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Enantioselective Recognition of Aliphatic Amino Acids by Organoselenium Modified β-Cyclodextrins*

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A series of novel organoselenium modified β-cyclodextrins (CDs) bearing an aromatic group 1–7 have been synthesized by a convenient method in satisfactory yields. Spectrophotometric titrations have been performed in aqueous buffer solution (pH 7.20) at 25.0°C to give the complex stability constants (K_s) and Gibbs free energy change ($-\Delta G^\circ$) for the 1:1 inclusion complexation of the six organoselenium modified β-cyclodextrins with some selected aliphatic amino acids. Inclusion complexation of mono-[6-(naphthylseleno-6-deoxy]-β-cyclodextrin 7 with aliphatic amino acids was too weak to be observed, which is attributable to the stronger self-inclusion of naphthylseleno moiety attached to the primary side of cyclodextrin into the cavity. However, the other modified β-cyclodextrins carrying one arylseleno moiety as a probe for differential UV spectrometry were found to recognize not only the size and shape but also the chirality of amino acids. Among arylseleno CDs 1–6, 3 showed the highest enantioselectivity of 27 for *L*-Ala over the antipodal *D*-Ala. The molecular recognition ability and enantioselectivity for amino acids of these seven modified β-cyclodextrins are discussed from the viewpoints of the size/shape-fit concept, substituent effect and the multipoint recognition mechanism. The inclusion complexation of these modified β-cyclodextrins with *L*/*D*-amino acids may be more explicitly understood in terms of the complementary geometrical relationship and the induced-fit interaction between the host and the guest.

Keywords: Enantioselective recognition, modified cyclodextrin, amino acids, organoselenium, inclusion complexation

INTRODUCTION

Molecular recognition is currently a significant topic in supramolecular chemistry. Native cyclodextrins (CDs) and chemically modified cyclodextrins possessing fairly rigid and well-defined hydrophobic cavities have been employed successfully as molecular receptors to include a wide variety of organic, inorganic and biological molecules forming host-guest complexes or supramolecular species [1–10]. Therefore, a great deal of effort has been devoted to the synthesis of cyclodextrin derivatives in order to examine their molecular recognition ability, including multipoint and chiral recognition, and also to understand the nature of the noncovalent interactions in relation to the biological receptor–

* Molecular recognition study on a supramolecular system. Part 15.

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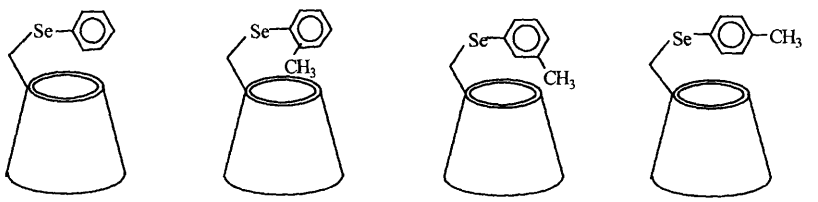
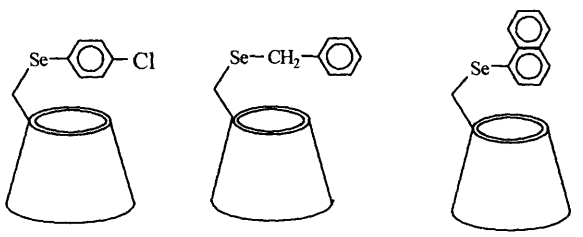
substrate interactions [11–15]. In recent years, some bifunctional cyclodextrins featuring the multipoint recognition and induced-fit interaction with the guest included in the cyclodextrin cavity, have been employed successfully in several areas of science and technology, such as enzyme mimetics [16], drug delivery systems [17], and chiral chromatography [18–26].

Our recent study on the chiral recognition of aromatic amino acids by binuclear copper(II)-cyclodextrin complexes indicates that the binuclear copper(II)-cyclodextrin complexes show preference for *D*-amino acids [8], while natural cyclodextrins favor *L*-amino acids. In the latest study on enantioselective recognition of amino acids by β-cyclodextrin-6-*o*-monophosphates, we found that the electrostatic interaction and intermolecular hydrogen bonding between host and guest can enhance both the molecular recognition ability and the enantioselectivity [27]. These results indicate that the microenvironmental change around the cavity of the cyclodextrins apparently governs the inclusion complexation phenomena to a considerable extent. Furthermore, the elucidation of the inclusion mechanism of CD derivatives is also helpful for our further understanding of the multipoint recognition and the induced-fit interaction hypothesis proposed for the selective binding of specific substrate by the biological receptor.

In the present study, we synthesized a series of organoselenium modified β-cyclodextrins **1**–**7**: mono-[6-(phenylseleno)-6-deoxy]-β-cyclodextrin **1**, mono-[6-(*o*-tolylseleno)-6-deoxy]-β-cyclodextrin **2**, mono-[6-(*m*-tolylseleno)-6-deoxy]-β-cyclodextrin **3**, mono-[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin **4**, mono-[6-(*p*-chlorophenylseleno)-6-deoxy]-β-cyclodextrin **5**, mono-[6-(benzylseleno)-6-deoxy]-β-cyclodextrin **6**, and mono-[6-(naphthylseleno)-6-deoxy]-β-cyclodextrin **7**, and investigated their inclusion complexation behavior with some selected *L*/*D*-aliphatic amino acids by the differential UV spectrometry in aqueous buffer solution (pH 7.20) at 25.0°C. The chromophoric aromatic group attached to the primary side of β-cyclodextrin, which must suffer substantial conformational change upon inclusion complexation with guest molecule, can act as a spectral probe to determine complex stability constants in differential UV spectrometry.



1 **2** **3** **4**



5 **6** **7**

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A series of *L*/*D*-aliphatic amino acids were selected as the guest molecules for this study in order to compare and examine the effects of size, shape, and chirality of the guest molecule upon inclusion complexation. The differential UV and induced circular dichroism (ICD) spectral study with modified β-cyclodextrins enables us to elucidate the conformation of the aromatic moiety in the host **1**–**7**. Under such circumstances, we can discuss the molecular recognition ability and enantioselectivity of organoselenium modified β-cyclodextrins **1**–**7** from the viewpoints of the size/shape-fit and the stereochemical complementary relationship between the molecular receptor (host) and model substrate (guest). It is another point of interest to examine the influence of the methyl substituent introduced to the aromatic ring sidearm on β-cyclodextrin upon its molecular recognition ability and enantioselectivity.

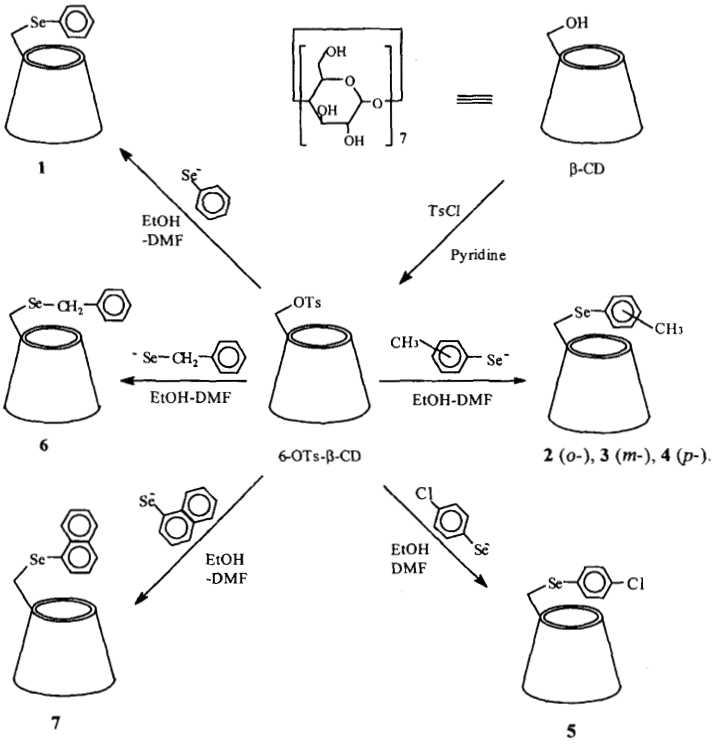
RESULTS AND DISCUSSION

Synthesis

Modified β-cyclodextrins were synthesized in preparatively satisfactory yields by using the 6-*o*-monotosylate of β-cyclodextrin as the starting material according to the following scheme:

CD Spectra

As can be seen from Figure 1, the circular dichroism (CD) spectrum of modified β-cyclodextrin **1** in aqueous solution showed a strong negative Cotton effect peak, corresponding to the ^1L_a band at 229 nm ($\Delta\varepsilon$ −2.86) and a weak positive Cotton effect for the ^1L_b band at 284 nm ($\Delta\varepsilon$ 0.66). Similarly, for the modified β-cyclodextrin **4**, the CD spectra (Fig. 2) showed a major negative Cotton effect peak ($\Delta\varepsilon$ −3.41) at 232 nm and a weak positive Cotton effect peak ($\Delta\varepsilon$ 0.99)



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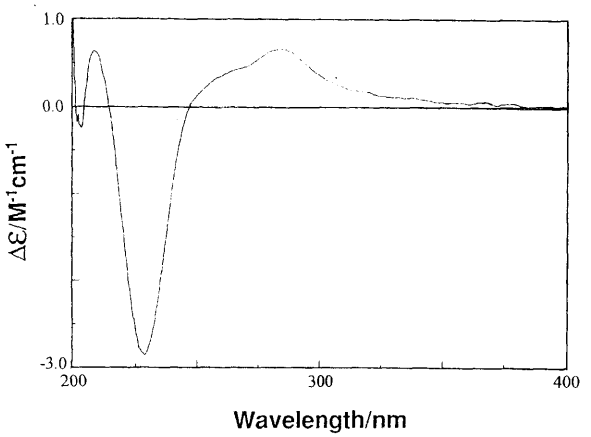

FIGURE 1 Circular dichroism spectrum of β-cyclodextrin derivative **1** (0.099 mmol·dm^{-3}) in buffer solution (pH 7.20) at room temperature.

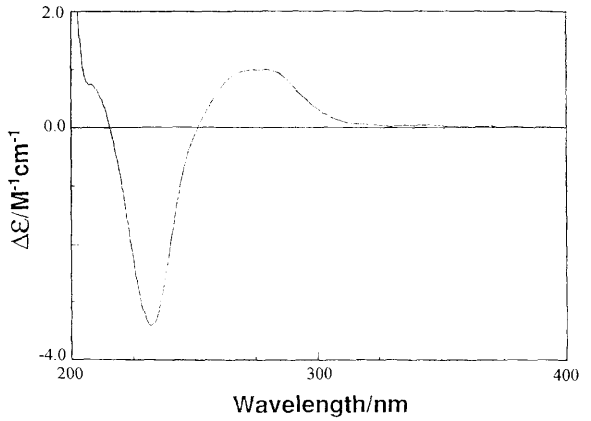

FIGURE 2 Circular dichroism spectrum of β-cyclodextrin derivative **4** (0.099 mmol·dm^{-3}) in buffer solution (pH 7.20) at room temperature.

at 279 n . According to the sector rule proposed by Kajta *t al.*, the Cotton effects observed for the ^1L_a and ^1L_b bands indicate that the aromatic moieties of both compounds **1** and **4** penetrate deeply into the hydrophobic cavity of cyclodextrin [30–32]. In addition to the structural similarities of the seven β-cyclodextrin derivatives, we can deduce that the aromatic moieties of the other modified cyclodextrins **2, 3, 5, 6,** and **7** are also embedded in the hydrophobic cavity of cyclodextrin. Furthermore, the results of CD spectra enable us to elucidate the conformation of the aromatic moiety in the host cyclodextrin derivatives. The aromatic group, originally attached to the rim of cyclodextrin cavity, must suffer substantial conformational changes upon guest inclusion, which may determine the complex stability constants to some extent.

UV Spectral Titrations

In the titration experiments using UV spectrometry, the absorption maximum of the modified cyclodextrins gradually increased in intensity upon addition of varying amounts of amino acids. Typical UV-vis spectral changes upon addition of amino acid to a modified cyclodextrin solution are shown in Figure 3. The enhanced absorbance at ca. 270 nm indicate that the formation of inclusion complex of the modified cyclodextrin with amino acids. With the assumption of a 1:1 stoichiometry, the inclusion complexation of amino acids (G) with β-cyclodextrin derivatives (H) is expressed by Eq. (1).

$$H + G \overset{K_s}{\rightleftharpoons} G \bullet H \qquad (1)$$

Under the conditions employed, the concentration of β-cyclodextrin derivatives is much smaller than those of amino acids, *i.e.*, $[H]_0 \ll [G]_0$. Therefore, the stability constant (K_s) of inclusion complex formed by the host and guest can be calculated according to the modified

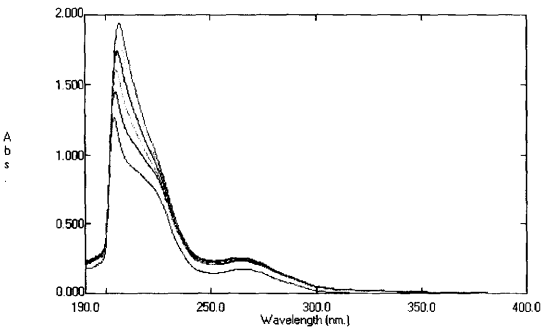

FIGURE 3 UV-vis spectra of **2** (1.04×10^{-4} mol·dm^{-3}) in the presence of *L*-serine, (a) 0; (b) 2.042; (c) 4.083; (d) 6.125; (e) 8.167; (f) 10.21 mmol·dm^{-3}; λ_{max} 264 nm.

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Hildebrand and Benesi Equation (2) [33, 34].

$$\frac{[G]_0[H]_0}{\Delta A} = \frac{1}{K_s \Delta\varepsilon} + \frac{[G]_0}{\Delta\varepsilon} \quad (2)$$

where $[G]_0$ and $[H]_0$ refer to the total concentration of amino acids and β-cyclodextrin derivatives, respectively, $\Delta\varepsilon$ is the difference between molar extinction coefficient for free and complexed β-cyclodextrin derivatives, ΔA denotes the changes in the absorbance of β-cyclodextrin derivatives upon addition of guest amino acids. For all guest molecules examined, the plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of $[G]_0$ give good straight lines. A typical plot was shown in Figure 4 for the inclusion complexation of cyclodextrin derivative **2** with *L*-serine, where the calculated $[G]_0[H]_0/\Delta A$ values are plotted against the $[G]_0$ to give an excellent linear relationship (r 0.996) with a slope of 1.14×10^{-3} mol·dm^{-3} and an intercept of 2.14×10^{-6} mol^2·dm^{-6}. The stability constant ($\log K_s$) and the free energy change ($-\Delta G°$) calculated from the slope and the intercept are listed in Table I, along with enantioselectivity ($\Delta\Delta G°$) calculated from $\Delta G°$ for inclusion complexation of *L*/*D*-amino acids by the modified β-cyclodextrins.

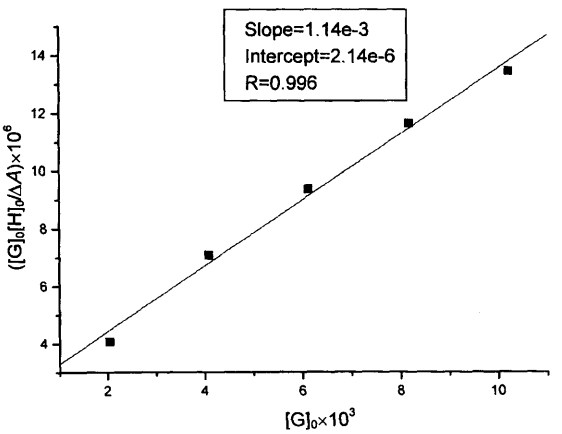

FIGURE 4 Typical plot of $[G]_0[H]_0/\Delta A$ *versus* $[G]_0$ for the inclusion complexation of cyclodextrin derivative **2** with *L*-serine in phosphate buffer solution (pH 7.20) at 25.0°C.

The results obtained verified the 1:1 stoichiometry of complexation as assumed above.

Molecular Recognition and Enantioselectivity

As can be seen from Table I, most of the modified β-cyclodextrins have shown higher enantioselectivity for *L*/*D*-alanine and leucine and lower enantioselectivity for *L*/*D*-serine and cysteine, although all the hosts possess roughly comparable complexing abilities. The size-fitted combination gives the strongest inclusion complexation. Somewhat unexpectedly, the inclusion complexation with β-cyclodextrin derivatives **1**, **4**, **5** and **6** show entirely opposite enantioselectivity for *L*/*D*-serine and cysteine, which possess only one different functional group, *i.e.*, OH *versus* SH. One reasonable explanation for this drastic inversion of enantioselectivity would be the intermolecular hydrogen bonding, since the serine's hydroxyl can form an intermolecular hydrogen bond with the CD's hydroxyl upon inclusion complexation, while the mercapto of cysteine cannot do so. This behavior typically demonstrate the crucial role of cooperative weak interactions working between the host and guest.

In order to visualize the inclusion complexation behavior of modified β-cyclodextrins with amino acids, the changing profiles of free energy change ($-\Delta G°$) upon complexation with **1**–**6** are shown in Figure 5. Molecular recognition ability and relative enantioselectivity of β-cyclodextrin **1**–**7** for amino acids will be discussed below in terms of the size/shape-fit, induced-fit, substituent effect and multipoint recognition mechanism.

Mono-[6-(phenylseleno)-6-deoxy]-β-cyclodextrin (1) and Mono-[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (6)

It is interesting to compare the molecular-binding ability of host compounds **1** and **6** with a sidearm of different chain length. Possessing

TABLE I Stability constants (log K_s) and Gibbs free energy changes ($-\Delta G°$) for the inclusion complexation of amino acids with β-cyclodextrin derivatives **1**–**7** in 0.1 mol·dm^{-1} phosphate buffer solution (pH 7.2) at 25.0°C

host	guest	log K_s	$-\Delta G°$/kJ.mol^{-1}	$-\Delta\Delta G°$/kJ.mol^{-1}*
1	*L*-Ala	1.96	11.2	3.4
	D-Ala	2.55	14.6	
	L-Ser	2.00	11.4	−1.6
	D-Ser	1.71	9.76	
	L-Cys	2.00	11.4	2.0
	D-Cys	2.35	13.4	
	L-Leu	2.46	14.0	0.1
	D-Leu	2.47	14.1	
	L-Pro	2.00	11.4	
	L-Ile	2.67	15.2	
2	*L*-Ala	4.19	23.9	−8.1
	D-Ala	2.76	15.8	
	L-Ser	2.73	15.6	0.9
	D-Ser	2.89	16.5	
	L-Cys	2.56	14.6	0.6
	D-Cys	2.66	15.2	
	L-Leu	3.10	17.7	1.5
	D-Leu	3.37	19.2	
	L-Pro	3.47	19.8	
	L-Ile	3.38	19.3	
3	*L*-Ala	2.77	15.8	1.4
	D-Ala	3.01	17.2	
	L-Ser	2.98	17.0	1.1
	D-Ser	3.17	18.1	
	L-Cys	2.42	13.8	−0.7
	D-Cys	2.30	13.1	
	L-Leu	2.97	16.9	−3.0
	D-Leu	2.44	13.9	
	L-Pro	3.95	22.5	
	L-Ile	2.80	16.0	
4	*L*-Ala	2.69	15.4	2.9
	D-Ala	3.20	18.3	
	L-Ser	2.92	16.7	−3.9
	D-Ser	2.25	12.8	
	L-Cys	2.42	13.8	1.2
	D-Cys	2.63	15.0	
	L-Leu	2.63	15.0	3.6
	D-Leu	3.26	18.6	
	L-Ile	2.39	13.6	
5	*L*-Ala	3.31	18.9	−3.1
	D-Ala	2.76	15.8	
	L-Ser	2.86	16.3	−2.8
	D-Ser	2.37	13.5	
	L-Cys	2.19	12.5	2.1
	D-Cys	2.56	14.6	
	L-Leu	2.50	14.3	3.0
	D-Leu	3.03	17.3	
	L-Pro	2.65	15.1	
	L-Ile	3.54	20.2	
6	*L*-Ala	2.34	13.4	−3.1
	D-Ala	1.80	10.3	
	L-Ser	2.34	13.4	−0.8
	D-Ser	2.20	12.6	
	L-Cys	2.41	13.8	1.9
	D-Cys	2.75	15.7	
	L-Leu	2.45	14.0	4.4
	D-Leu	3.23	18.4	
7	All amino acids used		No inclusion observed	

* The log K_s values are the average of three independent runs: error < 5% of the reported value. $\Delta\Delta G°$ signifies the difference of the free energy changes for the complexation behavior with *L*/*D*-amino acids ($\Delta\Delta G° = \Delta G°_D - \Delta G°_L$).

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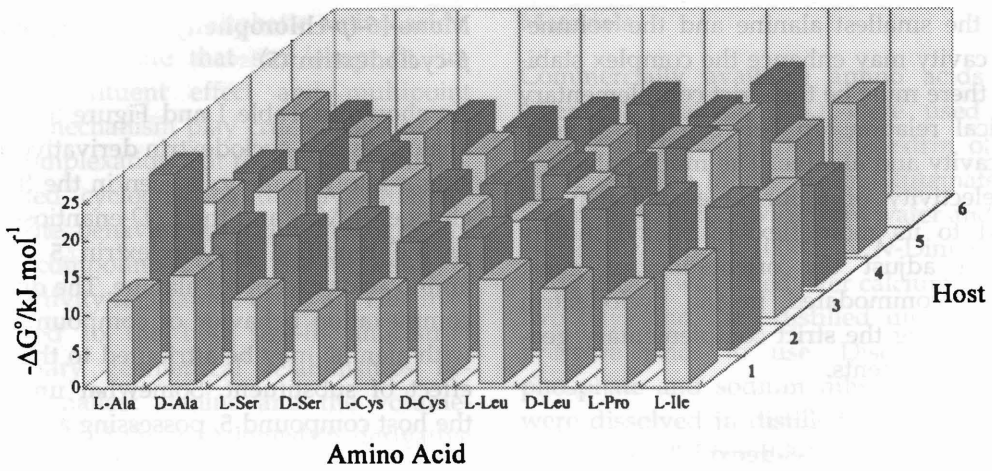

FIGURE 5 Gibbs free energy changes ($-\Delta G°$) as a function of amino acids for the including complexation of modified β-cyclodextrins **1**–**6** with some amino acids in phosphate buffer solution at 25.0°C.

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higher structural flexibility compared with **1**, host **6** can adjust the orientation of aromatic moiety attached to the primary side of β-cyclodextrin in order to maximize the stereochemical complementary relationship between host and guest, ultimately giving more tight inclusion complex with guest molecule. As can be seen from Table I and Figure 5, the free energy changes ($-\Delta G°$) for inclusion complexation with **1** are appreciably lower than those for **6**. The molecular recognition behavior of both **1** and **6** is highly sensitive to the chain length and shape of the alkyl group in amino acids. For **1**, the $\Delta G°$ value increases monotonically with increasing number of the methylene group in all of the examined cases of *L*-amino acids, *i.e.*, *L*-Ala < *L*-Pro < *L*-Leu < *L*-Ile. On the other hand, the compound **6** shows the highest molecular selectivity up to 26.9 between *D*-Leu and *D*-Ala among the amino acids examined. This seems reasonable, since the induced-fit interaction between the hydrophobic cavity of the host compound and the side chain of guest amino acids enhances the complex stability of more complex and hydrophobic *D*-leucine than simpler *D*-alanine.

It is also very interesting that β-cyclodextrin derivatives can recognize not only the size but also chirality of the amino acids. As can be seen from Table I and Figure 5, the enantiomers of *L*/*D*-amino acids show substantially different K_s values and Gibbs free energy changes ($-\Delta G°$), yielding good to excellent chiral recognition. Host compounds **1** and **6** show the same order of *L*/*D* enantioselectivities around 1.4–1.9 for *L*/*D*-serine. On the contrary, both of them show the same *D*/*L* enantioselectivities up to 2.2 for *D*/*L*-cysteine. Unexpectedly, for the smallest alanine, modified β-cyclodextrins **1** and **6** exhibit appreciably higher chiral recognition; the enantioselectivities are 3.9 ($\Delta\Delta G° = -3.4\,\mathrm{kJ\cdot mol^{-1}}$) and 3.5 ($\Delta\Delta G° = 3.1\,\mathrm{kJ\cdot mol^{-1}}$), respectively. However, for the largest leucine, compound **1** cannot recognize the chirality of *D*/*L*-leucine, whereas the compound **6** shows the highest chiral recognition for *D*/*L*-leucine; the *D*/*L* enantioselectivity is 6.0 ($\Delta\Delta G° = -4.4\,\mathrm{kJ\cdot mol^{-1}}$).

Examinations of CPK molecular models indicate that the higher enantioselectivity of **1** and **6** for alanine over serine and cysteine may be attributed to molecular chirality of the guests and the aromatic group originally perching on the edge of β-cyclodextrin cavity. Since the aromatic moiety embedded in the host compound is expected to reduce the volume of β-cyclodextrin cavity. The best size-fit relationship

between the smallest alanine and the volume-reduced cavity may enhance the complex stability, and there must be the strict complementary geometrical relationship between the β-cyclodextrin cavity and alanine. The much enhanced enantioselectivity of **6** for *D*-leucine may be attributed to its more flexible benzyl moiety which can adjust the orientation of guest molecule accommodated in the cyclodextrin cavity, satisfying the strict complementary geometrical requirements.

Mono-[6-(*o*-tolylseleno)-6-deoxy]-β-cyclodextrin (2), Mono-[6-(*m*-tolylseleno)-6-deoxy]-β-cyclodextrin (3), and Mono-[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin (4)

The structural difference among host compounds **2**–**4** is only the location of the methyl group in the benzene ring. As can be seen from Table I and Figure 5, inclusion complexation of the *p*-isomer **4** affords more stable complexes with all of *D*-amino acids than the corresponding *L*-isomer except for the *D*-serine, giving fairly good *D*/*L* enantioselectivity: *i.e.*, 3.2 ($\Delta\Delta G^\circ = -2.9\,\mathrm{kJ\cdot mol^{-1}}$) for alanine, 1.6 ($\Delta\Delta G^\circ = -1.2\,\mathrm{kJ\cdot mol^{-1}}$) for cysteine, 4.3 ($\Delta\Delta G^\circ = -3.6\,\mathrm{kJ\cdot mol^{-1}}$) for leucine, and 4.7 ($\Delta\Delta G^\circ = 3.9\,\mathrm{kJ\cdot mol^{-1}}$) for serine. As compared with compound **4**, the *o*-isomer **2** displays the very high *L*/*D* enantioselectivity for alanine up to 27. However, compound **2** only shows poor *D*/*L* enantioselectivities around 1.3–1.9 for serine, cysteine and leucine. Contrary to the *o*- and *p*-isomer, inclusion complexation with the *m*-isomer **3** displays relatively high *L*/*D* enantioselectivities up to 3.4 ($\Delta\Delta G^\circ = 3.0\,\mathrm{kJ\cdot mol^{-1}}$) for leucine and weak *D*/*L*-enantioselectivities around 1.5–1.7 for alanine and serine. One possible explanation for drastic differences between the *o*- and *p*-tolyl hosts (**2** and **4**) and the *m*-tolyl host (**3**) would be the substituent effect, the *m*-substituent might be able to adjust the orientation of the tolyl moiety to bind more precisely the amino acids with particular size/shape or chirality.

Mono-[6-(*p*-chlorophenylseleno)-6-deoxy]-β-cyclodextrin (5)

As shown in Table I and Figure 5, a tendency analogues to β-cyclodextrin derivative **4**, possessing a *p*-tolyl moiety, is seen in the free energy change ($-\Delta G^\circ$) and the *L*/*D*-enantioselectivities of the modified β-cyclodextrin **5** for all the amino acids except for alanine. The difference in complexation behavior of compounds **4** and **5** with alanine may be attributed to the electronic effect of substituent. Somewhat unexpectedly, the host compound **5**, possessing a *p*-chlorophenyl chromophore, gave enhanced enantioselectivities for all the amino acids examined. These results indicate that the microstructural change of the host molecule apparently governs the complexation phenomena to some extent besides the size and shape of the guest molecule [8].

Mono-[6-(naphthylseleno)-6-deoxy]-β-cyclodextrin (7)

As can be seen from Table I, no inclusion of compound **7** was observed for all the amino acids examined. One reasonable explanation is that the naphthyl moiety of **7** has been embedded into the β-cyclodextrin cavity to form tight intermolecular inclusion complex through self-inclusion. We have reported that modified cyclodextrins give highly stable complexes with some naphthalene derivatives whose stability constants are as high as 10^5 [14]. This indicates that naphthalene derivatives nicely fit into the cavity fulfilling the strict size/shape-fit relationship. Therefore, guest amino acid molecule cannot compete with the naphthyl substituent embedded into the β-cyclodextrin cavity of compound **7**.

CONCLUSIONS

In this paper we investigated the inclusion complexation behavior of seven modified cyclo-

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dextrins with a series of aliphatic amino acids. These results indicate that size/shape-fit, induced-fit, substituent effect and multipoint recognition mechanism play crucial roles in the inclusion complexation. For the smallest alanine, the modified cyclodextrins display different, even opposite, behavior upon chiral recognition. Especially, compound **2** gives the highest *L/D* enantioselectivity for alanine up to 27. This may be attributed to the best size-fit and strict complementary geometrical relationships between the smallest alanine and the volume-reduced cavity of the β-cyclodextrin derivative caused by sidearm's self-inclusion. However, all the host compounds except for **3** show the same trends in *L/D* (or very weak *D/L*) enantioselectivity for serine and *D/L* enantioselectivity for cysteine and leucine. One possible explanation for the unusual trends observed for compound **3** is the effect of *m*-substitution. The *m*-tolylseleno moiety can adjust orientation to satisfy the strict complementary geometrical requirements for the inclusion of *D*-serine, *L*-cysteine and *L*-leucine. The *D*-isomers of cysteine and leucine afford more stable complexes with all of host compounds may be attributed to the strict induced-fit and complementary geometrical relationships between host and guest. The selectivity inversion of serine and cysteine indicates that hydrogen-bonding play an important role in inclusion complexation.

EXPERIMENTAL SECTION

General procedure

Elemental analyses were performed on a Perkin-Elmer-240 instrument. ^{1}H NMR spectra were recorded at 200 MHz in [D]$_6$-dimethyl sulfoxide ([D]$_6$-DMSO) on a Bruker AM200 spectrometer. FT-IR and UC spectra were obtained on a Nicolet FT-IR 5DX and Shimadzu UV-2401 spectrometer, respectively. Circular dichroism (CD) spectra were recorded on a JASCO J-720 spectropolarimeter.

Materials

Commercially available amino acids (Tianjin Chemical Reagents Co.) were used without further purification. β-Cyclodextrin of reagent grade (Suzhou Monosodium Glutamate Works) was recrystallized twice from water and dried in vacuo for 12 h at 100°C. *N,N*-Dimethylformamide (DMF) was dried over calcium hydride for two days and then distilled under a reduced pressure prior to use. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for UV-vis spectral titration.

Synthesis of Mono-[6-(phenylseleno)-6-deoxy]-β-cyclodextrin (1)

Mono-[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (6-OTs-β-CD) was prepared by a reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in dry pyridine [28]. Compound **1** was synthesized by the reaction of mono-[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (6-OTs-β-CD) with diphenyl diselenide [29a] according to the following procedures. Sodium borohydride (0.037 g, 1 mmol) was added to the yellow solution of diphenyl diselenide (0.156 g, 0.5 mmol) in dry ethanol (50 ml) with stirring under nitrogen at room temperature. Once the solution turned to colorless, a solution of mono-[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin (1.29 g, 1 mmol) in dry DMF (75 ml) was added dropwise into the solution and heated to 60°C for 2 h with stirring. The resultant solution was evaporated under a reduced pressure to give light-yellow powder, which was dissolved in a minimum amount of hot water, and then the solution was poured into acetone (100 ml). The precipitate formed was filtrated to give white powder. The crude product was purified by three recrystallization from water and dried in vacuo to give a pure sample (yield 45%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO,

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25 °C, TMS): δ2.8–3.9(m, 40 H), 4.0–4.6(m, 8 H), 4.8–5.2(m, 7 H), 5.3–5.8(m, 14H), 7.1–7.9(m, Ar 5H). IR(KBr): ν = 3386.5, 2914.5, 1731.7, 1698.5, 1629.2, 1600.7, 1558.2, 1537.6, 1513.6, 1397.7, 1363.5, 1302.6, 1273.5, 1232.8, 1170.3, 1149.3, 1073.2, 1023.2, 939.7, 883.5, 830.0, 774.6, 751.5, 726.9, 699.1, 661.6 cm^{-1}. UV/vis (water): λ_{max} (ε) = 268.4 nm (870). $C_{48}H_{74}O_{34}Se \cdot 2H_2O$ (1310.1): calcd C 43.48, H 5.93; found C 43.57, H 5.55.

Synthesis of Mono-[6-(*o*-tolylseleno)-6-deoxy]-β-cyclodextrin (2)

Compound **2** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and di(*o*-tolyl) diselenide [29b], according to the procedures similar to those employed in the synthesis of **1** (yield 40%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO, 25°C, TMS): δ2.22(3H), 3.1–3.8(m, 40H), 4.0–4.7(m, 8H), 4.8–5.2(7H), 5.3–5.8(m, 14H), 7.0–7.7(m, Ar 4H). IR(KBr) ν = 3320.5, 2908.5, 1653.2, 1599.6, 1407.9, 1363.6, 1330.1, 1297.2, 1237.7, 1148.9, 1072.6, 1021.9, 940.0, 843.6, 749.3, 697.8, 658.3 cm^{-1}. UV/vis (water): λ_{max} (ε) = 263.6 nm (2048). $C_{49}H_{76}O_{34}Se \cdot 5H_2O$ (1378.2): calcd C 42.66, H 6.29; found C 42.64, H 5.89.

Synthesis of Mono-[6-(*m*-tolylseleno)-6-deoxy]-β-cyclodextrin (3)

Compound **3** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and di(*m*-tolyl) diselenide [29b], according to the procedures similar to those employed in the synthesis of **1** (yield 42%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO, 25°C, TMS): δ2.23(3H), 3.1–3.8(m, 40H), 4.0–4.7(m, 8H), 4.8–5.2(7H), 5.3–5.8(m, 14H), 7.0–7.4(m, Ar 4H). IR(KBr) ν = 3323.5, 2908.5, 1646.6, 1597.8, 1571.5, 1509.1, 1406.3, 1363.4, 1330.2, 1296.7, 1270.3, 1230.0, 1148.7, 1072.0, 1022.5, 937.5, 889.7, 852.2, 749.8, 697.9, 665.4 cm^{-1}. UV/vis (water): λ_{max} (ε) = 267.0 nm (2266). $C_{49}H_{76}O_{34}Se \cdot 4H_2O$ (1360.1): calcd C 43.27, H 6.22; found C 43.43, H 6.08.

Synthesis of Mono-[6-(*p*-tolylseleno)-6-deoxy]-β-cyclodextrin (4)

Compound **4** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and di(*p*-tolyl) diselenide [29a], according to the procedures similar to those employed in the synthesis of **1** (yield 47%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO, 25°C, TMS): δ2.1(3H), 3.1–3.8(m, 40H), 4.0–4.6(m, 8H), 4.8–5.2(7H), 5.3–5.8(m, 14H), 7.1–7.7(m, Ar 4H). IR(KBr) ν = 3383.0, 2914.0, 1371.8, 1698.0, 1632.0, 1556.3, 1512.7, 1397.8, 1364.9, 1297.3, 1267.4, 1233.8, 1149.3, 1072.9, 1023.3, 939.6, 890.2, 799.4, 772.9, 751.5, 699.7, 660.2 cm^{-1}. UV/vis (water): λ_{max} (ε) = 224.8 nm (9788), 266.8 nm (1262), 272.8 nm (1161). $C_{49}H_{76}O_{34}Se \cdot 2H_2O$ (1324.1): calcd C 44.40, H 6.09; found C 44.32, H 6.01.

Synthesis of Mono-[6-(*p*-chlorophenylseleno)-6-deoxy]-β-cyclodextrin (5)

Compound **5** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and di(*p*-chlorophenyl) diselenide [29c], according to the procedures similar to those employed in the synthesis of **1** (yield 55%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO, 25°C, TMS): δ3.3–4.1(m, 40H), 4.6–4.8(m, 8H), 4.8–5.4(7H), 5.5–6.2(m, 14H), 7.4–7.8(m, Ar 4H). IR(KBr) ν = 3333.0, 2913.0, 1656.2, 1474.5, 1410.7, 1364.8, 1333.5, 1306.8, 1250.7, 1151.1, 1074.1, 1022.7, 1000.1, 941.0, 834.5, 809.4, 751.1, 700.3, 663.8, 604.8 cm^{-1}. UV/vis (water): λ_{max} (ε) = 225.6 nm (10140), 268.0 nm (1472), 273.0 nm (15470). $C_{48}H_{73}O_{34}SeCl \cdot 6H_2O$ (1419.6): calcd C 40.70, H 6.05; found C 40.41, H 5.70.

Synthesis of Mono-[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (6)

Compound **6** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and dibenzyl diselenide [29d], according to the procedures similar to those employed in the synthesis of **1** (yield 50%). ^{1}H NMR (200 MHz, [D]$_6$-DMSO,

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25°C, TMS): δ3.1–3.9(m, 40H), 4.1–4.6(m, 8H), 4.8–5.2(9H), 5.3–5.8(m, 14H), 7.3(m, Ar 5H). IR(KBr) ν = 3369.0, 2912.5, 1730.9, 1701.5, 1638.6, 1615.4, 1574.6, 1536.7, 1514.6, 1398.6, 1365.0, 1336.5, 1302.9, 1273.9, 1235.1, 1149.4, 1127.1, 1073.8, 1022.3, 938.4, 885.6, 789.7, 769.3, 692.7, 658.7 cm^{-1}. UV/vis (water): λ_{max} (ε) = 260.2 nm (613). $C_{49}H_{76}O_{34}Se{\cdot}6H_2O$ (1396.2): calcd C 42.15, H 6.35; found C 42.12, H 6.10.

Synthesis of Mono-(6-naphthylseleno)-6-deoxy]-β-cyclodextrin (7)

Compound **7** was prepared from mono-[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and dinaphthyl diselenide [29e], according to the procedures similar to those employed in the synthesis of **1** (yield 55%). ^1H NMR (200 MHz, [D]$_6$-DMSO, 25°C, TMS): δ3.2–3.8(m, 40H), 4.3–4.6(m, 8H), 4.8–5.2(9H), 5.6–6.0(m, 14H), 7.3–8.2(m, Ar 7H). IR(KBr) ν = 3306.5, 2906.5, 1655.0, 1630.3, 1589.5, 1507.9, 1473.7, 1407.4, 1363.4, 1327.7, 1291.7, 1264.2, 1148.1, 1070.2, 1022.3, 934.2, 848.8, 788.6, 749.8, 697.4, 669.4 cm^{-1}. UV/vis (water): λ_{max} (ε) = 224.6 nm (44680), 284.8 nm (6074). $C_{52}H_{76}O_{34}Se{\cdot}3H_2O$ (1378.2): calcd C 45.32, H 6.00; found C 45.42, H 5.76.

Spectral Measurements

The complex stability constants of modified β-cyclodextrins **1–7** with some selected amino acids were determined by the UV spectrometry. The UV spectral titrations of a series of solutions containing β-cyclodextrin derivatives **1–7** (5×10^{-5} mol·dm^{-3}) were performed in buffered aqueous solution (pH 7.20) at 25.0 °C.

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