Recognition of Helicity by Native Cyclodextrins. Highly Enantioselective Complexation of Tetrahelicene Dicarboxylic Acid with β-Cyclodextrin

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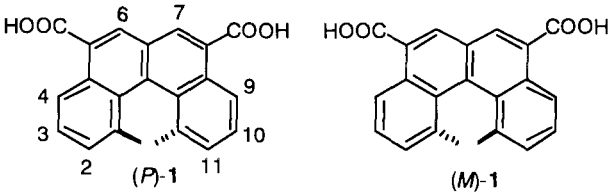
Recognition of the helicity of 1,12-dimethylbenzo[c]-phenanthrene-5,8-dicarboxylic acid (**1**) by cyclodextrins (CDxs) has been studied by means of ^{1}H NMR spectroscopy. The binding constant (K) for the (M)-**1**-β-CDx complex is 18700±1700 dm^3 mol^{-1} which is much larger than that of the (P)-**1**-β-CDx complex (2200±100 dm^3 mol^{-1}). The results sugget the formation of the hydrogen bonds between the CO_2^- groups of **1** and the OH groups of twisted β-CDx in water.

Lots of studies have been done with chiral recognition by cyclodextrins (CDxs).[1] Most examples, however, show the low ability of CDxs to discriminate between enantiomers of guests in aqueous solutions, differences in ΔG values ($\Delta\Delta G$) between guest enantiomers for complexation with CDxs being mostly less than 1 kJ mol^{-1}.[2] The present communication reports distinct chiral recognition ($\Delta\Delta G$ = 5.2 kJ mol^{-1}) by β-CDx toward the helicity of a chiral tetrahelicene, 1,12-dimethylbenzo[c]phenanthrene-5,8-dicarboxylic acid (**1**). It has been reported briefly that the conformation of achiral benzo[c]phenanthrene is fixed to take a (P)-helicity upon complexation with γ-CDx.[3]

Yamaguchi et al.[4] synthesized **1** and isolated the (M)- and (P)-isomers by a diastereomer method using (-)-quinine. Figure



1 shows the ^{1}H NMR spectra of a mixture of (M)-**1** and (P)-**1** in D_2O at pD 7.0 in the absence and the presence of native CDxs and heptakis(2,3,6-tri-O-methyl)-β-CDx (TMe-β-CDx). Under the conditions, **1** exists as a dianion form.[5] Each signal of **1** except for H2(H11) was split into two signals and shifted to lower magnetic field upon complexation with native β-CDx. Table 1 shows the binding constants (K) determined from the ^{1}H NMR titrations. The K value of the (M)-**1**-β-CDx complex is much larger than that of the (P)-**1** complex. The $\Delta\Delta G$ value for the **1**-β-CDx system is 5.2 kJ mol^{-1} which is anomalously large value among the enantioselectivities reported for the CDx systems. In most cases, K values for complexes of native CDxs are less than 10^3 dm^3 mol^{-1}.[6] Judging from the CPK molecular model, the size of **1** is too large to be included wholly into the β-CDx cavity. It is expected that an anionic guest hardly penetrates into a hydrophobic cavity of CDx. Therefore, the unusually large K value of the (M)-**1**-β-CDx complex might be explained by two or more cooperative binding forces, but not by simple one.

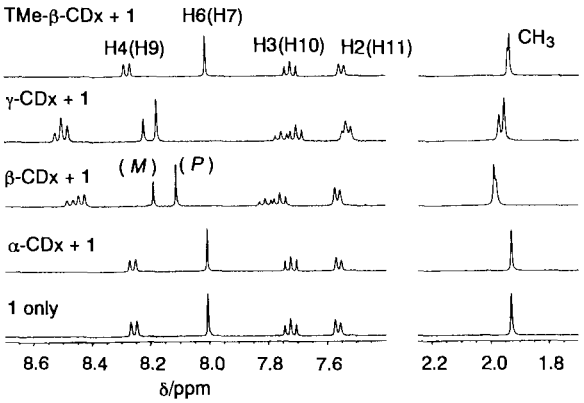


Figure 1. ^{1}H NMR spectra of a mixture of (M)-**1** and (P)-**1** (2 x 10^{-3} mol dm^{-3}) in D_2O in the absence and the presence of CDxs (0.01 mol dm^{-3}) at pD 7.0 and 25 °C. Sodium 3-(trimethylsilyl)propionate-d_4 was used as an external standard.

The signals of the protons near the CO_2^- groups of **1** (H4, H6, H7, H9) shift more remarkably than those located far from the hydrophilic groups (H2, H3, H10, H11, CH_3). This suggests that the hydrophilic part of **1** near two CO_2^- groups is located at the hydrophobic part of the host leading to extensive dehydration from **1**. The relatively large upfield shifts of the signals due to the protons at the 3- and 5-positions of β-CDx upon complexation of (M)- or (P)-**1** indicate that **1** penetrates into the host cavity from the secondary OH group side of β-CDx.[7] The ROESY spectra also support the penetration of **1** from the secondary OH group side. As shown in Figure 1, **1** does not interact with TMe-β-CDx which can act as a host for hydrophobic guests. In a previous paper, we demonstrated that TMe-β-CDx is an excellent host for discriminating between (R)- and (S)-enantiomers of the binaphthyl derivatives having an axial chirality.[8]

The pK_a values of **1** in water in the presence of β- and γ-

Table 1. Complexation of enantiomers of **1** with native CDxs.

Host	Guest	pK_a[a]	K / dm^3 mol^{-1}	$\Delta\Delta G$ / kJ mol^{-1}
β-CDx	(M)-**1**	3.1	18700±1700	
β-CDx	(P)-**1**	3.6	2200±100	5.2
γ-CDx	(M)-**1**	4.1	3100±100	
γ-CDx	(P)-**1**	4.1	690±20	3.7

[a] The pK_a values were determined spectrophotometrically for the aqueous solution of 1 x 10^{-4} mol dm^{-3} **1** in the presence of 0.01 mol dm^{-3} CDx at 25 °C.

CDxs are listed in Table 1. Stepwise dissociation of **1** could not be measured. The pK_a value of (*M*)-**1** is smaller than that of (*P*)-**1** in the presence of β-CDx. The pK_a values of both enantiomers of **1** in the presence of γ-CDx are much larger than that of the (*M*)-**1**-β-CDx system. The increase in pK_a can be explained by a microscopic environment effect which is arisen from the inclusion of **1** into the hydrophobic CDx cavity.[9] The important point is that pK_a of the (*M*)-**1**-β-CDx complex is significantly smaller than that of the (*P*)-**1** complex. Under the experimental conditions ([**1**] = 1 x 10^{-4} mol dm^{-3}, [β-CDx] = 0.01 mol dm^{-3}), most of both (*M*)- and (*P*)-**1** molecules form the complex. Therefore, the difference in the pK_a values between the (*M*)- and (*P*)-isomers of **1** should be ascribed to the difference in the structures of the complexes. All results obtained in this study can be explained by a hydrogen-bonded complex of **1** and β-CDx.[10] The smaller pK_a value of the (*M*)-**1** complex, which is much more stable than the (*P*)-**1** complex, can be understood as that (*M*)-**1** forms the stable hydrogen-bonded complex where two CO_2^- groups form two hydrogen bonds with the OH groups of β-CDx, while the formation of two hydrogen bonds is relatively more difficult in the case of (*P*)-**1** because of steric reason. The helicity of the monomethyl ester of **1** could not be recognized by β-CDx under the same conditions, suggesting the importance of two hydrogen-bonds in the present system. Similar participation of hydrogen bonding has been assumed in the complexation of bilirubin (BR) with β-CDx.[11,12] However, further careful studies need to conclude the formation of the hydrogen bonds in water.

The ^{1}H NMR spectrum shown in Figure 1 indicates that α-CDx does not interact with **1**. The size of the α-CDx cavity is too small to include **1**. The effects of γ-CDx on the ^{1}H NMR spectrum of **1** are somewhat different from those of β-CDx (Figure 1). Namely, in the case of γ-CDx system, the signal due to the H2(H11) proton, which is located far from the CO_2^- group, shifts to higher magnetic filed and the splitting of the methyl proton signal becomes remarkable. These results suggest that **1** is included into the γ-CDx cavity more deeply compared with the case of β-CDx. Less suitable fitting for forming two hydrogen bonds might cause the smaller *K* value and deep inclusion might result in the higher pK_a value of the (*M*)-**1**-γ-CDx complexes compared with the (*M*)-**1**-β-CDx complex.

The enantioselectivity can be evaluated from the $\Delta\Delta G$ value. Most $\Delta\Delta G$ values reported for enantioselective complexation with CDxs are less than 1 kJ mol^{-1}.[2] Recently, large $\Delta\Delta G$ values have been reported for the chiral recognition of binaphthyl derivatives such as anionic 1,1'-binaphthyl-2,2'-diyl phosphate (**2**) and neutral 1,1'-binaphthyl-2,2'-dicarboxylic acid (**3**) by TMe-β-CDx, the $\Delta\Delta G$ values being 3.9 and 4.5 kJ mol^{-1} for **2** and **3**, respectively.[8] The $\Delta\Delta G$ value for the **1**-β-CDx system is larger than those for binaphthyl derivatives. The recognition of the axial chirality of the binaphthyl derivatives[8] and 1,7-dioxaspiro[5,5]undecane[13] as well as the conformational enantiomerism of BR[11,12] and benzo[c]phenanthrene[3] induced by native CDxs can be regarded as the recognition of the helical structures of these guest compounds. It can be concluded, therefore, that the CDxs are the good hosts for discriminating between the (*P*)- and (*M*)-helix structures of guests. We found that (*M*)-**1** is selectively bound to noncyclic dextrins such as maltotetraose, maltoheptaose, maltohexaose, and moaltoheptaose.[14] These noncyclic oligosaccharides tend to take the (*P*)-helix structures.[15] We are speculating that CDxs have chiral twisted-structures in solution which are preferable for discriminating between (*M*)- and (*P*)-helix isomers.

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5 Although the pK_a value of **1** could not be determined accurately because of the precipitation of **1** in the CO_2H form at lower pH range, it was estimated to be below 3.

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