CHEMISTRY LETTERS, pp. 1495 - 1498, 1991.

NMR Studies of Conformation of Viologen-appended β-Cyclodextrin

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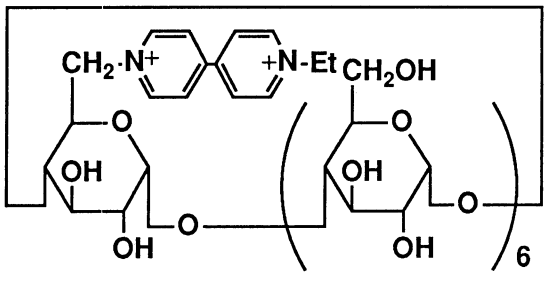
The conformation of viologen-appended β-cyclodextrin was studied by the combination of some kinds of NMR spectroscopic techniques. The long axis of viologen moiety directs approximately perpendicular to the z-axis of β-cyclodextrin but deviates from the center of cavity. Viologen moiety faces the glucopyranose unit B. Its conformational change after making inclusion complex was also studied.

Cyclodextrin (CDx) has a hydrophobic cavity and can make inclusion complexes with many kinds of guests. The hydrophobic cavity of CDx can be used to control a reaction through a microsolvent effect and a steric effect.[1] In order to improve these properties many modified CDx's were synthesized, but in many cases orientations of substituents have not been determined. It is necessary to make clear the conformation of modified CDx, especially the orientation of substituent, to understand the property of modified CDx. We recently demonstrated that the combination of two dimensional (2D) NMR was powerful to investigate the conformation and configuration of modified CDx.[5] Inoue and co-workers also reported the conformational study of modified CDx using NMR.[6] We lately presented viologen-appended β-cyclodextrin ($CDxEV^{2+}$) as a new photosensitized reduction system.[2-4] The photosensitized reduction of viologen residue of $CDxEV^{2+}$ could be controlled with addition of a guest. In this paper, we want to describe the NMR studies of conformation of $CDxEV^{2+}$, especially the orientation of viologen residue.

The 1D ^1H NMR spectrum of $CDxEV^{2+}$ is too complicated to make assignment of its peaks. But the combination of 2D NMR spectra can give many information for the assignment of peaks of $CDxEV^{2+}$. The method of assignment is the following way. At first, peaks were grouped into some spin systems of pyranose units by using HOHAHA spectrum. HOHAHA spectrum is useful to extract a spin system of pyranose unit from an overlapping



$CDxEV^{2+}$

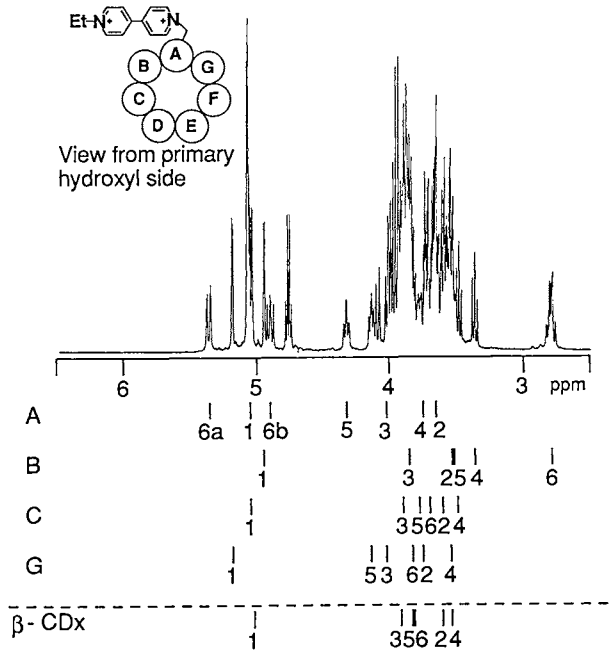


Fig. 1. 500 MHz ^{1}H NMR spectrum of $CDxEV^{2+}$ in D_2O only in the region of resonances for cyclodextrin.

spectrum region. $CDxEV^{2+}$ has peaks for anomeric protons around 5 ppm. Four peaks of them were resolved but the other three peaks were overlapping. Therefore the peaks belonging to four pyranose units could be grouped but the other peaks could not be grouped. Next, all grouped peaks were assigned to protons of each pyranose unit by COSY spectrum. Finally, the sequence of pyranose units was determined by ROESY spectrum. H_1 of a pyranose unit and H_4 of the adjacent pyranose unit are close enough to give NOE. ROESY spectrum is superior to NOESY spectrum to observe NOE in the case of medium-size molecule such as cyclodextrin.[7]

The glucopyranose unit which had largely down-field shifted resonances for H_{6a} and H_{6b} due to the modification with viologen moiety at C_6 position was defined as the glucopyranose unit **A** (**G-A**). The other glucopyranose units were labeled from **G-B** to **G-G** as shown in Fig. 1.[10] The glucopyranose unit of which the H_4 resonance had the negative crosspeak with the H_1 resonance of **G-A** in ROESY spectrum was identified as **G-B.** In a similar way, **G-C** and **G-G** could be determined.

The result of assignment is shown in Fig. 1. **G-B** is a un-modified glucopyranose unit but its resonances for H_{6a} and H_{6b} are abnormally shifted to up-field. This shift is probably attributed to the anisotropic ring current effect from viologen residue. On the other hand, resonances for H_5 and H_3 of **G-A** and **G-G** are shifted to down-field. These shifts are probably due to the electrostatic effect of pyridinum cation and/or anisotropic ring current effect from viologen residue. These indicate that viologen residue faces to **G-B**.

Next, the conformation around C_5-C_6 bond was analyzed. A measured coupling constant, $J_{5,6a}$ or $J_{5,6b}$, is the averaged value of component coupling constants in the three rotamers, gg, gt, and tg, weighted by their fractional populations.[8] On the basis of observed coupling constants, the populations of rotamers around C_5-C_6 bond can be analyzed. The coupling constants ($J_{5,6a}$ and $J_{5,6b}$) of **G-A** and **G-B** could be determined, because their H_6 resonances were separated from other resonances. The coupling constants of these resonances were estimated as the ABX spin system with the spin-simulation program on a Varian's VXR5000S system (Table 1). Both in **G-A** and **G-B**, the rotamer tg scarcely existed, because of steric and/or stereoelectronic interaction.

It is well known that the rotamer tg of D-glucose monomer is little present because of unfavorable parallel 1,3-interaction between C_4-O and C_6-O.[8] In **G-A**, the rotamer gt was major component. This means that viologen residue faces to **G-B**.

From the above considerations and the examination of CPK molecular models, the three dimensional structure of $CDxEV^{2+}$ was estimated as shown in Fig. 2. The angle between the long axis of viologen moiety and the plane through primary hydroxyl groups of each glucose residue is about 30 degrees. The viologen residue deviates from the center of cavity and faces to **G-B**. The primary hydroxyl side has room to include a guest despite of modification at the C_6 position and viologen residue could stack with a photosensitizer at the edge of hydrophobic cavity.

Yamamoto and co-workers had studied the conformation of 6-O-α-glucopyranosyl α-cyclodextrin by NMR.[9] They mentioned that the degeneracy of H_1 resonance was removed by the complexation with p-nitrophenol. The analysis of coupling constants revealed that the dihedral angle between H_1 and H_2 of the glucopyranose unit having a branching glucopyranose unit at the C_6 position was over 10 degrees smaller than those of other units. After making complex with p-nitrophenol, this dihedral angle changed to normal value but the dihedral angles of all units slightly differed from one another. We used 1-adamantane carboxylic acid as a guest in the case of $CDxEV^{2+}$. 1-Adamantane carboxylic acid is round in shape, is well bound to $CDxEV^{2+}$ (K_b = 4.76 x10^4 ($mol^{-1}dm^3$)), and does not exert the ring current effect. So, the extent of distortion of the cavity of $CDxEV^{2+}$ can be evaluated by making the inclusion complex with this guest. Only dihedral angle between H_1 and H_2 of **G-A** was slightly larger than those of **G-B**, **G-C**, and **G-G** before making the complex with this guest (Table 2). After making the complex, the former dihedral angle decreased by 5 degrees but changes of others were small. The degeneracy of H_1 resonances of **G-D** - **G-F** was not removed after making the inclusion complex. H_2 - H_6 resonances partially degenerated after making the inclusion complex. This suggests that the cavity of $CDxEV^{2+}$ is distorted before making the inclusion complex. This conformational change would take place around the α–1,4 linkage rather than the C_1 - C_2 bond. The consideration of

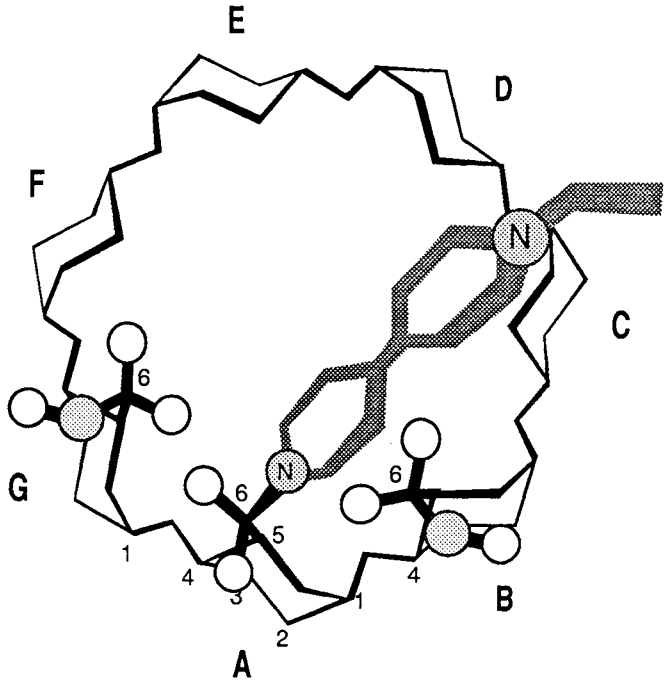


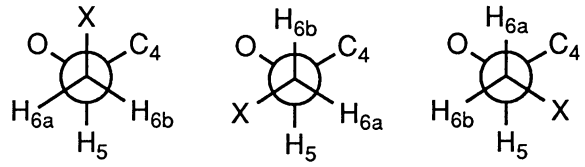
Fig. 2. Structure of viologen-appended β-cyclodextrin as determined by NMR.

Table 1. Calculated Fractional Population of Rotamers of C_5-C_6 Bond, and Observed Coupling Constants ($J_{5,6a}$, $J_{5,6b}$) of **G-A** and **G-B**

	P_{gg}	P_{gt}	P_{tg}	$J_{5,6a}$	$J_{5,6b}$
G-A	0.14	0.86	≈ 0	1.8	9.8
G-B	0.58	0.42	≈ 0	1.8	5.5

$J_{5,6a} = 1.7P_{gg} + 1.9P_{gt} + 11.1P_{tg}$

$J_{5,6b} = 1.5P_{gg} + 11.1P_{gt} + 2.1P_{tg}$



gg gt tg

Table 2. Coupling Constants $J_{1,2}$ and Dihedral Angle between H_1 and H_2 in the Absence and the Presence of Adamantane Carboxylic Acid (ACA)

	Glucose unit	G-A	G-B	G-C	G-G
Without ACA	$J_{1,2}$	3.41	3.66	3.66	3.66
	Dihedral angle	48	45	45	45
With ACA	$J_{1,2}$	3.91	3.66	3.66	3.91
	Dihedral angle	43	45	45	43

detail conformational change after making a inclusion complex is now in progress.

We are grateful to Nihon Shokuhin Kako Co. LTD. for providing us with β-cyclodextrin. This work was supported by a Grant for International Joint Research Project from the NEDO Japan.

References

1) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag (1978).

2) Y. Du, A. Nakamura, and F. Toda, *Bull. Chem. Soc. Jpn.*, **63**, 3351 (1990).

3) Y. Du, T. Harada, A. Nakamura, and F. Toda, *Chem. Lett.*, **1990**, 2235.

4) Y. Du, A. Nakamura, and F. Toda, *J. Incl. Phenom.*, in press.

5) H. Ikeda, Y. Nagano, Y. Du, T. Ikeda, and F. Toda, *Tetrahedron Lett.*, **31**, 5045 (1990).

6) W. Saka, Y. Yamamoto. Y. Inoue, R. Chûjô, K. Takahashi, and K. Hattori, *Bull. Chem. Soc. Jpn.*, **63**, 3175 (1990).

7) A. A. Bothner-By, R. L. Stephens, J. Lee, C. D. Warren, and R. W. Jeanloz, *J. Am. Chem. Soc.* **106**, 811 (1984).

8) D. G. Streefkerk, M. J. A. DE Bie, and J. F. G. Vliegenthart, *Tetrahedron*, **29**, 833 (1973).

9) Y. Yamamoto, Y. Kanda, Y. Inoue, R. Chûjô, and S, Kobayashi, *Chem. Lett.*, **1988**, 495.

10) Some investigators label glucopyranose units in a clockwise direction as viewed from primary hydroxyl side.

(Received May 18, 1991)