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Synthesis of Oxacalixarenes Incorporating Nitrogen Heterocycles: Evidence for Thermodynamic Control

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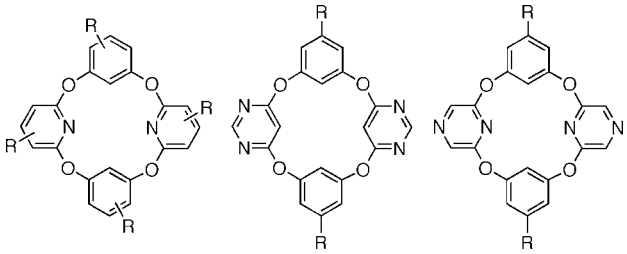
ABSTRACT



Oxacalix[2]arene[2]hetarenes are formed in a single step by cyclooligomerization of *meta*-diphenols with meta-dichlorinated azaheterocycles. The high selectivity for cyclic tetramer formation results from thermodynamic product control. Macrocycles as large as oxacalix[5]arene[5]-hetarenes have been isolated under nonequilibrating conditions.

Calixarenes, or [1$_n$]metacyclophanes, remain one of the premier platforms in supramolecular chemistry and molecular design.[1] Incorporation of non-carbon bridging atoms into the calixarene skeleton to form heterocalixarenes continues to be actively investigated as a means to expand calixarene structural diversity.[2] Although methods for heterocalixarene synthesis with a variety of bridging atoms (nitrogen,[3] sulfur,[4] silicon[5]) have been developed, those for oxacalixarenes remain quite scarce.[6] Our group has previously reported the synthesis of oxacalix[4]arenes by nucleophilic aromatic substitution of *meta*-diphenols with 1,5-difluoro-2,4-dinitrobenzene (**1**).[7] The method exhibited unusually high yields and selectivity for the tetrameric cyclooligomer and tolerated a wide range of functional groups on the nucleophilic component. However, oxacalixarene formation remains

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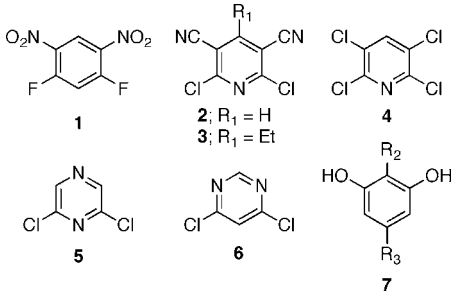
limited with respect to the electrophilic component.[8] We now report the synthesis of oxacalixarenes using electrophilic azaheterocyclic components **2**−**6**, affording macrocycles with embedded pyridines, pyrazines, and pyrimidines. This broadened electrophile scope allows facile access to oxacalixarenes with tunable sites for hydrogen bonding, metal coordination, or further chemical manipulation. Furthermore, we present evidence that the high selectivity for cyclotetramer formation observed in these macrocyclizations results from thermodynamic product control.

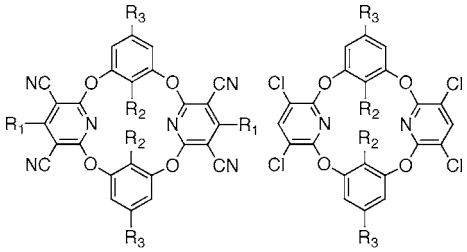


We initially explored the cyclization of 2,6-dichloropyridine **2**[9] with diphenols **7** under our previously reported oxacalix[4]arene formation conditions (1:1 nucleophile/electrophile ratio, Cs_2CO_3, DMSO, 25 °C).[7] Accordingly, condensation of **2** with methyl-3,5-dihydroxybenzoate (**7a**) was complete in less than 30 min and provided nearly quantitative conversion to oxacalix[2]arene[2]pyridine **8a** as analyzed by ^{1}H NMR spectroscopy (95% isolated yield, Table 1, entry 1). Additional linear and cyclic oligomeric species were not observed under the reaction conditions. Pyridine **2** also reacted efficiently with olivetol (**7b**), furnishing oxacalixarene **8b** in 93% yield (entry 2). Dihydroxylated oxacalix[2]arene[2]pyridines were also accessible by cyclization using ethyl gallate (**7c**, entry 3) and 4-*tert*-butylpyrogallol (**7d**, entry 4), providing macrocycles **8c** and **8d** in 86% and 84% yields, respectively.

Ethyl substitution on the pyridine ring was tolerated in the cyclization; pyridine **3**[10] required 1 h for condensation with orcinol (**7e**) and afforded oxacalix[2]arene[2]pyridine **9e** in 89% yield (entry 5). Ethyl gallate (**7c**) also reacted analogously with **3**, providing dihydroxylated oxacalixarene **9c** in 84% yield (entry 6).

We previously reported that 2,3,5,6-tetrachloropyridine (**4**) is sufficiently electrophilic to undergo bicyclooxacalixarene formation at elevated temperatures.[11] Analogously, pyridine **4** condensed with **7b** at 120 °C (Cs_2CO_3, DMSO, 18 h) to form oxacalix[2]arene[2]pyridine **10b** in 88% yield (entry 7). Attempts to cyclize **4** with **7a**, however, initially afforded a mixture of products at the elevated reaction temperature due to partial saponification of the methyl esters. Fortunately, addition of powdered 4 Å molecular sieves as a water scavenger substantially reduced the saponification, allowing the isolation of oxacalix[2]arene[2]pyridine **10a** in 70% yield (entry 8).

Table 1. Synthesis of Oxacalix[2]arene[2]pyridines Using Electrophilic Pyridines **2**−**4**[a]



entry	electrophile	nucleophile	product (yield)[b]
1	**2** (R_1 = H)	**7a** (R_2 = H, R_3 = CO_2Me)	**8a** (95%)
2	**2** (R_1 = H)	**7b** (R_2 = H, R_3 = *n*-pentyl)	**8b** (93%)
3	**2** (R_1 = H)	**7c** (R_2 = OH, R_3 = CO_2Et)	**8c** (86%)
4	**2** (R_1 = H)	**7d** (R_2 = OH, R_3 = *t*-butyl)	**8d** (84%)
5	**3** (R_1 = Et)	**7e** (R_2 = H, R_3 = CH_3)	**9e** (89%)
6	**3** (R_1 = Et)	**7c** (R_2 = OH, R_3 = CO_2Et)	**9c** (84%)
7	**4**	**7b** (R_2 = H, R_3 = *n*-pentyl)	**10b** (88%)[c]
8	**4**	**7a** (R_2 = H, R_3 = CO_2Me)	**10a** (70%)[c,d]

[a] Reaction conditions: 1 equiv of electrophile, 1 equiv of nucleophile, 2 equiv of Cs_2CO_3, DMSO, 25 °C. [b] Isolated yield. [c] Reaction run at 120 °C for 18 h. [d] 4 Å molecular sieves were added.

The sufficient reactivity of **4** to nucleophilic substitution prompted us to investigate alternative electrophilic azaheterocycles for oxacalixarene formation. We reasoned that the presence of two aromatic nitrogen atoms in 2,6-dichloropyrazine (**5**) and 2,6-dichloropyrimidine (**6**) could sufficiently stabilize the anionic intermediates arising during nucleophilic substitution, potentially obviating the need for additional electron-withdrawing substituents. Reaction optimization was conducted using pyrazine **5** and orcinol (**7e**), and product distributions were found to vary dramatically with reaction temperature. At 50 °C (Cs_2CO_3, DMSO, 18 h), **5** and **7e** condensed to form a mixture of cyclooligomers from which was isolated cyclotetramer **11e** (36% yield), cyclohexamer **12e** (18% yield), cyclooctamer **13e** (11% yield), and cyclodecamer **14e** (6% yield) (Table 2, entry 1). The material balance consisted of larger cyclooligomers and polymeric species. Increasing the reaction temperature favored formation of cyclotetramer **11e**, such that conducting the reaction at 120 °C provided **11e** in 87% isolated yield (entry 2). Only trace amounts of larger oligomers were detected under these conditions. Furthermore, the unpurified cyclooligomeric mixture obtained at 50 °C (entry 1) could be equilibrated to produce >80% of tetramer **11e** by resubjection to the reaction conditions at 120 °C (18 h reaction time). Pyrazine **5** also condensed efficiently at 120 °C with resorcinols **7a** and **7b** (4 Å sieves were added in the reaction of **7a**), providing oxacalix[2]arene[2]pyrazines **11a** and **11b** in 81% and 91% yield, respectively (entries 3 and 4).

(8) Oxacalix[4]arenes have been synthesized using nitrated benzenes (refs 6b−d,h,i, 7), cyanuric chloride (ref 6g), and perfluorinated pyridines (ref 6e).

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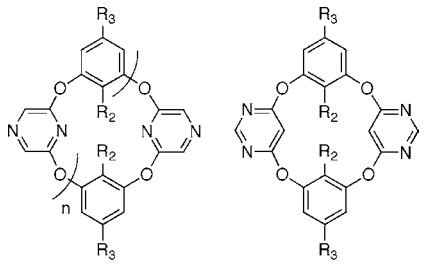
Table 2. Synthesis of Oxacalixarenes Using Electrophiles **5** and **6**[a]



11 (n=1) **12** (n=2)
13 (n=3) **14** (n=4)

15

entry	nucleophile	electrophile	temp (°C)	product (yield)[b]
1	**7e** (R_2 = H, R_3 = CH_3)	**5**	50	**11e** (36%)[c]
2	**7e** (R_2 = H, R_3 = CH_3)	**5**	120	**11e** (87%)
3	**7a** (R_2 = H, R_3 = CO_2Me)	**5**	120	**11a** (81%)[d]
4	**7b** (R_2 = H, R_3 = *n*-pentyl	**5**	120	**11b** (91%)
5	**7e** (R_2 = H, R_3 = CH_3)	**6**	50	**15e** (12%)
6	**7e** (R_2 = H, R_3 = CH_3)	**6**	120	**15e** (91%)
7	**7b** (R_2 = H, R_3 = *n*-pentyl	**6**	120	**15b** (90%)

[a] Reaction conditions: 1 equiv of electrophile, 1 equiv of nucleophile, 2 equiv of Cs_2CO_3, DMSO, 18 h. [b] Isolated yield. [c] **12e** (18%), **13e** (11%), and **14e** (6%) were also isolated. [d] 4 Å molecular sieves were added.

Pyrimidine **6** showed a reactivity profile similar to that for pyrazine **5**. The condensation of **6** and **7e** at 50 °C formed primarily polymeric material, such that only 12% of cyclotetramer **15e** was isolated (entry 5). Larger cyclooligomers were also formed but were difficult to purify from the reaction mixture. At 120 °C, no polymeric products could be detected and cyclotetramer **15e** was obtained in 91% yield (entry 6). Pyrimidine **6** also reacted efficiently with **7b** to give 90% of oxacalix[2]arene[2]pyrimidine **15b** (entry 7).

All oxacalix[4]arenes that have appeared in the literature adopt 1,3-alternate conformations in both the solid-state and solution, regardless of functional group substitution on the aromatic rings.[6e,g,h,7] X-ray quality crystals of oxacalix[2]arene[2]pyrazine **11e** were obtained by slow evaporation from acetone (Figure 1).[12] As expected, the 1,3-alternate solid-state conformation is observed for **11e**. Conjugation between the oxygen bridges and the pyrazine rings is evident by comparison of the C−O bond lengths between the oxygen bridges and the aromatic ring carbon atoms; the C−O bond lengths of the pyrazine carbons (1.36 Å average length) are significantly shorter than those of the benzene ring carbons (1.40 Å average length). The angle between pyrazine ring planes is 99.6°, creating a centroid−centroid distance of 6.7 Å (Figure 1a). A smaller 41.3° angle exists between benzene ring planes, and this creates a more closely spaced cavity between these rings with a centroid−centroid distance of 5.27 Å (Figure 1b).

There are no published investigations of product control elements in nucleophilic substitution-based oxacalixarene

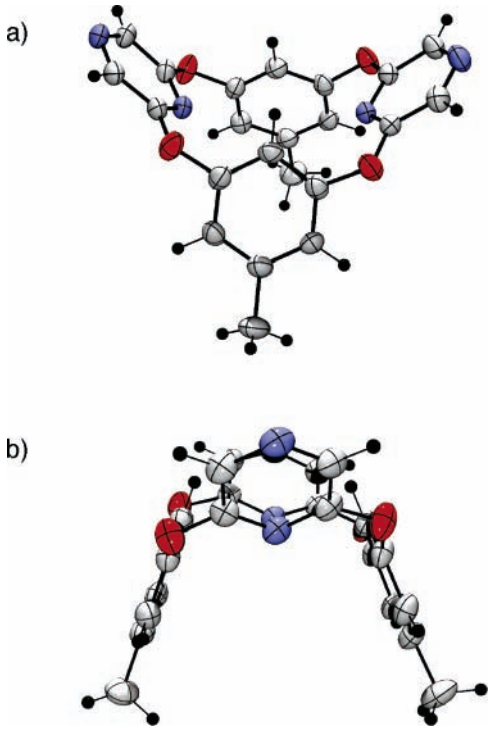


Figure 1. X-ray crystal structure of **11e** (thermal ellipsoids at the 50% probability level; oxygen = red, nitrogen = blue, carbon = gray, hydrogen = black). Figure 1b is rotated approximately 90° with respect to Figure 1a.

formation. Macrocyclization reactions using electrophile **1**,[6b−d,7] cyanuric chloride,[6g] or fluorinated pyridines[6e] were reported to selectively form oxacalix[4]arenes. Larger cyclooligomers, however, were recently isolated in cyclocondensations of **1** with hydroxylated porphyrins.[6h,13] As described above, pyridines **2** and **3** at 25 °C and **4** at 120 °C selectively form oxacalix[2]arene[2]pyridines. Electrophiles **5** and **6** efficiently form cyclotetramers at higher temperatures yet furnish a mixture of linear and cyclic oligomers at lower temperatures. These data suggest that oxacalix[4]arenes are thermodynamically favored over alternative linear and cyclic species and that the reaction outcomes at 25 °C for **2** and **3** and at 120 °C for **4**−**6** reflect thermodynamic product control.[14,15] Conversely, the more complex product mixtures obtained at 50 °C for **5** and **6** are likely kinetic product distributions.

To further investigate the thermodynamic reversibility of oxacalixarene formation during nucleophilic substitution,

(12) Crystallographic data for **11e**: M = 400.39, monoclinic space group $C2/c$, a = 15.6963(10) Å, b = 10.9386(7) Å, c = 22.5637(14) Å, β = 90.8420(10)°, V = 3873.7(4) Å^3, Z = 8, R_I = 0.0461, R_w = 0.1307, GOF = 1.053.

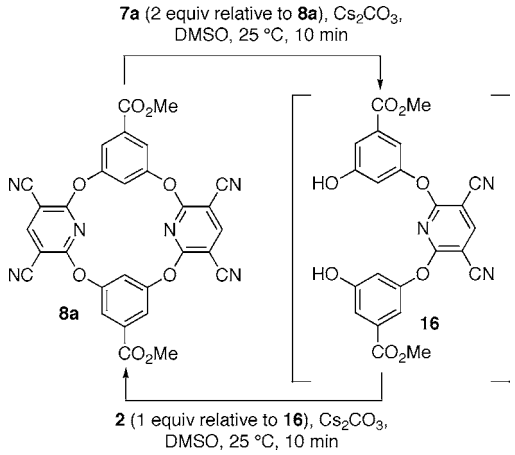
(13) An oxacalix[6]arene has also been formed by Ullmann coupling of resorcinol with 1,3-difluoro-2-nitrobenzene (ref 6i).

(14) For investigations into thermodynamic product control for calix[4]arene formation, see: (a) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742−745. (b) Dhawan, B.; Chen, S.-I.; Gutsche, C. D. *Makromol. Chem.* **1987**, *188*, 921−950. (c) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: London, 1989; pp 50−59. (d) Weinelt, F.; Schneider, H.-J. *J. Org. Chem.* **1991**, *56*, 5527−5535. (e) Vocanson, F.; Lamartine, R. *Supramol. Chem.* **1996**, *7*, 19−25.

(15) Reversibility has been reported for thiacalixarene formation by nucleophilic substitution: Freund, T.; Kübel, C.; Baumgarten, M.; Enkelmann, V.; Gherghel, L.; Reuter, R.; Müllen, K. *Eur. J. Org. Chem.* **1998**, *63*, 555−564.

cyclotetramer **8a** was resubjected to the cyclization conditions and an additional 2.0 equiv of nucleophile **7a** was added (Scheme 1). After only a 10 min reaction time, **8a** is

Scheme 1. Reversibility Experiment for Cyclization of **8a**



completely consumed by **7a**. The major product formed is linear trimer **16**, reflecting the supplied 2:1 nucleophile/electrophile ratio. Oxacalixarene **8a** is reformed, again in 10 min, upon restoration of a 1:1 nucleophile/electrophile ratio by addition of electrophile **2**. Thus, nucleophilic addition to the pyridine rings in **8a** is reversible under the cyclization conditions, even at very short reaction times. Developing an understanding of these control elements will prove critical for efficient access to larger cyclooligomers and will render nucleophilic substitution-based oxacalixarene formation suitable for methods such as dynamic covalent chemistry.[16]

In conclusion, oxacalix[2]arene[2]hetarenes are readily synthesized in a single step by nucleophilic aromatic substitution of meta-dichlorinated azaheterocycles with *meta*-diphenols. Thermodynamic product control is responsible for the high selectivity for cyclotetramer formation. Our continuing investigations into the synthesis and applications of these macrocycles will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**−**16** and X-ray crystallographic data for compound **11e** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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