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^{1}H NMR Study of the Inclusion Complexes of Chiral Aromatic Guests with β-Cyclodextrin and Its Derivatives: Discrimination of Aromatic Protons and Chiral Recognition

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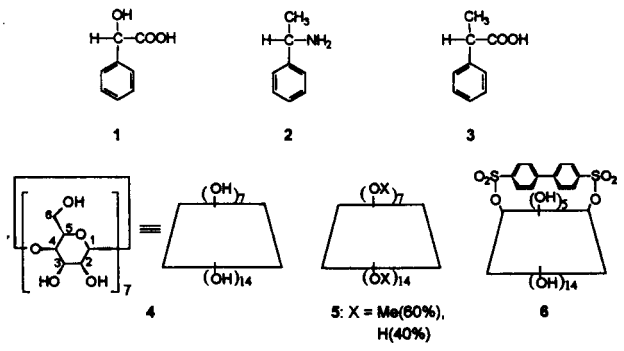
The effects of β-CD, Me-β-CD, and biphenyl capped β-CD on ^{1}H NMR spectra of mandelic acid **1**, α-methylbenzylamine **2** and 2-phenylpropionic acid **3** were investigated. Enantiomeric recognition was observed for mandelic acid **1** by all the hosts used, for α-methylbenzylamine **2** by β-CD and Me-β-CD, and for 2-phenylpropionic acid **3** by Me-β-CD. In the presence of biphenyl-capped β-CD, *o*-, *m*-, and *p*-protons of the phenyl groups of the guests are discriminated due to ring current of the capped biphenyl group. The splitting pattern of the phenyl protons indicates that the phenyl group of the guests is inserted into the β-CD cavity from the secondary hydroxyl side and positioned in close proximity to the capped biphenyl ring. The magnitude of the upfield shifts of H3 and H5 protons of β-CD upon binding of guests **1-3** is similar to that caused by ephedrine or pseudoephedrine, suggesting that the substitution at benzylic carbon atom has little effect on the depth of the insertion of the phenyl group into the β-CD cavity and stability of the inclusion complexes.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six(α), seven(β), and eight(γ) D-glucopyranose units linked by α(1,4) linkages and possess hydrophobic cavities. They form inclusion complexes with a variety of substrates.[1,2] It is known that the interaction between CDs and the substrate causes chemical shift changes of both the host and the guest protons in NMR spectra.[2~11] The changes in the chemical shifts provide information on the structure and stability of the CD-guest inclusion complexes.[2~5] Since the CD cavities have chiral environment, CDs and their derivatives can form diastereomeric inclusion complexes with chiral guests. NMR spectroscopy has been used for investigation of chiral recognition properties of CD cavities and elucidation of optical purity of chiral substances.[6~10] β-CD has a better-fitted cavity for aromatic groups and more readily available than the other CDs and thus much of NMR works with CDs were carried out with β-CD. Recently, there have been several reports on the improvement of chiral recognition properties by using functionalized β-CD.[8~11] Uccello-Barretta *et al.* reported that permethylated β-CD is a versatile and promising host for NMR chiral analysis.[10] Here, we report ^{1}H NMR study of the inclusion complexes of chiral aromatic substrates **1-3** with β-CD **4**, methylated β-CD (Me-β-CD) **5**, and biphenyl-capped β-CD **6**. The capped β-CD **6** is used since the compound exhibits enhanced binding affinity to aromatic guests,[12] compared to β-CD itself, and considerable ring current effect of the capped biphenyl ring on the chemical shifts of guest protons is expected. We investigated the ability of the hosts to recognize chirality of the guest molecules, and determined the chemical shift changes of the host and guest protons induced upon complexation. Chiral recognition of the guest molecules by the hosts **4-6**, and discrimination of phenyl protons by the host **6** are demonstrated.

Experimental

Materials. Biphenyl-capped β-CD **6** was synthesized by reacting β-CD with 4,4′-biphenyldisulfonyl chloride in pyridine as described by Tabushi.[13] β-CD (from Aldrich) was used after drying for a day in a vacuum oven at 100 ℃, and 4,4′-biphenyldisulfonyl chloride (from Aldrich) was used after recrystallization in chloroform. Me-β-CD **5** was obtained from Cyclolab in Hungary, and *R*-, *S*-, *R/S*-mandelic acid



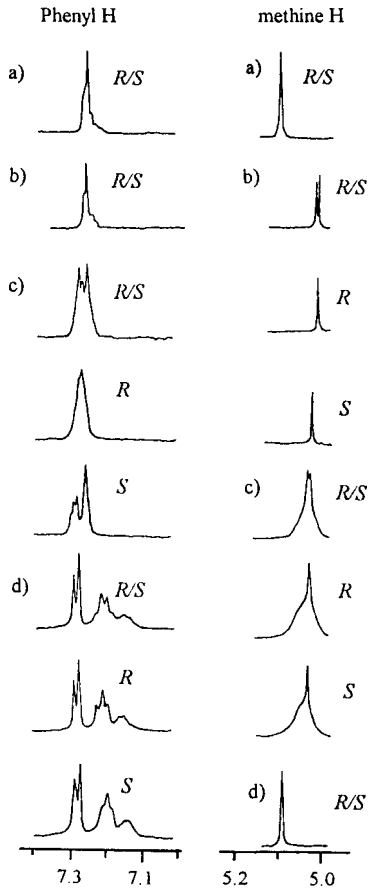


Figure 1. ^{1}H NMR Spectra of mandelic acid in D_2O: a) in host-free solution, b) in β-CD, c) in Me-β-CD, d) in biphenyl-capped β-CD media. In c), methine proton is overlapped with H1 proton of glucose unit of the host.

1, *R*-, *S*-, *R/S*-α-methylbenzylamine **2**, and *R*-, *S*-, *R/S*-2-phenylpropionic acid **3** were purchased from Aldrich and used as received.

^{1}H NMR Studies. Solutions of the substrates and the hosts in D_2O were prepared for NMR measurements. In case of **3**, acetone-d_6 was used as a co-solvent to dissolve the substrate and the final solvent composition was 10 : 1 D_2O-acetone-d_6. The concentrations of the hosts were *ca.* 10 mM for β-CD and 23-40 mM for Me-β-CD and capped-β-CD, and the ratios of [guest]/[host] were maintained to be *ca.* 1. ^{1}H NMR measurements were performed at 25 ℃ with a Bruker AMX 500 (500 MHz) spectrometer, and all chemical shifts are reported in δ (ppm) relative to the residual solvent (H_2O) at 4.63 ppm.

Results and Discussion

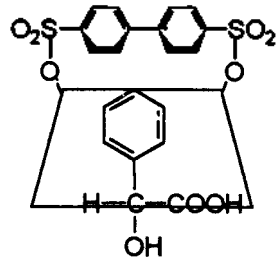
Mandelic Acid 1. Figure 1 shows the ^{1}H NMR spectra of mandelic acid **1** in D_2O without host and in the presence of β-CD **4**, Me-β-CD **5**, and capped-β-CD **6**. The spectra show clearly that the addition of the hosts results in the proton signals of the guest molecule to move considerably, but the extent of the shift change varies with the nature of host molecules and protons. Table 1 summarizes the chemical shift changes (Δδ), $\Delta\delta = \delta_{\text{host free}} - \delta_{\text{host}}$.

The Δδ value for the methine proton is much greater in β-CD or Me-β-CD medium than in biphenyl-capped β-CD. Enantiorecognition is observed in the signal of the methine proton in the presence of β-CD and Me-β-CD: the result in β-CD is consistent with a literature.[8] The difference of chemical shifts between the enantiomers is 0.005 ppm and the *S*-enantiomer is less upfield-shifted than the *R*-enantiomer in both β-CD and Me-β-CD. However, in the presence of the capped β-CD, Δδ of the methine proton is rather

Table 1. ^{1}H NMR Chemical Shift Changes (Δδ) of Various Aromatic Guests in the Presence of β-CD, Me-β-CD, and Biphenyl-capped β-CD[a]

Host	[G]/[H]	H_{phenyl}	$H_{methine}$	H_{methyl}
		mandelic acid		
β-CD	1.0	<0.01 (*R/S*)	0.095 (*R*), 0.090 (*S*)	
Me-β-CD	1.2	<0.02 (*R/S*)	0.087 (*R*), 0.082 (*S*)	
Capped-β-CD	1.0	<0.01 (*R/S*, *o*-)	0.020 (*R/S*)	
		0.078 (*R*, *m*-), 0.093 (*S*, *m*-)		
		0.139 (*R/S*, *p*-)		
		α-methylbenzylamine		
β-CD	0.9	—[b]	−0.060 (*R*), −0.066 (*S*)	−0.071 (*R/S*)
Me-β-CD	1.3	—[b]	−0.033 (*R*), −0.042 (*S*)	−0.052 (*R/S*)
Capped-β-CD	0.9	0.060[c] (*R/S*, *m*-)	-0.076 (*R/S*)	−0.052 (*R/S*)
		0.198[c] (R/S, p-)		
		2-phenylpropionic acid		
β-CD	0.9	—[b]	—[d]	0.005 (*R/S*)
Me-β-CD	1.1	—[b]	—[d]	−0.007 (*R*), −0.020 (*S*)
Capped-β-CD	1.1	0.045[c] (*R/S*, *m*-)	—[d]	0.050 (*R/S*)
		0.142[c] (*R/S*, *p*-)		

[a] Δδ is obtained by subtracting the chemical shift in the presence of the host from the chemical shift in the absence of the hosts. [b] Precise Δδ is unable to be determined because of the complex nature of the phenyl peaks, but the peak positions are not much changed. [c] Differences relative to the chemical shift of the *ortho* protons. [d] The peak is hidden under the host peaks.



Scheme 1. Model of the complexation between biphenyl-capped β-CD **6** and mandelic acid **1**.

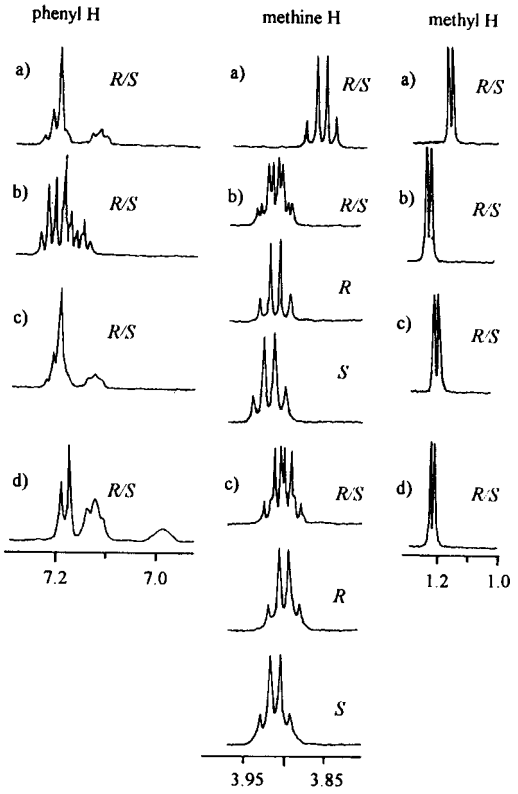


Figure 2. ^{1}H NMR Spectra of α-methylbenzylamine in D_2O: a) in host-free solution, b) in β-CD, c) in Me-β-CD, d) in biphenyl-capped β-CD media. Methine proton in d) is partially overlapped with the host peaks and not shown here.

small and no appreciable discrimination between the enantiomers is observed. The difference in chemical shifts of the enantiomers can be attributed to the formation of diastereomeric host-guest complexes.

The signals of the phenyl protons are hardly resolved in the absence of the hosts as well as in the presence of β-CD and Me-β-CD. However, in the presence of the biphenyl-capped β-CD, the signal is split into three distinct portions with area ratio of 2 : 2 : 1, which can be easily assigned from the area ratio and splitting patterns (see below): the most downfield portion comes from *ortho*-protons of the phenyl ring, the middle portion from *meta*-protons and the most upfield peak from *para*-proton. The *meta*-protons of the phenyl ring show enantiomeric discrimination and the difference in Δδ between the enantiomers is 0.015 ppm and the *R*-enantiomer is less upfield-shifted than the *S*-enantiomer. The *para*-proton is also partially resolved between the enantiomers. This is a great contrast to the behavior observed in the presence of β-CD or Me-β-CD.

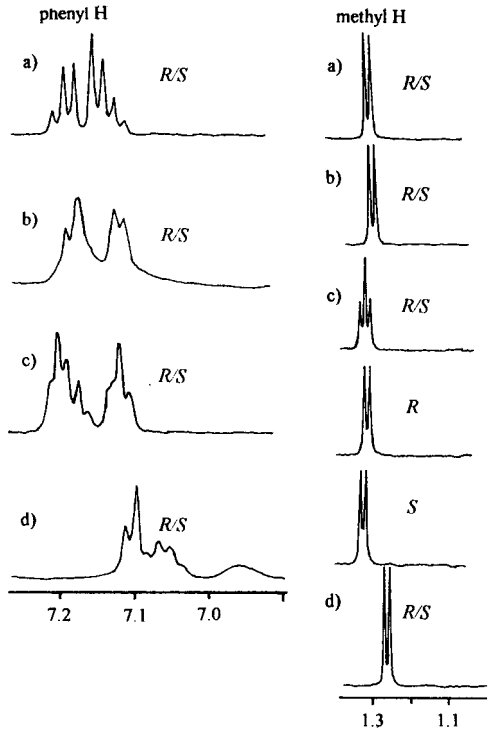


Figure 3. ^{1}H NMR Spectra of 2-phenylpropionic acid in 10 : 1 D_2O-acetone-d_6: a) in host-free solution, b) in β-CD, c) in Me-β-CD, d) in biphenyl-capped β-CD media. Methine proton is hidden by the host peaks in all cases.

Since the primary hydroxyl side of β-CD moiety of the biphenyl-capped β-CD is blocked by the capping, the phenyl ring of mandelic acid is inserted into the cavity of the host from the secondary hydroxyl side and positioned in close proximity to the capped biphenyl group as shown in Scheme 1. The splitting of the phenyl peaks into *o*-, *m*-, and *p*-protons in the presence of biphenyl-capped β-CD can be explained by the ring current effects of the biphenyl ring of the host on the phenyl protons of the guest: the proton closer to the biphenyl group would experience greater effect giving the order of upfield shift as *ortho*-<*meta*-<*para*-protons. The cavity of the capped β-CD would be shallow, compared to β-CD or Me-β-CD, and thus deep insertion of the guest into the cavity would be prohibited. This seems to result in the methine proton to be hardly located inside the cavity and thus the environment around the methine proton would be mostly achiral. This would be a reason why no enantiomeric resolution is observed for the proton in the presence of the biphenyl-capped β-CD.

α-Methylbenzylamine 2 and 2-Phenylpropionic acid 3. Figures 2 and 3 show the ^{1}H NMR spectra of α-methylbenzylamine **2**, and 2-phenylpropionic acid **3**, respectively, in the absence and in the presence of the hosts. In contrast to mandelic acid, the methine signal as well as the methyl peaks of α-methylbenzylamine move downfield in the presence of the hosts. In case of 2-phenylpropionic acid, the me-

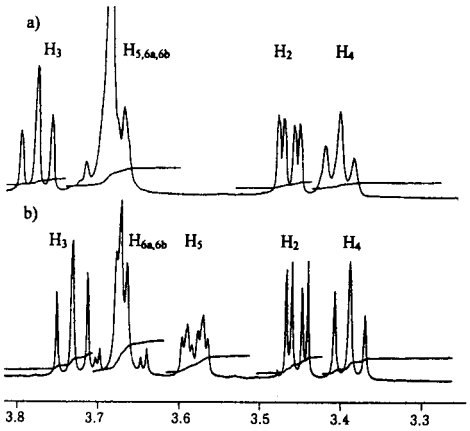


Figure 4. ^{1}H NMR Spectra of β-CD in D_2O: a) guest-free solution, b) in the presence of mandelic acid. For the assignment of peaks, see reference 15.

thyl peaks move upfield in β-CD and the capped β-CD, but downfield in Me-β-CD. In the presence of biphenyl-capped β-CD, the phenyl groups of both α-methylbenzylamine and 2-phenylpropionic acid are again split into *ortho-*, *meta-*, and *para*-protons of the area ratio of 2 : 2 : 1 as observed for mandelic acid. The chemical shift changes of α-methylbenzylamine and 2-phenylpropionic acid are included in Table 1.

It can be seen from Figure 2 that the methine proton of the racemic mixture of α-methylbenzylamine appears as two separate quartets in the presence of β-CD and Me-β-CD. The chemical shift differences between the enantiomers are 0.006 ppm and 0.009 ppm, respectively, and the *S*-enantiomer is more downfield-shifted than the *R*-enantiomer in both cases. No appreciable enantiomeric resolution in the methine proton of α-methylbenzylamine is observed in the capped β-CD, which is reminiscent of the case of mandelic acid in the same host. This might be also explained by the shallowness of the capped β-CD cavity and the binding model shown in Scheme 1. Neither the methyl doublet nor the phenyl peaks of α-methylbenzylamine are discriminated between the enantiomers in any hosts studied here.

In the ^{1}H NMR spectra of 2-phenylpropionic acid **3**, the methine proton is hidden by the host peaks and couldnt be analyzed. Figure 3 indicates that phenyl and methyl protons of 2-phenylpropionic acid show no enantiomeric differences in the presence of β-CD. However, the methyl doublets show enantiomeric discrimination in the presence of Me-β-CD with the chemical shift difference of 0.013 ppm, where the *S*-enantiomer appears at lower field than the *R*-enantiomer.

Effects of the Guest Binding on the ^{1}H NMR Spectra of β-CD. It is known that inclusion of aromatic guests in the CD cavity usually induces a net upfield shift of H3 and H5 protons of glucose units of β-CD which are located on the inner surface of the cavity due to the ring current effects of the aromatic guest, whereas protons H1, H2, and H4 which are on the outer surface of the cavity are little affected upon the complexation.[3,4,14] Figure 4 shows the ^{1}H NMR spectra of β-CD in the absence and in the presence of mandelic acid. It is evident from Figure 4 that the shifts of proton signals of β-CD upon the inclusion of mandelic acid into the cavity follow the general pattern. The chemical shift changes (Δδ) of β-CD protons are summarized in Table 2. Similar trends were observed in the ^{1}H NMR spectra of β-CD in the presence of α-methylbenzylamine and 2-phenylpropionic acid and those Δδ values are also included in Table 2. In case of Me-β-CD and capped β-CD, we have been unable to determine the chemical shift changes of the hosts caused by the guests because of peak overlaps. Rekharsky *et al.*[4] suggested that the magnitude of the upfield shifts, Δδ(H5) and Δδ(H3), and their relative ratio, Δδ(H5)/Δδ(H3), may be used respectively as qualitative measures of the complex stability and the depth of inclusion of the guest into the cavity: the proton H5 is on the narrower rim region, whereas the proton H3 is on the wider rim region, and the Δδ(H5)/Δδ(H3) ratio becomes greater as the guest penetrates deeply into the cavity. The change of chemical shift of the CD protons upon binding of guests **1-3** is similar to that caused by ephedrine or pseudoephedrine,[4] indicating that only phenyl group is included in the CD cavity and substituents attached to benzylic carbon atom contribute little to the inclusion complexation with β-CD. Based on the correlation between thermodynamic parameters of the complexation and the chemical shift changes,[4] the binding constants of the guests **1-3** with β-CD are estimated to be about 100 M^{-1}.

So far, we have described the effects of β-CD, Me-β-CD, and biphenyl capped β-CD on ^{1}H NMR spectra of various aromatic guests and have shown that the hosts cause chemical shift changes of the guest molecules. The sign and magnitude of Δδ are dependent upon the hosts and specific protons of guests. Enantiomeric recognition was observed for mandelic acid by all the hosts used, for α-methylbenzylamine by β-CD and Me-β-CD, and for 2-phenylpropionic acid by Me-β-CD. In the presence of biphenyl-capped β-CD, *o-*, *m-*, and *p*-protons of the phenyl groups of the guests are discriminated due to ring current of the capped biphenyl group. The splitting pattern of the phenyl protons indicates that the phenyl group of the guests is inserted into the β-CD cavity from the secondary hydroxyl side and positioned in

Table 2. ^{1}H NMR Chemical Shift Changes (Δδ) of β-CD's Protons in the Presence of Various Aromatic Guests

Guest	[G]/[H]	H1	H2	H3	H4	H5	H6	H5/H3
mandelic acid	1.0	0.02	0.02	0.05	0.02	0.12	0.03	2.2
α-methylbenzylamine	0.9	0.01	0.01	0.05	<0.01	0.11	0.03	2.0
2-phenylpropionic acid	0.9	<0.01	−0.01	0.08	−0.02	0.12	<0.01	1.5

[a] Δδ is obtained by subtracting the chemical shift in the presence of the guest from the chemical shift in the absence of the guest.

close proximity to the capped biphenyl ring. The magnitude of the upfield shifts of H3 and H5 protons of β-CD upon binding of the guests **1-3** is similar to that caused by ephedrine or pseudoephedrine, suggesting that the substitution at benzylic carbon atom has little effect on the depth of the insertion of the phenyl group into the CD cavity and stability of the inclusion complexes.

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Solvent Effects on the Solvolysis of 1-(4-Methoxyphenyl)-1-phenyl-2,2,2-trifluoroethyl Chloride. Influence of an Electron-Withdrawing α-Substituent on Carbonium Ion Center

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Solvolysis rates of 1-(4-methoxyphenyl)-1-phenyl-2,2,2-trifluoroethyl chloride (**1**) and 1-(4-methoxyphenyl)-1-phenylethyl chloride (**2**) were measured in a variety of aqueous binary solvents, and the solvent effect was treated with the Grunwald-Winstein equation. The solvent effect on the solvolysis of **1** failed to give a single linear correlations using the ordinary Y or Y_{Cl}, but exhibited the wide split pattern which could not be related to the solvent nucleophilicity. The improved correlations with Y_{BnCl} and extended dual-parameter treatment, log $(k/k_o)=mY_{Cl}+hI$ $(m_\Delta Y_\Delta)$, were observed for the solvolysis of **1**. These results suggest that the incipient cationic charge in the solvolysis of **1** is delocalized strongly into the aryl-rings in the transition state. While the solvent effect on the solvolysis of **2** is better correlated with Y or Y_{Cl} than Y_{BnCl} but the linearity is not satisfactory. The correlation is comparably improved by the use of the extended Grunwald-Winstein equation, log $(k/k_o)=0.81Y_{Cl}+0.26N_{OTs}$ ($R=0.994$, $SD=\pm 0.12$), indicating the cationic charge of reaction center of **2** was localized mostly in the transition state.

Introduction

The influence of an electron withdrawing α-substituent in carbonium ion center developed in solvolytic displacement has been studied with important subject.[1] In the previous paper,[2] we have treated the substituent effect on the solvolysis of 1-(4-methoxyphenyl)-1-aryl-2,2,2-trifluoroethyl chlorides based on the Yukawa-Tsuno equation[3] in 80% aqueous ethanol, $\log(k/k_o)=\rho[\sigma^o+r(\sigma^+-\sigma^o)]$, where r is resonance demand, which is the parameter measuring the degree of resonance interaction between the reaction center and benzene π-system. From the small $|\rho|$ and r values ($\rho=-1.84$ and $r=0.918$) in comparison with 1-aryl-1-(trifluoromethyl)ethyl tosylates ($\rho=-6.09$ and $r=1.59$),[4] we concluded that the carbocationic charge in the transition state was dispersed mostly by a strong p-π donor, p-methoxy group.