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NMR Investigations of Inclusion Complexes between β-Cyclodextrin and Naphthalene/Anthraquinone Derivatives

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Abstract

A ^{1}H and ^{13}C NMR study on the inclusion complex between β-cyclodextrin and naphthalene, 1,5-dichloronaphthalene and 9,10-anthraquinone was carried out in order to define the stoichiometry of the association and the possible conformations. The upfield variation of the chemical shifts from the protons locate inside the cavity (H-3, H-5) coupled with the downfield variation of the other protons which locate outer sphere of the β-CD (H-1, H-2, H-4 and H-6,6′) provided clear evidence of the inclusion phenomena. The NMR spectra revealed the formation of 1:1 inclusion complex in which aromatic ring of the guest is tightly held by the host cavity. The signal degeneration of ^{1}H & ^{13}C NMR spectra still exist for naphthalene and 1,5-dichloronaphthalene upon complexation revealed a symmetrical conformation of the guest molecules in the cavity of β-cyclodextrin, respectively. However, in 9,10-anthraquinone, the signal degeneration of ^{1}H & ^{13}C NMR spectra was removed upon complexation which revealed an unsymmetrical conformation of the guest molecule inside the cavity. According to theoretical calculations and NMR studies, the possible conformations of the inclusion complexes are given here.

Introduction

Cyclodextrins are cyclic organic compounds obtained by enzymatic transformation of starch. Among the class of ''host'' molecules, the β-cyclodextrin (β-CD) is one of the most abundant natural oligomers and corresponds to the association of seven glucose units [1–3] which cavity exhibits a hydrophobic character whereas the exterior is strongly hydrophilic (Figure 1). This peculiar structure allows various guest molecules to be included in the cavity via non covalent bonds to form what is called inclusion complexes. In the field of environmental research, the inclusion ability of cyclodextrins has attracted considerable attention for the merit of stabilizing and increasing the solubility of labile xenobiotics [4–9]. As the β-CD molecule is notably well-known to greatly affect the chemical behavior of many pesticides (absorption [10], solubility, stability [11], decomposition rate [12]), we decide to investigate a study about its capacity of complexation in aqueous solution with 1,5-dichloronaphthalene, naphthalene and 9,10-anthraquinone which are widely used in the synthesis of pesticides (Figure 2).

Materials and methods

Reagents

Solid reagents (β-CD, naphthalene, anthracene, 1,5-diaminonaphthalene) were purchased from Aldrich and were used without further purification. 1,5-Dichloronaphthalene was synthesized from 1,5-diaminonaphthalene [13] and 9,10-anthraquinone was synthesized from anthracene [14] according to the previously reported methods.

NMR experiments

NMR spectra were obtained with a Varian Mercury AS400 instrument. All the experiments 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 2.5 ppm (^{1}H NMR) and 40.10 ppm (^{13}C NMR) due to residual solvents, present at impurities (DMSO), was used as internal reference.

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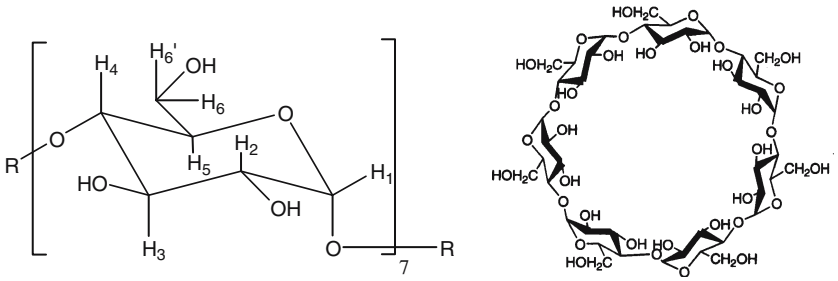

Figure 1. Structure of β-Cyclodextrin.

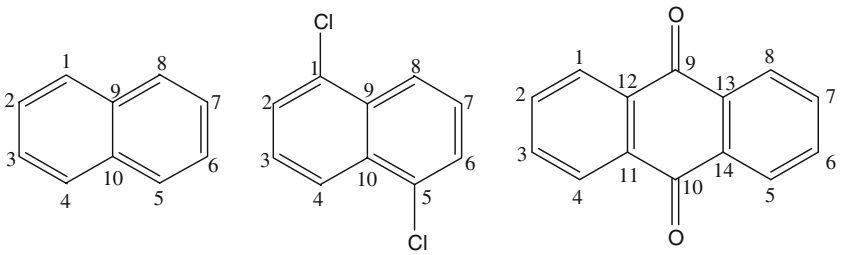

Figure 2. Structure of guest molecules.

Results and discussion

NMR results and analysis

For each molecule, we observed the difference in the chemical shifts between free β-CD, aromatic compounds and their inclusion complexes.

^{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, 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 bonds, electrostatic force, dipole–dipole interaction, dispersion force, etc. Hence, the variations of NMR chemical shifts in the complexes will be in a small scale (less than 0.30 ppm in ^{1}H NMR and less than 8 ppm in ^{13}C NMR) in comparison with the corresponding free guest molecules and β-cyclodextrin.

Tables 1–15 lists the ^{1}H NMR and ^{13}C NMR chemical shifts of the inclusion complexes in comparison to free β-cyclodextrin.

β-Cyclodextrin 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 [15]. 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 [16, 17]. The other β-CD protons (H1, H2, H4 & H6) located outside the cavity show downfield shifts in their chemical shifts upon complexation. The magnitude of chemical shifts ranges less than 0.05 ppm. On the other hand, signals for the guest protons will probably show downfield shift changes upon complexation with β-CD, which are shown in Tables 1 and 3. However, in Table 5, the protons in 9,10-anthraquinone move upfield upon complexation ranging from 0.24 to 0.30, which is attributed to the intermolecular hydrogen bonds between hydroxyl groups in β-CD and the carbonyl groups in anthraquinone. After the formation of hydrogen bonds, the electronic density in the carbonyl groups decreases and the resonance system between the carbonyl groups and benzene will decrease, the electronic density in benzene will increase in comparison to free

Table 1. ^{1}H NMR chemical shift corresponding to naphthalene in the presence and absence of β-CD

Naphthalene	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-2,3,6,7	7.32(q)	7.52(q)	0.20
H-1,4,5,8	7.67(q)	7.91(q)	0.24

Table 2. ^{1}H NMR chemical shifts corresponding to β-CD in the presence and absence of naphthalene

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-1	4.82(d)	4.84(d)	0.02
H-3	3.64(t)	3.63(t)	−0.01
H-6,6′	3.64(t)	3.68(t)	0.04
H-5	3.59(d)	3.56(d)	−0.03
H-4	3.34(t)	3.37(t)	0.03
H-2	3.29(d)	3.32(d)	0.03

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

1,5-Dichloronaphthalene	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-2,6	7.59(d)	7.82(d)	0.23
H-3,7	7.44(t)	7.67(t)	0.23
H-4,8	8.18(d)	8.19(d)	0.01

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

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-1	4.82(d)	4.83(d)	0.01
H-3	3.64(t)	3.63(t)	−0.01
H-6,6′	3.64(t)	3.67(t)	0.03
H-5	3.59(d)	3.57(d)	−0.02
H-4	3.34(t)	3.37(t)	0.03
H-2	3.29(d)	3.30(d)	0.01

anthraquinone which results in the upfield shift of the protons in anthraquinone upon complexation. In the cases of naphthalene and 1,5-dichloronaphthalene, there are no hydrogen bonds between host–guest molecules. The ^{1}H NMR chemical shifts are in agreement with those reported by Thakkar and Demarco [17(a)], who mentioned that downfield shifts should be observed for guest protons and upfield shifts for β-CD protons, upon hydrophobic interactions between both partners.

In Tables 1 and 3, signal degeneration still exists for naphthalene and 1,5-dichloronaphthalene upon complexation, which reveals symmetrical conformations of the guest molecules inside the cavity of β-cyclodextrin. However, in Table 5, the signal degeneration is removed for H-1,4 & H-5,8; H-2,3 & H-6,7. H-1,4 & H-2,3 move upfield in a larger magnitude than H-5,8 & H-6,7. Its NMR results exhibit an unsymmetrical conformation of

Table 5. ^{1}H NMR chemical shifts corresponding to 9,10-anthraquinone in the presence and absence of β-CD

9,10-Anthraquinone	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-1,4	8.32(q)	8.08(q)	−0.24
H-2,3	7.81(q)	7.51(q)	−0.30
H-5,8	8.32(q)	8.21(q)	−0.11
H-6,7	7.81(q)	7.93(q)	0.12

Table 6. ^{1}H NMR chemical shifts corresponding to β-CD in the presence and absence of 9,10-anthraquinone

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
H-1	4.82(d)	4.84(d)	0.02
H-3	3.64(t)	3.63(t)	−0.01
H-6,6′	3.64(t)	3.67(t)	0.03
H-5	3.59(d)	3.57(d)	−0.02
H-4	3.34(t)	3.36(t)	0.02
H-2	3.29(d)	3.30(d)	0.01

Table 7. ^{13}C NMR chemical shifts corresponding to naphthalene in the presence and absence of β-CD

Naphthalene	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-2,3,6,7	125.75	126.57	0.82
C-1,4,5,8	127.84	128.32	0.48
C-9,10	133.45	133.61	0.16

Table 8. ^{13}C NMR chemical shifts corresponding to β-CD in the presence and absence of naphthalene

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-1	102.58	102.57	−0.01
C-2	72.80	73.03	0.23
C-3	73.80	73.68	−0.12
C-4	81.55	82.20	0.65
C-5	72.53	72.66	0.13
C-6	63.09	60.56	−2.53

9,10-anthraquinone inside the cavity of β-cyclodextrin upon complexation. ^{1}H NMR spectra provide a clear evidence for the analysis of conformations of the inclusion complexes.

The stoichiometry of the inclusion complexes is obtained directly from the integration of the ^{1}H NMR spectra. β-Cyclodextrin forms 1:1 inclusion complexes with naphthalene, 1,5-dichloronaphthalene and 9,10-anthraquinone.

^{13}C NMR spectra were obtained from proton broad band 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.

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

1,5-Dichloronaphthalene	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-1	131.91	131.72	−0.19
C-2	127.02	128.38	1.36
C-3	126.66	128.18	1.42
C-4	123.70	124.03	0.33
C-9	131.91	131.72	−0.19

Table 10. ^{13}C NMR shift corresponding to β-CD in the presence and absence of 1,5-dichloronaphthalene

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-1	102.58	102.57	−0.01
C-2	72.80	73.03	0.23
C-3	73.80	73.67	−0.13
C-4	81.55	82.18	0.63
C-5	72.53	72.66	0.13
C-6	63.09	60.56	−2.53

Table 11. ^{13}C NMR chemical shift corresponding to 9,10-anthraquinone in the presence and absence of β-CD

9,10-Anthraquinone	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-1,4	127.25	126.17	−1.08
C-2,3	134.11	131.81	−2.30
C-5,8	127.25	128.63	1.38
C-6,7	134.11	135.18	1.08
C-9,10	183.14	Too weak to be detected	–
C-11,12	133.61	126.60	−7.01
C-13,14	133.61	127.37	−6.24

Table 12. ^{13}C NMR chemical shifts corresponding to β-CD in the presence and absence of 9,10-anthraquinone

β-CD	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
C-1	102.58	102.56	−0.02
C-2	72.80	73.04	0.24
C-3	73.80	73.67	−0.13
C-4	81.55	82.18	0.63
C-5	72.53	72.66	0.13
C-6	63.09	60.56	−2.53

In Table 7, there are three signals in the inclusion complex which are assigned as C-2,3,6,7, C-1,4,5,8 & C-9,10, respectively, the same number as that of free naphthalene. The results show a symmetrical conformation of naphthalene included in the cavity of β-CD, which is in accordance with the ^{1}H NMR result. Similar result is obtained in that of 1,5-dichloronaphthalene, which also reveals a symmetrical conformation for the inclusion complex. However, in the inclusion complex of 9,10-anthraquinone (Table 11), the signal degeneration is removed upon complexation, C-1,4 & C-5,8, for instance. C-9,10 experiences a largest up-field shift which is attributed to strong hydrogen bondings between carbonyl groups and hydroxyl groups in the secondary side of β-CD. The loss of signal degeneration also reveals an unsymmetrical conformation of 9,10-anthraquinone in the cavity of β-CD which is in accordance with the result analysis of ^{1}H NMR spectrum.

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 [19] (Figure 3). 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 [20]. 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 [20–22]. 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 resonances 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. The ^{1}H NMR chemical shifts in hydroxyl groups of β-CD move downfield upon complexation with naphthalene and 1,5-dichloronaphthalene. In 9,10-anthraquinone, the carbonyl groups in C-9,10 form three strong hydrogen bonds with OH-2, OH-3 and OH-6. Due to the fast exchange between H atoms, the three OH signals merge to form a broad peak.

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

OH	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
OH(2)	5.52(d)	5.70(d)	0.18
OH(3)	5.48(s)	5.66(s)	0.18
OH(6)	4.26(t)	4.44(t)	0.18

Theoretical studies

The following figure (Figure 4) 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 [15]. From the above data in Figure 4, naphthalene and 1,5-dichloronaphthalene will be included inside the cavity of β-cyclodextrin completely. 9,10-Anthraquinone will be partly included inside the cavity. According to the molecular sizes of

Table 13. ^{1}H NMR chemical shifts corresponding to the hydroxyl protons of β-CD in the presence and absence of naphthalene

OH	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
OH(2)	5.52(d)	5.73(d)	0.21
OH(3)	5.48(d)	5.69(d)	0.21
OH(6)	4.26(t)	4.46(t)	0.20

Table 15. ^{1}H NMR chemical shifts corresponding to the hydroxyl protons of β-CD in the presence and absence of 9,10-anthraquinone

OH	δ(ppm) (free)	Complex δ (ppm)	$\Delta\delta$ (ppm)
OH(2)	5.52(d)	4.17(broad)	–
OH(3)	5.48(s)	4.17(broad)	–
OH(6)	4.26(t)	4.17(broad)	–

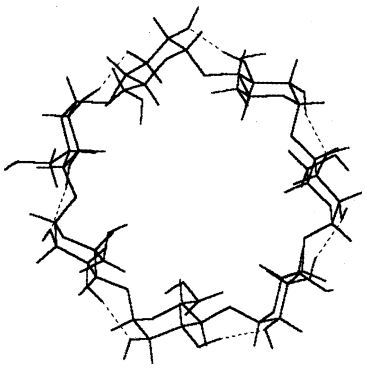

Figure 3. Hydrogen bonds around the secondary CD's side.

guest molecules, β-CD will form 1:1 inclusion complexes with naphthalene, 1,5-dichloronaphthalene and 9,10-anthraquinone, respectively, which is in accordance with the integration results of NMR spectra.

NMR study of the complex geometry

Cyclodextrins have an overall shape reminiscent of truncated cone with an internal cavity, which is predominantly hydrophobic. The internal cavity is open at the two ends, which have different diameters and are therefore referred to as the wide and narrow rings. Only proton H3 and H5 (henceforth called *H3 and *H5) from each sugar unit face the internal cavity and they are located near the wide and narrow ring, respectively. They can be used therefore to probe the internal cavity of cyclodextrins for the presence of a guest molecule and to understand the nature of this interaction.

Preliminary indications of the solution structure of the complex are derived by a proton chemical shift analysis. For instance, the observed largest chemical shift changes upon complex formation are those exhibited by *H3 and *H5 with an upfield shift. Since *H3 and *H5 face the cavity of the cylindrical structure of β-CD, their chemical shift changes are most likely due to the presence of one of the aromatic rings of guest molecules. On the other hand, the largest chemical shift variation observed in the whole guest molecules is attributed to the effect induced by the nuclei on the inner surface of β-cyclodextrin complexes.

For naphthalene, the chemical shift variations of H2,3,6,7 and H1,4,5,8 are very close. From the molecular size of naphthalene, together with the ^{1}H & ^{13}C NMR data analysis, we can conclude that naphthalene will be included in the cavity of β-cyclodextrin in the rather symmetrical conformation shown in Figure 5.

The chemical shift variations of 1,5-dichloronaphthalene are classified into two groups: H-2, 6 and H-3, 7 own the same variations which are much bigger than H-4,8. In combination with the molecular size information of 1,5-dichloronaphthalene, as well as the ^{1}H NMR & ^{13}C NMR data analysis, the inclusion complex will behave as the rather symmetrical conformation shown in Figure 5.

In the complex between anthraquinone and β-CD, unlike in free β-cyclodextrin, the three OH signals (OH-2, OH-3, OH-6) disappear from their original areas (δ5.52, δ5.48, δ4.26), instead, they form a broad peak at δ4.17 together which is due to the fast exchange of H atoms in the hydrogen bondings system of OH-2, OH-3 and OH-6. The formation of a broad peak means the OH groups form different hydrogen bonds with the carbonyl group (C-9, C-10) in anthraquinone. In combination with the ^{1}H & ^{13}C NMR spectra, 9,10-anthraquinone probably forms the unsymmetrical conformation in the liquid state with β-cyclodextrin shown in Figure 5.

Conclusion

The inclusion interactions between naphthalene, 1,5-dichloronaphthalene and 9,10-anthraquinone and β-cyclodextrin were studied systematically by ^{1}H NMR & ^{13}C NMR. NMR studies provided evidence that the interaction was an inclusion phenomenon since the modifications obtained for the β-CD signals involved

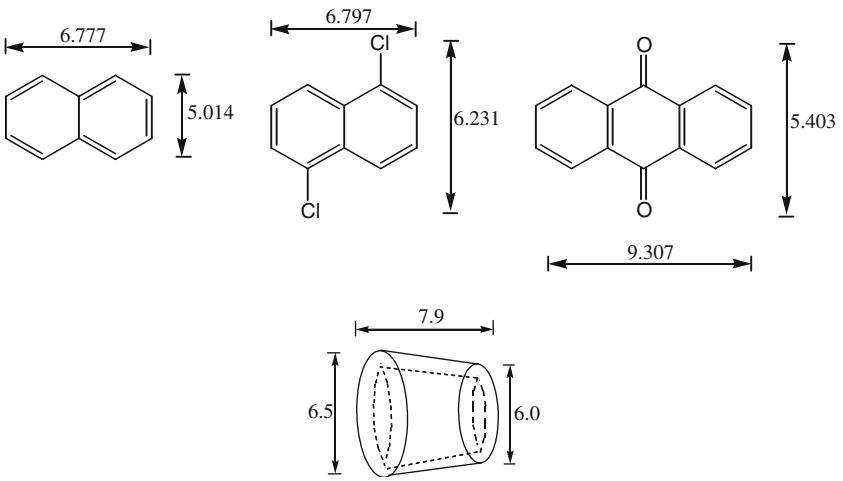

Figure 4. Molecular sizes of guest and host molecules (unit: Å).

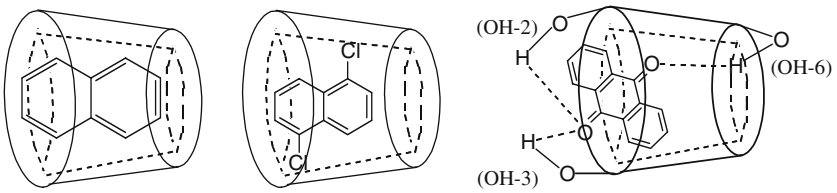

Figure 5. Possible conformations of the inclusion complexes.

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 naphthalene, 1,5-dichloronaphthalene and 9,10-anthraquinone. There are strong hydrogen bonds between 9,10-anthraquinone and β-CD upon complexation. The ^{1}H NMR & ^{13}C NMR spectra of naphthalene and 1,5-dichloronaphthalene reveal rather symmetrical conformations of the guest molecules in the inclusion complex, which is different to that of 9,10-anthraquinone. According to theoretical studies and NMR data analysis, we depicted the probable conformation of the inclusion complexes in liquid state.

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