



The influence of cosolvents on hydrophilic and hydrophobic interactions. Calorimetric studies of parent and alkylated cyclomaltooligosaccharides in concentrated aqueous solutions of ethanol or urea

Giuseppina Castronuovo*, Marcella Niccoli

Department of Chemistry, University Federico II of Naples, Complesso Universitario Monte S. Angelo, Via Cintia I-80126 Naples, Italy

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ABSTRACT

Heats of dilution in water and in aqueous 7 mol kg⁻¹ urea and 3 mol kg⁻¹ ethanol of binary solutions containing cyclomaltohexaose, cyclomaltoheptaose, cyclomaltooctaose, 2-hydroxypropyl-cyclomaltohexaose (HP α CD), 2-hydroxypropyl-cyclomaltoheptaose (HP β CD), methyl-cyclomaltohexaose (Me α CD), methyl-cyclomaltoheptaose (Me β CD) and 2-hydroxypropyl-cyclomaltooctaose (HP γ CD) have been determined at 298.15 K by flow microcalorimetry. The purpose of this study is to gain information about the influence of urea and ethanol, which have different effects on water structure, on hydrophilic and hydrophobic interactions. The pairwise interaction coefficients of the virial expansion of the excess enthalpies were evaluated and compared to those previously obtained for binary solutions of cyclomaltohexaose and cyclomaltoheptaose. The particular behaviour of cyclomaltooligosaccharides in water is put in evidence with respect to that shown by simple oligosaccharides. The values of the interaction coefficients greatly change in dependence of the solvent medium. They are negative in water for unsubstituted cyclomaltooligosaccharides, and positive for the alkyl-substituted ones, thus marking the major role of the hydrophobic interactions. In concentrated aqueous ethanol, coefficients are negative, while they are positive in concentrated aqueous urea. Urea solvates the hydroxyl group provoking the attenuation of hydrophilic and hydrophobic interactions. Instead, the presence of the cosolvent ethanol, which lowers the relative permittivity of the medium, enhances the strength of hydrophilic interactions.

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1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are (1–4)-linked cyclic glucooligosaccharides. The most commonly studied of these substances are cyclomaltohexaose (α CD), cyclomaltoheptaose (β CD) and cyclomaltooctaose (γ CD) with 6, 7 and 8 glucose units, respectively.^{1,2} The primary and secondary hydroxyl groups of the glucose units make the exterior of the molecule hydrophilic, while the interior surface of the truncated cone structure (the cavity), normally considered as the site of the guest molecule, is largely hydrophobic. The hydrophobic cavities allow inclusion complexes to form with a large variety of organic and inorganic compounds in different solvents, including water.^{2–7} Applications have been described of molecular modelling techniques to the study of the static and dynamical features of CDs, as well as their participation in the formation of inclusion complexes.⁸

In preceding papers from this laboratory, efforts were made to understand the factors determining the formation of the complexes between CDs and alkylated substances in solution.^{9–12} The

purpose of the present study is to obtain more information about the forces acting in the binary aqueous solutions of parent and chemically modified CDs. To that, a calorimetric study at 298 K is reported of the heats of dilution in water and in concentrated aqueous urea or ethanol of cyclomaltohexaose (α CD), cyclomaltoheptaose (β CD), cyclomaltooctaose (γ CD), 2-hydroxypropyl-cyclomaltohexaose (HP α CD), 2-hydroxypropyl-cyclomaltoheptaose (HP β CD), methyl-cyclomaltohexaose (Me α CD), methyl- β -cyclomaltoheptaose (Me β CD) and 2-hydroxypropyl-cyclomaltooctaose (HP γ CD). Urea and ethanol have different effects on water structure: the former is a well-known chaotropic agent, while the latter is a prevalingly hydrophobic structure maker. We shall analyze how the modifications induced in the structure of water by the two cosolvents modify the interactions between pairs of hydrated molecules. Through this kind of study, we hope it will be possible to relate the properties of the binary solutions with the inclusion requirements in the host–guest complexes.

The parameters that are most commonly used to characterize nonbonding interactions in solution are the pairwise coefficients of the virial expansion of the excess thermodynamic properties of a solution.^{13–15} The physical meaning of these parameters is linked to the variations in thermodynamic properties when two

* Corresponding author. Tel.: +39 081 674239; fax: +39 081 674090.
E-mail address: giuseppina.castronuovo@unina.it (G. Castronuovo).

hydrated molecules are brought from an infinite separation, where solute–solvent interactions are dominant, to a finite separation where solute–solute, water-mediated interactions are operating. Then, they are very useful to get information about the mechanism through which two hydrated molecules interact in solution. The model of overlapping hydration spheres of hydrated molecules accounts qualitatively for the sign and magnitude of these coefficients. Just on the basis of the signs and values of the enthalpic pair interaction coefficients, it has been already inferred that parent CDs in aqueous solutions are very particular substances, since they behave very differently from other simple saccharides, rather resembling higher molecular weight polyhydric alcohols.^{16,17} Cyclomaltooligosaccharides, especially their alkylated derivatives, are essential in pharmaceutical applications as they provide versatile carrier and delivery systems for drug molecules.^{18–23} From that arises the importance of further investigating their binary solutions in different aqueous solvents. Indeed, the possibility to modify the forces acting in these solutions by changes in the structure of the solvent can be useful when designing new cyclomaltooligosaccharides derivatives with more suitable characteristics to include specific drugs.

2. Results

Heats of dilution were measured at 298 K in water, and in the presence of a constant amount of ethanol or urea. For the investigated systems, dilution is an exothermic or endothermic process and the derived enthalpic interaction coefficients are positive or negative, respectively.

In Table 1, the pairwise enthalpic interaction coefficients are reported for the binary aqueous solutions of parent and modified CDs. In the same Table, some literature data are also shown with the aim of presenting a complete thermodynamic framework of the behaviour of the cyclomaltooligosaccharides studied in this laboratory.^{9,16,26–28}

In water, the coefficients for unsubstituted CDs are large and negative, the most negative characterizing the smallest cyclomaltooligosaccharide, α CD. On the contrary, methyl- and hydroxypropyl-substituted CDs are characterized by large and positive pairwise enthalpic interaction coefficients. Methyl derivatives are characterized by coefficients which are larger than those for the hydroxypropyl derivatives. It should be noted that the enthalpic coefficient reveals to be a useful parameter to distinguish among CDs of different degree of substitution. For instance, the coefficient for Me β CD (DS = 12) is 24,000 J kg mol⁻², while that for Me β CD (DS = 10–14) is 28,000 J kg mol⁻². The same occurs for HP β CD,

DS = 3 and DS = 6.3, whose coefficients are 4812 and 15,498 J kg mol⁻², respectively.

In 3 mol kg⁻¹ ethanol, coefficients for parent CDs become more negative than in water, while those for the alkylated derivatives change from positive to negative. The more positive the value of the coefficient in water, much more pronounced is the change in its value on passing to ethanol (as an example, see Me β CD, DS = 12).

In 7 mol kg⁻¹ urea, all coefficients are positive. Parent CDs change from negative in water to positive in urea, cyclomaltooctaose presenting the largest difference. Instead, methyl and hydroxypropyl derivatives have only a small decrease in the positive values of their coefficients. In Table 1, three data refer to α CD, β CD and Me β CD in phosphate buffer: coefficients are positive, thus indicating a behaviour qualitatively similar to that in urea.

3. Discussion

The structure of the smallest cyclomaltooligosaccharide, α CD, in water can be assumed to resemble that of α CD hexahydrate in the crystalline state. Namely, the ‘void’ molecule of α CD has two water molecules entrapped in the cavity, hydrogen-bonded to each other and to two glucopyranose rings.^{29,30} The pairwise enthalpic interaction coefficient for α CD is negative: on the basis of this sign, it can be classified as a prevalently hydrophilic structure-breaking solute.³¹ According to an interaction model that provides the presence of configurations between two hydrated molecules stabilized by the juxtaposition of groups having the same action on water structure, the negative sign is due to the juxtaposition of the external hydrated hydroxyl groups.³² For β CD and γ CD, coefficients are negative, too, but smaller than that for α CD, thus indicating that the larger macrocycles are structure breaker solutes less effective than α CD. Literature reports that α CD undergoes a tense \rightarrow relaxed transition upon formation of a complex,³⁰ hydrogen-bonded water molecules being squeezed out of the cavity, relaxing to the bulk. To the contrary, β CD and γ CD do not experience that conformational transition, and they would present relaxed conformations even in the absence of a guest, with the larger cavities more exposed to bulk solvent. The negative coefficients characterizing parent CDs in water make their behaviour to be different from that of other saccharides, which are characterized by positive coefficient. Cyclization is a factor that greatly influences interactions between molecules, since the rigidity of the cycles, compared to the flexibility of a linear chain, leads to face-to-face configurations stabilized by hydrophilic interactions which act through the juxtaposition of hydroxyl groups. As a fact, parent CDs mimic the behaviour of some higher members of polyols, whose enthalpic interaction

Table 1
Pairwise enthalpic interaction coefficients^a for parent and modified cyclomaltooligosaccharides in water and in aqueous mixed solvents, at 298 K

Substance	Water	Ethanol 3 mol kg ⁻¹	Na ₂ HPO ₄ 0.5 mol kg ⁻¹	Urea 7 mol kg ⁻¹
α CD	-3920 \pm 60 ^b	-7130 \pm 50	1360 \pm 60 ^c	2760 \pm 60 ^d
Me α CD (DS 11)	18,200 \pm 800	-5200 \pm 300		12,530 \pm 60
2HP α CD (DS 4.5)	9400 \pm 200	-1400 \pm 100		8500 \pm 200
β CD	-2800 \pm 200 ^e	-10,300 \pm 300 ^e	4200 \pm 100 ^f	1200 \pm 30 ^d
Me β CD (DS 12)	24,100 \pm 300	-6300 \pm 200		15,000 \pm 400
Me β CD (DS 10–14)	28,400 \pm 500 ^f		68,000 \pm 1000 ^f	
2HP β CD (DS 3)	4800 \pm 100	-7100 \pm 700		7200 \pm 300
2HP β CD (DS 6.3)	15,500 \pm 200	-1000 \pm 200		10,700 \pm 600
γ CD	-3160 \pm 90	-10,900 \pm 300		5700 \pm 400
2HP γ CD (DS 4.5)	12,700 \pm 200	-2700 \pm 300		11,900 \pm 200

^a Units: J kg mol⁻². Errors reported are the 95% confidence limits.

^b Ref. 16.

^c Ref. 26.

^d Ref. 27.

^e Ref. 28.

^f Ref. 9.

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