Journal of Inclusion Phenomena and Macrocyclic Chemistry **45:** 1–7, 2003.

The Comparison of the Orientation of Sodium 3-Hydroxy-2-Naphthalenecarboxylate in the Cavity of β-Cyclodextrin and Heptakis-(2,3,6-Tri-*O*-Methyl)-β-Cyclodextrin

ZHENG-PING YI, JUN HU and HUI-LAN CHEN*
State Key Laboratory and Institute of Coordination Chemistry, Department of Chemistry, Nanjing University, Nanjing, 210093, P.R. China

(Received: 2 October 2000; in final form: 6 October 2002)

Key words: conformational analysis, ^{1}HNMR, 3-hydroxy-2-naphthalenecarboxylate, β-cyclodextrin, heptakis-(2,3,6-tri-*o*-methyl)-β-cyclodextrin

Abstract

Conformational analysis of inclusion complexes of sodium 3-hydroxy-2-naphthalenecarboxylate with β-cyclodextrin and heptakis-(2,3,6-tri-*o*-methyl)-β-cyclodextrin in D_2O was investigated by 1D and 2D ^{1}HNMR measurements. The results show that part of the naphthyl group of sodium 3-hydroxy-2-naphthalenecarboxylate is situated in the 2,3-OH side of the β-cyclodextrin cavity asymmetrically while the whole naphthyl group is included in the heptakis-(2,3,6-tri-*o*-methyl)-β-cyclodextrin cavity with the caboxylate and hydroxy group close to the 6-OCH_3 group.

Introduction

As a class of important supramolecular hosts, cyclodextrins(CDs) can include a variety of guests into their hydrophobic cavities [1–9]. Interest in CDs has been extended to their applications in controlling the release of volatile substances and improving the often poor aqueous solubility of apolar drug molecules [10–12]. Furthermore, due to the conformational fit caused by inclusion of the guest into the CDs cavity, CDs can be used as catalyst themselves: they may change reaction rate as well as increase the reaction selectivity. The orientation of the guest in the CDs cavity is thought to play an important role [8, 13–17]. Hirai *et al.* reported that the carboxylation of benzoic acid and 4-biphenylcarboxylic acid with carbon tetrachloride and copper powder in aqueous alkali can proceed with 100% selectivity in the presence of β-CD [14]. However, the reaction cannot take place without β-CD.

Permethylation of β-CD to form the heptakis-(2,3,6-tri-*o*-methyl)-β-cyclodextrin (TMβ-CD) greatly improves its aqueous solubility, an important property for many applications [10, 11]. Compared to β-CD and its inclusion complexes, TMβ-CD and its inclusion complexes have been studied less comprehensively.

The modern NMR technique, in particular the 2D method, is a powerful tool for the structural and conformational analysis of the inclusion complexes of CDs [7, 10, 11, 18–25].

In our previous work [26], the thermodynamic parameters of inclusion complexation of β-CD and TMβ-CD with sodium 3-hydroxy-2-naphthalenecarboxylate (3h2n) in aqueous solutions were measured by the fluorescence method. At pH 7.0, both β-CD and TMβ-CD form 1:1 complex with 3h2n with formation constants of 1140 and 309 M^{-1}, respectively. Since NMR spectroscopy can give additional and more detailed information on the solution conformation of these inclusion complexes, it is helpful to carry out 1D and 2D ^{1}HNMR spectra on these complexes to determine the orientation of 3h2n in the cavity of β-CD and TMβ-CD. Such investigations not only have theoretical significance, but may also contribute to the study of cyclodextrin-catalyzed selective substitution of 3-hydroxy-2-naphthalenecarboxylic acid and its analogues, which are useful chemical raw materials and fluorescent compounds [27, 28].

Results and discussion

Figure 1 shows the position numbers of protons in β-CD, TMβ-CD and 3h2n. Figure 2 depicts the 500 MHz ^{1}HNMR spectra of β-CD, 3h2n and their inclusion complex in D_2O at 300K, pD = 7.0. The resonance of free β-CD protons was assigned according to references [29]. That of 3h2n ring protons was ascribed on the basis of anticipated electron density differences in the naphthalene ring: there are electron density increases for Hd, He, and Hg caused by the 3-OH group [30]. The assignments of the proton signals of the 3h2n part of the inclusion complex can be easily ascertained from the correlation in the 2D NOESY spectrum (Figure 3). Those of the β-CD part were undertaken by 2D COSY measurement (see Figure 4). The chemical shifts of β-CD, 3h2n, their in-

* Author for correspondence.

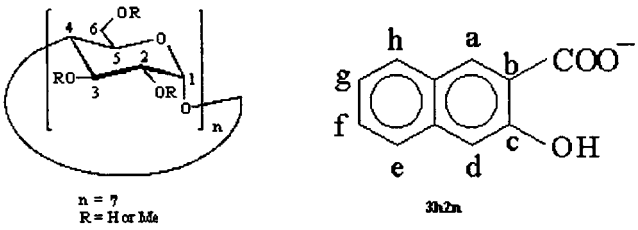
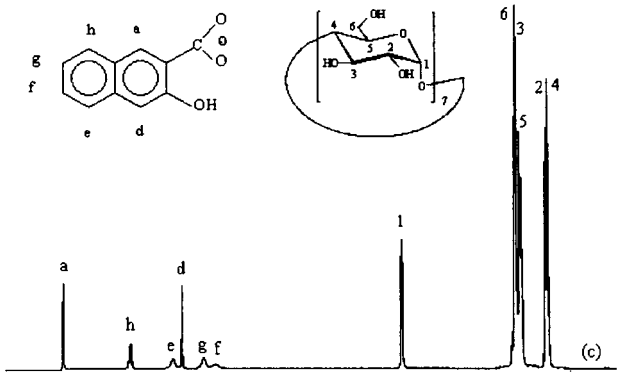


Figure 1. Position numbers of protons in β-CD, TMβ-CD and 3h2n.



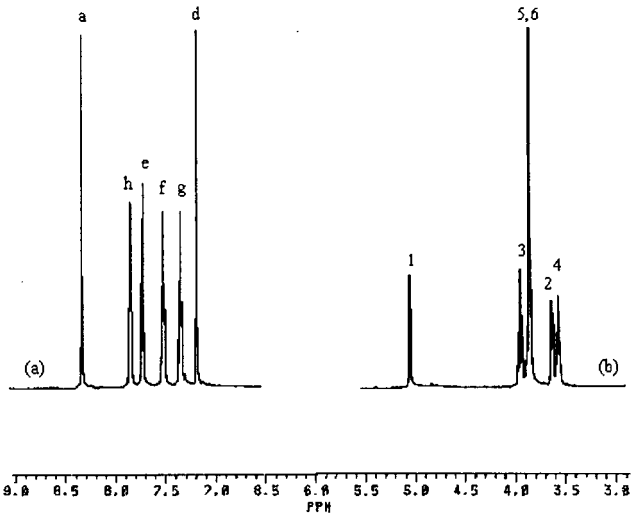


Figure 2. The 500 MHz ^{1}HNMR spectra of β-CD (C = 0.01 M), 3h2n (C = 0.02 M) and their inclusion complex (C = 0.02 M) in D_2O at 300 K, pD = 7.0.

clusion complex and the chemical shift difference Δ as well as the complexation induced shifts corresponding to 100% complexation Δ_0 are listed in Table 1. Δ_0 was obtained by the following equations:

$$|\Delta| = |\Delta_0| - [(\Delta/x)(\Delta_0/K_a)]^{0.5} \quad (1)$$

$$|\Delta_0| = (2|\Delta| + |\Delta|/x/K_a + [(2|\Delta| + |\Delta|/x/K_a)^2 - 4\Delta^2]^{0.5})/2 \quad (2)$$

where Δ is the difference between the observed chemical shift of the proton in the complex and that for the same proton in the free component, x and K_a are the corresponding concentration and formation constant of the complex [29, 31].

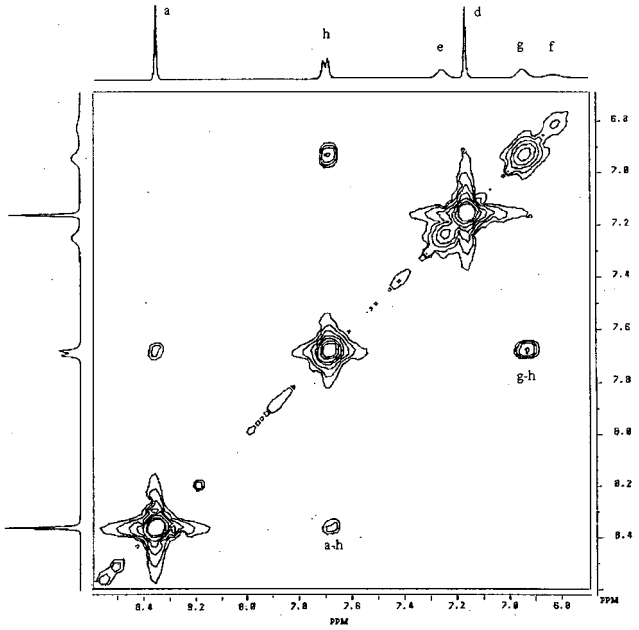


Figure 3. Portion of the 2D NOESY spectrum of β-CD-3h2n complex in D_2O at 300 K, C = 0.02 M, pD = 7.0.

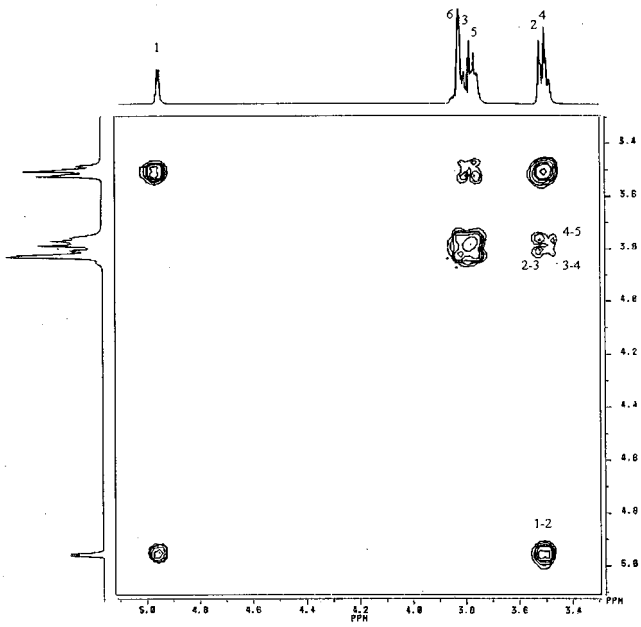


Figure 4. Portion of the 2D COSY spectrum of β-CD-3h2n complex in D_2O at 300 K, C = 0.02 M, pD = 7.0.

From Figure 2 and Table 1, we can see that (1) β-CD and 3h2n do form 1:1 inclusion complex as we proposed in our previous work. (2) There are dramatic differences between the chemical shifts of the protons and the contour of the spectrum for 3h2n in the presence and absence of β-CD. For example, two sharp triple peaks Hf and Hg become two broad and short single peaks. Such distinctly changed spectra for aromatic cyclodextrin inclusion complexes have been rarely reported in literature. Generally, broad and short peaks in ^{1}HNMR mean that there are several medium-speed-exchanged equilibriums for the inclusion complex in the solution. Since the size of the β-CD cavity matches the naphthyl group of 3h2n, they may form relatively rigid in-

Table 1. The chemical shifts (ppm) of 3h2n, β-CD, TMβ-CD, their inclusion complex and the chemical shift differences Δ (ppm) as well as the complexation induced shifts corresponding to 100% complexation Δ_0 (ppm) in D_2O at 300K, pD = 7.0

Proton	3h2n	β-CD	complex	Δ	Δ_0	TMβ-CD	complex	Δ	Δ_0
H1		5.06	4.97	–0.09	–0.11	5.28	5.18	–0.10	–0.13
H2		3.64	3.54	–0.10	–0.12	3.34	3.24	–0.10	–0.13
H3		3.97	3.80	–0.17	–0.21	3.67	3.49	–0.18	–0.24
H4		3.58	3.50	–0.08	–0.10	3.74	3.66	–0.08	–0.11
H5		3.88	3.76	–0.12	–0.15	3.85	3.72	–0.13	–0.17
H6a		3.88	3.83	–0.05	–0.06	3.64	3.55	–0.09	–0.12
H6b						3.86	3.77	–0.09	–0.12
2-OMe						3.51	3.45	–0.06	–0.08
3-OMe						3.60	3.53	–0.07	–0.09
6-OMe						3.38	3.35	–0.03	–0.04
Ha	8.34		8.35	+0.01	+0.01		8.40	+0.06	+0.08
Hd	7.20		7.15	–0.05	–0.06		7.19	–0.01	–0.01
He	7.72		7.24	–0.48	–0.59		7.68	–0.04	–0.05
Hf	7.51		6.82	–0.69	–0.85		7.36	–0.15	–0.20
Hg	7.36		6.93	–0.43	–0.53		7.23	–0.13	–0.17
Hh	7.87		7.68	–0.19	–0.23		8.02	+0.15	+0.20

clusion complex. Besides, in our previous work, it was concluded that there was hydrogen bonding between hydroxy groups of β-CD and 3h2n [26]. Therefore, 3h2n cannot rotate freely in the β-CD's cavity, leading to the broad and short peaks.

In the presence of 3h2n, all of the resonance of β-CD shifted upfield due to the magnetic anisotropy effect of the naphthalene ring of 3h2n. The most remarkable shifts are observed for H3 and H5 protons in the interior of the cavity of β-CD, indicating the insertion of 3h2n into the β-CD cavity. As for the protons in the naphthyl group, all proton signals but Ha shifted to higher field in this order: Hf (0.85 ppm) > He (0.59 ppm) > Hg (0.53 ppm) > Hh (0.23 ppm) > Hd (0.06 ppm). The downfield shift of the proton signal is mainly ascribable to a van der Waals deshielding effect which has been commonly observed [32, 33]. However, there is no generally accepted explanation on the scarcely reported upfield shift of the guest proton signals [32, 34]. One possibility is an electric-field effect caused by the ethereal oxygen atoms in β-CD which may change the electron density of a naphthalene ring near them [32]. The signal of the proton should shift upfield when the effect causes an increase in the electron density around a proton in a naphthalene group.

Figure 5 exhibits NOE cross-peaks caused by the interactions between β-CD and 3h2n. The cross-peak connecting the Ha of 3h2n to H3 of β-CD is clearly observed while the intensity of the correlation between Ha and H5 is much weaker. This means that Ha is located nearer to H3 than to H5. The correlation between Hh of 3h2n and H3 of β-CD is obvious while that between Hh and H5 couldn't be found, indicating Hh is situated close to H3 but far from H5. In addition, since Hd has no obvious cross-peaks with protons of β-CD, it is far from H3 and H5 compared to Ha. Due to the medium-speed-exchanged equilibriums in the solution, the intensity of some NOE signals decreased greatly. Therefore, no correlation between He, Hf, Hg of 3h2n and protons of β-CD was observed. The possible conformation of β-CD-3h2n inclusion complex in D_2O is proposed as shown in Figure 6a: part of the naphthyl group of 3h2n is included in β-CD cavity asymmetrically with hydrophilic carboxylate and hydroxy group left outside the hydrophobic cavity. Compared to the hydroxyl group, the stronger proton acceptor carboxylate anion [26] is closer to the 2,3-OH of β-CD to form hydrogen bond. This structure also agrees with the fact that H3 and H5 of β-CD have larger upshifts than other β-CD protons.

Figure 7 depicts the 500 MHz ^{1}HNMR of TMβ-CD, 3h2n and their inclusion complex in D_2O at 300K, pD = 7.0. Free TMβ-CD proton signals were assigned according to the 2D COSY (Figure 8) spectrum and the references [18–20]. The resonance of the 3h2n and TMβ-CD parts of the inclusion complex can be assigned from the correlation in the 2D NOESY spectrum (Figures 9 and 10) and the references [18–20, 32]. The chemical shifts of TMβ-CD, 3h2n and their inclusion complexes as well as Δ, Δ_0 are also listed in Table 1.

As can be seen from Table 1, all of the resonance of TMβ-CD also shifted upfield due to the magnetic anisotropy effect of the naphthalene ring of 3h2n with the interior H3 and H5 protons shifting most remarkably. As for the protons in the naphthyl group, signals of Ha and Hh shifted downfield while those of Hd, He, Hf and Hg shifted upfield.

It is interesting to note that the shape of NMR peaks of 3h2n changed little in the presence of TMβ-CD compared to β-CD. After β-CD is permethylated into TMβ-CD, its flexibility increases greatly [11] while its ability to form hydrogen bond decreases substantially. Therefore, 3h2n can rotate freely in its cavity.

In the 2D NOESY spectrum, the cross-peaks connecting the Ha resonance of 3h2n to the H5, H3 and OCH_3 protons at

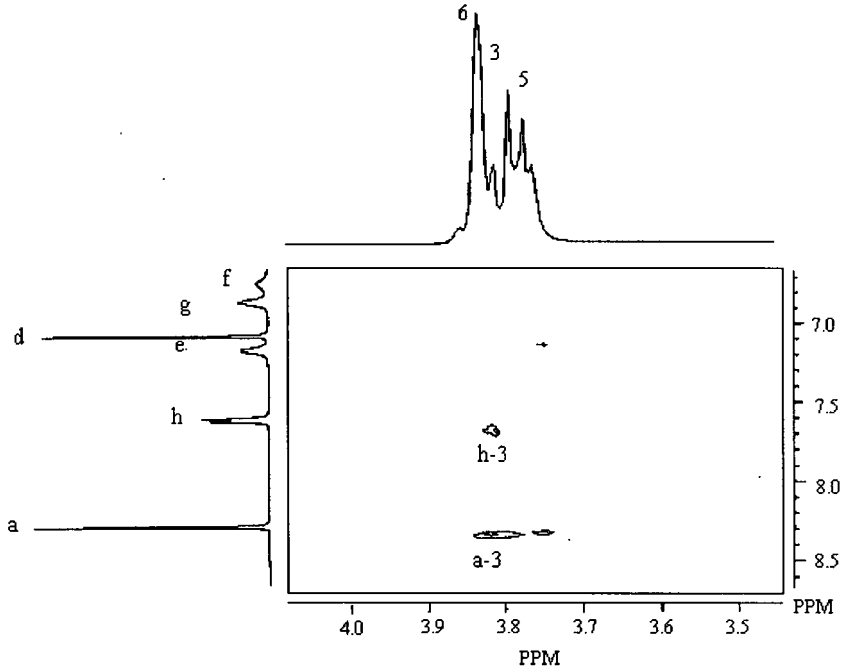


Figure 5. Portion of the 2D NOESY spectrum of β-CD-3h2n complex in D_2O at 300 K, C = 0.02 M, pD = 7.0.

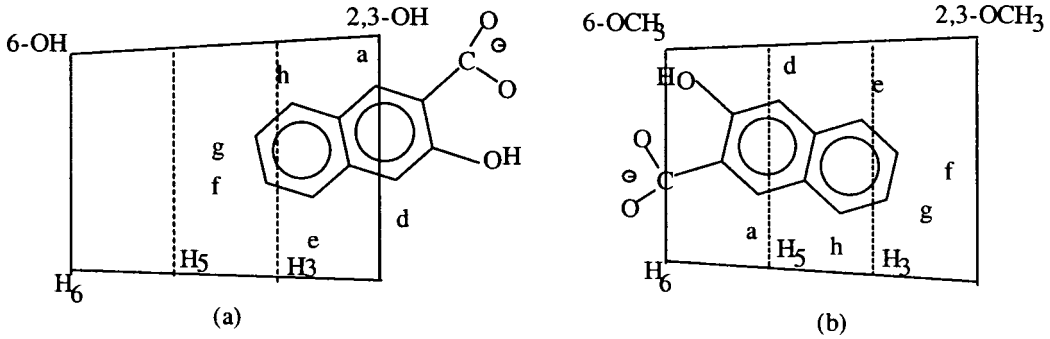


Figure 6. Proposed conformation of the β-CD-3h2n and TMβ-CD-3h2n inclusion complexes. The dashed lines H3 and H5 show planes comprised of the corresponding atoms of β-CD and TMβ-CD.

6 position of TMβ-CD are clearly observed. This indicates that the Ha proton is situated close to these protons of TMβ-CD. The cross-peaks connecting the Hd proton to the H5 and H3 protons can also be seen clearly but that to 6-OCH_3 protons couldn't be found, which means that Hd proton is situated near H5 and H3 protons but far away from 6-OCH_3 protons. The cross-peaks connecting the He, Hf, Hg and Hh atoms of 3h2n to the H3 atom of TMβ-CD can also be seen, indicating that He, Hf, Hg and Hh atoms of 3h2n are included in the TMβ-CD cavity. The correlation between the Hf proton and the 2-OCH_3 protons is clear while that between the Hg and the 2-OCH_3 protons is obscure, suggesting that the Hf atom of 3h2n is nearer to the 2-OCH_3 protons of TMβ-CD than the Hg atom. In addition, the correlation between Hf, Hg and 3-OCH_3 could not be found. Therefore, the 2-OCH_3 group may point to the molecular axis of TMβ-CD while 3-OCH_3 group points outside the cavity.

From what has been discussed above, the conformation of the TMβ-CD-3h2n inclusion complex in D_2O is proposed as shown in Figure 6b: the whole naphthyl group of 3h2n is embedded into the cavity of TMβ-CD asymmetrically with the carboxylate and hydroxy group near the 6-OCH_3 group. The hydroxy group of 3h2n is closer to the 6-OCH_3 group to facilitate the formation of hydrogen bond since the carboxylate anion cannot form hydrogen bond with the 6-OCH_3 group.

Conclusions

Methylation of β-CD affects the orientation of 3h2n in the cavity of β-CD: part of the naphthyl group of sodium 3-hydroxy-2-naphthalenecarboxylate is situated in the 2,3-OH side of the β-CD cavity while the whole naphthyl group is included in TMβ-CD cavity with the carboxylate and hydroxyl groups close to the 6-OCH_3 group. Due to the greater flexibility of TMβ-CD after permethylation, the conformation of TMβ-CD can change substantially to accommodate the entire naphthyl group. When 3h2n forms an inclusion complex with β-CD, it is the carboxylate anion that is close to the hydroxyl group of β-CD since the carboxylate anion is a stronger proton acceptor than hydroxyl group of 3h2n

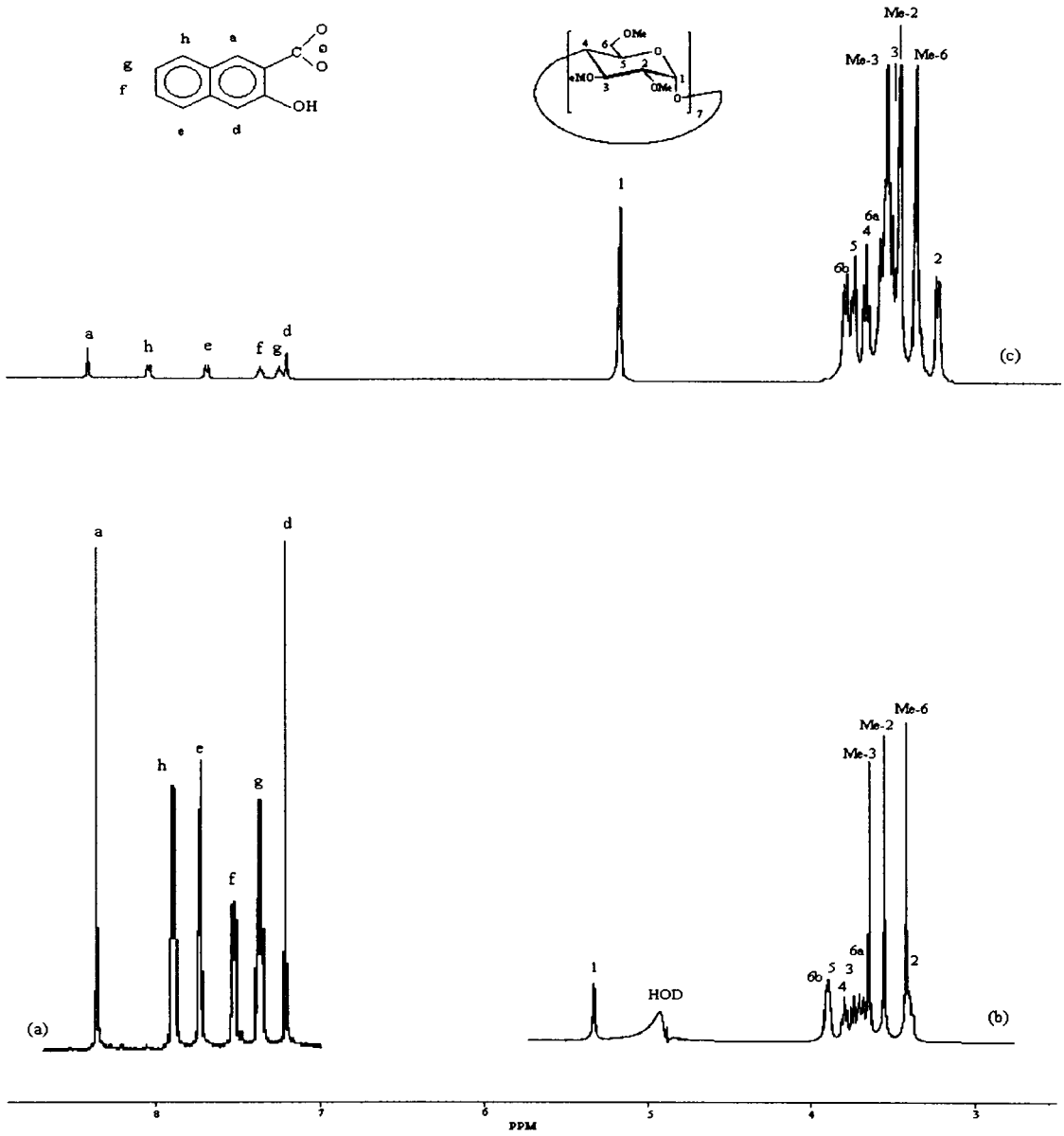


Figure 7. The 500 MHz ^{1}HNMR spectra of TMβ-CD (C = 0.02 M), 3h2n (C = 0.02 M) and their inclusion complex(C = 0.04 M) in D_2O at 300 K, pD = 7.0.

[26]. However, when 3h2n forms an inclusion complex with TMβ-CD, it is the hydroxyl group of 3h2n that is near to the 6-OCH_3 group of TMβ-CD because TMβ-CD cannot donate proton to form hydrogen bond with carboxylate anion of 3h2n. These results support the conclusion in our previous work: hydrogen bonding between the hosts and guests plays a very important role in the formation of the β-CD-3h2n complex [26].

Obviously, the effect of the β-CD and TMβ-CD cavities on the protons of the naphthyl group of 3h2n is different, which may lead to different reaction selectivity of the protons of naphthyl group.

Experimental section

β-CD was purchased from Nanjing Food Ferment Institute, recrystallized twice from water and dried in *vacuum* at 80 °C for 24 hours. TMβ-CD was bought from Sigma. 3-Hydroxy-2-naphthalenecarboxyic acid (3h2na) was recrystallized from ethanol. Sodium 3-hydroxy-2-naphthalenecarboxylate was prepared by mixing excessive 3h2na with 0.1 M NaOH. After having been stirred for 1 hour, the reaction mixture was filtered to remove excessive 3h2na. The filtrate was dried by rotary evaporation. The obtained powder was further dried in vacuum at 80 °C overnight. D_2O was used as solvent, G. R. grade. The β-CD-3h2n inclusion complex solution was prepared by mixing 0.02 M β-CD and 3h2n in D_2O at 60 °C. That of TMβ-CD-3h2n was prepared by mixing 0.04 M TMβ-CD and 3h2n. Other regents used were A. R. grade.

1D and 2D ^{1}HNMR spectra were recorded on a BRUKER AM-500 spectrometer at 300 K (external standard: DSS at δ = 0.00 ppm). The 2D COSY spectrum was acquired in a sweep width of 3000 Hz, 512 × 2048 data points. The 2D NOESY spectrum was acquired in a sweep

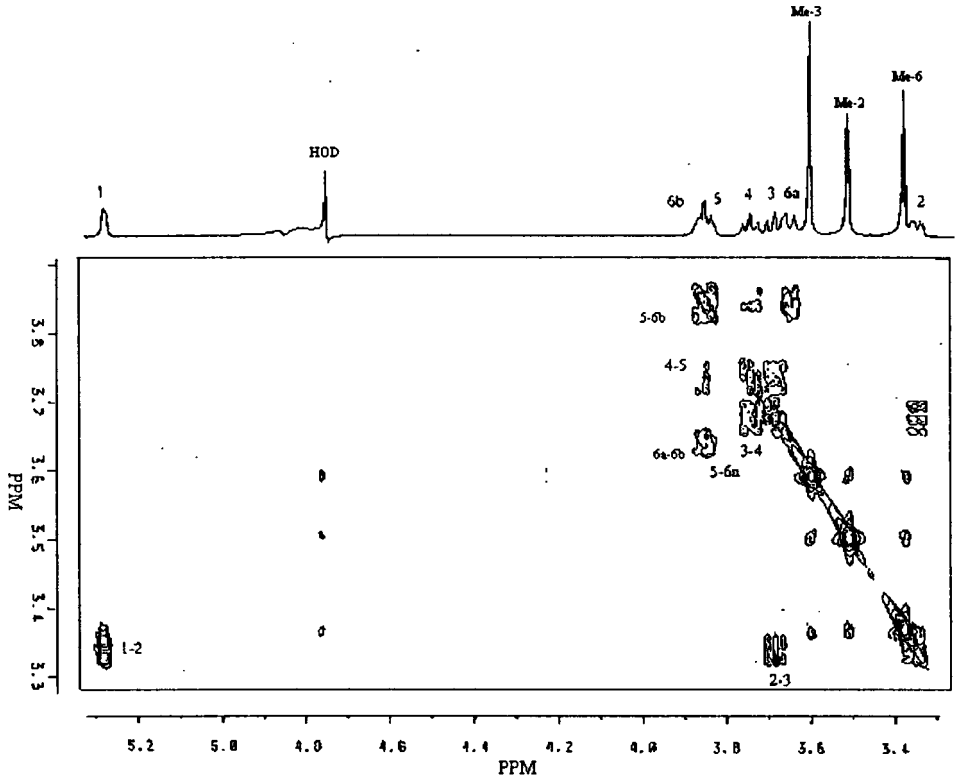


Figure 8. The 2D COSY spectrum of TMβ-CD in D_2O at 300 K, C = 0.04 M, pD = 7.0.

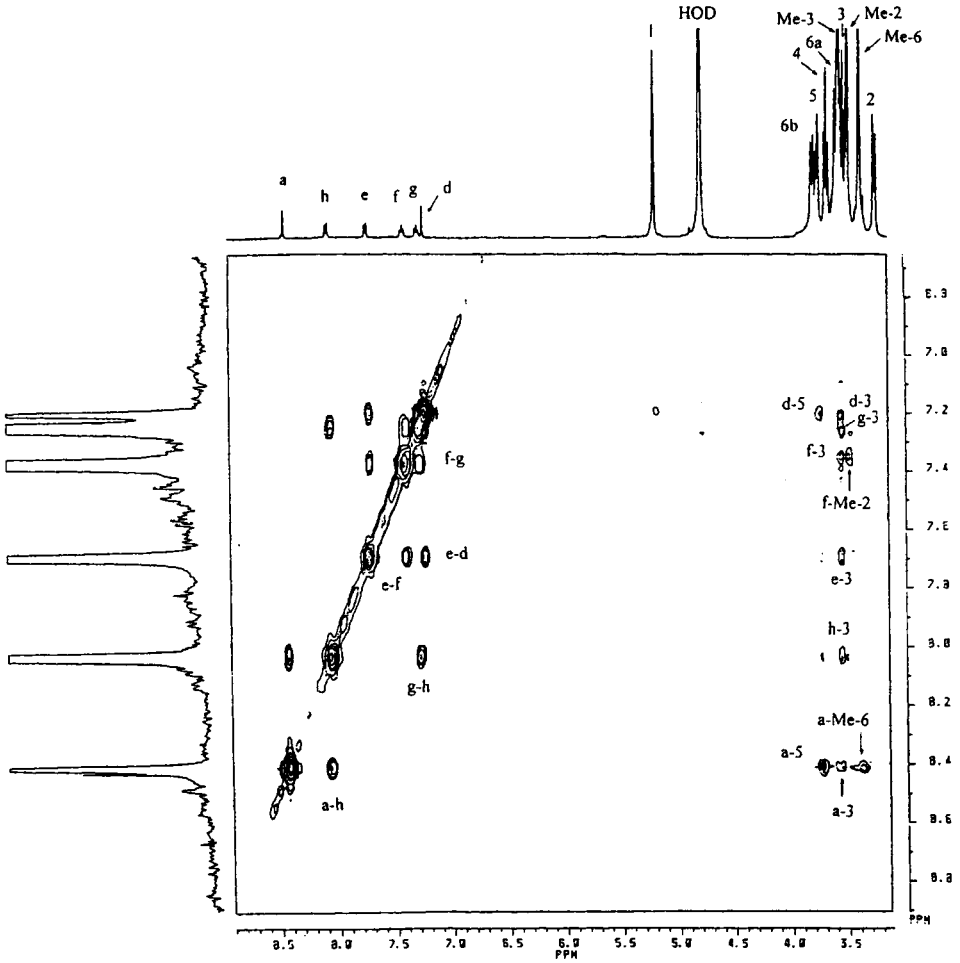


Figure 9. Portion of the 2D NOESY spectrum of TMβ-CD-3h2n complex in D_2O at 300 K, C = 0.04 M, pD = 7.0.

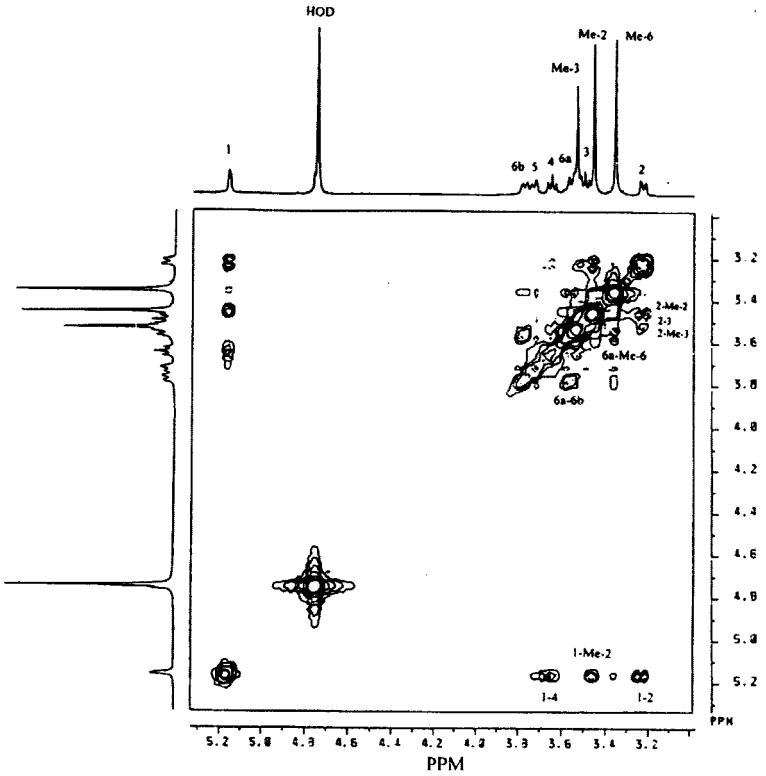


Figure 10. Portion of the 2D NOESY spectrum of TMβ-CD-3h2n complex in D_2O at 300 K, C = 0.04 M, pD = 7.0.

width of 3000 Hz, 150 ms mixing time, 512 × 2048 data points.

Acknowledgement

This research is supported by National Science Foundation of China (No. 29671019).

References

1. M.L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer Verlag, Berlin (1978).
2. J. Szejtli: *Cyclodextrins and Their Inclusion Complexes*, Academiai Kiado, Budapest (1982).
3. S. Li and W.C. Purdy: *Chem. Rev.* **92**, 1457 (1992).
4. J. Szejtli: *J. Incl. Phenom. Mol. Recogn. Chem.* **14**, 25 (1992).
5. G. Wenz: *Angew. Chew. Int. Ed. Engl.* **33**, 803 (1994).
6. J. Szejtli: *Chem. Rev.* **98**, 1743 (1998).
7. H.-J. Schneider, F. Hacket, V. Rudiger and H. Ikeda: *Chem. Rev.* **98**, 1755 (1998).
8. K. Takahashi: *Chem. Rev.* **98**, 2013 (1998).
9. A.R. Hedges: *Chem. Rev.* **98**, 2035 (1998).
10. J.R. Johnson, N. Shankland, and I.H. Sadler: *Tetrahedron* **41**, 3147 (1985).
11. A. Botsi, K. Yannakopoulou, B. Perly, and E. Hadjoudis: *J. Org. Chem.* **60**, 4017 (1995).
12. K. Uekama, F. Hirayama, and T. Irie: *Chem. Rev.* **98**, 2045 (1998).
13. E. Iglesias and A. Fernandez: *J. Chem. Soc. Perkin Trans. 2*, 1691 (1998).
14. H. Hirai, Y. Shiraishi, H. Mihori, K. Saito, and T. Kawamura: *Poly. J. (Japan).* **28**, 91 (1996).
15. H. Hirai, Y. Shiraishi, H. Mihori, and T. Kawamura: *Poly. J. (Japan).* **27**, 1064 (1995).
16. M. Komiyama: *J. Chem. Soc. Perkin Trans. 1*, 2031 (1989).
17. M. Komiyama and H. Hirai: *J. Am. Chem. Soc.* **105**, 2018 (1983).
18. K. Kano and M. Tatsumi: *J. Org. Chem.* **56**, 6579 (1991).
19. A. Botsi, K. Yannakopoulou, E. Hadjoudis, and B. Perly: *Magn. Reson. Chem.* **34**, 419 (1996).
20. A. Botsi, B. Perly, and E. Hadjoudis: *J. Chem. Soc. Perkin Trans. 2*, 89 (1997).
21. H.-J. Schneider, T. Blatter, and S. Simova: *J. Am. Chem. Soc.* **113**, 1996 (1991).
22. S. Hamai, H. Ikeda, and A. Ueno: *J. Incl. Phenom. Mol. Recogn. Chem.* **31**, 265 (1998).
23. S. Hamai and K. Hori: *Supramol. Chem.* **10**, 43 (1998).
24. H. Nakashima, Y. Takenaka, M. Higashi, and N. Yoshida: *J. Chem. Soc. Perkin Trans. 2*, 2096 (2001).
25. N. Yoshida: *J. Chem. Soc. Perkin Trans. 2*, 2249 (1995).
26. Zheng-Ping Yi, Hui-Lan Chen, Zheng-Zi Huang, Qing Huang, and Jun-Sheng Yu: *J. Chem. Soc. Perkin Trans. 2*, 121 (2000).
27. Wei Wen-De: *Comprehensive Handbook of Organic Materials*, Chemical Industry Press, Beijing (1998) p. 651.
28. P.J. Kovi and S.G. Schulman: *Anal. Chem.* **45**, 989 (1973).
29. L. Luo, Y. Chen, H. Chen, and W. Tang: *Spectroscopy Lett.* **29**, 449 (1996).
30. L. Prajer-Janczewska, A. Postawka, and J. Wroblewski: *Spectroscopy Lett.* **11**, 9 (1978).
31. D.R. Alston, T.H. Lilley, and J.F. Stoddart: *J. Chem. Soc. Chem. Commun.* **22**, 1600 (1985).
32. K. Kano, Y. Kato, and M. Kodera: *J. Chem. Soc. Perkin Trans. 2*, 1211 (1996).
33. S. Li and W.C. Purdy: *Anal. Chem.* **64**, 1405 (1992).
34. T.T. Ndou, S. Mukundan, and I.M. Warner: *J. Incl. Phenom. Mol. Recogn. Chem.* **15**, 9 (1993).