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ORIGINAL ARTICLE

The structure of inclusion complex of β-cyclodextrin with p-nitrophenoxyacetic acid in solution and the solid state

Min-Jie Guo · Chun-Hua Diao · Zuo-Liang Jing · Bin Dong · Zhi Fan · Min Wang

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Abstract The inclusion complex (**1**) of with β-cyclodextrin-*p*-nitrophenoxyacetic acid was synthesized and characterized. Its inclusion behavior was investigated by means of X-ray crystallography and NMR spectroscopy in solution and in the solid state. The crystallographic study shows that one β-cyclodextrin co-crystallize with one *p*-nitrophenoxyacetic acid, and 17 water molecules in the Monoclinic system with unit cell constants: $a = 18.6864(16)$, $b = 24.961(2)$, $c = 16.6644(14)$ Å, $\beta = 105.129(5)°$. Two β-cyclodextrins are held together by hydrogen bonds to form head-to-head dimers. The disordered guest molecule molulates itself to attain the most stable accommodation into the cavity in which the nitro group is located at the dimer interface while the carboxyl group buried in the primary hydroxyl groups of β-CD. The further 2D NMR spectroscopy investigation in solution supports the inclusion mode of the solid state.

Keywords β-Cyclodextrin · Inclusion complex · Crystal structure · *p*-Nitrophenoxyacetic acid

Introduction

Cyclodextrins (CDs) are a unique family of naturally occurring organic compounds. These macrocyclic compounds have an apolar cavity that can include a wide variety of guest molecules into the host CD cavity to form supramolecular inclusion complexes without formation of covalent bonds in solution and/or in solid state [1–4]. The unique structural features and fascinating properties enable these molecules to be ideal prototypes for examining intermolecular interactions associated with molecular recognition and assembly [5–8]. Therefore, there has been increasing interest in the inclusion complexes formed by CD and all kinds of guest molecules in order to understand the weak interactions associated with the inclusion process. The large numbers of investigations indicate that several factors contribute to the stabilization of the inclusion complexes: hydrogen bonding and polar interactions between the guest and host molecules, and the shape and size of the guest [9–19]. However, the mechanisms of molecular recognition and inclusion are still complicated.

To get insight into the conformation and mechanism of the noncovalent interactions of inclusion complexes at the molecular level, in present study, we prepared the inclusion complex of β-CD with *p*-nitrophenoxyacetic acid (β-CD-*p*-NPOAA), and investigated its binding behavior by means of X-ray crystallography and NMR spectroscopy in the solid state and in solution. It is of our particular interest to elucidate the weak interaction and the binding behavior of the inclusion complexation on β-CD complexes.

Experimental

Reagents

β-CD of reagent grade was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use, *p*-NPOAA was commercially available and used without further purification.

M.-J. Guo · C.-H. Diao · Z.-L. Jing · B. Dong · Z. Fan (✉)
College of Sciences, Tianjin University of Science and Technology, Tianjin 300222, People's Republic of China
e-mail: zhifan@tust.edu.cn

M. Wang
Key Laboratory of Industrial Microbiology, Ministry of Education, School of Biological Engineering, Tianjin University of Science and Technology, Tianjin 300222, People's Republic of China

Apparatus

Elemental analyses was performed on a Perkin-Elmer 2400C instrument. ^{1}H NMR spectra were recorded in D_2O on a Varian Mercury VX300 spectrometer. The X-ray intensity data were collected on a Saturn-70 Rigaku CCD Area Detector System equipped with a micro focus molybdenum target of Micro-Max-007 rotating anode (Mo Kα radiation $\lambda = 0.71073$ Å) operated at 50 kV and 16 mA and a confocal monochromator. During data collection, no intensity decay was observed. Data collection, reduction and absorption correct were performed by program Crystalclear [20]. The structure was eventually solved employing SHELXD [21].

Synthesis of complex **1**

The ethanol solution of *p*-NPOAA (0.5 mmol, 30 mL) was added dropwise to an aqueous solution of β-CD (0.5 mmol, 40 mL) and stirred at 60 °C for 6 h. Then the solution was cooled to room temperature, and the precipitate was obtained by slow evaporation of the solution. The crude product was recrystallized from water to give white solid **1** in 76% yield. Data for **1**: ^{1}H NMR (D_2O, ppm) δ 8.07–8.10 (d, 2H), 6.92–6.95 (d, 2H), 4.89–4.90 (m, 7H), 4.60 (s, 2H), 3.40–3.80 (m, 42H). Anal. Calcd for $C_{50}H_{77}NO_{40}\cdot 18H_2O$: C, 36.25; H, 6.88, N, 0.85. Found: C, 36.40; H, 6.67, N, 0.63.

Crystals of **1** was obtained from aqueous solution. A small amount of **1** was dissolved in hot water to make a saturated solution, which was then cooled to room temperature. After removal of the precipitates by filtration, the resultant solution was kept at room temperature for 1 week. The crystal formed was collected along with its mother liquor for X-ray crystallographic analysis.

Results and discussion

The crystal structure of **1**. The crystal data, experimental and refinement parameters of **1** are shown in Table 1. In the β-CD and *p*-NPOAA complex, β-CD forms a 1:1 complex with *p*-NPOAA, as shown in Fig. 1. Every glucose residue of β-CD has a $^4C_1$ chair conformation, and seven glycosidic oxygen atoms make up a plane (O4-plane) within 0.0540 Å. No disordered atom has been found in the host molecule. The primary hydroxyl groups having a *gauche-gauche* orientation point outward from the cavity, except atoms O62, O64 and O65 which have *gauche-trans* orientation point to the cavity. The parameters describing the macrocyclic conformation of **1** are presented in Table 2, the sevenfold symmetry of the β-CD appears to be well maintained. This is also reflected in the O4(n)···O4($n-1$) distances [average 4.38 Å] and O4($n+1$)···O4(n)···O4($n-1$) angles [128.5428°]. The latter is equal to the angle of the regular heptagon (128.5714…°).

Table 1 The crystal data, experimental and refinement parameters of **1**

	Crystal **1**
Molecular formula	C50 H111.25 N O57.13
M_r (g mol^{-1})	1640.65
Crystal system	Monoclinic
Space group	C2
Z	4
a (Å)	18.6864(16)
b (Å)	24.961(2)
c (Å)	16.6644(14)
β (°)	105.129(5)
V(Å^3)	7503.3(11)
ρ_{calcd} (g cm^{-3})	1.452
F (000)	3501
Absorption coefficient (mm^{-1})	0.134
Crystal size (mm)	0.40 × 0.38 × 0.20
Correction method	Multi-scan
Range scanned θ (°)	2.07 to 27.79
Index range	$-24 \le h \le 24$, $-31 \le k \le 32$, $-21 \le l \le 21$
Data/restraints/parameters	16902/263/1143
Final R indices [$I > 2$sigma(I)]	R1 = 0.0498, wR2 = 0.1300
R indices (all data)	R1 = 0.0548, wR2 = 0.1347
Largest diff. peak and hole (e Å^{-3})	0.589 and −0.671

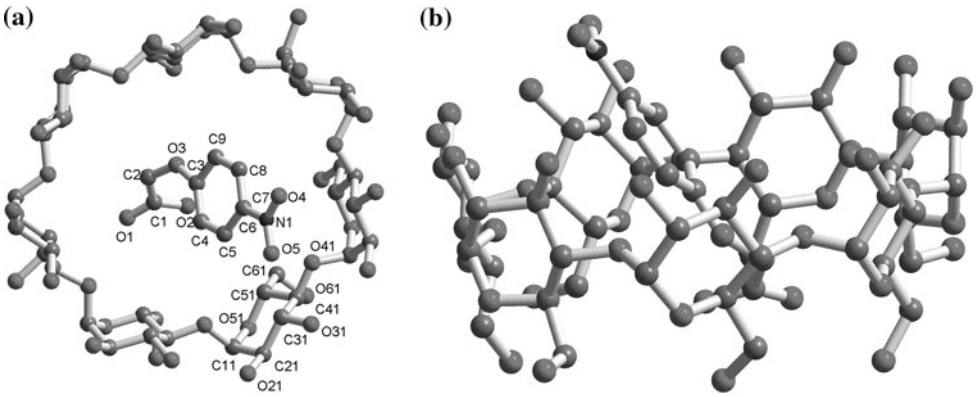

Fig. 1 An diagram showing the β-CD and *p*-NPOAA molecule and the numbering scheme: **a** Top and **b** side views of the complex

Table 2 Geometrical data describing the β-CD unit of the compound

	O4(n)–O4 (n − 1) (Å)	O4(n)–O4 (n + 1)–O4(n + 2) (°)	C4(n)–O4 (n)–C1(n + 1) (°)	Tilt angle (°)[a]	Deviation of O(4) atom (Å)[b]
G1	4.431	130.1	117.5	21.9	0.0342
G2	4.343	122.3	119.0	25.9	−0.0691
G3	4.247	132.9	116.6	30.0	−0.0159
G4	4.563	131.0	118.0	23.2	0.0954
G5	4.362	123.2	119.4	23.2	−0.0458
G6	4.297	129.4	117.3	29.2	−0.0582
G7	4.432	130.8	117.9	27.7	0.0594

[a] The tilt angle is defined as an angle made by the O4 plane and the plane through C1, C2, O4 and O4′

[b] The deviation of each O4 atom from the plane through O4 atoms

The disordered guest is included into the β-CD cavity in which the nitro group points to the second hydroxyl groups. The angle between the molecular axis of the disordered guest and the perpendicular axis to the O4 plane of β-CD is 32.9° and 35.4°, respectively. And the aromatic ring center of *p*-NPOAA are shifted from the O4 plane center to the second sides of β-CD by 1.54 and 1.31 Å, respectively. Which show that the guest molecule could adjust position of itself to occupy most of the available space in the cavity, and that the structural active adjustability would facilitate the occurrence of host–guest interaction and stabilize the inclusion complex.

Two β-CD molecules form a head-to-head dimer which the secondary hydroxyl sides face each other and are linked by means of hydrogen-bonds producing a barrel-like structure in the interior of which a pair of guest molecules is accommodated, as shown in Fig. 2.

In the dimeric structure, the both *p*-NPOAA molecules are placed in the central cavities of β-CD molecules, with the nitro group protruding from the region of the second

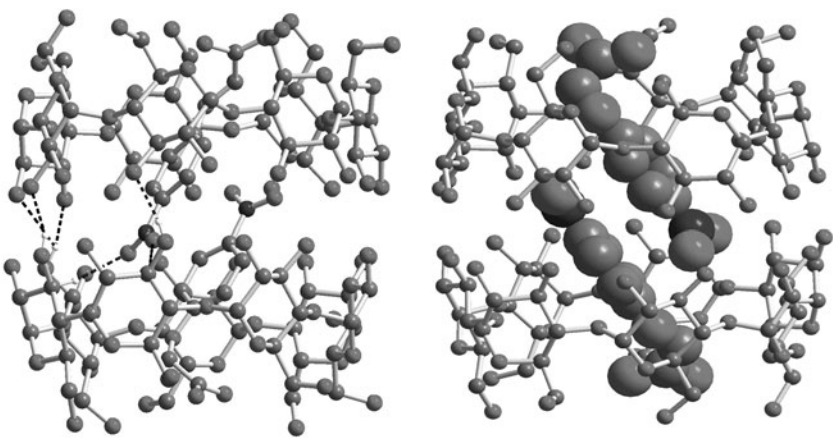

Fig. 2 Stereoscopic view of the β-CD dimer with the guest molecules inside the cavity. Intermolecular hydrogen bond interactions are drawn by *dotted lines*

hydroxyl groups and the carboxyl group buried in the primary hydroxyl groups of β-CD. The aromatic ring enters the cavity of the β-CD and makes van der Waals contacts with the atoms constructing the inside wall of the β-CD cavity, while the two oxygen atoms in the nitro group, O4 and O5, is hydrogen bonded to the adjacent β-CD ($d_{[O4B\cdots H35B\text{-}C35A]} = 3.488(8)$ Å, $\Phi_{[O4B\cdots H35B\text{-}C35A]} = 169.5(17)°$, $d_{[O5B\cdots H36B\text{-}C36A]} = 3.350(3)$ Å, $\Phi_{[O5B\cdots H36B\text{-}C36A]} = 156.4(18)°$). In addition, the carboxyl oxygen atom, O1, and the methylene form the hydrogen bond with the adjacent β-CD ($d_{[O1B\cdots H66E\text{-}C66C]} = 3.246(3)$ Å, $\Phi_{[O1B\cdots H66E\text{-}C66C]} = 115.5°$, $d_{[O65C\cdots H2A\text{-}C2B]} = 3.141(3)$ Å, $\Phi_{[O65C\cdots H2A\text{-}C2B]} = 132.0(17)°$). Although the ether oxygen atom (O3) does not have any hydrogen bonds with hydroxyl groups, it seems to form weak electrostatic interactions with the hydrogen atoms attached to the C-5 atoms. Since all of the C-5 hydrogen atoms in the β-CD direct to the center of the torus, the center of the C-5 plane is very much suited for an electronegative ether oxygen atom (O3). The distance between O3 and H54 and H55 are 2.914 and 3.340 Å, suggesting that the weak electrostatic interaction certainly exists between O3 and the C5 hydrogen atoms. As a result, These interactions between the host and guest are thought to determine the position and the orientation of the guest in the cavity, giving rise to the inclusion mode.

Comparing the title complex with the inclusion complexes of β-CD and *p*-nitro-benzoic acid, they show the similar inclusion geometries. In the dimeric struture of *p*-nitro-benzoic acid [22], the distance between aromatic ring centroids is 4.86 Å, and the dihedral angle is 0.3°. In the present study, the distance between aromatic ring centroids is 4.56 Å, and the dihedral angle is 26.5°. Showing that the guest molecule can adjust it's position and the orientation in β-CD cavity to some extent according to it's size/shape. So we think that the study will further our understanding of the molecuar recognition of substrate receptors together with published reports.

Crystal structures of the β-CD inclusion complexes are classified into three types according to the host–guest interactions and the chemical nature of β-CD and the guest molecule. In this inclusion complex, as shown in Fig. 3, the β-CD molecules complexed to *p*-NPOAAs form a layer-type structure in which the primary hydroxyl sides are open to the intermolecular space of the adjacent layer. Adjacent layers are shifted by half a molecule. The interspace between the adjacent layers is filled with water molecules. It should be noted that the water molecules filled with the layer interspace participate in interactions with β-CD to form the hydrogen bonds, typically bridging hydroxyl groups of β-CD molecules of the next layer, which contribute to stabilization of the layer-type structure.

The inclusion behavior of **1** in aqueous solution. In order to understand the formation mechanism of the inclusion complex from solution to the solid state, ^{1}H ROESY experiments have been performed on a Varian Mercury VX300 spectrometer. As shown in Fig. 4, the ROESY spectrum of **1** exhibits clear NOE cross-peaks (peaks A–E) between the protons of β-CD and *p*-NPOAA in complex **1**, which demonstrates that the *p*-NPOAA molecule is deeply included into the cavity of β-CD. Further information about the orientation of the guest molecule in the cavity of the β-CD moiety may be reasonably deduced according to the relative intensity of these cross-peaks. As illustrated in Fig. 4, the clear correlation between Hm and H3 (peaks A)

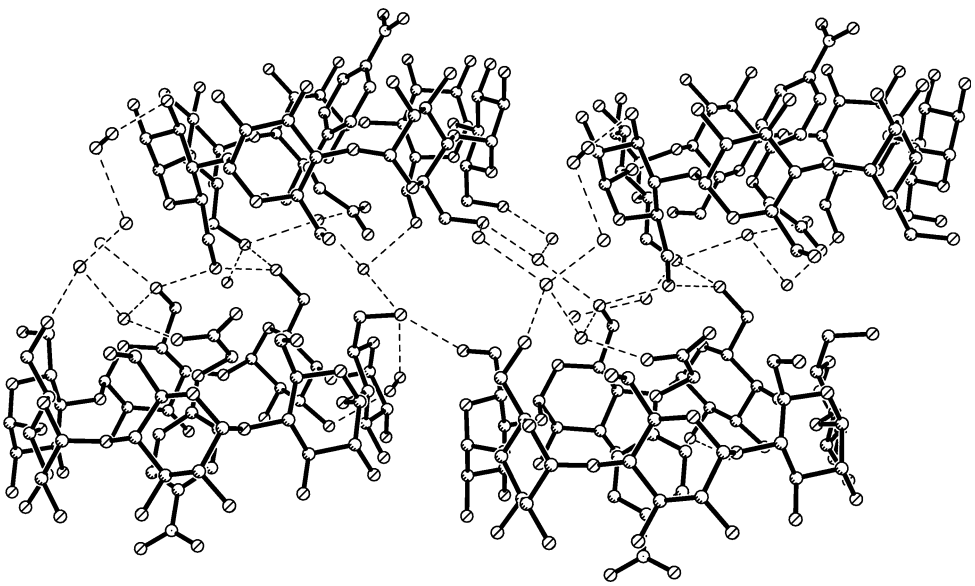

Fig. 3 The layer-type molecular packing structure of the inclusion complex **1**. Intermolecular hydrogen bond interactions are drawn by *dotted lines*

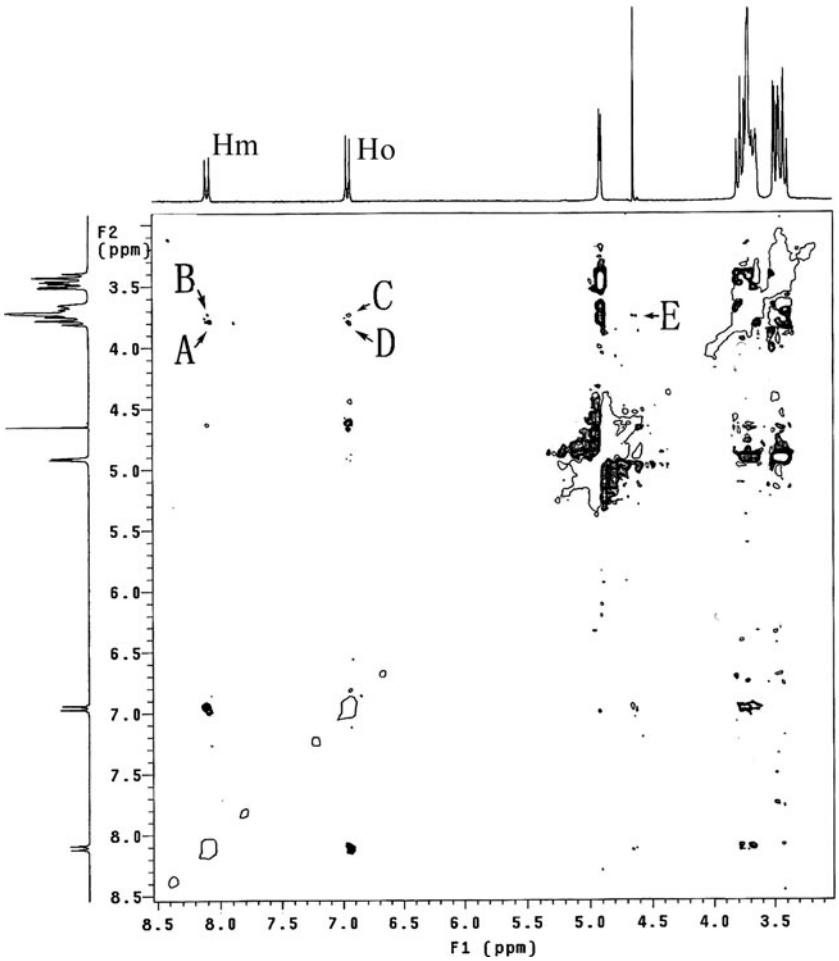

Fig. 4 ^{1}H ROESY spectra (300 MHz) of **1** ([**1**]) 1.04×10^{-3} M) with a mixing time of 300 ms in D_2O at 298 K

is stronger than that between Hm and H5 (peaks B), which imply that Hm must be close to H3, while the correlation between Ho and H5 (peaks C) is weaker than that between Ho and H3 (peaks D), implying that Ho must be close to H3. Furthermore, the correlation of H-CH_2 with H5 (peaks E) indicates that the methylene in the *p*-NPOAA must be close to the primary hydroxyl side of *β*-CD. These results unequivocally indicate that the solution conformation is consistent with the solid state structure.

Conclusion

The inclusion behavior of *β*-CD with *p*-NPOAA was studied in solution and in the solid state. In the crystal structure, the *β*-CD molecules form dimers and these dimers are arranged like coins in a roll constructing infinite linear supramolecular architecture along the crystallographic *c*-axis in which the *p*-NPOAA molecules are embedded. The *p*-NPOAA molecules prefer to occupy most of the available space in the cavity, and prefer to protrude with their polar COOH and NO_2 groups at hydroxyl group sides. On the other hand, the *p*-NPOAA molecules are maintained in positions to form hydrogen bonding with the surrounding hydroxyl groups and water molecules which stabilize the layer structure. We suggest that this system provides a data for the study of the inclusion mechanism and the interrelationship between steric effects and weak binding interactions.

Supplementary data

Complete crystallographic data for the structural analyses for compound **1** has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 664798. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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References

1. Wenz, G.: Cyclodextrins as building blocks for supramolecular structures and functional units. Angew. Chem. Int. Ed. Engl. **33**, 803–822 (1994)
2. Saenger, W., Jacob, J., Gessler, K., Steiner, T., Hoffmann, D., Sanbe, H., Koizumi, K., Smith, S.M., Takaha, T.: Structures of the common cyclodextrins and their larger analogues—beyond the doughnut. Chem. Rev. **98**, 1787–1802 (1998)
3. Liu, Y., Yu, Z.-L., Zhang, Y.-M., Guo, D.-S., Liu, Y.-P.: Supramolecular architectures of β-cyclodextrin-modified chitosan and pyrene derivatives mediated by carbon nanotubes and their DNA condensation. J. Am. Chem. Soc. **130**, 10431–10439 (2008)
4. Connors, K.A.: The stability of cyclodextrin complexes in solution. Chem. Rev. **97**, 1325–1357 (1997)
5. Matei, I., Nicolae, A., Hillebrand, M.: Fluorimetric and molecular mechanics study of the inclusion complex of 2-quinoxalinylphenoxathiin with β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. **57**, 597–601 (2007)
6. Frixa, C., Scobie, M., Black, S.J., Thompson, A.S., Threadgill, M.D.: Formation of a remarkably robust 2:1 complex between β-cyclodextrin and a phenyl-substituted icosahedral carborane. Chem. Commun. 2876–2877 (2002)
7. Liu, L., Guo, Q.-X.: The driving forces in the inclusion complexation of cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. **42**, 1–14 (2002)
8. Liu, Y., Zhao, Y.-L., Zhang, H.-Y., Song, H.-B.: Polymerir rotaxane constructed from the inclusion complex of β-cyclodextrin and 4,4′-dipyridine by coordination with Ni(II) ions. Angew. Chem. Int. Ed. Engl. **42**, 3260–3263 (2003)
9. Harata, K.: Structural aspects of stereodifferentiation in the solid state. Chem. Rev. **98**, 1803–1827 (1998)
10. Aree, T., Schulz, B., Reck, G.: Crystal structure of β-cyclodextrin complexes with formic acid and acetic acid. J. Incl. Phenom. Macrocycl. Chem. **47**, 39–45 (2003)
11. Caira, M.R., Vries, E.D., Nassimbeni, L.R., Jacewicz, V.W.: Inclusion of the antidepressant paroxetine in β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. **46**, 37–42 (2003)
12. Fan, Z., Diao, C.-H., Yu, M., Jing, Z.-L., Chen, X., Deng, Q.-.L.: An investigation of the inclusion complex of β-cyclodextrin with 8-nitro-quinoline in the solid state. Supramol. Chem. **18**, 7–11 (2006)
13. Wang, E.-J., Lian, Z.-X., Cai, J.-W.: The crystal structure of the 1:1 inlcusion complex of β-cyclodextrin with benzamide. Carbohydr. Res. **342**, 767–771 (2007)
14. Caira, M., Griffith, V., Nassimbeni, L.: X-ray structural comparison of the modes of inclusion of meclofenamate sodium and diclofenac sodium by β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. **32**, 461–476 (1998)
15. Liu, Y., Chen, G.-S., Zhang, H.-Y., Song, H.-B., Ding, F.: Interaction between beta-cyclodextrin and 1, 10-phenanthroline: uncommon 2:3 inclusion complex in the solid state. Carbohydr. Res. **339**, 1649–1654 (2004)
16. Liu, Y., Zhong, R.-Q., Zhang, H.-Y., Song, H.-B.: A unique tetramer of 4:5 b-cyclodextrin-ferrocene in the solid state. Chem. Commun. **17**, 2211–2213 (2005)
17. Yang, Z.-X., Chen, Y., Liu, Y.: Inclusion complexes of bisphenol A with cyclomaltoheptaose (β-cyclodextrin): solubilization and structure. Carbohydr. Res. **343**, 2439–2442 (2008)
18. Lisnyak, Y.V., Martynov, A.V., Baumer, V.N., Shishkin, O.V., Gubskaya, A.V.: Crystal and molecular structure of β-cyclodextrin inclusion complex with succinic acid. J. Incl. Phenom. Macrocycl. Chem. **58**, 367–375 (2007)
19. Chatziefthimiou, S.D., Yannakopoulou, K., Mavridis, I.M.: β-Cyclodextrin trimers enclosing an unusual organization of guest: the inclusion complex β-cyclodextrin/4-pyridinealdazine. Cryst. Eng. Commun. **9**, 976–979 (2007)
20. Uson, I., Sheldrick, G.M.: Advances in direct methods for protein crystallography. Curr. Opin. Struct. Biol. **9**, 643–648 (1999)
21. Sheldrick, G.M., Schneider, T.R.: SHELXL: high-resolution refinement. Methods Enzymol **277**, 319–343 (1997)
22. Fan, Z., Diao, C.-H., Guo, M.-J., Du, R.-J., Song, Y.-F., Jing, Z.-L., Yu, M.: An investigation of the inclusion complex of β-cyclodextrin with p-nitrobenzoic acid in the solid state. Carbohydr. Res. **342**, 2500–2503 (2007)