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DETERMINATION OF ENTHALPIC INTERACTION COEFFICIENTS BY ITC MEASUREMENTS
2-Hydroxypropyl-β-cyclodextrin in aqueous solution of NaCl

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Abstract

Aqueous solutions of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) at different concentrations of NaCl (0–1.90 mol) were studied by isothermal titration calorimetry (ITC) at 298.15 K. The thermal effects obtained were analysed according to the thermodynamic approach developed by McMillan and Mayer. The calculated enthalpic pair coefficients of HP-β-CD in water and in aqueous solutions of NaCl were analysed taking into consideration electrostatic and structural changes caused by the presence of NaCl in solution.

Keywords: cyclodextrins, enthalpic interaction coefficients, isothermal titration calorimetry

Introduction

Cyclodextrins (CDs) are oligosaccharides consisting of glucopyranoside units linked together by α-1,4 bonds to form macrocyclics. The characteristic structure of CDs, such as their toroidal shape, the partially hydrophobic cavity, the hydrophilic outer surface and the possibility to modulate the size of the cavity changing the number of glucopyranoside units, gives these macromolecules the ability to form inclusion complexes with many organic molecules. These properties make CDs useful as tools to generate aqueous drug solutions without the use of organic solvents or other additives which are unsafe for pharmacological applications [1].

It has sometimes been observed that the formation of CDs-drug inclusion complexes produces a decrease of CD solubility. This effect, which limits the use of CDs in solutions, does not occur or decreases if a polymer soluble in water or an electrolyte is present in the solution [2]. Although the formation of CDs inclusion complexes has been widely investigated, the influence of a polymer or an electrolyte on the equilibrium of complexation has not been studied systematically and the use of these additives, often involved in drug formulations, is empiric.

A correct analysis of experimental data resulting from studies on the inclusion complexes formed in the presence of additives requires some preliminary studies on the solutions of CDs. In particular it is interesting to verify which modifications in the structure of aqueous solutions of CDs are induced by the presence of an additive. For this purpose we

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carried out a calorimetric study on the properties of aqueous solutions of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) widely used as excipient, at increasing of NaCl concentration. These calorimetric measurements were carried out following a novel method presented in this paper. The main advantage of this method is that it requires small quantities of substance and can therefore be applied on substances available only in small quantities, for example, compounds extracted from biological systems. The thermal effects obtained were analysed according to the thermodynamic approach developed by McMillan and Mayer [3] and considering NaCl solutions as solvents.

Experimental

Hydroxypropyl-β-cyclodextrin (HP-β-CD – Aldrich) was used as received. The average molar substitution is 0.8 (M_w=1460 g mol^{-1}; *m. p.* 267°C). Since CDs are hygroscopic, the correct concentration value of each stock solution was evaluated by using the procedure reported in literature [4].

NaCl (SigmaUltra) was dried in an oven at about 620 K for 24 h. For each NaCl concentration, a stock solution was prepared (Table 1). These solutions were used as solvents in the preparation of HP-β-CD solutions.

Propanol solution was prepared using 1-propanol with a stated purity >99.5% (Carlo Erba) without further purification.

All solutions were prepared by weight using conductivity water.

The accuracy of the apparatus and method was tested by perfoming dilution experiments in water of a 10 mass% aqueous 1-propanol solution.

The calorimetric measurements were carried out using an LKB 2277 (TAM) microcalorimeter equipped with a Thermometric 2250 titration unit. The calorimetric vessel was charged with 0.9 cm^3 of solvent (water or aqueous solutions of NaCl). The vessel was inserted in the calorimeter and left to equilibrate for 12 h. The samples of HP-β-CD, dissolved in aqueous NaCl solution and the propanol solution were charged into a 250 μL Hamilton syringe connected with a calorimetric vessel using a thin hypodermic needle. The syringe was positioned in a computer operated motor drive (Thermometric's Lund pump). In each series of dilution experiments of propanol solutions and of HP-β-CD solutions 11 injections of 10 μL and 20 injections of 12 μL were made at a rate of 1 μL s^{-1} respectively. The heat output $\Delta H(m_{N-1}\rightarrow m_N)$ per injection was determined by peak integration to time. The thermal effects associated to the friction produced by each injection resulted negligible in all experiments.

The values of the enthalpies were obtained from:

$$\Delta H(m_{N-1}\rightarrow m_N)=\frac{\Delta H(m_{N-1},m_N)}{n_p} \tag{1}$$

where N indicates the number of injection and n_p, the amount of HP-β-CD present in each volume V_{injected} injected was calculated as follows:

$$n_p=V_{\text{injected}}\delta_{\text{solution}}m_0^{\text{I}} \tag{2}$$

Table 1 Experimental values of $\Delta H\,(m_{N-1}\rightarrow m_N)$ of HP-β-CD in water and in aqueous solutions of NaCl as a function of N, m_N and m_{N-1}

m_{NaCl}=0 mol kg^{-1}				m_{NaCl}=0.1844 mol kg^{-1}			
N	m_{N-1}	m_N	$\Delta H\,(m_{N-1}\rightarrow m_N)^a$	N	m_{N-1}	m_N	$\Delta H\,(m_{N-1}\rightarrow m_N)^a$
1	0	0.00345	–1530	1	0	0.00372	–1961
2	0.00345	0.00690	–1474	2	0.00372	0.00745	–1908
3	0.00690	0.0103	–1456	3	0.00745	0.0112	–1831
4	0.0103	0.0138	–1427	4	0.0112	0.0149	–1778
5	0.0138	0.0172	–1388	5	0.0149	0.0186	–1725
6	0.0172	0.0207	–1370	6	0.0186	0.0223	–1701
7	0.0207	0.0241	–1336	7	0.0223	0.0261	–1680
8	0.0241	0.0276	–1331	8	0.0261	0.0298	–1612
9	0.0276	0.0310	–1291	9	0.0298	0.0335	–1580
10	0.0310	0.0345	–1283	10	0.0335	0.0372	–1544
11	0.0345	0.0379	–1206	11	0.0372	0.0410	–1491
12	0.0379	0.0414	–1178	12	0.0410	0.0447	–1443
13	0.0414	0.0448	–1154	13	0.0447	0.0484	–1385
14	0.0448	0.0482	–1125	14	0.0484	0.0521	–1319
15	0.0482	0.0517	–1106	15	0.0521	0.0559	–1234
16	0.0517	0.0552	–1079	16	0.0559	0.0596	–1199
17	0.0552	0.0556	–1034	17	0.0596	0.0632	–1185
18	0.0556	0.0620	–1015	18	0.0632	0.0670	–1103
				19	0.0670	0.0707	–1052
				20	0.0707	0.0745	–1967
				21	0.0745	0.0782	–1926

m_{NaCl}=0.3547 mol kg^{-1}				m_{NaCl}=0.7144 mol kg^{-1}			
N	m_{N-1}	m_N	$\Delta H\,(m_{N-1}\rightarrow m_N)^a$	N	m_{N-1}	m_N	$\Delta H\,(m_{N-1}\rightarrow m_N)^a$
1	0	0.00376	–3471	1	0	0.00369	–4993
2	0.00376	0.00748	–3391	2	0.00369	0.00733	–4850
3	0.00748	0.0111	–3301	3	0.00733	0.0109	–4714
4	0.0111	0.0147	–3237	4	0.0109	0.0145	–4649
5	0.0147	0.0183	–3123	5	0.0145	0.0179	–4559
6	0.0183	0.0218	–3082	6	0.0179	0.0214	–4494
7	0.0218	0.0253	–3032	7	0.0214	0.0248	–4300
8	0.0253	0.0287	–2940	8	0.0248	0.0281	–4295
9	0.0287	0.0321	–2935	9	0.0281	0.0314	–4160
10	0.0321	0.0354	–2872	10	0.0314	0.0347	–4024
11	0.0354	0.0387	–2757	11	0.0347	0.0379	–3905

Table 1 Continued

m_{NaCl}=0.3547 mol kg^{-1}				m_{NaCl}=0.7144 mol kg^{-1}			
N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H\,(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{\mathrm{a}}$	N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H\,(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{\mathrm{a}}$
12	0.0387	0.0420	–2687	12	0.0379	0.0411	–3798
13	0.0420	0.0452	–2576	13	0.0411	0.0442	–3726
14	0.0452	0.0484	–2520	14	0.0442	0.0473	–3583
15	0.0484	0.0515	–2457	15	0.0473	0.0504	–3514
16	0.0515	0.0546	–2396	16	0.0504	0.0534	–3462
17	0.0546	0.0576	–2337	17	0.0534	0.0564	–3429
18	0.0576	0.0606	–2213	18	0.0564	0.0593	–3348
19	0.0606	0.0636	–2149	19	0.0593	0.0622	–3279
20	0.0636	0.0666	–2106	20	0.0622	0.0651	–3173
21	0.0666	0.0695	–2018	21	0.0651	0.0679	–3060

m_{NaCl}=0.9070 mol kg^{-1}				m_{NaCl}=1.1022 mol kg^{-1}			
N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H\,(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{\mathrm{a}}$	N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H\,(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{\mathrm{a}}$
1	0	0.00372	–4954	1	0	0.00375	–5309
2	0.00372	0.00738	–4784	2	0.00375	0.00745	–5047
3	0.00738	0.0110	–4681	3	0.00745	0.0111	–4939
4	0.0110	0.0146	–4627	4	0.0111	0.0147	–4798
5	0.0146	0.0181	–4558	5	0.0147	0.0182	–4736
6	0.0181	0.0215	–4404	6	0.0182	0.0217	–4602
7	0.0215	0.0250	–4354	7	0.0217	0.0252	–4517
8	0.0250	0.0283	–4232	8	0.0252	0.0286	–4358
9	0.0283	0.0317	–4124	9	0.0286	0.0320	–4253
10	0.0317	0.0350	–4011	10	0.0320	0.0353	–4099
11	0.0350	0.0382	–3842	11	0.0353	0.0386	–3940
12	0.0382	0.0414	–3753	12	0.0386	0.0418	–3667
13	0.0414	0.0446	–3594	13	0.0418	0.0450	–3521
14	0.0446	0.0477	–3554	14	0.0450	0.0482	–3398
15	0.0477	0.0508	–3410	15	0.0482	0.0513	–3244
16	0.0508	0.0538	–3273	16	0.0513	0.0543	–3166
17	0.0538	0.0568	–3183	17	0.0543	0.0574	–3031
18	0.0568	0.0598	–3092	18	0.0574	0.0604	–2943
19	0.0598	0.0627	–2997	19	0.0604	0.0633	–2809
20	0.0627	0.0656	–2864	20	0.0633	0.0663	–2667
21	0.0656	0.0684	–2723	21	0.0663	0.0692	–2437

Table 1 Continued

m_{NaCl}=1.2890 mol kg^{-1}				m_{NaCl}=1.5048 mol kg^{-1}			
N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{a}$	N	$m_{\mathrm{N-1}}$	m_{N}	$\Delta H(m_{\mathrm{N-1}}\rightarrow m_{\mathrm{N}})^{a}$
1	0	0.00378	–8246	1	0	0.00373	–9611
2	0.00378	0.00751	–7861	2	0.00373	0.00741	–9480
3	0.00751	0.0112	–7914	3	0.00741	0.0110	–9266
4	0.0112	0.0148	–7751	4	0.0110	0.0146	–9886
5	0.0148	0.0184	–7500	5	0.0146	0.0182	–8499
6	0.0184	0.0219	–7225	6	0.0182	0.0216	–8328
7	0.0219	0.0254	–6975	7	0.0216	0.0251	–8202
8	0.0254	0.0288	–6918	8	0.0251	0.0285	–8000
9	0.0288	0.0322	–6716	9	0.0285	0.0318	–7817
10	0.0322	0.0356	–6625	10	0.0318	0.0351	–7412
11	0.0356	0.0389	–6346	11	0.0351	0.0384	–7096
12	0.0389	0.0422	–6233	12	0.0384	0.0416	–6929
13	0.0422	0.0454	–6058	13	0.0416	0.0448	–6816
14	0.0454	0.0486	–5959	14	0.0448	0.0479	–6660
15	0.0486	0.0517	–5860	15	0.0479	0.0510	–6630
16	0.0517	0.0548	–5450	16	0.0510	0.0540	–6275
17	0.0548	0.0579	–5248	17	0.0540	0.0570	–6229
18	0.0579	0.0609	–5020	18	0.0570	0.0600	–5923
19	0.0609	0.0639	–4975	19	0.0600	0.0630	–5907
20	0.0639	0.0668	–4750	20	0.0630	0.0659	–5702
21	0.0668	0.0697	–4439	21	0.0659	0.0687	–5421

[a] J mol^{-1}

$\delta_{\mathrm{solution}}$ and m_0^{I} are the density and the concentration of the solution located in the syringe respectively; m_0^{I} is expressed as moles of solute in 1 g of solution. The densities of HP-β-CD solutions in water and in NaCl solutions were assumed to be that of pure water and those of binary solutions of NaCl in water calculated using data reported in literature [5]. The density of the 10 mass% aqueous 1-propanol solution was calculated using literature data [6].

The instrument was calibrated electrically.

Theoretical background

According to the thermodynamic treatment developed by McMillan–Mayer the excess enthalpy, $H^{\mathrm{E}}(m_{\mathrm{x}})$, of a solution containing m_{x} moles of the solute x and 1 kg of water is given by the following expression:

$$H^{\mathrm{E}}(m_{\mathrm{x}})=h_{\mathrm{xx}}m_{\mathrm{x}}+h_{\mathrm{xxx}}m_{\mathrm{x}}^{2}\ldots \tag{3}$$

where h_{xx} and h_{xxx} are two coefficients which measure the enthalpic contribute associated to the interactions of a pair and of a triplet of solute molecules. In the case of concentrated solutions it is necessary to consider higher terms in m_x.

The coefficients h_{xx} and h_{xxx} are usually obtained from measurements of enthalpy of dilution, solution or mixing. For the main calorimetric techniques the interaction coefficients are calculated analysing the dependence of the experimental data on m_x by expressions reported in literature [7]. We think that the titration calorimetry, thanks to its high sensitivity and the possibility to carry out sequential measurements using small quantities of substance, is very useful in the determination of interaction coefficients.

The general process of dilution experiment described in the previous section can be schematised as follows.

At the beginning of the experiment the cell is charged with n_c moles of water. The first aliquot of solution that will be injected in the cell contains n_p moles of solute and n_s moles of water. Therefore, the total enthalpy of the initial state has two contributions:

$$\text{initial state} \begin{cases} \text{syringe: } n_p H^{\Phi}(m_0) + n_S H_w^0 \\ \text{cell: } n_c H_W^0 \end{cases}$$

where H_w^0 is the molar enthalpy of pure water and $H^{\Phi}(m_0)$ is the apparent molar enthalpy of the solution at the concentration m_0 that is the concentration of the solution used to fill the syringe. After the first injection the total enthalpy of the final state becomes:

$$\text{final state} \quad \text{cell: } n_p H^{\Phi}(m_1) + n_c H_w^0 + n_s H_w^0$$

where $H^{\Phi}(m_1)$ is the apparent enthalpy of the solution at the concentration m_1 that is the concentration of the solution obtained in the cell after the first injection.

The enthalpic change resulting from the process, $\Delta H(m_0, m_1)$, is given by the difference of the total enthalpy of the final state and that one of the initial state:

$$\begin{aligned} &\Delta H(m_0, m_1) = \\ &n_p H^{\Phi}(m_1) + n_c H_w^0 + n_s H_w^0 - n_p H^{\Phi}(m_0) - n_c H_w^0 - n_s H_w^0 = \\ &n_p [H^{\Phi}(m_1) - H^{\Phi}(m_0)] \end{aligned} \tag{4}$$

The second injection produces a change in the concentration of the solution in the cell from the concentration m_1 to the concentration m_2 and a dilution of the second aliquot of solution injected from the concentration m_0 to the concentration m_2:

$$\text{initial state} \begin{cases} \text{syringe: } n_p H^{\Phi}(m_0) + n_S H_w^0 \\ \text{cell: } n_p H^{\Phi}(m_1) + n_c H_w^0 + n_s H_w^0 \end{cases}$$

$$\text{final state} \quad \text{cell: } 2n_p H^{\Phi}(m_2) + n_c H_w^0 + n_s H_w^0 + n_s H_w^0$$

where $H^{\Phi}(m_2)$ indicates the apparent enthalpy of the solution at the concentration m_2 that is the concentration of the solution obtained in the cell after the second injection.

The enthalpic change associated to the second injection, $\Delta H(m_1,m_2)$, has the following expression:

$$\begin{aligned}&\Delta H(m_1,m_2)=\\&2n_\mathrm{p}H^\Phi(m_2)+n_\mathrm{c}H^0_\mathrm{w}+2n_\mathrm{s}H^0_\mathrm{w}-n_\mathrm{p}H^\Phi(m_1)-n_\mathrm{c}H^0_\mathrm{w}-2n_\mathrm{s}H^0_\mathrm{w}-n_\mathrm{p}H^\Phi(m_0)=\\&n_\mathrm{p}[2H^\Phi(m_2)-H^\Phi(m_1)-H^\Phi(m_0)]\end{aligned} \tag{5}$$

The N^th injection produces a change in the concentration of the solution in the cell from the concentration $m_{\mathrm{N}-1}$ to the concentration m_N and a dilution of the N aliquot of solution injected from the concentration m_0 to the concentration m_N:

$$\text{initial state}\begin{cases}\text{syringe: } n_\mathrm{p}H^\Phi(m_0)+n_\mathrm{S}H^0_\mathrm{w}\\ \text{cell: } (N-1)n_\mathrm{p}H^\Phi(m_{\mathrm{N}-1})+n_\mathrm{c}H^0_\mathrm{w}+(N-1)n_\mathrm{s}H^0_\mathrm{w}\end{cases}$$

$$\text{final state}\quad \text{cell: } Nn_\mathrm{p}H^\Phi(m_\mathrm{N})+n_\mathrm{c}H^0_\mathrm{w}+Nn_\mathrm{s}H^0_\mathrm{w}$$

where $H^\Phi(m_\mathrm{N})$ and $H^\Phi(m_{\mathrm{N}-1})$ indicates the apparent enthalpy of the solution at the concentration m_N and $m_{\mathrm{N}-1}$, respectively.

The enthalpic change associated to the N^th injection, $\Delta H(m_{\mathrm{N}-1}, m_\mathrm{N})$ is expressed by:

$$\begin{aligned}&\Delta H(m_{\mathrm{N}-1},m_\mathrm{N})=\\&Nn_\mathrm{p}H^\Phi(m_\mathrm{N})+n_\mathrm{c}H^0_\mathrm{w}+Nn_\mathrm{s}H^0_\mathrm{w}-(N-1)n_\mathrm{p}H^\Phi(m_{\mathrm{N}-1})-n_\mathrm{c}H^0_\mathrm{w}-Nn_\mathrm{s}H^0_\mathrm{w}-n_\mathrm{p}H^\Phi(m_0)=\\&n_\mathrm{p}[NH^\Phi(m_\mathrm{N})-(N-1)H^\Phi(m_{\mathrm{N}-1})-H^\Phi(m_0)]\end{aligned} \tag{6}$$

which can be rewritten as:

$$\begin{aligned}&\Delta H(m_{\mathrm{N}-1}\to m_\mathrm{N})=\frac{\Delta H(m_{\mathrm{N}-1},m_\mathrm{N})}{n_\mathrm{p}}=\\&(N-1)\lfloor H^\Phi(m_\mathrm{N})-H^\Phi(m_{\mathrm{N}-1})\rfloor+\lfloor H^\Phi(m_\mathrm{N})-H^\Phi(m_0)\rfloor\end{aligned} \tag{7}$$

where the two terms $[H^\Phi(m_\mathrm{N})-H^\Phi(m_{\mathrm{N}-1})]$ and $[H^\Phi(m_\mathrm{N})-H^\Phi(m_0)]$ indicate the change of the enthalpy associated with an increase of the concentration of the solution, from $m_{\mathrm{N}-1}$ to m_N, and that one associated to a decrease of the concentration of the solution, from m_0 to m_N, respectively.

According to the definitions of apparent and excess quantity it is possible to do the following substitution:

$$H^\Phi(m_\mathrm{N})-H^\Phi(m_{\mathrm{N}-1})=H^\mathrm{E}(m_\mathrm{N})-H^\mathrm{E}(m_{\mathrm{N}-1}) \tag{8}$$

$$H^\Phi(m_\mathrm{N})-H^\Phi(m_0)=H^\mathrm{E}(m_\mathrm{N})-H^\mathrm{E}(m_0) \tag{9}$$

which allows to introduce Eq. (1) in Eq. (7) and finally to obtain the following equation:

$$\Delta H(m_{N-1}\rightarrow m_N)=(N-1)\lfloor h_{xx}(m_N-m_{N-1})+h_{xxx}(m_N^2-m_{N-1}^2)\rfloor+ \\ h_{xx}(m_N-m_0+h_{xxx}(m_N^2-m_0^2) \quad (10)$$

which relates the experimental thermal effects with the concentrations m_N, m_{N-1} and m_0 by means of the enthalpic coefficients h_{xx} and h_{xxx} and can be used to calculate the values of these coefficients.

When the volume of the solution injected into the vessel is much smaller than the volume of solution already present in the cell and the density of all solutions involved is almost unitary it is possible to do the following approximations:

$$m_N=Nm_1 \quad (11)$$

$$m_{N-1}=m_1(N-1) \quad (12)$$

which make the dependence of $\Delta H(m_{N-1}\rightarrow m_N)$ on the concentration of the solutions simplified and hence the analysis of experimental data easier.

The equation obtained:

$$\Delta H(m_{N-1}\rightarrow m_N)=h_{xx}[m_1(2N-1)-m_0]+h_{xxx}\{m_1^2[1+3N(N-1)]-m_0^2\} \quad (13)$$

can be further simplified if $m_1<<1$. In that case we obtain that $\Delta H(m_{N-1}\rightarrow m_N)$ depends linearly on N:

$$\Delta H(m_{N-1}\rightarrow m_N)=2h_{xx}m_1N-[h_{xx}(m_1+m_0)+h_{xxx}m_0^2] \quad (14)$$

The values of the intercept and of the slope obtained from the linear regression of experimental $\Delta H(m_{N-1}\rightarrow m_N)$ *vs.* N allow to calculate h_{xx} and h_{xxx}:

$$h_{xx}=\frac{\text{slope}}{2m_1} \quad (15)$$

$$h_{xxx}=-\frac{\text{intercept}+\dfrac{\text{slope}}{2m_1}(m_1+m_0)}{m_0^2} \quad (16)$$

Results and discussion

The accuracy of the apparatus and method was tested by performing dilution experiments in water of a 10 mass% aqueous 1-propanol solution as suggested in literature [8]. Experimental $\Delta H(m_{N-1}\rightarrow m_N)$ of 5 replicates have an average deviation of 0.8% from $\Delta H(m_{N-1}\rightarrow m_N)$ calculated introducing h_{xx}= 558 J kg mol^{-2} and h_{xxx}= 158 J mol^{-1}(mol kg^{-1})$^{-2}$ [9] in Eq. (10).

As an example, experimental and calculated $\Delta H(m_{N-1}\rightarrow m_N)$ of a dilution experiment are plotted in Fig. 1 as a function of m_N. They show a linear dependence on m_N. The linear regression all set of data were used to calculate, by extrapolation to m_N=0, $\Delta_{dil}H_m^{\infty}$, the enthalpy of dilution at infinite dilution. The experimental $\Delta_{dil}H_m^{\infty}=-1588\pm11$ J mol^{-1} differs slightly from $\Delta_{dil}H_m^{\infty}=-1628\pm12$ J mol^{-1} reported by Olofsson *et al.* [9]. A better

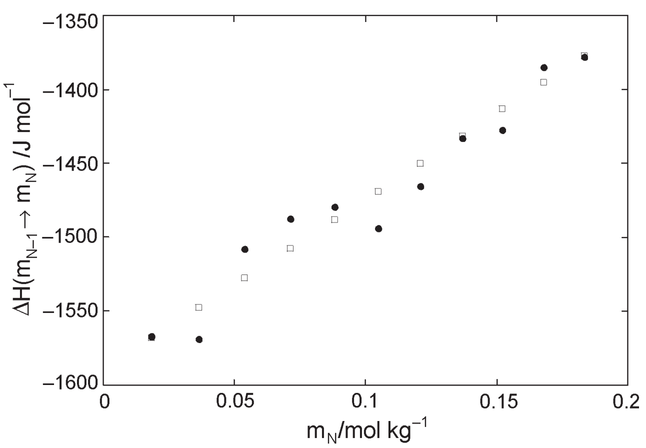

Fig. 1 Experimental (•) and calculated (□) $\Delta H(m_{N-1}\rightarrow m_N)$ of a 10 mass% aqueous 1-propanol solution

agreement is observed between our data and $\Delta_{\text{dil}}H_{\text{m}}^{\infty}=-1572\pm44$ J mol^{-1} and $\Delta_{\text{dil}}H_{\text{m}}^{\infty}=-1557\pm20$ J mol^{-1} calculated by Franks *et al.* [10] and Briggner and Wadsö [8] data respectively.

The experimental values of $\Delta H(m_{N-1}\rightarrow m_N)$ as a function of N, m_N and m_{N-1} obtained from HP-β-CD dilution experiments are reported in Table 1. For each of the studied system $\Delta H(m_{N-1}\rightarrow m_N)$ is negative and depends linearly on N. As an example we report in Fig. 2 the plot regarding a solution of HP-β-CD at an intermediate NaCl concentration 0.9070 mol kg^{-1}. The linear dependence observed is in agreement with the one expected according to Eq. (14). The slopes and intercepts obtained by the linear regression of experimental data were used to calculate h_{xx} and h_{xxx} from Eqs (15) and (16). The enthalpic pair and triplet interaction coefficients of HP-β-CD in water and in aqueous solutions of NaCl are reported in Table 2.

Table 2 Enthalpic pair and triplet interaction coefficients of HP-β-CD in water and in aqueous solutions of NaCl

m_{NaCl}/mol kg^{-1}	h_{xx}/kJ kg mol^{-2}	h_{xxx}/kJ kg^2 mol^{-3}
0.000	4.31±0.10	–2.22±0.19
0.1844	6.75±0.14	–5.7±0.2
0.3547	9.51±0.15	–5.7±0.2
0.7144	12.9±0.3	–6.7±0.5
0.9070	14.8±0.2	–10.1±0.4
1.1022	18.9±0.3	–16.6±0.5
1.2890	24.1±0.5	–17.2±0.7
1.5048	27.9±0.8	–18.6±1.4

The values of h_{xx} and of h_{xxx} in water are positive and negative respectively in agreement with results obtained by De Lisi *et al.* [11]. The difference between the values reported here (h_{xx}=4.31 kJ kg mol^{-1} and h_{xxx}=–2.22 kJ kg^2 mol^{-2}) using HP-β-CD with an average molar substitution 0.80 and those obtained by De Lisi *et al.* (h_{xx}=11.32 kJ kg mol^{-1} and h_{xxx}=–14.0 kJ kg^2 mol^{-2} using HP-β-CD with an average molar substitution 0.43 may be ascribed to the difference in the average molar substitution for each glucopyranose. In fact, it is known that the functionalisation of one or more primary and secondary OH groups strongly modifies the physicochemical properties of CD since it modifies the number of intra and inter molecular H bonds and can introduce new hydrophobic interactions [2].

The enthalpic pairwise coefficients in aqueous solutions are related to the change in the enthalpy of the solution that occurs when two hydrated molecules are brought from an infinite to a finite distance [12]. At infinite distance solute molecules interact only with the solvent being each solute molecule surrounded by solvent molecules which constitute the shell of hydratation. At finite distance two hydrated solute molecules approach each other and interact. It does not indicate that molecules necessarily come into contact [13]. Therefore, the enthalpic interaction coefficient is the result of different effects of electrostatic nature and changes in the overall structure such as the partial desolvation of the solutes and the reorganization of the solvent. The enthalpic contribute of each of these terms and, consequently, the overall effect depends on the structure of the molecule considered (shape, size, polarity, presence of particular moieties).

Wood *et al.* [14] carried out a systematic study of the dependence of experimental h_{xx} values on the molecular structure and developed an additivity principle which provides useful information to understand the interaction process between solute molecules. Unfortunately, the Savage and Wood principle cannot be used for a quantitative evalutation of h_{xx} of HP-β-CD in water, since the formation of intra molecular H bonds makes the principle not valid [14].

The enthalpic pair coefficients of HP-β-CD in aqueous solutions of NaCl are all positive as well as that one in water. This indicates that the presence of NaCl does not produce changes in the kind of interactions involved even though it modifies the mass of

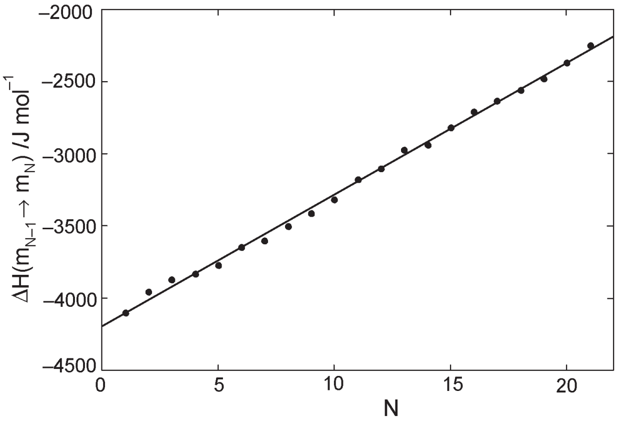

Fig. 2 Experimental values of $\Delta H\,(m_{N-1}\rightarrow m_N)$ of HP-β-CD in aqueous solutions of NaCl 0.9070 mol kg^{-1} as a function of N

each of them. In addition, the experimental h_{xx} shows a linear dependence on the molality of NaCl as shown in Fig 3. A similar trend was reported by Castronuovo *et al.* [15] for α-CD at pH 11.3: h_{xx} increases at increasing of the phosphate buffer concentration.

At the best of our knowledge, in literature the effect produced by the addition of an electrolyte on the interactions between two molecules of a non-electrolyte has not been extensively studied. Studies on the interactions between alkali metal halides and small molecules [16, 17] were carried out in different experimental conditions and provide the coefficients h_{xy} associated to the interaction of a non-electrolyte x with an electrolyte y and not the effect produced by the presence of the electrolyte on h_{xx}. In contrast to what regards electrolytes, the homotattic coefficients of amino acids in the presence of non-electrolytes have been the objects of study. In the case of glycine [12, 18] it was observed that h_{xx} decreases by increasing the concentration of ethanol and increases at increasing concentration of urea. A similar behaviour was observed for leucin [12]: h_{xx} increases and decreases at increasing of urea and ethanol concentration, respectively. The observed behaviours can be partially explained considering the changes of the dielectric properties of the solvent induced by the presence of additives [19]. The addition of urea, as well as the addition of NaCl, produces an increase of the dielectric constant of the medium which reduces the electrostatic interactions between solute molecules in solution. This gives rise to a decrease of negative H_{ij} contributions which are usually which an usually associated to electrostatic interaction. On the contrary, the addition of ethanol produces a decrease of the dielectric constant of the solvent and leads to an increase of electrostatic interactions.

In addition to electrostatic effects it is also necessary to take into consideration the ability of additives of changing the structure of water and, consequently, the above-named structural effects [12, 18, 19]. In particular in the water-rich regions ethanol has kosmotropic properties and it is a water structure maker whereas urea and NaCl have chaotropic properties and they are water structure breakers [20]. It means that water molecules in solution of urea or NaCl are less structured and, conse-

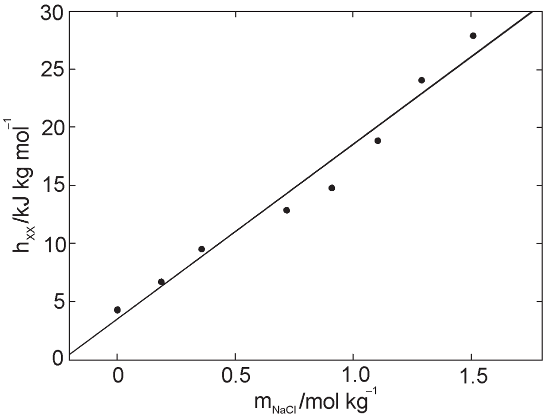

Fig. 3 Enthalpic pair interaction coefficients of HP-β-CD in aqueous solutions of NaCl as a function of NaCl molality

quently, have a lower enthalpic contribution than in pure water or in ethanol water. The release of water molecules upon the interaction of two solute molecules from the hydration cosphere to a less structured solvent produces a higher enthalpic change than in pure water.

The interaction coefficients of triplet h_{xxx} are opposite in sign to the corresponding pair term as observed for the most of the systems reported in literature. The values of h_{xxx} are of difficult interpretation and their dependence on the molecular structure have never been the object of systematic analysis like that performed by Savage and Wood.

Conclusions

The enthalpic interaction coefficients of HP-β-CD in aqueous solutions at increasing NaCl concentration were evaluated by calorimetric measurements performed using isothermal titration calorimetry.

The enthalpic pair and triplet coefficients HP-β-CD in water and in aqueous solutions of NaCl are positive and negative, respectively. In particular, the enthalpic pair coefficients increase at increasing NaCl concentration. This trend has been explained taking into account the increase of the dielectric constant and changes in the structure of the solvent produced by the presence of NaCl.

References

1 T. Loftsson and M. E. Brewster, J. Pharm. Sci., 85 (1996) 1017.
2 U. Uekama, F. Hirayama and T. Irie, Chem. Rev., 98 (1998) 2045.
3 W. McMillan and J. Mayer, J. Phys. Chem., 13 (1945) 176.
4 R. De Lisi, A. Inglese, S. Milioto and A. Pellerito, Langmuir, 14 (1998) 6045.
5 J. F. Millero, J. Phys. Chem., 74 (1970) 356.
6 C. Dethlefsen, P. G. Søresen and A. Hviott, J. Solution Chem., 13 (1984) 191.
7 J. E. Desnoyers, G. Peròn, L. Avédikian and J. P. Morel, J. Solution Chem., 5 (1976) 631.
8 L. E. Briggner and I. Wadsö, J. Biochem. Biophys. Methods, 22 (1991) 101.
9 G. Olofsson, D. Berling, N. Markova and M. Molund, Thermochim. Acta, 347 (2000) 31.
10 F. Franks, M. Pedley and D. S. Reid, J. Chem. Soc., Faraday Trans. 1, 72 (1976) 359.
11 R. De Lisi, S. Milioto and N. Muratore, Langmuir, 16 (2000) 4441.
12 G. Castronuovo, V. Elia, C. Postiglione and F. Velleca, Thermochim. Acta, 339 (1999) 11.
13 C. de Visser, G. Perron and J. E. Desnoyers, J. Am. Chem. Soc., 99 (1977) 5894.
14 R. H. Wood and L. H. Hiltzik, J. Solution Chem., 9 (1980) 45.
15 G. Castronuovo, V. Elia, A. Iannone, M. Niccoli and F. Velleca, Carbohydr. Res., 325 (2000) 278.
16 Lu Yan, Bai Tongchun, Xie Wei and Lu Jinsuo, Thermochim. Acta, 319 (1998) 11.
17 Lu Yan, Cheng Qingtang, Chen Yanbin, Bai Tongchun and Lu Jinsuo, Thermochim. Acta, 334 (1999) 29.
18 Li Shuqin, Hu Xingen, Lin Ruisen and Zong Hanxing, Thermochim. Acta, 342 (1999) 1.
19 Shao Shuang, Hu Xingen and Lin Ruisen, Thermochim. Acta, 604 (2000) 93.
20 K. D. Collins and M. W. Washbaugh, Quarterly Review of Biophysics, 18 (1985) 342.