Recognition of Planar Chirality by Cyclodextrins

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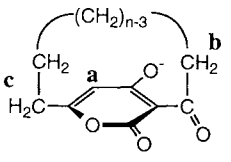
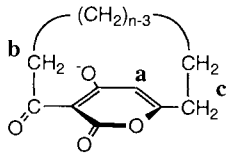
Recognition of planar chirality of 14-hydroxy-12-oxabicyclo[9.2.2]pentadecane-1(14),11(15)-diene-1,13-dione (C8) and 16-hydroxy-14-oxabicyclo[11.2.2]heptadecane-1(16),13(17)-diene-2,15-dione (C10) by native and *O*-methylated cyclodextrins has been studied by NMR spectroscopy. The cyclodextrins prefer the (*R*)-enantiomers of C8 and C10, which might well fit with asymmetrically twisted cavities of cyclodextrins.

Cyclodextrins (CDs) are composed of chiral glucopyranose units and they form diastereomeric isomers upon complexation with racemic molecules. In most cases, there is the difference in stability between diastereomers.[1] Such a characteristic of CDs has been utilized for analysis of chiral compounds by HPLC, GLC, and capillary electrophoresis.[2] It has been known that native and chemically modified CDs enantioselectively complex with various compounds having central and axial chirality. Especially, CDs well recognize the axial chirality of the binaphthyl derivatives[3] and the helicity of a tetrahelicene dicarboxylic acid.[4] In spite of numerous studies on chiral recognition by CDs, no example has been reported with recognition of planar chirality. In the present study, we challenged to make up such a lack in CD chemistry. We used 14-hydroxy-12-oxabicyclo[9.2.2]pentadecane-1(14),11(15)-diene-1,13-dione (C8) and 16-hydroxy-14-oxabicyclo[11.2.2]-heptadecane-1(16),13(17)-diene-2,15-dione (C10) as the guests having planar chirality.[5] The optical resolution of (±)-C8 and (±)-C10 has been carried out by deriving these cyclophanes to the imine derivatives of (*R*)-1-phenylethylamine.[5]



(*R*)-enantiomer

n = 8 : (*R*)-C8
n = 10 : (*R*)-C10



(*S*)-enantiomer

n = 8 : (*S*)-C8
n = 10 : (*S*)-C10

The pK_a value of C10 was roughly estimated to be ca. 4 by measuring pH-dependent absorption spectral change of C10 in water. Figure 1 shows ^{1}H NMR spectra of C10 in D_2O at pD 7.0 (Na_2CO_3) in the absence and the presence of various CDs. Except for TMe-γ-CD, the addition of CDs causes the splitting of the signal due to the H-a proton of C10. The splitting of the signal is ascribed to the difference in binding behavior between the enantiomers of C10. Broadening of the NMR signals of the guest indicates the formation of the complexes between C10 and CDs even in the case of TMe-γ-CD.

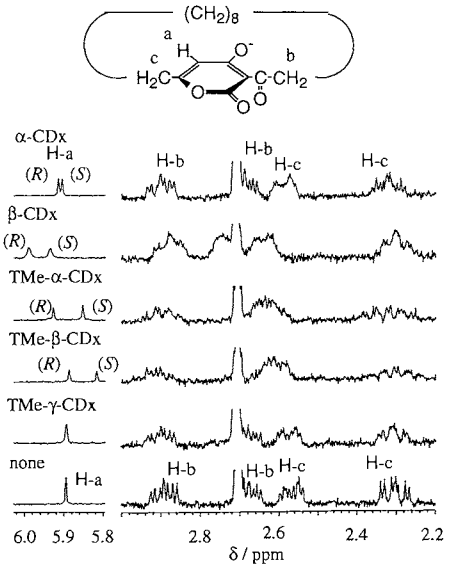


Figure 1. ^{1}H NMR spectra of (±)-C10 in D_2O at pD 7.0 and 25 °C in the absence and the presence of CDs. [(±)-C10] = 1 x 10^{-3} mol dm^{-3}, [CD] = 1 x 10^{-2} mol dm^{-3} except for β-CD (1 x 10^{-3} mol dm^{-3}).

Noncyclic dextrins such as maltose, maltotriose, maltohexaose, and maltoheptaose do not show any effect on the ^{1}H NMR spectrum of C10. Therefore, inclusion of the C10 molecule into the CD cavities seems to be important for splitting of the H-a signal. Essentially the same results were obtained for C8 (the data were not shown herein).

The binding constants (*K*) for complexation were determined from the ^{1}H NMR titration curves which were analyzed by a non-linear least-squares method. The results are summarized in Table 1. The *K* values are mostly small. The *K* values for the β-CD complexes, however, are especially large. Probably, the size fitting between host and guest is important for stabilizing CD complex of ionic guest. As shown in Table 1, native and *O*-methylated CDs prefer the (*R*)-enantiomers of C8 and C10, though the enantioselectivity of each CD ($\Delta\Delta G$) is not satisfactorily high.

The ROESY spectra of the (*R*)- and (*S*)-C10-TMe-α-CD systems show the cross peaks between the protons of methylene envelope as well as the H-a proton of C10 and the OCH_3 protons at the 3-positions of TMe-α-CD. No other cross peak was detected. The ROESY spectra clearly indicate that the hydrophobic part of C10 penetrates into the hydrophobic cavity of the host and consequentially the hydrophilic β-keto ester part of C10 is exposed to the aqueous bulk phase. Figure 2 shows the complexation-induced shifts (CIS) of the proton signals due to C10. Completely opposite effects of TMe-α-CD on CIS

Table 1. Binding constants (K) for complexation of C10 and C8 with various CDs in D_2O at pD 7.0 and 25 °C

Host	Guest	K/dm^3 mol^{-1}	K_R/K_S	$\Delta\Delta G$/kJ mol^{-1}
α-CD	(*R*)-C10	22±2	1.2	0.4
	(*S*)-C10	19±2		
β-CD	(*R*)-C10	730±70	1.5	1.0
	(*S*)-C10	490±60		
TMe-α-CD	(*R*)-C10	43±4	1.2	0.4
	(*S*)-C10	37±4		
TMe-β-CD	(*R*)-C10	74±5	1.2	0.4
	(S)-C10	64±4		
α-CD	(*R*)-C8	16±3	1.1	0.2
	(*S*)-C8	15±3		
β-CD	(*R*)-C8	560±30	1.3	0.6
	(*S*)-C8	440±30		
TMe-α-CD	(*R*)-C8	22±2	1.8	1.5
	(*S*)-C8	12±2		
TMe-β-CD	(*R*)-C8	7±3	0.9	0.3
	(*S*)-C8	8±3		

were observed for the (*R*)- and (*S*)-enantiomers of C10. On the basis of these results, we assumed the plausible structures of the complexes as exhibited in Figure 3. We have claimed that the asymmetrically twisted structure of CD is essential to achieve chiral recognition by the CD.[4,6] Each enantiomer of C10 also has an asymmetrically distorted structure as shown in Figure 3. Of course, the directions of distortion are inverse each other between the enantiomers. Assuming the (*R*)-C10-TMe-α-CD complex as the standard, the (*S*)-enantiomer has to turn through 180° along the long axis of this molecule to fit to the asymmetrically twisted hole of CD. Therefore, the environment around each proton of the guest enantiomer may differ from that of its antipode.

Meanwhile, the absorption maximum (λ_{max}) of the (*R*)- and (*S*)-enantiomers of C10 at 298.4 nm in water shifts to 306.8 and

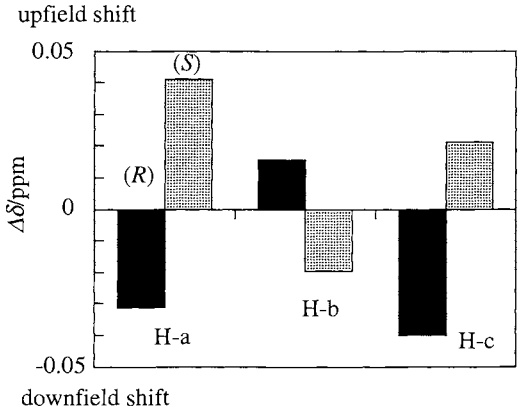


Figure 2. Changes in the proton chemical shifts of C-10 (1 x 10^{-3} mol dm^{-3}) upon addition of TMe-α-CD (1 x 10^{-2} mol dm^{-3}) in D_2O at pD 7.0 and 25 °C.

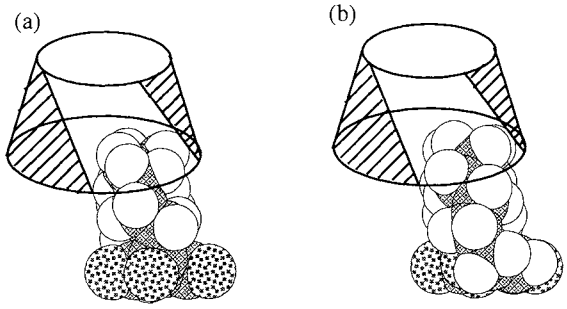


Figure 3. Plausible structures of (a) (*R*)-C10-TMe-α-CD and (b) (*S*)-C10-TMe-α-CD complexes.

313.7 nm, respectively, upon addition of 1 x 10^{-2} mol dm^{-3} β-CD, suggesting that the keto ester part of C10 is placed at the hydrophobic environment. Very slight shifts in λ_{max} were measured for the TMe-α-CD systems. No marked difference was observed in CIS between the (*R*)- and (*S*)-enantiomers of C10 (1 x 10^{-3} mol dm^{-3}) in D_2O containing β-CD (2 x 10^{-3} mol dm^{-3}). Such results of CIS are inconsistent with those for the C10-TMe-α-CD system. The inconsistency might be explained by the difference in binding sites between the TMe-α-CD complex and the β-CD complex. Judging from the larger bathochromic shift of (*S*)-C10, the hydrophilic ring part of (*S*)-C10 seems to penetrate into the β-CD cavity more deeply than that of (*R*)-C10. Detailed study by means of NMR spectroscopy could not be carried out because of the broadening of the NMR signals of C10 upon addition of β-CD. Although the ability of TMe-α-CD to discriminate between the enantiomers of C10 and C8 is not so high, the TMe-α-CD-C10 system is very suggestive. Namely, the present study supports our previous assumption that the asymmetrically twisted structure of CD plays the essentially important role for chiral discrimination.[4,6] Such a mechanism might be applied generally to chiral recognition by CDs.

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References and Note

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