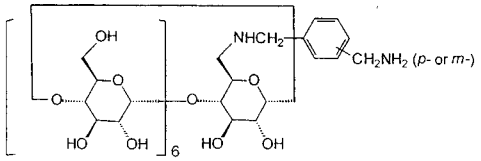
Notes

Chiral Discrimination of Phenylacetic Acid Derivatives by Xylylenediamine-Modified β-Cyclodextrins

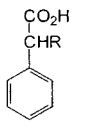
Kwanghee Koh Park,* Han Sung Lim, and Joon Woo Park†

Department of Chemistry, Chungnam National University, Taejon 305-764, Korea
†Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
Received September 26, 1998

Cyclodextrins (CDs) are cyclic oligosaccharides and have hydrophobic cavities capable of forming inclusion complexes with a variety of organic molecules in aqueous solution. They have attracted widespread interest as enzyme mimic[1] and have been applied in various types of chemical analysis.[2] It is known that the inclusion complexation between CDs and the substrate causes chemical shift changes of both the host and the guest protons in NMR spectra. Since the cavities of CDs are chiral, CDs and their derivatives form diastereomeric inclusion complexes with chiral guests. Thus chiral discrimination is usually observed in NMR spectra of the complexes due to the difference in the stability and/or the difference in the complexation-induced chemical shifts between the diastereomeric complexes.[3,4] Though the difference in stability of the complexes is required for resolution of the enantiomers by HPLC using CDs and their derivatives, large difference in the complexation-induced chemical shift with similar stability is desirable for better discrimination of the enantiomers by NMR spectroscopy. In the present study, we synthesized xylylenediamine-modified β-CDs **1** and investigated the inclusion complexation behavior with the aromatic guests **2a-b** by NMR spectroscopy. The modified β-CDs **1** exhibit the desired properties of chiral shift reagents for **2a** and **2b**.



1a, *p*-; **1b**, *m*-



2a, R=OMe; **2b**, R=CH_3

1a and **1b** were prepared by reacting mono(6-O-tosyl)-β-CD[5] with the corresponding xylylenediamine in DMF and characterized by NMR and FAB MS data. ^{1}H NMR spectra of the HCl salts of **1** show characteristic peaks at δ 7.6, 5.2-5.05, and 4.45-4.25 with the integral ratio of 4 : 7 : 4, which correspond to the phenyl protons, anomeric protons of β-CD moiety, and four protons of two methylene groups in the xylylenediamine moiety, respectively. ^{1}H NMR spectra of **1** in free base form don't show the peaks at δ 4.45-4.25: the peaks of two methylene groups in the unprotonated xylylenediamine moiety appear more upfield and overlap with β-CD peaks at δ 4.0-3.5.

To test the ability of **1** as chiral shift reagent for various aromatic guests, NMR spectra of the equimolar (15 mM) mixtures of **1** and racemic substrates **2** in D_2O were taken. The methoxy protons of (*R*/*S*) **2a** are clearly split into two singlets, and the methyl doublet of (*R*/*S*) **2b** is partially split into two doublets in the presence of the hosts **1** (Figure 1**)**. No noticeable difference in the effects of **1a** and **1b** on the ^{1}H NMR spectra of **2a** and **2b** is observed. The methine protons of **2a** and **2b** are hard to be analyzed due to overlap with either HOD peak (in case of **2a**) or β-CD peak (in case of **2b**). In agreement with a previous report on **2b**,[4] the enantiodiscrimination of the racemic **2a** or **2b** is not observed in the

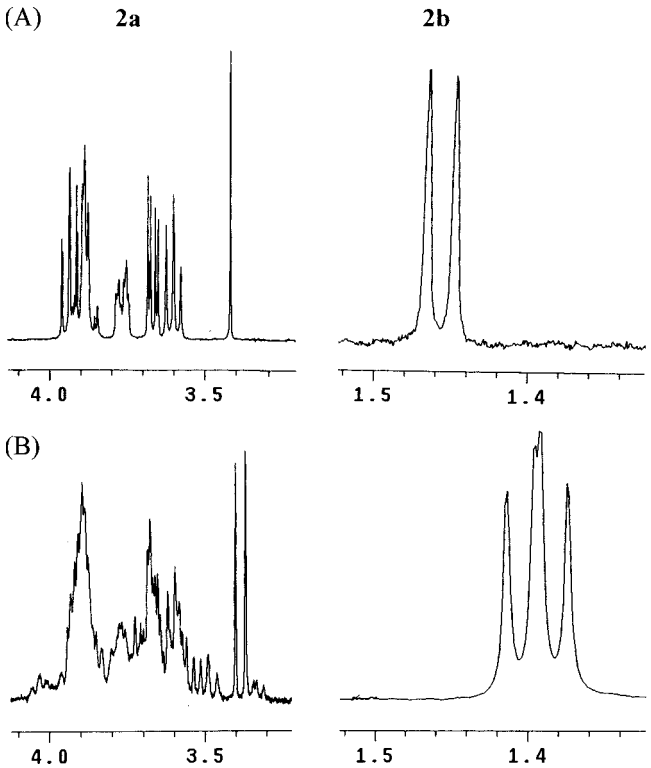


Figure 1. ^{1}H NMR spectra of α-methoxyphenylacetic acid **2a** in δ4.1-3.2 region and 2-phenylpropionic acid **2b** in δ 1.35 1.50 region in D_2O at 25 °C in the presence of β-CD (A) or *p*-xylylenediamine-modified β-CD **1a** (B). The concentrations of the host and the guest are equimolar (15mM). The mixtures with **1b** gave essentially the same spectra as those with **1a**.

presence of native β-CD. On the other hand, the addition of the hosts **1** causes no additional peak separation in the spectra of α-methylbenzylamine whereas native β-CD splits its methine quartet into two quartets.[4] Dipolar interaction between the guests **2a**-**2b** and the hosts **1** might be responsible for the better enantiodiscrimination for the acidic guests by the amine-functionalized hosts.

Enantiomeric compositions of **2a** are determined by using **1a** as a chiral solvating agent. NMR spectra of the synthetic mixtures of various ratios of (*R*) and (*S*)-**2a**[6] were taken in the presence of equimolar (15 mM) concentration of **1a** (data not shown). It was found that the integration ratios of methoxy protons corresponding to the respective enantiomers reflect the actual concentration ratios in the synthetic mixtures.

To delineate the origin of the chiral discrimination by **1**, we carried out the NMR titration of (*R*) or (*S*)-**2a** with *p*-xyxlylenediamine-modified β-CD **1a**.[7] A series of NMR spectra of (*R*) or (*S*)-α-methoxyphenylacetic acid in the presence of the host **1a** with varying concentration ratios of the host to the guest, [**1a**]/[**2a**] at fixed concentration of [**2a**] = 3 mM and ionic strength of [NaCl] = 40 mM were taken. The addition of the host moves the methoxy protons of **2a** upfield and the magnitudes of the observed chemical shift changes, Δδ of the methoxy protons are measured. The dependence of Δδ on the concentration of **1a** is shown in Figure 2.

Assuming 1 : 1 complexation between the host and the guest, Δδ is related to the ratio between the initial concentrations of the host and the guest, $[H]_o/[G]_o = \gamma$, and the binding constant of the guest with the host, *K*, by equation (1).[7]

$$\Delta\delta = 0.5\,\Delta\delta_c\,[1 + \gamma + 1/K[G]_o - \{(\gamma - 1 + 1/K[G]_o)^2 + 4/K[G]_o\}^{1/2}] \quad (1)$$

where $\Delta\delta_c$ is the chemical shift change expected when all of the guest molecules form the complex. The experimental data fit well with the equation (see Figure 2) and the binding constants of **2a** with **1a** are found to be essentially the same between the enantiomers: 71(±12) M^{-1} for the *R*-isomer and 73(±13) M^{-1} for the *S*-isomer. The $\Delta\delta_c$ value of the *S*-isomer is 0.140 ppm and is about 3.3 times greater than that of *R*-isomer. The binding constants between **2a** and native β-CD were also determined similarly. Since the chemical shift of methoxy protons of **2a** remains unchanged by the addition of β-CD**,** we titrated 5 mM β-CD solution with **2a**. All the C-H protons of β-CD move upfield by the addition of **2a** and the chemical shift changes for H3 and H5 protons of β-CD[4] are most significant. The analysis of Δδ *vs* [**2a**] data gives the binding constant as 90(±5) M^{-1} for both *R*- and *S*- isomers. Also no noticeable difference in $\Delta\delta_c$ value between the enantiomers is observed: $\Delta\delta_c$ value for H3 proton is 0.178 ppm.

To get information about the structures of the host-guest complexes and the origin of chiral discrimination by **1a**, we carried out molecular modeling calculation. The minimum energy conformation of **1a** was that the xylyl group is deeply embedded into the cavity of β-CD and the terminal ammonium group locates at the wider opening (secondary face) of β-CD. Inclusion of phenyl group of **2a** to **1a** from the secondary face appears to be favored by ca. 5 kcal/mol, compared to that from the primary face. Figure 3 shows the energy-minimized structures of **1a**/**2a** complexes formed by inclusion from the secondary face. Both carboxylate and methoxy oxygen atoms of *S*-enantiomer form hydrogen bonds with hydrogen atoms of C_2-OH and C_3-OH of the G7 glucose ring, respectively: we label the glucose rings of β-CD clockwise when viewed from the primary face as G1, G2 . . G7 starting from the functional group-appended ring. On the other hand, only a carboxylate oxygen atom is hydrogen bonded to either C_3-OH of G3 or C_2-OH of G4 in the *R*-enantiomer. We believe that such difference in the structure of the complexes results in difference in the complexation-induced chemical shift of the guest molecule. For the native β-CD, the opening of the secondary face may be too wide and the guest molecule may be rattle around inside the cavity giving no appreciable chiral discrimination. The gas phase modeling also suggested that the complexation is

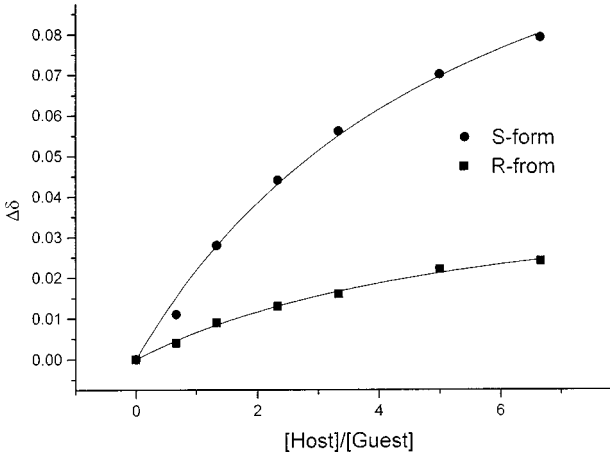


Figure 2. Variation of the observed chemical shift changes, Δδ of the methoxy protons of the guests, (*R*) and (*S*) α-methoxyphenylacetic acid **2a** in the presence of the host, *p*-xylylenediamine-modified β-CD **1a** with the ratios of [Host]/[Guest]. The concentration of guest was fixed at 3.0 mM and ionic strength of the media was held constant at 0.040 M with NaCl.

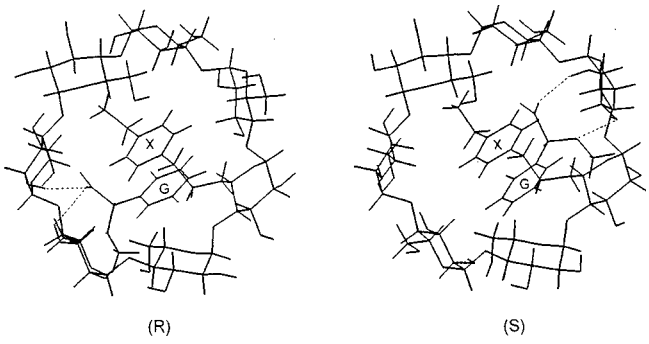


Figure 3. Stereoview of the inclusion complexes of (*R*) and (*S*) α-methoxyphenylacetic acid **2a** with *p*-xylylenediamine-modified β-CD **1a**. View is from the primary hydroxyl side of the host with oblique angle. The phenyl groups of the host and the guest molecules are marked as X and G, respectively. Hydrogen-bondings are shown as dotted lines.

favored energetically by 24.0 kcal/mol for the *R*-isomer and 24.6 kcal/mol for the *S*-isomer. The 0.6 kcal/mol difference between the two enantiomers seems to be too small to affect the binding constant significantly. This accords well with our result.

In conclusion, we have demonstrated the synthesis of *p*- or *m*-xylylenediamine-modified β-CD **1** and their ability of chiral discrimination for guests **2a** and **2b**. The discrimination arises not from the difference in the stability of complexes but from the structures of complexes formed by inclusion of phenyl group from the secondary face of β-CD. Molecular modeling suggests that the xylyl group is deeply embedded in the cavity of β-CD. This, combined with electrostatic interaction, results in induced-fit and specific orientation of the anionic guest molecule inserted from the secondary face of β-CD. The methoxy oxygen atom of the *S*-isomer is hydrogen bonded with hydrogen atom of hydroxy group of β-CD, while such hydrogen bonding is not feasible for the *R*-isomer.

Experimental Section

(*R*), (*S*), and (*R/S*) forms of **2a** were prepared from the corresponding mandelic acid by a reported procedure.[6] ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 spectrometer. HCl salts of the hosts **1** and sodium salts of the guests **2a**-**b** were used for NMR sample preparation. Molecular model calculation was performed using CVFF force field in the Insight II/Discover program package.[8]

Xylylenediamine Modified β-Cyclodextrins (1a) and (1b). 1a and **1b** were prepared by reacting mono(6-O-tosyl)-β-CD[5] with 5-7 molar excess of the corresponding xylylenediamine in dry DMF at 75-80 °C for 20 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in minimum amount of water. The product was precipitated by addition of acetone. The precipitates were collected, dissolved in minimum amount of water, re-precipitated by addition of acetone, and then purified by cation-exchange chromatography on a Sephadex CM-25 column.[9] The cation exchange chromatography was carried out by loading the acidified aqueous solution of the product to a Sephadex CM C-25 column and then eluted with linear gradient of NaCl (0-1.0 M). NaCl contained in the product was removed by filtration after selective solubilization of the product in DMF. The analytically pure products **1a** and **1b** were obtained in yields of *ca.* 20%. ^{1}H NMR spectra in D_2O at 25 °C, δ (relative to the residual solvent at 4.810): **1a**·2HCl 7.596 (s, 4H), 5.168 (d, 1H, *J*=3.6), 5.15-5.07 (m, 5H), 5.053 (d, 1H, *J*=3.6), 4.415 (d, 1H, *J*=13), 4.320 (d, 1H, *J*=13), 4.269 (s, 2H), 4.20-4.13 (m, 1H), 4.05-3.50 (m, 39H), 3.48-3.35 (m, 2H); **1b**·2HCl 7.64-7.58 (m, 4H), 5.177 (d, 1H, *J*=3.2), 5.14-5.06 (m, 6H), 4.431 (d, 1H, *J*=14), 4.331 (d, 1H, *J*=14), 4.271 (s, 2H), 4.21-4.15 (m, 1H), 4.05-3.52 (m, 39H), 3.41-3.32 (m, 2H). FAB MS: 1253.4672 for **1a**, and 1253.4679 for **1b** (calcd for $C_{50}H_{80}O_{34}N_2$+H^+ 1253.4671).

Acknowledgement. This work was supported by the Center for Biofunctional Molecules and by the Ministry of Education of the Republic of Korea through the Basic Science Research Institute Program (BSRI-97-3433). NMR spectra were taken at the Center for Research Facilities at Chungnam National University. Authors thank Miss S. K. Lee and Prof. S. Lee of Ewha Womans University for molecular model calculation.

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