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Per(3-deoxy)-γ-cyclomannin: a non-glucose cyclooligosaccharide featuring inclusion properties

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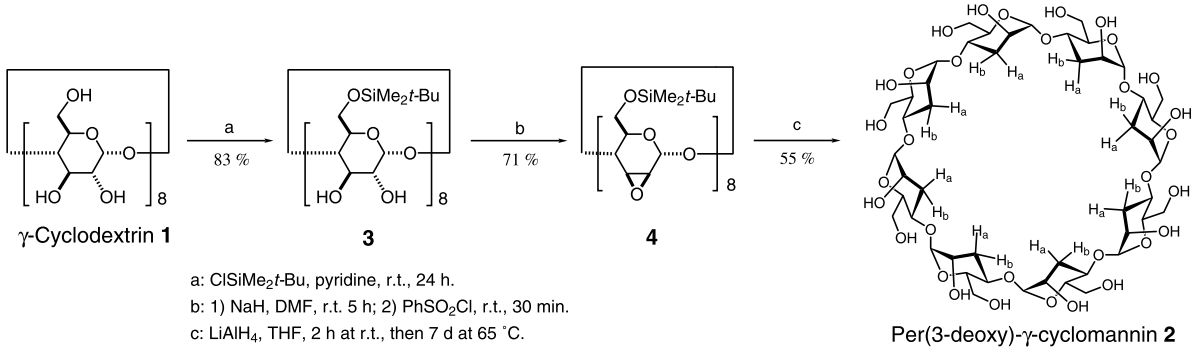
Abstract—Per(3-deoxy)-γ-cyclomannin has been efficiently synthesized by a three-step procedure starting from natural γ-cyclodextrin, and proved to be capable of binding naphthalenesulfonate in aqueous solution and solubilizing C_{60} in water. For the first time it was spectrally evidenced that a non-glucose cyclooligosaccharide did form inclusion complexes with conventional organic guest molecules.

Cyclodextrins, a series of cyclooligosaccharides formed during the enzymatic degradation of the linear amylose components of starch, have attained a unique and special status in supramolecular chemistry.[1] The hydrophobic cavities of these torus-like molecules turn out to be the havens for a wide range of guest molecules in aqueous solutions while their two rims provide the opportunity to improve or develop specific functions.[1,2] These particular features of cyclodextrins have been well documented and have found wide applications in chemical, pharmaceutical, biomedical and materials sciences.[3] In contrast to the wealth of knowledge on cyclodextrins, our knowledge on the molecular recognition properties of cyclooligosaccharides other than cyclodextrins has been surprisingly poor.[4] A limited range of cyclooligosaccharides[5] other than cyclodextrins, such as cyclooligo-(1→6)-α-glucopyranosides, cyclooligo-(1→2)-α-glucopyranosides, cyclooligo-(1→2)-β-fructofuranosides, are available by enzymatic or bacterial action on their corresponding linear components but their capability of binding organic guests has not been yet documented. During the last decades, much effort has been directed to the chemical synthesis of cyclooligosaccharides[6] from their corresponding monosaccharide units with the ultimate goal to create novel water-soluble chiral molecular receptors possessing specific complex formation properties that are sufficiently different and unique to be able to compete with those of cyclodextrins. Most of non-glucose cyclooligosaccharides presently known have been thus



Scheme 1. Synthesis of per(3-deoxy)-γ-cyclomannin.

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prepared synthetically but usually in such minute amounts as to preclude investigation into their inclusion behavior because of the tedious multistep procedures and the difficulty in controlling the regio- and stereoselectivity. Two of the authors[7] reported a four-step strategy for the facile access to cycloaltrins starting from the corresponding natural cyclodextrins. Unfortunately this series of non-glucose cyclooligosaccharides again failed in demonstrating inclusion ability towards normal organic guests. Therefore, non-glucose cyclooligosaccharides with inclusion ability still remain to be a challenge. In this paper, we report an efficient three-step-preparation of per(3-deoxy)-γ-cyclomannin **2** from γ-CD **1** (Scheme 1) and provide spectral evidence for its inclusion binding towards conventional organic guests.

Per(6-silyl)-per(2,3-mannoepoxy)-γ-cyclodextrin **4** was prepared from γ-cyclodextrin by the modification of the procedure used for the preparation of the β-analog.[8] Reduction of the epoxide **4** was carried out in THF by using $LiAlH_4$ as reducing agent and the reaction was traced by TLC. The reaction mixture was taken in water and chromatographed on a reversed-phase column to afford the pure product **2** in 55% yield.[9] Kelly[10] reported that the reduction of the β-analog with $LiAlH_4$ or $AlH(i\text{-}Pr)_2$ gave a complicated mixture. However, our procedure surely enables an efficient reduction and subsequent deprotection of **4** in a one-pot reaction. The isolated **2** demonstrated the pseudo-molecular ions at $m/z=1169$ $[M+H^+]$ and 1191 $[M+Na^+]$ in the FAB-MS spectrum.

Its NMR spectra (Fig. 1) clearly demonstrates a C_8 symmetry and two upfield shifted protons resonating at δ 2.01 and 1.95 ppm as two ddd's with strong second order effects from each other. ^1H–^1H COSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC experiments indicate that they are geminal protons bound to the C-3 carbon that also resonates in a very high field (δ 31.9). This means the reduction occurs at the C-3 carbons. Both the H-2 and H-4 protons are shifted to much lower fields (δ 3.84 and 3.93), while the H-1, H-5 and H-6 protons (at δ 4.72, 3.89 and ~3.78, respectively) are not significantly affected in comparison with the corresponding chemical shifts of γ-cyclodextrin.

The small $J_{1,2}$ (3.3 Hz) and large $J_{3a,4}$ and $J_{4,5}$ spin–spin coupling constants (both 8.1 Hz), which can be roughly derived by directly reading the ^1H NMR spectrum, suggest that the proton H-1 be in an equatorial disposition while the protons H_a-3, H-4 and H-5 all be axially located. This observation supports the $^4C_1$ conformation of the 3-deoxymannoside units and a hydrophobic cavity is thus expected to form with all the 2-OH groups axially located outside. Compared with γ-CD, there are only half the number of secondary hydroxyl groups in per(3-deoxy)-γ-cyclomannin **2**. Therefore, the cavity of per(3-deoxy)-γ-cyclomannin is expected to have stronger hydrophobicity. Its capability of binding hydrophobic guests in aqueous solution is unambiguously evidenced by taking sodium 2-naphthalenesulfonate and fullerene C_{60} as the guests.

Addition of naphthalenesulfonate to the NMR solution of **2** results in upfield shift of all the proton signals of **2**, which is consistent with the shielding effect of the aromatic ring (Fig. 2).[10,11] The signals of the inward-cavity-located protons H-2 and H-5 are obviously shifted faster than those of H-6 ones and finally get superimposed with the latter ones. The shifting behaviors of the two geminal protons of C-3 offer

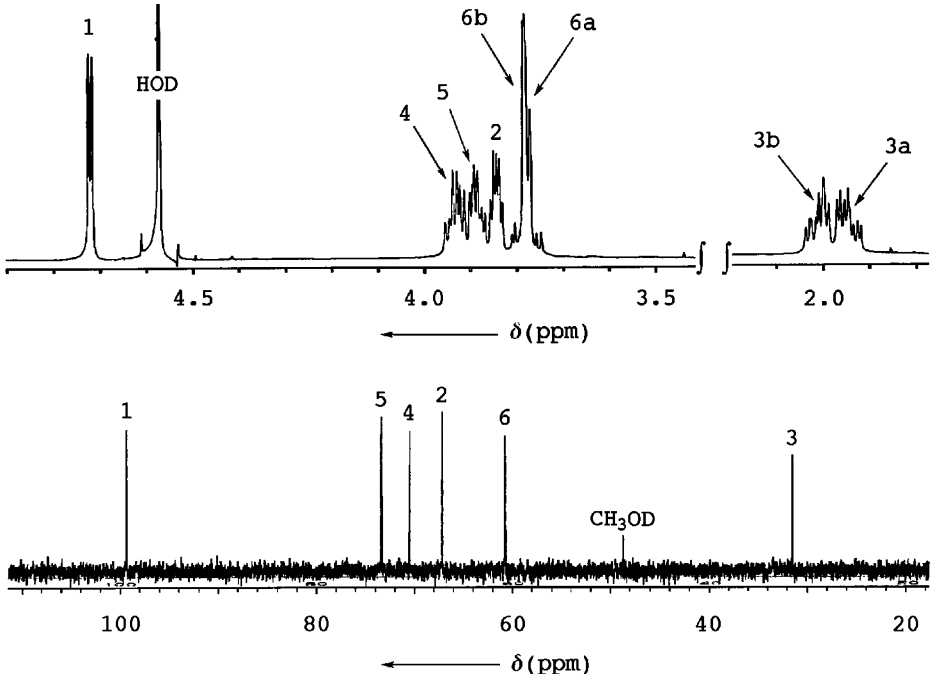

Figure 1. ^1H NMR spectrum (top, 500 MHz) and ^{13}C NMR spectrum (bottom, 125 MHz) of **2** in D_2O (CH_3OH int.).

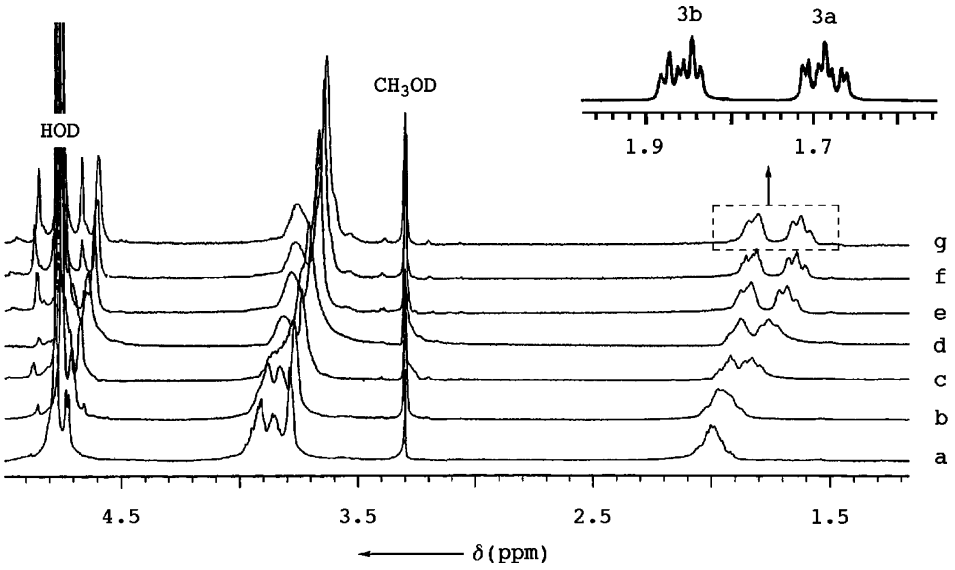

Figure 2. ^{1}H NMR spectra of **2** (300 MHz, 3 mM **2** in D_2O, CH_3OH int.) in the absence (a) and in the presence of (b) 5 mM, (c) 17 mM, (d) 30 mM, (e) 48 mM, (f) 60 mM and (g) 69 mM sodium 2-naphthalenesulfonate. The inset was recorded on a 500 MHz NMR spectrometer.

even more important evidence for the binding. The right one, which shows an axial–axial coupling to H-4 and is therefore located inwards to the cavity, is subjected to a stronger shielding effect and is shifted to the higher field faster than the left one. As a result, the second order effect between them is significantly reduced and the normal ddd splitting pattern is observed for both protons (Fig. 2, inset).

Solubilization of fullerene C_{60} in water has been attracting particular interest because of its potential biological applications.[12] Compound **2** is very efficient in solubilizing C_{60} in water. By heating C_{60} (5 mg) and **2** (20 mg) in pyridine (2 ml) at 60°C, the C_{60} becomes partially solubilized. After evaporation of the solvent, the residue is taken in distilled water (10 ml) and filtered through a polymer membrane (cellulose acetate, 0.4 μm) to give a clear solution. The UV–vis spectrum of this filtrate and that of C_{60} in CH_2Cl_2 are shown in Figure 3. C_{60} in CH_2Cl_2 shows absorbance peaked at 257 and 329 nm. The filtrate also demonstrates strong absorption around 255 nm and in the range of 310 ~ 410 nm. The absorbance around 255 nm is quite similar to that of C_{60} in CH_2Cl_2 while that in the range of 310 ~ 410 nm is different. Three peaks (347, 359 and an end peak at 392 nm) are observed instead of a single peak of C_{60} in CH_2Cl_2. The concentration of C_{60} in this filtrate is estimated to be ca. 2.8×10^{-5} M by assuming that the molecular absorptivity of C_{60}-**2** complex at 347 nm is the same as that of C_{60} in CH_2Cl_2 solution ($\varepsilon=5.65\times10^4$ at λ_{max} 329 nm). This result indicates that the solubility of C_{60} in the presence of **2** is comparable with that in the presence of γ-cyclodextrin.[13]

In summary, we described a three-step synthesis of per(3-deoxy)-γ-cyclomannin **2** from the natural γ-cyclodextrin, and proved for the first time that a non-glucose cyclooligosaccharide binds conventional organic molecules such as naphthalensulfonate in aqueous solution and efficiently solubilizes C_{60} in water.

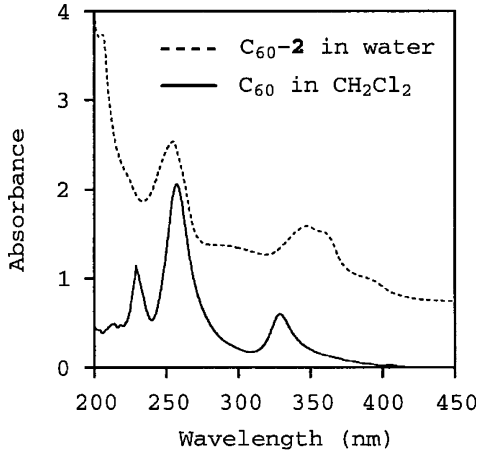

Figure 3. UV–vis absorption spectra of C_{60} in CH_2Cl_2 and the C_{60}-**2** inclusion complex in water.

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Preparation of ***3***: Dried γ-CD (4 g, 3.08 mmol) was dissolved in dry pyridine (30 mL). To this solution was added dropwise pyridine solution (20 mL) containing *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol). The reaction mixture was stirred at rt for 24 h, and then poured into 400 mL ice-water. The resultant precipitates were dissolved in ethyl acetate (150 mL), washed with 5% HCl solution, saturated $NaHCO_3$ solution and distilled water. After dried over anhydrous Na_2SO_4 the solvent was removed to afford (6.26 g, 92%) of crude product. Column chromatography of the crude product on silica gel with ethyl acetate–ethanol–water (18:4:1) as eluent gave the pure **3** (5.69 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 4.83 (1H, d, $J=2.7$), 3.94∼3.85 (2H, m), 3.65 (1H, d, $J=10.5$), 3.56∼3.53 (2H, m), 3.44 (1H, d, $J=9.0$), 0.83 (9H, s), 0.00 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 102.0, 81.7, 73.6, 73.4, 72.5, 61.6, 25.9, 18.3, −5.1, −5.2.

Preparation of ***4***: Sodium hydride (65% in mineral oil, 540 mg, 14.6 mmol) was washed with hexane, dried under vacuum and added to a dry DMF (25 mL) solution containing **3** (1 g, 0.45 mmol). After the resultant mixture was stirred at 60°C for 5 h, benzenesulfonyl chloride (767 mg, 4.35 mmol) was added and the reaction mixture was stirred for an additional 30 min. Propanol (5 mL) was then added carefully and ice-water (200 mL) was added to precipitate the cyclodextrin species. The precipitates were filtered off and dissolved in 100 mL benzene, washed successively with dilute hydrochloric acid, aqueous $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with an eluent of benzene–ethyl acetate (4:1) to afford **4** (665 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 5.15 (1H, s), 4.04 (1H, d, $J=9.0$), 3.85 (1H, dd, $J=3.4$, $J=9.3$), 3.66 (1H, d, $J=11.4$), 3.50 (1H, m), 3.30 (1H, d, $J=3.4$), 3.08 (1H, d, $J=3.5$), 0.84 (9H, s), 0.00 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 96.2, 69.5, 68.0, 62.2, 53.8, 49.4, 25.9, 18.3, −4.9, −5.1.

9. *Preparation of* ***2***: $LiAlH_4$ (60 mg, 1.58 mmol) was added to a solution of **4** (100 mg, 0.048 mmol) in THF (25 ml) cooled at 0°C and the resultant solution was stirred at rt for 2 h and then at 65°C for 7 days until no further changes can be detected on TLC. After cooled down to room temperature, the reaction mixture was treated by the addition of ethyl acetate (1 ml) to decompose the excess $LiAlH_4$. After evaporation of the solvent, the residue was taken in distilled water (50 ml), adjusted to neutral pH with 1 M HCl, filtered and applied to reversed-phase chromatography on a Merck pre-packed Lobar column (LiChrom Rp-18, size B). A gradient elution of the column from 5% to 30% aqueous EtOH afforded the title product **2** in good yield (31 mg, 55%). Anal. calcd for $C_{48}H_{80}O_{32}$: C, 49.31; H, 6.90. Found: C, 49.46; H, 7.10. FAB-MS: m/z 1169 [M+H$^+$] and 1191 [M+Na$^+$]. ^{1}H NMR (500 MHz, D_2O, CH_3OH int.: $\delta_{\mathbf{CH}}=3.30$): δ 1.95 (ddd, 1H, H_a-3), 2.01 (ddd, 1H, H_b-3), 3.77 (dd, 1H, H_a-6), 3.79 (dd, 1H, H_b-6), 3.84 (ddd, 1H, H-2), 3.89 (ddd, 1H, H-5), 3.93 (td, 1H, H-4), 4.72 (d, 1H, H-1). $J_{1,2}=3.33$, $J_{2,3a}\approx3.6$, $J_{2,3b}\approx5.9$, $J_{3a,3b}=13.6$, $J_{3a,4}=8.1$, $J_{3b,4}=5.4$, $J_{4,5}=8.1$, $J_{5,6a}\approx5.3$, $J_{5,6b}\approx3.3$, $J_{6a,6b}\approx12.4$. ^{13}C NMR (125 MHz, D_2O, CH_3OH int.: $\delta_{\mathbf{C}}=49.0$): δ 31.9 (C-3), 61.0 (C-6), 67.4 (C-2), 70.7 (C-4), 73.6 (C-5), 99.4 (C-1).

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