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ORIGINAL ARTICLE

^{1}H and ^{13}C NMR investigations of inclusion complexes between β-cyclodextrin and naphthalenediamines/phenol derivatives

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Abstract Three inclusion complexes between β-CD and 1,5-naphthalenediamine, 1,8-naphthalenediamine, ethyl *p*-hydroxylbenzoate are synthesized and identified via ^{1}H and ^{13}C NMR spectra, respectively. The possible conformations of the inclusion complexes are depicted.

Keywords β-Cyclodextrin · Inclusion complex · NMR

Introduction

β-Cyclodextrin (β-CD) is a macrocyclic oligosaccharide consisting of seven D-glucose units by α-(1 $\rightarrow$ 4) glycosidic bonds [1]. It has the shape of a truncated cone and is amphiphilic with apolar cavity coated by C–H groups and O-4, O-5 atoms, and hydrophilic rims with O-6-H groups on the narrower side, and O-2-H, O-3-H groups on the wider side (Fig. 1).

CDs are well known for their ability to form inclusion complexes [2] with various types of guest molecules as shown by crystallographic results [3]. Such beneficial property of CDs has been applied in many industries, e.g., foods, pharmaceutics, agriculture [4]. However, inclusion geometry and stoichiometry of the complexes are different from guest to guest. Therefore, a general direction for predicting the authentic CD inclusion complexes is not accessible. As for the identification of the inclusion complexes, there are various methods among which NMR technique is one of the most effective methods. In this paper, we synthesized the inclusion complexes between β-CD and ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine, 1,8-naphthalenediamine, respectively, which were identified by means of NMR technique. Meanwhile, we depicted the possible conformations of the guest molecules inside the cavity of β-CD. The formation of supramolecular complexes paved a way to study the organic reactions in aqueous media instead of organic media.

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Materials and methods

Reagents

Solid reagents (β-CD, ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine, 1,8-naphthalenediamine) were purchased from Aldrich and were used without further purification.

General preparation method of inclusion complexes

1.04 g (0.001 mol) of β-CD is dissolved in 70 ml of deionized water. 5×10^{-4} mol of substrate powder is dissolved in 5 ml of DMSO and the clear mixture is added to the aqueous β-CD solution drop wisely. Let the mixture stir at room temperature for 2 h. Collect the precipitate. Recrystallize it from deionized water twice. Dry in vacuo.

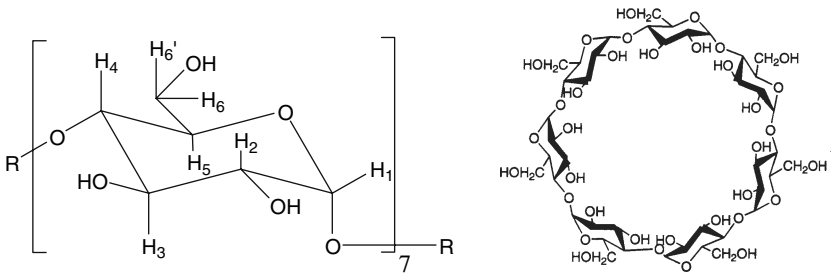

Fig. 1 Structure of *β*-cyclodextrin

NMR experiments

NMR spectra were obtained with a Varian Mercury AS400 instrument. All the experiments of the inclusion complexes were recorded using DMSO-d_6 as solvent. The solutions were transferred in 5 mm NMR tubes, giving a sample total volume of 600 µl. The probe temperature was regulated to 300 K. The resonance at 2.48 ppm (^{1}H NMR) and 40.04 ppm (^{13}C NMR) due to residual solvents, present at impurities (DMSO), was used as internal reference.

Results and discussion

NMR results and analysis

For each molecule, we observed the difference in the chemical shifts between free *β*-CD, aromatic guest molecules and their inclusion complexes (Fig. 2).

^{1}H NMR and ^{13}C NMR chemical shifts provided unambiguous evidence on the formation of the complexes. The effects were qualitatively used.

The assignments of NMR signals (^{1}H and ^{13}C NMR spectra) of the inclusion complexes are obtained in comparison with those of free host and guest molecules, respectively, together with the ^{3}J coupling constants, signal splitting and other necessary information, since there are no direct chemical bonds formed between host and guest molecules in the complexes. The interaction forces between host and guest molecules are Van der Waals forces such as hydrogen bondings, electrostatic force, dipole-dipole interaction, dispersion force, etc. Hence, the variations of NMR chemical shifts in the complexes will be in a small scale in comparison with the corresponding free guest molecules and *β*-CD.

Tables 1, 2, 3, 4, 5, 6 list the ^{1}H NMR chemical shifts of the inclusion complexes in comparison to free *β*-CD.

β-CD is a truncated right cylindrical cone shaped molecule, 7.9 Å high, with a hollow tapered cavity whose top and bottom dimensions are 6.5 Å and 6.0 Å [5]. The most likely mode of complexation of the guest involves insertion of the less polar portion into the cavity of the *β*-CD from the wider side resulting in major upfield shifts in the signals for H-3 and H-5 protons of *β*-CD, since these are positioned inside the cavity. This is attributed to the ring current of the guest molecules that is included into the cavity [6, 7]. The magnitude of chemical shifts ranges less than 0.05 ppm (Tables 2, 4, 6). In Tables 1, 3, 5, signal degeneration still exists for ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine and 1,8-naphthalenediamine upon complexation, which reveals symmetrical conformations of the guest molecules inside the cavity of *β*-CD. ^{1}H NMR spectra provide a clear evidence for the analysis of conformations of the inclusion complexes.

In Table 1, the chemical shifts of hydrogen atoms of ethyl *p*-hydroxylbenzoate move upfield upon complexation in the range of 0.10–1.70 ppm. The greatest shift is caused by the hydroxyl group (1.70 ppm), which is due to the decomposition of intermolecular hydrogen bondings between hydroxyl of ethyl *p*-hydroxylbenzoate (Fig. 3). In free ethyl

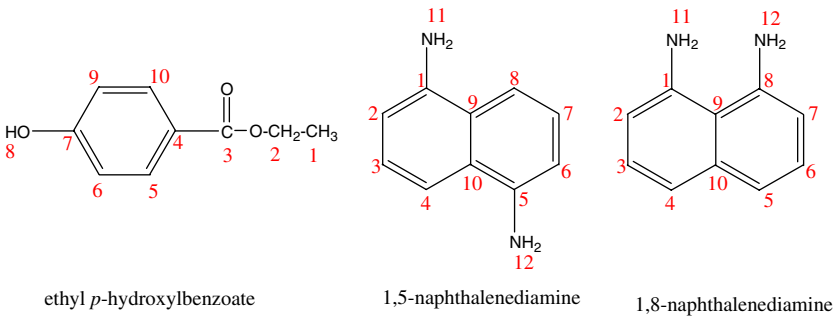

Fig. 2 Structure of guest molecules

ethyl *p*-hydroxylbenzoate 1,5-naphthalenediamine 1,8-naphthalenediamine

Table 1 ^{1}H NMR chemical shift corresponding to ethyl *p*-hydroxylbenzoate in the presence and absence of *β*-CD

Ethyl *p*-hydroxylbenzoate	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ* (ppm)
H-1	1.39(t)	1.27(t)	–0.12
H-2	4.36(q)	4.22(q)	–0.14
H-5,10	7.95(d)	7.78(d)	–0.17
H-6,9	6.93(d)	6.82(d)	–0.11
H-8	7.70(s)	6.00(s)	–1.70

Table 2 ^{1}H NMR chemical shifts corresponding to *β*-CD in the presence and absence of ethyl *p*-hydroxylbenzoate

β-CD	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ*(ppm)
H-1	4.82(d)	4.81(d)	–0.01
H-3	3.64(t)	3.60(t)	–0.04
H-6,6′	3.64(t)	3.64(t)	0
H-5	3.59(d)	3.54(d)	–0.05
H-4	3.34(t)	3.36(t)	0.02
H-2	3.29(d)	3.28(d)	–0.01

Table 3 ^{1}H NMR chemical shifts corresponding to 1,5-naphthalenediamine in the presence and absence of *β*-CD

1,5-Naphthalenediamine	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ*(ppm)
H-2,6	6.62(d)	6.57(d)	–0.05
H-3,7	7.07(t)	7.03(t)	–0.04
H-4,8	7.23(d)	7.19(d)	–0.04
H-11,12	5.41(s)	5.39(s)	–0.02

Table 4 ^{1}H NMR chemical shifts corresponding to *β*-CD in the presence and absence of 1,5-naphthalenediamine

β-CD	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ*(ppm)
H-1	4.82(d)	4.81(d)	–0.01
H-3	3.64(t)	3.62(t)	–0.02
H-6,6’	3.64(t)	3.66(t)	0.02
H-5	3.59(d)	3.54(d)	–0.05
H-4	3.34(t)	3.33(t)	–0.01
H-2	3.29(d)	3.28(d)	–0.01

Table 5 ^{1}H NMR chemical shifts corresponding to 1,8-naphthalenediamine in the presence and absence of *β*-CD

1,8-Naphthalenediamine	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ*(ppm)
H-2,7	6.53(d)	6.54(d)	0.01
H-3,6	7.15(t)	7.02(t)	–0.13
H-4,5	7.15(d)	6.94(d)	–0.21
H-11,12	4.40(s)	5.42(s)	1.02

Table 6 ^{1}H NMR chemical shifts corresponding to *β*-CD in the presence and absence of 1,8-naphthalenediamine

β-CD	*δ* (ppm) (free)	Complex *δ* (ppm)	Δ*δ*(ppm)
H-1	4.82(d)	4.81(d)	–0.01
H-3	3.64(t)	3.60(t)	–0.04
H-6,6’	3.64(t)	3.66(t)	0.02
H-5	3.59(d)	3.55(d)	–0.04
H-4	3.34(t)	3.36(t)	0.02
H-2	3.29(d)	3.30(d)	0.01

p-hydroxylbenzoate, the intermolecular hydrogen bondings between hydroxyl groups exist which cause the downfield shift of OH*. Upon complexation with *β*-CD, they are completely destroyed and hence, move upfield. The upfield shift of OH* of the guest molecule inevitably affects the electronic density of benzene ring and cause the upfield shift of the guest molecules.

1,5-Naphthalenediamine only forms very weak molecular interactions with *β*-CD upon complexation, as there aren't pronounced chemical shift variations for the guest molecule. The variation of N–H* chemical shift is only -0.02 ppm which indicates the hydrogen bondings between N–H and O–H of *β*-CD (Table 3) are very weak although they do exist according to the broad peak configuration of N–H* in its NMR spectrum.

In Table 5, the N–H signal moves to 5.42 ppm from 4.40 ppm for 1,8-naphthalenediamine upon complexation. The above phenomena can be accounted for hydrogen bondings. Before complexation, the two amino groups form six-membered intramolecular hydrogen bondings (Fig. 3), the intramolecular hydrogen bondings are damaged upon complexation and the weaker hydrogen bondings between N–H and O–H formed (like that of 1,5-naphthalenediamine). Due to the decomposed intramolecular strong hydrogen bondings and the existence of weak hydrogen bondings upon complexation, N–H* move to nearly free aromatic amino group area (*δ* = 5.42 ppm, similar to that of 1,5-naphthalenediamine).

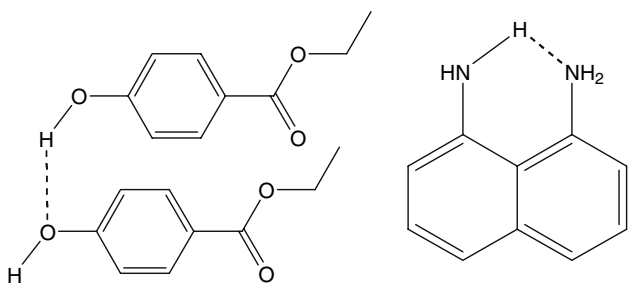

Fig. 3 Hydrogen bondings in ethyl *p*-hydroxylbenzoate and free 1,8-naphthalenediamine

The stoichiometry of the inclusion complexes is obtained directly from the integration of the ^{1}H NMR spectra. β-CD forms 1:1 inclusion complexes with ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine and 1,8-naphthalenediamine.

Tables 7, 8, 9, 10, 11, 12 list the ^{13}C NMR chemical shifts of the inclusion complexes in comparison to those of free β-CD.

^{13}C NMR spectra were obtained from proton broadband decoupling ^{13}C{^{1}H}. ^{13}C NMR shifts extended over a much larger scale than proton shifts which evidenced the existence of an interaction between the guest molecule and the interior of the host cavity, with a partial or complete inclusion on the torus and, hence complexation.

In Tables 7, 9, 11, the same amount of carbon signals for the guest molecules in the inclusion complexes to that of the corresponding free guest molecules reveals the signal degeneration still exists for the guest molecules, eg. C-5,10 and C-6,9 (Table 7) for ethyl *p*-hydroxylbenzoate, C-1,5 and C-2,6 (Table 9) for 1,5-naphthalenediamine, C-1,8 and C-2,7 for 1,8-naphthalenediamine (Table 11). The above phenomena reveal the symmetrical conformations of the three guest molecules inside the inclusion complexes, which are in accordance with the ^{1}H NMR results.

Tables 13, 14, 15 list the ^{1}H NMR chemical shifts of the hydroxyl groups of β-CD in the inclusion complexes in comparison to free β-CD.

Table 7 ^{13}C NMR chemical shifts corresponding to ethyl *p*-hydroxylbenzoate in the presence and absence of β-CD

Ethyl *p*-hydroxylbenzoate	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1	14.30	14.93	0.63
C-2	61.19	60.77	–0.42
C-3	167.55	166.27	–1.28
C-4	122.18	121.14	–1.04
C-5,10	131.99	132.03	0.04
C-6,9	115.39	115.99	0.60
C-7	160.77	162.63	1.86

Table 8 ^{13}C NMR shift corresponding to β-CD in the presence and absence of ethyl *p*-hydroxylbenzoate

β-CD	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1	102.58	102.61	0.03
C-2	72.80	73.07	0.27
C-3	73.80	73.72	–0.08
C-4	81.55	82.20	0.65
C-5	72.53	72.70	0.17
C-6	63.09	60.61	–2.48

Table 9 ^{13}C NMR chemical shifts corresponding to 1,5-naphthalenediamine in the presence and absence of β-CD

1,5-Naphthalenediamine	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1,5	144.33	145.02	0.69
C-2,6	107.39	108.30	0.91
C-3,7	124.24	125.12	0.88
C-4,8	109.92	110.74	0.82
C-9,10	123.65	124.41	0.76

Table 10 ^{13}C NMR chemical shifts corresponding to β-CD in the presence and absence of 1,5-naphthalenediamine

β-CD	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1,	102.58	102.60	0.02
C-2	72.80	73.02	0.22
C-3	73.80	73.72	–0.08
C-4	81.55	82.17	0.62
C-5	72.53	72.69	0.16
C-6	63.09	60.60	–2.49

Table 11 ^{13}C NMR chemical shifts corresponding to 1,8-naphthalenediamine in the presence and absence of β-CD

1,8-Naphthalenediamine	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1,8	144.44	146.70	2.26
C-2,7	111.49	110.83	–0.66
C-3,6	126.15	126.78	0.63
C-4,5	119.63	118.15	–1.48
C-9	117.02	116.66	–0.36
C-10	136.93	137.38	0.45

Table 12 ^{13}C NMR shift corresponding to β-CD in the presence and absence of 1, 8-naphthalenediamine

β-CD	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
C-1	102.58	102.59	0.01
C-2	72.80	73.02	0.22
C-3	73.80	73.72	–0.08
C-4	81.55	82.17	0.62
C-5	72.53	72.69	0.16
C-6	63.09	60.59	–2.5

Table 13 ^{1}H NMR chemical shifts corresponding to the hydroxyl protons of β-CD in the presence and absence of ethyl *p*-hydroxylbenzoate

OH	δ (ppm) (free)	Complex δ (ppm)	Δδ(ppm)
OH(2)	5.52(d)	5.72(d)	0.20
OH(3)	5.48(s)	5.67(s)	0.19
OH(6)	4.26(t)	4.44(t)	0.18

Table 14 ^{1}H NMR chemical shifts corresponding to the hydroxyl protons of β-CD in the presence and absence of 1,5-naphthalenediamine

OH	δ (ppm) (free)	Complex δ (ppm)	$\Delta\delta$(ppm)
OH(2)	5.52(d)	5.75(d)	0.23
OH(3)	5.48(d)	5.66(d)	0.18
OH(6)	4.26(t)	4.44(t)	0.18

Table 15 ^{1}H NMR chemical shifts corresponding to the hydroxyl protons of β-CD in the presence and absence of 1,8-naphthalenediamine

OH	δ (ppm) (free)	Complex δ (ppm)	$\Delta\delta$(ppm)
OH(2)	5.52(d)	5.73(d)	0.21
OH(3)	5.48(s)	5.66(s)	0.18
OH(6)	4.26(t)	4.44(t)	0.18

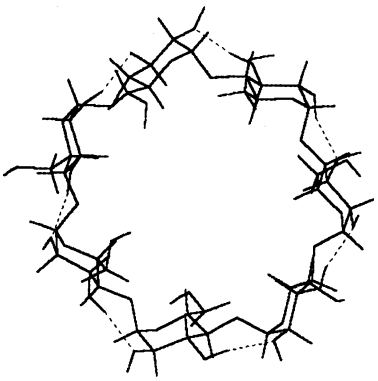

Fig. 4 Hydrogen bondings around the secondary CD's side

The secondary hydroxyl groups at the wider rim, from intramolecular bonds in which the OH-3 group of one glucose unit is interacting with the OH-2 group of the neighboring glucose unit. This leads to a belt of hydrogen bondings around the secondary CDs side that gives the whole molecule a rigid structure [8] (Fig. 4). The belt of hydrogen bonding still exists upon complexation. The primary OH-6 functions placed at the small rim's torus are not participating in intermolecular hydrogen bondings, and therefore can rotate so as to block partially the cavity. Protons involved in hydrogen bondings are much more deshielded than ''free'' protons. This kind of resonance displacement in the range of about 1 ppm has been ascribed previously to hydrogen bondings between secondary OH groups in cyclodextrins. In *DMSO-d_6*, OH signals are separated quite clearly and their couplings to the vicinal C–H protons can well be analyzed unlike in protic solvents such as water in which intermolecular exchange between solute and solvent is too fast on the NMR time scale for the observation of separate OH signals. The resonance of OH-2 and OH-3 are assigned to appear in DMSO between 5.2 and 5.6 ppm, clearly separated from the signals of the free, more shielded OH-6 groups between 4.2 and 4.6 ppm. Upon complexation, weak hydrogen bondings form between the hydroxyl groups of β-CD and the corresponding guest molecules which causes the downfield shifts of OH* signals of β-CD.

Theoretical studies and probable conformations of the inclusion complexes

The following Figure (Fig. 5) lists the molecular sizes of the guest molecules.

The molecular sizes are obtained by running minimal energy of molecules in MM2 software in CS chem3D Pro.

The hydrophobic cavity's diameters of β-CD are 6.0–6.5 Å, the height is 7.9 Å [5]. From the above data in Fig. 5, 1,5-naphthalenediamine and 1,8-naphthalenediamine will be included inside the cavity of β-CD; ethyl *p*-hydroxylbenzoate will be partly included inside the cavity.

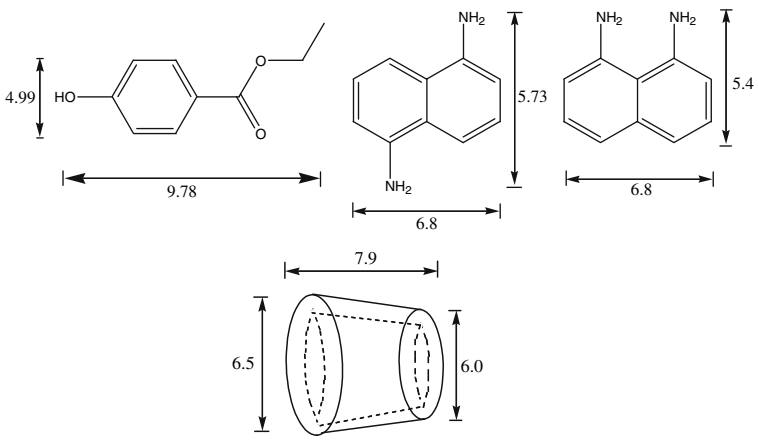

Fig. 5 Molecular sizes of guest and host molecules (unit: Å)

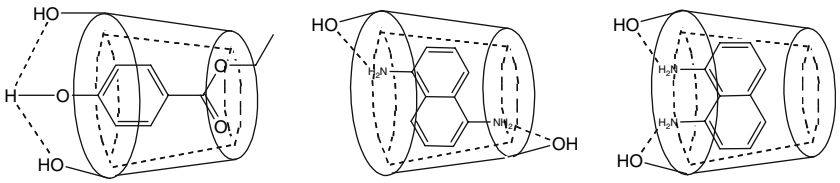

Fig. 6 Possible conformations of the inclusion complexes

According to NMR data analysis, the three guest molecules will form symmetrical conformations inside the cavity of β-CD. The possible conformations of the three inclusion complexes are depicted in Fig. 6. Meanwhile, since the host-guest molecular interaction is weak Van der Waals force as hydrogen bonding, dipole–dipole attraction, etc, the guest molecules will not be stabilized in the cavity of β-CD but stay in a dynamic conformation around the symmetrical conformations described in Fig. 6 which are the most stable conformations.

Conclusion

The inclusion interactions between ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine, 1,8-naphthalenediamine and β-CD were studied systematically by ^{1}H NMR and ^{13}C NMR. NMR studies provided evidence that the interaction was an inclusion phenomenon since the modifications obtained for the β-CD signals involved hydrogen atoms that were oriented forward the cavity. Inclusion behavior of β-CD and the aromatic guests depends on the size fit between guest and host. We obtained inclusion ratio (1:1) for ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine and 1,8-naphthalenediamine. The ^{1}H NMR and ^{13}C NMR spectra of ethyl *p*-hydroxylbenzoate, 1,5-naphthalenediamine and 1,8-naphthalenediamine reveal rather symmetrical conformations of the guest molecules in the inclusion cavities. According to theoretical studies and NMR data analysis, we depicted the probable conformation of the inclusion complexes in liquid state. Since the host-guest molecular interaction is weak Van der Waals force, the guest molecules will exhibit dynamic conformations around the symmetrical conformations in general.

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