

Cambiarenes: Single-Step Synthesis and Anion Binding of a Clip-Shaped Macrocyclic Host with a Redox-Active Core

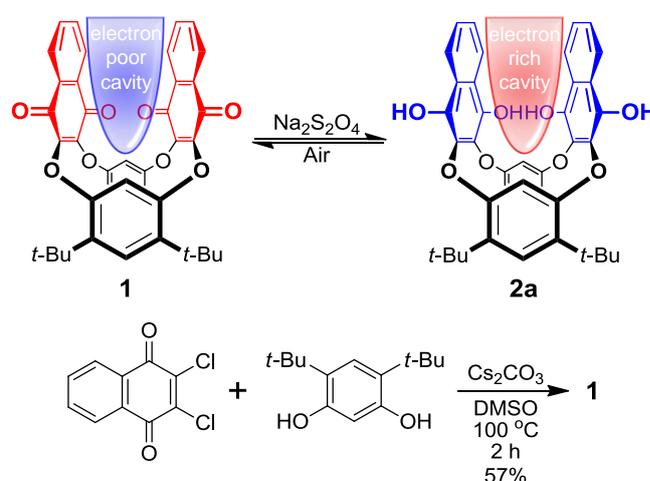
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Abstract: We report the synthesis of a novel macrocyclic host molecule that forms in a single step from commercially available starting materials. The core of the macrocycle backbone possesses two quinone rings and, thus, is redox-active. Host-guest binding involving the clip-shaped cavity indicates selective binding of pyridine *N*-oxides based on the electron density of and steric bulk of the anionic oxygen.

Electronically tunable systems offer a distinct advantage for the construction of supramolecular structures.^[1] By harnessing electronic features like oxidation state, well-defined macrocycles that can be switched between two different states have been generated. For example, Diederich^[2] and others^[3] have shown that the incorporation of quinone rings within^[3a,c,e] or onto^[2,3b,d] the macrocyclic backbone lead to changes in the electronic features of these supramolecular hosts. However, these structures require multi-step syntheses and often lead to hosts that exhibit non-specific guest binding. On the other hand, macrocyclic host molecules accessible in one step have revolutionized the field of supramolecular chemistry (e.g., calixarenes,^[4] resorcinarenes,^[5] pillararenes^[6]), but they often bind guest molecules utilizing a static benzenoid core (e.g. via cation- π interactions).¹ Our goal was to combine the synthetic utility of a single-step macrocyclization with the structural utility of an electronically dynamic supramolecular system. Herein we report the synthesis of a redox-active macrocycle that shows selective binding of pyridine *N*-oxide guests, based on electronic and steric features, primarily through anion- π ^[7] interactions.

Initially, the synthesis of cambiarene^[8] **1** was achieved in one step from the readily available and inexpensive starting materials 2,3-dichloro-1,4-naphthoquinone and 4,6-di-*tert*-butylresorcinol (Scheme 1).^[9] Expanding on our previous study of similar substitution reactions,^[10] the synthesis employed sterically bulky *tert*-butyl groups at the 4- and 6-positions of the diphenol which prevented the formation of a furan, and led to good yields (57%) of the macrocycle. The reaction can be scaled up using

less solvent and changing the base to K₂CO₃ to improve economy, with only a slight reduction in yield (49%, 1.8 g).



Scheme 1. Supramolecular redox properties and synthesis of cambiarene **1**.

Single crystals of cambiarene **1** with 4-methylpyridine *N*-oxide (**3a**) (1:1 ratio) as the guest in the form of 1·(**3a**)·(toluene)·0.08H₂O were grown via slow-evaporation from a solution of toluene to yield orange-yellow rod-like single crystals suitable for single-crystal X-ray diffraction (SCXRD).

The host cambiarene **1** exhibits a two-walled conformation (centroid-distances of aromatic rings: 6.83 Å; quinone rings is 5.54 Å) with both phenyl rings oriented the same direction (Figure 1). The conformation is reminiscent of the 1,3-alternate conformation of related calix[4]arenes.^[4] The walls are slightly twisted (37.2°) via the ethereal linkages. A salient feature of the X-ray structure is the inclusion of **3a** as guest. The guest is situated with the *N*-oxide functionality directed into the cavity of **1**. The geometry contrasts to four-walled calix[4]pyrroles,^[11] with guest molecule **3a** being sustained within the cavity of the host primarily through anion- π [O-centroid: 2.940(2), 2.843(2)], π - π [N-centroid 3.420(1), 3.418(1)], and C-H...O forces (C(7)-H...O = 3.213(2), C(29)-H...O = 3.393(2)). The cambiarene **1** self-assembles in a unidirectional manner to form columns along the *a*-axis.

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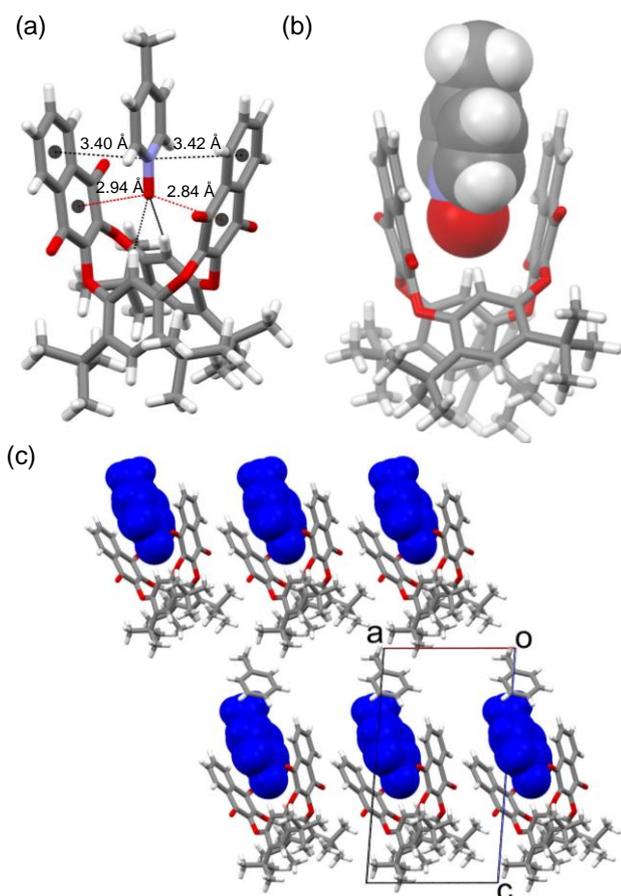
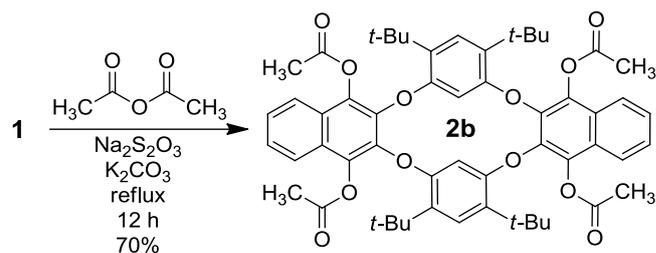


Figure 1. X-ray structure of **1·(3a)·(toluene)·0.08H₂O**: (a) cambiarene **1** host demonstrating cavity length and (b) pyridine *N*-oxide in cavity, and (c) packing along the *b*-axis.

Cyclic voltammetry (CV) analysis of **1** revealed three reversible features at ca. -2.33 V, -2.08 V, -1.35 V vs Fc/Fc⁺ and one irreversible feature at +0.23 V vs Fc/Fc⁺.^[9a] Analysis of CVs collected at scan rates of 10, 25, 50, 100, 200, 300 mV/s indicate all electrochemical features are diffusion controlled.^[12] When **1** was subjected to chemical reduction in methanol with NaBH₄ or Na₂S₂O₄ the orange solution would become colorless (**2a**), but over time with exposure to air the orange color would return.^[9a] Changing the reaction conditions to acetic anhydride and K₂CO₃ with Na₂S₂O₄ afforded the air-stable acylated, reduced macrocycle (**2b**) in good yield (Scheme 2).

Single crystals of cambiarene **2b** were grown from vapor-diffusion as **2b** was dissolved in ethyl acetate and hexanes was diffused through the solution to yield colorless plate-like crystal suitable for SCXRD (Figure 2). Cambiarene **2b** adopts a conformation similar to **1**, with a two-walled conformation (centroid-distances of aromatic rings: 5.21 Å; keto rings is 6.39 Å) with both phenyl rings oriented in the same direction. The two walls are also slightly twisted from planarity (28.0-30.3°). Macrocycles of **2b** pack in a manner that generates an interdigitated structure.



Scheme 2. Reductive acylation of cambiarene **1**.

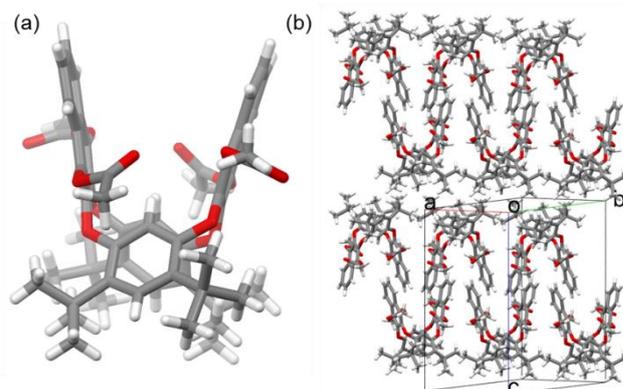
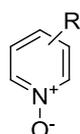


Figure 2. X-Ray crystal structure of cambiarene **2b** (a) single host molecule and (b) interdigitated assembly of macrocycles.

Consistent with the X-ray structure of **1:3a**, Job's method of continuous variation indicated the formation of a 1:1 complex in solution.^[9a] ¹H NMR titration experiments in benzene-*d*₆ revealed a $K_a = 252 \text{ M}^{-1}$ (Table 1).^[13] The binding appears to be predominantly due to anion- π interactions^[7] between the anionic oxygen of **3a** and the π -cavity of **1**.^[9a] While these interactions in non-specific binding systems tend to be on the order of ca. 10^1 M^{-1} ,^[7] binding of the pyridine *N*-oxide with two π -faces in this cavity was over an order of magnitude stronger.

To further probe the specificity of the solution state host-guest interaction the electron density on the oxide was decreased via modification of the group at the 4-position (**3a-c**, Table 1). This led to a decrease in the binding constant indicating that the binding can be modulated by tweaking the electronic parameters of the guest. Next the ability of the host to accommodate steric bulk around the anionic oxygen was probed. Moving the methyl group to the 2-position of the pyridine ring (**3d**) did not lead to a significant decrease in binding, but changing it to an isopropyl group revealed a marked decrease (**3e**). These results indicate that host **1** is selective for not only an electron rich guest but one of a size compatible with that of the narrow cavity.



3a: R = 4-CH₃ **3d:** R = 2-CH₃
3b: R = H **3e:** R = 2-*i*Pr
3c: R = 4-CF₃

Table 1. Binding constants (K_a) of the 1:3 host-guest binding complex.

| | 3a | 3b | 3c | 3d | 3e |
|---|-----------|-----------|-----------|-----------|-----------|
| K_a (M ⁻¹) ^[a] | 252 | 231 | 134 | 241 | 45 |
| Confidence Interval ^[a] | ±33.3 | ±7.35 | ±10.1 | ±23.5 | ±5.3 |
| R_σ ^[b] | -0.17 | 0 | 0.54 | - | - |

[a] ¹H NMR titration experiments and data analysis were performed as outlined in reference 14. [b] The σ_p values¹⁵ are shown as an independent measure of electron donating/withdrawing capacity of the R groups at the 4-position of the pyridine ring.

In conclusion, we have synthesized a new redox-active macrocycle for host-guest binding in good yields and in a single step from commercially available starting materials. The binding appears to be selective for flat guest molecules with a sterically unencumbered electron rich atom that binds via anion- π interactions. Future work will focus on modifying the solubility properties of cambiarenes in both redox forms to study a wider range of guest molecules, which could lead to applications such as solid sensor devices, targeted drug delivery, and carbon sequestration.

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Keywords: supramolecular chemistry • host-guest systems • macrocyclization • quinones • redox chemistry

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- [8] a) The term "cambiarene" was based on the latin verb "cambiare" which means "to change". b) Following the precedent of calixarenes this molecule would be a cambi[4]arene. c) Following IUPAC nomenclature guidelines this molecule would be termed an "oxaquinonacyclopheane", which is a name we have utilized in prior presentations.
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