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General Mechanism for Chiral Recognition by Native and Modified Cyclodextrins

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Abstract

A general mechanism for chiral recognition by native and modified cyclodextrins has been proposed by reconsidering the data reported so far. Cyclodextrins in aqueous solution adopt asymmetrically twisted structures, which seems to be the origin of chiral recognition.

Introduction

Studies on chiral recognition by cyclodextrins (CDs) started when Cramer and Dietsche [1] found partial optical resolution of the derivatives of mandelic acid by β-CD in 1959. In spite of various investigations, no general mechanism for chiral recognition by CDs has been presented. In order to discuss the mechanism for chiral recognition, it might be important to find good systems where enantioselective complexation proceeds in appropriate efficiency. As had been recognized, CDs generally show low ability to discriminate between enantiomers of various guests [2]. However, highly enantioselective complexation of native and modified CDs has recently been found to occur in certain systems (vide infra). Such findings make it possible to discuss general mechanism for chiral recognition by CDs.

Recognition of central chirality

α-Amino acids are typical guests having central chirality. Very few examples have been reported with chiral recognition of native α-amino acids by native CDs, because of very small binding constants (*K*s) for these systems. For example, Cooper and MacNicol briefly reported that the anionic forms of (*R*)- and (*S*)-Phes are bound to α-CD with the *K* values of 20.6 and 15.9 M^{-1}, respectively [3]. Although the data are not satisfactory to discuss the mechanism for chiral recognition, a plausible structure of the (*R*)-Phe-α-CD complex can be drawn as shown in Figure 1 where a hydrophobic phenyl group is located at the inside of the CD cavity. The rest of the substituents of (*R*)-Phe at the secondary OH side of α-CD are arranged in the order CO_2^- (large, L) $\rightarrow$ NH_2 (medium, M) $\rightarrow$ H (small, S) when eye travels in a clockwise direction. Is such arrangement found in other systems? Since there is no study which shows appreciable differences in *K* values between the enantiomers of α-amino acids, the data on chiral discrimination obtained by analytical methods such as HPLC, CE, and MS using CDs as chiral separators are considered in the present study. Table 1 summarizes a part of the reported results in analytical chemistry [4–7]. In all cases, the (*R*)-enantiomers are the preferable guests for native CDs. Assuming that a hydrophobic part of the α-amino acid is incorporated into the CD cavity at the secondary OH side, the arrangement of the rest of the substituents is the same as that shown in Figure 1.

We tried to use Coulomb interactions to increase *K* values for complexation of amino acids with CD [8]. Then heptakis(6-amino-6-deoxy)-β-CD in a protonated form (per-NH_3^+-β-CD) and heptakis(6-carboxymethylthio-6-deoxy)-β-CD in a dissociated form (per-CO_2^--β-CD) were used as the cationic and anionic CDs, respectively. *N*-Acetyl amino acids in the dissociated forms and amino acid methyl es-

Table 1. Enantioselectivity of native CDs for α-amino acids

Run	Host	Guest	Selectivity	Analysis[a]	Ref
1	β-CD	Phe	*R*	HPLC	4
2	β-CD	Ser	*R*	HPLC	4
3	β-CD	Val	*R*	HPLC	4
4	α-CD	Tyr	*R*	MS	5
5	α-CD	Trp	*R*	MS	5
6	β-CD	Trp	*R*	MS	5
7	β-CD	DnsGlu[b]	*R*	HPLC	6
8	β-CD	DnsAsp[b]	*R*	HPLC	6
9	β-CD	DnsSer[b]	*R*	HPLC	6
10	β-CD	DnsTrp[b]	*R*	HPLC	6
11	γ-CD	DnsVal[b]	*R*	CE	7
12	γ-CD	DnsLeu[b]	*R*	CE	7
13	γ-CD	DnsAsp[b]	*R*	CE	7

[a]MS and CE represent mass spectroscopy and capillary electrophoresis, respectively.
[b]Dns represents a dansyl group.

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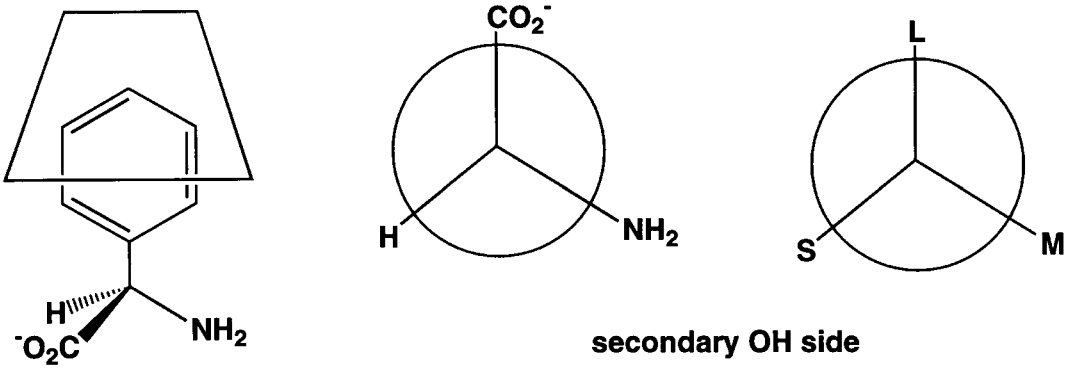

Figure 1. Plausible structure of the (*R*)-Phe-α-CD complex. L, M, and S represent large, medium, and small in sizes of substituents.

Table 2. Chiral recognition of ionic amino acid derivatives by charged CDs[8]

Run	Host	Guest	K/M^{-1}	Selectivity
1	per-NH_3^+-β-CD	(*S*)-AcTrp	2310 ± 90	*S*
2		(*R*)-AcTrp	1420 ± 50	
3		(*S*)-AcPhe	2180 ± 130	*S*
4		(*R*)-AcPhe	2000 ± 130	
5		(*S*)-AcLeu	2480 ± 130	*S*
6		(*R*)-AcLeu	2380 ± 110	
7		(*S*)-AcVal	2090 ± 160	*S*
8		(*R*)-AcVal	1310 ± 80	
9	per-CO_2^--β-CD	(*S*)-TrpME	380 ± 20	*R*
10		(*R*)-TrpME	550 ± 30	
11		(*S*)-PheME	1520 ± 150	*R*
12		(*R*)-PheME	1570 ± 150	
13		(*S*)-PGlyME	260 ± 10	*R*
14		(*R*)-PGlyME	280 ± 10	

ters in the protonated forms were used as the anionic and cationic guests, respectively. The results are listed in Table 2. The detailed study by NMR reveals that the ionic guests are bound to the oppositely charged CDs through both Coulomb and van der Waals interactions and the guest is anchored by electrostatic interactions between the charged substituent of the guest and the oppositely charged arms of the host. Consequently, an asymmetric carbon of the guest seems to be located at the primary OH side of the charged CD. The enantioselectivity is quite opposite between cationic and anionic CDs. Plausible arrangement of the substituents of the guests at the primary OH sides of the cationic and anionic CDs is shown in Figure 2. The direction of the size order (L → M → S) for both ionic CDs is counterclockwise at the primary OH sides, which corresponds to clockwise direction in the case where the eye is placed at the secondary OH sides. With chiral recognition of α-amino acids and their derivatives, it might be concluded generally that both native and modified CDs prefer the enantiomers with the substituent arrangement of L → M → S in the clockwise direction when the complexes are viewed from the secondary OH sides of CDs.

Mikolazyk and Drabowicz found relatively good optical resolution of isopropoxy methyl sulfoxide ($(CH_3)_2CHO$-S(O)-CH_3 by β-CD (optical purity of the resolved (*S*)-enantiomer = 68.2%) [9]. We reported that the K values for complexation of (*R*)- and (*S*)-1-(1-pyrenyl)ethanols by hexakis(2,3,6-tri-*O*-methyl)-α-CD (TMe-α-CD) are 565 ± 14 and 421 ± 43 M^{-1}, respectively [10]. These two examples may be used to discuss the recognition of central chirality because of relatively high enantioselectivity. The reasonable structures of the complexes are shown in Figure 3. It is rational that the most hydrophobic isopropoxy group in the sulfinyl compound is included into the CD cavity. Meanwhile, 1-(1-pyrenyl)ethanol seems to be hang to the secondary OH side of TMe-α-CD shallowly, because the CD cavity is too small to include the guest. The hydrophilic OH group of the guest should face to the aqueous bulk phase. The arrangement of the substituents of these systems at the secondary OH sides of the CDs is also L → M → S in the clockwise direction. On the basis of the "rock and key" concept that is generally applied to inclusion phenomena of CDs, it can be concluded that CDs have asymmetrically twisted structures in aqueous media.

Recognition of axial chirality

As indicated in Table 3, CDs well discriminate between enantiomers of binaphthyl derivatives having axial chirality [11–14]. Native β-CD as well as peralkylated β-CDs prefers the (*S*)-enantiomer of 1,1′-binaphthyl-2,2′-diyl phosphate anion (BNP). Especially, heptakis(2,6-di-*O*-methyl-3-*O*-ethyl)-β-CD (EtDMe-β-CD) well recognizes axial chirality of BNP ($\Delta\Delta G$ = 3.3 kJ mol^{-1}). Since optically active binaphthyl compound has an asymmetrically twisted configuration, strong complexation seems to occur if the CD has the asymmetrically twisted cavity which fits the shape of the guest enantiomer. The ethyl groups in EtDMe-β-CD may enhance the asymmetric distortion of the CD cavity.

Recognition of helicity

Le Bas et al. briefly mentioned that achiral benzo[c]phenanthrene (tetrahelicene) adopts the (*P*)-conformation in the γ-CD cavity [15]. This is the CD-induced conformational enantiomerism. 1,12-Dimethylbenzo[c]phenanthrene-5,8-dicarboxylic acid

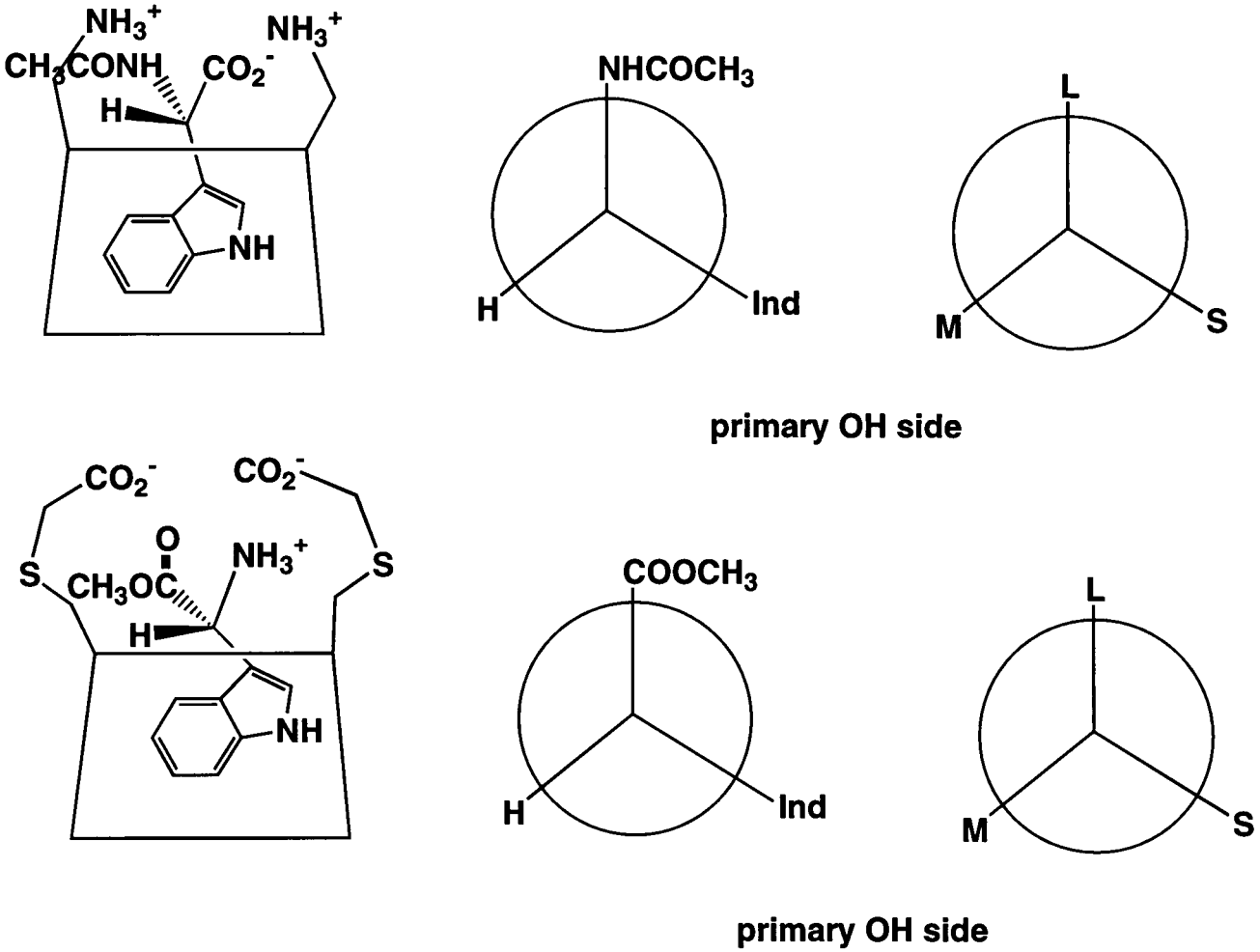

Figure 2. Structures of the (*S*)-AcTrp-per-NH_3^+-β-CD and (*R*)-TrpME-per-CO_2^--β-CD complexes. Ind represents the indole moiety.

Table 3. Recognition of axial chirality of 1,1′-bi-2-naphthol (BN), BNP (anion), and 1,1′-binaphthyl-2,2′-dicarboxylic acid (undissociated form, BNC) by CDs

Run	Host	Guest	K/M^{-1}	Selectivity	Ref.
1	β-CD	(*S*)-BN	280	*S*	11
2	β-CD	(*R*)-BN	230		11
3	β-CD	(*S*)-BNP	920 ± 54	S	12
4	β-CD	(*R*)-BNP	451 ± 21		12
5	β-CD	(*S*)-BNC	~ 0	*R*	13
6	β-CD	(*R*)-BNC	28		13
7	TMe-β-CD	(*S*)-BN	$(5 \pm 1) \times 10^4$ M^{-2}	*S*	14
8	TMe-β-CD	(*R*)-BN	17 ± 0.1		14
9	TMe-β-CD	(*S*)-BNP	370 ± 33	*S*	12
10	TMe-β-CD	(*R*)-BNP	175 ± 11		12
11	TMe-β-CD	(*S*)-BNC	114 ± 4	*R*	13
12	TMe-β-CD	(*R*)-BNC	691 ± 42		13
13	EtDMe-β-CD	(*S*)-BNP	954 ± 61	*S*	12
14	EtDMe-β-CD	(*R*)-BNP	254 ± 18		12

(HDC) is the chiral compound having helicity [16], which is excellently recognized by native β-CD [17] as well as non-cyclic oligosaccharides such as maltohexaose (G6) and maltoheptaose (G7) [18] as shown in Table 4. Although the original papers report that (*M*)-HDC dianion is enantioselectively bound to the saccharides, the representation of the absolute configurations in these papers [17, 18] as well as in the paper on the synthesis of HDC [16] is totally opposite and needs to be corrected. The cavity of β-CD well fits the (*P*)-configuration of the HDC dianion. The difference in ΔG values between (*P*)- and (*M*)-HDCs is 5.2 kJ mol^{-1}, which might be the highest enantioselectivity in chiral recognition by CDs reported so far. The NMR study indicates that the binding site of the HDC dianion is the secondary OH side of β-CD. On the basis of these data, it can be concluded that the shape of β-CD cavity is asymmetrically distorted to fit right-handed helix configuration of the guest upon complexation. Such a conclusion can be derived since the enantioselectivity in this system is enormously high.

Tris(1,10-phenanthroline)ruthenium ($Ru(phen)_3^{2+}$) complex is a unique chiral guest having helicity. The positive charge is located at the center of this complex which is surrounded by three phenanthroline molecules. No sterically projected part exists in this molecule. Therefore, $Ru(phen)_3^{2+}$ might be the best guest to judge whether asymmetrically twisted structure of CD is essential for chiral recognition or not. Since no interaction was observed between

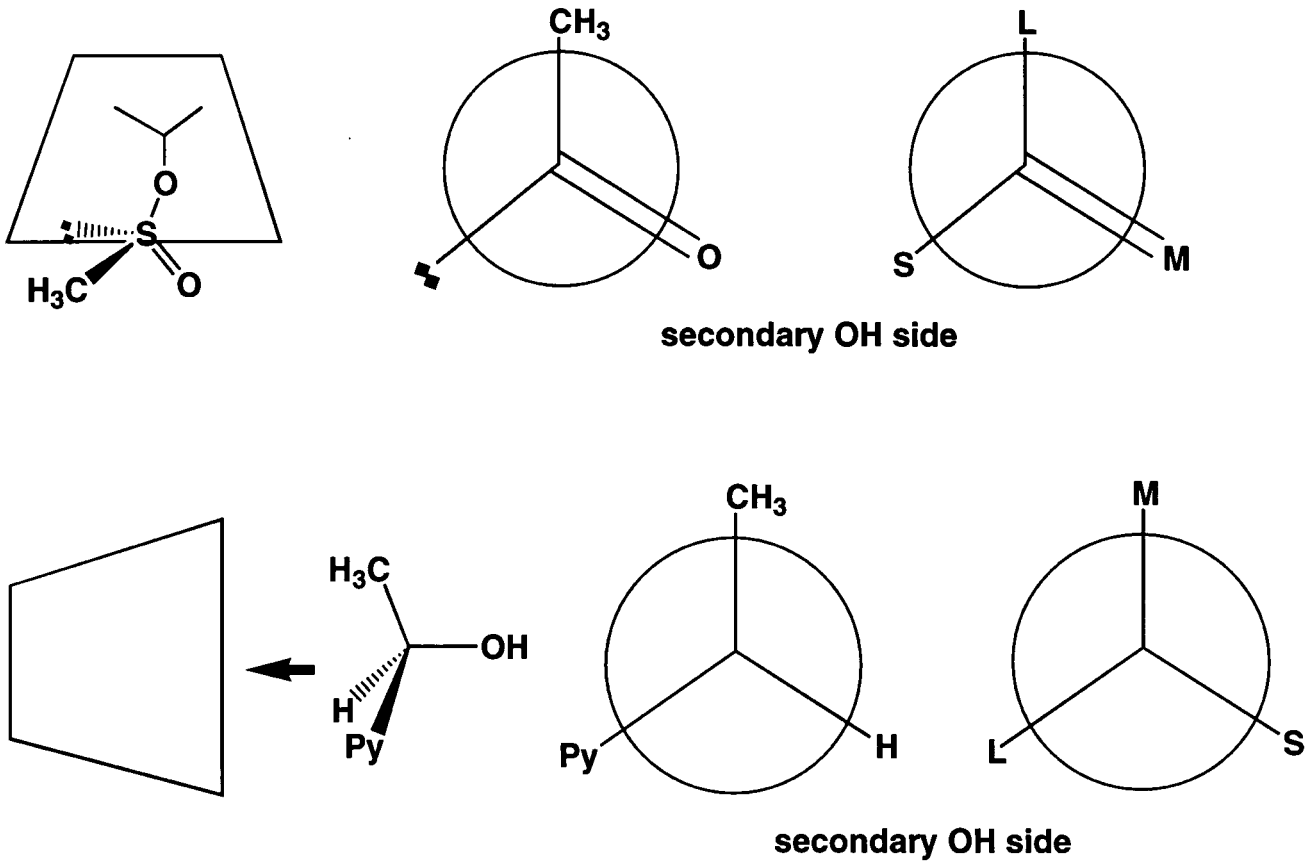

Figure 3. Structures of the (*S*)-isopropoxy methyl sulfoxide-β-CD and 1-(1-pyrenyl)ethanol-TMe-α-CD complexes.

Table 4. Enantioselective complexation of the HDC dianion with native CDs and G7

Entry	Host	Guest	K/M^{-1}	Ref
1	β-CD	(*P*)-HDC	18700 ± 1700	17
2	β-CD	(*M*)-HDC	2200 ± 100	17
3	γ-CD	(*P*)-HDC	3100 ± 100	17
4	γ-CD	(*M*)-HDC	690 ± 20	17
5	G7	(*P*)-HDC	82 ± 7	18
6	G7	(*M*)-HDC	45 ± 5	18

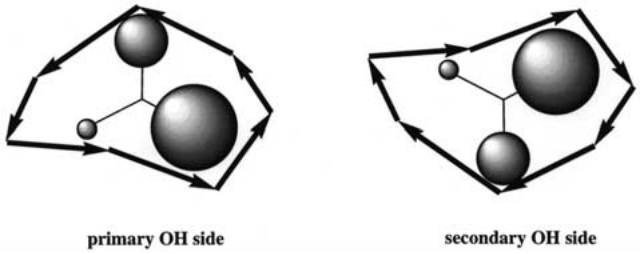

Figure 4. Top and bottom views of an asymmetrically twisted cavity of CD in which a chiral guest molecule is included. The arrow represents a glucopyranose unit.

Table 5. Chiral recognition of $Ru(phen)_3^{2+}$ and $Ru(bpy)_3^{2+}$ by per-CO_2^--β-CD and TMe-α-CD

Run	Host	Guest	K/M^{-1}
1	per-CO_2^--β-CD	Δ-$Ru(phen)_3^{2+}$	1250 ± 50
2	per-CO_2^--β-CD	Λ-$Ru(phen)_3^{2+}$	590 ± 40
3	per-CO_2^--γ-CD	Δ-$Ru(phen)_3^{2+}$	1140 ± 50
4	per-CO_2^--γ-CD	Λ-$Ru(phen)_3^{2+}$	890 ± 40
5	TMe-α-CD	Δ-$Ru(phen)_3^{2+}$	54 ± 4
6	TMe-α-CD	Λ-$Ru(phen)_3^{2+}$	108 ± 4
7	TMe-α-CD	Δ-$Ru(bpy)_3^{2+}$	59 ± 4
8	TMe-α-CD	Λ-$Ru(bpy)_3^{2+}$	77 ± 4

native CDs and $Ru(phen)_3^{2+}$, anionic per-CO_2^--β-CD was used as the host [19]. The results are summarized in Table 5. $Ru(phen)_3^{2+}$ is bound to per-CO_2^--β-CD through both Coulomb and van der Waals interactions and, therefore, the guest is located at the primary OH side of the host. In this case, the host prefers the Δ-isomer of the guest. Meanwhile, the guest weakly interacts with TMe-α-CD whose secondary OH side is the binding site. The Λ-enantiomer is the preferable guest. A smaller Ru complex $(Ru(bpy)_2^{3+}$, bpy = 2,2′-bipyridine) shows the same tendency. These results suggest that primary and secondary OH sides of CDs show opposite enantioselectivity for guests with helicity.

General mechanism for chiral recognition

Most of the data on chiral recognition by CDs suggest that CDs tend to distort asymmetrically upon inclusion of a guest. Plausible shape can be deduced from the results on chiral recognition of α-amino acid derivatives (Figure 4). Such a distorted structure can be prepared by twisting a CD cavity regularly [19]. The X-ray analysis also shows that large CDs such as CD9, CD10, and CD14 having nine, ten, and fourteen glucopyranose unites take twisted structures [20]. Twisting is assumed to occur by altering ordinary cis-orientation of the glucose units to trans-one.

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