

## Structure and internal motion of solvated beta-cyclodextrine: a molecular dynamics study

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### Abstract

A 5 ns molecular dynamics simulation was performed on a system constituting 512 water molecules and one  $\beta$ -cyclodextrin molecule in a cubic cell with a 26 Å length. The internal motion of the solute molecule was investigated and compared with reports from Molecular Mechanics, Neutron Scattering and Molecular Dynamics. The  $\beta$ -cyclodextrin structure is markedly distorted with the majority of the primary hydroxyl groups pointing towards the inner cavity. The structure and dynamics of the water molecules in the first solvation shells were also investigated. An average number of 25 water molecules compose the inner shell forming a network of hydrogen bonds with the cyclodextrin hydroxyl groups. © 1997 Elsevier Science B.V.

*Keywords:* Cyclodextrin; Polysaccharides; Molecular dynamics

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### 1. Introduction

Cyclodextrins are cyclic oligomers of 1  $\rightarrow$  4 linked  $\alpha$ -D-glucose monomers which form inclusion complexes with several molecules. Owing to this ability, cyclodextrins have been the subject of a considerable number of studies in the past two decades [1–3]. Most of these studies focused on the inclusion complexes of cyclodextrins as well as on the use of these molecules as an environment for chemical reactions [4–6]. More recently these molecules have been employed in chromatography to separate constitutional isomers and enantiomers [7,8]. Subsequently these molecules are of great interest to a wide range of scientists in many fields of chemistry.

The structural features of cyclodextrins have also been investigated. Such studies mainly deal with the inclusion complexes in the solid state [9–11] or in solution phase [12].

In recent years several theoretical investigations have been reported [13–20] most of which have focused on the inclusion process. Few have been concerned with the inherent structural features of cyclodextrins [13,14], with no investigations performed on a fully solvated cyclodextrin structure.

In this paper we have applied molecular dynamics (MD) to the study of  $\beta$ -cyclodextrin in water with the aim of testing the ability of the commonly used force fields to describe the BCD–water interactions. We report here the results of a 5 ns MD simulation of a system constituting a BCD molecule and 512 water molecules.

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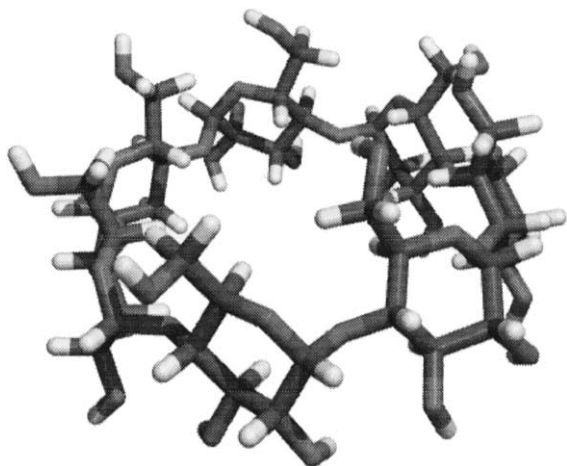


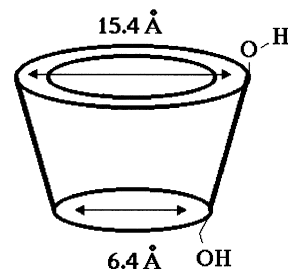
Fig. 1. The  $\beta$ -cyclodextrin molecule.

## 2. Materials and methods

The  $\beta$ -cyclodextrin (BCD) host molecule is shown in Fig. 1. It consists of seven D-glucopyranose monomers connected by  $\alpha$ -(1–4) linkages. Topologically this molecule can be represented by a toroid in which the primary and secondary hydroxyl groups are placed on the smallest and the largest circumferences, respectively (Scheme 1). No hydroxyl group is present within the toroid cavity which, accordingly, has a pronounced hydrophobic character. As a consequence, the ability of the BCD to form inclusion complexes in aqueous solution derives from its cavity, the interior of which is less polar than water.

## 3. Computational details

The MD experiments were performed employing the DLPOLY2 [21] program. The AMBER plus GLYCAM [22] force field was used with the necessary adaptations, while the BCD partial atomic charges were calculated by the Gasteiger method [23]. In the simulation all atoms and water molecules are free to move and all atoms are treated explicitly. The starting  $\beta$ -cyclodextrin structure for the simulation was taken from the 'BCDEX04' entry of the Cambridge Crystallographic Database. The DLPOLY utility *wateradd* was employed to add 512 rigid Simple Point Charge



Scheme 1. Topology of the  $\beta$ -cyclodextrin ring.

(SPC) [24] water molecules to a cubic box with unit cell dimensions  $a = b = c = 26.00 \text{ \AA}$ . Periodic boundary conditions were adopted and a cut-off radius  $R_c = 10 \text{ \AA}$  was applied to the non-bonded interactions; the Ewald summation method was employed to evaluate the coulombic interactions with a dielectric constant value of 1.0. The system was coupled to a thermal bath of  $T_0 = 298 \text{ K}$  [25] using a temperature relaxation time of 0.1 ps. This value makes the temperature coupling weak enough to avoid any significant effect on the atomic properties of the system [14]. Calculations were carried out on an IBM RS6000 and on a CRAY T3D at CINECA (Italy).

A 500 ps MD equilibration run on the BCD–water system was performed in the NPT ( $T = 298 \text{ K}$ ,  $P = 1 \text{ atm}$ ) ensemble. The trajectory was then collected over the next 2000 ps allowing the system to adjust its volume. The run was stopped after 2000 ps as no significant variation in the cell volume and in the total energy was observed during the final 1000 ps. The final

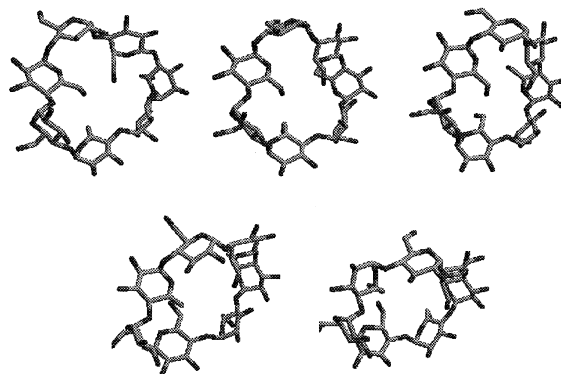


Fig. 2. Snapshots from the 30 ps movie of the BCD internal motion. The hydrogen atoms and the water molecules are omitted for ease of view.

Table 1

Distances between the glycosidic oxygen atoms (OS) in residues  $i$ ,  $i + 1$ , and  $i + 2$

Residue number	$R_{i,i+1}$ (Å)	$R_{i,i+2}$ (Å)
OS1	5.32	8.66
OS2	4.76	8.73
OS3	4.49	6.88
OS4	4.65	8.61
OS5	4.35	7.56
OS6	4.59	9.23
OS7	4.70	7.40

cubic cell dimensions were  $a = b = c = 25.45$  Å. The endpoint of the NPT run was used as starting configuration for a 5000 s trajectory in the NVT ensemble ( $T = 298$  K) which was recorded for the analysis.

#### 4. Results and discussion

A 30 ps movie of the internal motion in the BCD molecule was extracted from the trajectory. Snapshots from the movie are shown in Fig. 2. The BCD structure is strongly deformed and the primary hydroxyls are mostly rotated towards the interior of the cavity; this results in closing of the bottom rim of the BCD molecule. Also, a network of interglucose primary OH bonds forms, in agreement with the radial distribution function shown in Fig. 3. This evidences the propensity for the primary hydroxyls to form small clusters maximising the hydrogen bonding cooperativity [26]. These findings agree well with the reports of a Molecular Mechanics investigation on symmetry breaking in cyclodextrins [13]. The mean distances

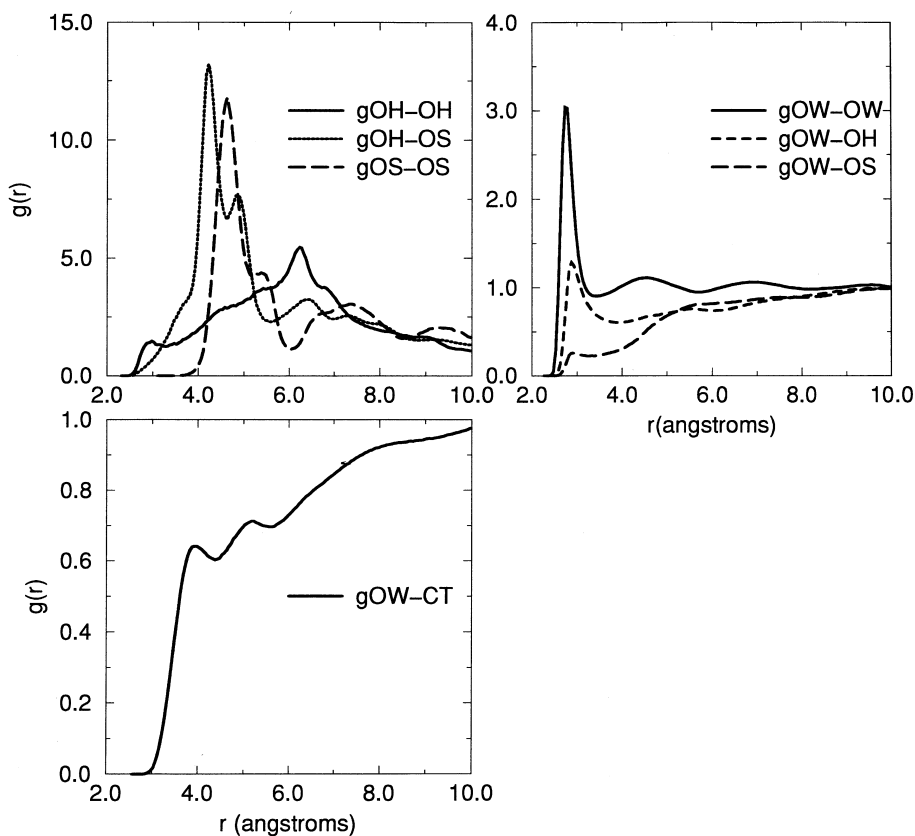


Fig. 3. (1st row, left) Radial Distribution Functions between the BCD hydroxyl (OH) and glycosil (OS) oxygen atoms. In the equilibrium conformation the hydroxyl groups of the BCD molecule link together and with the glycosidic oxygens via the formation of hydrogen bonds, as evidenced by the first peaks of the  $g(r)$ . The successive peaks reflects the periodicity of the BCD molecule. (1st row, right) Radial Distribution Functions between the water oxygen atoms (OW) and the BCD hydroxyl (OH) and glycosidic (OS) oxygen atoms. (2nd row) Radial Distribution Functions between the water oxygen atoms (OW) and the BCD carbon atoms (CT).

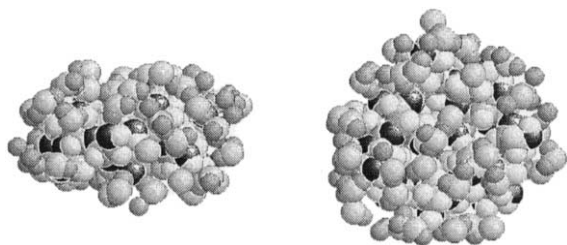


Fig. 4. Snapshots along the  $z$ -axis and the  $x$ -axis of the equilibrium conformation after a 5 ns MD run. Only the water molecules within 3.5 Å from the BCD atoms are represented in the 'spacefill' model.

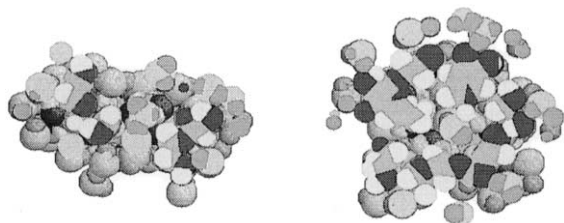


Fig. 5. Sections along the  $y$ - $z$  and  $x$ - $y$  planes of the BCD-water complex. A couple of water molecules are enclosed in the cavity.

between neighbouring glycosidic oxygen atoms (OS) calculated for the set of configurations in Fig. 2 are shown in Table 1 and indicate the extent of the deformation of the system. In the symmetric model the distances between the OS atoms (residues  $i$  to  $i + 1$ )

are about 4.5 Å and between residues  $i$  to  $i + 2$  are about 8.5 Å.

The cage of water molecules around the BCD is shown in Fig. 4. Only water molecules within a radius of 3.5 Å of the BCD oxygen atoms are represented. Water molecules in the first solvation shells form a network of hydrogen bonds with both the primary and secondary hydroxyl groups.

The radial distribution function between the BCD hydroxyl oxygen atoms (OH) and the water oxygen atoms (OW) (Fig. 3) reveals the existence of two shells of water molecules around the BCD molecule at  $R = 3$  and  $R = 5.4$  Å, respectively. The  $g_{OW-OW}$  function is almost equal to that computed for bulk water [27]. The BCD glycosidic oxygens (OS) interact to a negligible extent with the water molecules. This is probably due to the repulsion of the hydrophobic carbon skeleton of the BCD ring.

The snapshots in Fig. 4 also show the existence of void spaces on the BCD surface corresponding to the hydrophobic carbon atoms of the BCD skeleton. This visual impression is confirmed by the examination of the radial distribution function between the water oxygens and the BCD carbon atoms in Fig. 3. The plot evidences the hydrophobic effect of the inner cavity of the BCD molecule. The first shell of water molecules is 3.8 Å away from the BCD carbon atoms. The position of the first peak agrees with

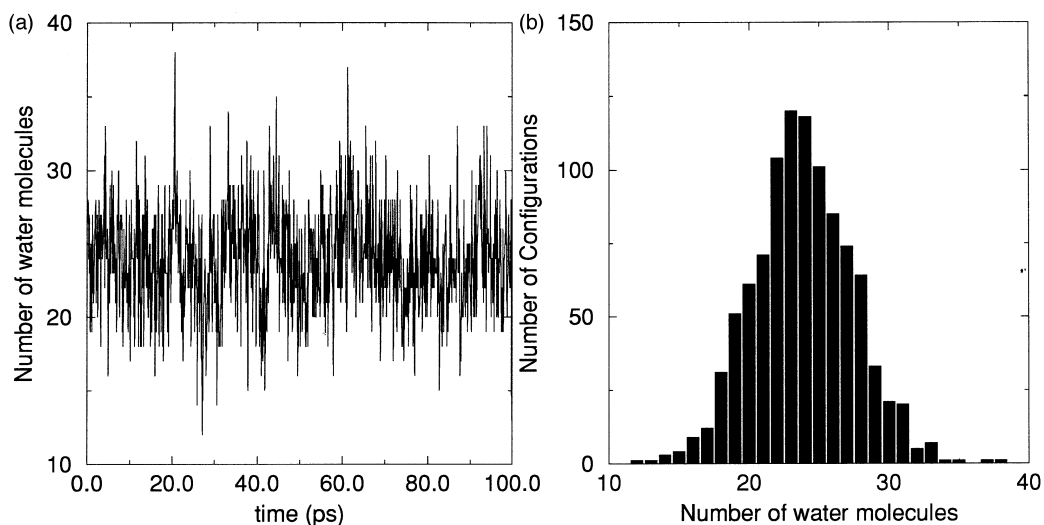


Fig. 6. (a) Fluctuation of the NWM over a 1000 uniformly sampled configuration. (b) Distribution of the NWM over a 1000 uniformly sampled configuration.

the report of about 3.6 Å for the methane–water system [28].

The water molecules move onto the surface of the BCD molecule where they form a pattern corresponding to the BCD oxygen atoms. Only seldom do one or two water molecules penetrate briefly into the cavity (Fig. 5).

The fluctuations of the number of water molecules (NWM) in the first solvation shell are shown in Fig. 6a. The data were collected at 0.1 ps regular steps from a 100 ps sample. The distribution of the NWM is shown in Fig. 6b.

Small fluctuations around the mean value of 25 water molecules occur within a time interval that can be roughly indicated to be 25–30 ps.

## 5. Conclusions

An analysis of the BCD–water structure has been undertaken employing molecular dynamics and empirical force fields. Both inter and intramolecular hydrogen bond networks have been highlighted, thus agreeing with data from Molecular Mechanics [13], Molecular Dynamics [14,29], and Neutron/X-Ray diffraction [30,31] studies. Moreover, we wish to point out that the overall structure of the BCD molecule markedly differs from the highly symmetric ones usually reported in the literature. The BCD molecule spends most of its time in asymmetric conformations with the primary hydroxyl ring closed off. The results reported here validate the force field we employed and, in a future perspective, will allow us to undertake investigation of the dynamics of a guest molecule inclusion in the presence of the solvent.

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## References

- [1] J. Szejtli, Cyclodextrins and Their Inclusion Complexes, Akademiai Kiado, Budapest, 1982.
- [2] M.L. Bender, M. Komiyama, Cyclodextrin Chemistry, Springer-Verlag, Berlin, 1978.
- [3] J. Szejtli, Proc. 1st Int. Symp. Cyclodextrin, 1981, p. 469.
- [4] Y. Kawajiri, N. Motohashi, J. Chem. Soc. Chem. Comm., (1989) 1336.
- [5] M. Komiyama, Y. Takeshige, J. Org. Chem. 1336 (1989) 54.
- [6] W.S. Chung, N.J. Turro, J. Silver, W.J. leNoble, J. Am. Chem. Soc. 1202 (1990) 112.
- [7] R.W. Souter, Chromatographic Separation of Stereoisomers, CRC Press, Boca Raton, 1985.
- [8] S.G. Allenmark, in: W.J. Lough (Ed.), Chiral Liquid Chromatography, Blackie and Son, London, 1989.
- [9] J.A. Hamilton, L. Chen, J. Am. Chem. Soc. 5833 (1988) 110.
- [10] B. Klar, B. Hingerty, W. Saenger, Acta Crystallogr. B 1154 (1980) 36.
- [11] C. Betzel, W. Saenger, B. Hingerty, G.M. Brown, J. Am. Chem. Soc. 6269 (1984) 106.
- [12] F.V. Bright, G.C. Catena, J. Huang, Am. Chem. Soc. 1343 (1990) 112.
- [13] K.B. Lipkowitz, J. Org. Chem. 6357 (1991) 56.
- [14] J. Kohler, in: J.M. Goodfellow (Ed.), Molecular Dynamics. Applications in Molecular Biology, MacMillan Press, London, 1991.
- [15] J. Kohler, M. Hohla, M. Richters, W.A. Koenig, Chem. Ber. 119 (1994) 127.
- [16] E. Alvira, C. Civiola, J.I. Garcia, J.A. Mayoral, Tetrahedron Lett. 2129 (1995) 36.
- [17] V.B. Luzhkov, C.A. Venanzi, J. Phys. Chem. 2312 (1995) 99.
- [18] M.E. Amato, K.B. Lipkowitz, G.M. Lombardo, G.C. Pappalardo, J. Chem. Soc. Perkin Trans. 2 (1996) 321.
- [19] P. Ivanov, D. Salvatierra, C. Jaime C, J. Org. Chem. 7012 (1996) 61.
- [20] G. Fronza, A. Mele, E. Redenti, P. Ventura, J. Org. Chem. 909 (1996) 61.
- [21] DLPOLY2 is a package of molecular simulation routines written by W. Smith and T.R. Forester, copyright the Council for the Central Laboratory of the Research Councils, Daresbury Laboratory, Nr Warrington (1994–6).
- [22] R.J. Woods, R.A. Dwek, C.J. Edge, B. Fraser-Reid, J. Phys. Chem. 3832 (1995) 99.
- [23] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, J. Hermans, in: B. Pulmann (Ed.), Intermolecular Forces, Reidel, Dordrecht, 1981.
- [24] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, J. Hermans, J. Phys. Chem. 3684 (1984) 81.
- [25] J.E.H. Koehler, W. Saenger, B. Lesyng, J. Comput. Chem. 1090 (1987) 8.
- [26] E. Clementi, Lectures Notes in Chemistry 2, 1976.
- [27] C.H. Bridgeman, A.D. Buckingham, N.T. Skipper, Chem. Phys. Lett. 209 (1996) 253.
- [28] K.B. Lipkowitz, G.A. Anderson, in: G. Wipff (Ed.), Computational Approaches in Supramolecular Chemistry, Kluwer Acad., Dordrecht, 1994.
- [29] T. Steiner, S.A. Mason, W. Sanger, J. Am. Chem. Soc. 6184 (1990) 112.
- [30] T. Steiner, W. Sanger, R.E. Lechner, Mol. Phys. 1211 (1991) 6.
- [31] T. Steiner, S.A. Mason, W. Sanger, J. Am. Chem. Soc. 5676 (1991) 112.