Communication

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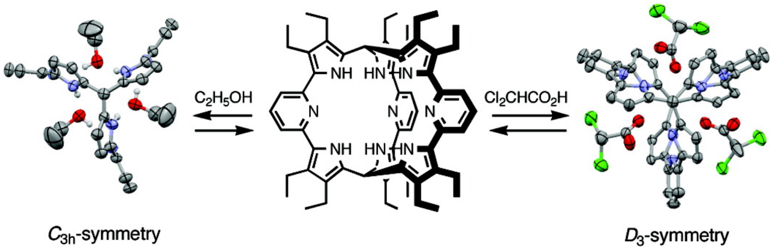

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Cryptand-like Porphyrinoid Assembled with Three Dipyrrylpyridine Chains: Synthesis, Structure, and Homotropic Positive Allosteric Binding of Carboxylic Acids

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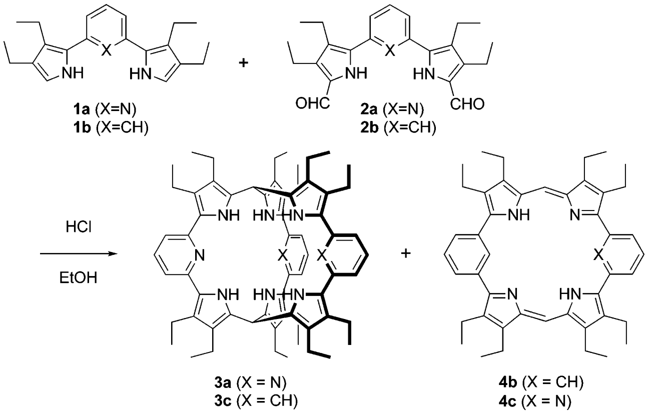
Artificial receptors showing homotropic positive allosteric effect are drawing considerable attention in view of the exquisite reaction control in many biological processes based on those allosteric effects,[1] but there are a limited number of successful examples.[1−4] Bridging two rigid subunits composed of multibinding sites by metal ions[3] or bifunctional ligands[4] is one of the more successful strategies that takes advantage of entropy penalty in binding the first ligand. It is even more difficult to demonstrate how positive cooperativity is realized in binding monofunctional ligands. Herein we describe new cryptand-like porphyrinoid assembled with three dipyrrylpyridine chains for this purpose. Cryptand-like hosts can provide not only an inside space but also three crevices toward ligands.[5] The latter binding mode which allows the incorporation of large ligands at multiple binding sites has potential application but has not been well explored. One such molecular design is cryptand-like calixpyrrole constructed by three tripyrrane chains which was used for anion binding at a single crevice.[5a] Since three crevices can influence each other through partitions or via the central cavity, the cryptand-like structure is a promising scaffold for cooperative ligand binding. Of great importance in our receptor is that the π-conjugated pyrrole and pyridine are involved in the hydrogen bondings with ligands at different crevices, which leads to strong homotropic positive allostericity in binding carboxylic acids.

It is exceptional that cryptand-like bicyclic calixpyrrole was formed by the conventional MacDonald-type condensation between α-free tripyrrane and tripyrrane dialdehyde, because it usually gives monocyclic compounds.[5a] The reaction of 2,6-bis(3,4-diethyl-2-pyrryl)pyridine **1a**[6] and the corresponding dialdehyde **2a** in 2:1 molar ratio in HCl/ethanol at reflux for 1 h afforded 48% yield of the bicyclic hexapyrrole **3a**, whereas the reaction of the benzene analogues with a 1,3-phenylene spacer, **1b**[6] and **2b**, gave ordinary monocyclic tetrapyrrole **4b** in 76% yield under the same reaction conditions (Scheme 1). The monocyclic hybrid tetrapyrrole **4c** was also obtained in 30% yield, if **1a** and **2b** were allowed to react in 2:1 molar ratio. However, the reverse combination of dipyrrole and dialdehyde, **1b** and **2a**, in 2:1 molar ratio afforded both the bicyclic hybrid hexapyrrole **3c** and the monocyclic tetrapyrrole **4c** in 19 and 71% yield, respectively. Since protonation at the pyridine nitrogen activates the dialdehyde **2a** and deactivates the dipyrrole **1a** for their coupling reaction, the product yields are superior in the reactant combination of **1b** and **2a** to any other combination. The hybrid tetrapyrrole **4c** would be protonated both at the pyridine nitrogen and the pyrrolenine nitrogens under strongly acidic conditions. The resulting tricationic species would undergo nucleophilic attack by **1b** at the *meso*-like carbons to lead to **3c**, while **1a** is not so reactive as to attack this trication because of the protonation of **1a** itself. The nucleophilic reactivity of **1a** seems sufficient toward highly reactive monocyclic tetracation generated from the reaction of **1a** and **2a** under acidic conditions, thus giving **3a**.

Scheme 1. Synthesis of Bicyclic Hexapyrroles (**3a**, **3c**) and Monocyclic Tetrapyrroles (**4b**, **4c**)



The crystals of **3a** grown from ethanol−CHCl$_3$ showed well-resolved ^{1}H NMR signals due to EtOH at δ 3.60 (quartet) and 1.13 (triplet) at 20 °C in CDCl$_3$ with EtOH/**3a** molar ratio of 3/1. These EtOH signals are shifted to δ 2.6 (CH$_2$) and 0.4 (CH$_3$) with broadening upon lowering the temperature to −60 °C (Supporting Information). These facts are indicative of binding three EtOH molecules by **3a**.

X-ray crystallography of **3a**·(EtOH)$_3$ showed C_{3h} symmetric structure where two pyrrole rings in one dipyrrylpyridine chain are tilted to the same side of the central pyridine plane with a N−C−C−N torsion angle of 35.6°.[7] As a consequence, two pyrrole NH bonds in one chain and the pyridine nitrogen lone pair orbital in the next chain are pointing to one focal point. This structural feature promotes binding of an ethanol molecule in each crevice of **3a** through three hydrogen bondings (Figure 1). Ethanol OH proton (H$_{O1}$) is bonded to the pyridine nitrogen (N2) with 2.864 Å O1−N2 distance, and the ethanol oxygen (O1) is bonded to two pyrrole NH protons (H$_{N1}$) belonging to the next dipyrrylpyridine chain with 3.093 Å N1−O1 distance. These hydrogen-bonded protons were found in the difference Fourier map in the X-ray analysis, and structural refinement was performed. They lie close to the N-to-O lines with N1−H$_{N1}$−O1 and O1−H$_{O1}$−N2 angles of 164.2 and 170.2°, respectively, and with N1−H$_{N1}$ and O1−H$_{O1}$ distances of 0.84 and 0.83 Å, respectively. The bond angles around O1 shows ideal tetrahedral geometry: 106.5° (C13−O1−H$_{O1}$), 108.1° (C13−O1−H$_{N1}$), 113.3° (H$_{N1}$−O1−H$_{O1}$), and 107.2° (H$_{N1}$−O1−H$_{N1}$).

UV−vis titration of **3a** (8.92 μM) in CH$_2$Cl$_2$ with CF$_3$CO$_2$H (TFA) showed two straight lines that intersect at the [TFA]/[**3a**] ratio near 3, which is the case known as the mole ratio method to determine stoichiometry using very strongly binding ligands. Yellow coloration as a 416 nm band develops with tailing up to 550 nm is indicative of protonation at the pyridine nitrogen. A binding

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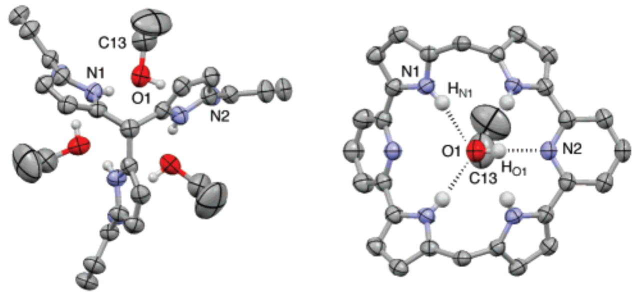


Figure 1. Ortep drawing (50% thermal ellipsoids) of **3a**·$(EtOH)_3$ viewed along the C_3 axis; pyrrole-β ethyl groups are omitted for clarity (left). Partial structure (side view) showing only one crevice with a EtOH ligand: N1-H_{N1}, 0.84; H_{N1}-O1, 2.27; O1-H_{O1}, 0.83; H_{O1}-N2, 2.05 Å (right).

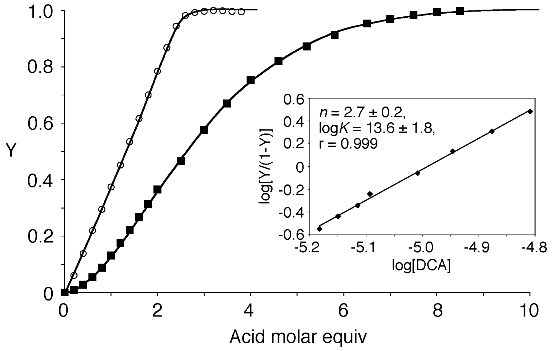
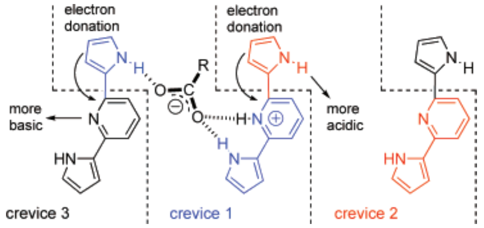


Figure 2. Binding isotherms based on the UV−vis titration of **3a** ([**3a**] = 8.92 μM) with dichloroacetic acid (DCA) at 420 nm (filled square) and trifluoroacetic acid (TFA) at 416 nm (circle) in CH_2Cl_2 at 293 K. (Inset) Hill plot for the binding of DCA to **3a**. $Y = \Delta abs/\Delta abs(max)$.

isotherm for Cl_2CHCO_2H (DCA) showed a sigmoidal response characteristic of positive cooperativity between three binding sites (Figure 2). Cooperativity was estimated by the Hill coefficient ($n = 2.7 \pm 0.2$) and the association constant ($\log K = 13.6 \pm 1.8$) on the basis of the Hill plot ($\log(Y/1 - Y) = n \log [DCA] + \log K$). In the ^1H NMR titration of **3a**·$(EtOH)_3$ (7.1 mM) in $CDCl_3$ with TFA at −50 °C, a singlet at δ 10.9 (6H) due to the pyrrole-NH of **3a**·$(EtOH)_3$ decreased in intensity with increasing two singlets at δ 11.6 (6H) and 11.9 (3H) due to the pyrrole-NH and pyridinium-NH, respectively, of **3a**·$(TFA)_3$. No other porphyrinoid species such as **3a**·(TFA) and **3a**·$(TFA)_2$ was detected during titration, and **3a**·$(EtOH)_3$ was completely replaced by **3a**·$(TFA)_3$ at 3 molar equiv of TFA (Supporting Information). These UV−vis and ^1H NMR titrations clearly indicate that the strong positive allosteric effect is operating in binding carboxylic acids to **3a**.

X-ray crystallography of **3a**·$(DCA)_3$ complex shows that a carboxylate ion bridges two pyrrole NH protons belonging to different dipyrrylpyridine chains with N−O distances of 2.749 and 2.908 Å.[7] These hydrogen bondings force the host molecule in pseudo-D_3 symmetric conformation where two pyrrole nitrogens in one dipyrrylpyridine chain are directed to the opposite sides of the central pyridine plane (Scheme 2 and Supporting Information). Protonation at the pyridine nitrogen in the first crevice causes electron attraction from the π-conjugated pyrroles to make the pyrrole belonging to the second crevice more acidic. Moreover, the hydrogen bonding at the pyrroles in the first crevice causes electron donation to the π-conjugated pyridines to make pyridine belonging to the third crevice more basic. Binding two ligands to **3a** strengthens both the pyridine basicity and pyrrole acidity in the remaining free crevice to further enhance binding the third ligand. This polarization of the π-conjugated chains and the reorganization in D_3 symmetric conformation rationalize the remarkable positive cooperativity in binding carboxylic acids.

Scheme 2. Mechanism for Positive Allosteric Binding of Carboxylic Acids with **3a**



Dipyrrylpyridines are known as molecular cleft receptors used for binding enolates.[8] The present work points out that fabrication with three units of dipyrrylpyridine into the cryptand-like structure gives rise to the new molecular crevice receptor with the positive cooperativity in binding carboxylic acids. It is also remarkable that the dual binding mode, C_{3h} or D_3 type, of this receptor can responds to structurally different ligands. Further study of molecular recognition using these crevice receptors is now going on in our laboratory.

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Supporting Information Available: Synthetic procedures and characterization data for all compounds, including VT-NMR spectra of **3a**·$(EtOH)_3$, details of UV−vis and ^1H NMR binding studies, and X-ray crystallographic data of **3a**·$(EtOH)_3$ and **3a**·$(DCA)_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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