Carbon-13 NMR Study on the Cyclodextrin Inclusion Complexes in Solution

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A correlation between the penetration depth of the carbon atoms of 4-nitrophenolate, benzoic acid, 4-nitrophenol and 2,6-dimethyl-4-nitrophenolate in the cavity of α-cyclodextrin and the changes of their ^{13}C-chemical shifts has been investigated. By use of this relationship and the observed changes of the ^{13}C-chemical shifts of 3-nitrophenol on the complex formation with α-cyclodextrin, the time-averaged conformation of the α-cyclodextrin–3-nitrophenol complex is determined.

The attention to the catalyses by cyclodextrins, cyclic oligosaccharides composed of 6—8 glucose units, has been increasing. This mainly comes from the inclusion complex formation of cyclodextrins with the substrates prior to the catalytic function in the similar way as enzymatic reactions, resulting in specificities.[1]

Although almost all of the reactions catalyzed by cyclodextrins are carried out in aqueous solutions, little is known on the positions of the substrates in the cavities of cyclodextrins. The information on the structures of inclusion complexes is quite important, since the characteristics of the cyclodextrin-catalyzed reactions are mainly due to the formation of the complexes.

In the previous paper,[2] the time-averaged conformations of the complexes of α-cyclodextrin with 4-nitrophenol and benzoic acid as well as their anions were determined by fitting the changes of the ^{1}H-chemical shifts of α-cyclodextrin to the calculated values of the anisotropic shielding effects of the aromatic rings of the guest compounds.

This paper describes the extension of the previous study to the ^{13}C-NMR spectroscopy. The relationship between the positions of the carbon atoms of the guest compounds in the cavity of α-cyclodextrin and the changes of the ^{13}C-chemical shifts of these atoms is shown for the complex of α-cyclodextrin with 4-nitrophenolate, benzoic acid, 4-nitrophenol, and 2,6-dimethyl-4-nitrophenolate. Furthermore, the conformation of the complex of α-cyclodextrin with 3-nitrophenol is determined by use of this relationship.

Experimental

Materials. The guest compounds and α-cyclodextrin were purified by recrystallization. Deuterium oxide (the minimum purity 99.75%) from Merck Co. was used as the solvent for the ^{13}C- and ^{1}H-NMR measurements.

Spectrometry. ^{13}C-NMR spectra were taken at ambient temperature (about 25 °C) on a JEOL PFT-100 spectrometer operating at 25.03 MHz, connected with JEOL EC-100 computer. The ^{13}C-chemical shifts were determined with the accuracy of ±0.01 ppm by use of sodium formate as the internal standard. The assignments of the signals were made according to the literatures for 4-nitrophenolate,[3] benzoic acid[4] and 4-nitrophenol,[3] and by using the additivity rule[5] for 2,6-dimethyl-4-nitrophenol and 3-nitrophenol. The changes of the ^{13}C-chemical shifts of the guest compounds (Δ_C's) on the complex formation with α-cyclodextrin were determined with the accuracy of ±0.05 ppm by plotting the observed changes of the ^{13}C-chemical shifts *vs.* the concentration of α-cyclodextrin.

^{1}H-NMR spectra were measured at 60 °C by use of JEOL PS-100 spectrometer. Assignments of the signals of α-cyclodextrin followed the literature.[6]

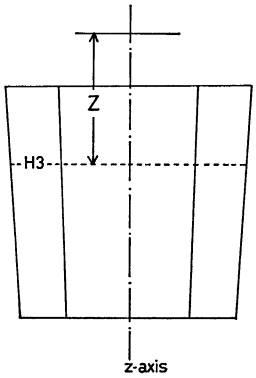


Fig. 1. Schematic drawing showing the definition of *Z*. ---H3--- shows the plane comprised of the six H-3 atoms of α-cyclodextrin.

Determination of the Time-averaged Position of the Guest Compound by ^{1}H-NMR Spectroscopy. The time-averaged position of the guest compound in the cavity of α-cyclodextrin was determined by the following method, the detailed description of which was made in the previous paper;[2]

1) The change of the ^{1}H-chemical shifts of the H-3 and H-5 atoms of α-cyclodextrin due to the complex formation with the guest compound were experimentally determined.

2) The magnitudes of the anisotropic shielding effects of the aromatic ring of the guest compound on the H-3 and H-5 atoms were calculated by using the table of Johnson and Bovey.[7]

3) The optimal position of the guest compound was determined by shifting the aromatic ring along the longitudinal axis (z-axis) of the cavity of α-cyclodextrin. In the optimal position, the calculated values of the shielding effects of the guest compound on the both H-3 and H-5 atoms show the maximal agreements with the corresponding observed values.

and

4) The optimal position was taken as the time-averaged position of the aromatic ring of the guest compound.

The position of the center of the aromatic ring and the carbon atoms of the guest compounds were expressed in terms of the heights (*Z*, in Å) from the plane comprised of the six H-3 atoms of α-cyclodextrin as shown in Fig. 1.

Results

Time-averaged Positions of the Guest Compounds in the Cavity Determined by the ^{1}H-NMR Spectroscopy. Table 1 shows the heights of the centers of the aromatic rings (Z-values) of 4-nitrophenolate, benzoic acid, 4-nitrophenol and 2,6-dimethyl-4-nitrophenolate, determined by the ^{1}H-NMR spectroscopy as described

TABLE 1. PENETRATION DEPTH (THE Z VALUE) FOR THE CENTER OF THE AROMATIC RING OF THE GUEST COMPOUND AND THE OBSERVED AND CALCULATED CHANGES OF THE ^{1}H-CHEMICAL SHIFTS OF THE H-3 AND H-5 ATOMS OF α-CYCLODEXTRIN

Guest compound	Z of the center of the aromatic ring/Å[a)]	^{1}H-Chemical shift change/ppm[b)]			
		H-3		H-5	
		Obsd	Calcd	Obsd	Calcd
4-Nitrophenolate[c)]	−1.1	+0.20	+0.21	−0.05	−0.08
Benzoic Acid[c)]	−0.1	+0.41	+0.40	−0.08	−0.09
4-Nitrophenol[c)]	−0.7	+0.25	+0.26	−0.04	−0.08
2,6-Dimethyl-4-nitrophenolate	−1.4	+0.15	+0.15	−0.06	−0.08

a) The negative sign refers to the shallower penetration with respect to the plane composed of the six H-3 atoms of α-cyclodextrin. b) The positive sign shows the increase in the shielding. c) From Ref. 2.

TABLE 2. VALUES OF Δ_c AND Z FOR THE COMPLEX FORMATION OF α-CYCLODEXTRIN WITH VARIOUS GUEST COMPOUNDS

Guest compound	Carbon atom[a)]	Δ_c/ppm[b)]	Z/Å[c)]
4-Nitrophenol	C-1	+0.25	−1.8
	C-2	−1.05	−0.4
Benzoic acid	C-3	−1.61	+0.6
	C-4	+0.14	−0.8
	C-5	−0.28	−1.5
4-Nitrophenol	C-6	−0.27	−1.3
	C-7	−1.26	0.0
2,6-Dimethyl-4-nitrophenolate	C-8	+0.59	−2.1
	C-9	+0.10	−0.8

a) The numbering system is shown in the legend for Fig. 2. b) The positive sign refers to the increase in the shielding. c) The negative sign shows the shallower penetration with respect to the plane comprised of the six H-3 atoms.

in the Experimental Section. The agreements between the observed values of the changes of the ^{1}H-chemical shifts and the calculated ones are fair for both the H-3 and H-5 atoms.

The conformations of the inclusion complexes can be definitely determined from the Z-values of the centers of the aromatic rings listed in Table 1, since the directions of the penetrations of the guest compounds were known.[8,9] 4-Nitrophenolate, 4-nitrophenol and 2,6-dimethyl-4-nitrophenolate form the complexes with α-cyclodextrin in which the nitro groups are located inside the cavity with the hydroxyl group and phenoxide oxygen atoms protruding from the secondary hydroxyl side of the cavity.[8] In the α-cyclodextrin–benzoic acid complex, the carboxyl group penetrates as a head from the secondary hydroxyl side.[9] Thus, the Z-values for all of the carbon atoms of the guest compounds were determined as shown in Table 2.

Relationship between the Penetration Depth and the Change of the ^{13}C-Chemical Shift. Table 2 lists the changes of the ^{13}C-chemical shifts (Δ_c) as well as the Z-values for the complex formations of α-cyclodextrin with 4-nitrophenolate, benzoic acid, 4-nitrophenol, and 2,6-dimethyl-4-nitrophenolate.

A fair correlation between Δ and Z are found as shown in Fig. 2. The seven points except for those of the C-4 and C-9 atoms showed linearity. As the carbon atom was included more deeply in the cavity, its chemical shift moved from the values in the absence of α-cyclodextrin towards the lower magnetic field to a greater extent. The C-4 and C-9 atoms, both of which have the Z-values of around −0.8 A, showed almost the identical Δ_c values (+0.1 ppm), although the corresponding points considerably deviated from the linear straight line for the other seven points.

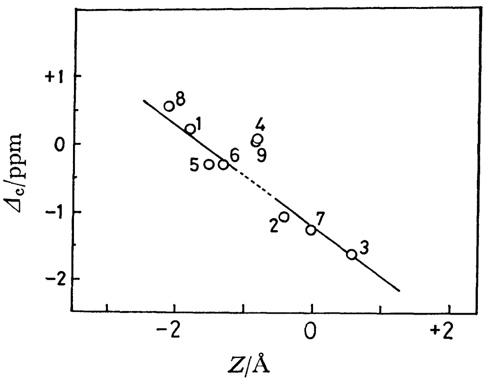
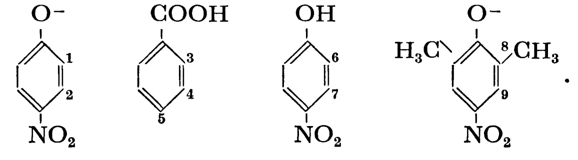


Fig. 2. Plot of the changes of the ^{13}C-chemical shifts (Δ_c in ppm) of the guest compounds on the inclusion complex formation with α-cyclodextrin *vs.* the penetration depth (Z in Å).
The positive sign in Δ_c shows the increase in the shielding, and the positive sign in Z shows the deeper penetration with respect to the plane (Z=0) comprised of the six H-3 atoms of α-cyclodextrin; the numbering system of the carbon atoms of the guest compounds are as follows;



The most important conclusion from Fig. 2 is that Δ_c is virtually governed only by the penetration depth in the cavity. The positions of the carbon atoms with respect to the substituents in the guest compounds are less important. Thus, the relationship in Fig. 2 is applicable to other guest compounds, especially to the substituted benzenes.

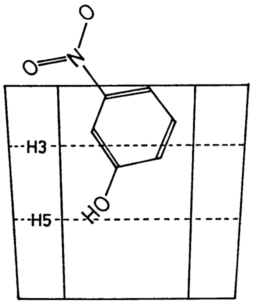


Fig. 3. The time-averaged conformation of the α-cyclodextrin-3-nitrophenol complex.
---H3--- and ---H5--- show the planes comprised of the six corresponding atoms of α-cyclodextrin.

Application of the Relationship between Δ_c and Z to the Complex Formation of α-Cyclodextrin with 3-Nitrophenol. The time-averaged position of 3-nitrophenol in the cavity of α-cyclodextrin can be estimated as shown in Fig. 3. Here, the Z-values of the carbon atoms of 3-nitrophenol are determined by use of the observed Δ_c's and the relationship in Fig. 2. The Δ_c's for the C-10, C-11, and C-13 atoms are evaluated from the straight line, and that for the C-12 atom, which is located at $Z=-0.9$ A, is taken as the average of the values for the C-4 and C-9 atoms. The agreements between the observed values of Δ_c and the calculated values are fair as shown in Table 3.

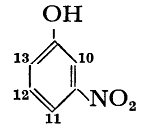
Supports for the conformation in Fig. 3 and thus the method for the determination were provided by the ^{1}H-NMR spectroscopy. The magnitudes of the anisotropic shielding effects of the aromatic ring of 3-nitrophenol on the H-3 and H-5 atoms, respectively, of α-cyclodextrin can be calculated to be +0.30 and −0.05 ppm. These values were determined by averaging the magnitudes of the shielding effects of the aromatic ring on the six H-3 or H-5 atoms, each of which are estimated by using the table of Johnson and Bovey.[7] These values are in fair agreements with the observed values (+0.29 and −0.05 ppm, respectively).

Penetration of the hydroxyl group of 3-nitrophenol in the cavity rather than the nitro group was further confirmed by the absorption spectroscopy. Table 4 shows the dissociation constant (K_d) of the inclusion complexes of α-cyclodextrin with 3-nitrophenol, 2-methyl-3-nitrophenol, and 4-methyl-3-nitrophenol, determined at 25 °C in 0.1 mol dm^{-3} HCl by using the change of the absorbance at 340 nm. The methyl substitution in the ortho position of the hydroxyl group prevents the complex formation with α-cyclodextrin, although the methyl substitution in the para-position of the hydroxyl group enhances it. These results are consistent with the conformation shown in Fig. 3, since the steric hindrance around the hydroxyl group shows larger effect on the complex formation than the steric hindrance around the nitro group does.

TABLE 3. VALES OF Δ_c AND Z FOR THE α-CYCLODEXTRIN-3-NITROPHENOL COMPLEX

Carbon atom[a]	Z/Å[b]	Δ_c/ppm[c] Obsd	Calcd
10	−0.4	−0.78	−0.92
11	−1.9	−0.13	+0.16
12	−0.9	0.00	+0.12
13	+0.4	−1.45	−1.48

a) The numbering system is as follows:



b) The negative sign shows the shallower penetration with respect to the plane composed of the six H-3 atoms. c) The positive sign shows the increase in the shielding.

TABLE 4. THE EQUILIBRIUM CONSTANT (K_d) OF THE DISSOCIATION OF THE INCLUSION COMPLEX OF α-CYCLODEXTRIN[a]

Guest compound	K_d/10^{-2} mol dm^{-3}
3-Nitrophenol	1.7
2-Methyl-3-nitrophenol	2.2
4-Methyl-3-nitrophenol	0.065

a) At 25°C in 0.1 mol dm^{-3} HCl.

Discussion

It has been shown that the ^{13}C-NMR spectroscopy as well as the ^{1}H-NMR spectroscopy[2] can be applicable to the determination of the time-averaged positions of the guest compounds in the cavity. An advantage of the ^{13}C-NMR spectroscopy over the ^{1}H-NMR spectroscopy is that it can provide the direct informations on the positions of all the carbon atoms of the guest compounds and thus on the directions of the penetrations of the guest compounds in the cavity. However, only the position of the aromatic ring of the guest compound in the cavity can be determined by use of the ^{1}H-NMR spectroscopy. The positions of the carbon atoms of the guest compounds can be estimated by ^{1}H-NMR spectroscopy only when the directions of the penetrations are determined by other methods. In the complex formations of 4-nitrophenolate and 4-nitrophenol, for example, the absorption spectroscopy showed the penetration of the nitro group as a head, since the steric hindrance due to the methyl substitution(s) around the nitro group exhibited much larger suppression of the complex formations than the steric hindrance around the hydroxyl group or phenoxide ion does.

The deviations for the C-4 and the C-9 atoms from the straight line in Fig. 2 are associated with the secondary hydroxyl groups of α-cyclodextrin which are located around $Z=-1.0$ A. Apolar property near the hydroxyl groups is smaller than estimated from the Z-value.

The penetration of the hydroxyl group in the cavity in the α-cyclodextrin–3-nitrophenol complex is attributable to the attraction of the dipole of the nitro group of 3-nitrophenol mainly by the negative charge at the O-2 oxygen atom of α-cyclodextrin. The O-2 oxygen atoms are located near the nitro group, since the corresponding secondary hydroxyl groups orient inside the cavity. In the α-cyclodextrin–4-nitrophenol complex, however, the interaction between the nitro group and the negative charge is less important because of the larger distance between them, resulting in the penetration of the more apolar nitro group in the cavity.

The conformation of the α-cyclodextrin–3-nitrophenol complex in solution in Fig. 3 is consistent with that in the crystal[10] where the benzene ring is located near the secondary hydroxyl side of the cavity. The complex in the crystal, however, has the nitro group inside the cavity, whereas that in solution has the hydroxyl group inside the cavity. This discrepancy is probably associated with the process of the crystallization.

Small discrepancies between the observed and calculated values of Δ_c's for the C-10 and C-11 atoms (Table 3) are due to the minor contribution of the inclusion complex where the nitro group penetrates the cavity as a head, in addition to the major contribution of the inclusion complex where the hydroxyl group penetrates the cavity as a head (Fig. 3).

Conclusion

1) A correlation between the penetration depth of the carbon atoms of the aromatic guest compounds and the changes of the ^{13}C-chemical shifts was found.

2) The time-averaged conformation of the α-cyclodextrin–3-nitrophenol complex in solution was determined by use of the relationship.

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