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A new dissolution microcalorimeter: calibration and test

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Abstract

A new batch microcalorimetric vessel for the determination of enthalpies of dissolution of small amounts of easily or slightly soluble solids was developed at University of Lund, Sweden and was tested at University of Porto, Portugal.

The vessel forms part of a series of twin heat conduction microcalorimeters. In a series of consecutive dissolution steps up to four samples, each 0.1–3 mg, can be injected into a solvent chamber of the vessel, volume 20 ml. The high stability of the baseline allows solution experiments to be extended over several hours.

All measurements reported were conducted at 298.15 K and with water as the solvent. The calorimeter was calibrated chemically by dissolution of potassium chloride. The performance of the instrument was further tested by measurements of the enthalpies of dissolution of acetanilide and adenine, 18.25±0.56 and 31.78±0.64 kJ mol^{-1}, respectively. No concentration dependence was found. The results are in good agreement with values in the literature.

Keywords: Dissolution microcalorimeter; Chemical calibration; Adenine; Acetanilide

1. Introduction

Calorimetric investigations of enthalpies of dissolution, $\Delta_{\text{sol}}H$, of pure chemical compounds—gases, liquids and solids—are important for discussion of solute–solvent interactions. In order to obtain data at infinite dilution such determinations are sometimes supplemented by measurements of enthalpies of dilution. To obtain the important value for the transfer of the molecules from the gas phase to infinite dilute solution it is, for liquid and solid compounds, required to know their enthalpy of vaporisation. However, such data are often poorly known, in particular for solids.

The temperature derivative of the enthalpy of dissolution at infinite dilution, i.e. the change in heat capacity, $\Delta_{\text{sol}}C_{\text{p}}^{\infty}$, is a very important property, especially for aqueous solutions, including biochemical systems. Such values together with heat capacity values for corresponding pure compound, C_{p}^{*}, will lead to the partial molar heat capacity for the compound at infinitely dilute solution, $C_{\text{p},2}^{\infty}$,

$$C_{\text{p},2}^{\infty} = C_{\text{p}}^{*} + \Delta_{\text{sol}}C_{\text{p}}^{\infty} \quad (1)$$

In particular at investigations of aqueous solutions of simple, partially hydrophobic compounds, the function $C_{\text{p},2}^{\infty}$ has been much used, e.g. in discussions of ‘hydrophobic hydration’ [1–9].

The precise calorimetric determination of enthalpies of dissolution of solid compounds has recently also become an area of significant practical interest. In particular, for the pharmaceutical industry it has become important to characterise solid materials with respect to their content of different polymorphic forms

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[10–12] or degree of crystallinity [13]. Such measurements may not require results of the highest accuracy, whereas very precise determinations are often needed. Many substances of interest in this connection are slightly soluble in water and methods suitable for organic solvents are therefore important.

In the past, most determinations of $\Delta_{\mathrm{sol}}H_{\mathrm{m}}$ have been made by use of "macro solution calorimeters" of the semi-adiabatic type. Typically, such measurements require about 100 ml of solvent and 0.5 g of solute in each experiment. For easily soluble compounds such determinations can usually be made very accurate, better than 0.1% [14], provided that the dissolution process is short, less than about 30 min. For slow processes adiabatic calorimeters are preferable.

In cases where relatively small quantities of material are available it is normally preferable to use microcalorimetric techniques. Such methods are in many cases suitable both for fast and for slow processes. For solid and liquid solutes measurements can be conducted on the mg level, but the accuracy reached is much lower than that obtained on the macro-level.

For many years, the Lund laboratory has been active in the development of microcalorimeters for dissolution of gases, liquids and solids [15–17]. In all cases, the twin heat conduction principle has been employed. The instruments allow measurements to be conducted on the μW level over long periods of time (day). Flow insertion vessels, of different designs for gases, liquids and solids, were used. Liquids can be easily or (for hydrophobic compounds) slightly soluble [16], whereas gases preferably should be slightly soluble [15]. The instrument used for solids require slightly soluble solutes [17]. All three techniques were tested using water as solvent.

A disadvantage with the method used for solid solutes is that measured enthalpy values will refer to samples in equilibrium with their saturated solutions and not of the dry samples. In many cases, there will be no significant enthalpy difference between dry and wet samples. However, for compounds that strongly interact with the solvent (for example, molecules with cavities, like the macrocyclic compounds) the difference may be large. With the technique described in the present report, where a dry sample is 'injected' into the solvent, such problems are avoided. The present method is a batch technique, whereas the other methods in this series used flow techniques. Both easily and slightly soluble compounds can be investigated. Other instruments for the microcalorimetric measurement of dissolution of solids include the device described by Gill and Seibold [18] and commercial vessels available from Setaram [19].

The instrument that will be described in this report was designed and built several years ago at Thermochemistry, Chemical Center in Lund. However, the instrument was not carefully tested until the measurements reported here were conducted in the Porto laboratory. The present vessel has recently become part of the system of microcalorimeters that are marketed by Thermometric, Järfälla, Sweden.

2. Experimental

2.1. Instrument design and function

The instrument is a twin heat conduction microcalorimeter using semi-conducting thermocouple plates as sensors for the heat flow between the dissolution vessel and the heat sink. The calorimeter is positioned in a water bath, where the temperature is maintained to within $\pm 5 \times 10^{-4}\,^{\circ}\mathrm{C}$. The water bath, temperature controller and all peripheral units were built at Thermochemistry, Lund, Sweden.

The batch dissolution vessel is of the insertion type, meaning that it is taken out from the calorimeter for inspection after each series of experiments and is cleaned and charged outside the calorimeter. Up to four samples can be measured in consecutive dissolution steps, before the vessel has to be recharged.

Fig. 1 shows a picture of the dissolution vessel, with the solvent chamber (r) disconnected from the lid (l). The solvent chamber (volume 20 ml, diameter 27.5 mm) and the lid are made from acid-proof steel. A stirrer (q) of the "turbine" type [20], is fitted with a propeller in order to improve the turbulence in the solvent at the bottom of the solvent chamber. The shaft (p), made from a thin-walled stainless steel tube, is rotated by the motor (d), normally at 60 rpm. Between the lid and the motor are shown three aluminium cylinders (i) that serve as heat exchangers.

At the top of the vessel the upper part of one of the four sample injectors is indicated. A plastic plunger (a) is attached to a thin steel tube (b) (outer diameter 0.6 mm), which is guided into the wider steel tube (k),

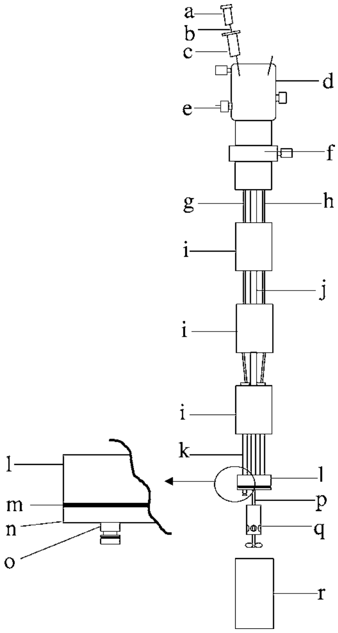

Fig. 1. The calorimetric vessel; a—plastic plunger; b—steel tube; c—injector cup; d—stirring motor; e—main tube wetting port; f—adjustable lock ring; g and h—injector guide tubes; i—heat sinks; j—main tube (stirrer shaft inside); k—wider steel tube; l—ampoule lid; m—Viton O-ring; n—Teflon sleeve; o—cartridge plunger; p–stirrer shaft; q—turbine stirrer with propeller; r—sample ampoule.

where it is attached to a second plunger, length 46 mm. Its function is to inject a cartridge with the sample into the solvent chamber. The lower end of the cartridge plunger (o) is seen in the large-scale figure at the left in Fig. 1. The figure shows the position of the plunger after the injection has taken place. Close to its tip is seen an O-ring, which is made from Kalrez (in order to minimise friction, cf. Section 2.3). The lower part of the lid is fitted with an O-ring (m), made from Viton, which together with a Teflon sleeve (n) provides a seal between the lid and the sample chamber. The Teflon sleeve protects the O-ring from (organic) solvent vapours. The reference vessel consists of a simple static vessel, which is similar to the sample chamber (r), volume 20 ml. It is made from acid-proof steel and is charged with solvent.

Fig. 2 shows the sample cartridge in a dismounted form, consisting of two half-tubes (a) and the bottom disk (b) that is fitted with an O-ring. The lower ends of the half-tubes are placed around the bottom disk and the parts are kept together by use of the “loading tube” (c). The sample (typically 0.1–3 mg, in the form of a tablet) is placed in the assembled cartridge. After weighing, the loading tool (d) is used to push the cartridge into a hole in the lid formed by the lower end of tube (k) in Fig. 1. The loading tube (c) will remain in the loading tool (d). The lower end of the cartridge plunger (o) (Fig. 1) will close the upper end of the sample cartridge by means of the Kalrez O-ring. The tube formed by the two half-tubes will thus be closed in both ends protecting the sample from interactions with solvent vapour and with the atmosphere. Fig. 3 shows a close view (from below) of the sample lid (l) (Fig. 1), with all four cartridges loaded into the holes in the lid. When the cartridge is pushed into the solvent chamber the two half-tubes and the bottom disk will be separated and the sample will be brought in contact with the solvent.

Data acquisition was performed through the SIGMA or ALPHA programs (Sven Hägg, Lund, Sweden). The area under the obtained voltage–time peaks was integrated using ORIGIN 6.

2.2. Materials

KCl obtained from Merck (p.a., ≥99.5%), was dried under vacuum during 4 h, at 70 °C [21]. The mass fraction of water was determined to be 0.01% by Karl Fisher coulometry. Acetanilide from BDH (organic analytical standard) and adenine from Serva (analytical grade) were used as received. The mass fraction of water, as determined by Karl Fisher coulometry, was 0.06% for acetanilide and 0.09% for adenine. The water used in the dissolution measurements was produced by a Milli-Q filtration system.

2.3. Experimental procedure

All dissolution experiments were performed at 298.15 K. The dissolution chamber and the reference vessel were charged with 17.0 ml of water and the stirring rate was 60 rpm. The sample cartridges were charged with 0.1–3 mg of substance and were weighed with a micro balance (±0.5 μg). Especially for substances that are in the form of powders, it is important to press the material to a tablet (using a modest pressure), before the sample is introduced into the cartridge. Otherwise the material might float

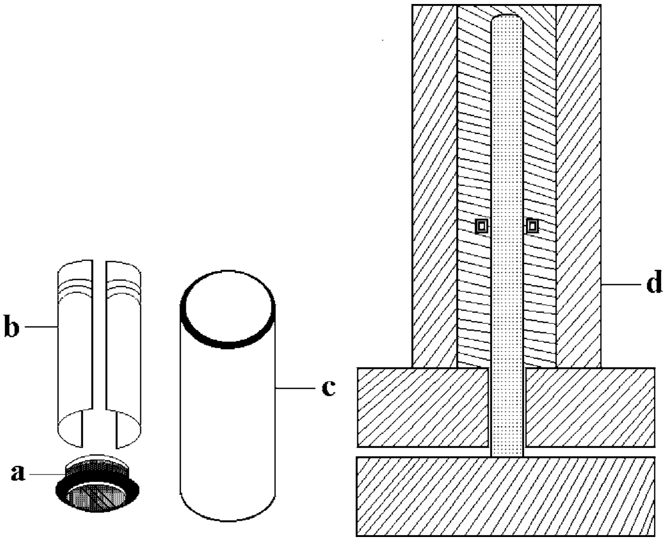

Fig. 2. Sample cartridge and loading tool; a—half-tubes; b—bottom part; c—loading tube; d—loading tool.

resulting in a very slow dissolution process. In all dissolution experiments reported here, the samples were in the form of tablets.

The equilibration time following that the vessel has been introduced into the calorimeter is about 3 h. The injection of the sample cartridges was accompanied by significant friction effects, which were different for the different cartridges and for the different injectors. A large number of blank experiments were therefore performed where empty cartridges were injected into water. In these experiments, and in the dissolution measurements, each cartridge was assigned to a certain injector.

The calibration constant for the instrument was determined by dissolution of potassium chloride [21]. Calibration experiments were conducted at different amplifications, in order to confirm the linearity of the amplifier. The calibration constant was calculated using enthalpies of dissolution reported in [22].

Fig. 3. Close view of the sample cartridges loaded into the vessel's lid.

Results of the chemical calibration and the overall performance of the instrument were tested by dissolution of the slightly soluble test compounds acetanilide and adenine [21]. The endpoint of a dissolution experiment is usually taken as the time when the calorimetric reaction curve has returned to its baseline value. However, in experiments where the dissolution process is very slow (as e.g. for adenine) the rate of heat evolution will be very low after the first few hours, and it can be difficult to judge when the dissolution process is completed. In the beginning of a series of measurements of very slow processes it is therefore advisable to check the dissolution chamber by visual inspection after each measurement.

3. Results and discussion

Uncertainty values for all results of the calorimetric measurements are reported as twice the standard deviation of the mean.

From four experiments conducted over periods of 15 h, the baseline stability (with stirring) was determined to be $0.029 \pm 0.001\ \mu W$ with a negligible baseline drift. These results suggest that the instrument is suitable to use with very slow dissolution processes (day).

Results obtained in the blank experiments with the empty cartridges were 13.8 ± 0.5 mJ for cup 1; 9.7 ± 0.3 mJ for cup 2; 6.3 ± 0.3 mJ for cup 3 and 1.5 ± 0.1 mJ for cup 4. These values were used to correct results of the dissolution experiments.

Fig. 4 shows a typical calorimetric dissolution curve for KCl. It is seen that the dissolution time of the samples was about 15 min. The experimental results for the dissolution of KCl are summarised in Table 1. The obtained mean value of the calibration constant was $\varepsilon = (2.14 \pm 0.06) \times 10^{-4}$ J (integral area)$^{-1}$.

3.1. Dissolution of acetanilide and adenine

Results for the dissolution of acetanilide and adenine are summarised in Tables 2 and 3, respectively. $\Delta_{\mathrm{sol}}H_{\mathrm{obs}}$ is the observed enthalpy changes calculated from the corrected calorimetric curves.

Typical dissolution curves for acetanilide and adenine in water are shown in Figs. 5 and 6, respectively. For both compounds, the dissolution processes are endothermic. However, initially short exothermic phases, caused by the "cartridge effect", are observed. It is seen that these dissolution experiments are much slower than that for KCl, 3–4 and 8–10 h for acetanilide and adenine, respectively. Similar values were also found by Nilsson and Wadsö

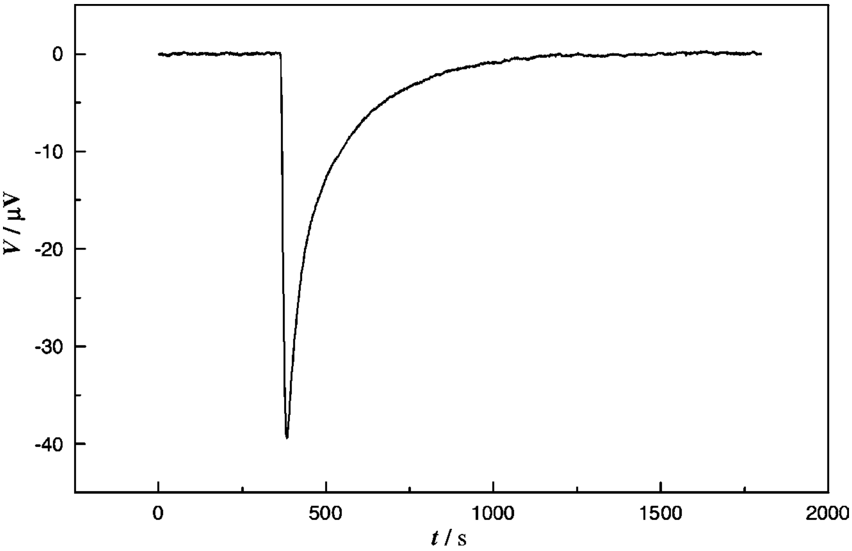

Fig. 4. Calorimetric curve for the dissolution of 0.1535 mg of KCl at 298.15 K.

Table 1
Results for the dissolution of KCl and calculated calibration constant, ε, at 298.15 K

Amplifier setting (μV)	m_{KCl} (mg)	$10^2\Delta_{\text{sol}}H$[a] (J)	$10^4\varepsilon$[b] ((J (integral area)$^{-1}$)	$10^4\varepsilon_{\text{mean}}$ (J (integral area)$^{-1}$)
30	0.1165	2.691	1.880	2.20 ± 0.15
	0.1381	3.191	2.499	
	0.1535	3.547	2.079	
	0.2159	4.989	2.389	
	0.2219	5.128	2.013	
	0.2354	5.441	1.912	
	0.2897	6.697	2.486	
	0.3128	7.231	2.101	
	0.3198	7.860	2.183	
	0.3400	7.393	2.494	
100	0.4234	11.35	7.299	2.13 ± 0.09[c]
	0.4904	9.794	8.038	
	0.4951	11.45	7.044	
	0.4963	11.47	6.683	
	0.5078	11.75	7.095	
	0.5214	12.06	6.618	
	0.5276	12.21	6.707	
	0.5684	13.15	7.196	
	0.5939	13.74	7.139	
300	0.8672	20.08	20.40	2.06 ± 0.04[c]
	0.8997	20.83	19.79	
	1.0220	23.67	20.41	
	1.0275	23.79	20.42	
	1.0879	25.19	21.35	
	1.1489	26.61	20.73	
	1.2700	29.43	21.31	

m_{KCl} is the sample mass, $\Delta_{\text{sol}}H$ the enthalpy change in the experiment and ε the calibration constant expressed in J per arbitrary unit of integral area. Mean value for the calibration constant at 30 μV, using all data: $(2.14 \pm 0.06) \times 10^{-4}$ J (integral area)$^{-1}$.

[a] $\Delta_{\text{sol}}H$ can be calculated from [22].

[b] $\varepsilon = n_{\text{KCl}}\Delta_{\text{sol}}H/(A_{\text{dissolution}} - A_{\text{empty cup}})$, where n_{KCl} is the amount of sample.

[c] The values given are the corresponding $\varepsilon_{\text{mean}}$ values calculated for the 30 μV amplifier setting. The uncertainty is twice the standard deviation of the mean.

when they measured these substances using the flow microcalorimetric vessel discussed above [17].

As discussed above, in the case of substances that dissolve very slowly, it is advisable to inspect the solution chamber after the experiments (at least for the first few experiments). We consider adenine (which normally is in the form of a quite hydrophobic powder) to be a difficult compound to handle in aqueous dissolution experiments and it is therefore a good test reaction [21], by which both instrument and experimental technique will be tested.

In Figs. 7 and 8, we show $\Delta_{\text{sol}}H_{\text{obs}}$ as a function of the amount of the solutes. For both acetanilide and adenine straight lines passing through zero are obtained, showing that the experimental enthalpies of dissolution are within uncertainty limits equal to the enthalpy values at infinite dilution, $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$. This is not surprising as the solute concentration was always very low (<1.4 mM). These values are listed in the third column of Tables 2 and 3.

For acetanilide, the mean value of $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ was 18.25 ± 0.56 kJ mol^{-1}, which is in very good agreement with the value obtained by Nilsson and Wadsö using the flow microcalorimetric technique, 18.13 ± 0.20 kJ mol^{-1} [17]. From solubility measurements (van't Hoff values) Logan derived the enthalpy value 19.7 kJ mol^{-1} [23]. As no error estimate was quoted for that value, and knowing that the errors tend to be large with the van't Hoff method, we consider the agreement to be fair.

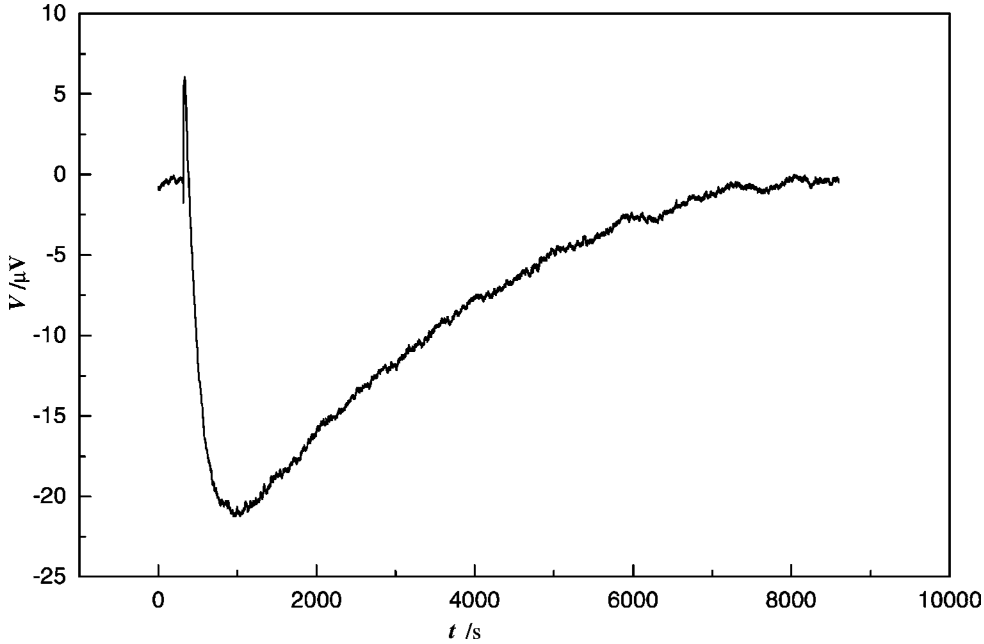

Fig. 5. Calorimetric curve for the dissolution of 2.5490 mg of acetanilide at 298.15 K.

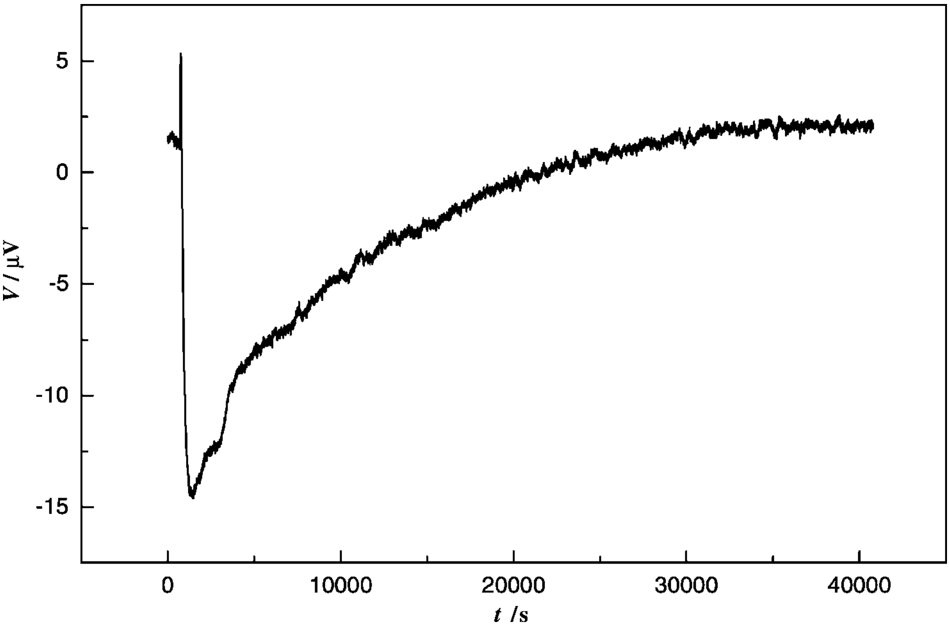

Fig. 6. Calorimetric curve for the dissolution of 3.1090 mg of adenine at 298.15 K.

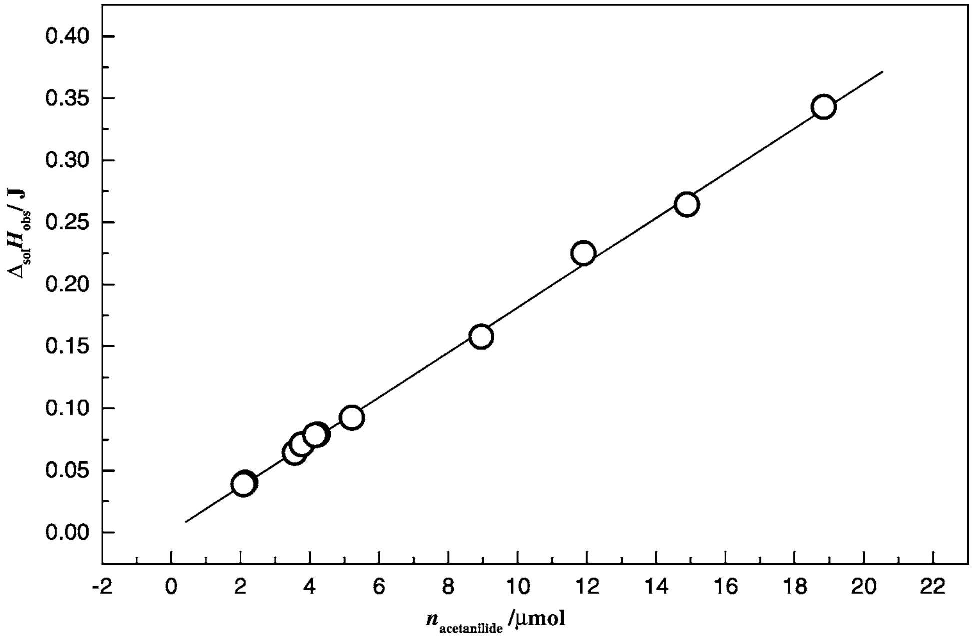

Fig. 7. Enthalpy of solution, $\Delta_{sol}H_{obs}$, as a function of the amount of acetanilide, at 298.15 K.

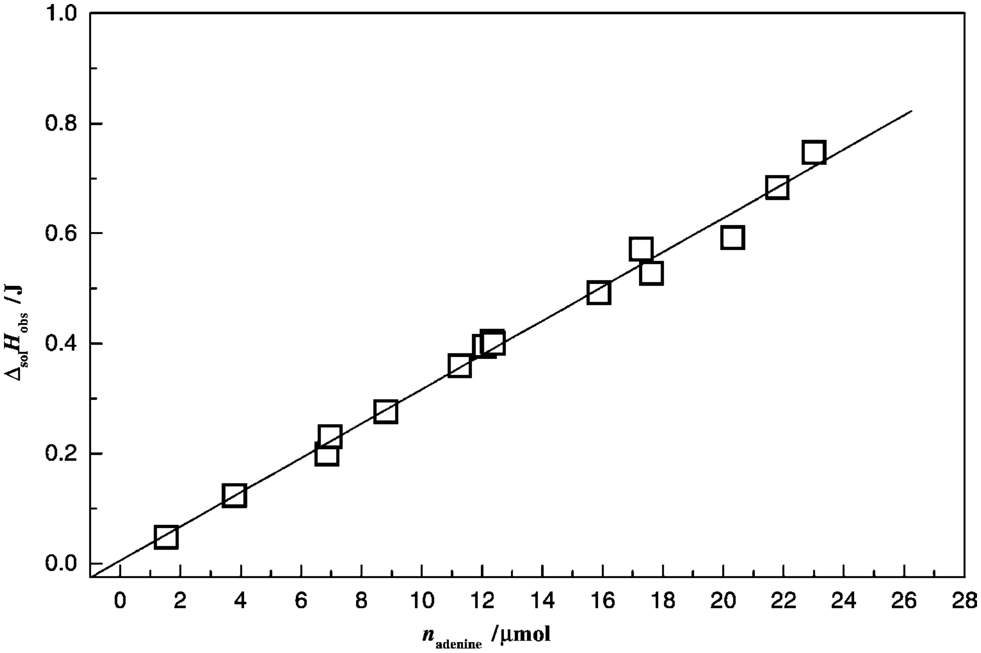

Fig. 8. Enthalpy of solution, $\Delta_{sol}H_{obs}$, as a function of the amount of adenine, at 298.15 K.

Table 2
Experimental results for the dissolution of acetanilide in water, at 298.15 K

$m_{\text{acetanilide}}$ (mg)	$\Delta_{\text{sol}}H_{\text{obs}}$ (J)	$\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ (kJ mol^{-1})
0.2903	0.03974	18.50
0.2832	0.03847	18.31
0.4841	0.06410	17.90
0.5116	0.07075	18.69
0.5733	0.07871	18.56
0.5624	0.07829	18.82
0.7073	0.09244	17.67
1.2120	0.1575	17.57
1.6105	0.2246	18.85
2.0149	0.2639	17.70
2.5490	0.3425	18.16

$m_{\text{acetanilide}}$ is the sample mass, $\Delta_{\text{sol}}H_{\text{obs}}$ the observed enthalpy change in the experiment and $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ the molar enthalpy of dissolution, at infinite dilution. Mean value, $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$: 18.25 ± 0.56 kJ mol^{-1}.

For adenine, the obtained mean value for $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ is 31.78 ± 0.64 kJ mol^{-1} which is in good agreement with the value obtained by Kilday, 32.3 kJ mol^{-1} [24], using an adiabatic calorimeter, as well as with the value 32.68 ± 0.66 kJ mol^{-1} obtained by Nilsson and Wadsö by the flow microcalorimetric method [17].

In summary, it is demonstrated that chemical calibration using KCl is a suitable calibration method for the present type of instruments used with water as the solvent. The results obtained in measurements of the slightly soluble test substances acetanilide and adenine agree well with literature values obtained with different methods. It is concluded that the method reported here can give results with an accuracy of about 4 J g^{-1}, for small samples ($\leq$3 mg) of slightly soluble compounds that may require up to 10 h to be dissolved.

An early version of the present version was used in measurements with an organic solvent [25]. A systematic study of the use with different organic solvents is in progress in the Porto laboratory.

Table 3
Experimental results for the dissolution of adenine in water, at 298.15 K

m_{adenine} (mg)	$\Delta_{\text{sol}}H_{\text{obs}}$ (J)	$\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ (kJ mol^{-1})
0.2064	0.0476	31.12
0.5110	0.1234	32.63
0.9417	0.2308	33.11
1.1893	0.2758	31.34
1.5211	0.3594	31.92
1.6320	0.3946	32.67
1.6650	0.4038	32.77
1.6732	0.4004	32.33
2.1449	0.4923	31.01
2.3343	0.5718	33.09
2.3805	0.5282	29.98
2.7451	0.5921	29.14
2.9441	0.6843	31.40
3.1090	0.7472	32.47

m_{adenine} is the sample mass, $\Delta_{\text{sol}}H_{\text{obs}}$ the observed enthalpy change in the experiment and $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ the molar enthalpy of dissolution, at infinite dilution. Mean value, $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$: 31.78 ± 0.64 kJ mol^{-1}.

Acknowledgements

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