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Encapsulation of Quinine by β-Cyclodextrin: Excellent Model for Mimicking Enzyme−Substrate Interactions

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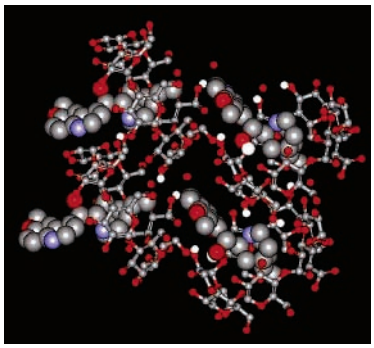

An inclusion complex formed by β-cyclodextrin and quinine has been investigated in solution and in the solid state, in which the quinoline ring and the aliphatic ring locate in different hydrophobic cavities, respectively. The study on the inclusion geometry and weak interactions shows that the difference in conformation for this complex is a result of three main packing arrangement considerations, which can provide an ideal model mimicking enzyme−substrate interactions.

The investigations on cyclodextrin (CD) complexes have attracted extensive attention in recent years because of their potential in several areas of science and technology.[1−4] In particular, the CD inclusion complexes serve as enzyme models to reveal enzyme−substrate interactions and have potential applications as drug carriers, providing an incentive to better understand the noncovalent interactions associated with the inclusion process.[5−9] These studies are based on the fact that the hydrophobic guests are included in the cavity of CD, so this calls attention to the need to consider not only the geometry of the CD−substrate complex but also the noncovalent interactions involved in the complex. Therefore, various kinds of β-CD inclusion complexes have been studied in detail so as to provide valuable information on the geometry and nonbonding interactions.[10−16] These studies showed that the inclusion process is influenced mainly by the shape and size of the guest and also by the hydrophobic nature of the interactions between the guest molecules and CD. On the other hand, the orientation of the guest molecule within the CD host is a crucial element of the enzyme−substrate interactions and is important for the design of drug molecules.[7] To the best of our knowledge, when the guest has only a kind of phenyl ring, the preferred arrangement is for host molecules to form the head−head dimers via hydrogen bonds, where guest molecules are usually accommodated in the large dimer cavity.[10−13] Although a few inclusion complexes display a slight change in the packing arrangement,[10a,15] their structures do not affect the geometry of CD−substrate complexes by the cooperative interactions between CD and the guest, and therefore, they could not be used as an ideal model for mimicking enzyme−substrate interactions.

We chose quinine as a guest molecule because quinine has not only two distinct functional groups (quinoline ring and aliphatic ring) and three chiral centers but also lots of binding sites that can form one or more hydrogen bonds with the hydroxyl group of β-CD. Therefore, the present study was undertaken to determine the binding behavior of quinine in the cavity of β-CD. Furthermore, the study on the inclusion behavior of the quinidine and β-CD is under consideration. Our particular interest is to investigate the conformation of the β-CD inclusion complex by means of the hydrophobic interaction and hydrogen-bonding selectivity and directionality, which represents a valuable model for understanding enzyme−substrate interactions.

The crystal structure reveals the 1:1 stoichiometry of the host and guest molecules. As shown in Figure 1, the aliphatic ring

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(1) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803−822.
(2) Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456−464.
(3) Liu, Y.; Zhao, Y.-L.; Zhang, H.-Y.; Song, H.-B. *Angew. Chem., Int. Ed.* **2003**, *42*, 3260−3263.
(4) (a) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1753. (b) Hedges, A. R. *Chem. Rev.* **1998**, *98*, 2035−2044.
(5) Strokopytov, B.; Knegtel, R. M. A.; Penninga, D.; Rozeboom, H. J.; Kalk, K. H.; Dijkhuizen, L.; Dijkstra, B. W. *Biochemistry* **1996**, *35*, 4241−4249.
(6) Schmidt, A. K.; Cottaz, S.; Driguez, H.; Schulz, G. E. *Biochemistry* **1998**, *37*, 5909−5915.
(7) (a) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011. (b) Zhang, B.-L.; Breslow, R. *J. Am. Chem.* Soc. **1997**, *119*, 1676−1681. (c) Murakami, Y.; Kikuchi, J.-I.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 6, 721−758.
(8) Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045−2076.
(9) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875−1917.
(10) (a) Harata, K. *Chem. Rev.* **1998**, *98*, 1803−1827. (b) Hamilton, J. A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 4379−4391. (c) Hamilton, J. A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 5833−5841.
(11) (a) Clark, J. L.; Stezowski, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 9880−9888. (b) Clark, J. L.; Booth, B. R.; Stezowski, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 9889−9895.
(12) (a) Liu, Y.; Zhong, R.-Q.; Zhang, H.-Y.; Song, H.-B. *Chem. Commun.* **2005**, *17*, 2211−2213. (b) Liu, Y.; Zhao, Y.-L.; Chen, Y.; Guo, D.-S. *Org. Biomol. Chem.* **2005**, *3*, 584−591. (c) Liu, Y.; Chen, G.-S.; Zhang, H.-Y.; Song, H.-B.; Ding, F. *Carbohydr. Res.* **2004**, *339*, 1649−1654.
(13) (a) Mieusset, J.-L.; Krois, D.; Pacar, M.; Brecker, L.; Giester, G.; Brinker, U. H. *Org. Lett.* **2004**, *6*, 1967−1970. (b) Udachin, K. A.; Ripmeester, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1080−1081.
(14) Stezowski, J. J.; Jogun, K. H.; Eckle, E.; Bartels, K. *Nature* **1978**, *274*, 617−619.
(15) Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1061−1062.
(16) (a) Harata, K.; Hirayama, F.; Arima, H.; Uekama, K.; Miyaji, T. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1159−1166. (b) Lou, L.-B.; Chen, H.-L.; Tang, W.-X.; Zhang, Z.-Y.; Mak, T. C. W. *J. Chem. Soc., Dalton Trans.* **1996**, 4425−4430.

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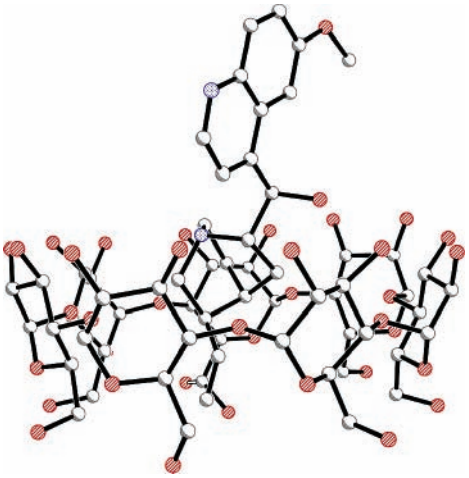

FIGURE 1. Unit structure of inclusion complex **1**.

and ethenyl of the guest molecule are buried fully in the interior of the β-CD torus, whereas the quinoline ring protrudes from the second hydroxyl region and is located above the β-CD torus with a dihedral angle of 98.4° with the β-CD ring. In comparison with the typical conformation of uncomplexed β-CD (average values for uncomplexed β-CD: rms deviation from planarity = 0.18 Å; radius of the O4 heptagon = 5.04 Å, values ranging between 4.86 and 5.18 Å; O4−O4′ distance = 4.31 Å, ranging between 4.20 and 4.50 Å),[17] the present β-CD shows a more regular shape (rms deviation from planarity = 0.10 Å; radius of the O4 heptagon = 5.07 Å, values ranging between 4.93 and 5.23 Å; O4−O4′ distance = 4.40 Å, ranging between 4.31 and 4.49 Å) despite an aliphatic ring included in its cavity.

The bulky quinoline moiety and nearly perpendicular dihedral angle between the quinoline ring and the β-CD ring suggest that two adjacent β-CDs could not form a head−head dimer via hydrogen bonds between two β-CDs, as observed in the previously reported inclusion complexes.[10−13] Thus, those β-CD molecules have to adopt a head−tail helical columnar packing superstructure through hydrogen-bonding interactions between the adjacent β-CDs and between β-CD and quinine, as shown in Figure 2.

Figure 3 shows the details of the host−guest interactions including both hydrogen-bonding and hydrophobic interactions between the guest molecule and β-CD. The aliphatic ring and ethenyl of quinine are fully inserted in the β-CD cavity from the second side of β-CD, and one nitrogen atom, N(2D), is hydrogen bonded to a second hydroxyl group of the adjacent β-CD ($d_{[N2D\cdots H20E-O20C]}$ = 2.008 Å, $\Phi_{[N2D\cdots H20E-O20C]}$ = 170.4°). Furthermore, the hydroxyl group in the quinine moiety interacts with another adjacent β-CD ($d_{[O36D\cdots H5-O5B]}$ = 2.001 Å, $\Phi_{[O36D\cdots H5-O5B]}$ = 151.9°) by hydrogen bonding. These interactions together with the hydrogen bonds between the adjacent β-CDs not only fix the position of the aliphatic ring in the cavity of β-CD but also stabilize the helical columnar superstructure. On the other hand, the bulky quinoline ring protrudes from the second side of β-CD and locates in the interface among the four adjacent β-CDs (A, B, C, and D). The orientation of the quinoline group is determined by intermolecular hydrogen bonds ($d_{[N1D\cdots O35B]}$ = 2.840 Å, $d_{[N1D\cdots O56B]}$ = 2.923 Å, $d_{[O56B\cdots O35B]}$ = 2.585 Å). It should be noted that once the hydrogen bonds

(17) Harata, K. In *Comprehensive Supramolecular Chemistry*; Stejtli, J., Osa, T., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, pp 279−304.

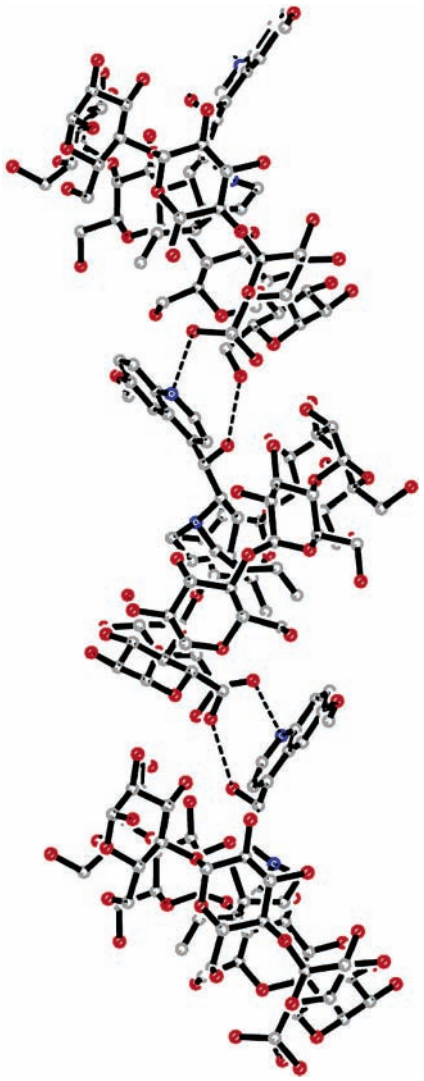

FIGURE 2. Head−tail helical column superstructure.

between the host and guest (N1D···O35B, N1D···O56B, O36D···O5B, and N2D···O20C) are established the interaction of the adjacent β-CDs appears to be strengthened. Interestingly, every four adjacent β-CDs form a hydrophobic "cavity" through hydrogen bonds, which could conform to the hydrophobic requirements of the quinoline ring. As a result, the whole guest molecule is located in the hydrophobic region, which results in the guest molecules being able to maximize the hydrophobic interaction to the β-CDs.

In comparison to previously reported crystals of inclusion complexes,[10−15] which prefer to form head−head dimers via hydrogen bonding and the guests included in the CD cavity and the dimmer interface, this complex gives a number of interesting changes in the molecular interactions and the binding pockets. For example, the aliphatic and quinoline rings are located in the distinctly different hydrophobic cavity; that is, the small aliphatic ring is included in the β-CD cavity, and the bulky quinoline ring perches in the hydrophobic cavity surrounded by the four β-CDs. In other words, the bulky guest molecule induces β-CDs to form a larger apolar environment for conforming to the requirements of the hydrophobic guest. Thus, the difference in conformation observed for this complex is due to three main packing arrangement considerations: the fit of

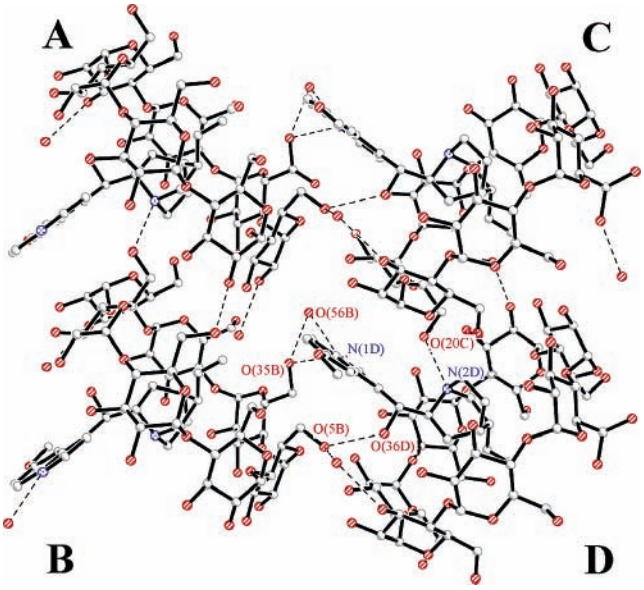

FIGURE 3. Stereodrawing of the title complex **1**. The hydrogen bonds are indicated by dash lines.

the aliphatic ring moiety inside the β-CD cavity, the hydrophobic requirements of the quinoline ring, and the hydrogen-bond formation requirements between N and O atoms of quinine with the hydroxyl group of β-CD. Tabushi and Kuroda think that the most important driving force for forming the inclusion complex is the hydrophobic interaction,[18] but Stoddart and Zarzycki consider that the extent of each contribution depends on the nature of the host, guest, and solvent molecules.[19] In this complex, the hydrophobic interaction is the driving force for the inclusion complex formation, and hydrogen bonding between the β-CDs and guests controls the position of the guest in the β-CD cavity; so, the inclusion complex formation results from the cooperative interactions between the β-CD and the guest, including the hydrophobic interaction and hydrogen bonding.

The conformation about the title complex in aqueous solution has also been investigated by ^{1}H ROESY experiments. The ROESY spectrum of the inclusion complex exhibits clear NOE cross peaks between the protons of the ethenyl/aliphatic ring in the quinine molecule and the protons of H3 and/or H5 in β-CD, which indicates that the ethenyl group and the aliphatic ring of the guest are included in the cavity of β-CD.

In summary, the present study illustrates the inclusion complex constructed by β-CD and quinine, in which the aliphatic and quinoline rings are located in the different hydrophobic regions, respectively. We suggest that this system represents an ideal model mimicking enzyme−substrate interactions, which will further our understanding of the binding mechanism of substrate receptors. This approach will provide valuable information on the selection of molecular conformations and interactions in nonconstraining binding environments for designing artificial enzymes.

Experimental Section

Synthesis of the Inclusion Complex Quinine−β-CD. The ethanol solution of quinine (1 mmol, 15 mL) was added dropwise to an aqueous solution of β-CD (1 mmol, 25 mL) and stirred at 75 °C for 5 h. Then, the solution was slowly cooled to room temperature and was refrigerated for a week, and the precipitate formed was filterd to obtain a white powder. The crude product was dissolved in hot water to make a saturated solution, and then the resultant solution was kept at a temperature of about 70 °C and was slowly evaporated for 5 days. The crystal formed was collected along with its mother liquor for the X-ray crystallographic analyses. Data for the inclusion complex: ^{1}H NMR (D_2O, 300 ppm) δ 8.59−8.61 (d, H), 7.85−7.89 (d, H), 7.54−7.56 (d, H), 7.31−7.39 (m, 2H), 5.45−5.78 (m, 2H), 4.89−4.91 (m, 7H), 4.80−4.82 (m, 2H), 3.85 (s, 3H), 3.38−3.80 (m, 42H), 2.90−3.20 (m, 3H), 2.45−2.60 (d, 2H), 2.21 (s, H), 1.45−1.83 (m, 5H). Anal. Calcd for $C_{62}H_{94}N_2O_{37}$−E12H_2O: C, 44.44; H, 7.10; N, 1.67. Found: C, 44.46; H, 6.96; N, 1.59.

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Supporting Information Available: Materials and instruments, X-ray diffraction analysis, crystal data, structure refinement, atomic coordinates, equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles, ^{1}H ROESY spectra, and the CIF files of quinine−β-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Tabushi, I.; Kuroda, Y. *Adv. Catal.* **1983**, *32*, 417−466.
(19) Stoddart, J. F.; Zarzycki, R. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*−*109*, 515−528.