Tetraarylporphyrins as Probes for Studying Mechanism of Inclusion-complex Formation of Cyclodextrins. Effect of Microscopic Environment on Inclusion of Ionic Guests

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The pK_a values and the ^{1}H NMR spectra of tetraarylporphyrins in the presence of cyclodextrins suggest that the microscopic environment of the positively polarized cavity of cyclodextrin promotes the inclusion of the anionic guest and prohibits the penetration of the cationic guest into the cyclodextrin cavity.

It has been known that anionic compounds can be included in a hydrophobic cavity of cyclodextrin (CDx).[1] Ion-dipole or dipole-dipole interaction has been assumed as a binding force for such a complexation. However, no detailed mechanism for penetration of the anionic guest into the CDx cavity has been studied so far. An anionic substituent R comes into the host cavity in the cases of modes 1 and 3 in Figure 1 while the

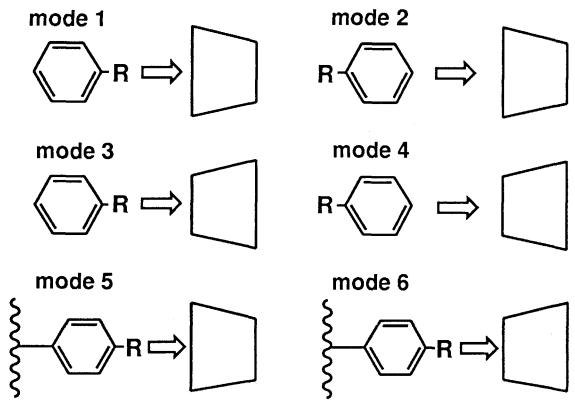
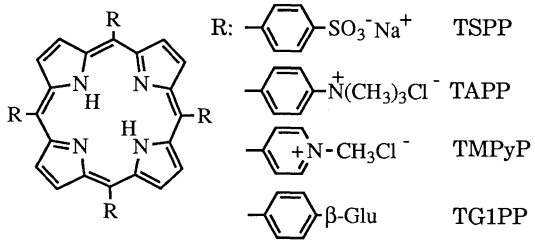


Figure 1. Penetration modes of substituted benzene and tetraarylporphyrin into a cyclodextrin cavity.

anionic group does not need to penetrate into the host cavity in the cases of modes 2 and 4. We cannot distinguish between the complexes formed via modes 1 and 4 and the complexes via modes 2 and 3. If one side of a guest molecule is blocked by a wall, the penetration mode are reduced to two types (modes 5 and 6). A porphyrin ring having phenyl groups at the periphery, which can act as guests of CDx, seems to be adequate to such a wall. In addition, pK_a of a protonated porphyrin is expected to be used as a measure to know the degree of penetration of the phenyl ring at the periphery. If deep penetration occurs, the pK_a value of the tetraarylporphyrin seems to decrease upon complexation. The interactions of the tetraarylporphyrins with native β- and γ-CDxs and with heptakis(2,6-di-*O*-methyl)-β-CDx (DMe-β-CDx) have been studied widely.[2] However, no study has been reported with the intention of investigating the inclusion mechanism. In the present study, we measured the pK_a values and the ^{1}H NMR spectra of the water-soluble tetraarylporphyrins in the absence and the presence of β-CDx, DMe-β-CDx, and heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx) to know the mechanism for the inclusion-complex formation of ionic guests.



The pK_a values of the conjugate acids of the tetraarylporphyrins in water in the absence and the presence of CDxs are listed in Table 1. It has been known that the sulfonatophenyl groups at the 5- and 15-positions of TSPP are included by two β-CDx molecules to form 1 : 2 complex in mode 5.[3] In this case, the pK_a value decreases moderately. Comparing with the large decrease in pK_a of the TSPP-TMe-β-CDx complex, it can be concluded that the sulfonatophenyl groups at the 5- and 15-positions are included shallowly in the β-CDx cavity. This conclusion was supported by the ^{1}H NMR data. Although the proton signal at the 2-position of the phenyl ring of TSPP (2 x

Table 1. The pK_a values of tetraarylporphyrins in the absence and the presence of CDxs[a]

Entry	Porphyrin	CDx	pK_a	-ΔpK_a
1	TSPP	none	5.4	0
2	TSPP	β-CDx	4.2	1.2
3	TSPP	DMe-β-CDx	2.2	3.2
4	TSPP	TMe-β-CDx	0.4	5.0
5	TAPP	none	3.0	0
6	TAPP	β-CDx	2.7	0.3
7	TAPP	DMe-β-CDx	2.2	0.8
8	TAPP	TMe-β-CDx	2.8	0.2
9	TMPyP	none	1.3	0
10	TMPyP	β-CDx	1.3	0
11	TMPyP	DMe-β-CDx	1.3	0
12	TMPyP	TMe-β-CDx	1.3	0
13	TG1PP[b]	none	4.6	0
14	TG1PP	β-CDx	4.2	0.4
15	TG1PP	DMe-β-CDx	2.7	1.9
16	TG1PP	TMe-β-CDx	1.2	3.4

[a] The pK_a values were determined by spectrophotometric titrations of the porphyrins (6 x 10^{-6} mol dm^{-3}) in water in the absence and the presence of CDx (1 x 10^{-2} mol dm^{-3}).
[b] This porphyrin free base forms the self-aggregate which is dissociated into the monomer upon addition of CDxs.

10^{-3} mol dm^{-3}) in D_2O shifts from 7.82 to 8.52 ppm upon dissociation of the TSPP dimer to the monomer by complexing with β-CDx (8 x 10^{-3} mol dm^{-3}), no peak-separation occurs between the protons of the included sulfonatophenyl groups at the 5- and 15-positions and the free ones at the 10- and 20-positions of the porphyrin. Meanwhile, TSPP forms a very stable and deep inclusion complex with TMe-β-CDx. Two sets of the ^{1}H NMR signals due to the included and free sulfonatophenyl groups were observed, indicating that the dissociation rate of the inclusion complex of TMe-β-CDx is significantly slow. The ROESY spectrum clearly shows the 1 : 2 inclusion complex formed via mode 5 where the sulfonatophenyl groups at the 5- and 15-positions are tightly included by TMe-β-CDx. In agreement with the NMR results, the pK_a value of the TSPP-TMe-β-CDx complex is much smaller than that of TSPP itself. This means that the center of the porphyrin ring is surrounded by a very hydrophobic environment provided by the TMe-β-CDx cavities.

In contrast with the anionic porphyrin, the cationic porphyrins such as TAPP and TMPyP hardly interact with CDxs. The decrease in the pK_a values (-ΔpK_a = 0.2-0.8) as well as the shifts of the ^{1}H NMR signals of TAPP upon addition of CDxs is very slight. No changes in both pK_a and ^{1}H NMR spectrum were observed with the TMPyP-CDx system. These results indicate that the cationic porphyrins hardly penetrate into the cavities of β-CDx, DMe-β-CDx, and TMe-β-CDx.

TG1PP, which is a nonionic porphyrin having the β-glucopyranosyl groups at the 4-positions of the phenyl groups, shows an inclusion behavior similar to that of TSPP. The ^{1}H NMR data suggest the formation of mode 5-type inclusion complexes. Water-insoluble 5,10,15,20-tetraphenylporphyrin (TPP) is solubilized only by TMe-β-CDx and the complex shows a very small pK_a value (-0.2).

The present study reveals that TMe-β-CDx includes deeply and tightly the neutral and anionic phenyl groups at the peripheries of the porphyrins. This means that the anionic substituent, $-SO_3^-$, easily penetrates into the hydrophobic CDx cavity. It was also found that the cationic aryl group cannot penetrate into the CDx cavity. What is the difference in inclusion phenomena between the anionic and cationic guests? The *p*-nitrophenolate anion is bound to α-CDx more strongly than undissociated *p*-nitrophenol.[1c] Such a novel result has been interpreted in terms of the ion-dipole interaction between the host and the guest.[1c] It has also been demonstrated that the orientation of *p*-toluic acid in the α-CDx and TMe-α-CDx cavities is dominated by the dipole-dipole interaction.[4] The molecular orbital calculations predict that the dipole-dipole interaction is effective in the case of α-CDx.[5] The MOPAC calculation exhibits that a large dipole moment of β-CDx (15.4 Debye) having a direction same as the C_7 symmetry axis of CDx exists at the center of the cavity. The secondary OH group side is polarized negatively. Meanwhile, the dipole moments of DMe-β-CDx and TMe-β-CDx having the same direction were calculated to be 6.46 and 0.71 Debye, respectively. The small dipole moment of TMe-β-CDx suggests that the dipole-dipole interaction does not contribute to the stabilization or instabilization of the TMe-β-CDx complexes of TSPP, TAPP, and TMPyP. A low ability of native β-CDx to include the cationic guest may be interpreted in terms of the instabilization of the complex due to the same direction of the dipole moments of the host and the guest if the inclusion occurs via mode 5. However, such an assumption cannot be applied for the complexation of TMe-β-CDx. Energy for dehydration from the guest may be considered to discuss the ease of complexation. The SO_3^- group is hydrated through hydrogen bonding as well as the ion-dipole interaction. On the other hand, the pyridinium group of TMPyP is solvated only through the ion-dipole interaction. It is hardly to assume, therefore, that the energy of dehydration from the cationic aryl groups is much larger than that from the anionic one. It is quite reasonable to consider the electrostatic interactions for inclusion of ionic guests in CDx cavity. Figure 2 shows the microscopic polarization of a glucopyranose unit due to the inductive effect. Since all carbon atoms of CDx are bound to the electronegative oxygen atoms and only the oxygen atoms at the 1-positions are located inside of the cavity, the inside of the CDx cavity is assumed to be composed of the positively polarized carbon atoms. The microscopically positive environment of the CDx cavity seems to promote the penetration of the anionic guest and to prohibit the inclusion of the cationic guest in the CDx cavity. Assuming the positively polarized microenvironment of the CDx cavity, all results obtained for the ionic guests can be explained reasonably. No evidence has been obtained for formation of the complex via mode 6. The importance of the local electric fields has also been demonstrated in the formation of the intermolecular hydrogen-bonded complexes.[6]

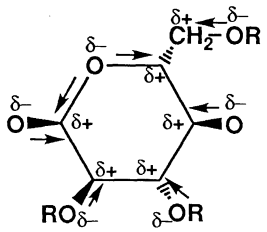


Figure 2. Microscopic polarization of glucopyranose which is an unit of β-CDx or TMe-β-CDx.

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