

Competitive processes of a chromophore modified α -cyclodextrin in the presence of a fluorescence polarity sensitive probe

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ABSTRACT

Steady-state fluorescence, time-resolved fluorescence, molecular mechanics (MM) and molecular dynamics (MD) were employed to study the thermodynamics of the complexation of 2', 3'-O-(*o*-xylylene)- α -cyclodextrin (X α CD), which is also capable of self-aggregation, with a fluorescent polarity sensitive probe, the 2-naphthalenecarboxylate (2MN), in aqueous solution. Dimerization and inclusion constants, as well as the thermodynamics parameters accompanying both processes were obtained. We also used MM and MD to investigate the conformational behavior for the isolated X α CD, the dimerization and inclusion processes and the geometry of the complexes and driving forces responsible for their formation. The results were compared with those obtained for other α -cyclodextrins in order to establish relationships between the dimer and complex structures and the thermodynamics of both processes.

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1. Introduction

Cyclodextrins (CDs) are donut shaped cyclic oligosaccharides composed of α (1 $\rightarrow$ 4)-linked D-glucopyranoside units which are widely used as host molecules in supramolecular chemistry [1,2]. The fact that they are water-soluble natural products, inexpensive, commercially available and nontoxic makes them very attractive as molecular platforms and starting materials for the construction of functional supramolecular systems [3,4]. Thus, the development of selective methods for the chemical CD functionalization has made it possible to access derivatives with improved chiral selectivity, molecular recognition or molecular self-assembly properties [5–9]. Among the modified CDs, the fluorophore-appended ones have been extensively investigated for their applications as chemosensors [10,11], photochemical microreactors [12,13] and antenna host molecules [14–16]. The chromophore covalently bonded to the CD core provide fluorescence properties to the host and are responsible for hindering, prompting or inducing self-association processes [17–22]. The tendency of the modified CD to undergo self-assembling will depend on the size and shape of the appended group, the flexibility and length of the spacer and the nature of the functional groups (methyl, hydroxypropyl, amine group, etc.) at the primary and secondary rims in the macrocyclic [23].

In the frame of an ongoing project aimed at designing multifunctional self-assembling CD derivatives for biomacromolecule complexation and delivery [24,25], we recently described the synthesis and characterization of 2',3'-O-(*o*-xylylene)-permethylated CDs (X m CD), in which a xylylene group was bonded to a glucopyranose unit through a bidentate-hinge [26]. We demonstrated the presence of an *open* $\rightleftharpoons$ *capped* conformational equilibrium in water solution, with the xylylene moiety adopting a quasi-perpendicular or quasi-parallel conformation with respect to the secondary rim of the CD, which was strongly temperature-dependent and significantly displaced to the *open* form. We also confirmed the existence of relatively stable (X m CD)₂ dimers in water [22,26]. The dimerization processes were accompanied by $\Delta H^\circ < 0$ and $\Delta S^\circ < 0$ with dimerization equilibrium constants (K_D) for X $m\alpha$ -, β - and γ CDs at 25 °C $\sim$ 180, $\sim$ 200 and $\sim$ 250 M⁻¹, respectively. The preferred dimer architecture resulted from the approaching of two *open* X m CDs monomers through their secondary faces (head–head), where both xylylene groups interact without penetrating in the cavity of the CD partner.

In addition, we studied and compared the complexation of methyl 2-naphthalenecarboxylate (2MN), a polarity fluorescence sensitive probe, with X m CDs and with their permethylated partners (m CDs) lacking the xylylene cap [27]. Binding constants for 1:1 2MN/X m CD complexes were higher than those for the corresponding 2MN/ m CD ones. Results also revealed that the cavities of X m CDs and m CDs were more hydrophobic than the cavity of their natural CD counterparts. Appending the xylylene hydrophobic moiety to

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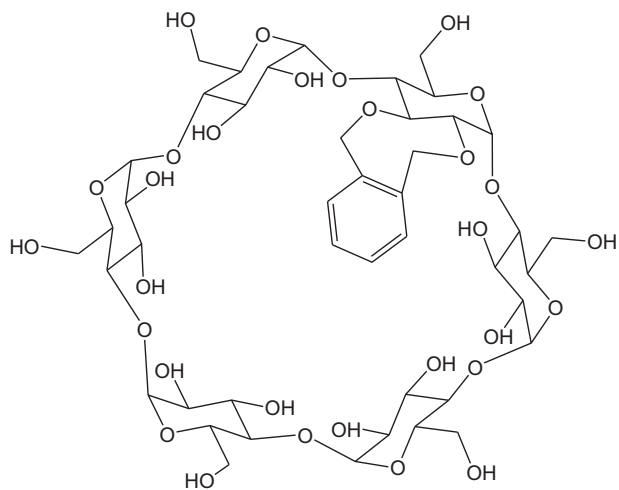


Fig. 1. Structure for 2',3'-O-(o-xylylene)-α-cyclodextrin, named XαCD.

the secondary face of the *m*CDs resulted in a rather similar apolar ($\epsilon \sim 30$) cavity microenvironments for the corresponding *Xmα*-, *Xmβ*- or *Xmγ*CDs [27]. In all cases, the presence of the aromatic moiety was critical in order to reach dimerization. Interestingly, the formation of head–head CD dimers was proposed to be the initial step in the formation of CD bilayers from amphiphilic CD derivatives in the presence of nucleic acids. These hierarchical self-association processes, leading to nanocomplexes that can be further decorated by host–guest chemistry, are strongly dependent on the hydrophobic/hydrophilic balance between both CD faces. In this context, exploring the effect of replacing the methyl ether groups by hydroxyl groups in *Xm*CDs in the conformational, self-association and complexation properties seemed very appealing [28,29].

In the present work the capabilities of 2',3'-O-(o-xylylene)-α-CD (XαCD) (Fig. 1), the Xy appended natural αCD, to dimerize and to form inclusion complexes with 2MN in water were investigated. Equilibrium constants and thermodynamics parameters were obtained for both competitive processes by using steady-state and time-resolved fluorescence techniques. To evaluate the influence of the chromophore group on the dimerization process, heterodimerization studies for XαCD with the natural αCD and the complexation of αCD with α, α'-dimethoxy-o-xylylene (oXy), a model for the aromatic cap, were also carried out. Molecular mechanics (MM) as well as molecular dynamics (MD) calculations were employed to study the XαCD conformational behavior, as well as to elucidate dimer and complex structures and to identify the driving forces responsible for their formation. Evaluating, understanding and rationalizing the influence of the appended group and the presence of methyl or hydroxyl groups at the primary and secondary faces of αCD on the dimer stability and the inclusion capabilities were the aim of this work. Studies in that direction could be particularly useful for designing modified cyclodextrins with characteristics that are better suited for promoting interactions with drugs and genetic material [30].

2. Experimental

2.1. Reagents and solution preparation

*Xmα*CD, *mα*CD, XαCD and oXy were prepared following previously reported methods [26,31]. CD aqueous solutions (water deionized by a Milli-Q system) were prepared by weight and stirred for 24 h prior to the measurements. XαCD/water solutions were in the 0.06–0.08 mM concentration range. Complexation (heterodimerization) of oXy (XαCD) with αCD was studied by keeping

the [oXy] ([XαCD]) constant $< 10^{-5}$ M (0.047 M) and changing the [αCD] in the 0–9.17 mM (0–7.99 mM) concentration range. Measurements with larger [XαCD] could not be carried out due to the appearance of a precipitate. A characteristic of XαCDs is that their solubility increases with temperature. 2,3-Butanedione (diacetyl, Aldrich) was used as a fluorescence quencher for Xy. Inclusion processes were studied using a saturated aqueous solution of 2MN ($\approx 3 \times 10^{-2}$ mM) by modifying the CD concentration in the 0.23–4.61 mM range. These solutions were prepared by weighting and addition of the solvent after being filtered by Millipore cellulose filters whose diameter was 0.5 μm.

2.2. Experimental details

Steady-state fluorescence measurements were recorded on an SLM 8100C AMINCO spectrofluorometer. The fluorescence decay measurements were achieved on a Time Correlated Single Photon Counting (TCSPC) FL900 Edinburgh Instruments Spectrometer with a thyatron-gated lamp filled with H₂. The time-resolved measurements were performed with a time window width of 200 ns with a total of 10,000 counts at the intensity maximum. Cylindrical quartz 2 mm inner path cells were used for all the experiments. Further details of the apparatus and methods are reported elsewhere [22,27].

2D NOESY spectra were recorded with a Bruker DRX 500 MHz NMR spectrometer using several mixing times between 0.2 and 1.0 s. For the preparation of the sample, a solution of XαCD was lyophilized twice with 99% D₂O and one final time with 99.99% D₂O (Sigma–Aldrich).

2.3. Determination of dimerization and inclusion constants

2.3.1. XαCD self-association process

If dimerization [22,26] of XαCD is described by the following equilibrium



Then, the association constant K_D expressed as

$$K_D = \frac{[(\text{X}\alpha\text{CD})_2]}{[\text{X}\alpha\text{CD}]^2} \quad (2)$$

can be related to the fluorescence intensity, I , at the maximum of the Xy emission band or measured as the area under the emission spectrum, and the total [XαCD] by the following equation:

$$I = \phi_{(\text{X}\alpha\text{CD})_2} [\text{X}\alpha\text{CD}] - (\phi_{(\text{X}\alpha\text{CD})_2} - \phi_{\text{X}\alpha\text{CD}}) \frac{(\sqrt{8K_D[\text{X}\alpha\text{CD}] + 1} - 1)}{4K_D} \quad (3)$$

where $\phi_{(\text{X}\alpha\text{CD})}$ and $\phi_{(\text{X}\alpha\text{CD})_2}$ are the proportionality constants (per chromophore unit) between fluorescence intensity and [XαCD] and [(XαCD)₂]. Both parameters are related to their fluorescence quantum yields and molar absorptivities at the excitation wavelength.

On the other hand a non-linear relationship between the weighted average lifetime (τ) obtained as described elsewhere [22,26] and [XαCD] can be derived as:

$$\langle \tau \rangle = \frac{2\tau_{\text{X}\alpha\text{CD}} + (\phi_{(\text{X}\alpha\text{CD})_2}/\phi_{\text{X}\alpha\text{CD}})\tau_{(\text{X}\alpha\text{CD})_2} \left(\sqrt{8K_D[\text{X}\alpha\text{CD}] + 1} - 1 \right)}{2 + (\phi_{(\text{X}\alpha\text{CD})_2}/\phi_{\text{X}\alpha\text{CD}}) \left(\sqrt{8K_D[\text{X}\alpha\text{CD}] + 1} - 1 \right)} \quad (4)$$

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