Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 54:165–170
DOI 10.1007/s10847-005-6288-x


# Preference Prediction for the Stable Inclusion Complexes Between Cyclodextrins and Monocyclic Insoluble Chemicals Based on Monte Carlo Docking Simulations

HYUNMYUNG KIM[1], KARPJOO JEONG[2], HYUNGWOO PARK[3] and SEUNHO JUNG[1,4,*]

[1]*Department of Advanced Technology Fusion, Konkuk University, 1 Hwayang-dong, Gwangjin-gu, Seoul, 143-701, South Korea;* [2]*College of Information and Communication, Bio/Molecular Informatics Center, Konkuk University, 1 Hwayang-dong, Gwangjin-gu, 143–701, Seoul, South Korea;* [3]*Korea Institute of Science and Technology Information, Yusong-Gu, Eoeun-Dong 52, Daejeon, 305–806, South Korea;* [4]*Department of Microbial Engineering, Konkuk University, 1 Hwayang-dong, Gwangjin-gu, Seoul, 143–701, South Korea*

(Received: 4 February 2005; in final form: 25 April 2005)

*Key words:* cyclodextrin, inclusion complex, Monte Carlo docking simulations, solubility, host-preference prediction

**Abstract**

Cyclodextrins (CDs) are useful functional excipients, which are being used to camouflage undesirable pharmaceutical characteristics, especially poor aqueous solubility, through the inclusion complexation process with insoluble drugs. The selection of more efficient cyclodextrin is important to improve the bioavailability of drugs. In this study, the complexing and solubilizing abilities toward poorly water-soluble monocyclic molecules of natural CDs (α-CD, *β*-CD, and γ-CD) were investigated using Monte Carlo (MC) docking simulations studies. These theoretical results closely agree with the experimental observation of the complex stability in water of the various guests–CD complexes. Host preferences, based on the experimentally determined stability constants between host CDs and guest molecules, show excellent correlation with the calculated interaction energies of corresponding complexes. The inclusion complex with the lower MC docking interaction energy shows a higher value of stability constant than that of the other complex, and the prediction accuracy of the preferred complex for 21 host–guest pairs is 100%. This result indicates that the MC docking interaction energy could be employed as a useful parameter to select more efficient cyclodextrin as a host for the bioavailability of insoluble drugs. In this study, *β*-CD shows greater solubilizing efficacies toward guest molecules than those of α-CD and γ-CD, with the exception of one case due to the structure of a guest molecule containing one lipophilic cyclic moiety. The surface area change of CDs and hydrogen bonding between the host and guest also work as major factors for the formation of the stable complex.

## Introduction

Aqueous solubility is a crucial physical property in pharmaceutical and environmental research. The solubility of biologically active compounds is often a limiting factor for their applicability. Therefore, the solubility enhancement of these compounds is an important task in pharmaceutical technology, because it leads to a better bioavailability and to more efficient application. Consequently, various approaches have been developed in order to enhance the bioavailability of lipophilic drugs. For example, several trials such as encapsulation by liposomes, formulation by organic solvent, and complexation with solubilizing agents have been performed. [1–3]. One of these is by enhancing the solubility, and, hence, the bioavailability, *via* complexing hydrophobic drugs with soluble cyclodextrins [4].

The cyclodextrins (CDs) are the macrocyclic molecules formed by α-(1 → 4) glycosidic links between D-glucose monomer units and adopt a toroid shape [5]. The non-polarity of the interior cavity of the cyclodextirn makes it ideal for solubilizing nonpolar solutes, whereas the polarity of its exterior helps it and its guest to become soluble in water [4–7]. The naturally occurring cyclodextrins contain 6, 7, and 8 glucose units and are designated α-, *β*-, and γ-CD, respectively. Except for differences in size, the overall geometries of the cyclodextrins are similar. In an aqueous solution, the slightly nonpolar cyclodextrin cavity is occupied by water molecules, which are energetically unfavored (polar–nonpolar interaction) and, therefore, can be readily substituted by an appropriate guest which is less polar than water [5].

* Author for correspondence. E-mail: shjung@konkuk.ac.kr

The use of more effective cyclodextrin is important in pharmaceutical fields. Several studies for the prediction of the aqueous solubility of complexes have been published in recent years [8–9]. In our previous MC docking simulation of paclitaxel–cyclodextrin complexes, we can explain why dimethyl-$\beta$-CD is a more efficient solubilizing agent of insoluble paclitaxel than natural $\beta$-CD by using the energetic and geometric preferences of complexes [8]. Faucci *et al*. predict the stability constant of complexes between selected four model drug molecules and several cyclodextrins using molecular modeling [9]. They used the results of NMR studies and stochastic methods based on molecular dynamics simulations. However, these approaches are hard to be applied to other complexes which have no experimental data and consume much time to execute molecular dynamics in water for the large set of complexes.

In the present study, the inclusion complexation of monocyclic organic guests with native CDs was investigated using Monte Carlo (MC) docking simulations. The purpose of our study was to predict which cyclodextrin is more practical to enhance the solubility of hydrophobic molecules. The inclusion complexes of CDs with monocyclic organic guest molecules were modeled and refined by molecular modeling methods to predict the solubility enhancement order between each pair of complexes. The intermolecular energies of the inclusion complexes were compared with experimental data and the driving forces were analyzed.

## Model and computational procedure

Molecular mechanics was performed with the Insight II/Discover program (version 2000, Molecular Simulation Inc. San Diego, USA) using a consistent force field (CFF91) on a SGI OCTANE 2 workstation (Silicon Graphics, USA) [10, 11]. The CDs structure was obtained by the energy minimization of a crystallographic geometry [12]. The three dimensional structures of various organic compounds as guests were obtained directly from SciFinder, and they were optimized using the Insight II/Discover module [13, 14]. Figure 1 shows the structure of guest molecules which have one cyclic moiety.

Docking with the guest was carried out using the "GridDocking" [15] option in the Affinity module of Insight II, and the CFF91 force field for docking and scoring. The guest was initially set above the center of the cavity of CD with a distance of ~15Å. The solvation

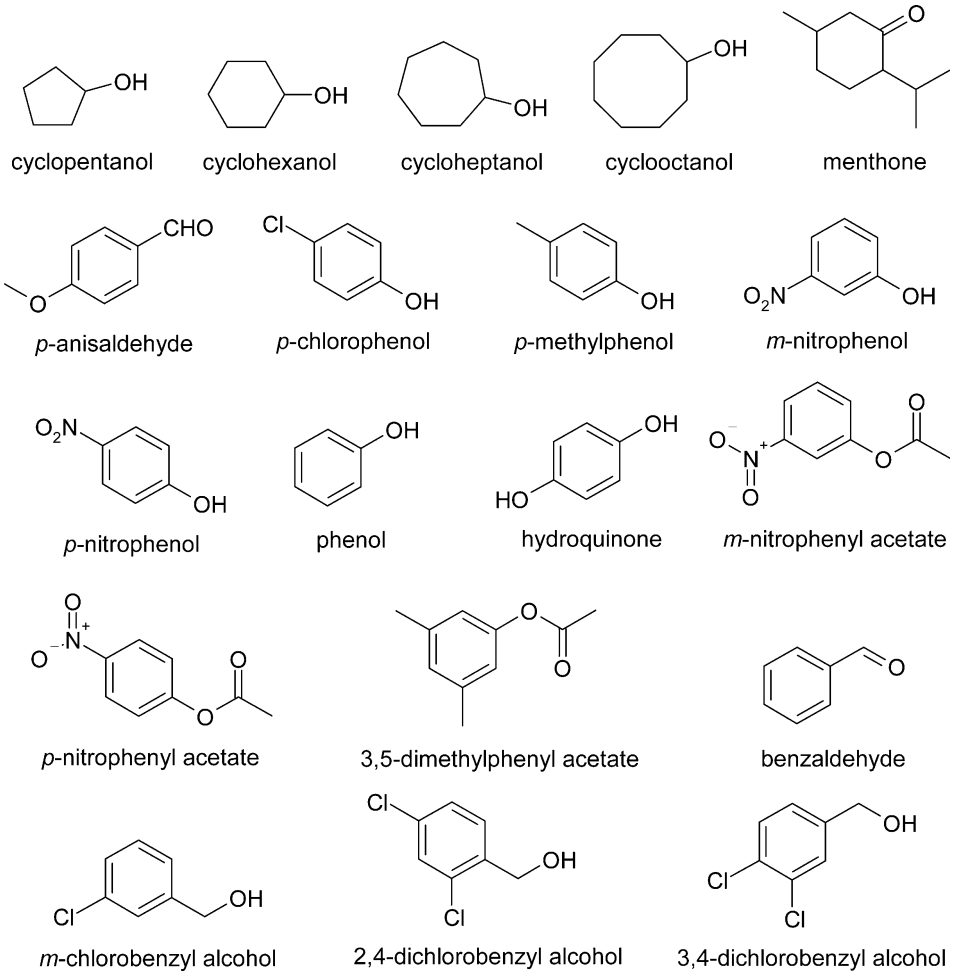


*Figure 1.* Structure of guest molecules.

grid is generated together with the van der Waals and electrostatics grids. The Monte Carlo docking simulations were performed on each complex, where the temperature was 298 K. The Monte Carlo docking simulations started by the conjugated gradient energy minimization of this initial configuration for 100 iterations and accepted the configuration as the first frame. During the course of a trial of a new configuration, a guest could make a maximum translational movement of Å to the $x$, $y$, $z$ axes and a maximum rotation of 180° around the $x$, $y$, and $z$ axes. A total of six degrees of freedom was present for this system (3 translational, 3 rotational). Each cycle began with a random change of up to five degrees of freedom among them [16]. If the energy of the resulting configuration was within 1000 kcal/mol of the last accepted one, it was subjected to 100 iterations of conjugated gradient energy minimization. The energy tolerance of 1000 k cal/mol was imposed to avoid significant overlap of the van der Waals radii in the random search. After the energy minimization, the resulting structure was accepted based on the following criteria: (a) an energy check with the Metropolis criteria at each temperature [17] and (b) a root-mean-squared displacement (RMSD) check, which compared the RMSD of the new configuration against those accepted so far. Configurations within 0.1 Å RMSD of pre-existing ones were discarded to avoid accepting similar configurations. The Monte Carlo (MC) docking simulations were performed until energy convergence. No cutoff was imposed on the calculation of non-bonded interactions, and a distance-dependent dielectric constant of $4r$ was used to mimic solvent screening during the conformational searches [18, 19]. Boltzmann averages of energies were evaluated at 298 K.

## Results and discussion

We predicted the solubility enhancement orders between CDs and guest molecules based on the MC docking simulations. The docking simulations were performed for total of 39 complexes between monocyclic organic guests and cyclodextrins (Table 1). The pathways of MC docking simulations showed a general tendency of inclusion complex formation and decreasing interaction energy. The interaction energy was defined as the difference between the sum of the energy of individual host and guest molecule and the energy of the inclusion complex [8]. Negative interaction energies obtained from the MC docking calculations indicate that complexation of guests into the cyclodextrin cavities is highly favored.

The fit of the entire or at least a part of the guest molecule in the cyclodextrin host cavity determines the stability of the inclusion complex. Therefore, the sta-

*Table 1.* The interaction energies (kcal/mol, $\Delta E_{\text{interaction}}$) for inclusion complexes of monocyclic organic guests with cyclodextrins in Monte Carlo docking simulations at 298 K

| Guest | $\Delta E_{\text{interaction}}$ | | | $K_F/K_L$[a] | Practical CDs[b] & reference |
|---|---|---|---|---|---|
| | α-CD | β-CD | γ-CD | | |
| Cyclopentanol | −27.97 | −35.53 | | 0.38 | β-CD [20] |
| Cyclohexanol | −30.08 | −34.08 | | 0.13 | β-CD [20] |
| Cycloheptanol | −25.37 | −36.90 | | 0.05 | β-CD [20] |
| Cyclooctanol | −25.67 | −44.42 | | 0.09 | β-CD [20] |
| Menthone | −27.95 | −34.79 | | 0.17 | β-CD [21] |
| *p*-Anisaldehyde | −24.87 | −40.21 | | 0.18 | β-CD [21] |
| *p*-Chlorophenol | −27.63 | −35.44 | | 0.71 | β-CD [22] |
| *p*-Methylphenol | −24.53 | −37.75 | | 0.11 | β-CD [22] |
| *m*-Nitrophenol | −21.06 | −40.41 | | 0.63 | β-CD [22] |
| *p*-Nitrophenol | −28.52 | −38.99 | | 0.45 | β-CD [22] |
| Phenol | −24.11 | −38.13 | | 0.39 | β-CD [22] |
| Hydroquinone | −26.87 | −36.25 | | 0.21 | β-CD [22] |
| *m*-Nitrophenyl acetate | −26.03 | −45.44 | | 0.04 | β-CD [23, 24] |
| *p*-Nitrophenyl acetate | −26.89 | −40.70 | | 0.05 | β-CD [23, 24] |
| 3,5-Dimethylphenyl acetate | −31.49 | −51.08 | | 0.50 | β-CD [23, 24] |
| Benzaldehyde | −30.27 | −32.33 | | 0.25 | β-CD [25] |
| Benzaldehyde | | −32.33 | −18.59 | 8.00 | β-CD [25] |
| Benzaldehyde | −30.27 | | −18.59 | 2.00 | α-CD [25] |
| *m*-Chlorobenzyl alcohol | | −43.79 | −29.56 | 285 | β-CD [26] |
| 2,4-Dichlorobenzyl alcohol | | −44.35 | −34.33 | 1.48 | β-CD [26] |
| 3,4-Dichlorobenzyl alcohol | | −32.37 | −45.32 | 0.13 | γ-CD [26] |

[a] $K_F/K_L$ is the ratio of experimental stability constant of the former complex ($K_F$) to that of the latter complex ($K_L$) for each pair of complexes in Table 1.

[b] Practical cyclodextrin complex has higher stability constant than that of the other cyclodextrin complex.

bility constant value of host–guest complexes is a useful index of the binding strength of the complex and is of great importance for the understanding and evaluation of the inclusion complex formation [27]. The interaction energies in the MC docking simulation for each inclusion complex compare with the stability constants derived from the experimental data [20–26]. The complex with the lower interaction energy shows a higher value of stability constant than that of the other complex for the same guest molecule, and the prediction accuracy of complex stability is 100%. The solubilization of organic molecules by cyclodextrins may be regarded as the partition of solutes from water into the cyclodextrin cavity, and the stability constants of CD–guest can be considered as partition coefficient [28]. Although the practical utility of CDs as efficient solubilizers depends on the stability constant and the intrinsic solubility of guests and CDs, it could be said that CDs with a higher stability constant in the complexes are more useful functional complexing agents for each guest because of the very low solubility of guests in an aqueous environment. Table 1 shows the interaction energies of complexes and practical CDs, the complexes (experimentally observed complexes) of which have a higher value of stability constant than those of the other complexes. Throughout the results, the MC docking interaction energy can guide researchers to a more efficient selection of cyclodextrin to improve an insoluble molecule's solubility.

Based on the properties of guests, the driving forces contributing to the complexation might vary. However, the guests in Figure 1 have homologous groups, such as lipophilic portion (monocyclic moiety) and hydrogen bonding portion (hydrogen bond donors and acceptors), and should have similar driving forces. It seems that hydrophobic interactions are more important than the electrostatic and hydrogen bonding interactions. This is also apparent through visual inspection of the docked complexes, as evident by insertion of the lipophilic portion of the molecule inside the cavity (Figure 2).

The Connolly surface area change of cyclodextrins between the free and complexed cyclodextrins is presented in Table 2. The Connolly surface area of $\beta$-CD slightly increased after complexation, but the surface area of $\alpha$-CD and $\gamma$-CD decreased a little. All guests used in this simulation have one cyclic moiety, which can safely fill the cavity of $\beta$-CD. However, $\alpha$-CD and $\gamma$-CD cannot provide the fitted space because they have small and large cavities, respectively, to accept the cyclic moiety. Through the MC docking simulations, the complex conformations, including cyclodextrins and guests in every step were minimized [8]. The changes in cyclodextrin structure with minimization were small, but they were enough to allow the host molecule to adjust and better accommodate the

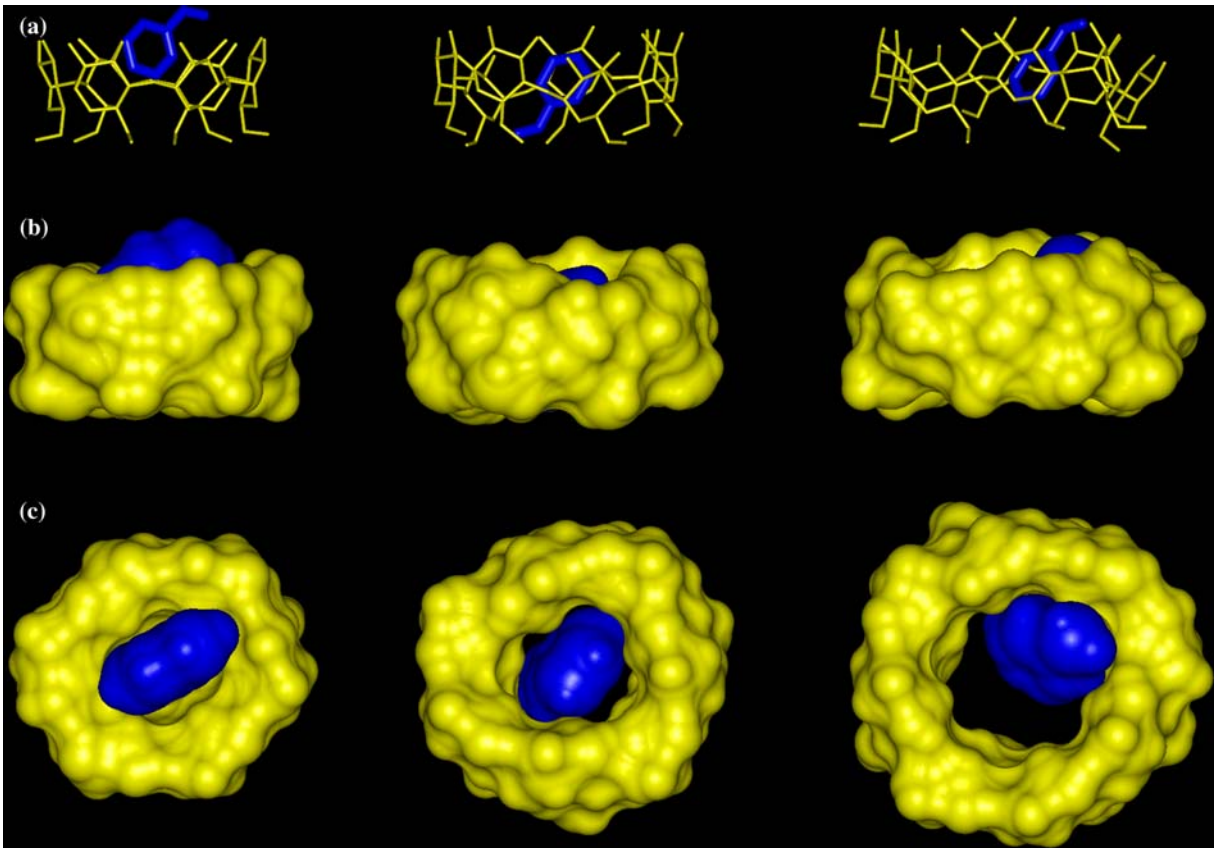


*Figure 2.* Low-energy inclusion complexes of benzaldehyde with each cyclodextrin; left: $\alpha$-CD, middle: $\beta$-CD, right: $\gamma$-CD, (A) lateral view. (B) lateral view with the Connolly surface. (C) axial view with the Connolly surface.

*Table 2*. The Connolly surface change of cyclodextrins between the free and complexed cyclodextrins

| Guest | ΔSA (Å$^2$) | | Practical CDs[a] |
|---|---|---|---|
| | α-CD | β-CD | |
| Cyclopentanol | −1.2 | 11.2 | β-CD |
| Cyclohexanol | −1.3 | 10.2 | β-CD |
| Cycloheptanol | −0.9 | 10.8 | β-CD |
| Cyclooctanol | −1.9 | 10.8 | β-CD |
| Menthone | −0.6 | 10.4 | β-CD |
| *p*-Anisaldehyde | −1.9 | 12.2 | β-CD |
| *p*-Chlorophenol | −2.3 | 10.0 | β-CD |
| *p*-Methylphenol | −0.9 | 12.1 | β-CD |
| *m*-Nitrophenol | −0.5 | 11.1 | β-CD |
| *p*-Nitrophenol | −1.1 | 11.1 | β-CD |
| Phenol | −0.9 | 12.3 | β-CD |
| Hydroquinone | −0.5 | 9.7 | β-CD |
| Benzaldehyde | −1.3 | 10.8 | β-CD |
| *m*-Nitrophenyl acetate | −2.0 | 11.7 | β-CD |
| *p*-Nitrophenyl acetate | −2.5 | 10.9 | β-CD |
| 3,5-Dimethylphenyl acetate | −1.5 | 10.8 | β-CD |
| | β-CD | γ-CD | |
| Benzaldehyde | 10.8 | −2.8 | β-CD |
| *m*-Chlorobenzyl alcohol | 9.9 | −2.3 | β-CD |
| 2,4-Dichlorobenzyl alcohol | 11.8 | −2.0 | β-CD |
| 3,4-Dichlorobenzyl alcohol | 11.7 | −1.1 | γ-CD |
| | α-CD | γ-CD | |
| Benzaldehyde | −1.3 | −2.8 | α-CD |

[a]Practical cyclodextrin complex has higher stability constant than that of the other cyclodextrin complex.

*Table 3*. Average number of hydrogen bonds between guest and cyclodextrin in the 10 low-energy complexes

| Guest | Hydrogen Bond | | Practical CDs[a] |
|---|---|---|---|
| | α-CD | β-CD | |
| Cyclopentanol | 0.7 | 1 | β-CD |
| Cyclohexanol | 0 | 1 | β-CD |
| Cycloheptanol | 0.3 | 1 | β-CD |
| Cyclooctanol | 0.6 | 1.2 | β-CD |
| Menthone | 0 | 1 | β-CD |
| *p*-Anisaldehyde | 0 | 0.9 | β-CD |
| *p*-Chlorophenol | 0 | 1 | β-CD |
| *p*-Methylphenol | 0.1 | 1 | β-CD |
| *m*-Nitrophenol | 0.6 | 1.2 | β-CD |
| *p*-Nitrophenol | 0.6 | 1.1 | β-CD |
| Phenol | 0.5 | 1.3 | β-CD |
| Hydroquinone | 0.5 | 1 | β-CD |
| Benzaldehyde | 0.4 | 0.7 | β-CD |
| *m*-Nitrophenyl acetate | 0 | 1 | β-CD |
| *p*-Nitrophenyl acetate | 0 | 1 | β-CD |
| 3,5-Dimethylphenyl acetate | 0 | 1.9 | β-CD |
| | β-CD | γ-CD | |
| Benzaldehyde | 0.7 | 0.1 | β-CD |
| *m*-Chlorobenzyl alcohol | 1.3 | 0.6 | β-CD |
| 2,4-Dichlorobenzyl alcohol | 0.9 | 0 | β-CD |
| 3,4-Dichlorobenzyl alcohol | 0.1 | 0.1 | γ-CD |
| | α-CD | γ-CD | |
| Benzaldehyde | 0.4 | 0.1 | α-CD |

[a]Practical cyclodextrin complex has higher stability constant than that of the other cyclodextrin complex.

guest molecule. The interaction between the cyclodextrins and guest molecules may be considered an induced fit, where the conformation of the host changes to produce a better fit [29]. To maximize the van der Waals interaction with the guest, β-CDs expand their surface of closely filled cavities and γ-CDs and α-CDs contract their surface of loosely and incompletely filled cavities to minimize empty space, respectively. The structure of the five low-energy complexes for benzaldehyde in cyclodextrins is shown in Figure 2. In each cyclodextrin benzaldehyde is complexed into the center of the cavity. However, the guest appears to be more deeply sequestered into β-CD and γ-CD than into α-CD in almost complexes. In the lateral and axial view, the empty space in the cavity of α-CD and β-CD complexes exists.

In addition to lipophilic portion, all guest molecules have more than one hydrogen bond donor or acceptor. Hydrogen bond formation between guest and cyclodextrin is also another important factor to form a stable inclusion complex [30]. Table 3 shows that the average number of hydrogen bonds between the guest and cyclodextrin in the 10 low-energy complexes. β-Cyclodextrin complexes, which generally form more stable complexes than other CDs, nearly all have one hydrogen bond with the exception of 3,4-Dichlorobezyl alcohol complex, which has a small number of hydrogen bonds. However, α-CD and γ-CD complexes have no or few hydrogen bonds, and their interaction energies are higher than β-CD complexes in most case. 3,4-Dichlorobenzyl alcohol cannot form a proper hydrogen bond with β-cyclodextrin because of the steric hindrance of 3-chloride moiety and forms a more stable complex with γ-CD than β-CD, which forms stable complexes with other guests.

Throughout this research, the Monte Carlo docking simulations for the prediction of solubility enhancement was very successful in overcoming the difficulties of predicting the solubilization of insoluble molecules by CDs. Complexation is a key factor in solubilization, but it is not the only factor. Additionally, the solubility of the cyclodextrin, the solubility of the solute, and the solubility of the complex determine the magnitude of solubilization. At this point, the accurate prediction of the magnitude of solubilization using host–guest interaction energy is unnecessary for the preference prediction of suitable cyclodextrins as a solubility enhancer with various guests. This theoretical approach will be very useful for a rapid determination of a suitable cyclodextrin as complexing agent of organic guest complexes solubilized by cyclodextrins in order to identify the best candidates for experimental characterization related with solubility enhancement. In this study, we focused on the inclusion complex of monocyclic guests with natural cyclodextrins, but will study this kind of the MC docking simulations

for various kinds of guests, such as aliphatic alcohol, monocyclic and multicyclic organic guests with aliphatic chains, and non-branching multicyclic guests and for modified cyclodextrins (CDs), such as dimethyl-$\beta$-CD, hydroxyethyl-$\beta$-CD, and hydroxypropyl-$\beta$-CD. Database on the information from these kinds of the MC docking simulations will be invaluable for the theoretical determination of both host molecules and their guest counterparts. We hope our approach to the MC docking simulations will be useful for the accurate prediction on the solubility enhancement relevant to the several bioindustrial fields, including the solubilization of insoluble drugs and the enhancement of guest stability.

## Acknowledgements

This study was supported by a grant of the MIC (Ministry of Information and Communication) through National Grid Infrastructure Implementation Project of KISTI (Korea Institute of Science and Technology Information) and partially supported by the Korea Research Foundation (KRF2004-F00019).

## References

1. U.S. Sharma and R.M. Straubinger: *Pharm. Res.* **11**, 889 (1994).
2. W.N. Waugh, L.A. Trissel, and V.J. Stella: *Am. J. Hosp. Pharm.* **48**, 1520 (1991).
3. U.S. Sharma, S.V. Balasubramanian, and R.M. Straubinger: *J. Pharm. Sci.* **84**, 1223 (1995).
4. W. Saenger: *Angew. Chem. Int. Ed. Engl.* **19**, 344 (1980).
5. J. Szejtli: *Chem. Rev* **98**, 1743 (1998).
6. G. Wenz: *Angew. Chem. Int. Ed. Engl.* **33**, 803 (1994).
7. I. Baussanne, J.M. Benito, C.O. Mellet, J.M.G. Fernandez, and J. Defaye: *ChemBioChem.* **2**, 777 (2001).
8. H. Kim, J. Choi, H.-W. Kim, and S. Jung: *Carbohydr. Res.* **337**, 549 (2002).
9. M.T. Faucci, F. Melani, and P. Mura: *Chem. Phys. Lett.* **358**, 383 (2002).
10. J.R. Maple, U. Dinur, and A.T. Hagler: *Proc. Natl. Acad. Sci. USA* **85**, 5350 (1988).
11. F. Melani, P. Mura, M. Adamo, F. Maestrelli, P. Gratteri, and C. Bonaccini: *Chem. Phys. Lett.* **370**, 280 (2003).
12. K. Harata: *Bull. Chem. Soc. Jpn.* **60**, 2763 (1987).
13. W.L. Jorgensen and E.M. Duffy: *Adv. Drug Deliv. Rev.* **54**, 355 (2002).
14. SciFinder: American Chemical Society, Columbus, OH (2004).
15. B.L. Luty, Z.R. Wasserman, P.F.W. Stouten, C.N. Hodge, M. Zacharias, and J.A. McCammon: *J. Comp. Chem.* **16**, 454 (1995).
16. T.N. Hart and R.J. Read: *Proteins* **13**, 206 (1992).
17. N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, and E. Teller: *J. Chem. Phys.* **21**, 1087 (1953).
18. S.J. Weiner, P.A. Kollman, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, S. Profeta, and P. Weiner: *J. Am. Chem. Soc.* **106**, 765 (1984).
19. L.T. Chong, Y. Duan, I. Massove, and P.A. Kollman: *Proc. Natl. Acad. Sci. USA* **96**, 14330 (1999).
20. Y. Matsui and K. Mochida: *Bull. Chem. Soc. Jpn.* **52**, 2808 (1979).
21. Y. Ikeda, K. Matsumoto, K. Kunihiro, T. Fuwa, and K. Uekama: *Yakugaku Zasshi* **102**, 83 (1982).
22. G.L. Bertrand, J.R. Faulkner, S.M. Han, and D.W. Armstrong: *J. Phys. Chem.* **93**, 6863 (1989).
23. K. Uekama: *Yakugaku Zasshi* **101**, 857 (1981).
24. K. Uekama, T. Fujinaga, F. Hirayama, M. Otagiri, and M. Yamasaki: *J. Pharm.* **10**, 1 (1982).
25. R.L. VanEtten, J.F. Sebastian, G.A. Glowes, and M.L. Bender: *J. Am. Chem. Soc.* **89**, 3242 (1967).
26. R.L. VanEtten, J.F. Sebastian, G.A. Glowes, and M.L. Bender: *J. Am. Chem Soc.* **89**, 3253 (1967).
27. F. Hirayama and K. Uekama: Methods of investigating and preparing inclusion compounds. In D. Duchene (Ed), *Cyclodextrins and their Industrial Uses*, Editions de Sante, Paris (1987), pp. 131–172.
28. X. Wang and M.L. Brusseau: *Environ. Sci. Technol.* **27**, 2821 (1993).
29. D.R. Black, C.G. Parker, and S.S. Zimmerman: *J. Comput. Chem.* **17**, 193 (1996).
30. W.Q. Tong, Lach J.L., Chin T.F., Guillory J.K., *Pharm. Res.* **8**, 951 (1991).