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Enthalpy of solution of α-cyclodextrin in water and in formamide at 298.15 K

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Abstract

A new dissolution microcalorimeter that can measure enthalpies of dissolution of slightly soluble solids was developed by Ingemar Wadsö at Lund University, and the prototype as well as the commercial vessel were tested in our laboratory. Recently we did report the testing of the prototype and we are now extending the previous investigation to measurements with an organic solvent in the commercial vessel. The instrument performance was found to be as good with formamide as with water.

The vessel was calibrated chemically (dissolution of KCl in water) and electrically, by means of a permanent and an insertion heater. The results obtained from the three methods are compared and discussed.

The enthalpy of dissolution of α-cyclodextrin, dry and hydrated with six water molecules, was determined in water and in formamide. The results are discussed in terms of the difference between water and formamide as regarding dissolution and binding to the cyclodextrin molecule.

Keywords: Dissolution microcalorimeter; Chemical calibration; Electrical calibration; α-Cyclodextrin; Formamide

1. Introduction

Calorimetric determination of enthalpies of dissolution, $\Delta_{sol}H$, of pure compounds is important for the discussion of solute-solvent interactions. The calorimetric determination of enthalpies of dissolution of solid compounds has recently become an area of significant practical interest, in particular for the pharmaceutical industry, where it is important to characterise drugs with respect solubility, content of polymorphic forms [1–3] or degree of crystallinity [4]. Many substances of interest in this connection are slightly soluble in water and methods that are suitable for organic solvents are therefore important.

A new dissolution microcalorimeter that can measure enthalpies of dissolution of slightly soluble solids has been developed by Ingemar Wadsö at Lund University, and the prototype as well as the commercial vessel were tested in our laboratory. Recently we did report the testing of the prototype [5]. We are now extending the previous investigation to measurements with an organic solvent in the commercial vessel, and the instrument performance was found to be as good with formamide as with water.

Cyclodextrins are cyclic oligosaccharides, formed by a variable number of D(+)glucopyranose units connected by α-1,4-linkages. They have hydrophobic cavities (formed by CH_2 and ether groups) and a hydrophilic exterior (hydroxyl groups). They are known to interact strongly with different types molecules, mainly by forming inclusion compounds, although in some cases the interaction via the hydroxyl groups has also been reported [6]. The major requirement seems to be that the guest molecule fits into the cyclodextrin cavity, and a variety of factors have been considered as driving forces for the binding process [7]. Solvent molecules can also form inclusion complexes with cyclodextrins [8], being water itself the most well-known example [9]. It is very important to be aware of this possibility, as many studies involving cyclodextrins are performed in organic media, and the possibility of solvent binding should be considered, and if present, corrected for [10]. Cyclodextrins

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have important technological applications in drug delivery systems [11–13], separation techniques and food industry [14,15].

In present work, the $\Delta_{sol}H_m$ of α-cyclodextrin, dry and hydrated (with 6 H_2O), was determined in water and in formamide by dissolution microcalorimetry. α-cyclodextrin interacts strongly with both solvents, which is reflected in very different values for the enthalpies of dissolution of dry and hydrated cyclodextrin. The results will be discussed in terms of the difference between water and formamide as regarding dissolution and binding.

2. Experimental

2.1. Instrument

The dissolution vessel (Thermometric AB, Sweden) is inserted in a twin heat conduction microcalorimeter (Thermometric AB, Sweden), which is positioned in a water bath of precisely controlled temperature ($\pm 5 \times 10^{-4}$ °C). Dissolution experiments were conducted with sample masses on the mg level and a solvent volume of 17.00 ml. The vessel has three injectors, thus allowing the successive injection of three samples without opening it. This vessel was characterized as regarding stability, noise level and "empty cups" thermal effect according to the methodology described before [5]. The instrument was calibrated chemically by dissolution of potassium chloride (KCl), and electrically by means of a permanent heater positioned in the channel and also by use of an insertion heater made at Lund University [16]. Data acquisition was performed through the SIGMA or ALPHA programs (Sven Hägg, Lund, Sweden).

2.2. Materials

KCl obtained from Merk (p.a., ≥99.5%), was dried under vacuum during 4 h, at 70 °C [17]. The mass fraction of water was determined to be 0.027% (w/w) by Karl Fischer coulometry (KF 737, Metrohm). α-Cyclodextrin (Sigma purity 100%) was kept inside a desiccator over a saturated solution of $Ca(NO_3)_2 \cdot 4H_2O$ during 1 week, in order to obtain α-cyclodextrin (CD) with 6 mol of water [17,18]. Due to the difficulty of obtaining and especially handling completely anhydrous CD, samples with different degrees of hydration (between 0.3 and 2.5% (w/w)) were used in the "dry" experiments. They were obtained by drying CD at 65 °C under vacuum for at least 4 h, and the mass fraction of water was determined thereafter by Karl Fischer coulometry. The water used in dissolution measurements was produced by a Milli-Q filtration system. The purity of formamide (Merck, p.a.) as determined by gas chromatography, was 99.08%. Its water content was checked in parallel to each experiment, and was always between 0.18 and 0.20% (w/w), as measured by Karl Fischer coulometry.

2.3. Experimental procedure

All dissolution experiments were performed at 298.15 K. The dissolution chamber and reference vessel were charged with 17.00 ml of solvent. The conducting tubes were dried with a flow of nitrogen prior to the introduction of the sample cartridge [5]. Stirring rates of 60 or 70 rpm were used. The sample cartridges were charged with 0.1–9.5 mg of substance and were weighed in a Mettler Toledo UMT2 micro balance (±0.5 μg). In most dissolution experiments the solid was pressed into tablets using a modest pressure, as described before [5]. In the case of hydrated CD in formamide, due to difficulty in complete dissolution of the tablet, the powder was inserted directly into the cartridges and very gently pressed with a plastic tool.

In the measurements with "dry" CD, all handling (tablet preparation and cartridge charge) was done in a controlled humidity environment, an AtmosBag filled with dry nitrogen. Each cartridge was closed inside the Atmosbag with a metal lid. After weighing, the lid was taken out and the cartridge was rapidly injected into the conducting tubes, previously dried.

Significant heat effects accompany the injection of the sample cartridges ("empty cups" thermal effect), which are different for the different cartridges and the different injectors, and also depend on the type of o-ring used. We used Viton o-rings for water experiments and Kalrez o-rings for formamide. Therefore, the "empty cups" thermal effect was determined independently by performing a large number of blank experiments for each injector, in each solvent.

The chemical calibration with KCl was performed as described before [5]. For the electrical calibration, both the permanent channel heater and an insertion heater were used. Calibrations were performed at different amplifier sensitivities. The time constant of the instrument was determined by electrical calibration under steady state conditions.

3. Results and discussion

Unless otherwise stated, the uncertainties are reported as twice the standard deviation of the mean.

The system has a very high stability, as the average value of potential difference readings over 16 h is determined to be 12.941 ± 0.001 μV, with a negligible baseline drift. The experimentally determined time constant (with the insertion heater) is 189 s.

The results obtained for the heat effect of the "empty cups" in water and formamide are presented in Table 1. These values were used to correct the results obtained on the dissolution experiments in the respective solvent. It can be observed that the values are higher in formamide. This must be mainly due to different heat of friction of the Kalrez o-rings as compared to the Viton ones.

Table 1
Thermal effects of “empty cups” in water and in formamide

Solvent	Thermal effects (mJ)		
	Cup 1	Cup 2	Cup 3
Water	−11.0 ± 0.4	−11.1 ± 0.8	−10.9 ± 0.8
Formamide	−24.5 ± 0.7	−17.1 ± 0.7	−18.6 ± 0.3

Table 2
Calibration constants ($\varepsilon_{\mathrm{chem}}$) from chemical calibration (dissolution of KCl at $T = 298.15\,\mathrm{K}$)

Amplifier setting (μV)	$10^4\ \varepsilon_{\mathrm{chem}}$[a] (J area^{-1})
30	2.28 ± 0.07[b]
100	7.38 ± 0.10[b]
300	21.4 ± 0.1[b]
$\varepsilon_{\mathrm{mean\text{-}chem}}$ is (2.20 ± 0.04) × 10^{-4} J area^{-1}[c]	

[a] $\varepsilon_{\mathrm{chem}}$ calculated as described in [5].

[b] The values are the mean value of at least eight independent experiments.

[c] Mean value of all calibration constants, referred to the 30 μV amplifier setting.

Table 3
Calibration constants ($\varepsilon_{\mathrm{elec}}$) from electrical calibration at $T = 298.15\,\mathrm{K}$

Amplifier setting (μV)		$10^4\ \varepsilon_{\mathrm{elec}}$ (J area^{-1})	
		Water	Formamide
Permanent heater ($R = 50.000\,\Omega$)	30	1.99 ± 0.02	1.99 ± 0.02
$\varepsilon^{\mathrm{P}}_{\mathrm{mean\text{-}elec}} = 1.99 \pm 0.02$[a]			
Insertion heater ($R = 50.915\,\Omega$)	30	2.16 ± 0.02	2.16 ± 0.03
	100	7.27 ± 0.07	7.23 ± 0.07
$\varepsilon^{\mathrm{I}}_{\mathrm{mean\text{-}elec}} = 2.17 \pm 0.02$[a]			

[a] Mean value of calibration constants for each heater type, calculated for the 30 μV amplifier setting.

3.1. The calibration constants

The calibration constants (ε) obtained from chemical and electrical calibrations, under different amplifier settings are summarized in Tables 2 and 3, respectively, where ε is the calibration constant expressed in J per integral area (in arbitrary units). The values obtained from chemical calibration ($\varepsilon_{\mathrm{chem}}$) are listed in Table 2. They are derived from the enthalpy of dissolution of KCl as described in detail before [5]. The results presented for each amplifier setting are the mean value of at least eight independent experiments. The overall mean value, referred to the 30 μV amplifier setting, is (2.20 ± 0.04) × 10^{-4} J (integral area)$^{-1}$.

The values obtained from electrical calibration ($\varepsilon_{\mathrm{elec}}$) are listed in Table 3. As expected, the solvent media has no effect on the value of the calibration constant, since we are dealing with a heat conduction calorimeter. On the other hand, the $\varepsilon_{\mathrm{elec}}$ values do depend significantly on the position of the heater—when two different types of heater are used, a permanent heater positioned in the channel (heating source outside the vessel) and an insertion heater (heating source inside the vessel), and all other conditions are the same, the area of voltage–time peak is smaller in the later case, as shown in Fig. 1.

Further, the calibration constant value (2.17 ± 0.02) × 10^{-4} J (integral area)$^{-1}$ (insertion heater) is in excellent agreement with the one obtained by chemical calibration with KCl (2.20 ± 0.04) × 10^{-4} J (integral area)$^{-1}$. This is a very important result, as it confirms the calibration constant value obtained by chemical calibration for the present vessel, stresses once again the importance of performing chemical and electrical calibrations and of being aware of the importance of heater position in calorimetric calibration procedures [16,19].

3.2. The dissolution of α-cyclodextrin in water and formamide

Typical calorimetric curves for the dissolution of hydrated and dry CD in water and in formamide are shown in Figs. 2 and 3. The dissolution of hydrated CD is endothermic in both solvents, whereas the dry CD’s dissolution is exothermic.

As stated in the experimental procedure, due to the extreme difficulty in handling completely dry cyclodextrin, we did dissolution experiments with varying degrees of hydration, all at very low hydration states. The enthalpy of

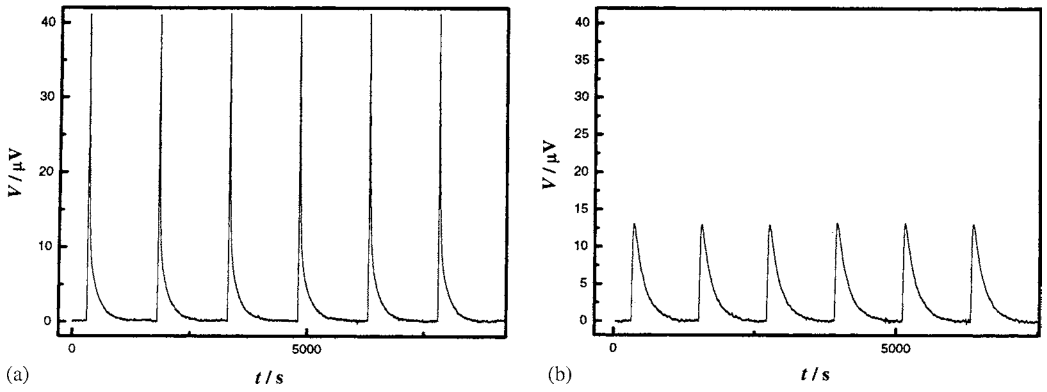

Fig. 1. Calorimetric potential–time curves for electrical calibration with 17 ml water: (a) with a permanent heater positioned in the channel ($R = 50.000\,\Omega$, $I = 5.000\,\mathrm{mA}$, $t = 12\,\mathrm{s}$); (b) with an insertion heater ($R = 50.915\,\Omega$, $I = 5.000\,\mathrm{mA}$, $t = 12\,\mathrm{s}$).

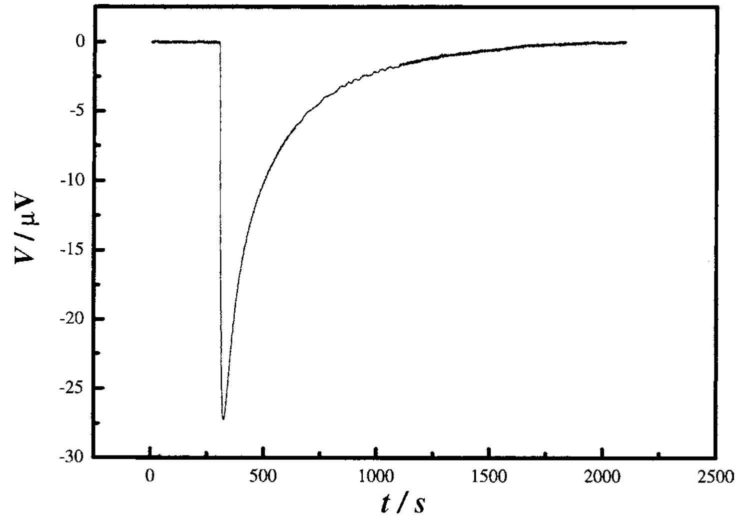

Fig. 2. Calorimetric curve for the dissolution of 8.870 mg of hydrated cyclodextrin in formamide at 100 μV.

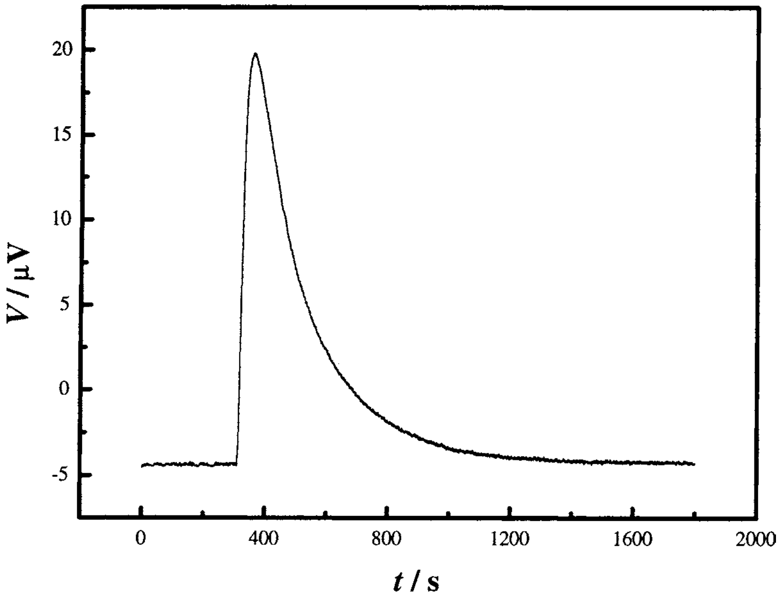

Fig. 3. Calorimetric curve for dissolution of 1.571 mg of "dry" cyclodextrin in water ($n_{H_2O}/n_{\alpha\text{-CD}} = 0.503$) at 100 μV.

solution ($\Delta_{sol}H_m$) is then plotted as a function of the ratio $n_{H_2O}/n_{\alpha\text{-CD}}$ as shown in Figs. 4 and 5, for water and formamide, respectively. A linear regression is performed in both cases, and the enthalpy of solution of the "dry" cyclodextrin is taken as the intercept of these plots. The obtained values are listed in Table 4.

Table 4
Enthalpies of solution, $\Delta_{sol}H_m$ of α-cyclodextrin in water and in formamide at $T = 298.15$ K

	Water	Formamide
$\Delta_{sol}H_m$ (α-CD, hydrated)/kJ mol^{-1}	+31 ± 1	[+7.7; +17.0] +19.7 ± 0.9[a]
$\Delta_{sol}H_m$ (α-CD, dry)/kJ mol^{-1}	−60 ± 1	−81 ± 3

[a] [20].

The enthalpy of solution of hydrated α-cyclodextrin in water was easily determined. However, when we did the same experiments in formamide, an unacceptable dispersion was obtained, despite a large number of experiments. We thus only report an interval of the minimum and maximum obtained values (Table 4). In a previous study, this value was determined to be $\Delta_{sol}H_m = +(19.7 \pm 0.9)$ kJ mol^{-1}, by macro-solution calorimetry with an LKB 8700 [20]. Let us try to understand why it was possible to determine it by macro-solution (volume of solvent 100.0 ml and mass of sample around 0.5 g). It is known that α-CD·6H_2O has two water molecules inside its cavity, being the others distributed in the exterior [9], and that these water molecules can be totally or partially exchanged with a ligand upon complex formation [21–23]. Further, as stated in the introduction, other solvent molecules can also form inclusion

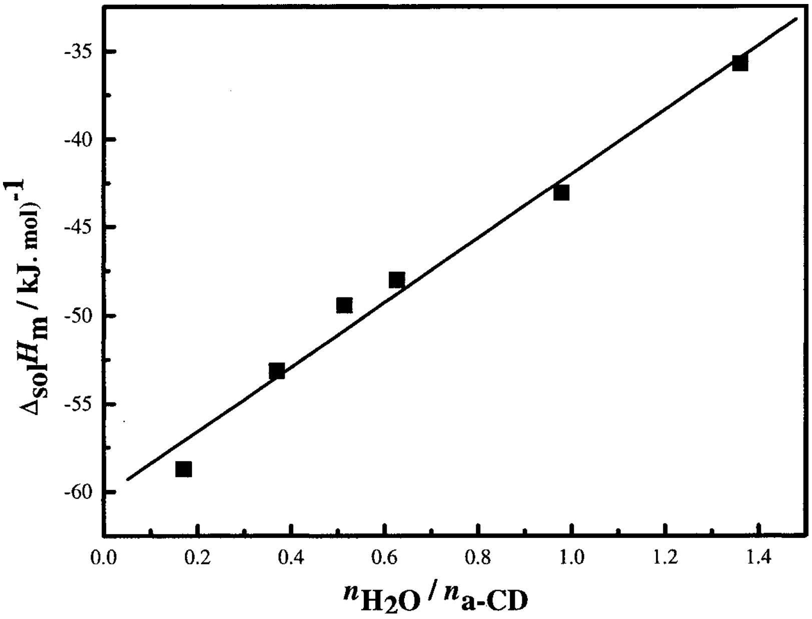

Fig. 4. Enthalpy of solution, $\Delta_{sol}H_m$, of "dry" cyclodextrin in water as a function of the ratio $n_{H_2O}/n_{\alpha\text{-CD}}$.

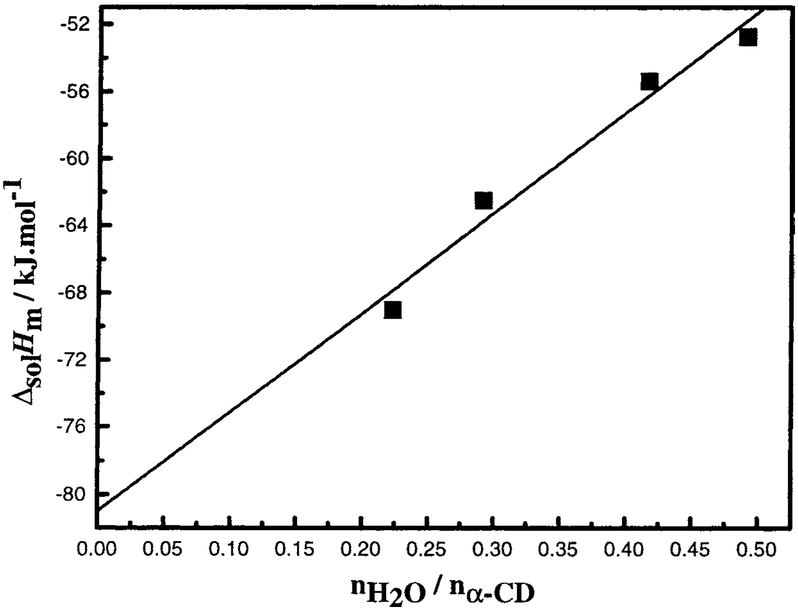

Fig. 5. Enthalpy of solution, $\Delta_{sol}H_m$, of "dry" cyclodextrin in formamide as a function of the ratio $n_{H_2O}/n_{\alpha\text{-CD}}$.

complexes with CD [8,23]. Thus, the dissolution reaction of hydrated CD in a solvent other than water is a complex one, as we have to consider the dissolution process and the solvent competition (as a ligand) for the cyclodextrin cavity. The enthalpy of dissolution of the dry CD, as determined here, is exothermic in both solvents, whereas for the hydrated CD endothermic values were obtained. This indicates that both solvents can complex with the empty cyclodextrin, being the process largely exothermic. The endothermic value obtained for the dissolution of hydrated cyclodextrin in water is then solely the result of the dissolution process, whereas the exothermic value for the dry compound reflects the sum of the two processes, dissolution and complex formation. This justifies the difficulties encountered that led us to modify the experimental procedure, where we changed from using tablets (where the compound is firmly pressed) to using the compound just gently pressed inside the cup, as stated above (see Section 2.3). We did this change as we had observed that it was impossible to dry the CD when it was in tablet form, as it always kept a significant amount of water. For the same reason, it is easy then to understand why it was possible to determine previously the value by macro-calorimetry—in that case the solid is not pressed into tablets, and further, since the size of the sample is much larger, any inhomogeneity in water content is less important, in relative terms.

It is interesting to deduce some important results from these values. From a simple thermodynamic cycle we can obtain the enthalpy change for the formation of the α-CD·6H$_2$O:

$$\begin{tikzcd}
\alpha\text{-CD (dry)} \arrow[rr, "\Delta_{\mathrm{sol}} H_{\mathrm{m}}\ (\mathrm{CD, dry})"] \arrow[dr, "\Delta H\ (\alpha\text{-CD}.\ 6H_2O)"'] & & \alpha\text{-CD (aqueous sol.)} \\
& \alpha\text{-CD}.\ 6H_2O \arrow[ur, "\Delta_{\mathrm{sol}} H_{\mathrm{m}}\ (\alpha\text{-CD}.\ 6H_2O)"'] &
\end{tikzcd}$$

The obtained value is ΔH (CD·6H$_2$O) $= -(91 \pm 1)\,\mathrm{kJ\,mol^{-1}}$, which shows that the enthalpy change for the process of complex formation between water and CD is largely exothermic.

In the case of the dissolution of CD·6H$_2$O in formamide we have to consider several processes simultaneously, namely the dissolution process and the possibility of competition of formamide with water in complex formation. Using the value $\Delta_{\mathrm{sol}}H_{\mathrm{m}} = -(19.7 \pm 0.9)\,\mathrm{kJ\,mol^{-1}}$ for the dissolution of hydrated CD in formamide [20] and the value $\Delta_{\mathrm{sol}}H_{\mathrm{m}} = +(1.17 \pm 0.01)\,\mathrm{kJ\,mol^{-1}}$ for the enthalpy of solution of water in formamide [24], we can construct the thermodynamic cycle:

$$\begin{tikzcd}
\alpha\text{-CD}.\ 6H_2O \arrow[rr, "+91\,\mathrm{kJ\cdot mol^{-1}}"] \arrow[dr, "+19.7\ \mathrm{kJ\cdot mol^{-1}}"'] & & \alpha\text{-CD} + 6\ H_2O \arrow[dl, "\Delta H"'] \arrow[dl, bend left, "6\times 1.17=7.02\ \mathrm{kJ\cdot mol^{-1}}"] \\
& \alpha\text{- CD (in formamide)} + 6\ H_2O\ \text{(in formamide)} &
\end{tikzcd}$$

From this cycle we can obtain the value $\Delta H = -78\,\mathrm{kJ\,mol^{-1}}$, which represents the enthalpy change for the process of transferring dry cyclodextrin to formamide. This value is very similar to the one obtained here for the enthalpy of solution of dry cyclodextrin in formamide, $\Delta_{\mathrm{sol}}H_{\mathrm{m}} = -(81 \pm 3)\,\mathrm{kJ\,mol^{-1}}$. This agreement suggests that formamide can displace the two water molecules, being a stronger ligand, as it is assumed in the cycle that all the water is displaced. Further, the enthalpy of solution of dry cyclodextrin is more negative in formamide than in water, $-(81 \pm 3)$ and $-(60 \pm 1)\,\mathrm{kJ\,mol^{-1}}$, respectively. A similar result was obtained by Danil de Namor et al. [8] for CD in dimethylformamide, namely, $-107\,\mathrm{kJ\,mol^{-1}}$.

The enthalpy of transfer of CD from water to formamide can also be calculated, $\Delta_{\mathrm{trans}}H_{\mathrm{m}} = -21\,\mathrm{kJ\,mol^{-1}}$, showing that the transfer is enthalpically favoured. The obtained value is of the same magnitude of the one obtained by Danil de Namor et al. [8] for the transfer of α-cyclodextrin from water to dimethylformamide, $-44\,\mathrm{kJ\,mol^{-1}}$.

The present work shows that this vessel's performance is as good with an organic solvent as with water. As regarding cyclodextrin, the obtained values allow us to suggest a value for the enthalpy of formation of the aquo-complex, and indicate that formamide is a stronger ligand than water. These results stress the importance of considering the possibility of complex formation with the solvent when performing ligand-binding studies with cyclodextrins in non-aqueous solvents.

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