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Evaluation of Host-Guest Interaction of Cyclodextrins with DL-Alanine β-Naphthylamide by ^{1}H NMR Spectroscopy

Yuko YAMASHOJI,* Minoru TANAKA, and Toshiyuki SHONO
Department of Applied Chemistry, Faculty of Engineering,
Osaka University, Suita, Osaka 565

The host-guest interaction of cyclodextrins (CDs) with L-alanine β-naphthylamide hydrobromide (L-AN) and DL-AN hydrochloride (DL-AN) was studied by ^{1}H NMR. The inclusion complex formation of the guests with β- and γ-CDs in aqueous solution was confirmed by remarkable changes in their chemical shifts. In the case of α-CD, such remarkable changes were not induced, indicating weak or no interaction between the host and the guests.

Cyclodextrins (CDs) are water soluble cyclic oligosaccharides consisting of six or more α-1,4-linked glucose units and called α-, β-, and γ-CDs for six-, seven-, and eight-unit compounds, respectively. One of the well-known properties of CDs is their ability to recognize chirality of guest molecules by including them into the cavities.

In a previous paper,$^{1)}$ we have described the preliminary separation of some racemates on chemically bonded β-CD stationary phases in high-performance liquid chromatography (HPLC). The chiral recognition and separation of DL-AN was successfully attained by this HPLC process using methanol-1% triethylammonium acetate (30:70) at pH 5.1 as an eluent.

NMR spectroscopy is one of the powerful techniques to investigate the mechanism of CD inclusion complex formation process and the structure of their complexes in both the solution and solid state. Recent high resolution NMR spectrometers have especially offered much information about these interests. However, there are only a few reports dealing with chiral recognition of CDs by NMR.$^{2-4)}$

In this communication, we describe the host-guest interaction of α-, β-, and γ-CDs with DL- and L-AN and the distinct chiral recognition of β-CD in aqueous solution.

NMR spectra were measured by a Bruker AM-600 spectrometer (600 MHz) at 20 °C. The concentrations of CDs and the guest compounds were 2.0 X 10^{-3} mol dm^{-3} in D_3PO_4-NaOD buffer at pD 6.0 (ionic strength μ=0.05). ^1H-chemical shifts (ppm) were measured, relative to an external standard of sodium 2,3-dimethyl-2-silapentane-5-sulfonate (DSS) with an accuracy of ± 0.0012 ppm.

Table 1. ^1H-chemical shift changes of α-, β-, and γ-CDs in D_2O at pD 6.0 after addition of DL- or L-AN

	α-CD		β-CD		γ-CD	
Guest	DL	L	DL	L	DL	L
Ratio[a)]	1.16	1.02	1.37	0.79	1.46	1.55
$\Delta\delta_1$	0.02	0.04	0.06	0.05	0.09	0.08
$\Delta\delta_2$	0.02	0.03	0.05	0.04	0.05	0.05
$\Delta\delta_3$	0.05	0.07	0.17	0.15	0.09	0.14
$\Delta\delta_4$	0.02	0.04	0.06	0.05	0.09	0.08
$\Delta\delta_5$	0.02	0.02	0.28	0.24	0.25	0.25
$\Delta\delta_6$	0.02	0.02	0.13	0.12	0.14	0.12
$\Delta\delta_{6'}$	0	0	0.13	0.11	0.11	0.11

a) Mol of guest / mol of CD.

Table 1 gives the 600 MHz ^1H NMR spectral data of CDs before and after addition of DL- or L-AN. The molar ratios of the added guest molecules to CDs were estimated from the integrated areas of their signals. Here, $\Delta\delta_i$ are defined as the chemical shift changes (ppm) of CDs before and after addition of the guests. After the addition, the large upfield shifts were induced for the H-3, H-5, and two H-6 proton resonances of β- or γ-CD. This is ascribed to the ring-current effect of the naphthyl group of the guest included in the host cavity, because these protons are located inside the cavity and strongly affected by the effect. On the other hand, the resonances of the external H-1, H-2, and H-4 protons gave much smaller upfield shifts. It is apparent that the $\Delta\delta_i$ values for β- or γ-CD are larger than those for α-CD (especially, for the H-3, H-5, and H-6 protons). This suggests deep insertion of the naphthyl group into the β- and γ-CD cavities.

Table 2 gives the chemical shifts and coupling constants of DL-AN in the absence of CD determined using ^1H-^1H homonuclear shift correlated spectroscopy (COSY) and J coupling resolved spectroscopy (2DJ). The ^1H-chemical shift changes of L-AN after addition of CDs are given in Table 3. The addition of γ-CD resulted in larger upfield shifts of all the naphthyl proton signals, compared with the β-CD addition. This fact is not convincingly explained by the formation of a 1:1 inclusion complex. It is suggested that the naphthyl protons are strongly affected by the ring current-effect due to the inclusion of the two guests into the host cavity. A large downfield shift of the H-a proton of L-AN was observed after the addition of β-CD. We speculate that the naphthyl moiety of the guest tightly fits into the β-CD cavity. This may bring about a conformational change by which the H-a proton experiences a stronger unshielding effect of the carbonyl group in the guest itself after complexation.

Table 2. Chemical shifts and coupling constants of DL-AN in the absence of CD

Proton	Chemical shift (ppm)	Coupling constant / J							
A	1.73(d)	J_{AB}	7.12						
B	4.33(q)	J_{BA}	7.12						
a	8.06(d)					J_{ab}	2.21	$J_{ac}=J_{ag}=J_{ad}$	0.74
b	7.55(dd)	J_{bc}	8.83			J_{ba}	2.21		
c	7.96(d)	J_{cb}	8.83					$J_{ca}=J_{cd}=J_{cg}$	0.74
d	7.95(d)	J_{de}	8.10			J_{df}	1.48	$J_{dc}=J_{da}=J_{dg}$	0.74
e	7.58(t)	J_{ed}	8.09	J_{ef}	6.80	J_{eg}	1.29	J_{ea}	0.74
f	7.61(t)	J_{fg}	8.04	J_{fe}	7.03	J_{fd}	1.48		
g	7.92(d)	J_{gf}	8.09			J_{ge}	0.92	$J_{ga}=J_{gc}=J_{gd}$	0.74

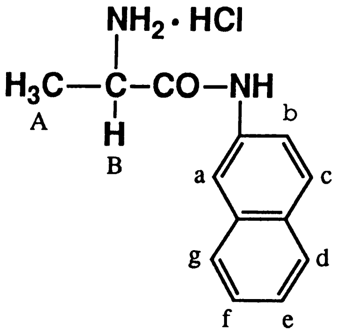

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Table 3. ^{1}H-chemical shift changes of L-AN after addition of α-, β-, and γ-CDs

	α-CD	β-CD	γ-CD
Ratio[a)]	1.02	0.79	1.55
$\Delta\delta CH_3$	0.07	0.05	0.03
$\Delta\delta CH$	0.06	0.04	0.09
$\Delta\delta$ a	0.02	-0.21	0.37
$\Delta\delta$ b	0.03	0.13	0.49
$\Delta\delta$ c	0.02	0.16	0.48
$\Delta\delta$ d	0.02	0.08	0.45
$\Delta\delta$ e	0.05	0.09	0.3
$\Delta\delta$ f	0.06	0.14	0.33
$\Delta\delta$ g	0.04	0.04	0.42

a) Mol of guest / mol of CD.

Addition of β-CD to a solution of DL-AN resulted in duplication of all proton resonances of the guest; the separations were about 0.01 - 0.03 ppm, as shown in Fig. 1. This is ascribed to the different orientation of the D- and L-enantiomers and to their severely restricted motion within the β-CD cavity (i.e., chiral recognition). This duplication in NMR spectra is compatible with the chiral separation in HPLC mentioned above.

Further investigations are now in progress to determine the stoichiometry and the structure of each inclusion complex.

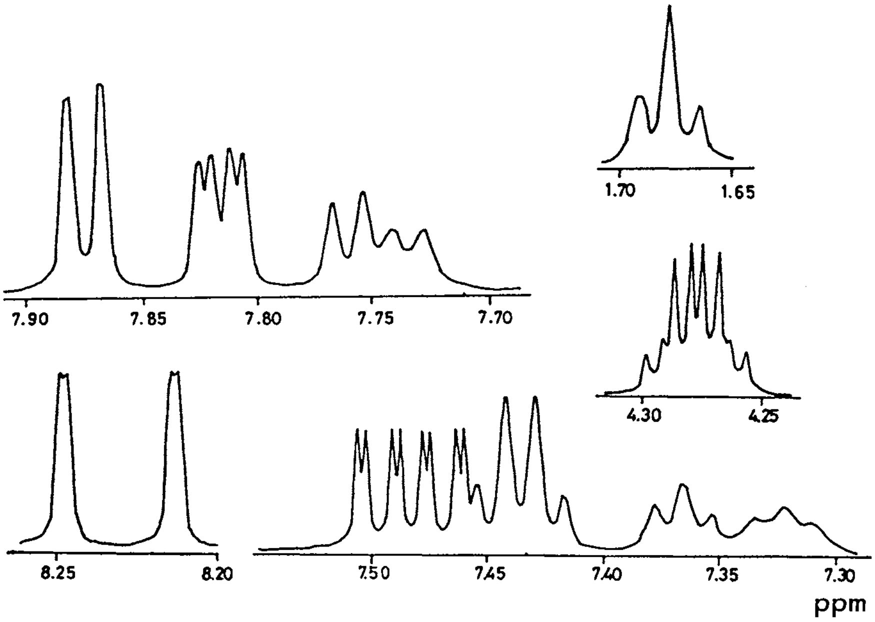

Fig. 1. 600 MHz ^{1}H NMR spectrum of DL-AN in the presence of β-CD (DL-AN/β-CD molar ratio=1.37) in D_2O at pD 6.0.

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