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Horning-Crown Macrocycles: Novel Hybrids of Calixarenes and Crown Ethers

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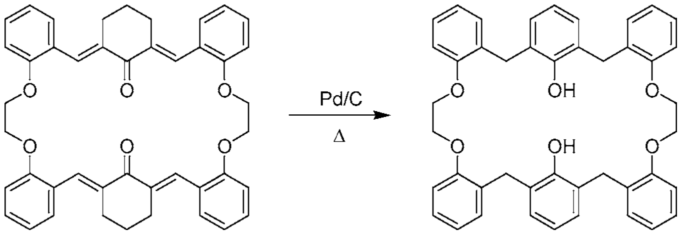
ABSTRACT



Novel macrocycles possessing ether linkages and 2,6-disubstituted phenolics were produced in one step and with 100% atom economy by isoaromatization of chameleon macrocyclic precursors possessing 2,6-diarylidenecyclohexanone moieties. Intramolecular hydrogen bonding of the phenolic hydrogen atoms influenced the shape of the macrocycles and dictated host–guest behavior.

In the preceding paper,[1] we reported a family of new macrocycles, members **1** and **3** of which were produced by “green” sequential Claisen−Schmidt condensations between aryl dicarboxaldehydes and cycloalkanones. We refer to the family as chameleon macrocycles. Its members can undergo simple yet broad structural transformations to afford new products that may bear only passing resemblance to the starting cycles. In an aspect illustrated herein, the yellow starting materials are converted to colorless hybrid macrocycles of calixarenes and crown ethers by migration of double bonds. As outlined below, we would like the new product family to be known collectively as Horning-crown macrocycles, in honor of E. C. Horning, whose work we have found highly beneficial for our present activities. About 60 years ago, Horning reported that 2,6-dibenzylphenol could be obtained by thermolysis of (2*E*,6*E*)-dibenzylidenecyclohexanone in the presence of a Pd catalyst.[2] He coined the word “isoaromatization” to describe the process.[3] Since then, similar conversions have been attempted, with variable degrees of success and under a range of conditions, including by homogeneous metal catalysis[4] and with acid in the absence of metal.[5] Nonetheless, the significant potential of Horning’s excellent work does not appear to have been widely exploited. Extension of his approach could facilitate efficient production of substituted phenolic derivatives from easily prepared masked phenols. Here, we have carried out one or, for the first time, more isoaromatizations in a single step to obtain novel macrocycles such as **2** or **4**.

The macrocycles have the phenolic functionality of calixarenes but not the bowl shape from which the name derives. They also have features reminiscent of crown ethers. Our chameleon dienone precursor macrocycles are constructed through a modular strategy. A diverse range of possible building blocks is available commercially. Others can be readily prepared, including by methods developed within our laboratory.[1,6] Hence diverse structural features and functional

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[1] Preceding Letter, this journal.
[2] Horning, E. C. *J. Org. Chem.* **1945**, *10*, 263.
[3] Horning, E. C. *Chem. Rev.* **1943**, *33*, 89.
[4] (a) Aizenshtat, Z.; Hausmann, M.; Pickholtz, Y.; Tal, D.; Blum, J. *J. Org. Chem.* **1977**, *42*, 2386. (b) Pickholtz, Y.; Sasson, Y.; Blum, J. *Tetrahedron Lett.* **1974**, 1263.
[5] Conia, J.-M.; Amice, P. *Bull. Soc. Chim. Fr.* **1968**, *8*, 3327.

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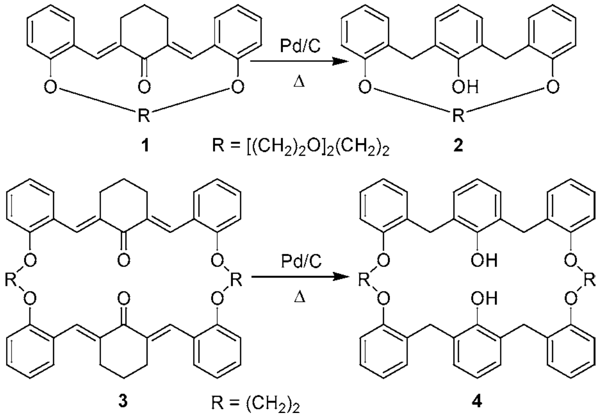
Scheme 1. Isoaromatization



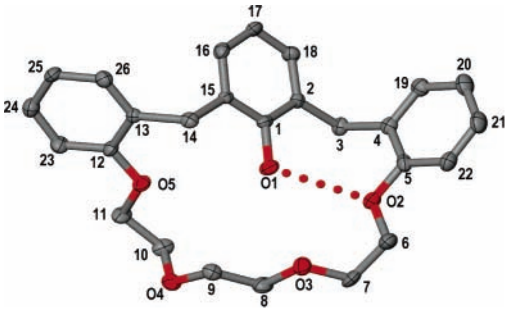


Figure 1. Molecular diagram for **2**. Ellipsoids are depicted at the 50% probability level, H atoms are omitted for clarity, and the hydrogen bond is indicated as a dotted line: *d* OH 0.94(4) Å, *d* H···O, 1.97(4) Å, O···O 2.889(3) Å, ∠ OH−O 166(3)°.

groups may be incorporated into the macrocyclic dienone precursors to afford broad structural diversity in the resultant phenol-ether macrocycles after isoaromatization. Thus in one step, compound **3** has undergone a transformation involving the removal of four enone olefinic groups and two ketonic carbonyls and the introduction of two disubstituted phenolic rings and four diaryl-substituted methylenes. The shape of the molecule has been transformed from an open-book to a butterfly shape with a large self-complementary cleft leading to highly stabilized clasped dimers. The shape of this now conformationally flexible cycle may be switched by alteration of the polarity of the environment.

Analyses of single-crystal structures were undertaken to confirm the chemical structure and conformation of the macrocycles in the solid state. Macrocycle **2** yielded crystals of suitable quality for X-ray diffraction by slow evaporation of an acetone solution.[7] Recrystallization of **4**, from a range of common solvents, resulted in crystalline solvates including the 2:4.5 solvate with aniline depicted here.[8] From the molecular diagrams presented in Figures 1 and 2, the three linked aromatic rings were significantly twisted with regard to each other. Theoretically, these molecules have a high degree of flexibility and several low energy conformations are possible.

Intramolecular hydrogen bonds from phenolic hydroxy group(s) to the oxygen atoms of the salicylyl ether linkers, however, fix the macrocycles into a twisted conformation, and these bonds are not readily disrupted, even by a variety of solvents. The macrocycle **4**, formed by two isoaromatization events, is particularly interesting in this regard. Some members exhibit a high degree of self-association in solvents such as CH_2Cl_2, PhMe, or $CHCl_3$, as evidenced by the concentration dependency of chemical shift values in their ^{1}H NMR spectra. Analysis of the crystalline aniline solvate revealed that the intramolecular hydrogen bonds created a more rigid structure than might normally have been envisaged. The macrocycles became twisted to afford a host molecule with a significant cleft. This in turn was filled by a second macrocycle molecule, in an excellent demonstration of self-complementarity. The resulting dimers showed short-range $\pi\cdots\pi$ interactions between the central pair of aromatic rings (salicylyl moieties), Figure 2.

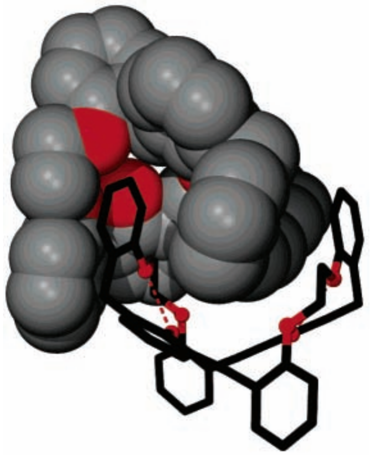


Figure 2. Perspective view of clasped dimers of **4** (as the aniline solvate). One macrocycle in twisted conformation is shown in stick form and the second with atoms depicted at van der Waals radii. Both macrocycles are crystallographically unique and, together with 4.5 molecules of aniline, constitute the asymmetric unit. Four unique intramolecular hydrogen bonds occur with the following geometry. O1A···O2A: *d* OH 0.85(4) Å, *d* H···O 1.94(4) Å, O···O 2.783(3) Å, ∠OHO 172(4)°. O4A···O5A: *d* OH 0.77(3) Å, *d* H···O 2.08(3) Å, O···O 2.841 (3) Å, ∠OHO 168(3)°. O1B···O2B: *d* OH 0.93(4) Å, *d* H···O 1.92(4) Å, O···O 2.831(3) Å, ∠OHO 168(3)°. O4B···O5BA: *d* OH 1.02(4) Å, *d* H···O 1.78(4) Å, O···O 2.789(3) Å, ∠OHO 170(3)°.

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(6) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L. Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107.

(7) **Crystal data for 2**: $C_{26}H_{28}O_5$, $M_r = 420.48$, orthorhombic, space group *Pbca*, $a = 9.7408(4)$, $b = 17.4668(7)$, $c = 25.7256(12)$ Å, $V = 4377.0(3)$ Å^3, $Z = 8$, $D_{calc} = 1.276$ g·cm^{-3}, μ(Mo Kα) = 0.088 mm^{-1}. Of 5262 unique reflections measured, 1762 $I > 2\sigma(I)$, R indices $[I > 2\sigma(I)]$ $R_1 = 0.0670$, $wR_2 = 0.0983$, GoF on $F^2 = 0.936$ for 281 refined parameters and 0 restraints.

(8) **Crystal data for 2(4)·4.5aniline**: $(C_{44}H_{40}O_6)_2\cdot(C_6H_7N)_{4.5}$, $M_r = 1749.60$, triclinic, space group $P\bar{1}$, $a = 15.8459(2)$, $b = 16.8743(3)$, $c = 19.5577(4)$ Å, $\alpha = 71.975(1)$, $\beta = 75.676(1)$, $\gamma = 72.658(1)$°, $V = 4377.0(3)$ Å^3, $Z = 2$, $D_{calc} = 1.242$ g·cm^{-3}, μ(Mo Kα) = 0.080 mm^{-1}. Of 22554 unique reflections measured, 9538 $I > 2\sigma(I)$, R indices $[I > 2\sigma(I)]$ $R_1 = 0.0681$, $wR_2 = 0.1462$, GoF on $F^2 = 0.943$ for 1205 refined parameters and 0 restraints.

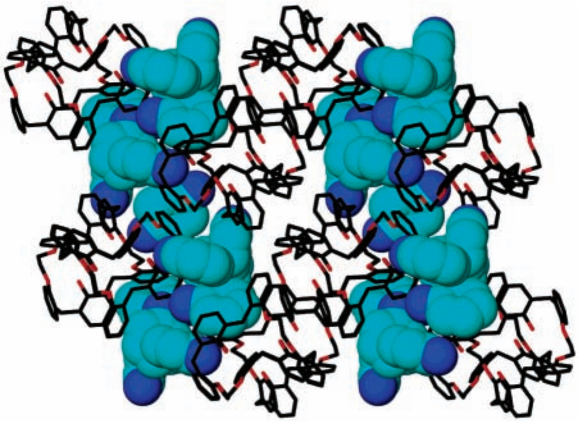

Figure 3. Packing diagram of the 2:4.5 complex of **4** with aniline viewed down *b*. Aniline guests are depicted in space-filling mode and macrocycle dimers are in stick mode. A significant volume of the cell is taken up by guest molecules, which are associated via weak CH···π interactions.

The dimers associated with aniline form a close packed structure as illustrated in Figure 3. Multiple crystal structure analyses of different solvates indicated that the lack of strong directional interactions between dimers in the solid state allows great variation in packing motifs and hence in guests accommodated.

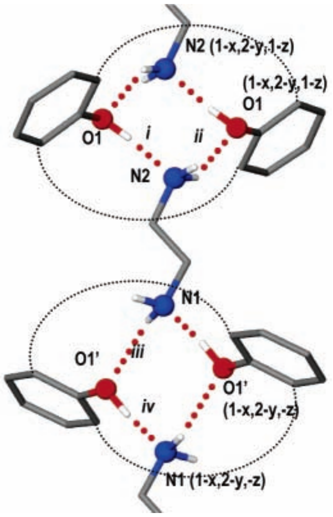

Figure 4. Hydrogen bond motif in the complex **4**·ethylenediamine·dichloromethane. Continuous columns of hydrogen-bonded host and guest propagate parallel to (001). Oxygen and nitrogen atoms are depicted as spheres, and hydrogen bonds are red dotted lines. Dashed arcs indicate connectivity of separate macrocycles. H-bond geometry: (i) *d* DH 0.88(2) Å, *d* H···A 1.74(2) Å, D···A 2.623(2) Å, ∠DHA 173(2) °; (ii) *d* DH 0.93(3) Å, *d* H···A 2.31(3) Å, D···A 3.111(3) Å, ∠DHA 144(2)°; (iii) *d* DH 0.95(3) Å, *d* H···A 2.33(3) Å, D···A 3.099(3) Å, ∠DHA 136(2)°; (iv) *d* DH 0.95(3) Å, *d* H···A, 1.72(3) Å, D···A 2.646(2) Å, ∠DHA 165(2)°.

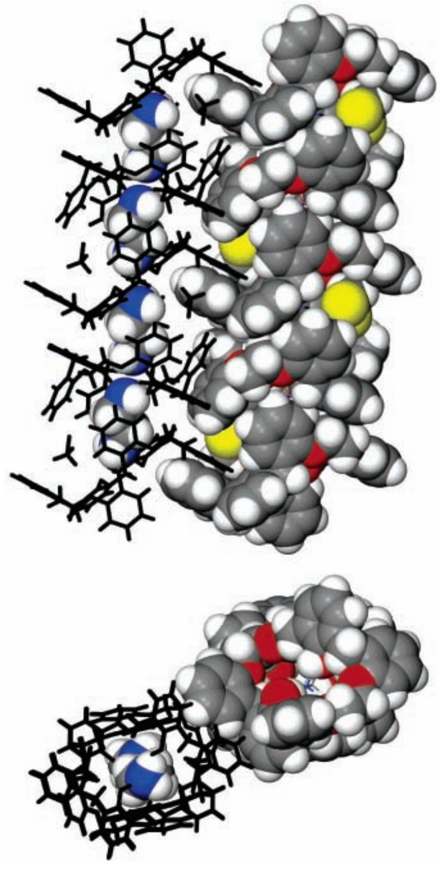

Figure 5. (Top) Packing diagram of **4** with ethylenediamine and dichloromethane viewed down [−100]. One column is depicted with guests in spacefill and hosts and dichloromethane in stick mode (black), whereas a second shows the host/solvent "insulation" in spacefill mode. The guest is completely contained. (Bottom) Columns viewed from above.

Although the self-association of molecules of **4** to form dimers is common to many solvates, the intramolecular hydrogen bonding may be disrupted by the introduction of amine bases stronger than aniline. Crystal structures of inclusion complexes with ethylenediamine/CH_2Cl_2[9] and phenylisopropylamine[10] were illustrative of the range of inclusion modes possible with these macrocycles.

In both cases, the amines acted as hydrogen bond acceptors, disrupting the intramolecular phenolic hydroxy to ether oxygen hydrogen bond, and the macrocycle adopted an open conformation. The linear diamine, by virtue of accepting hydrogen bonds from phenolics of different macrocycles (Figure 4), yielded a columnar packing motif

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(9) **Crystal data for 2·ethylenediamine·dichloromethane**: $C_{40}H_{44}O_6\cdot C_2H_8N_2\cdot CHCl_2$, M_r = 809.79, triclinic, space group $P\bar{1}$, a = 12.3043(3), b = 12.9833(3), c = 15.1589(4) Å, α = 78.598(1), β = 71.580(1), γ = 64.698(1)°, V = 2071.61(9) Å^3, Z = 2, D_{calc} = 1.298 g·cm^{-3}, μ(Mo Kα) = 0.209 mm^{-1}. Of 10015 unique reflections measured, 4831 $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] R_1 = 0.0511, wR_2 = 0.1088, GoF on F^2 = 0.900 for 532 refined parameters and 0 restraints.

(10) **Crystal data for 2·2phenylisopropylamine**: $C_{44}H_{40}O_6\cdot 2(C_9H_{13}N)$, M_r = 935.17, triclinic, space group $P\bar{1}$, a = 9.2697(3), b = 12.5253(3), c = 12.7887(4) Å, α = 98.471(1), β = 107.044(1), γ = 110.474(1)°, V = 1277.17(7) Å^3, Z = 1, D_{calc} = 1.216 g·cm^{-3}, μ(Mo Kα) = 0.077 mm^{-1}. Of 4653 unique reflections measured, 3158 $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] R_1 = 0.0737, wR_2 = 0.1951, GoF on F^2 = 1.062 for 329 refined parameters and 0 restraints.

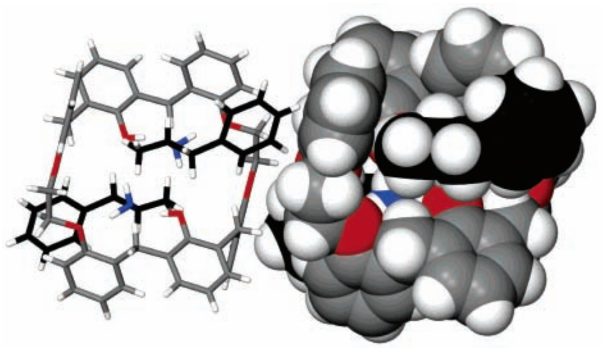

Figure 6. Packing diagram of **4** with phenylisopropylamine viewed down [−100]. Symmetrical balls composed of 1 macrocycle and 2 guests almost completely enclose the OH, -O-, and NH_2 groups in the core, presenting a lipophilic exterior. (Guest C atoms are colored black.)

in which the cycles surround the diamine guest in a motif reminiscent of a wire with insulated coating (Figure 5).

Two crystallographically independent $^1/_2$ macrocycles comprised the asymmetric unit, reflecting different conformations adopted to maximize enclosure of the guest. The "insulation" was rendered complete by inclusion of a molecule of CH_2Cl_2 to provide a column with a hydrophobic exterior. Polar OH and -O- groups were directed toward the interior and interacted with guest amines.

The complex with monoamine guest phenylisopropylamine contained no occluded solvent molecules, and a single unique host-to-guest hydrogen bond occurs (O1−H1O···N1G: *d* OH 0.87(5) Å, *d* H···N, 1.80(5) Å, O···N 2.651(4) Å, ∠ OH−N 165(4)°). Two guest amines were thus associated with each complete macrocycle, and a ball-like structure with lipophilic exterior formed, in which host and guest aromatic moieties were exposed. Remarkably, only a single short CH···π interaction was noted between individual balls (Figure 6), and these were otherwise associated by van der Waals interactions alone.

Horning-crown macrocycles offer scope for great diversity in incorporation of different structural elements during synthesis, and the products can be further derivatized after isoaromatization. Examples presented herein exhibited interesting characteristics, such as self-association and inclusion. Work in progress is directed toward broadening the range of synthetic examples, as well as exploring potential new applications.

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Supporting Information Available: Tables of atomic coordinates, bond lengths and angles, detailed experimental procedures and characterization, and crystal data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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