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Chemical calibration of Isothermal Titration Calorimeters: An evaluation of the dilution of propan-1-ol into water as a test reaction using different calorimeters, concentrations, and temperatures

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ABSTRACT

The use of a good chemical calibration or test reaction in Isothermal Titration Calorimetry is crucial for getting reliable enthalpy values that can be compared across different laboratories. Indeed most titration calorimeters are used to measure both equilibrium constants and molar enthalpies of reaction. But a necessary prerequisite for such measurements is to first perform the enthalpy measurement accurately and precisely. The values of the equilibrium constant(s) are then calculated by regression from an appropriate model. As such, we found it timely to extensively test a previously proposed test reaction, the dilution of propan-1-ol into water, using two calorimeters of different design (heat conduction and power compensation calorimeters) and sensitivity. Experiments were performed at 298.15 K for the previously suggested 10% mass fraction propan-1-ol solution, as well as for the lower concentrations of 5% and 2% mass fractions. Due to our capacity to use insertion heaters with one of the used calorimeters, which allows for very accurate calibration constants to be obtained, we also determined a value for the enthalpy of dilution of 10% mass fraction solution at 308.15 K, previously not available, and closer to the temperatures commonly used in titration experiments involving biological samples. The observed change in the enthalpy of dilution was found to decrease in absolute value, but to an extent that did not justify the determination of new values for the less concentrated solutions.

The values obtained with the two calorimeters are in excellent agreement, as well as with the values from the literature for the 10% mass fraction solution at 298.15 K. This reaction is thus again proposed as an excellent test reaction and the detailed conditions of their use depending on instrument sensitivity are suggested. In summary, the values for the enthalpies of dilution to infinite dilution $\Delta_{dil}H_m^{\infty}$ at 298.15 K are $-(1.540 \pm 0.021)$ kJ · mol^{-1}, $-(0.604 \pm 0.020)$ kJ · mol^{-1}, and $-(0.186 \pm 0.011)$ kJ · mol^{-1} for the 10%, 5%, and 2% mass fraction solutions, respectively, and at 308.15 K $-(1.486 \pm 0.017)$ kJ · mol^{-1} for the 10% mass fraction solution.

1. Introduction

Isothermal Titration Microcalorimetry (ITC) can easily provide the basic thermodynamic parameters of a reaction in solution, which in some cases cannot be directly obtained using other physical methods. In recent years, ITC alone or together with other techniques has been used in a variety of fields, such as general physical chemistry, pharmaceutical research, polymer/surfactant interactions, structural biology, or membrane/drug interactions [1–12]. Clearly ITC has proven to be an excellent tool with wide application scope, as it can provide basic thermodynamic data and contribute to the unraveling of the mechanisms of intermolecular interactions in different systems.

In any calorimetric titration measurement with instruments in the micro- or nano-sensitivity range, the most common procedure involves adding aliquots of the titrating solution (in the 10^{-3} cm^3 range) to a solution contained in the calorimetric cell (with volumes between 0.2 cm^3 and 1.5 cm^3), using solutions that typically have concentrations ranging from 10^{-6} mol · dm^{-3} to 10^{-3} mol · dm^{-3}. Therefore, extreme care must be taken in order to attain a good precision. Another very important but sometimes disregarded aspect is the accuracy of the obtained data, which requires accurate calibration. As it is known since the beginnings of calorimetry, in any accurate calorimetric work the use of appropriate calibration protocols is fundamental to ensure accurate data [3,13,14]. In fact, in many cases discrepancies between results

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reported from different laboratories can be accounted for by differences in calibration procedures and/or standards used, or even worse, due to the absence of use of a correct calibration procedure. To ensure the accuracy of the calorimetric results it is essential to make periodic calibrations of the ITC instrument, regarding its various components such as heat exchange, volume of the calorimetric cell and injected volumes [14].

Titration micro calorimeters are in some cases calibrated electrically, being that this calibration can be made with easiness and precision. However, electric calibration depends critically on the position of the heater (in heat conduction or power compensation calorimeters) [13]. In some of the instruments available in the market the electrical calibration cannot be performed by the user, and thus chemical calibration is a requirement [14].

In some cases the electrical calibration that can be made with the permanent heater provided with the instrument is not good enough for very accurate work. As shown by Briggner and Wadsö [13], the use of insertion heaters (located inside of the reaction vessel) provides very accurate calibration constants, as the heat is evolved inside the calorimetric cell as in subsequent titration experiments. Nevertheless, its use is not common, as they are usually "home-made devices" [13,15–17], and thus are not available to many users. Therefore, overall the need for simple and standardized chemical calibration procedures, tested for different equipments, is mandatory. Moreover, even in cases where electrical calibration with an insertion heater can be performed, a chemical test is appropriate, as it can provide an excellent test reaction for the results obtained with the instrument.

Previously we have done a systematic work in this respect for a Lund dissolution micro calorimetric vessel (prototype), as well as with the vessel as later commercialized by Thermometric AB, Sweden (now General Electric – GE) [15,18,19]. We have now decided to do a similar work for ITC by re-visiting a very simple test reaction proposed at Wadsö's lab [13], testing it with two instruments of different calorimetric design: 1 – the heat conduction calorimeter of Thermometric AB (GE Healthcare-Microcal, Piscataway, NJ, USA), equipped with 1 cm^3 titration cell, which has an air gap above the titrant solution (a non-constant volume calorimeter) (calorimeter A) and 2 – the power compensation VP-ITC (Microcal/GE Healthcare-Microcal, Piscataway, NJ, USA) (a constant volume, overflow type of calorimeter) (calorimeter B). Calorimeter A was used with a volume of solution of 0.9 cm^3 in the cell, as this has been shown to be the most appropriate volume of titrant for this type of calorimeter cell (nominally 1 cm^3) [13,15,20] and calorimeter B has a volume of $\approx$1.4 cm^3. These two instruments have different sensitivities and design, and thus we thought it appropriate to compare their performance in regards to the same test reaction. Further, due to the higher sensitivities available today as compared to the time the test reaction was proposed, we have tested the same reaction at 298.15 K for different starting concentrations. Finally, as in our Lab we have the possibility to use insertion heaters [15,17,18], we were able to provide an accurate value for the test reaction at another temperature.

In this work we have thus extensively studied the reaction test as previously proposed by Briggner and Wadsö [13] with three goals: (i) to evaluate the quality of results when initial concentrations of propan-1-ol lower than the previously suggested 10% mass fraction are used, as these are more suitable for the more sensitive instruments; (ii) to compare the performances of two widely used calorimeters of different design type; and (iii) to provide a new value for the test reaction at 308.15 K ($\Delta_{dil}H_m$) a more relevant temperature in biological studies (the values in the literature are at 298.15 K).

2. Experimental

2.1. Material

Insertion heater: an insertion heater (made at Thermochemistry, Lund University, Sweden) consisting of insulated manganin wire fitted to double copper leads (0.12 mm diameter) was used throughout. The copper leads (diameter 0.15 mm, length equals 50 cm (2 leads), 1.015 $\Omega \cdot m^{-1}$) are used to connect the heater to the power supply. The manganin part of the heater forms a horizontal ring (diameter about 10 mm), which encircles the stirrer shaft and is totally inserted in the calorimetric liquid. The initial section of the copper leads (few millimeters) is also immersed in water [13] but the remaining part is thermally stationed at the calorimeter shield (through the heat exchangers) which is maintained at a constant temperature. Thus, the amount of heat generated in the leads that goes into the calorimeter can be disregarded and we assumed that the heat generated in the leads goes to the surroundings. The total resistance (manganin + copper wire) and separately the resistance of the copper wires were measured by means of a HP nanovoltmeter, and thus the resistance of the copper wires (1.538 Ω) was subtracted from the total resistance measured, leading to the value of 66.00 Ω to the resistance of the heater (R).

Propan-1-ol solutions: propan-1-ol (mole fraction 0.999, Sigma–Aldrich) was used as received. Its water content was determined by Karl Fischer coulometric titration (Metrohm AG Herisau, Switzerland) and found to be less than 0.005% (w/w). The molar mass of propan-1-ol was taken as 60.097 $g \cdot mol^{-1}$. Solutions of concentrations 2%, 5%, and 10% mass fraction) were rigorously prepared by mass with an analytical balance (±0.00001 g) (Mettler-Toledo International Inc., Germany) and thus the concentrations were obtained with 5 significant figures.

All solutions were prepared with Milli Q gradient Ultra pure water (Millipore, Billerica, MA, USA). As the propan-1-ol solutions were used in the syringe, we needed to convert the concentration in molality as obtained after preparation into molarity. The data of relative densities measured by Pang and collaborators at 298.15 K and 308.15 K [21] were used to obtain a fitting curve (2nd degree polynomial) of the density as a function of mole fraction, and the densities of each of the solutions used were thus calculated from their mole fraction by interpolation with the fitting curve.

2.2. Instruments

Calorimeter A was a calorimetric unit that consisted of a twin heat conduction microcalorimeter (GE Healthcare, Piscataway, NJ, USA) placed in a water bath, and used with control units that were made at Lund University, Sweden [17]. A 7½ digit HP nano voltmeter is connected to the calorimetric channel and interfaced to the computer, where data acquisition and syringe pump control are performed through a modified version of the program LABTERMO [22]. A titration cell of 1 cm^3 volume equipped with a gold propeller (GE Healthcare, Piscataway, NJ, USA) was used throughout. The cell was charged with 0.9 cm^3 of water, accurately measured with a calibrated Gilson P100 pipette (V = 0.8943 cm^3). The experiments were performed in "fast mode", and the recorded curves dynamically corrected thereafter [20,23] using a time constant τ = 220 s, and subsequently integrated from the baseline. The areas so obtained (in $\mu V \cdot s$) were used to calculate the heat (Q).

Calorimeter B was a VP-ITC (GE Healthcare, Piscataway, NJ, USA). This calorimeter model uses a cell feedback network (CFB) to differentially measure and compensate for the heat produced or absorbed in the sample and reference cells. The two coin shaped cells are totally filled with liquid during operation, which is