Molecular Properties Related to the Anomalous Solubility of β-Cyclodextrin

Kevin J. Naidoo,*,† Jeff Yu-Jen Chen,† Jennie L. M. Jansson,‡,§ Göran Widmalm,‡ and Arnold Maliniak§

Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa, and Division of Physical Chemistry and Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

Received: December 4, 2003; In Final Form: February 18, 2004

Analyses of trajectories generated in molecular dynamics (MD) computer simulations and pulse-field-gradient spin−echo nuclear magnetic resonance (PGSE NMR) experiments were used to investigate the molecular origin of the anomalous solubility of β-cyclodextrin (CD) in water. The solubility of β-CD (seven glucose units) is 1 order of magnitude lower compared with α- and γ-CDs, which comprise six and eight glucose residues, respectively. The translational diffusion coefficients derived from NMR and MD are in good agreement and reveal a small but significant deviation from the molecular mass dependence. The β-CD is seen to increase the local water structure dramatically while its internal motion displays a smaller amplitude and faster relaxation of the macrocyclic structure compared with the two other compounds. These results collectively indicate that the relatively rigid macrocyclic structure of β-CD strongly affects the surrounding water ordering, thereby lowering the configurational entropy that results in the well-known anomaly of the β-CD water solubility.

Cyclodextrins (CDs) continue to attract considerable scientific attention due in part to the many spectacular applications related to guest−host and supramolecular chemistry. CDs can be described as shallow, truncated cones with a hydrophobic interior. The cavity selectively complexes guest molecules in aqueous solutions. Three of the most important cyclodextrins are α-CD, β-CD, and γ-CD in order of increased size. Because of its cavity size and relative ease of chemical modification, the derivatives of β-CD have been used commercially as drug carriers. An inhibiting property of β-CD has been its relatively low solubility in water compared with those of α- and γ-CDs that are nine and eleven times more soluble, respectively.[1] Therefore, a detailed understanding, based on molecular mechanisms, of the anomalous behavior of β-CD is important for catalytic, industrial, and pharmaceutical applications of CDs.[2,3]

We investigate the molecular origin of the solubility anomaly employing analyses of 5 ns trajectories generated in molecular dynamics (MD) computer simulations of α-, β-, and γ-CD solutions. In particular, we focus on investigations of local water structure and conformational dynamics of the CD molecules. In addition, translational diffusion measurements were performed on the three CDs (1 mM in D_2O) at 25 °C using a pulse-field-gradient spin−echo nuclear magnetic resonance (PGSE NMR) method.[4]

All simulations were carried out using a isothermal−isobaric ensemble (NPT) where the pressure and temperature were kept constant ($P = 1$ bar and $T = 300$ K) using the Langevin Piston method[5] as implemented in CHARMM.[6] We chose a relatively large piston mass (500 amu) and a low piston collision frequency (5 ps^{-1}) which results in a NPT ensemble with minimal effect on molecular motion for inhomogeneous systems[5,7] such as cyclodextrin solutions. A CHARMM-like force field specifically parametrized for carbohydrates[8] was used to model the CDs. The SPC/E water model[9] implemented with periodic boundary conditions was employed for description of the solvent. The α-, β-, and γ-CDs were immersed in simulation boxes of 4040 water molecules with the solution densities of 1.013 g/cm^3.

TABLE 1: Diffusion Coefficients ($\times 10^{10}$ m^2/s) of α-, β-, and γ−CD Determined from NMR and Calculated from MD Simulations within 95% Confidence Limits

method	α-CD	β-CD	γ-CD
NMR	2.292 ± 0.025	2.168 ± 0.015	2.097 ± 0.017
MD	2.535 ± 0.035	2.400 ± 0.060	2.375 ± 0.070

The diffusion constants collected in Table 1 were experimentally determined employing a PGSE NMR technique and calculated from the MD trajectories using the mean square displacement. The average diffusion coefficients of HDO in a standard sample and in the CD solutions were 1.900×10^{-9} and 1.895×10^{-9} m^2/s respectively, reflecting the accuracy of the diffusion measurements. In light of the viscosity difference ($\eta_{D_2O}/\eta_{H_2O} = 1.23$)[10] of the solvent in experiments and simulations, diffusion coefficients obtained from the MD trajectories are in a good agreement with those observed experimentally.

Results in Table 1 indicate molecular mass dependence with the slowest and fastest diffusion observed for γ- and α-CDs, respectively. The Stokes−Einstein equation provides a simple relationship between the diffusion coefficient and the molecular mass. Closer examination of the NMR and MD results reveals, however, a small but significant deviation from this model. The same trend in this deviation was observed for both NMR and MD.

The water structure around the cyclodextrins was analyzed using three-dimensional spatial distribution functions (SDFs),[11] shown in Figure 1. The chosen contours represent the probability of finding water molecules around the CD that is 50% higher compared with that in the bulk solvent. Thus, the SDFs reflect the local water density and can be related to the tendency of

* To whom correspondence should be addressed. E-mail: knaidoo@science.uct.ac.za. Fax: +27-21-689-7499.

† University of Cape Town.

‡ Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University.

§ Division of Physical Chemistry, Stockholm University.

10.1021/jp037704q CCC: $27.50
Published on Web 03/16/2004

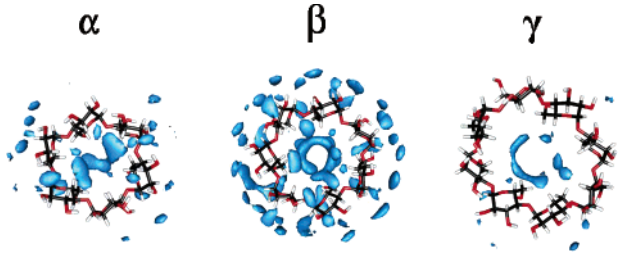

Figure 1. Contour plots of water spatial distribution functions corresponding to the probability density 50% above bulk water as calculated from the MD trajectories.

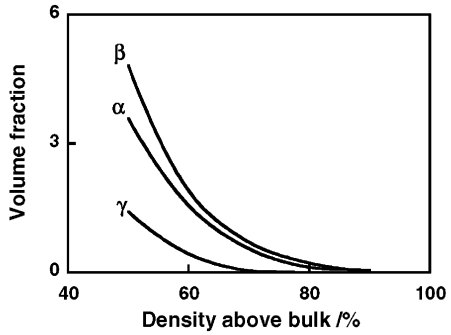

Figure 2. Volume fraction ($\times 10^4$) occupied by the structured water, derived from the SDFs for the CDs.

the CDs to limit the configurational entropy of the water as compared with the bulk region. We note that the least soluble, β-CD, induces strong order on the surrounding water, a result that is consistent with enthalpy−entropy compensation studies of α- and β-CD solutions.[12] The most soluble cyclodextrin, γ-CD, on the other hand, structures the water to a significantly lesser extent compared the other two CDs. The α-CD is an intermediate case. Thus, a strong correlation emerges between solubility and the extent to which the CDs interfere with the local water structure.

Calculating the volume of the contours associated with above bulk water probability densities for the three cyclodextrin solutions gives a more accurate assessment of the total fraction of water molecules that are localized around the three cyclodextrins compared with the bulk solvent. The results of these calculations are graphically illustrated in Figure 2.

The notion that CDs are rigid molecules based on early X-ray diffraction studies has been largely modified so that today CDs are accepted to be flexible.[3] The flexibility is related to the local fluctuations of the individual glucose rings and distortions of the macrocyclic structure.[13] Here we investigate the internal motion of the cyclodextrins in solution by removing the reorientational and translational dynamics of the CDs from the MD trajectories. The time scale and amplitude of the internal motion were estimated by calculating the root-mean-square (RMS) fit time correlation function, TCF, where RMS(t_a,t_b) is the best RMS fit obtained between structures at times t_a and t_b using a standard fitting procedure.[14] The TCF, $C_{RMS}(t)$, is defined (in Å) as $C_{RMS}(t) = \langle RMS(0,t) \rangle$.

The general behavior of the three TCFs shown in Figure 3 is similar. Initially, a perfect correlation between the molecular structures is observed, and therefore, RMS(0,0) = 0. Subsequently, the TCFs, i.e., difference between the structures, increase and reach a plateau in the long time limit. Two types of information can be derived from the TCFs: (i) a value of $C_{RMS}(t)$ corresponding to the plateau and (ii) a characteristic (relaxation) time required to reach the plateau. The value of the plateau can be interpreted as a generalized amplitude of the

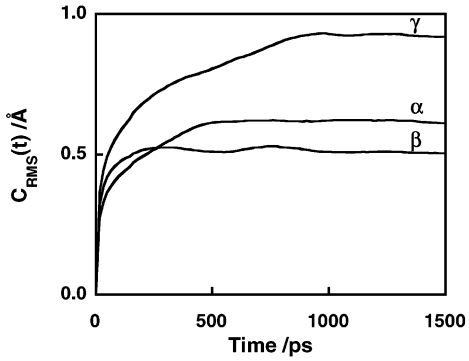

Figure 3. Time correlation functions (TCFs) of the RMS fit calculated for the three CDs.

internal motion, whereas the time to reach the plateau reflects the relaxation process of the macrocyclic ring toward the equilibrium structure. Again, a deviant behavior is observed for the β-cyclodextrin. The TCFs show that β-CD undergoes the most restricted macrocyclic ring motion and relaxes significantly faster than the other CDs. The levels of the plateau are 0.6, 0.5, and 0.9 Å, whereas the estimated relaxation times are 500, 200, and 850 ps for α-, β-, and γ-CDs, respectively. We conclude therefore that β-CD undergoes small amplitude fast librations. Furthermore, we can argue that the constrained motion of the β-CD is more likely to trap water molecules within its hydrophobic cavity and in the first hydration shell compared with the relatively flexible γ-CD, which interferes only to a minor degree with the surrounding solvent.

To further characterize the motional picture of the macrocyclic structure, additional analyses were performed: (a) pseudo torsion angles were constructed where the four atoms consisted of glycosidic oxygens and (b) the motion of the glucose units with respect to the normal of the CDs. These analyses resulted in distributions of angles (not shown), which clearly indicated the most restricted motion for β-CD.

In summary, the origin of the anomalous solubility of the β-cyclodextrin can be explained by its tendency to highly increase the local water structure in the cavity and around the molecule. The structuring of water can, in turn, be related to the restrained macrocyclic ring motions. Thus, the relatively "rigid" macrocyclic compound is not easily accommodated into the overall water structure compared with α- and γ-CDs. Remarkably, the increase in flexibility in the sequence β-, α-, and γ-CD correlates with the solubility pattern of the three cyclic oligosaccharides. We intend to investigate the details of conformational properties of the CDs using modern NMR techniques.[15]

Acknowledgment. This work was supported by the National Research Foundation (NRF-Pretoria), the Swedish International Development Cooperation Agency (SIDA), and the Swedish Research Council (VR). We thank Michelle Kuttel for helpful discussions.

References and Notes

(1) French, D.; Levine, D.; Pazur, J. H.; Norberg, E. *J. Am. Chem. Soc.* **1949**, *71*, 353−356. (b) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1753.

(2) Stezowski, J. J.; Parker, W.; Hilgenkamp, S.; Gdaniec, M. *J. Am. Chem. Soc.* **2001**, *123*, 3919−3926. (b) Jozwiakowski, M. J.; Connors, K. A. *Carbohydr. Res.* **1985**, *143*, 51−59. (c) Starikov, E. B.; Brasicke, K.; Knapp, E. W.; Saenger, W. *Chem. Phys. Lett.* **2001**, *336*, 504−510. (d) Manunzaa, B.; Deianaa, S.; Pintorea, M.; Gessab, C. *J. Mol. Struct. (THEOCHEM)* **1997**, *419*, 133−137.

(3) Dodziuk, H. *J. Mol. Struct.* **2002**, *614*, 33−45.

(4) Gibbs, S. J.; Johnson, C. S. *J. Magn. Reson.* **1991**, *93*, 395−402. (b) Lycknert, K.; Höög, C.; Widmalm, G. *J. Chem. Soc., Perkin Trans. 2* **2002**, 416−421.

(5) Feller, S. E.; Zhang, Y.; Pastor, R. W.; Brooks, B. R. *J. Chem. Phys.* **1995**, *103*, 4613−4621.

(6) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4* (2), 187−217.

(7) Kolb, A.; Dunweg, V. *J. Chem. Phys.* **1999**, *111*, 4453−4459.

(8) Kuttel, M. M.; Brady, J. W.; Naidoo, K. J. *J. Comput. Chem.* **2002**, *23*, 1236−1243.

(9) Berendsen, H. J. C.; Grigera, R. J.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269−6271.

(10) Mills, R.; Harris, K. R. *Chem. Soc. Rev.* **1976**, *5*, 215−231.

(11) Liu, Q.; Brady, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 12276-12286. (b) Naidoo, K. J.; Kuttel, M. M. *J. Comput. Chem.* **2001**, *22*, 445−456.

(12) Linert, W.; Margl, P.; Renz, F. *Chem. Phys.* **1992**, *161*, 327−338.

(13) Lipkowitz, K. B. *J. Org. Chem.* **1991**, *56*, 6357−6367.

(14) Kabsch, W. *Acta Crystallogr.* **1976**, *A32*, 922−923. (b) Kabsch, W. *Acta Crystallogr.* **1978**, *A34*, 827−828.

(15) Stevensson, B.; Landersjö, C.; Widmalm, G.; Maliniak, A. *J. Am. Chem. Soc.* **2002**, *124*, 5946−5947. (b) Stevensson, B.; Sandström, D.; Maliniak, A. *J. Chem. Phys.* **2003**, *119*, 2738−2746.