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Single-Step Synthesis of D_{3h}-Symmetric Bicyclooxacalixarenes

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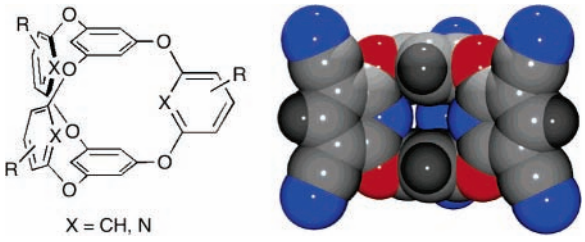
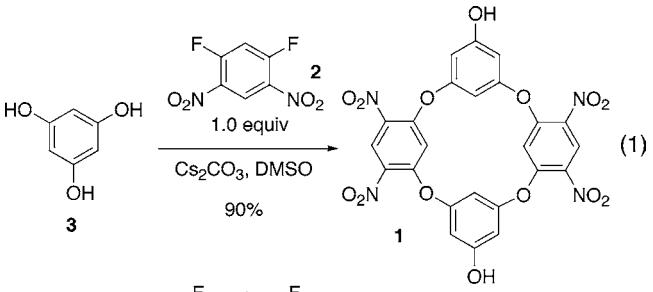
ABSTRACT



Bicyclooxacalixarenes are obtained in up to 95% yield by condensation of phloroglucinol with electron-poor meta-dihalogenated benzenes or pyridines. Single-crystal X-ray analysis reveals that these compounds adopt highly symmetrical, all-1,3-alternate cage-like structures.

Calixarenes continue to grow in popularity as scaffolds for studying molecular encapsulation, probing host−guest interactions, and constructing supramolecular systems and new materials.[1] The versatility of the calixarene framework is a result of its well-defined three-dimensional structure and potential for varied functionality on the upper and lower rims. However, after decades of research into their synthesis and applications, very few calixarenes can be accessed directly by cyclization of monomeric precursors. Instead the "almost unlimited possibilities"[1a] in calixarene structural diversity, particularly systems containing complex functional groups and bridged ring systems, result from extensive postcyclization derivatization or multistep fragment coupling strategies.[1a,d,e] Herein, we report a high-yielding, single-step synthesis of bridged calixarene frameworks with linking oxygen atoms, bicyclooxacalixarenes.[2,3] These compounds adopt D_{3h}-symmetric cage-like structures and constitute a new class of flexible scaffolds for molecular and supramolecular design.



Our laboratory recently reported the synthesis of dihydroxyoxacalix[4]arene **1** by condensation of 1,5-difluoro-2,4-dinitrobenzene **2** with phloroglucinol **3** in a 1:1 molar ratio (eq 1).[4] ^{1}H NMR spectroscopy and X-ray crystallography have established that oxacalix[4]arenes similar to **1** adopt a distorted 1,3-alternate conformation with the nucleophilic

(1) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713−1734. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (d) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: London, 2000. (e) Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, Netherlands, 2001. (f) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508.

(2) Bicyclocalixarenes were first synthesized and named by Böhmer to describe upper-rim bridged calixarenes in which "all macrocyclic ring systems have a calixarene structure": Berger, B.; Böhmer, V.; Paulus, E.; Rodriguez, A.; Vogt, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 96−99.

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component aromatic rings nearly parallel.[4,5] This conformation orients the pendant phenols on **1** in close proximity and spaced for potential bridging by a *meta*-phenylene linker such as an additional equivalent of **2**.[6] Such a bridge is readily installed, without preformation of **1**, by simply changing the reactant stoichiometry during calixarene formation. Thus, reaction of **2** and **3** in a 3:2 molar ratio under identical conditions for formation of **1** (Cs_2CO_3, DMSO, 25 °C, 1 h) furnished bicyclooxacalixarene **4** in 15% yield (eq 2). An optimized yield of **4** (70% conversion, 58% isolated yield) was obtained using NEt_3 base at elevated temperature (DMSO, 80 °C, 12 h). As is observed for other S_NAr-based oxacalix[4]arene formation reactions,[4,7] high dilution is not required to prevent polymerization, nor does use of ambient atmosphere or air-dried glassware negatively affect the isolated yield of **4**.

The ^{1}H NMR spectrum of bicycle **4** contains only three signals, consistent with an all-1,3-alternate solution structure, and no chemical shift change or broadening was observed over the temperature range 193−330 K (acetone-d_6). The high-field chemical shift observed for the inner-cavity protons (δ 5.52 in DMSO-d_6, δ 5.68 in acetone-d_6) is consistent with analogous chemical shifts observed for oxacalix[4]arenes that adopt 1,3-alternate solution conformations.[4,5,7] Excluding disorder in the nitro groups, bicycle **4** adopts a near-D_{3h}-symmetric, all-1,3-alternate conformation in the solid state (Figure 1);[8] the nucleophilic component benzene rings are eclipsed, and the electrophilic component rings point directly into the formed cavity. Conjugation between the bridging oxygen atoms and the nitro-bearing aromatic rings is supported by the significantly shorter C−O bond length between the oxygen bridges and the electrophilic component aromatic ring carbons (1.36 Å average bond length) versus the nucleophilic component aromatic ring carbons (1.40 Å average bond length). The cavity created by the bridged ring structure is extremely small, with a distance of only 3.0 Å between the interior hydrogen atoms and 4.83 Å between the centroids of the nucleophilic component aromatic rings.

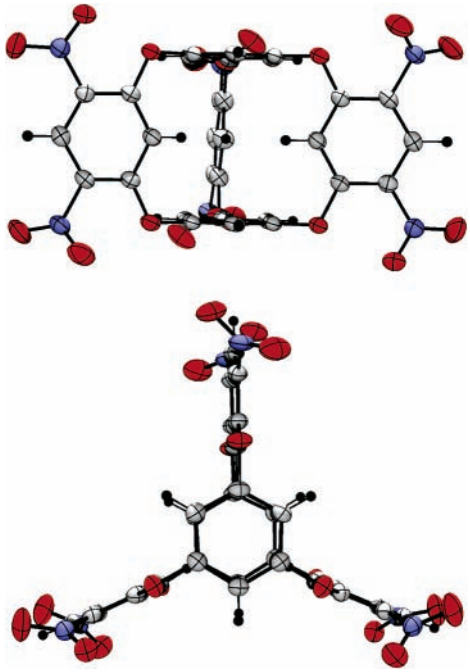


Figure 1. X-ray crystal structure of bicyclooxacalixarene **4** (thermal ellipsoids at the 50% probability level; oxygen = red, nitrogen = blue, carbon = gray, hydrogen = black).

2,6-Dihalogenated pyridine electrophiles were next explored as a means to expand structural diversity on the bicyclooxacalixarene interior and exterior surfaces. Condensation of commercially available 2,6-dichloro-3-nitropyridine **5** with phloroglucinol **3** forms bicyclooxacalixarenes **6a** and **6b** as a 3:1 (statistical) mixture of regioisomers in 80% yield (eq 3). Phloroglucinol **3** also readily condenses with both 2,6-dichloropyridine-3,5-dicarbonitrile **7**[9] and 2,6-dichloro-4-ethylpyridine-3,5-dicarbonitrile **8**,[10] furnishing bicyclooxacalixarenes **10** and **11** in 95 and 80% isolated yields, respectively (eq 4). The efficiency of these reactions is quite extraordinary, as in situ reaction monitoring shows that formation of **10** is quantitative to the detection limit of ^{1}H NMR spectroscopy. At elevated temperatures, 2,3,5,6-tetrachloropyridine **9** is also sufficiently electrophilic to react with **3**, furnishing bicycle **12** in 45% yield (eq 5).[11] However, this is not general for all 2,6-dihalopyridines, since no bicyclooxacalixarenes could be isolated using 2,6-dichloropyridine, 2,6-difluoropyridine, 2,3,5,6-tetrachloro-4-ethylpyridine, or 4-benzyl-2,3,5,6-tetrachloropyridine[12] as the electrophile.

The ^{1}H NMR data for bicyclooxacalixarenes **6** and **10**−**12** are again consistent with an all-1,3-alternate solution

(3) For other examples of bicyclocalixarenes and related annulated structures, see: (a) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811−6817. (b) Böhmer, V.; Dörrenbächer, R.; Frings, M.; Heydenreich, M.; de Paoli, D.; Vogt, W.; Ferguson, G.; Thondorf, I. *J. Org. Chem.* **1996**, *61*, 549−559. (c) Rajca, A.; Lu, K.; Rajca, S. *J. Am. Chem. Soc.* **1997**, *119*, 10335−10345. (d) Paulus, E. F.; Frings, M.; Shivanyuk, A.; Schmidt, C.; Böhmer, V.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2777−2782. (e) Zheng, Y. S.; Huang, Z. T. *Tetrahedron Lett.* **1998**, *39*, 5811−5814. (f) Baker, M. V.; Bosnich, M. J.; Williams, C. C.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1999**, *52*, 823−825. (g) Liu, J.-M.; Zheng, Y.-S.; Zheng, Q.-Y.; Xie, J.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron* **2002**, *58*, 3729−3736. (h) Baker, M. V.; Bosnich, M. J.; Brown, D. H.; Byrne, L. T.; Hesler, V. J.; Skelton, B. W.; White, A. H.; Williams, C. C. *J. Org. Chem.* **2004**, *69*, 7640−7652.

(4) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91−94.

(5) (a) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727−733. (b) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137−2147. (c) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412−15422.

(6) The strategy of employing electrophile **2** to bridge phenols on resorcinarenes has been employed by Rebek: Shivanyuk, A.; Far, A. R.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 1555−1558.

(7) Gilbert, E. E. *J. Heterocycl. Chem.* **1974**, *11*, 899−904.

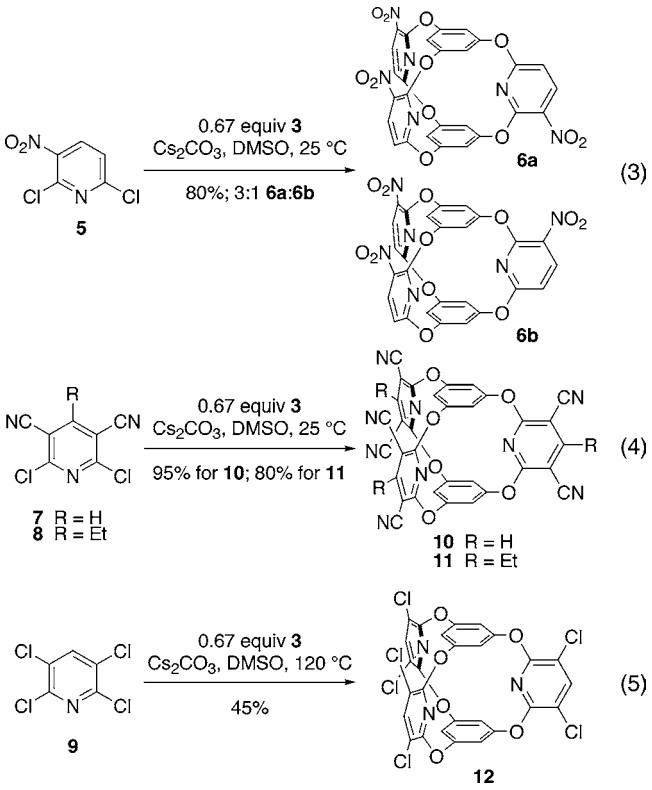
(8) Crystallographic data for **4**·acetone: M = 860.61, monoclinic space group $C2/c$, a = 9.3865(8) Å, b = 21.2279(17) Å, c = 18.8177(15) Å, β = 91.3940(10)°, V = 3748.4(5) Å^3, Z = 4, R_1 = 0.0559, R_w = 0.1647, GOF = 1.071.

(9) (a) Graffner-Nordberg, M.; Kolmodin, K.; Aqvist, J.; Queener, S. F.; Hallberg, A. *J. Med. Chem.* **2001**, *44*, 2391−2402. (b) Vilarelle, D. V.; Veira, C. P.; Quintela Lopez, J. M. *Tetrahedron* **2004**, *60*, 275−283.

(10) Gunther, L.; Dehnert, J. 2,6-Dichloro-3,5-dicyanopyridines. Ger. Offen. 2,206,506, 1973.

(11) 2,6-Dichloropyridines **5** and **7**−**9** also form oxacalix[2]arene[2]-pyridines via S_NAr reactions with resorcinols in high yield. Details of these oxacalixarene formations will be disclosed in a subsequent manuscript.

(12) Dua, S. S.; Gilman, H. *J. Organomet. Chem.* **1968**, *12*, 299−303.



conformation, and a near-D_{3h}-symmetric conformation is observed in the solid state for **10** (Figure 2).[13] Use of a 2,6-dichloropyridine electrophile has incorporated Lewis basic nitrogen atoms on the internal surface of the bicycle and has significantly expanded the volume of the formed cavity. The nitrogen atoms point directly into the cavity in a trigonal planar array, with an average distance of 2.74 Å from the nitrogen nuclei to the center of the cavity. Thus, bicycles **6** and **10**−**12** have the potential for inner-cavity metal−cation complexation, although long nitrogen−metal bond lengths and the close spacing of the capping benzene rings (4.49 Å between centroids) may preclude such a complex.[14] Investigations to this effect are ongoing.

(13) Crystallographic data for **10**·2EtOAc: M = 803.70, monoclinic space group $P2(1)/c$, a = 15.8519(11) Å, b = 11.8209(8) Å, c = 21.1429(15) Å, β = 105.6600(10)°, V = 3814.8(5) Å^3, Z = 4, R_1 = 0.0519, R_w = 0.1476, GOF = 1.074.

(14) Hansen, J.; Blake, A. J.; Li, W.-S.; Mascal, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3371−3376.

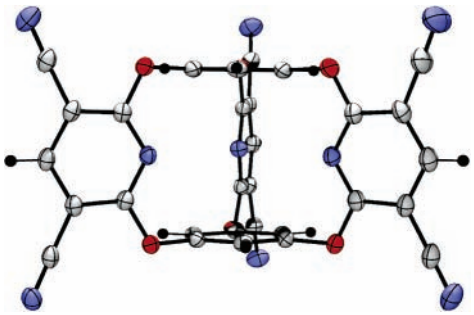


Figure 2. X-ray crystal structure of bicyclooxacalixarene **10** (thermal ellipsoids at the 50% probability level; oxygen = red, nitrogen = blue, carbon = gray, hydrogen = black).

In summary, we have described a simple, high-yielding procedure for the synthesis of bicyclooxacalixarenes by nucleophilic aromatic substitution of phloroglucinol with electron-poor meta-dihalogenated aromatics. Nitro, cyano, and chloro groups are easily incorporated onto the bicyclooxacalixarene external surface and nitrogen atoms on the internal surface. Due to their ease of synthesis, high-symmetry, and versatile functionality, bicyclooxacalixarenes constitute potentially powerful building blocks for construction of covalent and supramolecular systems.

Acknowledgment. The authors are grateful to Research Corporation (CC-6148) and Colby College for financial support of this work and to the NSF for funding the Colby College instrumentation facilities (CCLI-0088307, MRI-0115832, and MRI-0079569). Special thanks are due to the Bowdoin College MALDI HRMS facility funded by the NSF (MRI-0116416).

Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **6**, and **10**−**12** and X-ray crystallographic data for compounds **4** and **10** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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