J Therm Anal Calorim (2011) 103:641–646
DOI 10.1007/s10973-010-0965-8

Solvent effects on the complexation of 1-alkanols by parent and modified cyclodextrins. Calorimetric studies at 298 K

Giuseppina Castronuovo · Marcella Niccoli

Received: 14 May 2010 / Accepted: 9 July 2010 / Published online: 24 July 2010

Abstract The formation of complexes of parent and alkylated cyclodextrins (CDs) with 1-heptanol and 1-octanol has been studied calorimetrically at 298 K in water and in concentrated aqueous solutions of urea. The forces involved in the association process are discussed in the light of the signs and values of the thermodynamic parameters obtained: association enthalpy, binding constant, Gibbs free energy, and entropy. It was inferred that: (i) in water, the formation of complexes for parent and substituted *α*-cyclodextrins (*α*CDs) is determined by enthalpy. For parent and substituted *β*-cyclodextrins (*β*CDs), instead, hydrophobic interactions are the prevailing forces determining complexation, as indicated by the small and negative or positive enthalpies and by the high and positive entropies. (ii) In urea, hydrophilic interactions are attenuated. The formation of complexes with alkylated CDs does not occur. (iii) The analysis of the thermodynamic properties confirms that inclusion is a process dominated by hydration phenomena. Modifications experienced by the solvent water in the hydration shells of the interacting substances upon association determine the formation of the complexes.

Keywords Isothermal calorimetry · Cyclodextrins · 1-heptanol · 1-octanol · Inclusion complexes

Introduction

Natural cyclodextrins (CDs), cyclic oligomers of α-D-glucose, are the most suitable host molecules for the recognition in aqueous media of hydrophobic guest molecules. They are characterized by a fairly polar exterior and by a cavity which is nonpolar relative to the exterior and to the external aqueous environment. CDs are able to form complexes with a great variety of organic substances either in the solution or in the solid state [1–6]. Complexation is determined by a series of noncovalent intermolecular forces: hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, and dipole–dipole and ion–dipole interactions [1, 7–11]. In addition, another important effect determines inclusion: the rearrangement of water molecules originally surrounding both CD and guest molecule [12, 13].

Complexation induces changes in the physicochemical properties of the included substances: for instance, the aqueous solubility, stability, and bioavailability of apolar drugs are enhanced. CDs, especially their alkylated derivatives, provide versatile carrier and delivery systems for drug molecules [14–20]. The only obvious implication is that undesired biological effects (for example, hemolysis) of the employed CD derivative in solution should be eliminated or minimized. Indeed, the possibility to modify the forces acting in these inclusion processes by changes in the structure can be useful when designing new CDs derivatives with more suitable characteristics to include specific drugs.

Notwithstanding the extensive studies about the complexes of CDs, it is still a matter of debate which of the aforementioned contributions is responsible for the overall Gibbs energy of association. In preceding articles from this laboratory, efforts were made to understand the factors

G. Castronuovo (✉) · M. Niccoli
Department of Chemistry, University Federico II of Naples,
Complesso Universitario Monte S. Angelo, via Cintia,
80126 Naples, Italy
e-mail: giuseppina.castronuovo@unina.it

determining the formation of the complexes between CDs and alkylated substances, in water and in mixed solvents [21–27]. The thermodynamics of the interaction with substances of pharmacological interest under different experimental conditions was also studied [28]. To relate the properties of the binary solutions with the inclusion requirements in the host–guest complexes, binary solutions of parent and chemically modified CDs were investigated in different experimental conditions [29]. The present contribution, aimed to further explore the factors determining the formation of the complexes, deals with the interaction of 1-heptanol and 1-octanol with α-cyclodextrin (αCD), methyl-α-cyclodextrin (MαCD), 2-hydroxypropyl-α-cyclodextrin (HPαCD), β-cyclodextrin (βCD), methyl-β-cyclodextrin (MβCD), 2-hydroxypropyl-β-cyclodextrin (HPβCD) in water and in concentrated aqueous urea solutions. The association process was followed through isothermal microcalorimetry at 298 K. Knowledge of the values and signs of the thermodynamic parameters obtained—association enthalpy, binding constant, Gibbs energy, and entropy—makes it possible to propose hypotheses about the forces determining the interaction between CDs and the examined guest molecules.

Experimental

Materials

Cyclodextrins employed were purchased from Cyclolab, with the exception of αCD and βCD which were Sigma products. All substances were of the highest commercially available purity (98–99.5% minimum). For MβCD and HPβCD, the mean substitution degree is 11 and 4.5, respectively, as determined by NMR. For MβCD and HPβCD the mean substitution degree (DS) is 12 and 6.3, respectively, as determined by the same technique. All CDs were dried on phosphorus pentoxide under reduced pressure. Solutions were prepared by weight: water was twice distilled and filtered on a Millipore membrane.

Calorimetry

Measurements of the heats of mixing, ΔH_{mix}, of solutions of the CD (titrant) with solutions of 1-heptanol (titrate) or octanol were made at 298.15 ± 0.01 K with a thermal activity monitor (TAM) from Thermometric, equipped with a 3-mL titration vessel. Experimental details are described in preceding articles [27, 28]. Approximately, 30 injections (50 μL each) were made in each experiment, and at least two experiments were performed for each reaction. The estimated uncertainties are 1% in the molalities and 2% in the heat effects. Enthalpies of dilution of the titrant were determined, using the same number of injections and concentrations as in the titration experiments, and were subtracted from the enthalpies of mixing the reactants. The dilution of the titrate in the cell was assumed negligible.

Treatment of the data

Assuming that a 1:1 complex is formed when mixing two binary solutions, the standard molar enthalpy of association, $\Delta H_{\mathrm{a}}^{\circ}$, and the apparent association constant, K_{a}', are related to the actual molality of the CD host molecule, $m_{\mathrm{CD}}^{\mathrm{f}}$, and to the enthalpy of formation of a complex, or in general the enthalpy of interaction between solutes, ΔH^{*}, as follows [30]:

$$\Delta H^{*}/m_{\mathrm{L}} = \left(\Delta H_{\mathrm{a}}^{\circ\prime} K_{\mathrm{a}}' m_{\mathrm{CD}}^{\mathrm{f}}\right)/\left(1 + K_{\mathrm{a}}' m_{\mathrm{CD}}^{\mathrm{f}}\right) \tag{1}$$

ΔH^{*} is normalized to the total molality of the guest, m_{L}. Equation 1 can be rewritten in a linear form, more useful for fitting the data:

$$m_{\mathrm{L}}/\Delta H^{*} = 1/\Delta H_{\mathrm{a}}^{\circ\prime} + 1/\left(\Delta H_{\mathrm{a}}^{\circ\prime} K_{\mathrm{a}}' m_{\mathrm{CD}}^{\mathrm{f}}\right) \tag{2}$$

where the actual concentration of the guest molecule is given by:

$$m_{L}^{f} = m_{L} - [\Delta H^{*}/\Delta H^{*}(sat)]m_{CD} \tag{3}$$

The standard enthalpy and the association constant are obtained from Eqs. 2 and 3 by an iterative least square method, according to the procedure reported previously [27, 28]. In the absence of any information about the activity coefficients, only an apparent constant, K_{a}', can be determined. Consequently, the standard Gibbs energy and entropy, $\Delta G_{\mathrm{a}}^{\circ\prime}$ and $S_{\mathrm{a}}^{\circ\prime}$, obtained through the usual thermodynamic relations, suffer the same limitations.

Results

The thermodynamic association parameters for the interaction of the various parent and modified CDs with heptanol and octanol were determined at 298 K in water and in concentrated aqueous urea solutions. In the tables, the notation NA (No Association) is used to indicate that association does not occur, either because the heat of association is very small or because the solubility of the interacting substances is scarce, so that the corresponding thermal effect cannot be detected.

In Table 1, association constant, enthalpy, Gibbs energy, and entropy are reported for the interaction of 1-heptanol with parent and methyl-or hydroxypropyl-modified CDs, in water and in 7 mol kg^{-1} urea. For parent αCD and βCD, the formation of the complex is an exothermic process in both solvent media. However, in water,

Table 1 Association parameters for parent and substituted α and β cyclodextrins interacting with heptanol at 298 K, in water and in 7 mol kg^{-1} urea

Cyclodextrin	Solvent	ΔH°_{a} [a] /kJ mol^{-1}	K'_{a} [a] /kg mol^{-1}	$-\Delta G^{\circ\prime}_{a}$ [b] /kJ mol^{-1}	$T\Delta S^{\circ\prime}_{a}$ [c] /kJ mol^{-1}
α-CD	H_2O	−20.6 ± 0.8	(3.8 ± 0.2)10^2	14.7 ± 0.1	−5.9 ± 0.9
Methyl-α-CD (DS 11)	H_2O	−13.5 ± 0.5	(3.9 ± 0.5)10^2	14.8 ± 0.3	1.3 ± 0.8
2-hydroxypropyl-α-CD (DS 4.5)	H_2O	−8.7 ± 0.3	(4.5 ± 0.6)10^2	15.1 ± 0.3	6.4 ± 0.6
α-CD	Urea	−14.5 ± 0.1	(2.62 ± 0.04)10^2	13.8 ± 0.1	−0.7 ± 0.2
Methyl-α-CD	Urea	−9.2 ± 0.8	(4.4 ± 0.5)10	9.4 ± 0.3	0 ± 1
2-hydroxypropyl-α-CD	Urea	NA	–	–	–
β-CD	H_2O	−0.41 ± 0.04	(1.1 ± 0.3)10^3	17.4 ± 0.6	16.9 ± 0.7
Methyl-β-CD (DS 12)	H_2O	10.5 ± 0.3	(1.7 ± 0.1)10^2	12.7 ± 0.2	23.2 ± 0.5
2-hydroxypropyl-β-CD (DS 3)	H_2O	5.1 ± 0.4	(3.4 ± 0.5)10^2	14.5 ± 0.3	19.6 ± 0.7
2-hydroxypropyl-β-CD (DS 6.3)	H_2O	2.0 ± 0.2	(2.5 ± 0.5)10^2	13.7 ± 0.5	15.7 ± 0.7
β-CD	Urea	−3.8 ± 0.2	(5.1 ± 0.7)10^2	15.4 ± 0.3	11.7 ± 0.5
Methyl-β-CD	Urea	NA	–	–	–
2-hydroxypropyl-β-CD (DS 3)	Urea	NA	–	–	–

[a] Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3

[b] Errors are half the range of $\Delta G^{\circ\prime}_{a}$ calculated from the upper and lower error in K'_{a}

[c] Errors are the sum of the errors on free energy and enthalpy

enthalpy is very small for the wider βCD. The same occurs for the alkyl-substituted αCDs, with the exception of HPαCD, which does not form the complex in urea. For the substituted βCDs, association enthalpies in water are positive, while in urea no association is detected for both derivatives. Association entropies are negative only for the unsubstituted αCD, positive in all other cases, very large for parent and modified βCDs. Association constants are about $10^{2,}$ with the exception of MαCD in urea. The null contribution of entropy and the diminished favorable enthalpic contribution determine the smaller value of the constant.

In Table 2, the above-cited association parameters are reported for the interaction of the same CDs with 1-octanol. The overall thermodynamic framework is similar to that for 1-heptanol. In general, association constants are smaller, for an increased unfavorable enthalpic term, notwithstanding the large and positive entropies.

Discussion

According to the commonly accepted view, complexation of a CD with an alkylated guest molecule occurs through

Table 2 Association parameters for parent and substituted α and β CDs interacting with octanol at 298 K, in water and in 7 mol kg^{-1} urea

Cyclodextrin	Solvent	ΔH°_{a} [a] /kJ mol^{-1}	K'_{a} [a] /kg mol^{-1}	$-\Delta G^{\circ\prime}_{a}$ [b] /kJ mol^{-1}	$T\Delta S^{\circ\prime}_{a}$ [c] /kJ mol^{-1}
α-CD	H_2O	−22 ± 1	(2.2 ± 0.3) 10^2	13.4 ± 0.3	-9 ± 2
Methyl-α-CD (DS 11)	H_2O	−10.6 ± 0,7	(9 ± 3)10^3	16.8 ± 0,7	−6 ± 1
2-hydroxypropyl-α-CD (DS 4.5)	H_2O	−6,2 ± 0,2	(4 ± 2)10^3	21 ± 1	15 ± 1
α-CD	Urea	−12.9 ± 0.4	(8 ± 1) 10^2	16.6 ± 0.3	3.7 ± 0.7
Methyl-α-CD	Urea	NA	–	–	–
2-hydroxypropyl-α-CD	Urea	23 ± 6	27 ± 8	8.2 ± 0.8	31 ± 7
β-CD	H_2O	−1.19 ± 0.03	(3,1 ± 0,4)10^3	19.9 ± 0.3	18.7 ± 0.4
Methyl-β-CD (DS 12)	H_2O	4.8 ± 0.5	65 ± 9	10.3 ± 0.5	15.1 ± 0.8
2-hydroxypropyl-β-CD (DS 3)	H_2O	9 ± 0.5	58 ± 4	10.1 ± 0.2	19.1 ± 0.7
β-CD	Urea	−4.6 ± 0.3	(8.8 ± 1.3) 10^2	16.8 ± 0.4	12.2 ± 0.7
Methyl-β-CD	Urea	NA	–	–	–
2-hydroxypropyl-β-CD	Urea	NA	–	–	–

[a] Errors reported are the standard deviations as obtained by fitting the data to Eqs. 2 and 3

[b] Errors are half the range of $\Delta G^{\circ\prime}_{a}$ calculated from the upper and lower error in K'_{a}

[c] Errors are the sum of the errors on free energy and enthalpy

the inclusion of the alkyl chain into the prevailingly hydrophobic cavity. The functional group forms hydrogen bonds with the external hydroxyl groups on the rim of the macrocycle cavity, acting as a hook which prevents the further penetration of the alkyl chain [22, 27]. In general, the charged and hydrophilic functional groups of the guests, with the exception of the phenolic hydroxyl group, can be assumed to remain in the bulk solution before and after the association with the CD.

The present data, relative to the interaction between CDs and alkanols, show that association occurs through the same mechanism. In the modified macrocycles, however, the presence of the external alkyl groups causes the balance of the forces upon association to be different from that acting when natural CDs are involved. As a fact, enthalpies are negative for association processes involving parent CDs and modified αCDs, while they are positive when an alkylated *β*CD is the host molecule. Entropies are positive, with the exception of those relative to the complexation of heptanol by parent αCD in both solvents, and of octanol by αCD and MαCD. Upon inclusion, water molecules relax from an ordered microenvironment, namely, the cavity, and from the ordered hydrophobic hydration shells of the guest to a more disordered bulk. For the alkylated CDs, a further process must be considered: the relaxation of water molecules upon the interaction of the alkylated guest molecule with the hydrophobic exterior of the macrocycle.

Table 1 shows that modified and parent αCDs have almost the same binding constant for the association with heptanol, because of the balance between different enthalpic and entropic contributions. For instance, the constant for αCD and MαCD in water is quite the same, as determined by very different enthalpic contributions (-20.6 and -13.5 kJ mol^{-1}, respectively), and by entropic contributions opposite in sign. The smaller value of enthalpy for MαCD and 2-HPαCD, as respect to parent αCD, is due to the increased positive contribution of hydrophobic interactions caused by the substitution of hydroxyl groups with alkyl groups. In urea, the increased dielectric constant of the medium makes hydrophilic interactions to be attenuated, with the consequent attenuation of hydrophobic interactions, too. That is detected by a less negative enthalpy and by an almost null value of entropy. Hence, the value of the constant for MαCD is very small and the complex with 2-HPαCD does not form. For *β*CDs, the values of the constants slightly decrease because association enthalpies are positive, or small and negative. However, that unfavorable contribution is more than balanced by the high and positive entropies. The *β*CD cavity is rather large toward the inclusion of an alkyl chain that needs to be dehydrated only partially to be included. The last contribution is small, so that the entropic term should be mainly determined by the relaxation of water molecules from the cavity to the bulk.

For octanol, the thermodynamic framework is similar to that shown by heptanol. The substituted CDs in urea do not form complexes, probably for the increasingly positive enthalpic term. Only in the case of 2-HPαCD the constant has been determined. However, its very small value indicates the formation of a very weak complex. Moreover, the almost linear trend makes the asymptote value not well determined, as evidenced by the large error on the enthalpy.

Preceding studies concerning the interaction of alkylated substances with αCD led to the hypothesis that for alkyl chains longer than C_6–C_7, because of their flexibility, two adducts could form simultaneously having the included alkyl residue in a bent or in an extended form, whose concentration ratios depend on the alkyl chain length [31]. For alkyl chains shorter than six or longer than nine carbon atoms, only one adduct is present, in the extended or bent form, respectively, while for intermediate alkyl chains, both adducts are present. The whole thermodynamic framework concerning heptanol and octanol does not unravel any anomalous trend in the values of the thermodynamic parameters: the absence of any discontinuity leads to hypothesize that inclusion is ruled by a 1:1 stoichiometry, and only the adduct having the alkyl chain in the extended form is present. The absence of any jump in the values of the thermodynamic parameters characterizing the present data, relative to the alkylated CDs, indicates that a "cavity elongation effect" is operating. Namely, the alkyl substitution makes the cavity behave as if it were deeper than that of the parent CDs [8, 27, 32]. The interaction would occur mostly between the external alkyl groups and the alkyl chain of the alkanol, determining the positive sign of entropies. Alkyl chains even longer than those required for the unsubstituted CD would be needed for the formation of the adduct having a bent alkyl chain into the cavity. A shift toward negative entropies would detect that change in the association mechanism.

As outlined before, the formation of a complex between a CD and a prevailingly hydrophobic guest molecule is a process ruled by the changes experienced by the solvent water upon association: dehydration of the guest molecule, desolvation of the cavity, formation of a hydration shell for the complex. For the CDs derivatives, association occurs through the interaction between the hydrophobic hydration shells of the alkyl chain of the guest and the hydrated external alkyl group of the host. Upon inclusion, the relaxation to the bulk of the water molecules from these hydrated interacting groups determines a positive entropic contribution, an effect much more evident for *β*CDs, whose complexes are formed for the large, favourable entropies, notwithstanding the unfavourable enthalpic contribution. The value of enthalpy is determined by several effects, among them the disruption of hydrogen bonds between water molecules in the cavity, the dehydration of the included hydrophobic guest molecule, and the adaptation of the guest molecule to the CD cavity. The first two effects are endothermic, while the third one is exothermic. The internal diameter of α-CDs is about 4.9 Å, much smaller than that of *β*CD (about 6.2 Å), so the shape-matching between the host cavity and the guest inserting group is the major factor determining the association between the interacting molecules. For the narrower CD, then, the association is ruled prevailingly by the negative enthalpy, an indication of the prevalence of van der Waals interactions between the alkyl chain and the cavity.

Conclusions

The changes experienced by the solvent water molecules upon association control the formation of a complex between CDs and hydrophobic guest molecules. A compensatory enthalpy–entropy relationship exists [1–4, 33–36] for all processes dominated by aquation phenomena and ascribed to the modifications experienced by the solvent in the hydration cospheres of the interacting substances. For most complexes reported in the literature, a roughly linear trend is obtained when reporting $\Delta H^{\circ\prime}$ versus $\Delta S^{\circ\prime}$, and their compensation temperatures, T_C, lie in a relatively narrow range (250–315 K) [33–37]. In Fig. 1, $\Delta H^{\circ\prime}$ versus $\Delta S^{\circ\prime}$ for heptanol and octanol are reported, in water and in concentrated urea: the slope of the line corresponds to T_C and has the value of (307 ± 23)K. Then, the data were considered independently in each solvent. No differences were found: the compensation temperature was the same within the error, which can be considered as a further proof that, even in the presence of high concentrations of urea, association processes are dominated by changes in the hydration cospheres. Another quantitative correlation of the enthalpy–entropy compensation is performed by plotting $T\Delta S^{\circ\prime}$ versus $\Delta H^{\circ\prime}$ (Fig. 2) [36–38]. The $T\Delta S^{\circ\prime}$, at $\Delta H^{\circ\prime} = 0$, and the slope of the line (correlation coefficient = 0.90) are 13.9 ± 0.8 kJ mol^{-1} and 0.88 ± 0.07, respectively, values not far from those reported in the literature for complexes formed by modified CDs [1]. Accordingly, the slope indicates to what extent the enthalpic gain is canceled by entropic loss, while the positive intercept suggests that the complex is stabilized even in the absence of enthalpic contributions. The large entropic term confirms that the inclusion process is determined mainly by the changes experienced by water in the hydration shells of the interacting hydrated molecules.

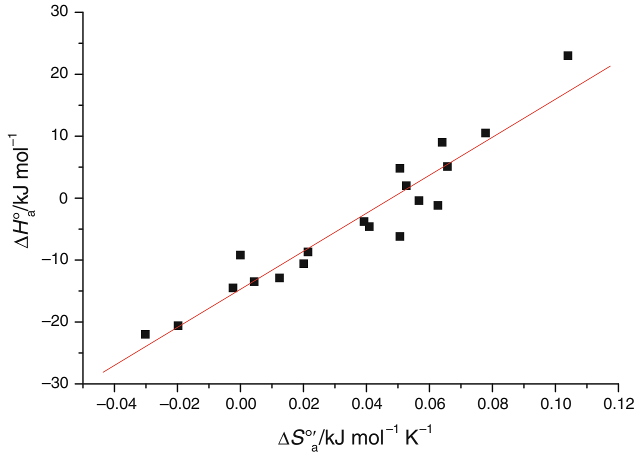

Fig. 1 Enthalpy–entropy compensation plot for the formation of native and modified cyclodextrins with heptanol and octanol, in water and in 7 mol kg^{-1} urea

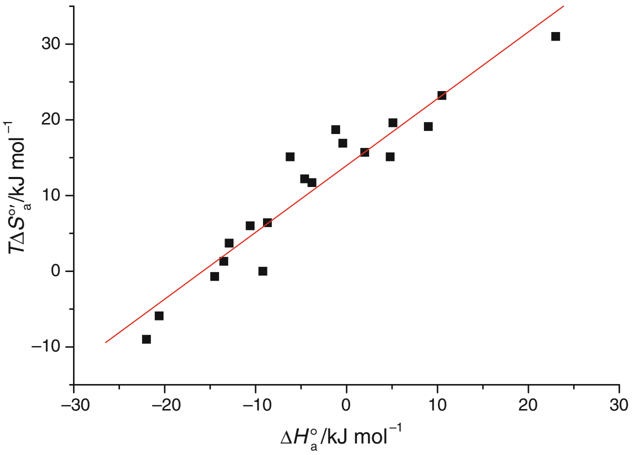

Fig. 2 Entropy–enthalpy compensation plot for the formation of native and modified cyclodextrins with heptanol and octanol, in water and in 7 mol kg^{-1} urea

References

1. Rekharsky MV, Inoue Y. Complexation thermodynamics of cyclodextrins. Chem Rev. 1998;98:1875–917.
2. Rekharsky MV, Inoue Y. Chiral recognition thermodynamic of *β*-cyclodextrin: the thermodynamic origin of enantioselectivity and the enthalpy–entropy compensation effect. J Am Chem Soc. 2000;122:4418–35.
3. Clarke RJ, Coates JH, Lincoln SF. Inclusion complexes of the cyclomalto–oligosaccharides (cyclodextrins). Adv Carbohydr Chem Biochem. 1988;46:205–11.
4. Connors A. The stability of cyclodextrins complexes in solution. Chem Rev. 1997;97:1325–57.
5. Bellia F, La Mendola D, Pedone C, Rizzarelli E, Saviano M, Vecchio G. Selectively functionalized cyclodextrins and their metal complexes. Chem Soc Rev. 2009;38:2756–81.
6. Zielenkiewicz W, Terekhova IV, Wszelaka-Rylic M, Kumeev RS. Thermodynamics of inclusion complex formation of

hydroxypropylated α- and β-cyclodextrins with aminobenzoic acids in water. J Therm Anal Calorim. 2010;101:15–23.

7. Rekharsky MV, Mayhew MP, Goldberg RN, Ross PD, Yamashoji Y, Inoue Y. Thermodynamic and nuclear magnetic resonance study of the reactions of α- and β-cyclodextrin with acids, aliphatic amines, and cyclic alcohols. J Phys Chem. 1997; 101:87–100.
8. Castronuovo G, Niccoli M, Varriale L. Complexation forces in aqueous solutions. Calorimetric studies of the association of 2-hydroxypropyl-β-cyclodextrin with monocarboxylic acids or cycloalkanols. Tetrahedron. 2007;63:7047–52.
9. Ross PD, Rekharsky MV. Thermodynamics of hydrogen bond and hydrophobic interactions in cyclodextrins complexes. Biophys J. 1996;71:2144–54.
10. Liu L, Guo Q-XJ. The driving forces in the inclusion complexation of cyclodextrins. J Inclusion Phenom Macrocycl Chem. 2002;42:1–14.
11. Liu L, Guo Q-XJ. Use of quantum chemical methods to study cyclodextrins chemistry. J Inclusion Phenom Macrocycl Chem. 2004;50:95–103.
12. Hallén D, Schön A, Shehatta I, Wadsö I. Microcalorimetric titration of α-cyclodextrin with some straight-chain alkan-1-ols at 288.15, 298.15, and 308.15 K. J Chem Soc Faraday Trans. 1992;88:2853–9.
13. Terechova IV, De Lisi R, Lazzara G, Milioto S, Muratore N. Volume and heat capacity studies to evidence interactions between cyclodextrins and nicotinic acids in water. J Therm Anal Calorim. 2008;92:285–90.
14. Brewster MF, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007;59:645–66.
15. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chem Rev. 1998;98:2045–76.
16. Junquera E, Ruiz D, Aicart E. Role of hydrophobic effect on the noncovalent interactions between salisilic acid and a series of β-cyclodextrins. J Colloid Interface Sci. 1999;216:154–60.
17. Todorova NA, Schwarz FP. The role of water in the thermodynamics of drug binding to cyclodextrins. J Chem Throdynam. 2007;39:1038–48.
18. Aki A, Ikeda H, Yukawa M, Iwase Y, Mibu N. Effect of pH on the formation of inclusion complexes between β-lactam antibiotics and 2-hydroxypropyl-β-cyclodextrin in aqueous solution. J Therm Anal Calorim. 2009;95:421–6.
19. Zielenkiewicz W, Terekhova IV, Marcinowicz A, Kozbial M, Poznanski J. Interactions of native and modified cyclodextrins with some B-vitamins. J Therm Anal Calorim. 2008;93:365–72.
20. Zielenkiewicz W, Terekhova IV, Kozbial M, Kumeev RS. Thermodynamic study on inclusion complex formation of riboflavin with 2-hydroxypropyl-β-cyclodextrin in water. J Therm Anal Cal DOI:10.1007/s10973-010-0858-x.
21. Castronuovo G, Elia V, Niccoli M, Velleca F. The effects of cosolvents on the complexation of α-cyclodextrin with alkylated substances. Calorimetric studies at 25 °C. J Inclusion Phenom Macrocycl Chem. 2002;44:229–34.
22. Castronuovo G, Elia V, Niccoli M, Velleca F, Viscardi G. Role of the functional group in the formation of the complexes between α-cyclodextrin and alkanols or monocarboxylic acids in aqueous solutions. A calorimetric study at 25 °C. Carbohydr Res. 1998; 306:147–55.
23. Andini S, Castronuovo G, Elia V, Gallotta E. Inclusion compounds in water. Calorimetric and spectroscopic studies of the interaction of cyclomaltohexaose (cyclodextrin) with alkanols at 25 °C. Carbohydr Res. 1991;217:87–97.
24. Castronuovo G, Elia V, Iannone A, Niccoli M, Velleca F. Factors determining the formation of complexes between alpha-cyclodextrin and alkylated substances in aqueous solutions: a calorimetric study at 25 °C. Carbohydr Res. 2000;325:278–86.
25. Castronuovo G, Elia V, Niccoli M, Velleca F. Study of the effects of cosolvents on the complexation of β-cyclodextrin with alkanols by calorimetry at 298 K. J Incl Phenom Macrocycl Chem. 2003;45:91–7.
26. Castronuovo G, Niccoli M, Velleca F. Complexation of modified cyclodextrins with hydroxylated substances in aqueous solutions. Calorimetric studies at 298 K. Phys Chem Chem Phys. 2003; 5:2658–62.
27. Castronuovo G, Niccoli M. Complexation of natural and methylated β-cyclodextrins with long chain carboxylic acids in aqueous solutions. Calorimetric studies at 298 K. J Inclusion Phenom Macrocycl Chem. 2005;53:69–76.
28. Castronuovo G, Niccoli M. Thermodynamics of inclusion complexes of natural and modified cyclodextrins with propranolol in aqueous solution at 298 K. Bioorg Med Chem. 2006;14:3883–7.
29. Castronuovo G, Niccoli M. The influence of cosolvents on hydrophilic and hydrophobic interactions. Calorimetric studies of parent and alkylated cyclomaltooligosaccharides in concentrated aqueous solutions of ethanol or urea. Carbohydr Res. 2008; 343:2771–5.
30. Eftink M, Biltonen R. Thermodynamics of interacting biological systems. In: Beezer AE, editor. Biological microcalorimetry. London: Academic Press; 1980. p. 343–412.
31. Castronuovo G, Elia V, Fessas D, Velleca F, Viscardi G. Thermodynamics of the interaction of α-cyclodextrin with monocarboxylic acids in aqueous solutions: a calorimetric study at 25 °C. Carbohydr Res. 1996;287:127–38.
32. Castronuovo G, Niccoli M. The cavity elongation effect. Calorimetric studies of the complexes of long-chain carboxylic acids with methyl-α-cyclodextrin in aqueous solutions. J Incl Phenom Macrocycl Chem. 2007;58:289–94.
33. Lumry R, Rajender S. Enthalpy–entropy compensation phenomena in water solutions of proteins and small molecules: a ubiquitous property of water. Biopolymers. 1970;9:1125–12227.
34. Grunwald E, Steel C. Solvent reorganization and thermodynamic enthalpy–entropy compensation. J Am Chem Soc. 1995;117: 5687–92.
35. Lo Meo P, D'Anna F, Gruttadauria M, Riela S, Noto R. Thermodynamics of binding between α- and β-cyclodextrins and some p-nitro-aniline derivatives: reconsidering the enthalpy–entropy compensation effect. Tetrahedron. 2004;60:9099–111.
36. Tabushi I, Kiyosuke Y, Sugimoto T, Yamamura K. Approach to the aspects of driving force of inclusion by α-cyclodextrin. J Am Chem Soc. 1978;100:916–9.
37. Inoue Y, Hakushi T, Liu Y, Tong L, Shen B, Jin D. Thermodynamics of molecular recognition by cyclodextrins. 1. Calorimetric titration of inclusion complexation of naphthalenesulfonates with α-, β-, and γ-cyclodextrins: enthalpy–entropy compensation. J Am Chem Soc. 1993;115:475–81.
38. Inoue Y, Liu Y, Tong L, Shen B, Jin D. Calorimetric titration of inclusion complexation with modified β-cyclodextrins. Enthalpy–entropy compensation in host–guest complexation: from ionophore to cyclodextrin and cyclophane. J Am Chem Soc. 1993; 115:10637–44.