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Complexation of hydrogen bonding-driven preorganized di- and hexacationic bisporphyrin receptors for $C_{60}C(CO_2^-)_2$ in aqueous and DMSO media

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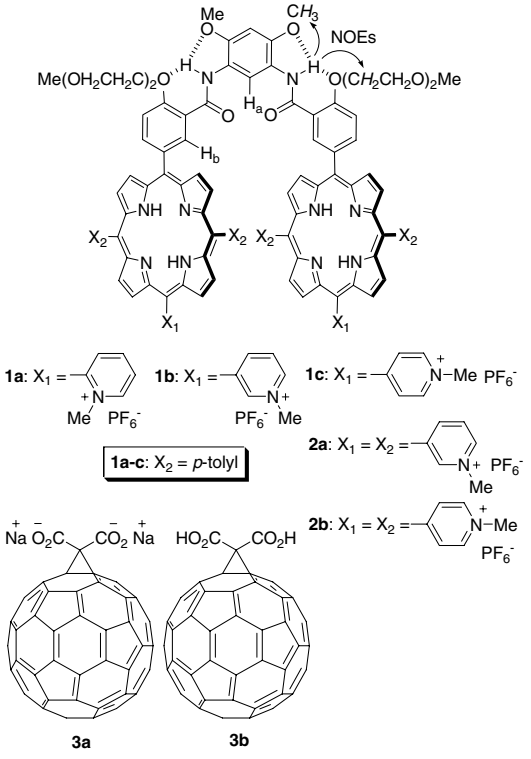
Abstract—This Letter reports the synthesis of three dicationic and two hexacationic receptors in which two porphyrin units are connected with an aryl amide linker. ^{1}H NMR and X-ray crystal structure analysis for model compounds show that in aqueous or DMSO medium the receptors could adopt preorganized U-styled conformation due to intramolecular hydrogen bonding-induced rigidity of the amide linker. ^{1}H NMR, UV–vis and fluorescent investigations revealed that the ionic receptors efficiently complex $C_{60}C(CO_2^-)_2$ in aqueous medium with cooperative intermolecular electrostatic and donor–acceptor interactions as driving forces. A 1:1 binding stoichiometry has been established for the complexes and the related association constants have been evaluated.

Hydrogen bonding is the non-covalent force that is widely used for stabilizing the compact conformations of both aliphatic and aryl amide-derived foldamers.[1,2] Studies on aliphatic oligoamides have been initially inspired by mimicking the folded secondary structures of natural peptides, and studies on their conformations are usually performed in aqueous media.[3] Due to the intrinsic rigidity and planarity of aryl amides, foldamers with the aryl amide backbones usually exhibit high structural predictability.[2] In many cases, the alkoxyl groups are introduced to the aryl rings to serve as proton acceptors, and the resulting molecules are of high solubility in less polar solvents like chloroform.[2] We recently initiated a program to develop foldamer-based synthetic receptors.[2c,4] By incorporating two porphyrins to the ends of the well-defined rigidified aryl amide backbones, we have assembled several hydrogen bonding-driven molecular tweezers[5] that complex fullerenes in chloroform or toluene of low polarity.[6] Considering the high competitiveness of water as proton acceptors,[7] further exploration of foldamer-based binding in aqueous media represents a new challenge. We herein report the synthesis of five ionic hydrogen bonded receptors **1a**–**c** and **2a**,**b** and their binding properties toward ionic C_{60} derivative **3a** in aqueous or polar organic media.



Keywords: Molecular tweezers; Hydrogen bonding; Aqueous medium; Porphyrin; Molecular recognition; C_{60} derivative.
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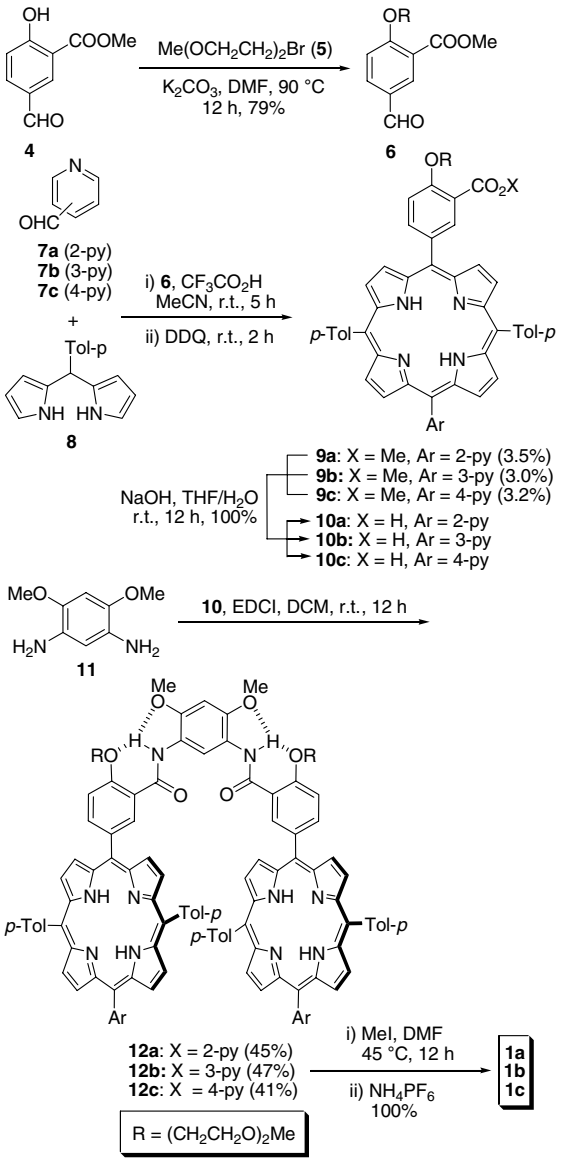
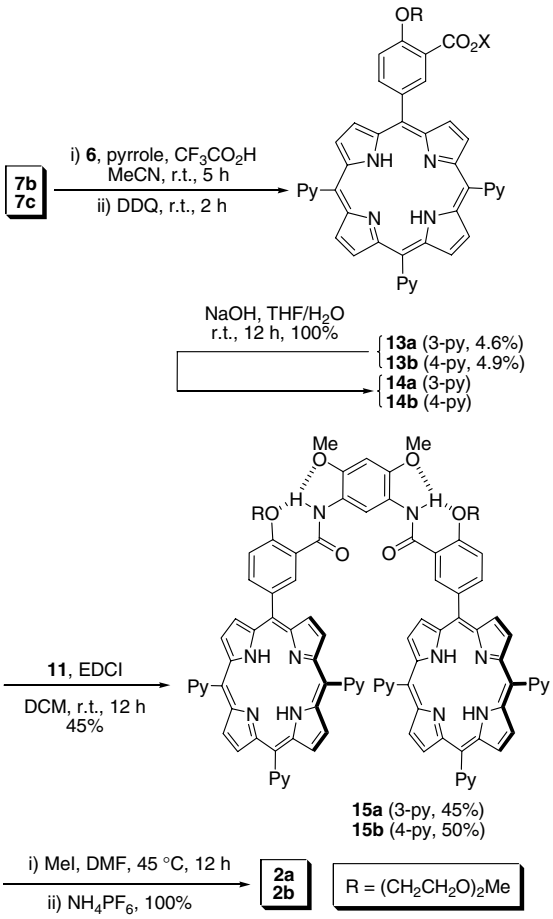


Scheme 1. Synthesis of compounds **1a**–**c**.



Scheme 2. Synthesis of compounds **2a** and **2b**.

The synthetic routes for **1a**–**c** are shown in Scheme 1. Compound **6** was first prepared in 79% yield from the reaction of **4**[8] with **5** and then treated with **7a**–**c** and **8**[9] in acetonitrile to afford porphyrins **9a**–**c** in 3.0–3.5% yields. Quantitative hydrolysis of the esters yielded acids **10a**–**c**, which were then coupled with **11**[10] to produce **12a**–**c** in 41–47% yields. Treatment of the porphyrins with excessive methyl iodide in DMF, followed by ion exchange with NH_4PF_6, gave rise to **1a**–**c** in quantitative yield. For the synthesis of **2a** and **2b** (Scheme 2), porphyrins **13a** and **13b** were first prepared from the reaction of pyrrole, **6** and **7b** or **7c** and then hydrolyzed to afford **14a** or **14b**. The acids were then coupled with **11** to give **15a** or **15b**, respectively. Hexamethylation of both intermediates with methyl iodide, followed by anion exchange with NH_4PF_6, produced **2a** or **2b** quantitatively. Porphyrins **1a**–**c** and **2a** and **2b** are soluble in water or polar organic solvents like DMSO or DMF, but insoluble in less polar solvents like chloroform.[11] Their structures have been characterized with the ^1H and ^{13}C NMR and mass spectroscopy.[12] The ^1H NMR spectrum of **1a** (in DMSO-d_6) was significantly more complicated than that of other molecules, which may be attributed to the formation of atropisomers because the methylation of the two pyridine units would confine their rotation around the C(py)–C(porphyrin) bonds.[13]

The folded conformations of the aryl amide backbones of the bisporphyrins in chloroform have been established.[6a,b] Previous ^1H NMR studies supported that intramolecular five- and six-membered N–H···OR hydrogen bonding could survive in aqueous and polar organic solvents.[14,15] In order to obtain more evidences, several model molecules have been prepared and for two of them, that is, **16** and **17**, single crystals suitable for X-ray analysis were successfully grown by evaporation of their solution in water and THF (4:1). Their solid state structures clearly revealed the formation of three-center intramolecular hydrogen bonding (Fig. 1). In addition, the stacking pattern and structural parameters of **17** are very close to those of its crystal grown from chloroform.[15a] 2D NOESY experiments in DMSO-d_6 also revealed important NOE connections between the NH signal and the neighboring OCH_3 and OCH_2 signals for the solutions of **1b** and **2a** (as shown in the above structure). All these results support that intramolecular hydrogen bonding exists in polar solvents for the aryl

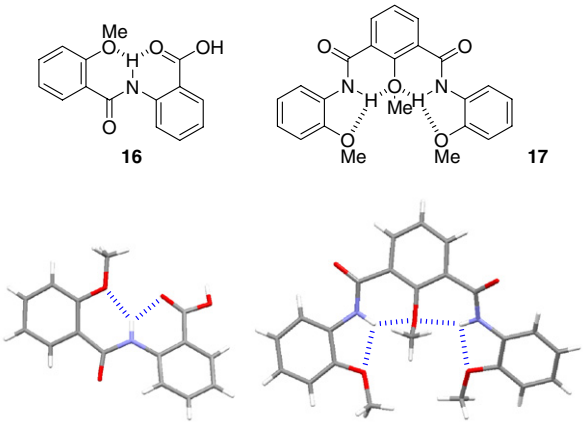


Figure 1. Compounds **16** and **17** and their crystal structures, highlighting the intramolecular hydrogen bonding. The single crystals were grown by slow evaporation of their solution in water and THF (4:1).

amide units of the ionic bisporphyrins and the whole molecules have a preorganized U-styled conformation.

Mixing **3a**[16] with the bisporphyrins in D_2O (pH 7) or DMSO-d_6 caused important change of the signals of the pyridine protons of the latter in their ^1H spectra. Accurate values of the change of the chemical shifts were not available due to the low resolution of the signals. Important upfield shifting was observed for the signals of **3a** in the ^{13}C NMR spectra of the mixture solutions. For example, the signals of the O=*C* and O=C–*C* of **3a** (5.0 mM in D_2O) in the presence of 1 equiv of **1b** moved upfield from 163.1 and 73.2 ppm to 159.7 and 71.1 ppm, respectively. The signals of the aromatic carbons of the C_{60} moiety also shifted upfield pronouncedly, although these signals could not be assigned separately due to overlapping. In contrast, no similar salient changes were observed for both the ^1H and ^{13}C spectra of the mixture solutions of neutral **3b**[16] and the cationic bisporphyrins of the identical concentration. These results suggested that (1) ion exchange occurred in the mixture solutions of **3a**, which gave rise to ionic porphyrin–C_{60} complexes, (2) the spherical moiety of **3a** of the complexes was orientated between the two porphyrin units of the ionic receptors. That is, sandwich-styled complexes were formed between the ionic receptors and **3a**, which were stabilized by both cooperative electrostatic and aromatic stacking interactions (Fig. 2). The fact that no interaction was observed between the cationic bisporphyrins and **3b** might be attributed to the low solubility of the latter. However, adding 1 equiv of **12a–c** to the solution of **3a** (5.0 mM) in DMSO-d_6 did not cause salient shifting for the signals of the latter in the ^{13}C NMR spectrum, which might be rationalized by considering the reduced preorganization of the linker of the bisporphyrins in the highly polar solvent. This result supports that electrostatic interaction was the major driving force for the formation of the complexes of **3a** with the ionic receptors. Such interaction would not only increase the preorganization of the porphyrin units of the receptors, promoting the porphyrin–C_{60} stacking, but also reduce the unfavorable

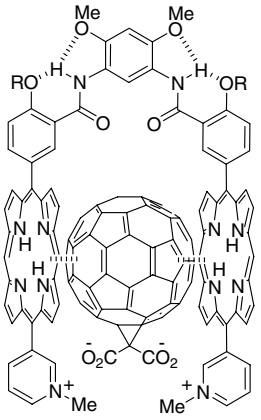


Figure 2. The formation of sandwich-styled complexes between ionic receptors (with **1b** as example) and **3a**.

binding entropic effect. In principle, other types of complexes with more complicated stoichiometry could also be formed between **2a** and **2b** and **3a** through further ion exchange. However, the above observations support that the 1:1 complexes should be most favorable (vide infra), in which the porphyin and fullerene moieties could interact remarkably.

Incremental addition of **3a** to the solution of the ionic receptors in water or DMSO caused significant bathochromic shift and reduction of the Soret band of the receptors in the UV–vis spectrum (Figs. 3 and 4). Similar results were not observed when replacing **3a** with **3b**. These observations were consistent with the above NMR experiments, supporting the formation of stable complexes between **3a** and the receptors. Job's plot analysis suggested a 1:1 binding mode for the complexes of both **1** and **2**, although the latter two receptors were hexacationic. This result implies that, upon the insertion of the first molecule of **3a** between the porphyrin units of **2**, molecules of **3a** that were electrostatically bound to **2** through further ionic exchange did not form significant donor–acceptor interaction with the porphyrin units of the receptors. On the base of the absorbance changes

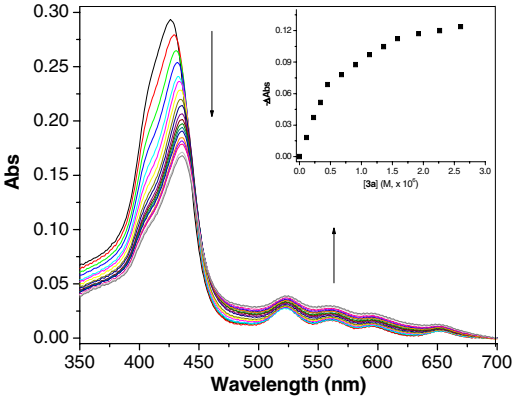


Figure 3. Absorption spectral changes of **1a** (2.1×10^{-6} M) upon addition of **3a** (0–2.7×10^{-6} M) in water at 25 °C (inset, the plot of the absorbance change vs [**3a**], the absorbance of **3a** had been subtracted from the spectra).

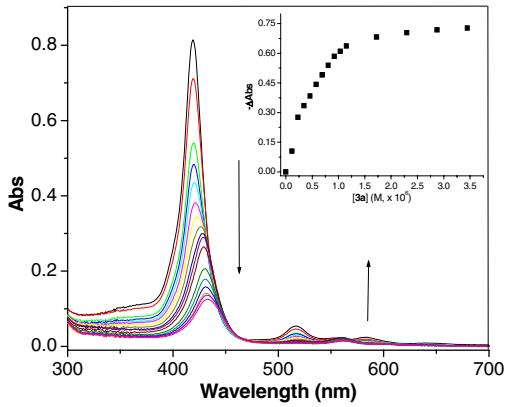


Figure 4. Absorption spectral changes of **2b** (2.1×10^{-6} M) upon addition of **3a** (0–3.5×10^{-6} M) in water at 25 °C (inset, the plot of the absorbance change vs [**3a**], the absorbance of **3a** had been subtracted from the spectra).

of the Soret band of the receptor (at 420 nm) in the UV–vis spectra with [**3a**] in water,[6b,17] we have determined the association constants (K_{assoc}'s) of complexes of **3a** with **1a**–**c** and **2a** and **2b** in water to be approximately 2.5 ($\pm$0.2) $\times 10^4$, 1.1 ($\pm$0.1) $\times 10^5$, 2.5 ($\pm$0.2) $\times 10^5$, 6.9 ($\pm$0.7) $\times 10^5$ and 2.1 ($\pm$0.2) $\times 10^6$ M^{-1}, respectively. Compared to that of **1b** and **1c**, the value of **1a** was notably lowered, which may be attributed to the existence of atropisomers for **1a** and also the possible steric hindrance of the methyl groups that were connected to its pyridine units. Generally, the values of hexacationic **2a** and **2b** are larger than that of their dicationic analogues, which should reflect their increased intermolecular electrostatic interaction.

The strong binding affinity of **3a** toward the ionic bisporphyrin receptors in water also caused substantial quenching of the emission of the latter. Fluorescent titration experiments were therefore also carried out for the system of **2b** and **3a** (Fig. 5), which gave rise to a K_{assoc} of ca. 2.0×10^6 M^{-1} for their 1:1 complex. This value was quite consistent with the result derived from the UV–vis titrations.

In conclusion, we have reported the synthesis of two series of water-soluble ionic bisporphyrin tweezers for

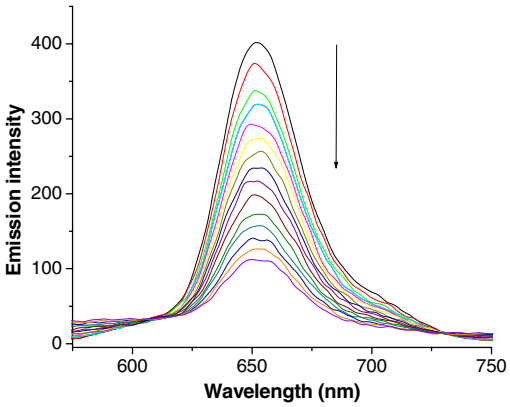


Figure 5. The change of the fluorescent spectra of **3b** (1.9×10^{-6} M) with the addition of **3a** (0–25 equiv) in water at 25 °C.

binding ionic C_{60} derivative. Intramolecular hydrogen bonding has been utilized to preorganize the U-styled conformation of the tweezers and intermolecular electrostatic attraction used as the major driving force for the binding. The high stability of the resulting complexes illustrates the efficiency of intramolecular hydrogen bonding in regulating the shape of conformation of synthetic receptors in water or highly polar organic solvents. Future works will point to the application of the cooperativity hydrogen bonding and electrostatic forces for assembling well-defined porphyrin–C_{60} supramolecular polymers in aqueous medium.

Acknowledgments

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11. The zinc porphyrin derivatives of these ionic receptors could be prepared, but they were found to be unstable in the solution possibly due to the strong electron-withdrawing ability of the methylated pyridines.

12. *Characterization data*: Compound **15a**. ^{1}H NMR ($CDCl_3$): δ −2.89 (s, 4H), 3.39 (s, 6H), 3.58 (t, $J = 6.2$ Hz, 4H), 3.81 (t, $J = 6.2$ Hz, 4H), 4.08 (s, 6H), 4.18 (t, $J = 6.3$ Hz, 4H), 4.69 (t, $J = 6.3$ Hz, 4H), 6.72 (s, 1H), 7.42 (d, $J = 5.4$ Hz, 2H), 7.75–7.78 (m, 6H), 8.21–8.24 (m, 2H), 8.48–8.50 (m, 6H), 8.73–8.99 (m, 22H), 9.06 (d, $J = 4.2$ Hz, 2H), 9.15 (s, 1H), 9.41–9.44 (m, 6H), 10.27 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 56.4, 59.1, 69.2, 69.4, 70.8, 72.0, 111.6, 116.0, 116.3, 121.2, 121.4 (d), 122.0, 131.0, 135.0, 137.7, 138.3, 140.9, 148.3, 149.2 (d), 153.6, 156.6, 162.6. MS (MALDI-TOF): m/z 1692 $[M]^+$. HRMS (MALDI-TOF): Calcd for $C_{102}H_{83}N_{16}O_{10}$: 1691.6478. Found: 1691.6446. Compound **2b**. ^{1}H NMR (DMSO-d_6): δ −3.13 (s, 4H), 3.18 (s, 6H), 3.72 (t, $J = 6.2$ Hz, 4H), 4.10–4.13 (m, 10H), 4.52 (s, 6H), 4.66 (s, 15H), 4.72 (4H), 7.05 (s, 1H), 7.76 (d, $J = 9.0$ Hz, 2H), 8.35–8.38 (m, 2H), 8.47–8.50 (m, 2H), 8.54–8.58 (m, 2H), 8.76 (s, 2H), 9.04–9.26 (m, 16H), 9.27–9.30 (m, 8H), 9.41–9.44 (m, 4H), 9.51 (d, $J = 6.3$ Hz, 2H), 9.90–9.96 (m, 7H), 10.52 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 41.1, 41.3, 41.5, 41.6, 41.8, 48.4 (d), 56.6, 58.1, 68.8, 69.5, 69.9, 71.4, 112.1, 112.9, 113.1, 118.5, 120.7, 121.6, 126.5, 133.3, 136.8, 140.2, 145.4, 147.7, 148.1, 156.9, 162.1. MS (MALDI-TOF): m/z 1781 $[M-6PF_6]^+$. HRMS (MALDI-FT): Calcd for $C_{108}H_{101}N_{16}O_{10}$: 1781.7854. Found: 1781.7842.

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