SHORT COMMUNICATIONS

Conformation of β -Cyclodextrin-2-Naphthalenecarboxylate Inclusion Complex in Aqueous Solution

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Beta-Cyclodextrin (β -CyD) is a cyclic oligomer composed of seven α -glucose units, and forms inclusion complexes with aromatic compounds in aqueous solution.^{1,2} Recently, we reported the selective synthesis of 2,6-naphthalenedicarboxylic acid from 2-naphthalenecarboxylic acid (2-NCA), carbon tetrachloride and copper powder in aqueous alkali by using β -CyD as catalyst.³ In this reaction, β -CyD formed an inclusion complex with the 2-naphthalenecarboxylate (2-NC) anion in the reaction mixture and positional selectivity should depend on the conformation of the inclusion complex.

The circular dichroism spectroscopy of β -CyD complexes with 2-NC anion and 2-naphthylacetate anion revealed that the structure of the 2-substituted naphthalene complex was an axial inclusion.⁴ However, the orientation of the guest molecule was not determined in this literature.⁴

Measurement of ¹H–¹H intermolecular nuclear Overhauser effect (NOE) promotes the investigation of the specific interaction between two different molecules from the information about short-range distances among proton

nuclei.⁵ The rotating frame Overhauser enhancement spectroscopy (ROESY) method is particularly useful for the NOE measurement of moderately large molecules (molecular weight of about 1000).^{6–8} From measurement of the ROESY spectra, Inoue *et al.*⁹ reported that *p*-nitrophenol is preferentially inserted into the cavity of 6-*O*-(α -D-glucopyranosyl)-cyclomaltohexaose with the nitro group first.

This paper describes the determination of the conformation of β -CyD–2-NC inclusion complex by measurements of the ¹H chemical shifts of β -CyD and the ROESY spectrum on the aqueous alkaline solution of β -CyD and 2-NC.

EXPERIMENTAL

The samples for ¹H NMR spectra of a solution of β -CyD (0.1 mol·L^{–1}) and a solution containing β -CyD (0.1 mol·L^{–1}) and 2-NC (0.1 mol·L^{–1}) were prepared in 1 wt% NaOD/D₂O by using 2-NCA as 2-NC. The ¹H NMR spectra were recorded at 400 MHz on a JNM-GX400 FT-NMR spectrometer at 27.0 °C. Two dimensional (2D) ROESY spectrum

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Figure 1. Positional numbers of protons in β -cyclodextrin (β -CyD) and 2-naphthalenecarboxylic acid (2-NCA).

was acquired in a sweep width of 2500 Hz. A spin-lock field was used during the mixing period of 1000 ms and 500 ms in order to minimize magnetization transfer through scalar couplings. Free induction decays which accumulated 128 times at each mixing time were stored in a matrix of 1024×128 . The data matrix was expanded to 1024×512 by zero-filling for column side was multiplied by the sinebell window function prior to the double Fourier transform. Chemical shifts are given in parts per million (ppm) downfield from that of tetramethylsilane in chloroform- d_1 using internal capillary.

RESULTS AND DISCUSSION

The C-1—C-6 protons on the glucose unit of β -CyD are defined as H-1—H-6, respectively, as shown in Figure 1. The C'-1—C'-8 protons on naphthalene group of 2-NCA are defined as the H'-1—H'-8, respectively (see Figure 1).

The 400 MHz ^1H NMR spectrum of a solution containing β -CyD ($0.1 \text{ mol} \cdot \text{L}^{-1}$) and 2-NC ($0.1 \text{ mol} \cdot \text{L}^{-1}$) was compared with that of a solution of β -CyD ($0.1 \text{ mol} \cdot \text{L}^{-1}$). The 2-NCA molecule was converted to 2-NC anion in aqueous alkaline solution. Table I shows the values of ^1H chemical shifts of β -CyD in the absence of 2-NC anion and the presence of 2-NC anion. In the presence of 2-NC anion,

Table I. Proton chemical shifts of β -CyD in the absence (δ_0) and presence (δ) of 2-naphthalenecarboxylate anion^a

Protons of β -CyD	δ_0/ppm^b	δ/ppm^c	$\delta - \delta_0/\text{ppm}^d$
H-1	4.92	4.88	-0.04
H-2	3.49	3.46	-0.03
H-3	3.85	3.76	-0.09
H-4	3.42	3.39	-0.03
H-5	3.77	3.50	-0.27
H-6	3.81	3.66	-0.15

^a Conditions: 400 MHz ^1H NMR at 27°C . ^b β -CyD ($0.1 \text{ mol} \cdot \text{L}^{-1}$) in 1 wt% NaOD/ D_2O solution. ^c β -CyD ($0.1 \text{ mol} \cdot \text{L}^{-1}$) and 2-naphthalenecarboxylate anion ($0.1 \text{ mol} \cdot \text{L}^{-1}$) in 1 wt% NaOD/ D_2O solution. ^d Sign - indicates upfield shift.

all the protons of β -CyD shifted upfield. The upfield shifts of the H-3 (0.09) and H-5 (0.27) atoms located in the interior of the cavity of β -CyD¹⁰ are remarkably larger than those of H-1 (0.04), H-2 (0.03), and H-4 (0.03) atoms located on the outer surface of β -CyD.¹⁰ The upfield shifts are due to the magnetic anisotropy effect of the naphthalene group. These facts indicate that the 2-NC molecule is included in the cavity of β -CyD.

Figure 2 illustrates the ROESY spectrum of the solution containing β -CyD and 2-NC anion, where the J -resolved spectrum of β -CyD is shown on abscissa and that of 2-NC on ordinate. The cross-peaks connecting the H-3 resonance of β -CyD to the H'-1, H'-3, H'-4, and

Figure 2. 2D-ROESY spectrum of a solution containing β -cyclodextrin ($0.1 \text{ mol} \cdot \text{L}^{-1}$) and 2-naphthalenecarboxylate anion ($0.1 \text{ mol} \cdot \text{L}^{-1}$) in 1 wt% NaOD/D₂O at 27.0°C. The projection spectra on the abscissa and ordinate, respectively, were obtained from the J -resolved 2D spectrum.

H'-8 resonances of 2-NC are clearly observed, and those to the H'-5, H'-6, and H'-7 resonances are observable. The cross-peaks connecting the H-5 resonance of β -CyD to the H'-1 and H'-3 resonances of 2-NC are remarkable. The intensity of the cross-peaks connecting the H-5 resonance of β -CyD to the H'-4 and H'-8 resonances of 2-NC are weak. However, the cross-peaks between the H-5 resonance of β -CyD and the H'-6 and H'-7 resonances of 2-NC do not appear. The intensity of the

cross-peak connecting the H-5 resonance to the H'-1 resonance is stronger than that of the cross-peak connecting the H-3 resonance to the H'-1 resonance.

These results indicate that the H'-1 and H'-3 atoms of 2-NC are located near the H-5 atom of β -CyD and the H'-4 and H'-8 atoms of 2-NC lie close to the H-3 atom of β -CyD. The H'-6 and H'-7 atoms of 2-NC are located far from the H-5 atom of β -CyD. Thus, the conformation of β -CyD-2-NC inclusion complex in

aqueous alkali can be proposed, as shown in Figure 3. In this figure, β -CyD is illustrated simply by its cavity: the inner diameter of cavity 6.0 Å for the primary hydroxyl side, 6.4 Å for the secondary hydroxyl side, and the depth of the cavity is 7.9 Å, according to the literature.¹¹ The 2-NC molecule is axially included in the cavity of β -CyD with an orientation which locates the carboxylate group at the primary hydroxyl side of β -CyD and the 5-, 6-, and 7-positions of 2-NC at the secondary hydroxyl side of β -CyD.

The reaction of 2-NCA with carbon tetrachloride and copper powder in aqueous alkali using β -CyD as catalyst gave 2,6-naphthalenedicarboxylic acid (NDA) in 67 mol%, 2,7-NDA in 10 mol%, and 1,6-NDA in 2.4 mol% yield.³

The 6-position of 2-NC was predominantly attacked by the active species formed from

carbon tetrachloride, copper powder and aqueous alkali in this reaction. The conformation of β -CyD-2-NC inclusion complex as shown in Figure 3 is located at the 5-, 6-, and 7-positions of 2-NC outside the β -CyD. The order of jutting-out is as follows:

6- > 7- > 5-position

When the 5-position of 2-NC is attacked by the active species, 1,6-NDA is produced. Consequently, the proposed conformation is consistent with the positional selectivity of the reaction.

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Figure 3. Proposed conformation of the β -cyclodextrin-2-naphthalene carboxylate inclusion complex; ----H-3 and ----H-5 show planes comprised of the corresponding atoms of β -cyclodextrin.