Mechanism for chiral recognition of binaphthyl derivatives by cyclodextrins

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The mechanism for chiral recognition of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNP) and 1,1′-binaphthyl-2,2′-dicarboxylic acid (BNC) by β-cyclodextrin (β-CDx) and heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx) has been investigated by ^{1}H NMR spectroscopy, thermodynamic parameters for complexation and molecular mechanics–molecular dynamics (MM–MD) calculations. TMe-β-CDx recognizes axial chiralities of the BNP anion and undissociated BNC, (*S*)-BNP and (*R*)-BNC being the preferable guest enantiomers. The ability of β-CDx to recognize the axial chiralities is inferior to that of TMe-β-CDx. ^{1}H NMR spectra suggest that (*S*)-BNP is shallowly bound to the wider side of the TMe-β-CDx cavity where a hydrophilic phosphate group is located inside the hydrophobic CDx cavity. Meanwhile, (*R*)-BNP seems to form the complex of TMe-β-CDx where the C_2 symmetry axis of (*R*)-BNP is perpendicular to the C_7 symmetry axis of TMe-β-CDx. The complexation of the preferable enantiomer of the guest with TMe-β-CDx is entropically favourable while that of the undesirable enantiomer of the guest is entropically unfavourable. The MM–MD calculations suggest that the orientation of the preferable guest is determined by the dipole–dipole interactions between the host and the guest. Similar orientation in the cases of the undesirable enantiomers may be prevented by steric factors. The positive entropy changes in the complexation of (*S*)-BNP and (*R*)-BNC seem to be ascribed to the extended dehydration from both the hydrophilic groups of the guest and the ethereal oxygen atoms of the wider side of the TMe-β-CDx cavity upon inclusion.

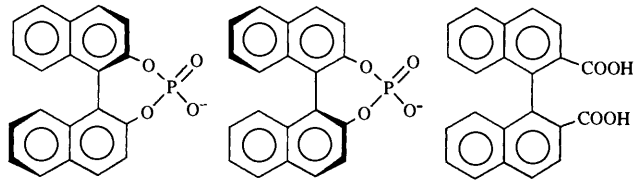
The ability of β-cyclodextrin (β-CDx) to discriminate between (*R*)- and (*S*)-enantiomers of guest molecules was reported for the first time by Cramer and Dietsche.[1] After their study on mandelic acid derivatives, partial optical resolution using α- and β-CDxs has been used to examine several racemates.[2] Fairly good resolution was achieved in the chiral phosphinate[3] and sulfinyl compound–β-CDx systems.[4] In most cases, however, the optical resolution by CDxs is not satisfactory compared with ordinary optical resolution using diastereoisomer formation.[2] More recently, CDx-mediated enantioselective reactions and chiral discrimination by CDxs in solutions have been studied widely.[5] However, detailed studies on the mechanisms for chiral recognition by CDxs have scarcely been carried out so far. Mikołajczyk and Drabowicz[4b] have demonstrated the 'three-point attachment model'[6] as a plausible mechanism for the chiral recognition of the sulfinyl compounds by β-CDx. Although this theory has been applied to chromatographic separation of enantiomers using host–guest chemistry,[7] no experimental evidence has been obtained in solutions to verify this mechanism. Recently, we reported the mechanism for the conformational enantiomerism of (4*Z*,15*Z*)-bilirubin IXα (BR) induced by β-CDx,[8] where hydrogen bonding between the CO_2^- groups of BR and the secondary OH groups of β-CDx promotes the conformational enantiomerism.[8b] Two hydrogen bonds and steric repulsion may participate in this system. Such a mode for chiral recognition is classified as the 'three-point binding mechanism'. A 'lock and key' mechanism presented by Fischer[9] in 1894 is also applicable for chiral recognition by CDxs.[10] We found the formation of a chiral pyrene excimer in the γ-CDx cavity.[11] Since there is no site of point interaction in this host–guest system, the lock and key principle interprets the formation of the pyrene dimer having (*M*)-helicity in the γ-CDx cavity. The mechanism for the conformational enantiomerism of dinaphthylmethane derivatives can also be understood by the lock and key concept.[12]

In the previous papers,[13] we demonstrated that permethylated β-CDx, heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx), well recognizes axial chiralities of binaphthyl derivatives such as 1,1′-bi-(2-naphthol), 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNP) and 1,1′-dihydroxy-2,2′-binaphthyl-3,3′-dicarboxylic acid. The present paper deals with the detailed mechanism for the chiral recognition of BNP and 1,1′-binaphthyl-2,2′-dicarboxylic acid (BNC) by TMe-β-CDx.

Table 1 Binding constants (K) for complexation of the enantiomers of BNP and BNC with β-CDx, DMe-β-CDx and TMe-β-CDx at 25 °C[a]

	K/dm^3 mol^{-1}		
	β-CDx	DMe-β-CDx	TMe-β-CDx
(*R*)-BNP	263 ± 24	207 ± 18	81 ± 3
(*S*)-BNP	346 ± 30	210 ± 16	398 ± 34
(*R*)-BNC	28	675 ± 18	691 ± 42
(*S*)-BNC	*ca.* 0	583 ± 28	114 ± 4

[a] The K values for the BNP and BNC complexes were determined in 0.067 mol dm^{-3} phosphate buffer at pH 5.5 and 0.20 mol dm^{-3} KCl–HCl buffer at pH 2.0, respectively.

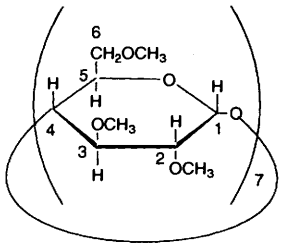


(*R*)-BNP (*S*)-BNP BNC

Results and discussion

Binding constants

Table 1 shows the binding constants (K) for complexation of dissociated BNP and undissociated BNC with β-CDx, heptakis(2,6-di-*O*-methyl)-β-CDx (DMe-β-CDx) and TMe-β-



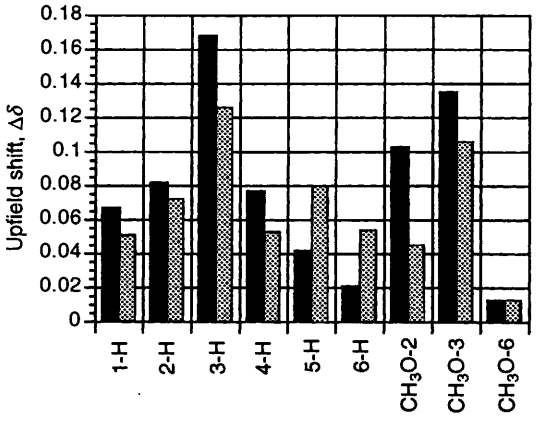
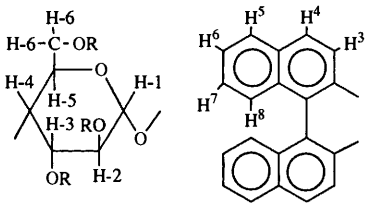


Fig. 1 Changes in the ^{1}H NMR chemical shifts of TMe-β-CDx (0.01 mol dm^{-3}) in D_2O upon addition of (*R*)- (■) and (*S*)-BNPs (▨). The concentration of BNP was 2 × 10^{-3} mol dm^{-3}

CDx in the buffer solutions at 25 °C. The BNC dianion scarcely interacts with CDxs. The *K* values were determined in the 0.067 mol dm^{-3} phosphate buffer at pH 5.5 for BNP and in the 0.20 mol dm^{-3} KCl–HCl buffer at pH 2.0 for BNC using the Benesi–Hildebrand equation[14] for the change in the absorption spectrum of the guest upon addition of the host. A good linear relationship between ΔOD^{-1} and $[CDx]^{-1}$ suggests the formation of a 1:1 complex in each system, ΔOD being the change in optical density of the guest upon addition of the host. In the case of BNP, the *K* value for (*S*)-BNP is larger than that for (*R*)-BNP in each CDx solution. As reported previously,[13] TMe-β-CDx is the best CDx to recognize the axial chirality of BNP amongst the three kinds of CDxs examined. On the contrary, each CDx prefers the (*R*)-enantiomer of undissociated BNC. The best CDx for BNC is also TMe-β-CDx.

NMR spectroscopy

The chemical shifts (δ) of the protons of TMe-β-CDx in D_2O (internal standard: HDO at δ 4.650) are 5.154, 3.203, 3.531, 3.616, 3.716, 3.716, 3.377, 3.468 and 3.211 ppm for the 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, CH_3O-2, CH_3O-3 and CH_3O-6



protons, respectively. The changes in the chemical shifts of the protons of TMe-β-CDx upon addition of (*S*)- and (*R*)-BNPs are shown in Fig. 1. The ^{1}H NMR titrations indicate that the TMe-β-CDx complex does not aggregate in D_2O until, at least, 2 × 10^{-3} mol dm^{-3} of (*R*)- or (*S*)-BNP has been added. All proton signals of the CDx shift to higher magnetic fields owing to a ring-current effect of the naphthalene moiety of BNP. The marked upfield shifts of the signals due to the 3-H, CH_3O-2 and CH_3O-3 protons clearly indicate that the BNP molecule is bound mainly to the wider side of the TMe-β-CDx cavity. The shift in δ for CH_3O-2 suggests that another naphthalene moiety

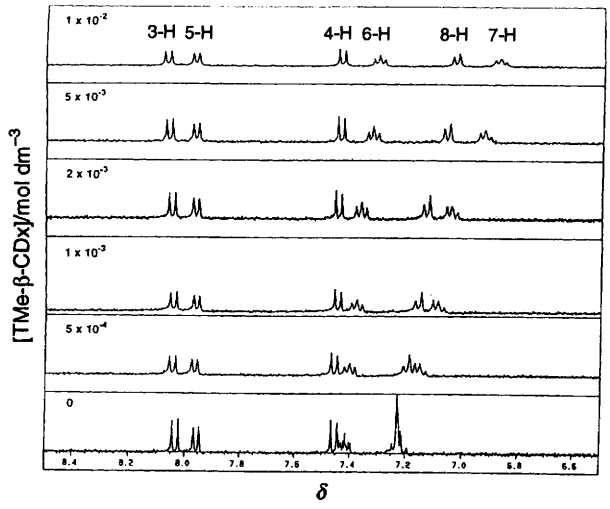
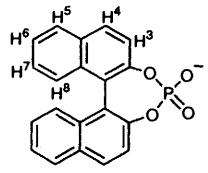


Fig. 2 ^{1}H NMR spectra of (*R*)-BNP (1 × 10^{-3} mol dm^{-3}) in D_2O in the absence and the prescence of various amounts of TMe-β-CDx



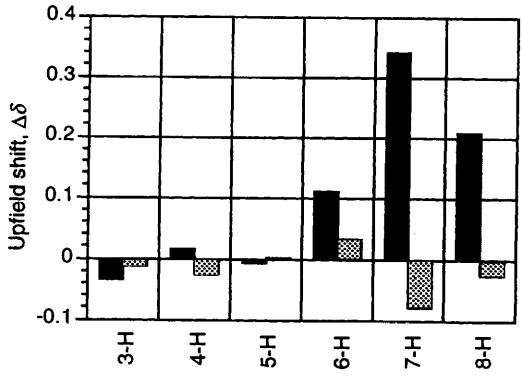
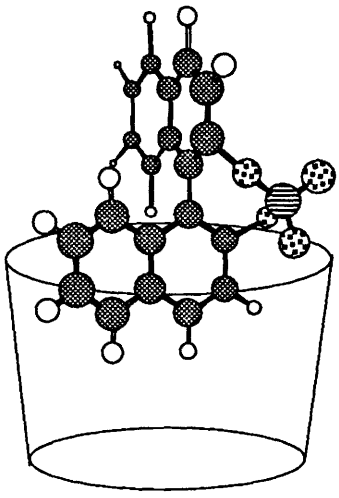


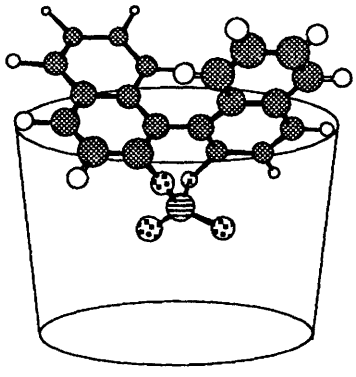
Fig. 3 Changes in the ^{1}H NMR chemical shifts of (*R*)- (■) and (*S*)-BNPs (▨) in D_2O upon addition of TMe-β-CDx (0.01 mol dm^{-3}). The concentration of BNP was 1 × 10^{-3} mol dm^{-3}.

is located outside the cavity to cover the wider side of the CDx toroid. Except for the 5-H and 6-H protons, each proton signal of the CDx in the (*R*)-enantiomer complex having the smaller *K* value appears at a higher magnetic field compared with that in the (*S*)-enantiomer complex having a larger *K* value. This suggests that a naphthalene moiety of (*R*)-BNP penetrates more deeply into the TMe-β-CDx cavity than that of (*S*)-BNP. The relatively large shifts of the 5-H and 6-H proton signals upon addition of (*S*)-BNP may indicate that (*S*)-BNP is also bound to the narrower side of the CDx cavity. A small shift in δ for the CH_3O-6 protons may suggest that the two hydrogen atoms of each CH_2 linkage at the 6-position of TMe-β-CDx are directed to the inside of the CDx cavity. Such a situation necessarily places the CH_3O-6 group at an outer position of the rim of the CDx cavity.

Fig. 2 shows the ^{1}H NMR spectra of (*R*)-BNP in the absence and the presence of various amounts of TMe-β-CDx. The marked upfield shifts of the 6-H, 7-H and 8-H proton signals and the slight downfield shifts of the 3-H and 4-H proton signals of (*R*)-BNP were observed when TMe-β-CDx was added (Fig. 3). The downfield shift of the proton signal of a guest molecule is mainly ascribed to a van der Waals deshielding effect and is observed commonly.[15] Although upfield shifts



(*R*)-BNP-TMe-β-CDx



(*S*)-BNP-TMe-β-CDx

Fig. 4 Hypothetical structures of the (*R*)- and (*S*)-BNP–TMe-β-CDx complexes deduced from the ^{1}H NMR data

of the guest signals are also observed in some inclusion phenomena,[16] no reasonable explanation has been presented. One possibility is a sort of an electric-field effect caused by the ethereal oxygen atoms in TMe-β-CDx having a large electronegativity. The ethereal oxygen atoms may alter the electron density of a naphthalene ring located near the ethereal oxygen atoms. When such an effect causes an increase in the electron density around a proton attached to a naphthalene moiety, the signal of the proton should shift to a higher magnetic field. If the electric-field effect is applicable to the present system, the 6-H, 7-H and 8-H protons of (*R*)-BNP seem to be located in the vicinity of the rim of the wider side of the TMe-β-CDx cavity. Then we assumed a hypothetical structure of the (*R*)-BNP–TMe-β-CDx complex as shown in Fig. 4. A C_2 symmetry axis of (*R*)-BNP is almost perpendicular to the C_7 symmetry axis of TMe-β-CDx. The 6-H and 7-H protons of the naphthalene moiety and the 8-H proton of another naphthalene moiety are located in the vicinity of the ethereal oxygen atoms of the wider side of the TMe-β-CDx cavity. As demonstrated in Fig. 3, the NMR data of (*S*)-BNP are quite different from those of (*R*)-BNP. Only the 5-H and 6-H protons of (*S*)-BNP show very small upfield shifts and other proton signals shift slightly to lower magnetic fields when TMe-β-CDx is added. The small downfield shifts of the proton signals due to 7-H and 8-H may be ascribed to the binding of this guest to the narrower side of the CDx cavity. A hypothetical structure of the (*S*)-BNP–TMe-β-CDx complex is also shown in Fig. 4. A very shallow inclusion complex is assumed. This model explains well the slight upfield shifts of the 3-H and 4-H protons of (*S*)-BNP. The

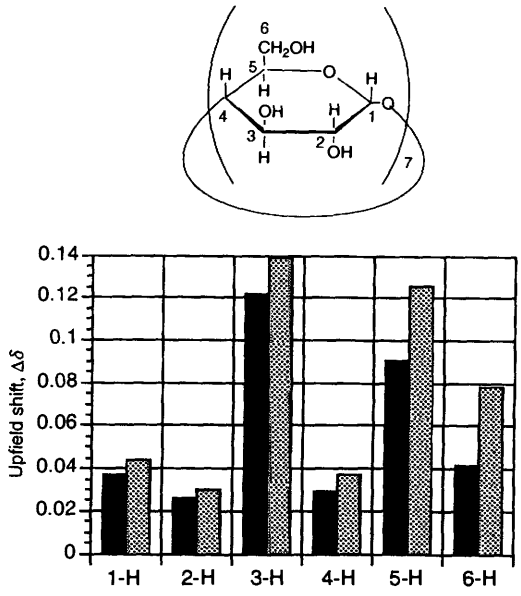


Fig. 5 Changes in the ^{1}H NMR chemical shifts of β-CDx (0.01 mol dm^{-3}) in D_2O upon addition of (*R*)- (■) and (*S*)-BNPs (▨). The concentration of BNP was 2×10^{-3} mol dm^{-3}.

compensation of the deshielding and shielding effects induced by the van der Waals and electric-field effects seems to cause the small shifts of these proton signals.

In order to obtain more information about the structures of the inclusion complexes of BNP, the ^{1}H–^{1}H NOESY spectra were measured. In the case of the (*R*)-BNP–TMe-β-CDx complex, the cross peaks were recorded between the 3-H, 4-H, 5-H and 8-H protons of (*R*)-BNP and both the CH_3 protons at the 2- and 3-positions of TMe-β-CDx. No other correlation was observed. The NOESY data clearly indicate that the main binding site is the wider side of the TMe-β-CDx cavity and the 3-H, 4-H, 5-H and 8-H protons of (*R*)-BNP are located near the larger rim of the CDx toroid. Although the correlation was observed between the 3-H, 4-H and 8-H protons of (*S*)-BNP and the CH_3 protons at the 2- and 3-positions of TMe-β-CDx, no cross peak was detected for the 5-H proton. The absence of the correlation between the 5-H of the guest and the CH_3 protons of the host suggests the formation of the shallow inclusion complex where the hydrophilic phosphate group penetrates into the CDx cavity and most of the hydrophobic naphthalene moieties exist outside the cavity.

The 161.7 MHz ^{31}P NMR spectra were measured for both the (*R*)- and (*S*)-BNP complexes. The δ value of (±)-BNP (1×10^{-4} mol dm^{-3}) in D_2O is 54.008 ppm (external standard: trimethyl phosphate). In the presence of 0.01 mol dm^{-3} of TMe-β-CDx, the signal shifts to 54.134 ppm for (*R*)-BNP and 54.171 ppm for (*S*)-BNP. Although $\Delta\delta$ for (*S*)-BNP is slightly larger than that for (*R*)-BNP, the difference in the $\Delta\delta$ values between the (*R*)- and (*S*)-enantiomers is too small to discuss the difference in the structures of the inclusion complexes.

Fig. 5 shows the changes in the ^{1}H NMR chemical shifts of β-CDx in D_2O upon addition of (*R*)- and (*S*)-BNPs. The signals due to the 3-H, 5-H and 6-H protons of β-CDx shift to higher magnetic fields upon addition of BNP. This clearly indicates that both the primary and secondary OH group sides of the β-CDx cavity are the binding sites for both the enantiomers. The $\Delta\delta$ values for (*S*)-BNP, which is the preferable guest, are larger than those for (*R*)-BNP. The shifts of the proton signals due to each BNP enantiomer upon addition of β-CDx are shown in Fig. 6. Since both the primary and secondary OH group sides of β-CDx are the binding sites for BNP, estimation of the structures of the complexes from the data shown in Figs. 5 and 6 should be almost meaningless. In any event, it is clear that there is no marked difference between the BNP enantiomers in the ^{1}H

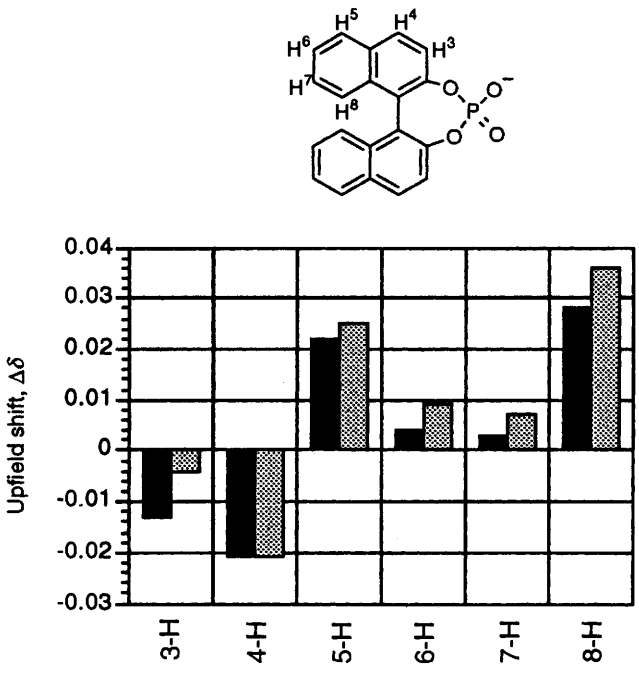


Fig. 6 Changes in the ^1H NMR chemical shifts of (*R*)- (■) and (*S*)-BNPs (▨) in D_2O upon addition of β-CDx (0.01 mol dm^{-3}). The concentration of BNP was 1×10^{-3} mol dm^{-3}.

NMR data. Probably, the structure of the inclusion complex of (*R*)-BNP is very similar to that of (*S*)-BNP. The NOESY data also indicate that the BNP molecule is bound to the primary OH group side as well as the secondary OH group side (the data are not shown herein). A macrocyclic conformation of β-CDx is stabilized by the intramolecular hydrogen bonds between the O(2) and O(3) OH groups of the adjacent glucopyranose units.[17] Therefore, the toroidal shape of β-CDx is hardly altered upon inclusion of a guest molecule. Meanwhile, the intramolecular hydrogen bonds cannot be formed in the case of TMe-β-CDx, the shape of this CDx is changeable upon inclusion of a guest having a relatively larger size.[18] The BNP molecule is too large to be included fully in the β-CDx cavity. Inclusion of such a large guest in the TMe-β-CDx cavity may cause the expansion of the wider side of this CDx. Such a complex seems to be much more stable than the complex bearing the BNP molecule at the narrower side of the TMe-β-CDx cavity, where the most part of the BNP molecule is exposed to the aqueous phase. This may be the reason why the BNP molecule is preferentially bound to the wider side of the TMe-β-CDx cavity.

The detailed NMR study on the complexation of undissociated BNC could not be undertaken because of a low solubility of this guest in water. The dissociated BNC complex is very unstable and its formation could not be detected spectroscopically.

Thermodynamic parameters

Table 2 shows the *K* values for complexation of the enantiomers of BNP and BNC with TMe-β-CDx as a function of temperature. The van't Hoff plots provided the thermodynamic parameters for complexation of the binaphthyl compounds with β-CDx and TMe-β-CDx and the results are summarized in Table 3. β-CDx shows a weak ability to discriminate between the (*R*)- and (*S*)-enantiomers of BNP. In the (*R*)- and (*S*)-BNP-β-CDx systems, the inclusion is promoted by the enthalpy changes (ΔH). The negative entropy changes (ΔS) suggest that hydrophobic interaction is not important in the complexation of BNP with β-CDx. There are many examples where the inclusions in the CDx cavities are enthalpically favourable and entropically unfavourable.[19]

Table 2 Binding constants for complexation of the enantiomers of BNP and BNC with TMe-β-CDx as a function of temperature

	K/dm^3 mol^{-1}			
T/K	(*R*)-BNP	(*S*)-BNP	(*R*)-BNC	(*S*)-BNC
288	351	454	812	154
293	306	394	754	136
298	263	346	691	114
303	230	301	636	100
308	195	261	577	85

Table 3 Thermodynamic parameters for complexation of the enantiomers of BNP and BNC with β-CDx and TMe-β-CDx

System	ΔH/kJ mol^{-1}	ΔS/J mol^{-1} K^{-1}
(*R*)-BNP–β-CDx	−22.0 ± 0.8	−25.9 ± 2.2
(*S*)-BNP–β-CDx	−21.1 ± 0.6	−19.8 ± 0.6
(*R*)-BNP–TMe-β-CDx	−12.9 ± 0.4	−6.9 ± 0.4
(*S*)-BNP–TMe-β-CDx	−12.1 ± 0.2	+10.1 ± 0.3
(*R*)-BNC–TMe-β-CDx	−11.9 ± 0.3	+12.0 ± 1.3
(*S*)-BNC–TMe-β-CDx	−22.7 ± 1.1	−35.4 ± 2.5

TMe-β-CDx recognizes the axial chiralities of BNP and BNC. The complexation of the guest having preferable chirality [(*S*)-BNP or (*R*)-BNC] with TMe-β-CDx is entropically favourable while that of the guest having undesirable chirality [(*R*)-BNP or (*S*)-BNC] is entropically unfavourable. It is found that the chiral recognition of the binaphthyl derivatives by TMe-β-CDx is the process controlled by the entropy term. Positive ΔS is usually explained by a hydrophobic effect. Matsui and Mochida[20] studied the binding forces in the inclusion of alkyl alcohols in the β-CDx cavity and concluded that binding of an alcohol whose molecular size fits well in the β-CDx cavity is dominated mainly by a van der Waals interaction because of effective van der Waals contacts between the host and the guest. In the case of a hydrophobic alcohol having a smaller size compared with the cavity size, hydrophobic interaction becomes a main binding force. Such an explanation was also applied to the inclusions of alicyclic carboxylate anions in the CDx cavities.[21] The BNP molecule is too large to be included fully in the β-CDx and TMe-β-CDx cavities. Judging from the results obtained for aliphatic alcohols[20] and alicyclic carboxylate ions,[21] it is assumed that binding of BNP to β-CDx or TMe-β-CDx is promoted by the van der Waals interaction and/or the dipole interaction, not by the ordinary hydrophobic interaction. In a previous paper,[22] we determined the thermodynamic parameters for complexation of 3-(4-hydroxyphenyl)butan-1-ol with β-CDx, DMe-β-CDx and TMe-β-CDx. This hydrophobic guest alcohol is found to be included in the TMe-β-CDx cavity through the van der Waals interaction (negative and large ΔH and ΔS) while the strong binding to β-CDx or DMe-β-CDx is entropically favourable (negative and small ΔH and positive ΔS). These findings indicate that a hydrophobic guest is not necessarily to be bound to TMe-β-CDx through the hydrophobic interaction. If the ordinary hydrophobic interaction is the driving force, the ΔS values should be positive in complexation of both the enantiomers of BNP with TMe-β-CDx. However, ΔS for the (*R*)-BNP–TMe-β-CDx complex is negative. The thermodynamic parameters obtained for the BNP–TMe-β-CDx system can be explained reasonably by the structures shown in Fig. 4. One naphthalene moiety of (*R*)-BNP penetrates into the CDx cavity and the hydrophilic phosphate group of (*R*)-BNP exists outside of the cavity. The van der Waals interaction may be the main binding force in such complexation, where binding is dominated by ΔH. Meanwhile, the hydrophilic phosphate group of (*S*)-BNP is located inside the CDx cavity. During penetration of (*S*)-BNP into the TMe-β-CDx cavity, the water

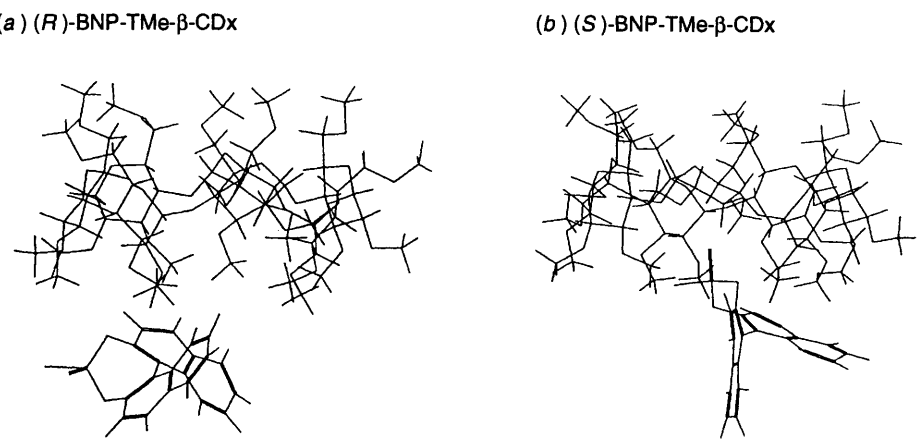


Fig. 7 Structures of the (*R*)- and (*S*)-BNP-TMe-β-CDx complexes proposed from the MM–MD calculations

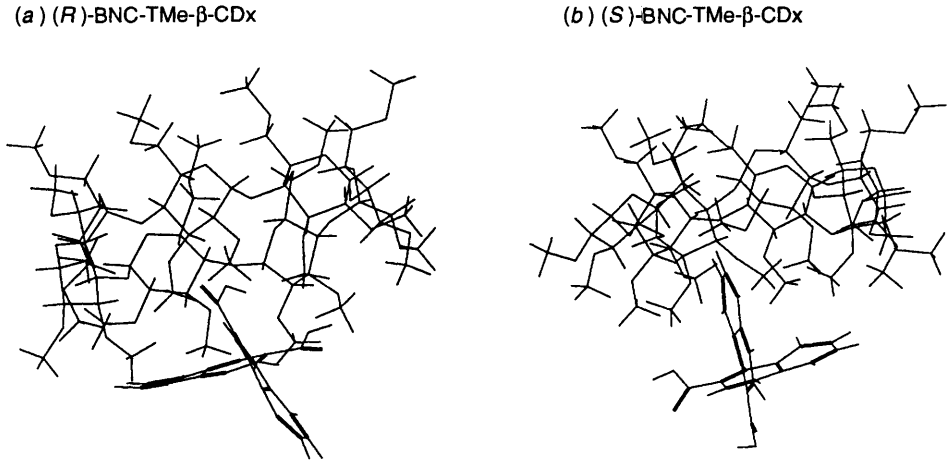


Fig. 8 Structures of the (*R*)- and (*S*)-BNC–TMe-β-CDx complexes proposed from the MM–MD calculations

molecules bound to the hydrophilic group need to be released from the BNP molecule. Two naphthalene moieties of (*S*)-BNP are located in the vicinity of the rim of the CDx cavity to cover the wider side of the TMe-β-CDx cavity, which may also cause the release of the water molecules from the ethereal oxygen atoms of TMe-β-CDx. Thus the complexation of (*S*)-BNP with TMe-β-CDx is accompanied by the release of lots of water molecules from both the host and the guest molecules leading to a positive ΔS. The same discussion is also acceptable for the enantioselective complexation of BNC with TMe-β-CDx.

The linear relationship has been known to exist between ΔH and ΔS for host–guest complexation.[19,23] The results obtained for the complexation of BNC with TMe-β-CDx are consistent with this enthalpy–entropy compensation concept. Namely, the complexation of (*R*)-BNC is entropically favourable and enthalpically unfavourable while that of (*S*)-BNC is entropically unfavourable and enthalpically favourable. The entropic gain in the case of the (*R*)-enantiomer is ascribed to the dehydration from both the host and the guest and the small enthalpy change seems to be due to the shallow binding of the guest (*vide infra*, see Fig. 8). On the contrary, the enthalpic gain and the entropic loss in the case of the (*S*)-enantiomer can be explained by the inclusion of a part of the naphthalene moiety of (*S*)-BNC through the van der Waals interaction without extensive dehydration. In order to discuss the enthalpy–entropy compensation in more detail, we need to accumulate lots of data of complexation of TMe-β-CDx.

Molecular mechanics–molecular dynamics calculations

The molecular mechanics (MM) and molecular dynamics (MD) calculations (Amber V. 4) were carried out to confirm the structures of the complexes postulated from the ^{1}H NMR and thermodynamic data. Before MM–MD calculations, the information about charges of the host and guest molecules was obtained from MOPAC calculations (PM3). The effects of water as a solvent were considered in the MM–MD calculations where a SHAKE method was applied. In the SHAKE method, the stretching mode of each bond is neglected. The results of the TMe-β-CDx complexes of (*R*)- and (*S*)-BNPs are shown in Fig. 7. The structures obtained from the calculations are in good agreement with those deduced from the NMR and thermodynamic data.

The MM–MD calculations were also carried out for the BNC–TMe-β-CDx system. The energy-minimized structures are shown in Fig. 8. As in the case of BNP, a hydrophilic CO_2H group of the preferable guest, (*R*)-BNC, is located inside the hydrophobic CDx cavity and the guest is bound shallowly to the TMe-β-CDx cavity. Meanwhile, both the CO_2H groups of the undesirable guest, (*S*)-BNC, are situated outside the cavity. These structures explain well the thermodynamic parameters (*vide supra*).

Mechanism for chiral recognition

We have to explain the reason(s) why the hydrophilic group of (*S*)-BNP or (*R*)-BNC is located inside the TMe-β-CDx cavity. In a previous paper,[18d] we demonstrated that a dipole–dipole interaction controls the orientation of toluic acids in the CDx cavities. When CDx has enough size to include a toluic acid molecule fully, the guest penetrates headlong into the CDx cavity from the wider side of the CDx cavity where the polar CO_2H group of the guest acts as a head. Such a novel orientation of the guest in the host cavity is dominated by the

dipole–dipole interaction. There are several papers which report the participation of the dipole–dipole interaction in the formation of inclusion complexes of CDxs.[24] In the case of (*S*)-BNP or (*R*)-BNC, the orientation of the guest in the TMe-β-CDx complex may be controlled by this interaction.

The complexation of the undesirable guests, (*R*)-BNP and (*S*)-BNC, with TMe-β-CDx may be promoted mainly by the van der Waals interaction. The dispersion force working between a naphthalene moiety located inside the CDx cavity and the CDx wall seems to be important. Probably, the orientation of the guest according to the dipole–dipole interaction is affected by steric hindrance. Since the ΔH values for complexation of the preferable guest enantiomers are negative and are not so small, the van der Waals interaction seems to be also important for complexation of these enantiomers. It is reasonable to assume that the van der Waals interaction gathers the host and the guest, and the dipole–dipole interaction controls the orientation of the guest in the complex when it is sterically possible.

It is worthwhile considering the contribution of hydrogen bonding to the present chiral recognition system. Bates *et al.*[25] reported the chiral recognition of the ephedrinium cation and its related ions by hexakis(6-*O*-octyl)-α-CDx at the electrode and in an organic solvent. In this case, the protonated amino groups of the guest molecules and the ethereal oxygens of the lipophilic CDx can act as the hydrogen-bond donors and acceptors, respectively. It has been demonstrated that the point interaction through hydrogen bonding between the host and the guest promotes the chiral recognition.[25] In general, however, it is very difficult to form a hydrogen bond in water because of strong hydration to the hydrogen-bonding sites of both host and guest. Moreover, there is no appropriate method to detect the hydrogen-bond formation in water. Because of these reasons, no direct evidence has been obtained in regard to hydrogen-bonded complexes of CDxs. In the previous paper, we proposed the structure of the BR-β-CDx complex where the CO_2^- groups of BR and the secondary OH groups of β-CDx interact through hydrogen bonding.[8] In the BNP–TMe-β-CDx system, however, there is no possibility of the chiral recognition by forming hydrogen-bonded complex because both the host and the guest act only as hydrogen-bond acceptors. Meanwhile, it is possible that the CO_2H groups of BNC interact with TMe-β-CDx through hydrogen bonding. The possibility of the hydrogen-bonding interaction between the CO_2H group of guest and the ethereal oxygen of TMe-β-CDx has previously been studied using benzoic acid derivatives as the guests.[18d] However, no experimental evidence for formation of a hydrogen bond has been obtained. There is no reason to consider the participation of a hydrogen-bonding interaction in the present system.

The following conclusion is derived from the present study. TMe-β-CDx discriminates between the (*R*)- and (*S*)-enantiomers of BNP or BNC. The marked chiral recognition in the present system is achieved by the difference in ΔS for complexation between the (*R*)- and (*S*)-enantiomers. The complexation of the preferable guest enantiomer shows a positive ΔS, while ΔS for the undesirable guest enantiomer is negative. The positive ΔS is ascribed to the dehydration from the hydrophilic head group of the guest and from the ethereal oxygen atoms of the wider side of the host cavity upon complexation. No point interaction participates in the present chiral recognition. Therefore, the 'lock and key' concept is applied to the mechanism of the chiral recognition of BNP and BNC by TMe-β-CDx.

Experimental

β-CDx (Nacalai) was purchased and an antioxidant contained in this material was extracted with THF using a Soxhlet extractor. TMe-β-CDx and DMe-β-CDx (Nacalai) were commercially obtained and used without further purification. The purities of TMe-β-CDx and DMe-β-CDx were checked by ^{1}H NMR spectroscopy. (±)-, (*R*)-(−)- and (*S*)-(+)-BNPs (Aldrich) were purchased and used without further purification. (±)-, (*R*)-(+)- and (*S*)-(−)-BNCs were prepared according to the procedures described in the literature.[26]

The ^{1}H NMR data were collected using a JEOL JNM-A400 (400 MHz) at 25 °C. The MM–MD calculations were carried out as previously reported.[27]

Acknowledgements

This work was supported by a Grant-in-Aid for Science and Research on Priority Areas, 'Asymmetric Synthesis of Chiral Molecules' (No. 07214236) and a Grant-in-Aid for Science Research (No. 07454169) from the Ministry of Education, Science and Culture, Japan.

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Paper 5/05129K
Received 1*st August* 1995
Accepted 25*th January* 1996