured error in the $\Delta_{\mathrm{sol}}H$ values recorded.

The sucrose data are interesting, because they were repeated with two sample masses. This was possible because, of the three test substances, sucrose has the smallest enthalpy of dilution. The data obtained using 7 mg samples show the largest standard deviation of all the systems investigated. However, when the sample mass was increased to 20 mg, the data showed the smallest standard deviation. It is likely that this is because of the large sample mass minimising the effect of the weighing error and suggests that, of those errors discussed above, the weighing error is the most significant.

Several conclusions can be drawn from the data discussed above. Principally, it appears that for the 20-mL micro solution ampoule, and presumably for other similar heat-conduction instruments, sucrose is a better test substance than KCl, when 20 mg of sample is used, because it has the smallest R.S.D. value. As discussed above, this appears to be because in this case the experimental errors are at a minimum (the error of cartridge breaking is inherent to the instrument assuming no frictional effects are introduced by the user). Tris, the manufacturer's recommended test substance, had the largest R.S.D. (if the 7 mg sucrose data are disregarded), although the data were within the manufacturer's limits. If the use of KCl is required, because of the need to use certified values, then it appears better to use the value of $\Delta_{\mathrm{sol}}H_{\infty}$ as the reference enthalpy, since this requires fewer corrections and more closely matches the experimental conditions employed. The data also show that even when used with care, it is not possible to record data with an R.S.D. of better than ±1% when using the 20-mL micro solution ampoule; this should be considered when setting repeatability limits for experimental data.

4. Summary

The proper selection of instrumentation for solution calorimetry measurements is governed by the sample to be investigated. If solid samples are available only in small quantities (likely during the preformulation characterisation of a newly synthesised pharmaceutical) or have a low enthalpy of solution, then the greater sensitivity and length of experimental measurement time suggest that an isothermal heat-conduction solution calorimeter would be the instrument of choice. Conversely, if samples are freely available, have a high enthalpy of solution or are liquid or semi-solid in nature then semi-adiabatic instruments are preferable. These considerations apply also to the selection of a chemical test reaction. While the dilution of KCl into water appears to be the best choice for semi-adiabatic instruments, the dilution of sucrose is a better choice for heat-conduction calorimeters. The R.S.D. in measurement of heat-conduction instruments when using this test substance is of the order of ±1%, although this will increase as smaller sample masses are used, and this should be taken into account when considering experimental data.

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