

Molecular Interpenetration within the Columnar Structure of Crystalline Anilino- β -cyclodextrin

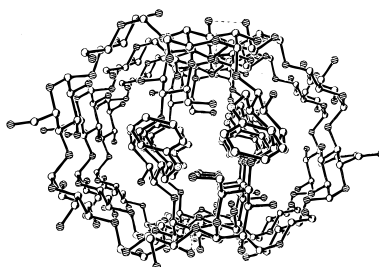
Yu Liu,^{*,†,‡} Chang-Cheng You,[†] Min Zhang,[†] Lin-Hong Weng,[†]
Takehiko Wada,[§] and Yoshihisa Inoue^{*,†,§}

Department of Chemistry, Nankai University, Tianjin 300071, China, and
Inoue Photochirogenesis Project, ERATO, JST, 4-6-3 Kamishinden,
Toyonaka 565-0085, Japan, and Department of Molecular Chemistry,
Osaka University, 2-1 Yamadaoka, Suita 565-0871, Japan

yuliu@public.tpt.tj.cn

Received May 25, 2000

ABSTRACT



A single crystal of mono(6-anilino-6-deoxy)- β -cyclodextrin was prepared, and its crystal structure was determined by X-ray crystallographic analysis, which clearly revealed that the anilino groups are consecutively included intermolecularly into the adjacent cyclodextrin cavities in the crystal, thus giving rise to a consolidated column, located on a 2₁-screw axis.

Cyclic oligosaccharides composed of six to eight linked D-glucopyranose units forming truncated conical structures such as α -, β -, and γ -cyclodextrins are widely used as enzyme mimics and molecular receptors in science and technology, as a result of their ability to bind small hydrophobic molecules in aqueous solution.¹ To improve their catalytic and complex-forming abilities, a wide variety of chemically modified cyclodextrins have been designed and prepared by introducing various functional groups to the macrocyclic ring.² β -Cyclodextrin is readily available and possess an appropriate cavity for accommodating monocyclic aliphatic and aromatic compounds, and therefore its deriva-

tives are of increasing interest. Recently, the conformations of many chemically modified cyclodextrins in aqueous solution have been carefully studied.^{3,4} Most studies indicate that the new hydrophobic substituents prefer to be self-induced included into the cavity of the parent cyclodextrin, forming an intramolecular complex. Upon accommodation of a guest molecule, the self-included substituent is driven out of the cavity, which enables the host to selectively bind guests. In this context, it is interesting to investigate and compare the conformations of a modified cyclodextrin in both solution and the solid state.

[†] Nankai University.

[‡] Inoue Photochirogenesis Project.

[§] Osaka University.

(1) (a) Szejtli, J. *Cyclodextrin Technology*; Dordrecht: Kluwer Academic, 1988. (b) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.

(2) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.

(3) (a) Ikeda, H.; Nakamura, M.; Ise, N.; Oguma, N.; Nakamura, A.; Ikeda, T.; Toda, F.; Ueno, A. *J. Am. Chem. Soc.* **1996**, *118*, 10980. (b) Kuwabara, T.; Nakajima, H.; Nanasawa, M.; Ueno, A. *Anal. Chem.* **1999**, *71*, 2844.

(4) (a) Liu, Y.; Han, B.-H.; Sun, S.-X.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 1487. (b) Liu, Y.; You, C.-C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 3630.

Single-crystal X-ray diffraction is an indispensable technique for determining the solid-state structures of cyclodextrins and their inclusion complexes, which not only reveals the geometries of host and guest molecules but also provides vital information regarding the host–guest interactions. Hence, a considerable amount of effort has been devoted toward a crystallographic study of native and modified cyclodextrins.^{5,6} In this Letter, we report the X-ray crystallographic study of mono(6-anilino-6-deoxy)- β -cyclodextrin (**1**), which is found in the solid state to behave as both a host (cyclodextrin cavity) and a guest (anilino moiety). In contrast, aqueous solution studies show that the anilino moiety prefers to be self-included in the cyclodextrin cavity, forming an intramolecular complex.

Mono(6-anilino-6-deoxy)- β -cyclodextrin (**1**) was prepared by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]- β -cyclodextrin⁷ with an excess of freshly distilled aniline in DMF according to the procedure described previously.⁸ A small amount of **1** was dissolved in hot water to make a saturated solution, which was then cooled to room temperature. After removing the precipitates by filtration, a small amount of water was added to the filtrate. The resultant solution was kept at 4 °C for a week. The crystal formed was collected along with its mother liquor for X-ray crystallographic analysis.⁹

The molecular structure of **1** is shown in Figure 1. As reported in several papers,¹⁰ all of the D-glucoses are in the

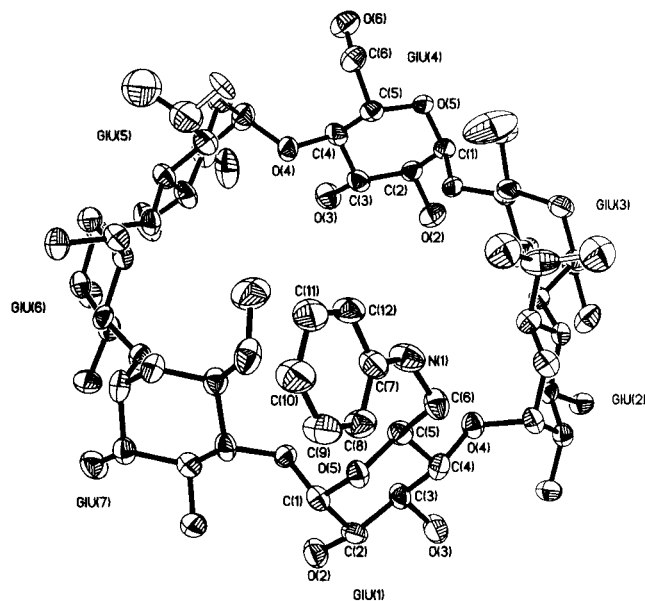


Figure 1. ORTEP representation of the molecular structure of **1**.

⁴C₁ chair conformation, and the secondary hydroxyl groups form the well-documented successive intra- and inter-glucose hydrogen bond network circling the rim of cyclodextrin. The

seven glycosidic oxygen atoms (O4) are coplanar within 0.13 Å forming a heptagon. The edge-to-edge distances of the heptagon are in the range of 4.99–5.08 Å, which indicates that the heptagon composed of O4 atoms is essentially regular. In other words, the cyclodextrin moiety has an approximate 7-fold axis and a round shape, indicating that the introduction of an anilino group does not significantly alter the original skeleton of native β -cyclodextrin. The O6 atoms in the GIU(2) and GIU(5) glucose residues are disordered, and the two conformers are statistically distributed. The anilino group of **1** is located just above the GIU(1) glucose residue, and the dihedral angle of C5–C6–N1–C7 is 94.4°.

A more interesting structural feature of the crystal is that the molecules are aligned along a screw axis, forming a helical columnar superstructure. As shown in Figure 2, the

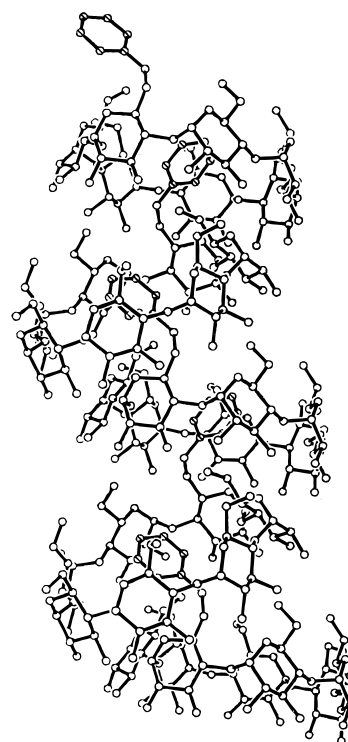


Figure 2. Side view of the columnar structure of **1**.

anilino group is intermolecularly included in the hydrophobic cavity of an adjacent cyclodextrin from the secondary hydroxyl side; thus a single molecule acts as both guest and host. Some of these structural features are similar to those reported for mono(6-phenylthio-6-deoxy)- β -cyclodextrin by Tabushi et al.^{10c} However, the cyclodextrin residues of **1** in a helical column are related by a 2₁ screw axis and inclined to this screw axis by 123.1°, while the thio analogue is stacked along a 4-fold screw axis. The anilino groups of **1**

(5) Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Smith, S. M.; Takaha, T. *Chem. Rev.* **1998**, 98, 1787.

(6) (a) Harata, K. In *Comprehensive Supramolecular Chemistry*, Vol. 3; Atwood, J. L., Davies, J. E. D., MacNicol D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; p 279. (b) Harata, K. *Chem. Rev.* **1998**, 98, 1803.

are spirally aligned in one direction through the column of compiled cyclodextrins and function as joints to bind the β -cyclodextrin rings.

The self-assembled structure of **1** further extends to a more sophisticated level, since the columns or channels associate with each other through hydrogen-bonding interactions along the *a* and *b* axes. As can be seen from Figure 3, many water



Figure 3. View down the columnar axis of **1**.

molecules fill the lattice space, and thus the hydrogen-bonding interactions occur either through direct association of the primary and secondary hydroxyl groups of cyclodextrin or through intervening water molecules.

Although it is not fully justified in general to elucidate the conformations in aqueous solution from crystal structures, the above results suggest that in solution there exists not

only monomers, where the anilino group is shallowly included intramolecularly into the cavities, but also dimers or even higher-order complexes in concentrated aqueous solution. The formation of dimeric and/or oligomeric complexes in aqueous solution has been reported for some 6-substituted cyclodextrins.¹¹ Hence, we further investigated the possible interaction of **1** with β -cyclodextrin using the circular dichroism spectroscopy. However, the circular dichroism spectra of **1** (0.1 mM) showed no significant changes upon addition of β -cyclodextrin up to 12 mM (near the solubility limit) in aqueous buffer solution. This result indicates that the anilino, which is originally self-included in the cavity as demonstrated by the circular dichroism and fluorescence spectroscopic studies, cannot be pulled out of the cavity to form intermolecular complexes with added β -cyclodextrin. In another work, we carefully studied the conformations of mono(6-*m*-toluidino-6-deoxy)- β -cyclodextrin, an analogue of **1**, by using 1D and 2D NMR spectroscopy, which revealed that in aqueous solution *m*-toluidino- β -cyclodextrin forms a stable intramolecular complex in which the *m*-toluidino group penetrates into its own cavity.¹² One probable explanation for the above phenomena is that only hydrophobic interactions dominate the formation of self-inclusion complexes in aqueous solution, whereas in the crystalline state both hydrogen-bonding and hydrophobic interactions contribute to the intermolecular interaction and make the columnar structure stable. Hence, the anilino derivative **1** may be concluded to form the polymeric complex only in the crystalline state.

Acknowledgment. This work was supported by the National Outstanding Youth Fund (Grant 29625203), Natural Science Foundation of China (Grant 29992590-8 and 29972029), Trans-Century Qualified Personal Fund (Sun-Light Plan) of Tianjin Municipality, and Tianjin Natural Science Fund (Grant 993601311), which are gratefully acknowledged. We also thank Dr. Guy A. Hembury and Ms. Makiko Niki at the Inoue Photochirogenesis Project for assistance in the preparation of the manuscript and for technical assistance, respectively.

Supporting Information Available: Crystal details, structure of unit cell, and CIF file for **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL000135+

(7) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860.

(8) Liu, Y.; Zhang, Y.-M.; Sun, S.-X.; Li, Y.-M.; Chen, R.-T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1609.

(9) The X-ray intensity data of **1** were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal-focus molybdenum-target X-ray tube ($\lambda = 0.71073$ Å) operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator. Data were collected to $2\theta_{\max} = 50.06^\circ$. **Crystal data for 1:** $C_{48}H_{75}O_{34}N \cdot nH_2O$; $M = 1210$ (excluding water molecules), orthorhombic, $a = 13.432(3)$ Å, $b = 19.025(4)$ Å, $c = 28.041(6)$ Å, $V = 7166(3)$ Å³, space group $P2_12_12_1$, $Z = 4$, $D_m = 1.225$ g cm⁻³, $\mu(\text{Mo K}\alpha) = 0.109$ mm⁻¹, $T = 298$ K. The structure was solved by using direct method and refined employing full-matrix least squares on F^2 (Siemens, SHELXTL, version 5.04). Convergence was achieved with $R_1 = 0.109$ and $wR_2 = 0.2661$ for 6160 data having $I > 2\sigma(I)$ (of 12601 independent reflections).

(10) (a) Mentzafos, D.; Terzis, A.; Coleman, A. W.; de Rango, C. *Carbohydr. Res.* **1996**, 282, 125. (b) Corradini, R.; Dossena, A.; Marchelli, R.; Panagia, A.; Startor, G.; Saviano, M.; Lombardi, A.; Pavone, V. *Chem. Eur. J.* **1996**, *2*, 373. (c) Kamitori, S.; Hirotsu, K.; Higuchi, T.; Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *J. Chem. Soc., Perkin Trans. 2* **1987**, 7.

(11) (a) Tong, L.-H.; Hou, Z.-J.; Inoue, Y.; Tai, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1253. (b) Jung, J. H.; Takehisa, C.; Sakata, Y.; Kaneda, T. *Chem. Lett.* **1996**, 147. (c) McAlpine, S. R.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4269.

(12) The conformations and structures of **1** and the *m*-toluidino analogue in aqueous phosphate buffer solution have been studied in detail by circular dichroism and fluorescence spectroscopy as well as time-correlated and fluorescence lifetime measurements, which was published in *Supramol. Chem.* (**2000**, in press).