Computational study of beta-cyclodextrin-water system

SILVIA PATACHIA, CATALIN CROITORU
Chemistry Department
“Transilvania” University of Brasov
Eroilor 29 Str., 500036
ROMANIA

Abstract: Beta-cyclodextrin is a cyclic oligosaccharide with large applications in medicine, pharmacy and food industry, due to its unique architecture which enables the formation of supramolecular aggregates with small molecular compounds. In this work, some aspects regarding the behavior of beta-cyclodextrin molecules in water at different concentrations have been simulated with specialized software and correlated with existent experimental data, in order to understand better the complexity of the BCD-water system and to define future applications.

Key-Words: beta-cyclodextrin, interactions, molecular dynamics, energy minimization, force field, MM2

1 Introduction
Beta-cyclodextrin [BCD] is a cyclic oligomer of glucose, comprised of 7 glucopyranoside units linked in 1-4 positions (fig. 1). It is obtained at industrial scale by enzymatic conversion of starch [1].

Due to this arrangement, the interior of the toroid is hydrophobic and thus able to host other hydrophobic molecules. In contrast, the exterior is hydrophilic enough to impart cyclodextrins (or their complexes) water solubility.

The formation of the inclusion compounds modifies the physical and chemical properties of the guest molecule, mostly in terms of its water solubility. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications: because inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions. In most cases, the mechanism of controlled degradation of the inclusion complexes of BCD is based on the pH change in different body humours, leading to the cleavage of hydrogen or ionic bonds between the host and the guest molecules [3].

Besides the above mentioned pharmaceutical applications for drug release, cyclodextrins can be employed in environmental protection: these molecules can effectively immobilize inside their rings toxic compounds, or can form complexes with stable substances, or sewage sludge, easing their separation. In the food industry cyclodextrins are employed for the preparation of cholesterol free products. The ability of cyclodextrins to form complexes with hydrophobic molecules has led to their usage in supramolecular chemistry. In particular, they have been used to synthesize certain mechanically interlocked molecular architectures, such as rotaxanes and catenanes.

Complex methods of analysis have failed to explain in every detail the mechanism of the BCD-small molecular compounds inclusion complex formation and
beta-cyclodextrin-water system behavior, such as the low solubility of BCD in water (1.1% wt.).

Modern methods for computational modeling of molecules play an important role in understanding the features of dissolution processes. Theoretical studies make it possible to explain the characteristics of the system obtained experimentally, and if there is not enough experimental data, to predict the behavior of the system in different situations [4].

To develop new applications of BCD in pharmacy and medicine, a thorough study of the mechanism of BCD dissolution in water needs to be done.

This task is a tedious one to be achieved experimentally, so we have simulated the dissolution of beta-cyclodextrin in water at different concentrations, and the conformation of the cyclodextrin-water hydrate at equilibrium has been computed.

The structures obtained for each cyclodextrin concentration have then been correlated to the density-concentration and refractive index-concentration dependences, in order to pertinently evaluate their significance.

2 Experimental

Beta-cyclodextrin has been purchased from Aldrich and has been used further without any purification/treatment. 20 mL of BCD solutions (0.2%, 0.5%, 0.8% and 1% wt.) have been prepared by adding a determined amount of BCD powder into Milli-Q distilled water.

The densities of the BCD solutions have been determined using the picnometric method.

The mass has been determined with a KERN-ABJ balance with $10^{-4}$ g precision.

The refraction index has been determined with a Pullfrich Karl-Zeiss refractometer, using the red filter of the mercury lamp ($\nu_e$) and $V_0F_4$ quartz prisms.

All measurements have been performed at 25°C.

The simulations of the BCD-water structures for different BCD concentrations have been performed on an Intel 2.83 GHz processor architecture using the ChemBio 3D Ultra software (developed by Cambridge Soft). MM2 force field has been used to minimize the energy of the studied system, before applying MM2 molecular dynamics for 300 K. For molecular dynamics calculations, 10000 iterations for every studied system have been performed, with an average speed of 10 frames/s.

Norman L. Allinger has developed MM2 force field, for a broad range of chemicals. It is designed to reproduce the equilibrium covalent geometry of molecules as precisely as possible. It implements a large set of parameters that is continuously refined and updated for many different classes of organic compounds.

The software calculates the total energy of the given system in initial state, and each iteration minimizes the total energy by moving the atoms of the system in a position that is energetically more favorable than the previous one. The modeling stops when the system reaches equilibrium (when the total energy of the system remains constant).

3 Results and discussion

The dependence of the density ($\rho$), respectively refractive index measured for the red filter of the mercury lamp ($n_e$) on BCD concentration is illustrated in Fig.3 and Fig. 4 for the BCD aqueous solutions:

![Fig. 3. Density dependence of aqueous BCD solutions on BCD concentration](image)

![Fig. 4. Refractive index of aqueous BCD solutions dependence on BCD concentration](image)

The results regarding the MM2 molecular dynamics of BCD aqueous solutions at 300 K are shown in figures 7 to 12. The BCD and the water molecules are represented separately in figure 6:
Fig. 6. *BCD and water molecules*

Fig. 7. *Water molecules*

Fig. 8. *0.1 % BCD aqueous solution*

Fig. 9. *0.2 % BCD aqueous solution*

Fig. 10. *0.4 % BCD aqueous solution*

Fig. 11. *0.5 % BCD aqueous solution*
As it can be seen from figure 3 and 4, the behavior of the BCD-water system is not ideal. The density respectively refractive index dependence on solution’s concentration is Boltzmannian. This means that BCD and water molecules associate themselves, probably through hydrogen bonds. At low cyclodextrin concentrations (below 0.5%) H-bonds between water molecules seem to be partially broken by BCD’s molecules that intercalated between them, forming new H-bonds that ensure the BCD dissolution. The simulation exhibits the BCD’s molecules surrounded by water molecules, forming a relatively homogeneous structure, with an increasing compactity when the BCD concentration increases. At 0.5% BCD, the molecular dynamic simulation evidences an interesting change of the system’s structure: water molecules seem to be rejected by the BCD molecules and an expansion of the system occurred. This could be correlated with the slope decreasing of the dependency between system’s density and BCD’s concentration and with the inflexion point from the graph of refractive index function of BCD’s concentration. At higher BCD’s concentrations, it could be seen that BCD’s molecules occupy closer positions that allow stronger interaction between OH groups from the neighbour molecules. The simulated structures evidence a more expanded state due to the interaction between molecules of BCD that have a specific molecular shape, difficult to be changed. At 4% of BCD, very close structure of the system to the pure BCD has been obtained, fact that suggests the phase separation, proved by BCD’s limit of solubility in water. The experimental data and the computational results are in good agreement.

**Conclusion**

Computational simulations of different systems comprising of water and beta-cyclodextrin in different concentrations have been performed using the MM2 force field approximation. The density and the refractive index of the aqueous solutions of beta-cyclodextrin have been determined experimentally and correlated with the computed simulations. It has been found that the simulated structures concord and explain the solutions density and refractive index dependencies, respectively, with the cyclodextrin concentration. Based on the information gathered from the computed simulations, further applications of beta-cyclodextrins as drugs’ solubilization enhancement in different solvents can be outlined.

**References:**