

# A molecular dynamics study of the inclusion of mono- and disubstituted benzenes in $\beta$ -cyclodextrin

B. Manunza,\* S. Deiana,\* M. Pintore,\* and C. Gessa†

\*DISAABA, Università di Sassari, Sassari, Italy

†Istituto di Chimica Agraria, Bologna, Italy

**Abstract:** The interaction between  $\beta$ -cyclodextrin and five mono- and disubstituted benzenes in water was investigated by means of molecular dynamics. The trajectories were calculated for each system, imposing a 1:1 host-guest stoichiometry with 512 water molecules. Periodic boundary conditions were adopted. The results account for the formation of stable adducts and the predicted geometry agrees with experimental circular dichroism data. © 1997 by Elsevier Science Inc.

**Keywords:** cyclodextrin, phenol, aniline, nitrobenzenes, molecular dynamics, inclusion complexes

## INTRODUCTION

Cyclodextrins are cyclic oligosaccharides that form inclusion complexes with several molecules. Owing to this ability, they have been the subject of studies concerning their stabilization of labile pesticides and the improvement of their residual activity. Although a considerable number of experimental studies about the inclusion have been carried out, there are still only a few theoretical studies on the inclusion process<sup>1, 2</sup>. Being interested in the investigation of pesticide inclusion into the cyclodextrin cavity, we tested the ability of some available force fields to describe the interactions that occur in the host-guest couple. To do this we performed a molecular dynamics investigation of the complex formation of phenol, *p*-nitrophenol, *p*-hydroxyphenol, aniline, and *p*-nitroaniline with  $\beta$ -cyclodextrin. These compounds were chosen because the properties of their adducts with the  $\beta$ -cyclodextrin mole-

cule are well known<sup>3-5</sup> so that they constitute a valid test for a molecular dynamics experiment.

## MATERIALS AND METHODS

The  $\beta$ -cyclodextrin (BCD) molecule is shown in Figure 1. It consists of seven D-glucopyranose monomers connected by  $\alpha(1\rightarrow4)$  linkages.

Topologically this molecule can be represented as a toroid in which the primary and secondary hydroxyl groups are placed on the smaller and larger 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 BCD to form inclusion complexes in aqueous solution derives from its cavity, whose interior is less polar than water.

The molecular dynamics (MD) experiments were performed employing the DLPOLY2<sup>6</sup> program. The AMBER plus GLYCAM<sup>7</sup> force field was used with the necessary adaptations, while the partial atomic charges were calculated by a semiempirical SCF-MO calculation using the AM1 Hamiltonian<sup>8</sup> and the program MOPAC<sup>9</sup>. Periodic boundary conditions were adopted. Calculations were carried out on an IBM RS6000.

Preliminary MD runs were done, in the absence of solvent, on systems composed of one guest and one host molecule in a cubic cell arrangement with  $a = b = c = 26.0$  Å. The systems were allowed to equilibrate in the NVT ensemble at 298 K for 150 ps. The final configurations were taken as the starting point for an MD simulation with 512 water molecules. The trajectories were computed in the NPT ensemble at  $P = 1$  atm. Each system was equilibrated at  $T = 298$  K for 100 ps, cooled to 0 K for 50 ps, and successively heated to 400 K in 100-K steps, 100 ps of simulation for each step. Finally, the system was equilibrated for 100 ps at 298 K, and a 200-ps trajectory was recorded.

Address reprint requests to: B. Manunza, DISAABA, Università di Sassari, V. le Italia 39, 07100 Sassari, Italy.

Paper submitted to Electronic Conference of the Molecular Graphics and Modelling Society, October 1996.

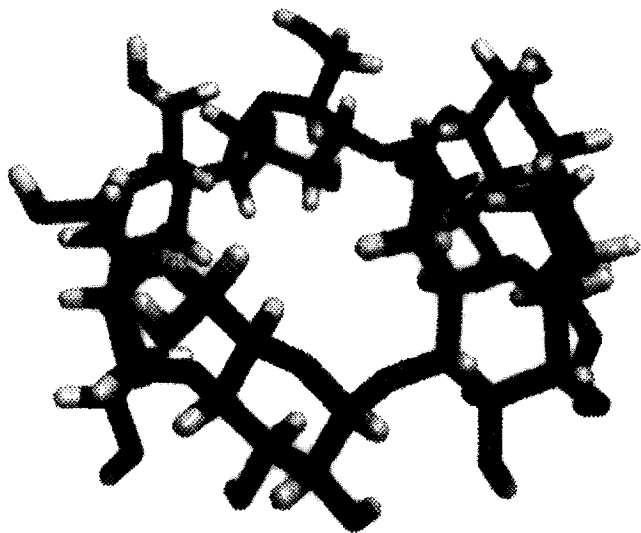
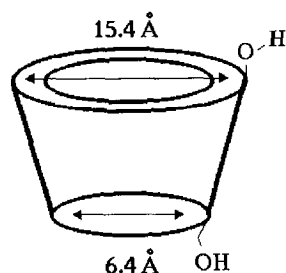


Figure 1. The cyclodextrin molecule.



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

## RESULTS AND DISCUSSION

### Aniline and phenol

Aniline and phenol are included with their molecular axis strongly inclined (Figure 2a, c, and d). The  $g(r)$  values (Figure 3a and b) indicate the formation of hydrogen bonds between the hydroxyl groups of the top torus in the BCD molecule and the N and O atoms of the guest molecules. These findings are compatible with Kamiya et al.<sup>5</sup> according to whom the phenolic hydroxyl group is reluctant to enter the hydrophobic BCD cavity and remains in the vicinity of the top torus with some preferred orientation. Both aniline and phenol molecular axes are strongly inclined as shown in Figure 2a, c, and d; this qualitatively agrees with circular dichroism data<sup>5</sup> reporting values of 27.5 and 19.6° for the inclination angle of the symmetry axis of phenol and aniline, respectively, from the cavity axis.

### *p*-Nitrophenol, *p*-hydroxyphenol, and *p*-nitroaniline

The *p*-nitrophenol molecule is included in a strictly axial way (Figure 2b), agreeing with literature data<sup>3,5</sup>. The  $g(r)$  values (Figure 3c) indicate a close association among the nitro group

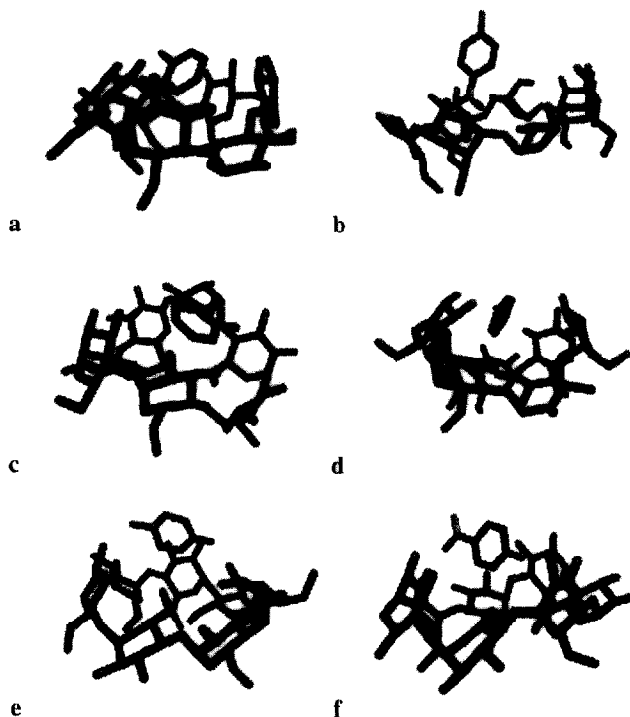


Figure 2. Snapshot taken after 200-ps trajectory of the complexes of the BCD with aniline (a), *p*-nitrophenol (b), phenol (c and d), *p*-hydroxyphenol (e), and *p*-nitroaniline (f). Hydrogen atoms and water molecules are omitted.

atoms and the hydroxyl groups of BCD. However, the molecule does not penetrate deeply into the host cavity as reported by nuclear magnetic resonance (NMR) investigations<sup>10</sup>. This may be due to a strong deformation observed in the BCD ring, being two of the monomers rotated about 90° with respect to the most stable conformation.

*p*-Hydroxyphenol and *p*-nitroaniline are included in a similar way (Figure 2e and f) and their polar groups strongly interact with the hydroxyl groups of the top torus, as indicated by the  $g(r)$  (Figure 3d and e). This trend is reasonable for *p*-hydroxyphenol, which forms hydrogen bonds with both its polar ends,<sup>3,5</sup> whereas *p*-nitroaniline is expected to enter deeper into the BCD cavity and with a small inclination angle. Our findings support the observation of Buvary and Barcza,<sup>4</sup> according to whom in the large BCD cavity the fit of the guest is not very tight; consequently, van der Waals forces are weaker and deviations from axial insertions are possible, so that hydrogen bonding may contribute to the interaction, even with the *para* isomers.

## CONCLUSIONS

The results reported here indicate a good qualitative agreement between the model and the experimental data. Future work should be devoted to fine-tuning the nonbonding interaction parameters in order to reproduce the experimental enthalpy data and improve the agreement between the experimental and the simulated geometries. We also hold that the force field

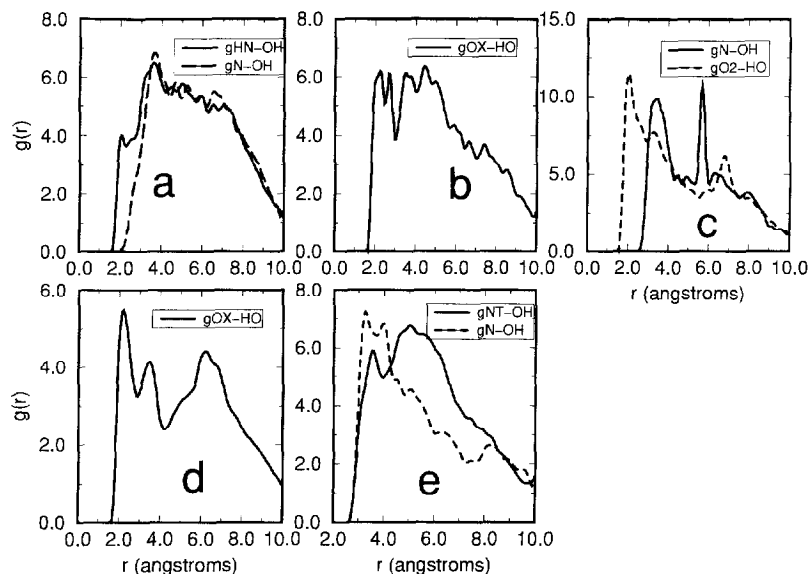


Figure 3. Radial distribution functions computed for the complexes of the BCD with aniline (a), between the aminic hydrogen atoms (HN), the nitrogen atom (N), and the BCD hydroxyl oxygen (OH); phenol (b), between the phenolic oxygen (OX) and the BCD hydroxyl hydrogen atoms; p-nitrophenol (c), between the nitrogen atom (N) and the BCD hydroxyl oxygens (OH) and between the nitro group oxygen atoms (O-2) and the BCD hydroxyl hydrogens (HO); p-hydroxyphenol (d), between the phenolic oxygen atoms (OH) and the BCD hydroxyl hydrogens (HO); p-nitroaniline (e), between the aminic nitrogen atom (NT), the nitro group nitrogen atom and the BCD hydroxyl oxygens (OH).

should be checked in an MD experiment involving only BCD and the solvent, in order to better describe the internal motion of the BCD ring, and we are currently working on this aspect.

## ACKNOWLEDGMENTS

Thanks are due to MURST and CNR for the financial support.

## REFERENCES

- 1 Fronza, G., Mele, A., Redenti, E., and Ventura, P.  $^1\text{H}$  NMR and molecular modeling study on the inclusion complex  $\beta$ -cyclodextrin-indomethacin. *J. Org. Chem.* 1996, **61**, 909–914
- 2 Jicsinszky, L. and Bako, I. IV *Int. Satellite Meeting, Conformational Studies on Carbohydrates*. La Thuile, Italy, 1996
- 3 Bertrand, G.L., Faulkner, J.R., Jr., Han, S.M., and Armstrong, D.W. Substituent effects of the binding of phenols to cyclodextrins in aqueous solution. *J. Phys. Chem.* 1989, **93**, 6863–6867
- 4 Buvári, A. and Barcza, L. Complex formation of phenol, aniline, and their nitro derivatives with  $\beta$ -cyclodextrin. *J. Chem. Soc. Perkin Trans.* 1988, **2**, 543–545
- 5 Kamiya, M., Mitsunashi, S., Makino, M., and Yoshioka, H. Analysis of the induced rotational strength of mono- and di-substituted benzenes included in  $\beta$ -cyclodextrin. *J. Phys. Chem.* 1992, **96**, 95–99
- 6 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, North Warrington, UK 1994–1996
- 7 Woods, R.J., Dwek, R.A., Edge, C.J., and Fraser-Reid, B. Molecular mechanical and molecular dynamical simulations of glycoproteins and oligosaccharides. 1. GLY-CAM\_93 parameter development. *J. Phys. Chem.* 1995, **99**, 3832–3846
- 8 Dewar, M.J.S., Zoebisch, E.G., Healy, E.F., and Stewart, J.J.P. AM1: A new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* 1985, **107**, 3902
- 9 Stewart, J.J.P. Program No. 455. *QCPE Bull.* 1983, **3**, 43
- 10 Inoue, Y., Okura, T., Miyata, M.Y., and Chujo, R. NMR studies on cycloamilose inclusion complexes with *p*-substituted phenols. *Carbohydr. Res.* 1984, **125**, 65