Complexation of 4,4′-Dipyridyl Derivatives Changed the Orientations of Metalloporphyrins Linked to the Cyclic Peptide Gramicidin S

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Pairs of Zn and Co(III) porphyrins linked to the natural cyclic β-sheet peptide, Gramicidin S, formed stable host-guest complexes with the 4,4′-dipyridyl derivatives in dichloromethane, in which the Cotton effects reflected the orientational changes of the metalloporphyrins upon the complexations.

Porphyrin-containing artificial receptors for diamines are of current interest because of their excellent chromophoric properties.[1] Circular dichroism (CD) spectroscopy has discriminated the chirality of the guest diamines[1a,1b] and elucidated the structure of the chiral hosts molecules.[1c,1d] We have linked two porphyrins to the natural cyclic peptide, Gramicidin S (Figure 1, **1**), and reported the solvent-dependent orientational change of two zinc-porphyrins in **3**.[2] We wish to report the host-guest capturing by this porphyrin-polypeptide hybrid, which is unique in the following points: 1) the metalloporphyrins are connected via flexible spacers (-$(CH_2)_3$-) to the peptide and may be brought together by the guest diamine, 2) the peptide framework is rigid with four intramolecular hydrogen bondings,[2] and 3) the self-associating character of the peptide might later form the supramolecular multiple host-guest assembly.

The host molecules **3–5** were synthesized via an intermediate (**2**)[2,3] and characterized by their ^{1}H NMR and FAB-MS spectra. To a 20 μM CH_2Cl_2 solution of **3**, a guest (**6** or **7**[4]) solution in CH_2Cl_2 was titrated at 25 °C. The absorptions of bis-zinc host (**3**) at 421, 550, and 589 nm shifted to 426, 562, and 603 nm, respectively, with clear isosbestic points for both guests, in which near-saturation was observed by adding 1.8 equivalents of the guest (not shown). The continuous variation method ([**3**]+[guest] was 20 μM) supported the formation of the host-guest 1 : 1 complex. The mixture of **3** and **6** (1 : 1 by mol) showed MALDI-TOF-MS (matrix, α-cyano-4-hydroxycinnamic acid) signals of $m/z = 2634$ ([**3**]$^+$) and 2790 ([**3** + **6**]$^+$), though only **3** was detected by FAB-MS. In toluene, the absorptions of **3** changed by adding **6** but the isosbestic points were not clear. Probably **3** acquired some assembled structure in toluene[2] and the addition of **6** caused the dissociation of the assembled **3** and then the successive coordination of **6**. In CH_2Cl_2 containing 20% MeOH or 5% CF_3CH_2OH, the addition of **6** slightly changed the UV spectra of **3**, indicating the weak coordination of **6** in these solvents.

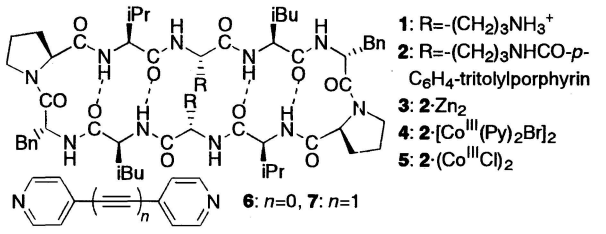

Figure 1. Structures of porphyrin-hosts and the guests.

The binding constants for the complexation, log *Ka*, were obtained from the UV-Vis data[5] and were 5.8 ± 0.1 for **3** + **6** and 4.8 ± 0.1 for **3** + **7**. Because the basicity of the two guests are similar,[4] the difference in the *Ka* values may be due to the size effect, that is, **7** might be too long to fit the host. As the control experiments, **3** was titrated by pyridine, and also the zinc tetraphenylporphyrin (TPP) by **6**. In both cases, the UV-Vis spectra did not change even when ≈40 equivalents of amines were added, which means the weak coordination of the monodentate pyridine to the host and also of **6** to the monomeric zinc porphyrin. The reported binding constant of pyridine to a doubly strapped bis-zinc etioporphyrins in the face-to-face fashion was 1/2000 compared with that of **6**.[1e] Hence, the coordination of the 4,4′-dipyridyl derivatives to **3** should be intramolecular bridging and not intermolecular bridging.

The bis-cobalt hosts (**4** and **5**, 4.0 μM) also changed their absorptions by adding **6** from 437/555 nm (Figure 2, line a) to 434/551 nm (line b), and from 411/546 nm to 439/555 nm, respectively, with clear isosbestic points. The continuous variation experiments indicated the 1 : 1 complexes in **4** + **6** and **5** + **6** below the molar ratio of the guest/host = 1, however, the addition of a large amount of **6** to **5** caused a further spectral change (λ_{max} 436 and 554 nm, Figure 2, line c). This is ascribed to the formation of the porphyrin/dipyridyl = 1/2 complex reflecting the six-coordination character of Co(III).[3b] In fact, pyridine coordinated to **5** under the same experimental conditions without any clear isosbestic points. Relatively strong and successive coordinations of two pyridines to ClCo(TPP) are known (log *Ka*s 4.98 and 3.62).[3b] The log *Ka* values were 6.8 ± 0.1 for **4** + **6** (binding of the first **6**), 6.9 ± 0.1 (K_1, binding of the first **6**) and 4.4 (K_2, binding of the second **6**) for **5** + **6**, and 6.6 ± 0.2 for **5** + **7**

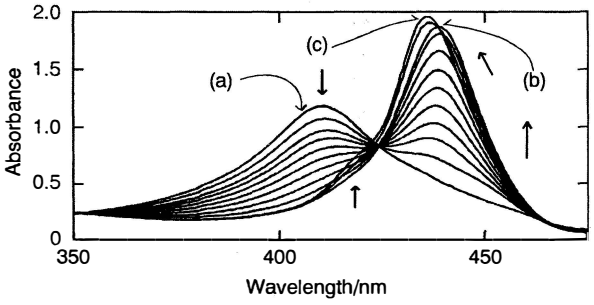

Figure 2. Titration of **5** (line a) in CH_2Cl_2 (4.0 μM) by **6** (0, 0.2, ... 1.6 (line b), 3.2, 6.4, 12.8 (line c) equivalents).

(binding of the first **6**). The larger binding constant of **5** than **4** may be due to its Lewis acidic character. Anyway, the cobalt hosts with such large association constants will be useful in future studies.

The CD spectra provided information as to the orientations of the porphyrin rings in the host-guest complexes (Figure 3). The exciton coupled CD appeared for **3** (20 μM in CH_2Cl_2, $\Delta\varepsilon_{426} = -75.5$ and $\Delta\varepsilon_{416} = 73.2\,M^{-1}\,cm^{-1}$) in the porphyrin region reflecting the chirality of the cyclic peptide.[2] The addition of **6** drastically decreased the split Cotton effects and a weak Cotton effect newly appeared at 424 nm with $\Delta\varepsilon = 23.7$ (Figure 3a). From its shape and the small $\Delta\varepsilon$ values, this new Cotton effect of **3** + **6** should be the induced CD, not the exciton-coupled CD. The edge-to-edge conformation of the two porphyrin rings in **3**[2] changed to the face-to-face orientation after sandwiching **6**. Interestingly, the shape of the CD spectra of **3** in pyridine was similar to that in CH_2Cl_2. Unfortunately, the structure of the peptide moiety was not clarified because the CD spectra of the amide or dipyridyl regions could not be measured in CH_2Cl_2. However, the conformation of the cyclic β-sheet peptide Gramicidin S is known to be rigid[2] and the peptide framework might be unchanged upon the complexations. The CD spectra of **5** also changed upon the addition of **6** (Figure 3b). A weak and complex CD appeared for **5** ($\Delta\varepsilon \approx 5.3$) in the porphyrin region, suggesting that the chlorocobalt complexes were somewhat polar and tended to separate. However, split Cotton effects appeared after the addition of **6** ($\Delta\varepsilon_{449} = -22.8$ and $\Delta\varepsilon_{431} = 31.5\,M^{-1}\,cm^{-1}$), which suggested that the binding of **6** brought two cobalt porphyrins together. To the best of our knowledge, this is the first example of cobalt porphyrins showing the exciton coupled Cotton effects and further investigation using the simpler chlorocobalt porphyrins is necessary.

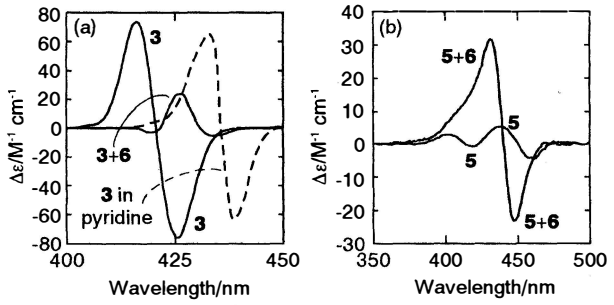

Figure 3. CD spectral changes of hosts (a) **3** and (b) **5** (20 μM in CH_2Cl_2) by the addition of three equivalents of **6**.

The binding of **6** was not successfully observed by the ^1H NMR spectroscopy because the host molecules aggregated and showed the broad signals in CD_2Cl_2 (1.0 mM) at such a high concentration. In CD_3OD or DMSO-d_6, the sharp NMR signals of **3**-**5** appeared indicating that **3**-**5** were dissolved as monomers, but unfortunately the binding was not observed at all in these solvents. In CD_2Cl_2-CD_3OD (4 : 1, v/v) and in CD_2Cl_2-CF_3CD_2OD (19 : 1, v/v), the sharp NMR signals of **3**-**5** appeared, but the binding phenomena were very weak. When two equivalent of **6** were added to **3** in CD_2Cl_2-CD_3OD (4 : 1, v/v), the signals of **6** was observed at δ 8.10 and 7.42 ppm (Figure 4a), which were

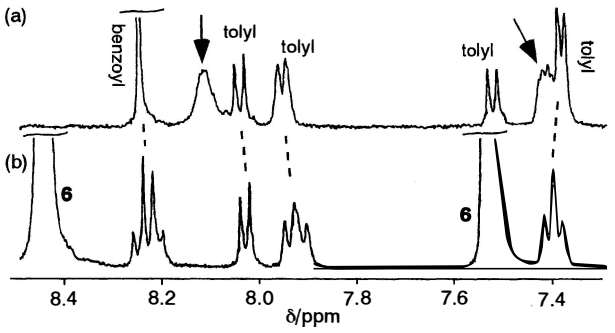

Figure 4. ^1H NMR spectra of (a) **3** + **6** (1 : 2) and (b) **3** + **6** (1 : 10) in CD_2Cl_2-20% CD_3OD. The arrows in (a) indicate the signals of **6**.

slightly high-field shifted from the chemical shifts of the free **6** in CD_2Cl_2 (δ 8.43 and 7.53). In CD_2Cl_2-CF_3CD_2OD (19 : 1, v/v), the signals of **6** was observed at δ 8.07 and 7.56 ppm when two equivalent of **6** was added to **3**. These facts showed that the binding of **6** in alcohol-containing solvent is very weak, because alcohols may prevent the coordination of dipyridyl. When the equimolar amount of **6** was added to **3**, only broad signals were observed in both solvent systems. At low temperature, the signals of **3** became too broad to assign. The signals derived from **3** did not changed when two equivalent of **6** was added (Figure 4a), but a little changed when 10 equivalent of **6** was added (Figure 4b). The benzoyl aromatic signal (δ 8.27) and one of the tolyl aromatic signals (δ 7.98) of the porphyrin in **3** increased their multiplicity. These facts suggest the conformational change occurred in **3** when the large amount of **6** was added. A further studies on the complexation phenomena and more complicated molecular assembly combining the coordination bonds and the hydrogen bondings are now underway.

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