Retardation of the Molecular Rotation of *p*-Nitrophenolate Ion in the Cavity of a Positively Charged Derivative of α-Cyclodextrin by Electrostatic Interactions

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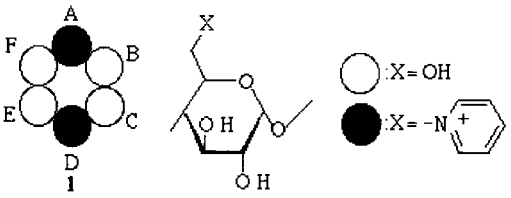
^{1}H NMR signal for the C(5)-H of A, D glucose residues of bis[6^A,6^D-(1-pyridinio)-6^A,6^D-deoxy]-α-cyclodextrin shifted downfield, whereas those of B, E and C, F residues shifted upfield, with the addition of *p*-nitrophenol at pD 11.3. This infers that the molecular rotation of the guest is retarded in the CD cavity.

The complexation of an aromatic molecule with cyclodextrin (CD) generally causes significant changes in the ^{1}H NMR chemical shifts of the C(3)- and C(5)-H's which locate in the interior cavity of CD.[1–3] The changes are caused by the diamagnetic anisotropy (ring-current effect) of the aromatic ring. Each of the C(3)- and C(5)-H's on the different glucose residues of CD receives identical shielding contribution from the included guest because of various averaging factors. The most effective one is that the molecular rotation of a guest within the CD cavity, together with the association–dissociation process of CD complexation, is rapid on NMR time-scale basis.[3] Recently, we have found that the negatively charged *p*-nitrophenolate ion (*p*NP) is strongly bound to a positively charged host, bis[6^A,6^D-(1-pyridinio)-6^A,6^D-deoxy]-α-CD (**1**), and shifts the ^{1}H NMR signals of the C(5)-H's of **1** to different directions depending on the position of glucose residues. There have been little reports on the regulation of molecular rotation of a guest within the CD cavity.[4–6] Our result is another important finding indicating that the molecular rotation of a guest within the CD cavity is retarded by the strong electrostatic interactions.



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Structure of the compound **1**

The host **1** was prepared according to the method previously reported.[7] The ^{1}H NMR spectra were measured at 298 K by a JEOL A400 FT-NMR spectrophotometer in D_2O containing 0.1M Na_2CO_3 (pD 11.3) using methanol as an internal standard (α = 3.343 ppm). The pD was took by a HORIBA D-21S pH meter by adding 0.4 to the pH read. A part of the ^{1}H NMR spectrum of **1** is shown in Figure 1A. The spectrum has changed to Figure 1B with the addition of *p*NP. The signals were assigned by the combination of HOHAHA, ROESY, and spin–lattice relaxation time techniques.[8] The corresponding

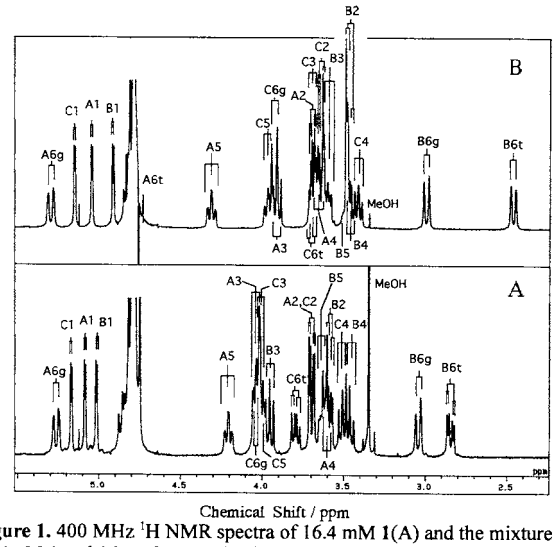
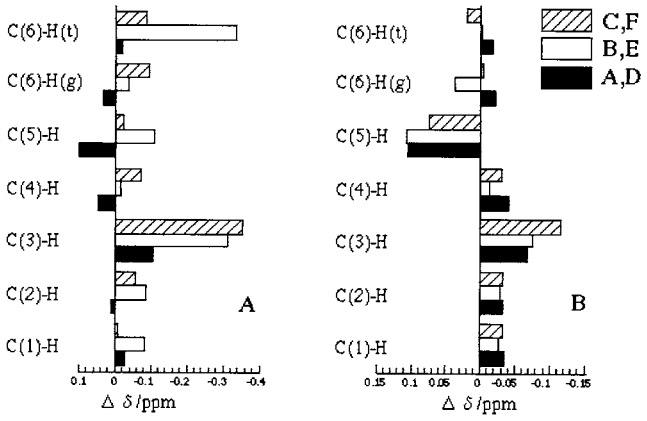


Figure 1. 400 MHz ^{1}H NMR spectra of 16.4 mM **1**(A) and the mixture of 16.4mM **1** and 16.4 mM pNP (B) in D_2O (pD 11.3) at 298 K.

spectral changes with the addition of *p*-hydroxybenzoic acid (*p*HBA) were also observed in D_2O containing 0.1 M KH_2PO_4–NaOH (pD 7.4) at 298 K.

The chemical shift changes of the CD protons with the addition of *p*NP and *p*HBA are summarized in Figure 2. The C(5)–H signals showed the most characteristic behavior: The proton signal due to A(D) glucose at δ = 4.20 showed downfield shift, while those of B(E) and C(F) glucose at δ = 3.53 and 3.94, respectively, showed upfield shifts with the addition of *p*NP. Although not so apparent as C(5)–H, the C(3)-H also



Fiure 2. Chemical shift changes in ^{1}H NMR signals of **1** induced by the addition of 2.0 mM pNP to 2.0 mM **1** (A) and 10.0 mM pHBA to 10.0 mM **1** (B).

showed diamagnetic anisotropy: That of the A(D) residue showed significantly smaller upfield shift than those of B(E) and C(F) residues. These results infer that the ring current of the *p*NP benzene ring gives different effects on glucose residues depending on their positions. The ROESY spectrum of a **1**-*p*NP system gave clear cross-peaks between the *m*-H of *p*NP and the C(5)–H of A(D) glucose, together with those between the *m*- and *o*-H's of *p*NP and the C(3)–H of A(D) glucose, indicating that *p*NP deeply penetrates into the CD cavity in such a manner that the nitro group locates in the vicinity of the pyridinio groups of **1**. It is probable that electrostatic interactions between the nitro and pyridinio groups are strong, since the binding constant (Ka = 11800 $mol^{-1}dm^3$) determined for a **1**-*p*NP system in H_2O at pH 11.3 and 298 K by UV/VIS measurement is much larger than that (Ka = 1870 $mol^{-1}dm^3$)[9] for an α-CD-*p*NP system. The internal rotation of the C–N bond linking the benzene ring to the nitro group in *p*NP will be retarded to a considerable extent by a rigid quinoid form with C=N bond, one of the resonance structures of *p*NP, as shown in Figure 3. Thus, once nitro group is trapped by the pyridinio groups of **1**, the benzene ring is also forced to be directed to the A and D glucose residues of **1**. In this orientation, the C(5)–H of A(D) residue locates in the lateral zone of the benzene ring and shifts downfield, whereas those of B(E) and C(F) residue locate above or below the benzene ring and shift upfield. This interpretation was also supported by ROESY spectrum : The cross-peaks between the *m*-H of *p*NP and the C(5)–H's of B(E) and C(F) residues are obviously lower than that of the C(5)–H of A(D) residue.

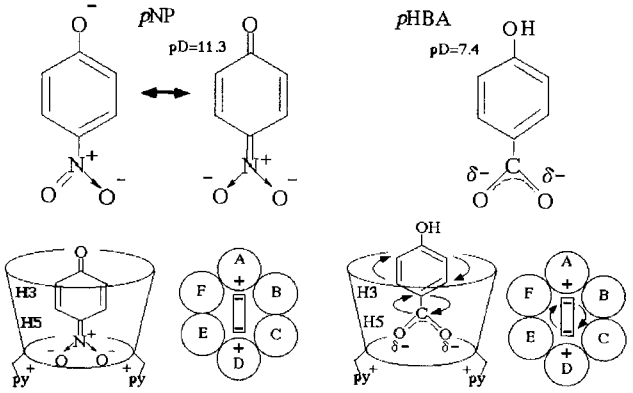


Figure 3. Upper: Schematic structures of *p*NP and *p*HBA. Lower: Molecular rotation of *p*NP (left: retarded) and *p*HBA (right: free) in the cavity of **1**.

Another interpretation would be possible that the observed anisotropy is caused by conformational changes of **1**, including the translocation of the pyridinio groups, upon complexation. However, *p*HBA, with a molecular structure very similar to *p*NP, caused little anisotropy in the chemical shifts of the C(5)–H and C(3)–H of **1** (Figure 2B). This indicates that the effect of such a conformational change is minor, if any. Since the carboxyl group of the *p*HBA is connected to the benzene ring by the freely rotating C–C bond, the benzene ring can freely rotate in the CD cavity, even when the carboxyl group is trapped by the pyridinio groups of **1**.

We also measured spin–lattice relaxation time (T_1) to confirm the above interpretations.[10] Complexation with **1** caused a marked decrease in T_1 of the *m*-H of *p*NP from 2.49 s to 0.85 s. This infers that the magnetic energy of the *m*-H is very effectively relaxes after complexation. Close van der Waals contact of the *m*-H with the C(5)–H of the A(D) glucose residue of **1** will be responsible for the rapid relaxation. The T_1 of the *o*-H was also decreased, though to a less extent, from 3.67 s to 1.53 s. The thermal fluctuation will be more vigorous at the *o*-H side of *p*NP than at the *m*-H side.

We have thus concluded that the free rotation of *p*NP in the cavity of **1** is retarded by strong electrostatic interaction.[7] The present study suggests that the electrostatic interactions are available for controlling the molecular motion or orientation of an ionic guest compound in the CD cavity and, then, for the design of enzyme-mimic modified CD.

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10 The T_1 values of *p*NP protons were determined for degassed D_2O solutions of 16.4 mmol dm^{-3} *p*NP in the absence and in the presence of 16.4 mmol dm^{-3} **1** at 298 K. In the presence of **1**, about 93% or more *p*NP was bound to **1**.