Carbohydrate Polymers 141 (2016) 99–105

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Conformation study of ε-cyclodextrin: Replica exchange molecular dynamics simulations

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ARTICLE INFO

Article history:
Received 23 January 2015
Received in revised form 4 September 2015
Accepted 8 October 2015
Available online 13 October 2015

Keywords:
Large-ring cyclodextrin
ε-Cyclodextrin
Replica exchange molecular dynamics
Conformational changes

ABSTRACT

There is growing interest in large-ring cyclodextrins (LR-CDs) which are known to be good host molecules for larger ligands. The isolation of a defined size LR-CD is an essential prerequisite for studying their structural properties. Unfortunately the purification procedure of these substances turned out to be very laborious. Finally the problem could be circumvented by a theoretical consideration: the highly advantageous replica exchange molecular dynamics (REMD) simulation (particularly suitable for studies of conformational changes) offers an ideal approach for studying the conformational change of ε-cyclodextrin (CD10), a smaller representative of LR-CDs. Three carbohydrate force fields and three solvent models were tested. The conformational behavior of CD10 was analyzed in terms of the flip (turn) of the glucose subunits within the macrocyclic ring. In addition a ranking of conformations with various numbers of turns was preformed. Our findings might be also helpful in the temperature controlled synthesis of LR-CDs as well as other experimental conditions, in particular for the host–guest reaction.

1. Introduction

Cyclodextrins (CDs) are produced from cyclodextrin glucanotransferase or amylomaltase from starch or similar substrates. They are cyclic α-1,4 linked oligosaccharides of D-glucopyranose units (Fig. 1a) with a hydrophobic nanoscale cavity and a hydrophilic outer surface. Generally, cyclodextrins and their derivatives are used to enhance water-solubility, stability and bioavailability of compounds of interest in pharmaceutical and food industries. The regular-ring CDs contain six, seven and eight α-D-glucopyranoside units known as α-CD, β-CD, and γ-CD, respectively, whereas the large-rings CDs (LR-CDs) are comprising more than eight units. The small-ring CDs prefer the doughnut shape, whereas LR-CDs may exist in various conformations. For example, based on the crystal structures ε-CD (CD10) (Jacob et al., 1998, 1999; Ueda, Endo, Nagase, Kobayashi, & Nagai, 1996) and ι-CD (CD14) (Harata, Endo, Ueda, & Nagai, 1998; Jacob et al., 1998, 1999) containing 10 and 14 D-glucose units, respectively, these CDs are stable in bent forms while CD26 with 26 D-glucose units shows a somewhat twisted form (Gessler et al., 1999; Nimz, Geßler, Usón, & Saenger, 2001). For small-ring CDs, the dihedral angles $\tau(O2_{(n)}\text{–}C1_{(n)}\text{–}C4_{(n+1)}\text{–}O3_{(n+1)})$ (Fig. 1a), determined for all glucose units are in the range from −60° to 60°. Contrary to these findings the τ angle of some glucose units which are connected in the larger CD moieties is found within much larger ranges.

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http://dx.doi.org/10.1016/j.carbpol.2015.10.018
0144-8617/

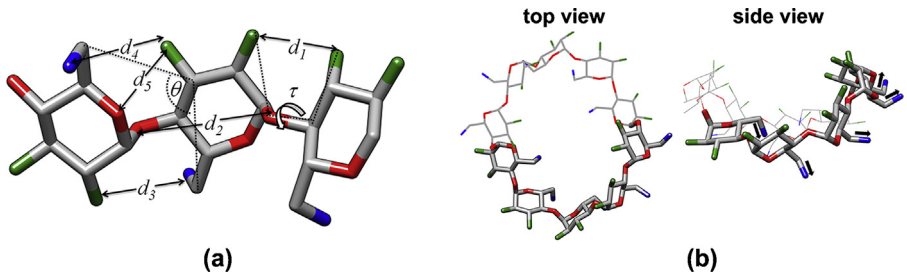

Fig. 1. (a) CD fragment showing the atomic labels and focused structural parameters, d_1[O2—O3′], d_2[O4—O4′], d_3[O2—O6′], d_4[O3—O6′], d_5[O3—O5′] and τ[O2—C1—C4′—O3′]. A turn between two glucose units is shown for the left glucose unit, whereas the two other glucose rings are within the band structure in cis position. (b) A helical band subunit is shown with five glucose rings (from the X-ray structure of CD10).

The crystal structure of CD10, C2 symmetry is observed. Two slightly twisted band subunits (Fig. 1b) are connected by two flips of glucose rings leading to a saddle-like conformation of **ε**-CD (Jacob et al., 1998, 1999; Ueda et al., 1996).

Besides a variety of researches on the physicochemical properties and host–guest interactions of small ring CDs (Cao & Wu, 2015; Fernandes et al., 2014; Hu, Tang, & Chu, 2014; Khuntawee, Wolschann, Rungrotmongkol, Wong-Ekkabut, & Hannongbua, 2015; Ogawa, Takahashi, & Yamamoto, 2015; Sangpheak, Khuntawee, Wolschann, Pongsawasdi, & Rungrotmongkol, 2014), the studies on LR-CDs (Dodziuk et al., 2003; Larsen, 2002; Larsen, Endo, Ueda, & Zimmermann, 1998; Wang et al., 2015) have been less mentioned. The larger ring size molecules are enabled to be good hosts, thus enhancing the solubility and efficiency of relatively large ligands (Ueda, 2002, 2004). In order to understand this behavior more clearly, the physicochemical and structural properties at a molecular level were investigated. In several publications, the dynamical behavior was described using MD simulation techniques starting from the crystal structures of CD10, CD14, and CD26 (Gotsev & Ivanov, 2007a) and larger macro-ring sized models (CD27–30, 35, 40, 48, 55, 70, 85, and 100) including intermediate conformations of available X-ray structures (CD11–13, CD15–18, and CD20–25) in either gas phase or in solution (Gotsev & Ivanov, 2007b, 2009; Gotsev, Ivanov, & Jaime, 2007; Ivanov, 2011, 2012; Ivanov & Jaime, 2004; Maestre, Beà, Ivanov, & Jaime, 2007; Shimada, Handa, Kaneko, & Takada, 1996; Shimada, Kaneko, Takada, Kitamura, & Kajiwara, 2000). The MD results of CDs with a degree of polymerization higher than 13 support the hypothesis for the existence of more than one cavity in LR-CDs.

In the process of enzymatic synthesis of CD, the CD conformations could be controlled by the number of glucopyranose monomers and experimental conditions (temperature and pH). However, the single conventional simulation of biological systems at low temperature condition trends toward a larger number of local minima. To overcome this multiple-minima problem, the replica exchange molecular dynamics simulation (REMD) which allows the exchange of non-interacting replicas of the system at several temperatures has been applied (Cheng, Cui, Hornak, & Simmerling, 2005; Hansmann, 1997; Nymeyer, Gnanakaran, & Garcia, 2004; Sugita & Okamoto, 1999). Therefore, to study the conformational changes of LR-CDs as well as the temperature effect on their structures, we apply REMD technique on one representative of LR-CDs, CD10, which has two flips (antitype) of glucose subunits at opposite sites in the macrocyclic ring. Additionally, REMD simulations have been carried out using different force fields as well as various solvation models based on generalized born (GB) implicit solvent. The replica exchange based conformational study of CD10 affords the instrument to control the physicochemical properties of this substance and subsequently its application.

2. Methods

A detailed description of the REMD method is given elsewhere (Sugita & Okamoto, 1999). The structure preparation and REMD simulations were performed by Amber10 package (Case et al., 2008) with the carbohydrate force field, glycam06 (Kirschner et al., 2008; Nutho et al., 2014; Tessier, Demarco, Yongye, & Woods, 2008). In addition, the glycam04 (Basma, Sundara, Calgan, Vernali, & Woods, 2001; Kirschner & Woods, 2001a,b) and hybrid force field, q4md-CD (Cezard, Trivelli, Aubry, Djedaini-Pilard, & Dupradeau, 2011) were also tested for reasons of comparison. The crystallographic structure of CD10 was taken from the Cambridge Crystallographic Data Centre CCDC (CCDC) entry code CCDC100656 as the starting structure (Jacob et al., 1998). For taking into account the solvent model effect, 50 ns REMD simulations were performed under three different GB implicit solvent models Igb1, Igb2, and Igb5 (Rungnim, Rungrotmongkol, Hannongbua, & Okumura, 2013). The initial structure of CD10 was fully minimized with 2000 steps of steepest descent (SD) method, followed by 1000 steps of conjugated gradient (CG) method. Here, all REMD simulations were performed with 16 replicas at temperatures ranging from 300 K to 600 K with interval steps of 20 K. This temperature protocol was found to be the most promising one for the present case. To equilibrate the systems at the assigned temperatures, a short MD simulation of 5 ns was performed prior to the REMD simulation. The REMD simulation was then done for 100 ns using the solvent model Igb5. Conformations at all temperatures were sampled at every 2 ps. The conformational change of CD10 was monitored through contour plots of the probability by the distances between the secondary hydroxyl groups of adjacent glucoses, d_1[O2$_{(n)}$—O3$_{(n+1)}$], and the distances between the glycosidic oxygen atoms, d_2[O4$_{(n)}$—O4$_{(n+1)}$], using the ptraj module in Amber10 package. In addition the conformational and temperature change correlation was investigated and the probabilities of each state were calculated.

3. Results and discussion

3.1. Crystal structure analysis

The basic structural properties of CD10 in the crystalline state are well understood. The distances of adjacent glucopyranose units d_1[O2—O3′], d_2[O4—O4′], d_3[O2—O6′], d_4[O3—O6′] and d_5[O3—O5′] as well as the dihedral angles τ(O2$_{(n)}$—C1$_{(n)}$—C4$_{(n+1)}$—O3$_{(n+1)}$) are summarized in Table 1. As a consequence of the C2 symmetry the distances of the second half of the CD rim are identical. The distance R5–R6 (as well as R10–R1) is much larger because of the flip of the glucopyranose ring.