Double Self-Inclusion by Rotating Glucopyranose Units in Per-*O*-methylated β-Cyclodextrin Moieties Attached to a Porphyrin in Aqueous Solution

Ryuhei Nishiyabu[a] and Koji Kano*[a]

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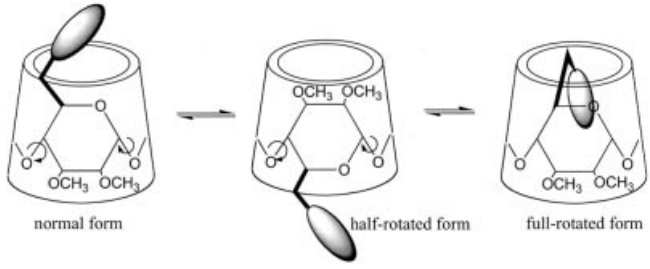
Double self-inclusion of the porphyrin part by two per-*O*-methylated β-cyclodextrin moieties, which were attached to the 4-positions of the phenyl groups of 10,20-bis(3,5-dicarboxylatophenyl)-5,15-diphenylporphyrin, occurred through 360° rotation of two glucopyranose units in the per-*O*-methylated cyclodextrin moieties. The self-inclusion proceeded quantitatively in aqueous solution. As the porphyrin ring was completely covered by two cyclodextrin moieties, no fluorescence quenching of the porphyrin by 9,10-anthraquinone-2-sulfonate took place. The intramolecular self-inclusion is achieved by destroying a hydrogen-bond belt at the secondary OH group side of the native cyclodextrin by *O*-methylation and extremely strong hydrophobic effects resulting from complexation of the porphyrin with per-*O*-methylated β-cyclodextrin.

Introduction

The truncated cone structures of native cyclodextrins (CDs) are stabilized by intramolecular hydrogen bonding between the secondary OH groups at the 2-positions and those at the 3-positions of adjacent glucopyranose units.[1] Rigidity of a CD is diminished upon *O*-methylation of all OH groups in the CD because of the disappearance of an intramolecular hydrogen-bond belt. Therefore, per-*O*-methylated CDs sometimes show characteristic behavior in their inclusion phenomena such as induced-fit type intermolecular complexation.[2] Theoretically, it is possible for a glucopyranose unit in a per-*O*-methylated CD to spin 360° about its glycosidic oxygen atoms (Scheme 1). In 1996, Bradshaw and co-workers reported the self-inclusion of 6^A,6^B-bis[*O*-(*p*-allyloxyphenyl)]heptakis(2,3-di-*O*-methyl)-β-cyclodextrin in DMF by full rotation of an allyloxyphenylated glucopyranose unit.[3] The normal and fully rotated forms were isolated in a 1:2 ratio. The equilibrium between the normal and half-rotated forms was previously discussed for per-*O*-benzylated β-CD, which has a bulky naphthyl moiety in $CDCl_3$.[4] Recently, Yamada et al. reported the full rotation of a glucopyranose unit in a per-*O*-methylated β-CD derivative that has a bulky bis(azobenzene) moiety attached to the narrower rim side of the CD in CD_3OD.[5] The equilibrium constant for the isomerism between the normal and fully rotated forms was determined to be 0.55 at 21 °C, which implies that about half of the bis(azobenzene)-loading CD molecules exist in the normal form. In the present study, we found perfect, double full rotation of the per-*O*-methylated glucopyranose units in a CD-porphyrin conjugate **1**, in which two per-*O*-methylated β-CD moieties are attached to 10,20-bis(3,5-dicarboxylatophenyl)-5,15-diphenylporphyrin (2DCP) as shown in Figure 1, to form a self-inclusion complex **2**. The equilibrium is completely shifted to **2** in aqueous solution.



Scheme 1. Flipping of a glucopyranose unit in per-*O*-methylated CD

Results and Discussion

The ^1H NMR spectrum of **1** in D_2O (Figure 2, a) shows seven singlet signals at δ = 0.30, 0.71, 1.30, 2.16, 2.58, 2.81, and 3.10 ppm (external standard: [D_4]3-(trimethylsilyl)propionate, TSP), which are assigned to the OCH_3 protons (see the Supporting Information; for supporting information see also the footnote on the first page of this article). The OCH_3 proton signals for the tetraethyl ester of **1** in $CDCl_3$ appear at δ = 3.20−3.74 ppm (Figure 2, b). It is clear that the signals for the OCH_3 protons of **1** in D_2O shift to higher

[a] Department of Molecular Science and Technology, Doshisha University,
Kyotanabe, Kyoto 610-0321, Japan
Fax: (internat.) + 81-774-65-6845
E-mail: kkano@mail.doshisha.ac.jp
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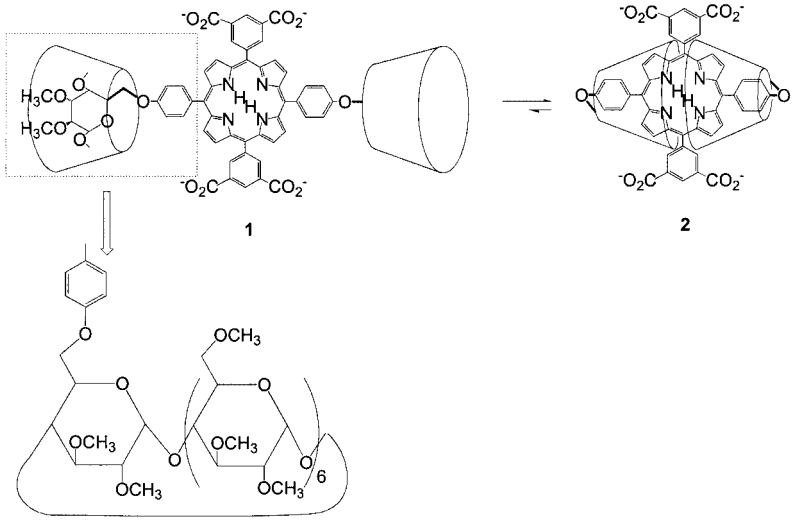

Figure 1. Double self-inclusion of **1** in aqueous solution

magnetic fields because of ring current effects caused by the porphyrin and/or benzene rings. There are six and fourteen OCH_3 groups at the primary and secondary OCH_3 sides, respectively, of a CD unit of **1**. In order to determine the side of the OCH_3 groups whose proton signals appear at higher magnetic fields, an HMBC spectrum (^{1}H-detected multiple-bond heteronuclear multiple quantum coherence spectrum) of **1** in D_2O was recorded (Figure 3). The ^{13}C NMR spectrum of **1** is so complex that complete assignment of each ^{13}C signal was not achieved. By comparing the ^{13}C NMR spectrum of **1** with that of heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMe-β-CD),[6] the signals of **1** were classified into four groups: the (C-1), (C-2, C-3, and C-4), (C-5 and C-6), and (2-, 3-, and 6-OCH_3) groups (see the Supporting Information). In the HMBC spectrum of **1**, a distinct correlation is observed between the seven proton signals in the 0.30−3.10 ppm range and the ^{13}C signals belonging to the (C-2, C-3, and C-4) group. No correlation is observed between the OCH_3 proton signals and the ^{13}C signals belonging to the (C-5 and C-6) group. The HMBC data clearly indicate that the proton signals in the 0.30−3.10 ppm range can be assigned to the secondary OCH_3 groups and not to the primary groups. The NMR spectroscopic data clearly show that the secondary OCH_3 groups of per-*O*-methylated β-CD moieties of **1** are placed on the porphyrin ring such that they receive the ring-current effects of the porphyrin ring. We confirmed that the dianion form of the 3,5-(dicarboxylato)phenyl group attached to the porphyrin ring cannot penetrate the TMe-β-CD cavity.[7] Intermolecular complexation of **1** can therefore be excluded. The NMR spectroscopic data can definitely be interpreted in terms of intramolecular self-inclusion of **1** to afford **2** in aqueous solution. The fact that the proton signals of the secondary OCH_3 groups appear over a wide range of higher magnetic fields indicates that many geometric relationships between the secondary OCH_3 groups and the porphyrin ring exist. As the CD moieties attached to the porphyrin ring of **2** cannot rotate freely,[8] each secondary OCH_3 group of **2** is subjected to a ring-current effect of the porphyrin ring to a different degree. We pre-

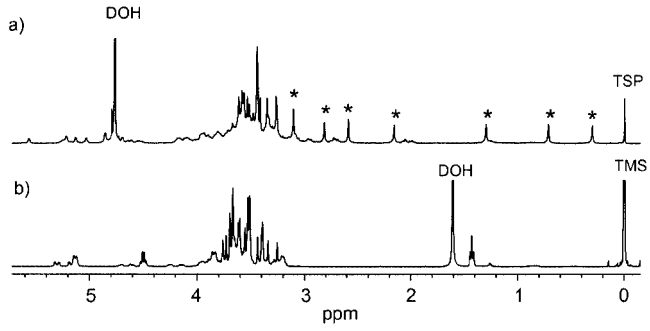

Figure 2. ^{1}H NMR spectra of **1** in D_2O (0.1 M phosphate buffer at pD = 7.0, TSP) (a) and the tetraethyl ester of **1** in $CDCl_3$ (TMS) (b)

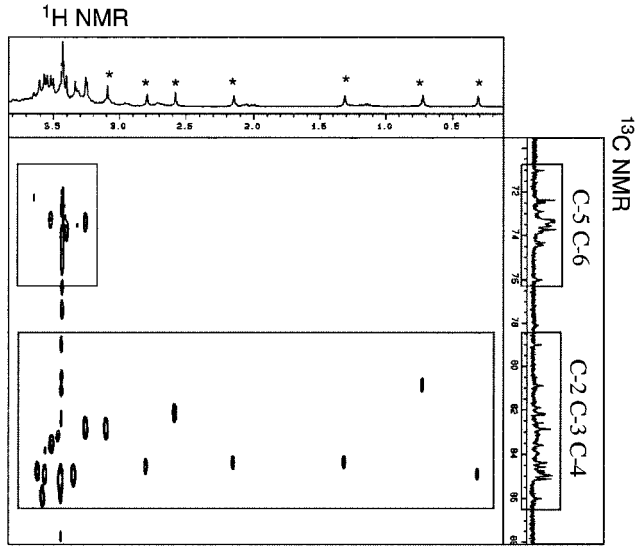

Figure 3. HMBC spectrum of **1** (0.075 M) in D_2O at 25 °C

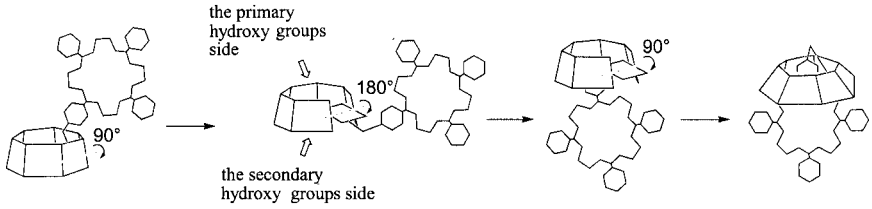

Figure 4. Schematic representation of self-inclusion by full rotation of the per-*O*-methylated glucopyranose units in **1**; in this figure, only single rotation is shown for clarity

viously found that the TMe-β-CD molecules deeply include the aryl groups at the 5- and 15-positions of 5,10,15,20-tetrakis(*p*-substituted phenyl)porphyrins.[9] Judging from the CPK molecular model, the per-*O*-methylated β-CD moieties of **2** have to be distorted upon deep inclusion of the aryl groups of the porphyrin.

The remaining problem is the stability of **2**. Seven distinguishable signals assigned to C-1 (carbon atoms at the 1-positions of the glucopyranose units) are observed at δ = 99.1, 99.2, 99.6, 99.9, 100.8, 101.5, and 103.5 ppm in the ^{13}C NMR spectrum of **1** in D_2O (see the Supporting Information). This result as well as the seven independent OCH_3 proton signals in the ^1H NMR spectrum can be interpreted in terms of either a very fast exchange between **1** and **2** or a very slow exchange because of the very stable nature of **2**. Four Q-bands are observed in the absorption spectrum of **1** in methanol, and are indicative of an ordinary etioporphyrin-type (see the Supporting Information). The shapes of the Q-bands of **1** in aqueous solution (pH = 7) are significantly different from those in methanol and are very similar to those of an extremely stable, intermolecular 1:2 complex of 2DCP and TMe-β-CD in aqueous solution.[10] The characteristic Q bands of **1** in aqueous solution suggest that **2** is predominantly formed. It has been known that fluorescence from water-soluble porphyrins is quenched by 9,10-anthraquinone-2-sulfonate (AQS) by means of both static and dynamic processes.[11] The fluorescence quenching of **1** and 2DCP in the absence and presence of TMe-β-CD by AQS was studied (see the Supporting Information). The fluorescence from 2DCP in aqueous solution without TMe-β-CD was quenched by AQS, and the Stern−Volmer constant (K_{SV}) was found to be 5500 M^{-1}. The absorption spectral titration indicates the formation of a ground-state complex of 2DCP and AQS (K = 4900±90 M^{-1}). Formation of such nonfluorescent complexes is well-known for the anionic porphyrin-anthraquinonesulfonate systems.[11,12] Meanwhile, the fluorescence quenching hardly occurred in the case of the intermolecular complex of 2DCP and TMe-β-CD (the K value for the 2DCP-TMe-β-CD 1:2 complex is too large to be determined).[10] This is due to an encompassing effect of TMe-β-CD. Quite similarly, the fluorescence from **1** was hardly quenched by AQS. These results definitely indicate that in aqueous solution **1** exclusively exists as its double inclusion form **2**.

The present study demonstrates the first example of perfect, intramolecular, double self-inclusion caused by full rotation of glucopyranose units to give the sole conformational isomer in aqueous solution. Such novel behavior is possible because of the following characteristics of the porphyrin-CD conjugate **1**:

1) Full rotation of the glucopyranose units is possible because of the absence of intramolecular hydrogen-bonding in per-*O*-methylated CD;

2) The per-*O*-methylated β-CD moieties of **1** have a great ability to include the tetraarylporphyrin in aqueous solution.[9]

In $CDCl_3$, no self-inclusion of the tetraethyl ester of **1** was observed (vide supra). This result is corresponding to the fact that intermolecular complexation of tetraarylporphyrins with TMe-β-CD to form 1:2 inclusion complexes hardly occurs in organic solvents.[9] The intramolecular double inclusion of **1** might be achieved by extremely strong hydrophobic effects that work in aqueous solution.[9,13]

The schematic representation for the self-inclusion of **1** is shown in Figure 4. Two CD moieties are not essential for self-inclusion. We found that the analogue of **1** that has only one per-*O*-methylated β-CD moiety shows the same intramolecular self-inclusion.

Experimental Section

The synthetic route and procedures of **1** are given in the Supporting Information.

1: ^1H NMR [400 MHz, 0.1 M phosphate buffer (D_2O), pD = 7.0, 25 °C, [D_4]3-(trimethylsilyl)propionate]: δ = 0.29−5.58 (per-*O*Me-β-CD), 7.41 (d, 4 H, phenyl), 8.34 (d, 4 H, phenyl), 8.59 (s, 4 H, phenyl), 8.75 (s, 2 H, phenyl), 8.96 (broad, β-pyrrole) ppm. MS (MALDI-TOF, dithranol matrix): m/z = 3624.7 (calcd. for [M + Na]$^+$: 3617.8).

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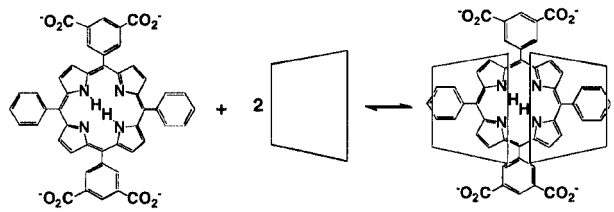
[10] Complexation of 2DCP with TMe-β-CD is represented as the following equation:



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