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Computational study on the conformations of CD38 and inclusion complexes of some lower-size large-ring cyclodextrins

Petko Ivanov [a,*], Emanouil Atanassov [b], Carlos Jaime [c]

[a] Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, ul. Acad. G. Bonchev, bloc 9, 1113 Sofia, Bulgaria
[b] Institute of Information and Communication Technologies, Bulgarian Academy of Sciences, ul. Acad. G. Bonchev, bloc 25A, 1113 Sofia, Bulgaria
[c] Universitat Autònoma de Barcelona, Departament de Química, Facultat de Ciències, E-08193 Bellaterra (Cerdanyola del Vallès), Spain

HIGHLIGHTS

- Limited number of modes determine the overall deformations of the macroring of CD38.
- A three-turn helix conformation shaped as a short tube was found for CD38.
- Computationally were examined for the first time inclusion complexes of LR-CDs.

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ABSTRACT

The conformations of CD38 were examined by conformational search with molecular dynamics simulations using the Glycam04 force field. The results were compared with previous ones for CD26, the largest cyclodextrin for which crystal data are available. Principal component analysis (PCA) was applied for post-processing of the simulation trajectories. Limited number of modes determine the overall deformations of the macroring of CD38. The longer perimeter of the macroring allowed the formation of a form not observed so far – a three-turn helix shaped as a short tube. In analogy with CD26, significant participation was monitored for conformations of CD38 with one-turn spirals at the opposite sides of the macroring linked together from the 'bottom' and from the 'top' with extended bridge spacers. Computationally were examined for the first time inclusion complexes of some lower-size LR-CDs, namely complexes of CD*n* (*n* = 13, 14, 26) with adamantane and of CD14 with 1-hydroxyadamantane. The macroring conformation of CD13 was not altered by the inclusion of the substrate molecule which acquired preferred positioning not in the middle of the cavity but rather close to the glucose residues at one of the sides. The same positioning of the small molecule in the cavity of the more flexible CD14 macroring enhanced the appearance of bent onto two conformation of this cyclodextrin. The most interesting behaviour presented the complex of CD26 with adamantane in which case the small molecule acts as a 'nucleation center' for the formation of a second helical turn about the substrate molecule.

1. Introduction

As a natural consequence of the long-lasting interest and the numerous applications of the native cyclodextrins (small cyclodextrins; α-CD, β-CD and γ-CD, respectively, cyclohexa-, cycloheptа-, and cyclooctaamylose), their larger analogues, the large-ring cyclodextrins (LR-CDs; CDs with a degree of polymerization (DP) higher than eight) [1–5], also attracted attention in recent years, and advances were marked in the study of their physicochemical properties [6–15], in spite of existing difficulties in their synthesis, isolation and purification. The existence of LR-CDs has been proven as products from the action of 4-α-glucanotransferases on amylose and amylopectin [2] almost a century later after the first evidences for the existence of cyclodextrins [16]. The expectations were that, in addition to the numerous well-known useful for the practice properties of the small cyclodextrins, namely to provide heterogeneous microenvironment to molecules, accommodated in their cavities, that acquire significantly modified properties compared to the free forms, some of the LR-CDs may have new, specific properties.

It took about twenty years after the first report for the existence of LR-CDs (DP = 9–14) [17] preparation method for LR-CDs mixtures to be worked out and δ-CD (DP = 9) [18] to be isolated and its crystal structure to be characterized [19]. This opened the renewed interest on LR-CDs: within very short time the crystal determinations of CD10 (ε-CD) [14,20–22], CD14 (ι-CD) [20,21], and CD26 (υ-CD) [23–25] were reported. Important further steps

* Corresponding author. Tel.: +359 29606177; fax: +359 28700225.
E-mail address: ivanov@bas.bg (P. Ivanov).

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related with the development of an effective purification method for LR-CDs [4] was the first chemical synthesis of a LR-CD – CD9 [26], as well as the synthesis of the first chemically modified LR-CD (CD9) [27].

Crystal structure determinations were so far successful only for four of them [28]. The difficulties in forming intramolecular and intermolecular hydrogen bonds, due to the high flexibility of their macrocyclic rings, as well as the low nucleation rates of sugars, that has to precede crystal growth [3], were considered to be the main cause for the low crystallinity of most LR-CDs. CD26 (cyclohexaicosaose) adopts in the crystal the shape of a figure eight in which each half contains two left-handed, single helical turns with six glucoses per repeat. At the 'upper' and 'lower' sides, the short helices are connected by two stretches of three glucoses containing one band flip each. The *flips* have the same geometries as in CD10 and CD14, i.e. the structure of CD26 hydrate is modular with elements taken from CD6 and CD10 and from V-amylose [23,24]. The two short single helices in CD26 are oriented antiparallel and contain channel-like cavities with similar width as found in α-CD [1]. The band-flips allow directional changes and avoid destabilization of the polysaccharide chain due to steric strain that would otherwise occur [21].

In analogy with the native CDs, the complexation properties of LR-CDs also have started to be studied [29,30]. LR-CDs may be good host molecules for relatively large guest compounds [6]. The inclusion complex forming ability of the large CDs varies greatly according to their size, suggesting that they, just like the small CDs, are able to present more or less suitable cavities dependent on the size and structure of the guest molecules. An increased flexibility of these molecules allows them either to present a more suitable cavity prior to complex formation or adapt to the guest molecules by an induced fit mechanism [2]. CD14, in particular, can be considered to possess two β-CD-like pseudo-cavities, suitable for complex formation. Since the large CDs are able to present a variety of cavity sizes, compared to the small CDs, they may be useful for special applications. δ-CD, for example, has demonstrated to form a stable complex with C_{70} Buckminsterfullerene that allows its solubilization in water [31]. It has been proven that η-CD (12 glucoses) is effective in the partial separation of carbon nanotubes [32]. Increased interest is evident from the literature on developing techniques for isolation of LR-CDs [33,34] and for examining the properties of these macromolecules as new polysaccharide-based biomaterials [35].

Systematic computational studies gave us deeper understanding about the preferred conformations of many LR-CDs and their deformation modes for conformational interconversions [36–47]. Two more problems we found however necessary to be examined and the results are presented in this report:

(i) The intriguing case CD38, for which expectations were expressed that may crystallize [23]. The least-soluble LR-CDs are those obtained in crystalline forms. Crystallization of CD10, CD14, and CD26 may occur because due to cyclization, they are conformationally restricted and have inherent molecular twofold symmetry so that the band-flips are diametrically opposed. Besides, they are internally stabilized by tight folding and intramolecular hydrogen bonding [23]. For these reasons, doubts were expressed whether CD24 or CD28 would crystallize – one is too short, the other too long to provide structural features as found for CD26; the best candidate may appear to be CD38, with V-helices three turns long [23].

(ii) Further natural step we considered to be the examination of inclusion complexes of LR-CDs. Computationally were examined for the first time inclusion complexes of some lower-size LR-CDs, namely complexes of CD*n* ($n = 13, 14, 26$) with adamantane and of CD14 with 1-hydroxyadamantane.

2. Computational details

For almost a decade duration of our project for large-ring cyclodextrins [36–47] we tried continuously to improve the computational protocol by using different force fields, as well as testing the importance of different parameters related to the conformational search with molecular dynamics, e.g. the shape and the size of the water box in which the CD is merged.

2.1. The conformational search based on molecular dynamics simulations

The MD simulation trajectories subjected to PCA (principal component analysis) analyses were obtained with the AMBER program (versions 10 [48] and 11 [49]) using the parameterization for carbohydrates, Glycam04 [48]. The simulations were run for aqueous solution (a box with TIP4P [50] water molecules) using the particle mesh Ewald (PME) method [51–54] for the treatment of the long-range electrostatics. A 9.0 Å distance cutoff was used for direct space nonbonded calculations and a 1.0×10^{-5} Ewald convergence tolerance for the inclusion of long-range electrostatic contributions. The 'solvateBox' command of LEaP was used to create cubic solvent box around the CD with buffer distances 20.0 Å between the walls of the box and the closest atoms of the solute. The dimensions of the periodic cubic boxes and the number of water molecules for CD38 were 76.4 Å and 13,401, respectively. The SHAKE option (tolerance 5.0×10^{-5} Å) was used for constraining bonds involving hydrogen atoms. Optimized geometries from previous studies were used as starting geometries of CD*n* ($n = 13, 14, 26$), whereas the starting geometry of CD38 was generated with molecular graphics using the crystal geometry of CD26 and adding one more turn of six glucoses to each two-turn helical portions of CD26. The same protocol from our previous studies was used for the preparation of the systems for the simulations [39,41,43]: (i) 5000 steps steepest descent and 200 steps conjugate gradient minimization of the LR-CD in gas-phase, followed by 5000 steps steepest descent and 400 steps conjugate gradient minimization of the whole (LR-CD or complex, plus water molecules) fully unrestrained system; (ii) 50,000 steps steepest descent minimization with holding the solute fixed with positional restraints; (iii) 25.0 ps unrestrained MD were run at 100 K on the water alone with holding the LR-CD constrained (this is the stage of the equilibration process where the bulk of the water relaxation takes place); (iv) gradual release of the restraints on the LR-CD in a series of minimizations and MD steps: 1000 steps minimization and 3.0 ps MD with 25.0 kcal mol^{-1} Å position restraints, followed by five rounds of 600 steps minimization, reducing the positional restraints by 5.0 kcal mol^{-1} Å each run; and (v) the process was completed with short MD simulation (NVT) after heating the system gradually to 298 K. Additional 500.0 ps simulation (NPT) was executed before starting the productive runs. The productive runs were performed with the recommended maximum time-step 2.0 fs when SHAKE is used, at 300 K and an average pressure 1.0 bar with isotropic position scaling. Samplings were taken every 2.0 ps. The duration of the MD conformational search for CD38 was 0.5 μs. Of particular importance when examining the modes of conformational interconversions and the dynamics of the intramolecular self-organization is the monitoring of the appearance and the disappearance of *band-flips* during longer simulation intervals (variation with the simulation time of the *flip* angle, O3(n)···C4(n)···C1($n + 1$) ···O2($n + 1$) – the dihedral flip between secondary hydroxyls of adjacent glucoses).

2.2. Principal component analysis

Principal component analysis (PCA), also called *quasiharmonic analysis* or *essential dynamics* method [55–57], is a very useful