Carbohydrate Research 343 (2008) 2439–2442

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Inclusion complexes of bisphenol A with cyclomaltoheptaose (β-cyclodextrin): solubilization and structure

Zi-Xin Yang, Yong Chen, Yu Liu *

Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

ARTICLE INFO

Article history:
Received 24 March 2008
Received in revised form 17 June 2008
Accepted 24 June 2008
Available online 2 July 2008

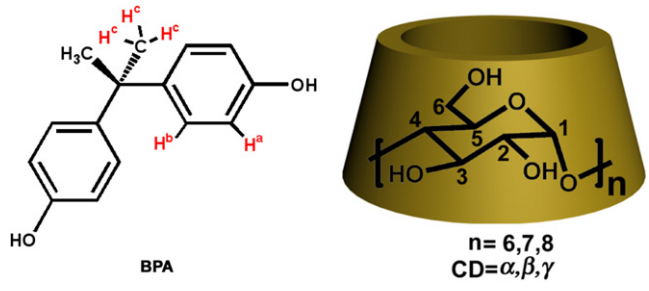
Keywords:
Cyclodextrin
Bisphenol A
Solubilization
Single-crystal X-ray structure

ABSTRACT

The inclusion complexation behavior and the solubilization effects of Bisphenol A (BPA, an endocrine-disrupting chemical) by cyclomaltohexaose, -heptaose, and -octaose (α-, β-, and γ-cyclodextrins) were investigated by ^{1}H NMR spectroscopy and by elemental analysis. The results showed that β- and γ-cyclodextrins gave the satisfactory solubilization ability to BPA up to 7.2×10^3 mg L^{-1} and 9.0×10^3 mg L^{-1}, respectively. X-ray crystallographic diffraction and ROESY spectroscopy were also employed to investigate the structure of the β-CD/BPA inclusion complex in both aqueous solution and the solid state. The result showed that this complex adopted a 2:2 stoichiometry in the solid state, that is, a head-to-head β-CD dimer accommodated two BPA molecules. The inclusion of BPA led to the desolvation of the β-CD cavity and the destruction of the circularly closed hydrogen-bond network in the secondary side of β-CD, which made the complex more soluble.

1. Introduction

Bisphenol A (BPA, Scheme 1) is widely used as a primary raw material in the manufacture of epoxy resins and polycarbonate. The human population is exposed to it from a wide range of materials to water. Unfortunately, BPA has been identified as an endocrine-disrupting chemical by the US Environmental Protection Agency, and the World Wide Fund for Nature,[1,2] since it can affect reproductive behavior of both humans and animals, inducing various diseases including cancer, and even endanger the balance of ecosystems.[3,4] Moreover, BPA is difficult to remove once it accumulates in the environment or in the human body due to its poor solubility (381 mg L^{-1} in water, 25 °C).[5] Therefore, research on the removal of BPA, including its detection, capture, solubilization, and degradation, has become very important and urgent. On the other hand, cyclomaltooligosaccharides (cyclodextrins, CDs), a class of cyclic oligosaccharides mainly with 6–8 D-glucose units linked by α-1,4-glucose bonds, play an important role in BPA research. For example, Del Olmo et al. reported a spectrofluorimetric method for the determination of BPA in water, utilizing its enhanced fluorescence after complexation by β-CD. [6] Deng et al. reported the enhanced photodegradation of BPA in the presence of β-CD under the UV light.[7] Kitano and co-workers and Aoki et al., respectively, synthesized the insoluble CD materials by cross-linking β-CD with epichlorohydrin[8] and locating β-CD on a gold electrode[9] or insoluble chitosan,[10] and investigated their absorption behavior with BPA. The merits of the inclusion complex of β-CD with BPA, their structural character and recognition thermodynamics were also studied. Del Olmo et al. first reported the stoichiometric 1:1 β-CD/BPA inclusion complex with a high association constant.[6] Kitano et al. examined their complexation in 9:1 water–methanol system using spectrofluorimetric and NMR measurements.[11] Jouini and co-workers further presented the optimized structural geometry of the β-CD/BPA complex by theoretical calculations.[12] However, the solubility of BPA in β-CD solution has not been given much attention, so that when a high concentration of β-CD/BPA solution is needed in the study (just as in 2D NMR study), unwanted methanol has to be introduced into the system. Herein, we wish to report the solubilization of various CDs with BPA, as well as the structural study of a β-CD/BPA complex in both water and the solid state. This study might provide some useful information about the depollution of BPA.



Scheme 1. Chemical structure and atomic numbering of CD and BPA.

* Corresponding author.
E-mail address: yuliu@nankai.edu.cn (Y. Liu).

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.06.018

2. Results and discussion

2.1. Solubilization

The solubilities of BPA in various CD solutions were obtained by the following procedures. An equimolar mixture of CD and BPA (1.3×10^{-3} mol) was combined in a sealed flask containing 20 mL of distilled water, and the mixture was placed in a thermostated water bath (the fluctuation was ±0.05 K) for 3 days at 25 °C. Then, 10 mL of supernatant was collected by filtration, and the solvent was removed under reduced pressure with a rotary evaporator. The solids were dried at 90 °C for 24 h and could be handled by weighing. Figure 1 displays the spectra of the resultant solid. As can be seen in Figure 1, the solids obtained from β-CD/BPA and γ-CD/BPA solutions showed clear ^{1}H NMR signals, but that obtained from the α-CD/BPA solution displayed no appreciable ^{1}H NMR signals that could be assigned to the BPA protons. These results indicate that only β-CD and γ-CD could form inclusion complexes with BPA. A comparison of the integral area of the BPA protons with that of the CD protons showed that the molar ratio between CD and BPA was 1:1 for β-CD/BPA and 1:0.8 for γ-CD/BPA. These ratios were further confirmed by the elemental analyses data.

Due to the good capability of forming inclusion complexes with BPA, both β-CD and γ-CD showed satisfactory solubilization of BPA. The water solubility of BPA, compared with that of free BPA (381 mg L^{-1}),[5] was dramatically increased to approximately 7.2×10^3 mg L^{-1} and 9.0×10^3 mg L^{-1} after inclusion complexation with β-CD and γ-CD, respectively. It should be noted that the solubility of β-CD in the β-CD/BPA system (3.6×10^4 mg L^{-1}) is higher than that of native β-CD (1.88×10^4 mg L^{-1}),[13] which might result from the destruction of the circularly closed hydrogen-bond network in the secondary side of native β-CD by the inclusion of BPA.[14] Moreover, the solubilization effects of BPA by β- and γ-CD was also determined by using simple UV–vis absorption by the way of monitoring the optical density at the peak position of BPA. The results showed that β-CD and γ-CD could enhance the water solubility of BPA to 6.1×10^3 mg L^{-1} and 8.4×10^3 mg L^{-1}, respectively, which were basically consistent with the results gotten from the gravimetric method.

2.2. Crystal structure of the β-CD/BPA complex

Figure 2 shows the crystal structure of the β-CD/BPA complex, which was triclinic system with the space group *P*1. As can be seen from Figure 2, one asymmetric unit of the β-CD/BPA complex consists of a head-to-head dimer containing two β-CDs and two BPAs. Each β-CD unit possesses an approximate 7-fold axis and maintains the round shape of the macrocycle, where every glucose residue of β-CD has a $^4C_1$ chair conformation, and the seven glycosidic oxygen atoms are basically coplanar. Two β-CD units composed of a hydrophobic cage where the phenol rings (ring 'a' and ring 'a'') of two BPA molecules were completely located, and this hydrophobic cage was stabilized by the cooperative contributions of seven hydrogen bonds between the secondary hydroxyl groups of two adjacent β-CD units, the hydrogen bonds between the hydroxyl groups of BPA and the secondary hydroxyl groups of β-CD units, as well as the π–π interaction between the a and a′ rings (centroid separation 3.947 Å) of BPA molecules. It is noteworthy that, in the crystal structure of the β-CD/BPA complex, no water molecules could be found in the β-CD cavities. This was obviously distinct with the crystal structure of native β-CD, where 6.13 water molecules were included in the cavity of β-CD.[14] This indicates that the inclusion of BPA resulted in an extensive desolvation effect, which was consistent with the reported result that the complexation of β-CD with BPA gave the positive entropic change (ΔS° = 24.4 J mol^{-1} K^{-1}) in aqueous medium.[12] In addition, the circularly closed O(2)–H···H–O(3) hydrogen-bond network, which existed in the secondary side of native β-CD,[14] was absent in the dimer, which may favor the solubilization of β-CD with the included BPA.

Furthermore, through the hydrogen bonds between the hydroxy groups of neighboring dimers as well as the hydrogen-bond network mediated by the water molecules around the dimers, the head-to-head dimer of β-CD/BPA self-assembled as a two-dimensional layer in the *x*, *y* plane (see Fig. S1 in the Supplementary data). Then, the two-dimensional layers were packed along *z*-axis to form the three-dimensional architecture by the hydrogen bonds among neighboring layers (see Figs. S2 and S3 in the Supplementary data).

2.3. Structure of β-CD/BPA complex in solution

To further investigate the structure of β-CD/BPA complex in water solution, ROESY experiments were performed at 25 °C in

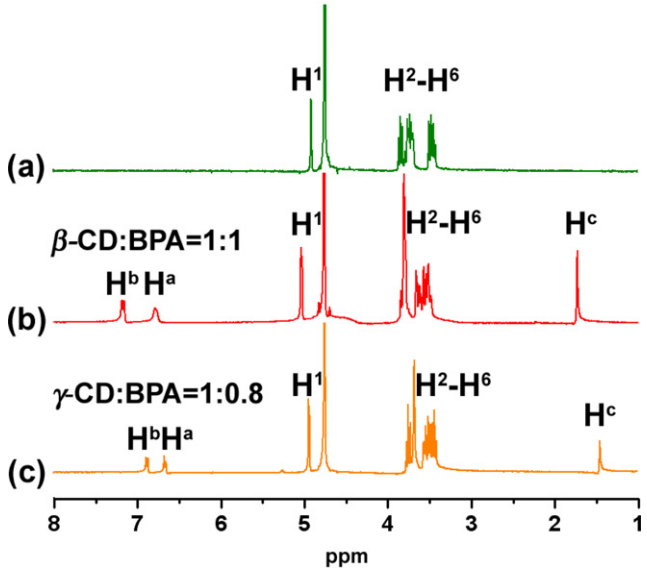


Figure 1. ^{1}H NMR spectra of the resultant solid dried from (a) α-CD + BPA, (b) β-CD + BPA, and (c) γ-CD + BPA solutions in D_2O at 25 °C.

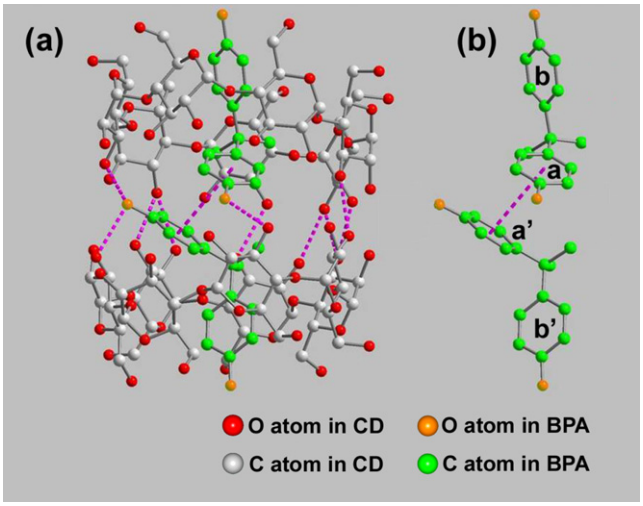


Figure 2. (a) The head-to-head dimer of β-CD/BPA complexes. H-atoms and solvent water molecules are omitted for clarity, and the molecules are colored by atom type. (b) The BPA molecules in the dimer.

D_2O. Since NOE cross-peaks between the protons that are closer than 0.4 nm in space will be observed in the ROESY spectrum, and the relative intensities of these cross-peaks depend on the spaces between the corresponding protons, the NOE correlations between the protons of BPA and the inner protons of β-CD cavity (H-3/H-5) should be determined by the ROESY spectrum when BPA is included in the β-CD cavity.[15,16] Jouini and co-workers reported a 1D ^{1}H NMR experiment on the β-CD/BPA complex in D_2O.[12] Herein, we further investigated the 2D ROESY spectrum of the β-CD/BPA complex to obtain its structural information in solution. As shown in Figure 3a, the ROESY spectrum of the β-CD/BPA complex displayed clear NOE cross-peaks between the H^a protons of BPA and the H-3/H-5 protons of β-CD (peaks A and B), as well as NOE cross-peaks between the H^b protons of BPA and the H-3/H-5 protons of β-CD (peaks C and D). These NOE cross-peaks indicate that the phenyl ring of BPA is deeply included in the hydrophobic cavity of β-CD. However, we could not present a reasonable single illustration to explain these observations. Considering the comparable intensity of peaks E and F (peaks E assigned to the NOE cross-peaks between the H^c protons of BPA and H-3 protons of β-CD, peaks F assigned to the NOE cross-peaks between the H^c protons of BPA and H-5 protons of β-CD), we deduced that the BPA molecule is included into the β-CD cavity in two different modes, as illustrated in Figure 3b.

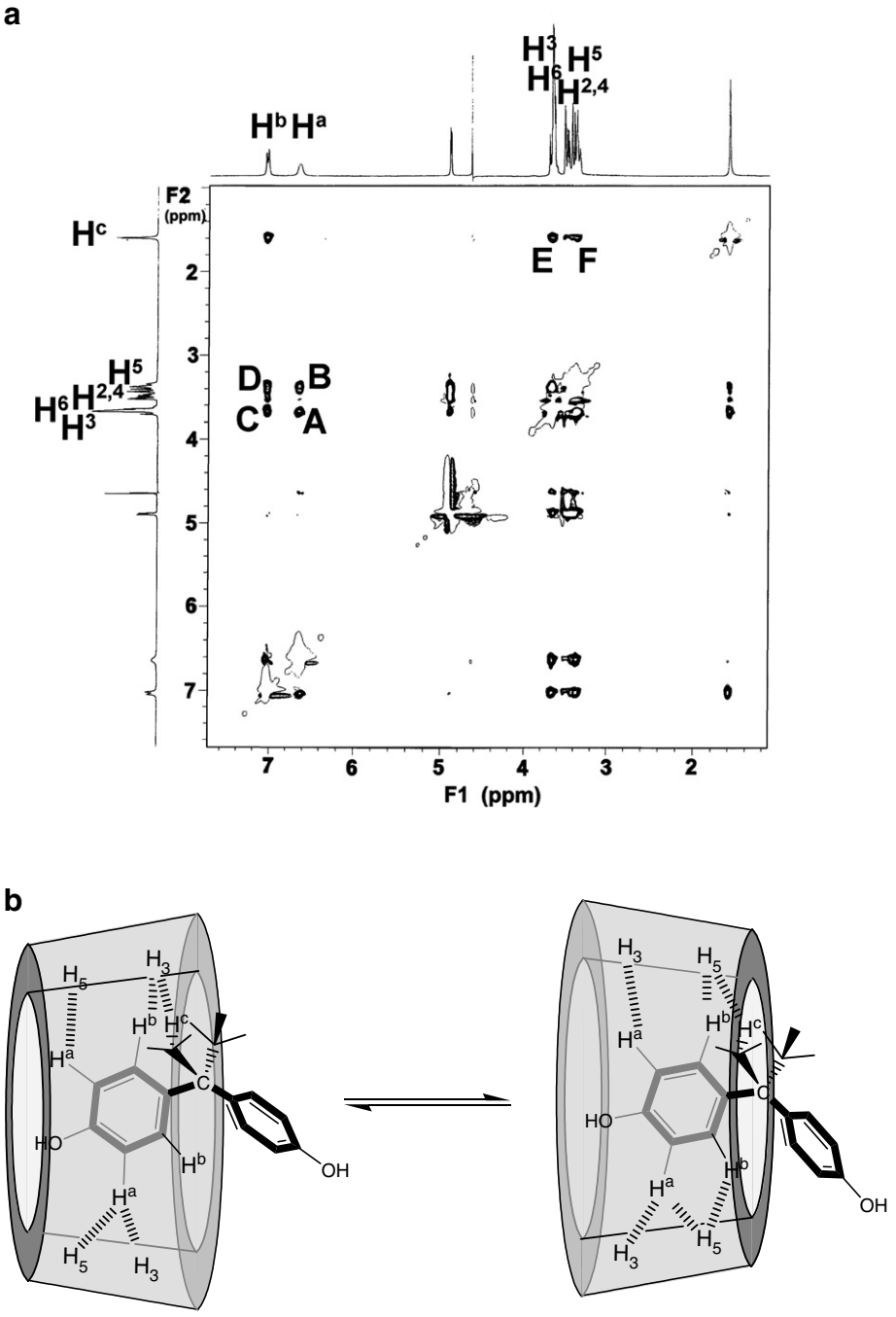


Figure 3. (a) ^{1}H ROESY spectrum of the β-CD/BPA complex (8×10^{-3} mol L^{-1}) in D_2O at 25 °C with a mixing time of 200 ms. (b) Possible structure of the complex in aqueous solution.

3. Conclusions

In summary, the solubilization abilities of various CDs with BPA were assessed, and the results showed that β-CD and γ-CD significantly enhanced the water solubility of BPA by 19 and 24 times, respectively. The structure of the β-CD/BPA complex was investigated in both water and the solid state, which demonstrated that the desolvation of β-CD cavity and the destruction of the circularly closed hydrogen-bond network in the secondary side of β-CD upon the BPA inclusion led to the satisfactory solubilization of β-CD with BPA.

4. Experimental

4.1. Materials and instruments

BPA was the commercially available product and was used after purification by recrystallization from toluene. The cyclomaltooligosaccharides (cyclodextrins, α-, β-, and γ-CD) were purchased from TCI and used as received. Distilled water was used for aqueous solutions. Elemental analyses were performed on a Perkin–Elmer 2400C instrument. ^{1}H NMR and ROESY (rotating frame Overhauser effect spectroscopy) spectra were recorded on a Varian Mercury VX300 spectrometer. UV spectra were performed on a Shimadzu UV-3600 spectrophotometer. The X-ray intensity data were collected on a Rigaku MM-007 rotating anode diffractometer equipped with a Saturn CCD Area Detector System using monochromated Mo K radiation at $T = 113(2)$ K. Data collection and reduction were performed by the program of CRYSTAL CLEAR. The structures were solved by using direct method and refined by full-matrix least-squares on F^2 (CRYSTALSTRUCTURE, SHELX97). Crystal data of β-CD/BPA: $C_{114}H_{215}O_{95.50}$, $M = 3113.86$, triclinic, space group $P1$, $a = 15.100(3)$ Å, $b = 15.623(4)$ Å, $c = 17.469(4)$ Å, $\alpha = 112.228(3)°$, $\beta = 96.882(2)°$, $\gamma = 104.303(2)°$, $V = 3590.5(14)$ Å^3, $Z = 1$, $D_c = 1.440$ mg/m^{-3}, λ(Mo Kα) = 0.71070 Å, $T = 113(2)$ K, $F(000) = 1663$, $\mu = 0.127$ mm^{-1}, approximate crystal dimensions $0.10 \times 0.08 \times 0.08$ mm^3, θ range = 1.50–25.00°, reflections collected/unique, 37 036/23 341 ($R_{int} = 0.0336$), final R indices [$I > 2\sigma(I)$] $R_1 = 0.0642$, $wR_2 = 0.1584$, R indices (all data): $R_1 = 0.0764$, $wR_2 = 0.1690$, goodness of fit on $F^2 = 1.068$.

4.2. Preparation of the β-CD/BPA complex

β-CD (0.5 g) and BPA (0.1 g) were dissolved in a little boiling water to make a supersaturated solution. Then, the solution was slowly cooled to room temperature, and the precipitate that formed was filtered to obtain the transparent crystal suitable for the X-ray crystallographic analysis. (0.41 g, yield 63%). ^{1}H NMR (300 MHz, D_2O): δ 7.03 (d, 4H, $J = 9.0$ Hz, H^b of BPA), 6.64 (d, 4H, $J = 9.0$ Hz, H^a of BPA), 4.93–4.85 (m, 7H, H^1 of β-CD), 3.80–3.20 (m, 42H, H$^{2-6}$ of β-CD). 1.62–1.52 (s, 6H, H^c of BPA). Anal. Calcd for $C_{42}H_{70}O_{35}\cdot C_{15}H_{16}O_2\cdot 7H_2O$: C, 45.97; H, 6.77. Found: C, 45.91; H, 6.81.

Acknowledgments

We thank the 973 Program (2006CB932900), NNSFC (20421202, 20673061, 20772062), and Key Project of Chinese Ministry of Education (No. 107026) for financial support.

Supplementary data

The detailed stereodrawings of the β-CD/BPA crystal. Complete crystallographic data for the structural analysis of β-CD/BPA have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 680225. 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, e-mail: deposit@ccdc.cam.ac.uk or *via*: www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.06.018.

References

1. Stapher, C. A.; Dorn, P. B.; Kleka, G. M. *Chemosphere* **1998**, *36*, 2149–2173.
2. Snyder, S. A.; Villeneuve, D. L.; Snyder, E. M.; Giesy, J. P. *Environ. Sci. Technol.* **2002**, *35*, 3620–3625.
3. Ike, M.; Chen, M. Y.; Jin, C. S.; Fujita, M. *Environ. Toxicol.* **2002**, *17*, 457–461.
4. Howdeshell, K. A.; Peterman, P. H.; Judy, B. M. *Environ. Health Perspect.* **2003**, *111*, 1180–1187.
5. Li, J. H.; Zhou, B. X.; Cai, W. M. *J. Chem. Eng. Data* **2007**, *52*, 2511–2513.
6. Del Olmo, M.; Zafra, A.; Gonzales-Casado, A.; Vilchez, J. *Int. J. Environ. Anal. Chem.* **1998**, *69*, 99–110.
7. Wang, G. H.; Wu, F.; Zhang, X.; Lu, M. D.; Deng, N. S. *J. Chem. Technol. Biot.* **2006**, *81*, 805–811.
8. Kitaoka, M.; Hayashi, K. *J. Incl. Phenom. Macro.* **2002**, *44*, 429–431.
9. Endo, H.; Nakaji-Hirabayashi, T.; Morokoshi, S.; Gemmei-Ide, M.; Kitano, H. *Langmuir* **2005**, *21*, 1314–1321.
10. Aoki, N.; Arai, R.; Hattori, K. *J. Incl. Phenom. Macro.* **2004**, *50*, 115–120.
11. Kitano, H.; Endo, H.; Gemmei-ide, M.; Kyogoku, M. *J. Incl. Phenom. Mol. Recognit. Chem.* **2003**, *47*, : 83–90.
12. Chelli, S.; Majdoub, M.; Jouini, M.; Aeiyach, S.; Maurel, F.; Chane-Ching, K. I.; Lacaze, P. C. *J. Phys. Org. Chem.* **2007**, *20*, 30–43.
13. Fromming, K.-H.; Szejtli, J. *Cyclodextrin in Pharmacy*; Kluwer: Dordercht, The Netherlands, 1994; Chapter 1, pp 33–34.
14. Betzel, C.; Saenger, W.; Hingerty, B. E.; Brown, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7545–7557.
15. Schneider, H. J.; Hacker, F.; Rüdiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755–1785.
16. Liu, Y.; Zhao, Y.-L.; Zhang, H.-Y.; Yang, E.-C.; Guan, X.-D. *J. Org. Chem.* **2004**, *69*, 3383–3390.