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Cage Molecules with Multiple Recognition Cavities: Quadruply Cyclodextrin-Linked Cofacial Porphyrins

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Abstract

Quadruply γ-cyclodextrin-linked cofacial porphyrin is synthesized from the one-pot reaction of pyrrole and acetylated γ-cyclodextrin $6^A,6^E$-bisbenzaldehyde by the Lindsey's method. Deacetylation affords the water-soluble derivative. Their spectroscopic properties are also described.

Keywords: cofacial porphyrins, γ-cyclodextrins, one-pot synthesis

Cofacial porphyrins have been extensively explored in biomimetic research. The covalently linked porphyrin dimers may be singly, doubly, triply or quadruply bridged by various linkers, such as crown ether [1], calixarene [2] and cyclophane [3]. Cyclodextrins are popular binding blocks for supramolecular structures, and the synthesis of cyclodextrin-linked porphyrins has been demonstrated to be a practical approach to construct biomimetic models for some naturally-occurring processes [4-9]. Thus, the cyclodextrin-linked cofacial porphyrins are expected to afford some effective artificial enzymes, in which cyclodextrins act as hydrophobic recognition sites and hydrophilic pendants to enable the investigation of the properties of the artificial enzymes in aqueous solution. Recently, we have synthesized *quadruply* γ-cyclodextrin-linked cofacial porphyrins **2-3** (Scheme 1). These compounds possess the hydrophobic cavities of γ-cyclodextrins and the cage composed of the four linkers and the two porphyrin rings, thus multiple recognition and catalysis could be expected. And **2** represents the first *one-pot* synthesis of *quadruply* linked cofacial porphyrins.[1] Here, we

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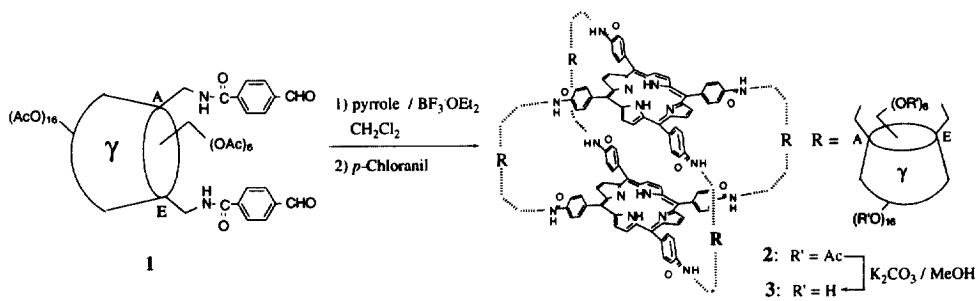

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Scheme 1 Synthesis of quadruply γ-cyclodextrin-linked cofacial porphyrins **2** and **3**.

describe the synthesis and spectroscopic properties of **2** and **3**.

The one-pot synthesis of **2** was carried out according to the Lindsey's standard protocol [10-11] using $BF_3{\cdot}OEt_2$ as the Lewis acid catalyst and *p*-chloranil as the in-situ oxidant (Scheme 1). Thus, acetylated γ-cyclodextrin $6^A,6^E$-bisbenzaldehyde **1**[2] (500 mg) was subject to condense with 2 equivalents of pyrrole in CH_2Cl_2 (20 cm^3) at room temperature. After stirred under N_2 for 1d, the reaction was readily oxidized. Purification of the product was accomplished by chromatography twice on a silica-gel column with a mixture of $CHCl_3$-MeOH (10 / 1, v / v) as the eluent, followed by preparative reverse-phase HPLC to afford **2** (32.5 mg, 5.22%). The deprotection of **2** by K_2CO_3 in aqueous MeOH and purification by chromatography on a reverse-phase column afforded **3** in 65% yield.

The structures of **2** and **3** were confirmed by MS spectra, ^1H and ^{13}C NMR spectra, etc.[3] Compound **2** exhibited the expected FAB MS spectrum with the m / z being 10318.2 ($[M+1]^+$; calculated mass 10317.4 for $C_{464}H_{548}N_{16}O_{248}$). The ^1H NMR spectrum of **2** showed the characteristic signals for the pyrroles at 9.12 ppm and the pyrrolic NHs at -2.79 ppm as well as other signals for phenyl rings and acetylated γ-cyclodextrins. And the proton integrations for the β-protons of pyrroles and the H1s of γ-cyclodextrins were consistent with a porphyrin-to-γ-cyclodextrin ratio of 1:2. The ^{13}C NMR spectrum of **2** afforded all the desired signals, such as the meso-carbons and α-carbons of pyrroles.[3] The features of the ^1H and ^{13}C NMR of **2** (for example, the singlet proton resonances for the pyrroles, only four

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1) The other reported *quadruply* linked cofacial porphyrins adopt the *stepwise* routes. See references 12-14.

2) Compound **1** was synthesized by the reaction of $6^A,6^E$-diamino-$6^A,6^E$-dideoxy-γ-cyclodextrin **4** with terephthalaldehydic acid in the presence of DCC, followed by acetylation. Compound **4** was prepared from the 6A, 6E regiospecifically trans-stilbene-4,4'-disulfonate capped γ-cyclodextrin [15] via the corresponding diazido-γ-cyclodextrin.

detected carbon signals for the C1s of γ-cyclodextrins, etc.) revealed the symmetrical structure of **2**. And **2** showed the typical Soret band and Q bands of free base porphyrins[4] and excitation at the Soret band maximum of **2** yielded its emission spectrum with a strong band at 650 nm. Furthermore, **2** showed much weaker fluorescence intensity than the tetraphenylporphyrin carrying four acetylated β-cyclodextrins,[5] which reflected the intramolecular quenching. These results substantiated that **2** had the cofacial porphyrin structure. For compound **3**, the MALDI-TOF-MS spectrum showed not the molecular ion peak but the peak at m / z 3348.7, corresponding to the molecular weight plus two K^+, *i.e.* $[M+2K]^{2+}$ (calculated m / z 3348.2). The ^1H and ^{13}C NMR of **3** were in agreement with the proposed structure.[3] And the characteristic UV-Vis and fluorescence spectra of porphyrins were also presented.[4]

The yield of **2** seems to be a little high, given the random combination of 12 molecules. However, much complexity has been shown in the synthesis of the present species. For example, the attempts to synthesize the α-cyclodextrin analogues of **2** proved unsuccessful. And several tedious separations were required to obtain the pure **2**, as described above. If **2** purified only by silica-gel column chromatography was used, the deacetylation of **2** and purification by chromatography on a reverse-phase column would afford other minor γ-cyclodextrin-porphyrin adducts, in addition to the main product **3**.

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3) The NMR data for Compound **2**: ^1H-NMR ($CDCl_3$, ppm) 9.12 (s, 16H, pyrrolic β-Hs); 8.39 (d, 16H, phenyl Hs), 8.27 (d, 16H, phenyl Hs); 7.56 (br, 8H, CONH); 5.51-5.30 (32H, H3); 5.26 (16H, H1), 5.22 (d, 8H, H1), 5.12 (d, 8H, H1); 4.91-4.12 (128H, H2, H5 and H6); 3.90-3.67 (32H, H4); 2.21-2.00 (264H, CH_3); -2.79 (s, 4H, pyrrolic NH). ^{13}C-NMR ($CDCl_3$,ppm) 171.61, 170.71, 170.65, 170.56, 170.50, 170.40, 169.55, 169.49, 169.42, 169.35, 167.89 (ester and amide carbonyls); 145.19, 135.36, 134.25, 134.10, 126.31, 124.77, 119.39 (phenyl rings, pyrrole and meso carbons); 97.28, 97.03, 96.17, 95.58 (C1); 79.61-69.10 (C2, C3, C4 and C5); 63.63, 62.58, 62.49, 43.05 (C6); 21.14-20.60 (CH_3). Compound **3**: ^1H-NMR (C_5D_5N, ppm) 9.28 (s, 16H, pyrrolic β-Hs); 8.97 (d, 16H, phenyl Hs); 8.56 (br, 8H, CONH); 8.32 (d, 16H, phenyl Hs); 5.72 (d, 8H, H1), 5.62 (d, 8H, H1), 5.55 (d, 8H, H1), 5.48 (d, 8H, H1); 4.83-3.81 (192H, H2, H3, H4, H5 and H6). ^{13}C-NMR (C_5D_5N, ppm) 170.19 (amide carbonyls), 103.61, 103.36, 103.40, 102.03 (C1); 86.16, 83.81, 82.42, 79.74 (C4), 74.58, 74.41, 74.09, 73.89, 73.65, 73.43, 73.34, 72.78 (C2, C3 and C5); 62.10, 61.14, 60.41, 42.50 (C6). It was difficult to assign the carbon signals for the phenyl rings, pyrroles and the meso-carbons in **3** because they were overlapped with those of pyridine.

4) UV-Vis spectral data (λ nm / ε 10^{-3} $mol^{-1}dm^3cm^{-1}$) for **2** in $CHCl_3$: 420.0 / 627, 515.5 / 30.6, 551.0 / 154, 590.0 / 11.0 and 645.5 / 7.31; **3** in H_2O: 427.2 / 44, 521.8 / 6.33, 556.8 / 4.99, 595.2 / 3.88 and 645.0 / 4.09.

5) We have also synthesized tetraphenylporphyrin **5** carrying four β-cyclodextrins at the primary hydroxyl side via the amide bonds, the analogues reported by Breslow et al [6-7]. Under the same conditions, the fluorescence intensity of **2** was about half of that of acetylated **5**, that is to say, each porphyrin of **2** exhibited only one fourth of the fluorescence intensity of acetylated **5**.

Compound **3** is slightly soluble in H_2O, and within the range of 0~1.42×10^{-5} M it was found that Beer's law (425 nm) was obeyed and the graph of fluorescence intensity (649 nm) versus the concentration was also linear, which indicated that the intermolecular interaction between the porphyrin rings could be neglected [16]. And **3** (1.29×10^{-6} M) in H_2O shows strong induced circular dichroisms (ICDs) with a negative Cotton effect at 425.8 nm ($\Delta\varepsilon$ = 2.97×10^{4} $mol^{-1}dm^{3}cm^{-1}$) and a positive Cotton effect at 431.4 nm ($\Delta\varepsilon$ = 3.30×10^{4} mol^{-1} $dm^{3}cm^{-1}$). The strong ICDs show the chiral exciton coupling between the Soret band transitions of the two porphyrin chromophores spatially correlated in the same molecule.

In summary, the present report focuses on the synthesis and spectroscopic properties of quadruply γ-cyclodextrin-linked cofacial porphyrins with multiple recognition cavities. The cofacial porphyrin cores in close proximity with cyclodextrins as the linkers enable π - π and / or hydrophobic interaction with an appropriate guest molecule. Thus, strong binding and multiple recognition could be expected. Further investigations on these properties as well as their applications in catalysis are under progress in our laboratory.

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