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Naphthalene-Based Calixarenes: Unusual Regiochemistry of a Friedel–Crafts Alkylation

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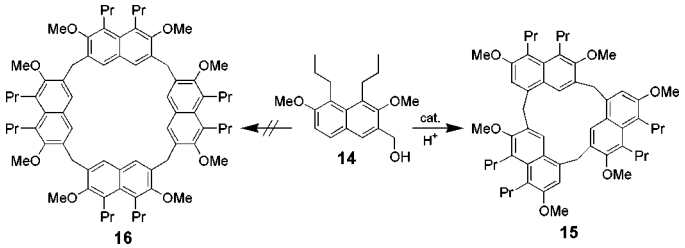
ABSTRACT



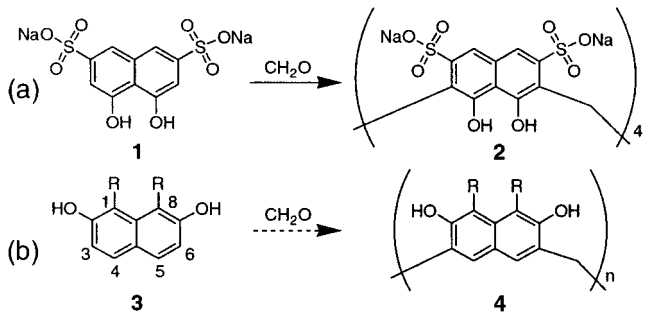
In the pursuit of naphthalene-based calixarenes, a Friedel–Crafts alkylation with unusual regiochemistry was observed. Treatment of carbinol 14 with catalytic triflic acid was expected to produce calixarenes of the class represented by 16. Instead, the major product was cyclic trimer 15, in which alkylation of each naphthalene ring occurred at the electronically deactivated position. The structure of compound 15 was assigned by 2-D NMR studies.

Since their first classification by Cram nearly two decades ago,[1] cavitands have received much attention in the field of molecular recognition.[2] Possessing rigid cavities, these bowl-shaped molecules have provided opportunity for the preparation of a myriad of molecular hosts. Owing to their ease of synthesis, resorcinarenes[3] often have been used as a starting block for a wide variety of cavitands.

We recently became interested in exploring the potentially unusual recognition properties of naphthalene-based cavitands. An obvious first step toward such molecules was the formation of naphthalene-based calixarenes. Only one such molecule was known, cyclotetrachromotropylene (**2**), which was synthesized by Poh (Scheme 1a).[4] The facile synthesis of this calixarene involved a condensation of chromotropic acid (**1**) with aqueous formaldehyde. Unfortunately, the substitution pattern of compound **2** is not conducive to cavitand formation.

We initially envisioned a reaction analogous to Högberg's resorcinarene synthesis,[3a] using 2,7-dihydroxynaphthalene (**3**, R = H) as the base aromatic unit (Scheme 1b). It has been

Scheme 1



(1) Cram, D. J. *Science* **1983**, *219*, 1177−1183.
(2) (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, England, 1994; Chapter 5. (b) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991−2005.
(3) (a) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498−4500. (b) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312.
(4) Poh, B.-L.; Lim, C. S.; Khoo, K. S. *Tetrahedron Lett.* **1989**, *30*, 1005−1008.

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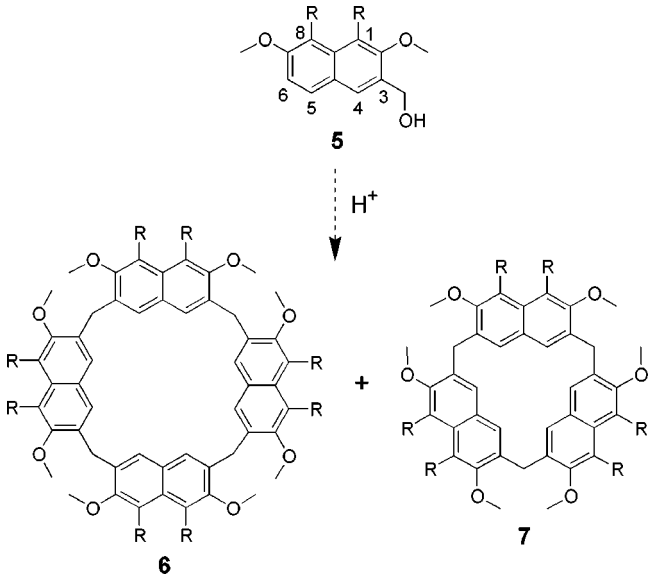
shown, however, that the C1 position of this compound is the most reactive site toward electrophiles such as formaldehyde.[5] Thus, we chose to block reaction at the 1 and 8 positions by utilizing 1,8-dialkyl derivatives of **3** (i.e., R = alkyl), forcing reaction at the C3 and C6 positions. Furthermore, symmetrical 1,8 substitution would avoid complications from the generation of regioisomers in the cyclized products.

Unfortunately, initial studies of 1,8-dialkyl-2,7-dihydroxynaphthalenes (**3**, R = alkyl) indicated that these derivatives were unstable to the acid and base conditions that are typically employed for calixarene formation. We circumvented these issues of instability by protecting the naphthols as methyl ethers.

Patterning our strategy after a convenient synthesis of octamethylcalix[4]resorcinarene,[6] we chose to integrate a carbinol moiety at C3 (Scheme 2). We anticipated that

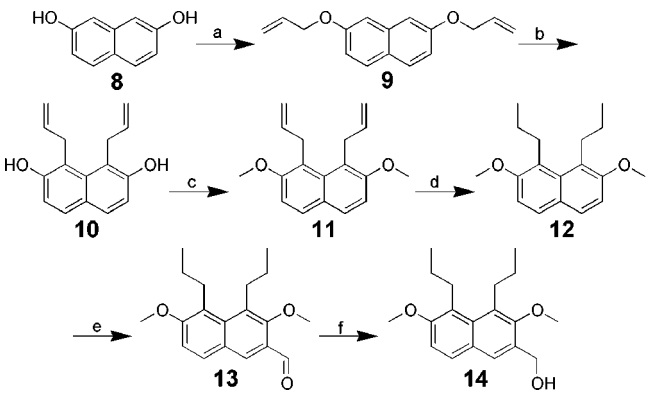
Scheme 2



treatment of a compound such as **5** with acid would generate a carbocation that would react at the remaining electrophilic carbon (C6) of a second unit of **5**, eventually producing calixarene oligomers such as **6** and **7**.

Therefore, 1,8-diallyl-2,7-dihydroxynaphthalene (**10**) was synthesized in two steps from 2,7-dihydroxynaphthalene (**8**) through an intramolecular Claisen rearrangement[7] (Scheme 3). Compound **10** was unstable even to silica and was taken on crude to the methylation reaction giving compound **11**. The allyl groups were reduced in order to prevent rearrangements under the acid-promoted calixarene formation conditions. The desired carbinol moiety was incorporated at C3 by formylation, followed by reduction. Electrophilic formylation of compound **12** ($TiCl_4$, $MeOCHCl_2$) gave low conversion to a mixture of regioisomers (ca. 1:1) of aldehyde-containing products. The lack of selectivity in the addition of this electrophile to compound **12** would portend the eventual outcome of the calixarene cyclization reaction.

Scheme 3[a]



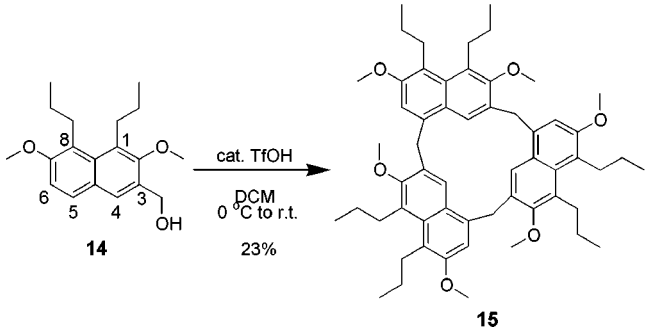
[a] Reagents and conditions: (a) allyl bromide, K_2CO_3, acetone, reflux, 77%; (b) *N*,*N*-diethylaniline, reflux; (c) CH_3I, K_2CO_3, THF, reflux, 53% (two steps); (d) H_2, Pd/C, EtOAc, 95%; (e) *n*-BuLi, TMEDA, Et_2O; DMF, 57%; (f) $NaBH_4$, EtOH, 92%.

Nevertheless, directed lithiation with *n*-BuLi, followed by quenching with *N*,*N*-dimethylformamide, gave aldehyde **13** as a single regioisomer, which was reduced to carbinol **14** upon treatment with sodium borohydride.[8]

In the event, compound **14** was dehydrated with acid to give calixarene-type products. A range of conditions were screened, varying both the type and concentration of acid, as well as reaction temperature. Mass spectrometry indicated that each reaction produced uncyclized dimer, trimer, and tetramer, as well as cyclic trimer and tetramer. The major product under most conditions was cyclic trimer.

Under optimal conditions, treatment of carbinol **14** with 0.1 equiv of trifluoromethanesulfonic acid at 0 °C, followed by warming to room temperature, gave 23% isolated yield of a single compound, which according to mass spectrometry, was a cyclic trimer. ^{1}H and ^{13}C NMR spectra did not support a fully symmetrical structure, such as **7**, as each naphthyl ring had two aromatic singlets and two different methoxy groups in the ^{1}H NMR spectrum. Atropisomerism was ruled out by variable temperature experiments. The spectra could be explained by a structure such as **15**, in which alkylation of the presumed cationic intermediate occurred at C5, meta to the methoxy carbon, rather than at C6 (Scheme 4).

Scheme 4



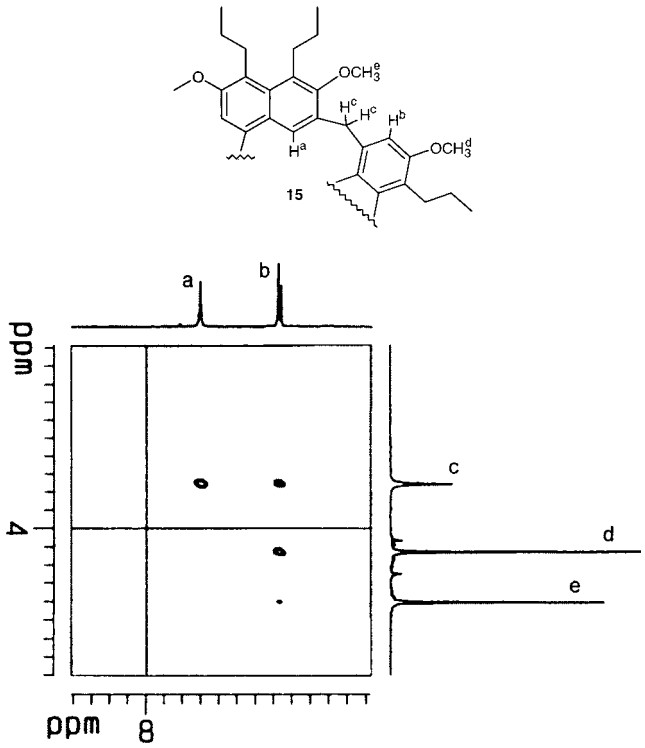


Figure 1. Expanded region of NOESY spectrum showing correlations between the two aromatic protons and methoxy/methylene protons of trimer **15**.

The structure of trimer **15** was confirmed by 2-D NMR. As shown in Figure 1, NOESY clearly indicates that the two aromatic protons are in distinct environments. Proton H^a, whose signal appears at 7.70 ppm, has a through space correlation only to the methylene protons (H^c), whereas proton H^b, at 7.30 ppm, is correlated to the methylene protons, as well as to both sets of methoxy protons. As expected for **15**, the correlation of proton H^b to the methoxy protons (H^d) at 3.85 ppm is stronger than to the protons (H^e) at 3.60 ppm. In addition, the methylene protons (H^c) correlate to the methoxy protons (H^e) at 3.60 ppm, yet they show no correlation to the other set of methoxy protons (H^d) at 3.85 ppm (spectral region not shown in Figure 1). This result is consistent only with C5 alkylation. Carbon-proton correlations (HMQC) also corroborate the structure of trimer **15**.

The unusual reactivity of this system is likely due to steric factors. The two propyl groups at the peri positions of the naphthyl ring of compound **14** are quite sterically congested. This situation is exacerbated by the flanking methoxy groups. Apparently, electrophilic substitution ortho to the methoxy groups entails a high steric penalty such that reaction at the C6 position in compound **14** is impossible. Thus, the sterically accessible position (C5) is the most reactive. This reactivity pattern is also observed in compound **12** since electrophilic formylation gave a mixture of regioisomers (vide supra), contrary to the typically high ortho/meta ratios seen with electrophilic addition to methoxy-substituted arenes.

In conclusion, a novel naphthyl calix[3]arene has been prepared. The synthesis of this trimer involves an unusual Friedel−Crafts alkylation at an electronically deactivated position of a sterically constrained naphthyl system. The recognition properties of this class of calixarenes are currently under investigation.

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds **11**−**15** and NOESY spectrum for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS.