

Self-assembly behavior of inclusion complex formed by β -cyclodextrin with α -aminopyridine

ZHAO Yanli & LIU Yu

Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
Correspondence should be addressed to Liu Yu (email: yuliu@public.tpt.tj.cn)

Received January 5, 2004

Abstract An inclusion complex (**1**) has been prepared by β -cyclodextrin with α -aminopyridine. The result of X-ray crystallographic analyses showed that the α -aminopyridine molecules in the β -cyclodextrin cavities possess two opposite orientations, i.e. the amine group of α -aminopyridine pointing to the primary side (**1a**, occupancy: 41.2%) or the secondary side (**1b**, occupancy: 58.8%) of β -cyclodextrin, forming two scalelike supramolecular aggregations. The studies of 2D NMR and circular dichroism spectra indicated that the α -aminopyridine molecule is deeply embedded in the β -cyclodextrin cavity to form host-guest inclusion complex, showing a circular dichroism spectrum induced by the chiral cavity of cyclodextrin. The results obtained are helpful for understanding the molecular recognition and aggregation mechanism between the host and guest.

Keywords: aggregation, crystal structure, cyclodextrin, hydrogen bonds, inclusion complex.

DOI: 10.1360/03yb0169

Cyclodextrins (α -, β - and γ -CDs), possessing the hydrophobic cavity, could form the host-guest or supramolecular inclusion complexes with a variety of guest molecules in solution and in the solid state^[1]. The supramolecular assemblies constructed by simple inclusion complexation of host CDs and guest molecules have attracted more and more attentions in recent years because of their potential to serve as molecular devices and molecular machines, as well as functional materials etc.^[2–6]. Our recent investigations have revealed that the resulting complex of β -CDs with guest molecules is the crucial step in the formation of polymeric rotaxane^[7].

On the other hand, several works have focused on the solution studies of CD complexes of aliphatic alcohols, amino acids, dyes molecules and so on, using a

variety of methods such as fluorescence spectrometry, UV-Vis spectrometry, and titration microcalorimetry^[8,9], providing important information for understanding the binding thermodynamics and molecular recognition of CDs in solution. However, there are few reports concerning the direct evidence for the formation of supramolecular complexes in the solid state. In order to compare the inclusion behaviors of β -CDs with guest molecule in solution and in the solid state, in the present paper, we report our investigations on an uncommon scalelike supramolecular aggregation **1** obtained by the resulting complex of β -CD with α -aminopyridine. The results of X-ray crystallographic analyses of aggregation **1** showed that α -aminopyridine molecule in the β -CD cavity possess two opposite orientation, i.e. the amine group of α -aminopyridine pointing to the primary side (**1a**) or

the secondary side (**1b**) of β -CD, leading to two different aggregation modes. Furthermore, the complexation behavior of β -CD with α -aminopyridine in solution was studied by 2D NMR and circular dichroism spectra, indicating that the α -aminopyridine molecule is deeply embedded in the β -CD cavity to form host-guest inclusion complex, giving a circular dichroism spectrum induced by the chiral cavity of cyclodextrin.

1 Experimental

1.1 Materials and instruments

α -Aminopyridine was purchased from Shanghai Reagent Factory and used without further purification. β -CD of reagent grade (Shanghai Reagent Factory) was recrystallized twice from water and dried *in vacuo* at 95°C for 24 h prior to use.

The X-ray intensity data were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal-focus molybdenum-target X-ray tube ($\lambda = 0.071073$ nm) operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator at $T = 293(2)$ K. The structures were solved by using direct method and refined, employing full-matrix least squares on F^2 (Siemens, SHELXTL, version 5.04). Elemental analyses were performed on a Perkin-Elmer

2400C instrument. ^1H NMR spectra were recorded in D_2O on a Varian INVOA 300 spectrometer. Circular dichroism (CD) and UV-Vis spectra were recorded in a conventional quartz cell (light path 10 mm) on a JASCO J-715S spectropolarimeter or a Shimadzu UV-2401PC spectrophotometer equipped with a PTC-348WI temperature controller to keep the temperature at 25°C.

1.2 Preparation of host-guest inclusion complex **1**

As shown in fig. 1, a mixture of β -CD (1 mmol) and α -aminopyridine (1 mmol) was allowed to react in aqueous solution (30 mL) with stirring at 30°C for 5 h. The solution was slowly cooled to 0°C, the precipitate formed was filtrated to give white powder. The crude product was recrystallized and purified from water and dried *in vacuo* to obtain a pure sample. The product was then dissolved in hot water to make a saturated solution, which was 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 room temperature for a week. The colorless crystal of **1** then formed was collected along with its mother liquor for the X-ray crystallographic analyses. Yield 63%. Anal. Calcd. (%) for $\text{C}_{47}\text{H}_{76}\text{O}_{35}\text{N}_2 \cdot 4\text{H}_2\text{O}$: C 43.39, H 6.51, N 2.15; found

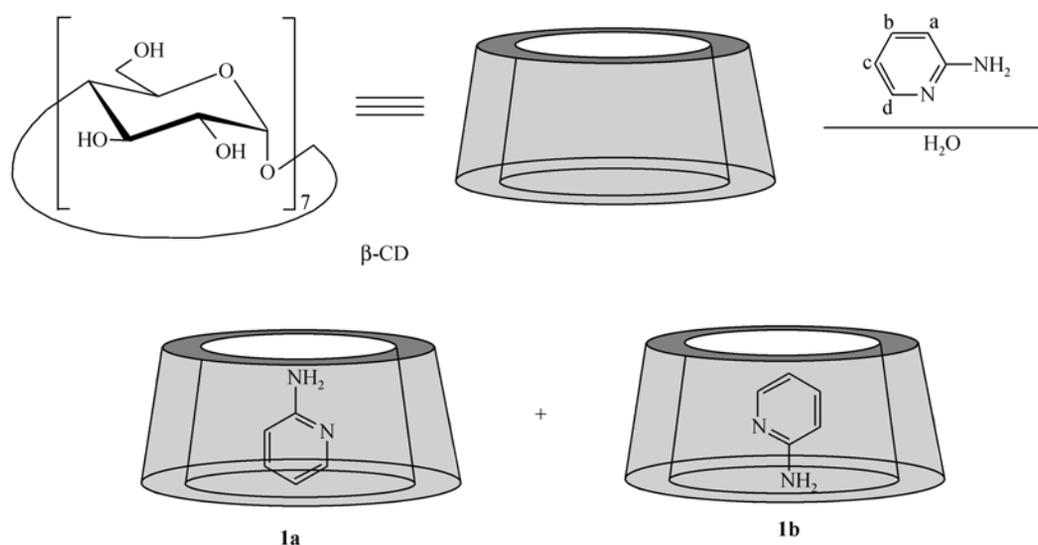


Fig. 1. Schematic representation of the formation of complex **1**. **1a**: The amine group of α -aminopyridine points to the primary side of β -CD, **1b**: the amine group points to the secondary side of β -CD.

(%): C 43.31, H 6.46, N 2.21. ^1H NMR (300 MHz, D_2O , TMS): δ 3.39—3.84 (m, 42H), 4.91—4.92 (d, 7H), 6.54—6.57 (d, 1H), 6.61—6.65 (m, 1H), 7.41—7.47 (m, 1H), 7.80—7.81 (d, 1H).

Crystal data for **1**: empirical formula $\text{C}_{47}\text{H}_{86}\text{N}_2\text{O}_{40}$; $M = 1319.18$ (including water molecules); crystal size = 0.34 mm \times 0.24 mm \times 0.20 mm; monoclinic; space group: $\text{P}2_1$; unit cell dimensions: $a = 1.5228(5)$ nm, $b = 1.0226(3)$ nm, $c = 2.1079(6)$ nm, $\beta = 110.612(8)^\circ$, $V = 3.0724(16)$ nm 3 ; $Z = 2$; $D_m = 1.426$ g/cm 3 ; $F(000) = 1404$; $1.03^\circ < \theta < 25.00^\circ$; data/restraints/parameters 7008 / 15 / 791; final R indices $R1 = 0.0884$, $wR2 = 0.2325$.

2 Results and discussion

2.1 Crystal structure

It is noted that the direct evidence for the formation of supramolecular aggregation constructed by β -CD with α -aminopyridine has been obtained in the solid state. In the molecular structure, every β -CD has an approximate 7-fold axis and maintains the round shape of the macrocycle. Every glucose residue of β -CD has a $^4\text{C}_1$ chair conformation, and seven glycosidic oxygen atoms are coplanar within 0.514 nm. Interestingly, α -aminopyridine molecule in the β -CD cavity shows two opposite orientation, i.e. the amine group of α -aminopyridine pointing to the primary side (**1a**, occupancy: 41.2 %) or the secondary side (**1b**, occupancy: 58.8 %) of β -CD, which is entirely different from the general inclusion types of β -CD with guest molecules in the solid state^[10,11]. Fig. 2(a) gives a molecular structure of **1a**. Every α -aminopyridine in the molecular structure is deeply included in the β -CD cavity with a dihedral angle of 38.1° between the plane of α -aminopyridine molecule and the heptagons composed of seven glycosidic oxygen atoms of the β -CD. The molecular structure of **1b** is shown in fig. 2(b). As compared with **1a**, every α -aminopyridine is deeply included in the β -CD cavity with a dihedral angle of 66.7° . Especially, the complexes **1a** and **1b** could further self-assemble to form head-to-tail scalelike polymeric supramolecule, which are shown in fig. 3. If the

unique assembly behavior is the result of the cooperative contributions of the van der Waals, hydrophobic and hydrogen bond interactions, then different orientations of α -aminopyridine in **1a** and **1b** should be ascribed to the 6 hydrogen bonds between host and guest: 4 of them come from the hydroxyl groups between the primary side of the β -CD and the secondary side of the next β -CD, and 2 of them involve the amine group of α -aminopyridine and the hydroxyl groups of the next β -CD. **1a** is oriented by the hydrogen bonds between the amine group and the hydroxyl groups of the secondary side of the next β -CD, but **1b** is oriented by the hydrogen bonds between the amine group and the hydroxyl groups of the primary side of the next β -CD. Furthermore, the guest molecule does not locate in the center of β -CD cavity in the aggregation. The spatial distance between the center of guest's aromatic ring and the center of the heptagons composed of seven glycosidic oxygen atoms of the β -CD is 0.112 nm for **1a** and 0.052 nm for **1b**. The special relative position might be attributed to the van der Waals interactions between the host and guest, and could be taken as one of the reasons forming the scalelike aggregation. On the other hand, the strong hydrogen bond network formed by the hydroxyl groups of the β -CD and intervening water stabilizes the aggregation and further extends the aggregation to a more complicated level. Therefore, the results of crystal structure not only indicated the formation of the supramolecular aggregation constructed by the β -CDs with α -aminopyridines, but also established a correlation between the conformation of aggregation and the host-guest binding mode.

In order to further discuss the forming mechanism of the scalelike aggregation, and the influence of guest to the relative position of cyclodextrins, we compared the crystal structures of **1** with native β -CD^[12]. β -CD crystallizes from water in monoclinic space group $\text{P}2_1$ with $a = 2.1261(6)$ nm, $b = 1.0306(3)$ nm, $c = 1.5123(4)$ nm, $\beta = 112.3(5)^\circ$, $V = 3.0658$ nm 3 . Per asymmetric unit is distributed with 11 water molecules and 6.13 of them are included in the β -CD

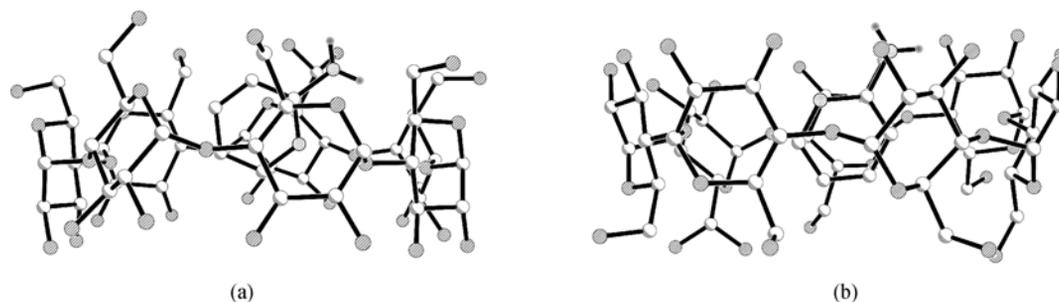


Fig. 2. The molecular structure of complex **1** (beside of the amine group's hydrogen atoms in α -aminopyridine, other hydrogen atoms were omitted). The amine group of α -aminopyridine points to (a) the primary side and (b) the secondary side of β -CD.

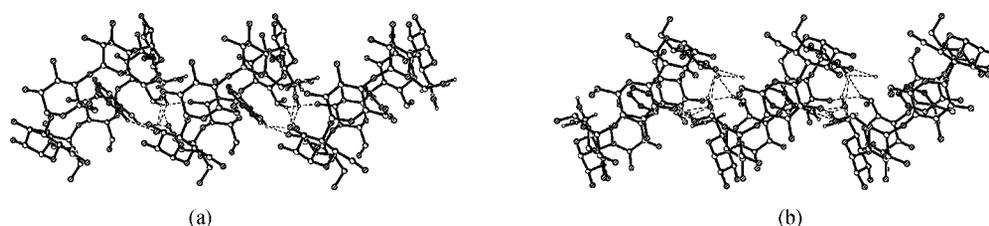


Fig. 3. The scalelike structure of **1** (only the hydrogen atoms involved in hydrogen bonds are given). The amine group of α -aminopyridine points to (a) the primary side and (b) the secondary side of β -CD.

cavity. The main driving force of the aggregation's formation is the hydrogen bond interactions between the hydroxyl groups of the primary and secondary side of the adjacent β -CDs. As compared with native β -CD, the crystal **1** belongs to monoclinic system with $a = 1.5228(5)$ nm, $b = 1.0226(3)$ nm, $c = 2.1079(6)$ nm, $\beta = 110.612(8)^\circ$, $V = 3.0724(16)$ nm³. In per asymmetric unit, 5 water molecules are totally located in the outside of β -CD cavity, which indicates the presence of stronger hydrophobic interactions between the cavity and guest. In the aggregation, except for the hydrogen bonds between the hydroxyl groups of the adjacent β -CDs, the amine group of α -aminopyridine in the cavity also participated in the hydrogen bond formations, which fixed the relative orientation of the scalelike aggregation. Therefore, the introduction of guest molecules not only altered the hydrogen bond network of the crystal structure, but also played a crucial role in controlling relative position of the host and guest.

2.2 ¹H NMR experiment

Usually, guest molecules included in CDs cavity show the chemical shifts in ¹H NMR spectra^[13].

Therefore, to study the binding behavior of **1** in solution, ¹H NMR experiments were performed at 25°C in D₂O, and the concentration of α -aminopyridine and **1** were 5.0×10^{-3} and 4.8×10^{-3} mol \cdot L⁻¹ respectively. The changes in the chemical shift of all the protons of the α -aminopyridine molecule are observed in the presence of β -CD relative to the free guest molecule, that is, the Ha, Hb, Hc, and Hd protons of α -aminopyridine molecule shift downfield ca. 12, 18, 15, and 12 Hz respectively, which indicate that a complex has formed between α -aminopyridine and β -CD.

2D NMR spectroscopy has recently become an important method for the investigation of the interaction as well as inclusion mode between host CDs and guest molecules, since the NOE cross-peaks between the protons that are closer than 0.4 nm in space will be observed in the NOESY or ROESY spectra and the relative intensities of these cross-peaks depend on the spaces between the corresponding protons. The height and diameter of the β -CD cavity are about (0.79 ± 0.01) nm and 0.60–0.65 nm, respectively. Therefore, while the guest molecule is included into the β -CD

cavity, the NOE correlations between the protons of the guest molecule and the protons of the β -CD cavity (H3 and H5) will be measured. On the other hand, according to the relative intensity of these cross-peaks^[13], it is possible to estimate the orientation of the guest molecule within the β -CD cavity. To obtain further evidence about the initial geometry of the inclusion mode of β -CD with α -aminopyridine molecule, 2D NMR spectroscopy experiment of **1** has been performed in D₂O at 25 °C. As shown in fig. 4, the ROESY spectrum of **1** displays clearly NOE cross-peaks between the H5/H3 protons of β -CD and the Ha and/or Hc protons of α -aminopyridine (peaks A), the H5/H3 and the Hb protons (peaks B), as well as the H5/H3 and the Hd protons (peaks C), which indicate distinctly that the α -aminopyridine in **1** is deeply included into the hydrophobic cavity from the primary or secondary side of β -CD, consistent with the crystal structure.

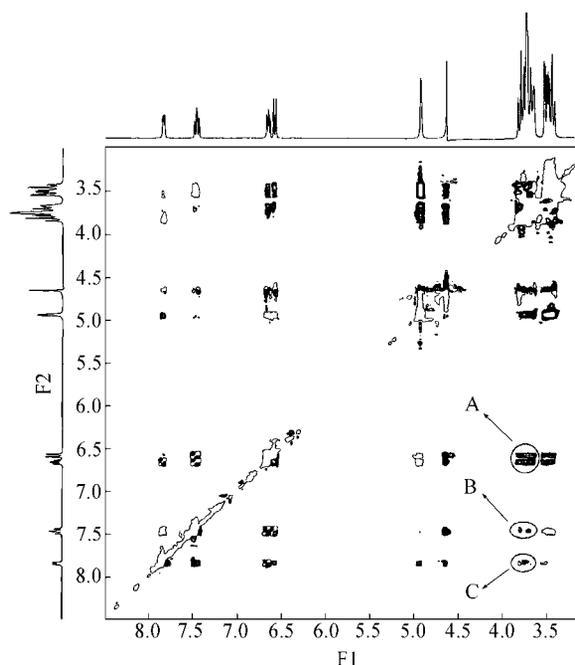


Fig. 4. ¹H ROESY spectrum of **1** ($4.8 \times 10^{-3} \text{ mol} \cdot \text{L}^{-1}$) in D₂O at 25 °C with a mixing time of 600 ms.

2.3 Induced circular dichroism spectrum

It has been demonstrated that the inclusion of chromophoric achiral guest in a chiral cavity of CDs

produces induced circular dichroism (ICD) signals at the wavelengths absorbed by the guest chromophore. Therefore, the ICD spectrum of **1** was measured in aqueous solution at 25 °C. As can be seen from fig. 5, the circular dichroism spectrum of **1** shows a moderate negative Cotton-effect peak at 217 nm ($\Delta\epsilon = -0.120 \text{ L}^{-1} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$), a weak positive Cotton-effect peak at 269 nm ($\Delta\epsilon = 0.013 \text{ L}^{-1} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$), and a weak negative Cotton-effect peak at 279 nm ($\Delta\epsilon = -0.013 \text{ L}^{-1} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$). According to the Kajtár's sector rule^[14], it is deduced that the α -aminopyridine molecule in **1** is entered into the β -CD cavity with an acclivitous orientation, which further support the investigations of the 2D NMR experiment and crystal structure on the conformation of **1**.

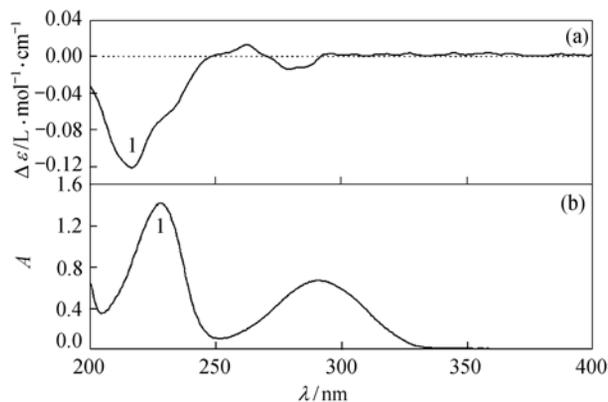


Fig. 5. (a) Circular dichroism and (b) absorption spectra of **1** ($4.8 \times 10^{-4} \text{ mol} \cdot \text{L}^{-1}$) in aqueous solution at 25 °C.

3 Conclusions

In conclusion, a novel host-guest inclusion complex was prepared by β -CD with α -aminopyridine. In the crystal structure of this complex, α -aminopyridine in the β -CD cavity possessed two opposite orientation, leading to two different aggregation modes. In solution, the α -aminopyridine not only was deeply embedded in the β -CD cavity to form host-guest inclusion complex, but also gave an ICD spectrum in the chiral cavity. The results obtained are helpful for understanding the molecular recognition and aggregation mechanism of β -CD.

Acknowledgements This work was supported by the National Natural Science Foundation of China (Grant Nos. 20272028 and 90306009).

References

1. Wenz, G., Cyclodextrin as building blocks for supramolecular structure and functional units, *Angew. Chem. Int. Ed.*, 1994, 33(8): 803—822.[\[DOI\]](#)
2. Nepogodiev, S. A., Stoddart, J. F., Cyclodextrin-based catenanes and rotaxanes, *Chem. Rev.*, 1998, 98(5): 1959—1976.[\[DOI\]](#)
3. Harada, A., Cyclodextrin-based molecular machines, *Acc. Chem. Res.*, 2001, 34(6): 456—464.[\[DOI\]](#)
4. Liu, Y., Li, L., Zhang, H. Y. et al., Bis(pseudopolyrotaxane)s possessing copper(II) ions formed by different polymer chains and bis(β -cyclodextrin)s bridged with a 2,2'-bipyridine-4,4'-dicarboxy tether, *Macromolecules*, 2002, 35(27): 9934—9938.[\[DOI\]](#)
5. Fan, Z., Zhao, Y. L., Liu, Y., Molecular self-assembly behavior of mono[6-O-6-(4-carboxyl-phenyl)]- β -CD in solution and solid state, *Chin. Sci. Bull.*, 2003, 48(15): 1535—1538.[\[DOI\]](#)
6. Ma, S. K., Wang, J. L., Li, A. X. et al., Synthesis and crystal structure of hydroquinone- β -cyclodextrin complex, *Chin. Sci. Bull.*, 2001, 46(5): 390—392.
7. Liu, Y., Zhao, Y. L., Zhang, H. Y. et al., Polymeric rotaxane constructed from the inclusion complex of β -cyclodextrin and 4,4'-dipyridine by coordination with nickel(II) ions, *Angew. Chem. Int. Ed.*, 2003, 42(28): 3260—3263.[\[DOI\]](#)
8. Rekharsky, M. V., Inoue, Y., Complexation thermodynamics of cyclodextrin, *Chem. Rev.*, 1998, 98(5): 1875—1917.[\[DOI\]](#)
9. Liu, Y., Kang, S. Z., Molecular recognition on supramolecular systems (XXXV)—Synthesis of novel β -cyclodextrin derivative bearing pyridinio group and its chiral discrimination of amino acids, *Science in China, Series B*, 2001, 44(3): 260—267.
10. Harata, K., Structural aspects of stereodifferentiation in the solid state, *Chem. Rev.*, 1998, 98(5): 1803—1827.[\[DOI\]](#)
11. Song, L. X., Meng, Q. J., You, X. Z., Cyclodextrins and their inclusion compounds, *Chinese J. Inorg. Chem. (in Chinese)*, 1997, 13(4): 368—374.
12. Betzel, C., Saenger, W., Hingerty, B. E. et al., Circular and flip-flop hydrogen bonding in β -cyclodextrin undecahydrate: a neutron diffraction study, *J. Am. Chem. Soc.*, 1984, 106(24): 7545—7557.
13. Schneider, H. J., Hacket, F., Rüdiger, V. et al., NMR studies of cyclodextrins and cyclodextrin complexes, *Chem. Rev.*, 1998, 98(5): 1755—1785.[\[DOI\]](#)
14. Kajtár, M., Horvath-Toro, C., Kuthi, E. et al., A simple rule for predicting circular dichroism induced in aromatic guests by cyclodextrin hosts in inclusion complexes, *Acta Chim. Acad. Sci. Hung.*, 1982, 110(3): 327—355.