Chiral recognition of an anionic tetrahelicene by native cyclodextrins. Enantioselectivity dominated by location of a hydrophilic group of the guest in a cyclodextrin cavity

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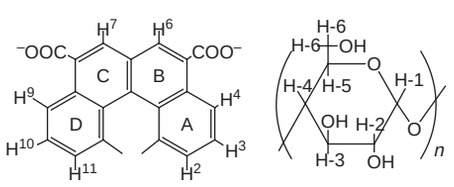
Received (in Cambridge) 3rd August 1998, Accepted 5th November 1998

Chiral recognition of 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylic acid (**1**) by native β- (β-CD) and γ-cyclodextrins (γ-CD) has been studied by means of ^{1}H NMR spectroscopy. The binding constant (*K*) for complexation of (*M*)-**1** with β-CD (18700 ± 1700 dm^3 mol^{-1}) is much larger than that for (*P*)-**1** (2200 ± 100 dm^3 mol^{-1}), $\Delta\Delta G$ being 5.2 kJ mol^{-1}. γ-CD forms less stable inclusion complexes (K = 3100 ± 100 and 690 ± 20 dm^3 mol^{-1} for (*M*)-**1** and (*P*)-**1**, respectively). The 2D ROESY spectra indicate that both CO_2^- groups of **1** are placed near the rim of the secondary OH group side of β-CD though the (*P*)-**1** molecule penetrates into the host cavity somewhat more deeply than the (*M*)-**1** molecule. The deeper penetration of the (*P*)-**1** molecule seems to be an enthalpically unfavourable but entropically favourable process because such a complexation needs dehydration from the CO_2^- group(s) of **1**. The enantioselectivity of β-CD toward **1** is dominated by the difference in the enthalpy changes due to the difference in the extent of penetration between the enantiomers of **1**. The 2D NMR spectra clearly indicate that at least one CO_2^- group of **1** is located inside of the γ-CD cavity resulting in extensive dehydration from the guest molecule. Such an endothermic process reduces the *K* value for the **1**-γ-CD complex. The difference in the structures of the complexes between the guest enantiomers might be ascribed to the chiral helix-structure of the CD taken upon complexation in water.

Since cyclodextrins (CD) are cyclic oligosaccharides composed of chiral glucopyranose units, a racemic guest yields diastereomeric isomers upon complexation with a host CD. If there is a difference in binding constants (*K*) between guest enantiomers, it is said that CD recognizes the chirality of the guest molecule. Lots of studies have been carried out with chiral recognition by CDs.[1] However, most examples show a poor ability of CDs to discriminate between the enantiomers of guests in aqueous solutions, differences in ΔG values ($\Delta\Delta G$) for complexation between guest enantiomers being mostly less than 1 kJ mol^{-1}.[2] Although molecular mechanics–molecular dynamics (MM–MD) calculations suggest the possibility of chiral recognition of α-amino acids such as tryptophan by native α-CD,[3] no data about the differences in binding constants (*K*) between the enantiomers have been reported. Improvements have been carried out by modifying native CDs. For example, protonated aminocyclodextrins are known as hosts which can recognize the central chirality of 1-phenylpropanoic acid,[4] mandelic acid and its derivatives[5] and *N*-acetylated α-amino acids[6] in their anionic forms. In these cases, however, the $\Delta\Delta G$ values for chiral recognition are still small. Metal complexes of cyclodextrins having ligand moieties show extremely large *K* values for complexation with native α-amino acids.[7] These complexes also show small $\Delta\Delta G$s. As a general conclusion, it might be said that the CDs are poor hosts for recognition of the central chirality. Meanwhile, recent studies reveal that heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMe-β-CD) shows an excellent ability to discriminate between the enantiomers of 1,1′-bi-2-naphthol, 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNP) and 1,1′-binaphthyl-2,2′-dicarboxylic acid (BNC).[8] In the case of BNC in a neutral form, the $\Delta\Delta G$ value for chiral recognition is 4.5 kJ mol^{-1}. Such a finding is epoch-making in CD chemistry because, in general, it has been assumed that CDs are trivial hosts in chiral recognition in spite of their wide use as chiral selectors in HPLC, GLC and capillary electrophoresis (CE).[9] In order to generalize the characteristic nature of CDs in chiral recognition, it is necessary to gather further examples which exhibit the high ability of CDs to discriminate between enantiomers of guests. In a previous communication,[10] we reported distinct chiral recognition by β-CD of the helicity of a chiral tetrahelicene, 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylic acid (**1**). This is the first example of the recognition of



1 CD

helicity by CD, though it has been reported briefly that the conformation of achiral benzo[*c*]phenanthrene is fixed to take (*P*)-helicity upon complexation with γ-CD.[11] The $\Delta\Delta G$ value for chiral recognition of **1** by β-CD is 5.2 kJ mol^{-1} which might be the largest in chiral recognition by CDs reported so far. The present paper is a continuation of the previous communication and reports further detailed results and the mechanism for chiral recognition.

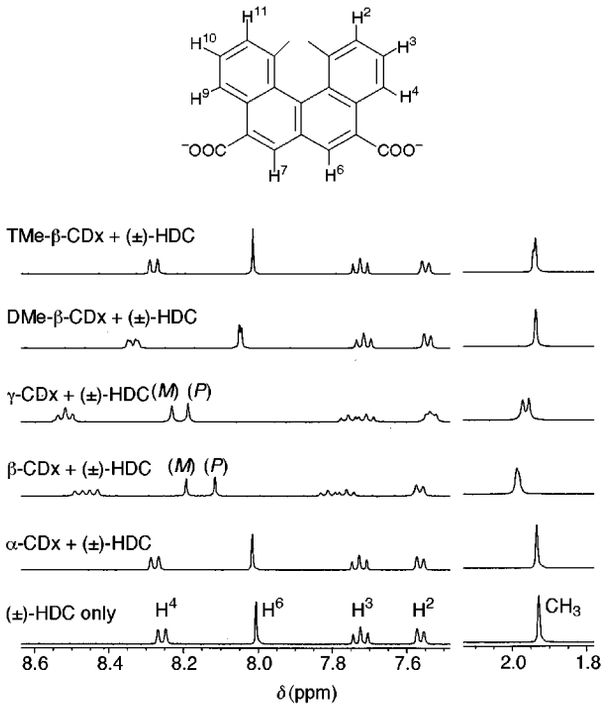


Fig. 1 ^{1}H NMR spectra of (±)-**1** (2×10^{-3} mol dm^{-3}) in D_2O at pD 7.0 and 25 °C in the absence and the presence of various CDs (1×10^{-2} mol dm^{-3}).

Results

^{1}H NMR spectra

Fig. 1 shows the ^{1}H NMR spectra of (±)-**1** in D_2O containing various CDs at pD 7.0. Under the conditions, tetrahelicene **1** exists as a dianion. The spectrum is not affected by α-CD, indicating no interaction between **1**, having a large molecular size, and α-CD with a relatively small cavity size. Upon addition of β-CD, the signal of each proton of **1**, except for $H^2(H^{11})$ and CH_3, shifts downfield and is split. Splitting of each signal is ascribed to a larger complexation-induced shift in chemical shift (CIS) of (*M*)-**1** as compared with that of (*P*)-**1**. Splitting of the signals of the $H^2(H^{11})$ and CH_3 protons, which are located at a hydrophobic part of **1**, is too small to be detected. Addition of γ-CD causes splitting of all signals due to **1**. The signals of (*M*)-**1** shift downfield more than those of (*P*)-**1**. The signals of the $H^2(H^{11})$ and CH_3 protons of **1** are also split by complexation with γ-CD. The effects of alkylated β-CDs such as heptakis(2,6-di-*O*-methyl)-β-CD (DMe-β-CD) and heptakis-(2,3,6-tri-*O*-methyl)-β-CD (TMe-β-CD) are not significant. In particular, TMe-β-CD does not interact with **1** at all. The cavity of TMe-β-CD is so hydrophobic that the hydrophilic dianion of **1** might not penetrate into such a host cavity.

Fig. 2 shows the CISs of β- and γ-CDs observed when (*M*)-**1** and (*P*)-**1** were added. All proton signals of the hosts shift upfield upon complexation because of the ring current effect of **1**. In the case of β-CD, the most remarkable upfield shift was observed with H-3 of β-CD, suggesting that **1** penetrates into the host cavity from the secondary OH group side of β-CD. The signals of H-1, H-2 and H-4, which are located at the outside of the host cavity, also shift upfield. A part of the **1** molecule might be situated outside of the cavity because the size of **1** is too large to be incorporated fully into the β-CD cavity. A characteristic of the γ-CD system is that CISs of H-5 and H-6 are larger than that of H-3. The **1** molecule seems to be incorporated into the γ-CD cavity more deeply than the case of β-CD.

A continuous variation method was applied to determine the stoichiometry of the inclusion complexes of **1** and CDs. The 1:1 complex of each enantiomer of **1** and β- or γ-CD was

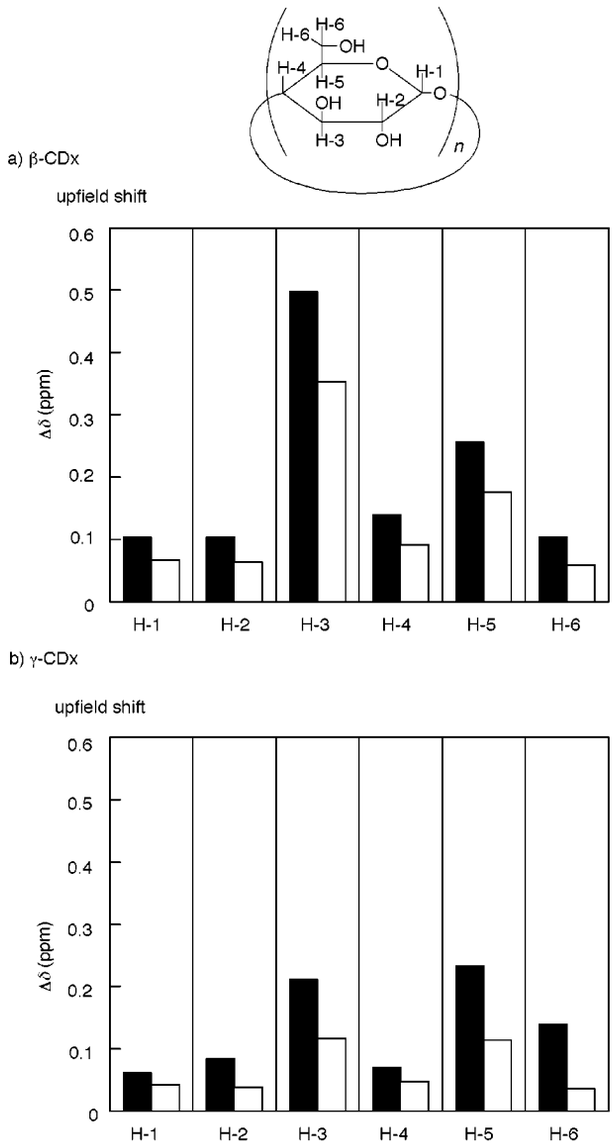


Fig. 2 Changes in the ^{1}H NMR chemical shifts of a) β-CD and b) γ-CD (5×10^{-4} mol dm^{-3}) in D_2O at pD 7.0 and 25 °C upon addition of (*M*)- and (*P*)-enantiomers of **1** (1×10^{-3} mol dm^{-3}), (■) (*M*)-**1**, (□) (*P*)-**1**.

suggested from the Job's plot for the changes in the chemical shifts of $H^4(H^9)$ and $H^6(H^7)$ (the data are not shown herein).

Binding constants and thermodynamic parameters

The binding constants (*K*) were determined from the ^{1}H NMR titration curves which were analyzed by a non-linear least-squares method.[12] The results are listed in Table 1. The *K* value for the (*M*)-**1**-β-CD complex is 18700 dm^3 mol^{-1} which is an anomalously large *K* for complexation of a dianionic guest with native β-CD. Meanwhile, the *K* value for the (*P*)-**1**-β-CD complex is relatively small (2200 dm^3 mol^{-1}), but still large for a guest with two negative charges. The difference in free energy changes for complexation between the (*M*)- and (*P*)-enantiomers ($\Delta\Delta G$), a measure of enantioselectivity, is 5.2 kJ mol^{-1} which might be the largest enantioselectivity in chiral recognition by CDs so far reported. From the viewpoint of size-fitting, γ-CD seems to bind **1** more strongly than β-CD. However, the *K* value of the γ-CD complex is much smaller than that of the β-CD complex against the same enantiomer of **1**. Still, γ-CD also shows a considerably high enantioselectivity ($\Delta\Delta G = 3.7$ kJ mol^{-1}).

Table 2 summarizes the temperature dependence of *K* and

Table 1 Binding constants K and enantioselectivities $\Delta\Delta G$ for complexation of **1** with β- and γ-CDs in D_2O at pD 7.0 and 25 °C and pK_a values of **1** in the presence of CDs at 25 °C[a]

Host	Guest	K/dm^3 mol^{-1}	$\Delta\Delta G$/kJ mol^{-1}	pK_a
β-CD	(*M*)-**1**	18700 ± 1700		3.1
β-CD	(*P*)-**1**	2200 ± 100	5.2	3.4
γ-CD	(*M*)-**1**	3100 ± 100		4.1
γ-CD	(*P*)-**1**	690 ± 20	3.7	4.1

[a] The K values were determined from the NMR titration curves measured for 1×10^{-3} mol dm^{-3} of **1** in D_2O. The pK_a values of **1** (1×10^{-5} mol dm^{-3}) in water containing CDs (1×10^{-2} mol dm^{-3}) were determined from the changes in the optical densities of **1** at 298.4 nm as a function of pH. In this case, the phosphate buffer (3.3×10^{-2} mol dm^{-3}) was mostly used to adjust pH.

Table 2 Binding constants K for complexation of the enantiomers of **1** with β- and γ-CDs as a function of temperature and thermodynamic parameters for complexation

System	T/K	K/dm^3 mol^{-1}	ΔH/kJ mol^{-1}	ΔS/J mol^{-1} K^{-1}
(*M*)-**1**-β-CD	288.15	37100	−51.1 ± 0.8	−90.1 ± 3.6
	298.15	18700		
	308.15	9750		
	318.15	4920		
(*P*)-**1**-β-CD	288.15	3720	−35.1 ± 1.1	−53.2 ± 2.7
	298.15	2200		
	308.15	1400		
	318.15	940		
(*M*)-**1**-γ-CD	288.15	4590	−30.2 ± 1.4	−34.4 ± 4.7
	298.15	3244		
	308.15	2037		
	318.15	1431		
(*P*)-**1**-γ-CD	288.15	818	−16.0 ± 0.3	0.45 ± 0.76
	298.15	678		
	308.15	543		
	318.15	438		

the thermodynamic parameters for complexation determined from the van't Hoff plots. Regardless of which enantiomer is used, the complexation of **1** with β-CD is enthalpically favourable and entropically unfavourable. As compared with the case of (*M*)-**1**, the complexation of (*P*)-**1** with β-CD is entropically more favourable but enthalpically less favourable. The smaller K values for the **1**-γ-CD system are ascribed to the larger ΔH values compared with the **1**-β-CD system. It is noteworthy that the complex formation of γ-CD shows a relatively large ΔS. In particular, a positive but small ΔS was obtained for the (*P*)-**1**-γ-CD system.

pK_a of 1

Measurement of pK_a of a guest carboxylic acid in the presence of CD is one of the methods which can be used to locate the position of the CO_2^- group of the guest. If the CO_2^- group is located inside of a CD cavity, the pK_a of the guest should be raised. The apparent pK_a values of (*M*)-**1** and (*P*)-**1** in water in the presence of β- and γ-CDs are shown in Table 1. Although the precipitation of **1** in the CO_2H form at lower pH prevented the determination of the precise pK_a of **1** in water, it was roughly estimated to be around 3.

In the presence of β-CD, the apparent pK_a values of the (*M*)- and (*P*)-enantiomers of **1** are 3.1 and 3.4, respectively. Successive acid–base equilibria of **1** due to two CO_2H groups of **1** could not be measured from the titration curves. The pK_a value of (*M*)-**1** indicates that the CO_2^- groups of the guest are located outside of the β-CD cavity while slightly deeper penetration is suggested with (*P*)-**1**.

Complexation with γ-CD causes a remarkable increase in the pK_a values of both enantiomers of **1**. ΔpK_a is around 1.0,

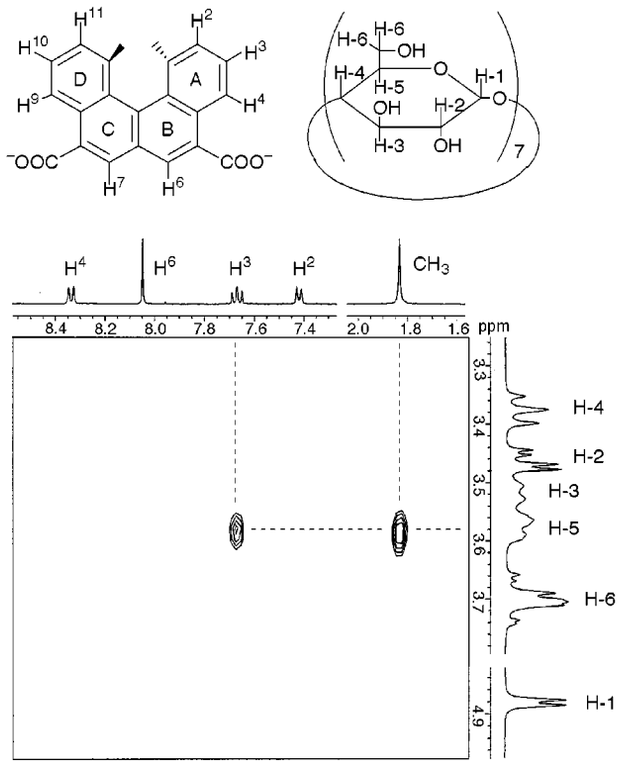


Fig. 3 ROESY spectrum of the β-CD-(*M*)-**1** system in D_2O at pD 7.0 and 25 °C. The spectrum was measured for the solution of a mixture of β-CD (5×10^{-3} mol dm^{-3}) and (*M*)-**1** (3×10^{-3} mol dm^{-3}) in N_2-saturated D_2O. The mixing time for the ROESY measurement was 250 ms.

indicating that at least one CO_2^- group of **1** is located on the inside of the γ-CD cavity.

Structures of complexes—ROESY spectra

Figs. 3 and 4 are the 2D ROESY spectra of the (*M*)-**1**- and (*P*)-**1**-β-CD systems in D_2O. The ROESY spectrum of the (*M*)-**1**-β-CD system (Fig. 3) shows correlations between the H-5 protons of the host and the CH_3 and H^3 protons of the guest. Such correlations clearly indicate that a hydrophobic part of the (*M*)-**1** molecule is located inside of the CD cavity. Since a Corey–Pauling–Koltun (CPK) molecular model does not allow simultaneous penetration of both rings A and D of **1**, ring A seems to penetrate into the CD cavity resulting in the protrusion of ring D.

The ROESY spectrum of the (*P*)-**1**-β-CD system is more complicated. The cross peaks between the H-6 protons of the host and the CH_3, H^2 and H^3 protons of the guest indicate a deeper penetration of ring A of (*P*)-**1** into the β-CD cavity. The cross peaks between the H-3 protons of the host and the CH_3, H^2(H^{11}) and H^4(H^8) protons of the guest were measured. If these correlating protons of the guest belong to ring D, it can be concluded that ring D of (*P*)-**1** is located at the rim of the secondary OH group side and the mobility of this enantiomer in the complex is restricted more seriously than that of (*M*)-**1**. The results of the 2D NMR spectroscopy are in good agreement with those of the pK_a measurements. The slightly larger pK_a value of (*P*)-**1** in the presence of β-CD can be interpreted in terms of the somewhat deeper penetration of ring A of (*P*)-**1** compared with the case of the (*M*)-**1**-β-CD system.

The ROESY spectra of the (*M*)-**1**- and (*P*)-**1**-γ-CD systems are shown in Figs. 5 and 6, respectively. It is noteworthy that the H^6(H^7) protons of both enantiomers of **1** interact with the H-5 protons of γ-CD. Such a result clearly indicates the deeper penetration of **1** to place the CO_2^- group(s) in the hydrophobic γ-CD cavity. The correlations between the CH_3, H^2(H^{11}) and

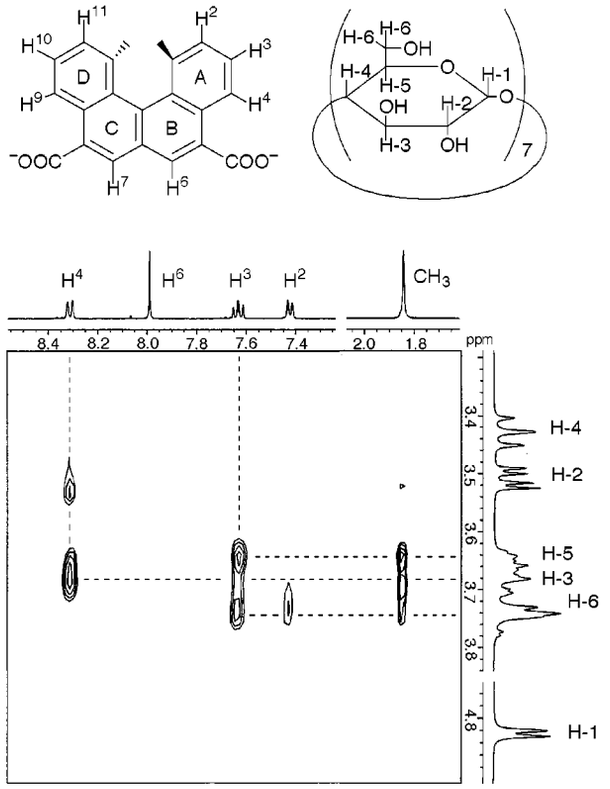


Fig. 4 ROESY spectrum of the β-CD-(*P*)-**1** system. The conditions of the measurement are the same as those of the (*M*)-**1** system.

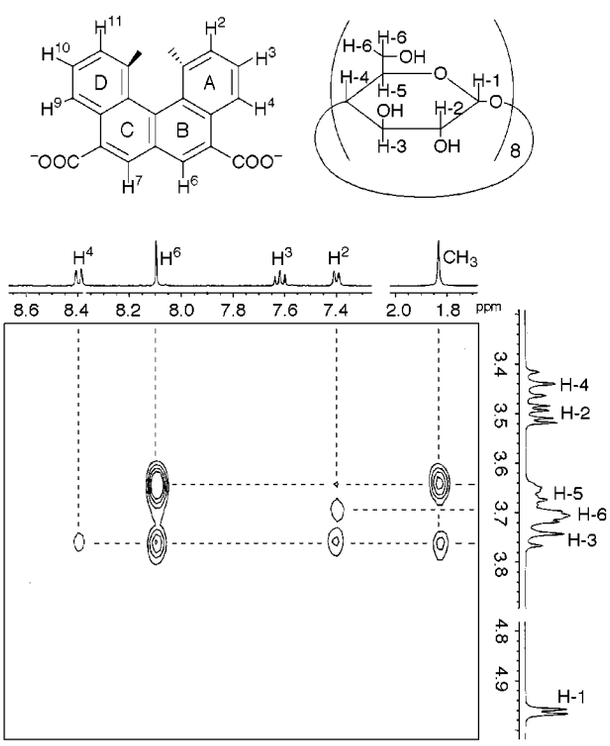


Fig. 5 ROESY spectrum of the γ-CD-(*M*)-**1** system in D_2O at pD 7.0 and 25 °C. The spectrum was measured for the solution of a mixture of γ-CD (1.5×10^{-2} mol dm^{-3}) and (*M*)-**1** (3×10^{-3} mol dm^{-3}) in N_2-saturated D_2O. The mixing time for the ROESY measurement was 250 ms.

$H^6(H^7)$ protons of the guest and the H-6 protons of the host are observed in the (*P*)-**1**-γ-CD system while such correlations are negligible in the (*M*)-**1**-γ-CD system. Stronger correlation with the H-6 protons in the (*P*)-**1** complex might be explained by the deeper penetration of this guest.

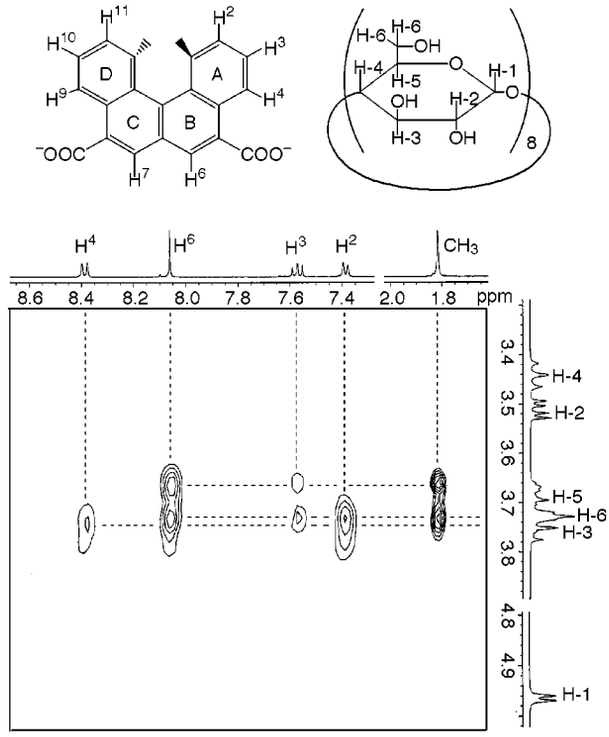


Fig. 6 ROESY spectrum of the γ-CD-(*P*)-**1** system. The conditions of the measurement are the same as those of the (*M*)-**1** system.

Discussion

The present study reveals the excellent ability of native CDs such as β- and γ-CDs to discriminate between (*M*)- and (*P*)-enantiomers of tetrahelicene dicarboxylate **1**. The high ability of TMe-β-CD to recognize the axial chirality of the binaphthyl derivatives has already been reported.[8] The chiral recognition of 1,7-dioxaspiro[5.5]undecane by TMe-β-CD,[13] the conformational enantiomerism of bilirubin induced by native CDs[14] and cationic CD,[15] γ-CD-induced conformational enantiomerism of pamoic acid[16] and the formation of an optically active pyrene-dimer in the γ-CD cavity[17] are also regarded as recognition of the chiral twisted-structures of the guest molecules. These results strongly suggest that the CDs are good hosts for recognizing chiral twisted-structures of some guests, though they are poor hosts for guests with central chirality.

In the case of the chiral recognition of the binaphthyl derivatives such as BNP and BNC by TMe-β-CD, the complexation of a preferred guest [(*S*)-BNP or (*R*)-BNC] is a process accompanied by a negative enthalpy change (Δ*H*) and a positive entropy change (Δ*S*) while the complexation of another enantiomer [(*R*)-BNP or (*S*)-BNC] is an entropically unfavourable process.[8c] The positive entropy change in complexation of (*S*)-BNP in an anionic form has been ascribed to dehydration from the guest as well as the host upon complexation. The BNP monoanion penetrates into the CD cavity from the secondary OCH_3 group side of TMe-β-CD to place the hydrophilic anion group (cyclic phosphate) on the inside of the hydrophobic CD cavity. Such a process is accompanied by dehydration from the phosphate anion group of BNP yielding the entropic gain. On the other hand, the phosphate anion group of (*R*)-BNP is located outside of the CD cavity. In this case, van der Waals interaction is the main driving force for complexation showing negative Δ*H* and negative Δ*S*. Similar entropic gain accompanied by extensive dehydration has been found in the complexation of *p*-methylbenzoate anion by protonated heptakis(6-amino-6-deoxy)-β-CD as well as native β-CD.[18] The thermodynamic parameters are very important for discussing mechanisms for chiral recognition by CDs as well as for formation of inclusion complexes.[19]

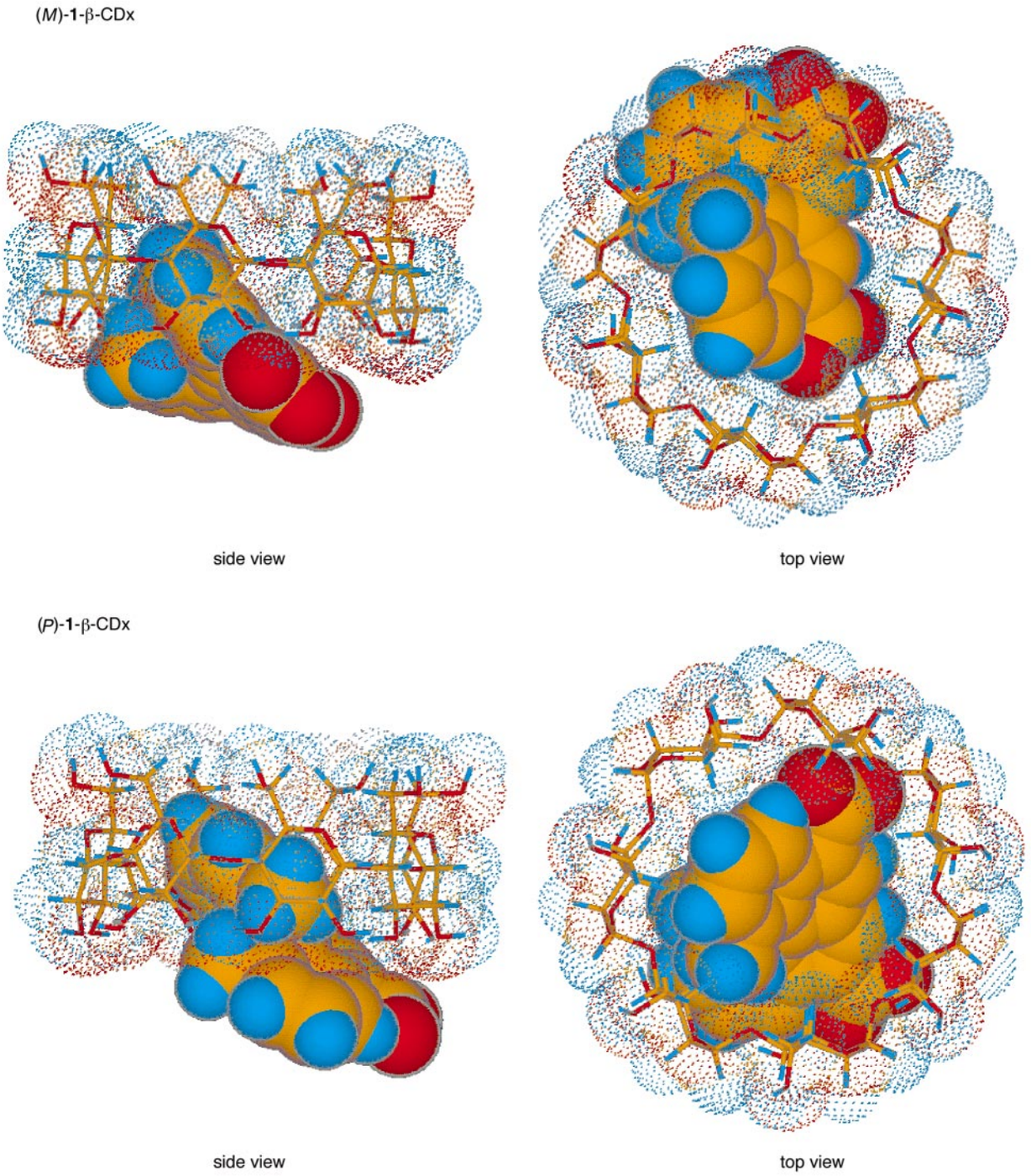


Fig. 7 Structures of the β-CD-(*M*)- and (*P*)-**1** complexes proposed from the ROESY spectra.

The thermodynamic behaviour in the complexation of **1** by β-CD apparently differs from that reported for the BNP and *p*-methylbenzoate anions. In spite of two CO_2^- groups of **1**, the complex formation of both enantiomers of **1** shows the negative and large entropy changes. Such a result strongly suggests that the CO_2^- groups of **1** bound to β-CD are located outside of the CD cavity. The results of the ^{1}H NMR spectroscopy as well as those of the pK_a measurements indicate the structures of the **1**-β-CD complexes in which two CO_2^- groups of **1** are placed outside of the CD cavity (Fig. 7). The enantioselectivity of β-CD toward **1** is controlled by the difference in the enthalpy changes. The complexation of (*P*)-**1**, the undesirable guest, is entropically more favourable but enthalpically less favourable than the complexation of (*M*)-**1**. Such a difference in the thermodynamic parameters might be interpreted in terms of the difference in the location of the CO_2^- groups of **1** in the inclusion complexes. As the ROESY spectra suggest, the (*P*)-**1** molecule penetrates into the CD cavity somewhat more deeply than (*M*)-**1** resulting in a partial penetration of the CO_2^- group of **1** into the β-CD cavity (Fig. 7). The partial penetration of the CO_2^- group needs dehydration from the (*P*)-**1** molecule to some extent. Such a process is enthalpically unfavourable but entropically favourable. In the case of (*M*)-**1**, two CO_2^- groups of **1** are distinctively located outside of the β-CD cavity. Therefore, the complexation of (*M*)-**1** does not need extensive dehydration from the guest.

The relatively small *K* values for the γ-CD complexes can also be explained in the same manner. The 2D NMR spectra clearly indicate the deep penetration of the molecule of **1** into the γ-CD cavity. At least one CO_2^- group of **1** is located inside of the γ-CD cavity. Such an inclusion requires the release of lots of water molecules from dianionic **1** yielding the enthalpic loss

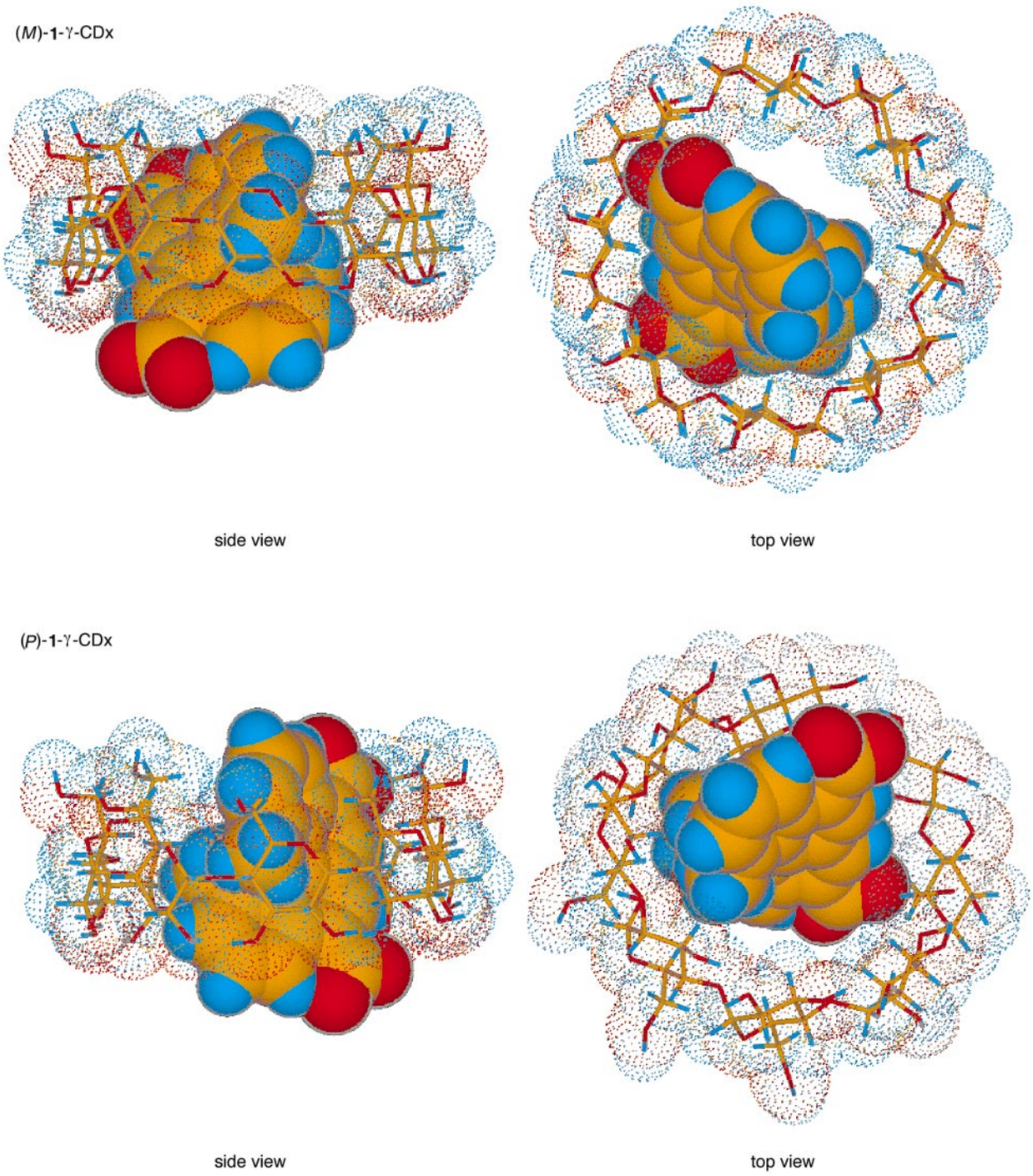


Fig. 8 Structures of the γ-CD-(*M*)- and (*P*)-**1** complexes proposed from the ROESY spectra.

and the entropic gain. Indeed, both ΔH and ΔS values for the γ-CD complexes are larger than those for the β-CD complexes, supporting more extensive dehydration from the guest. In particular, a small but positive ΔS value was obtained in the case of (*P*)-**1**. Such a positive ΔS value can be explained by the deep penetration of (*P*)-**1** which causes extensive dehydration from the CO_2^- group(s) of the guest. The ROESY spectra show that (*P*)-**1** penetrates into the γ-CD cavity more deeply than (*M*)-**1**. Thus, the results of the 2D NMR spectroscopy are in good agreement with those of the thermodynamic parameters. As a consequence, it might be concluded that the enantioselectivity of native β- or γ-CD toward **1** is dominated by the difference in the location of the hydrophilic CO_2^- group of **1** between the guest enantiomers. Penetration of the anionic group of a guest into a hydrophobic CD cavity has been interpreted in terms of an ion–dipole interaction between host and guest.[20]

The next problem is the reason why the location of a hydrophilic group of an enantiomer differs from that of another enantiomer. This question might be answered by assuming a chiral twisted-structure of CD complexed with a guest in water. It is known that noncyclic dextrin takes a right-handed helix structure.[21] One turn of the helix is composed of six or seven glucopyranose units. The cyclic structure of native CD is stabilized by intramolecular hydrogen bonding between the secondary OH groups of adjacent glucopyranoses.[22] In water, however, the hydration of the secondary OH groups of CD weakens intramolecular hydrogen bonding. Therefore, it might be reasonable to assume that the structure of native CD as well as permethylated CD tends to take a right-handed helix structure when it complexes with a guest. Such a chiral helical structure of a host should be suitable for recognizing axial chirality or helicity of a guest.

At present, we cannot explain the reason(s) for the abnormally large K values of the native CD complexes of dianionic **1** and the extremely weak interaction between **1** and TMe-β-CD.†

Experimental

α-, β- and TMe-β-CDs (Nacalai) were purchased and washed with THF using a Soxhlet extractor. γ-CD (Nacalai) was used as received. TMe-α-CD was prepared and purified in our laboratory using an ordinary method.[23] The purity of TMe-α- and -β-CDs were found by ^{1}H NMR to be satisfactory. Racemic tetrahelicene dicarboxylic acid **1** was prepared and its enantiomers were resolved by a diastereomer-method using quinine.[24] The ^{1}H NMR spectra were taken on a JEOL JNM-A400 (400 MHz) spectrometer in D_2O (CEA, 99.8%) using 3-trimethylsilyl[2,2,3,3-$^2H_4$]propionate (TSP, Aldrich) as an external standard. ROESY spectra were recorded with a spectral width of 3358 Hz. The 90° pulse was 33.3 μs, mixing time was 250 ms, delay time was 2.0 s and 512 × 512 data points were recorded. The pD values were adjusted by using Na_2CO_3 and DCl. The MM–MD calculations involving the effects of solvent were carried out as previously reported.[25]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas, 'New Polymers and Their Nano-Organised Systems' (No. 277/09232258), a Grant-in-Aid for Scientific Research B (10440211) and a subsidy to RCAST of Doshisha University from the Ministry of Education, Science, Sports and Culture, Japan.

† The possibility of hydrogen-bond formation between the CO_2^- groups of **1** and the OH groups of β-CD could be studied to explain the large K values. The cavity of TMe-β-CD might be too hydrophobic to include anionic **1**.

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