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Synthesis of Functionalized Acenaphthenes and a New Class of Homooxacalixarenes

Tayel A. AlHujran, Louise N. Dawe, and Paris E. Georghiou*

Departments of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada, A1B3X7

parisg@mun.ca

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ABSTRACT

The 5,6-dialkoxyethers of acenaphthene have been synthesized for the first time via modified Ullmann reaction conditions. Further modifications of the 5,6-dimethoxyacenaphthene allowed the synthesis of the first acenaphthene analogue of the octahomotetraoxacalixarenes. The X-ray structure of this new macrocycle and its complexation study with C_{60} are reported.

Acenaphthene (**1**) is a polycyclic aromatic hydrocarbon which is a well-known constituent of coal tar. It consists of a naphthalene ring with C-1 and C-10 peri-positions that are connected by an ethylene bridge. According to Hahn and Holmes,[1] acenaphthene was first isolated from coal in 1867 by Marcellin Berthelot, who later also synthesized it. Since acenaphthene occurs both naturally in coal tar and as a byproduct of many manufacturing processes, it is consequently found ubiquitously as a trace environmental pollutant or contaminant. A recent Scifinder search using the term "acenaphthene" revealed over 12 000 publications with the overwhelming majority of these concerned with its detection and analysis in environmental samples and other industrial applications. A much smaller list of publications deals with chemical reactions or transformations of the compound. Among the best-known are those involving the easily generated compounds acenaphthylene (**2**) and the 1,2-dioxo compound, acenaphenequinone (**3**) (Figure 1). In light of our own ongoing interest in the synthesis and development of the chemistry of naphthalene or naphthol ring-containing macrocyclic analogues[2] of the well-known calixarenes,[3] acenaphthene ring analogues have been a logical extension. The chemistry of acenaphthene has proven to be challenging, but we report herein the syntheses of 5,6-dialkoxy-functionalized acenaphthenes and the first acenaphthene-based analogue of the homooxacalixarenes.[4]

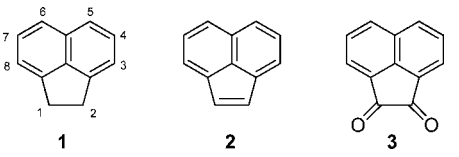

Figure 1. Structures of acenaphthene (**1**), acenaphthylene (**2**), and acenaphthenequinone (**3**).

Our first objective, as shown in the retrosynthetic scheme in Scheme 1, was the synthesis of **4**, which had a precedent from an earlier synthesis of calixnaphthalenes reported by our group[2,5] and requiring, in this case, 4-hydroxymethyl-5,

(1) Hahn, D. A.; Holmes, H. E. *J. Ind. Eng. Chem.* **1921**, *13*, 822–830and references cited therein.
(2) Georghiou, P. E.; Li, Z.; Ashram, M.; Chowdhury, S.; Mizyed, S.; Tran, A. H.; Al-Saraierh, H.; Miller, D. O. *Synlett* **2005**, 879–891.
(3) For a general overview of calixarenes, see: Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, UK, 1998.
(4) For a recent review of homooxacalixarenes, see:Cottet, K.; Marcos, P. M.; Cragg, P. J. *Beilstein J. Org. Chem.* **2012**, *8*, 201–226.
(5) Georghiou, P. E.; Ashram, M.; Li, Z.; Chaulk, S. G. *J. Org. Chem.* **1995**, *60*, 7284–7289.

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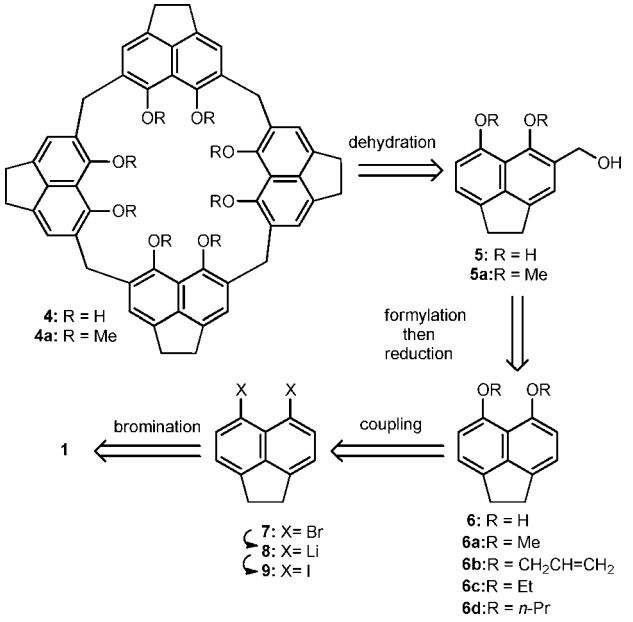
6-dihydroxyacenaphthene (**5**) or its dialkoxy derivative, **5a**, respectively, from **6** and **6a**.

Scheme 1. Retrosynthetic Analysis for "Calix[4]acenaphthenes" **4** and **4a**

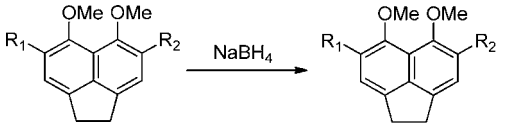


To the best of our knowledge, there are no reports dealing with the synthesis of C-5,C-6-dihydroxy- or dialkoxy-substituted acenaphthenes directly from readily available acenaphthene apart from a single report of **6b**[6] from a synthesis that requires using hazardous conditions. Instead, it was envisioned that 5,6-dibromoacenaphthene (**7**) could serve as a starting compound to be converted to the corresponding 5,6-dihydroxy product **6** (R = H) via a transmetalation–boronic ester oxidation sequence.[7] NBS-dibromination of acenaphthene to form **7** was relatively straightforward;[8,9] however, the transmetalation–boronic ester oxidation reaction to convert **7** to **6** via the in situ-generated **8** only afforded intractable products.

When the 5,6-dilithio intermediate **8** was instead quenched with iodine, 5,6-diiodoacenaphthene **9**[8] could be obtained in good yields, but it also failed to give the desired product under the same transmetalation–boronic ester reaction conditions. 5,6-Dimethoxyacenaphthene (**6a**) was eventually synthesized, however, using a modified Ullmann coupling methodology[10] in which **9** reacted with CuI and NaOMe (freshly prepared in situ). Nevertheless, both the lithiation and the iodination reactions presented practical limitations, so efforts were directed toward using **7** instead (see Table 1, Supporting Information). In summary, the use of CuCl and dioxane under modified Ullmann conditions clearly emerged as the best conditions and was used with in situ-generated NaOMe, NaOEt, and NaOPr and **7**, to form the corresponding 5,6-dialkoxyacenaphthenes **6a** and **6c**,**d** in good to excellent yields. With *n*-propoxide, 5-bromo-6-propoxyacenaphthene was also formed as a minor product.

Attempts at the synthesis of "octamethoxycalix[4]acenaphthene" **4a** via one-pot $Mg(OTf)_2$-catalyzed reactions of **6a** with trioxane under acetonitrile or toluene reflux conditions, or under microwave-assisted conditions,[11] failed and only unreacted starting material was recovered. A different approach, using a direct catalyzed cyclocondensation reaction of **5a** to form **4a** was then examined using an analogous approach that Dutasta used for $Sc(OTf)_3$-catalyzed synthesis of cyclotriveratrylenes.[12] The optimal route found to synthesize the required precursor **5a** in our hands was achieved via $NaBH_4$ reduction (Scheme 2) of 4-formyl-5,6-dimethoxyacenaphthene (**10**) which was synthesized in 90–95% yields via a Reiche formylation[13] reaction of **6a**.

Scheme 2. Synthesis of Mono- and Bis(hydroxymethyl)-acenaphthenes **5a** and **12**

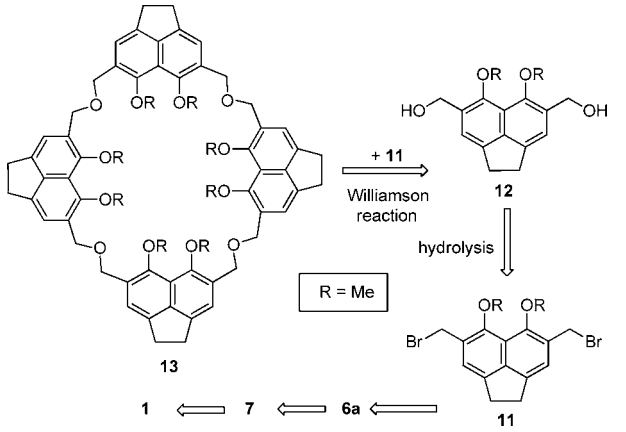


Unfortunately, using either $Sc(OTf)_3$ or other Lewis acids offered only trace amounts, which could not be purified, of the target macrocycle **4a** in the crude reaction mixture, as indicated by mass spectrometry, along with many other products by TLC examination. Since the above approaches met only with partial success and not with achieving the targeted acenaphthene macrocycle, our attention was therefore directed toward employing bis(bromomethyl)acenaphthene (**11**) and the corresponding bis(hydroxymethyl)acenaphthene (**12**). It was envisoned that by analogy with our previous synthesis of octahomotetraoxacalix[4]naphthalene (Zorbarene),[14] a Williamson ether-type coupling between **11** and **12** (Scheme 3) should produce the analogous octahomotetraoxacalix[4]acenaphthene (**13**).[15]

Bromomethylation of **6a** easily afforded **11**. The best synthetic route to form **12** from **11** required a sequence of

(6) Levchenko, A. I.; Moroz, R. A.; Zatolokin, E. I.; Sminych, V. V. Ger. Offen. DE 1802602 A 19700521, 1970.
(7) Torii, S.; Tanaka, H.; Siroi, T.; Akada, M. *J. Org. Chem.* **1979**, *44*, 3305–3310.
(8) Tanaka, N.; Kasai, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3020–3025.
(9) Neudorff, W. D.; Lentz, D.; Anibarro, M.; Schluter, A. D. *Chem.—Eur. J.* **2003**, *9*, 2745–2757.
(10) (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853–857. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456.
(11) Bew, S. P.; Sharma, S. V. *J. Org. Chem.* **2011**, *76*, 7076–7083.
(12) Brotin, T.; Roy, V.; Dutasta, J.-P. *J. Org. Chem.* **2005**, *70*, 6187–6195.
(13) (a) Merner, B. L.; Dawe, L. N.; Bodwell, G. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5487–5491. (b) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longmans: London, 1989.
(14) Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115–1121.
(15) **13** can also be considered to be a "tetraoxa[3.3.3.3](4,7)-acenaphthenophane".

Scheme 3. Retrosynthetic Analysis for Octahomotetraoxacalix[4]acenaphthene **13**



reactions in which **11** was first converted to the corresponding bisaldehyde **14** in 60−65% yields, using Kornblum's conditions.[16] $NaBH_4$ reduction of **14** afforded the desired compound **12** in near-quantitative yields.

Using Masci's methodology,[17] the base-mediated coupling of **11** with **12** afforded the target macrocycle **13** in an unoptimized yield of ~24%. Its ^1H NMR spectrum is very simple, confirming its highly symmetrical nature and showing only one sharp signal for all methylene bridges, which is consistent with fast conformational equilibration in solution. The position of the methyl signal of the methoxy groups appears at δ 3.61 ppm, which is upfield from the positions of the corresponding signals in the starting materials **11** and **12**, which appear at δ 3.99 and 3.84 ppm, respectively. Crystals of **13**, suitable for X-ray diffraction analysis, were obtained from the slow evaporation of a $CHCl_3$/hexane solution. Its structure is a calixarene-like *1,3-alternate* conformation having C_{2v} symmetry (Figure 2).[18]

The unit cell packing looking down the *c*-axis showed four significant-sized voids (Figure 3). The Platon Squeeze[19] procedure was applied to recover 228 electrons per unit cell in four voids that were sufficiently large to contain a small molecule (total volume 5143 Å^3). Discrete lattice solvent could not be modeled; however, each void contained 57 electrons, consistent with the presence of one hexane molecule (50 electrons). Interestingly, the ^{13}C NMR spectrum of these crystals indicated the presence of three additional aliphatic signals at δ 24.7, 30.1, and 36.7 ppm.

(16) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.

(17) Masci, B.; Finelli, M.; Varrone, M. *Chem.—Eur. J.* **1998**, *4*, 2018–2030.

(18) Crystal data for **15**: $C_{65.50}H_{67.50}O_{12}$, M_r = 1046.75, colorless prism, space group $I4_1/acd$ (no. 142), a = 27.6050(9) Å, c = 32.4280(13) Å, V = 24711.3(15) Å^3, Z = 16, D_c = 1.125 g/cm^3, F_{000} = 8904, μ(Mo Kα) = 0.77 cm^{-1}, T = 295(1) K, $2\theta_{max}$ = 59.8°, 5752 reflections collected, 5752 unique (R_{int} = 0.000). Final GoF = 1.160, $R1$ ($I > 2.00\sigma(I)$) = 0.0904, R(all reflections) = 0.1274, $wR2$(all reflections) = 0.2371. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 884592.

(19) Spek, A. L *J. Appl. Crystallogr.* **2003**, *36*, 7–13.

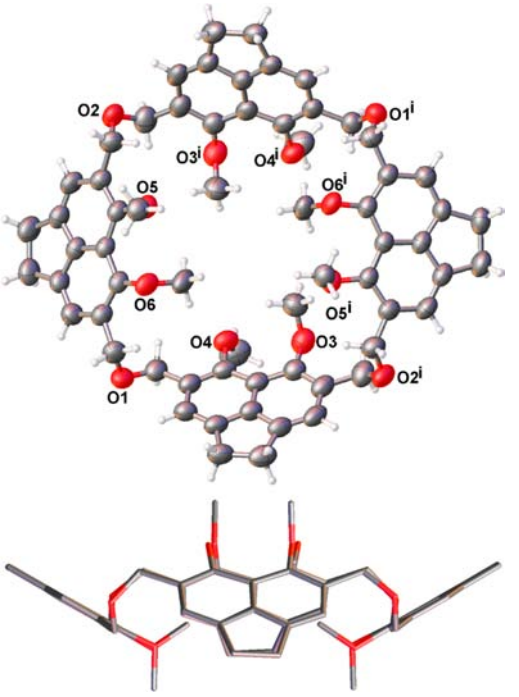


Figure 2. Top: 50% probability ellipsoid representation of **13** (symmetry code i = 1.25 − x, 1.25 − y, 0.25 − z). Bottom: capped stick representation of the 1,3-alternate conformation of **13** (H-atoms omitted for clarity).

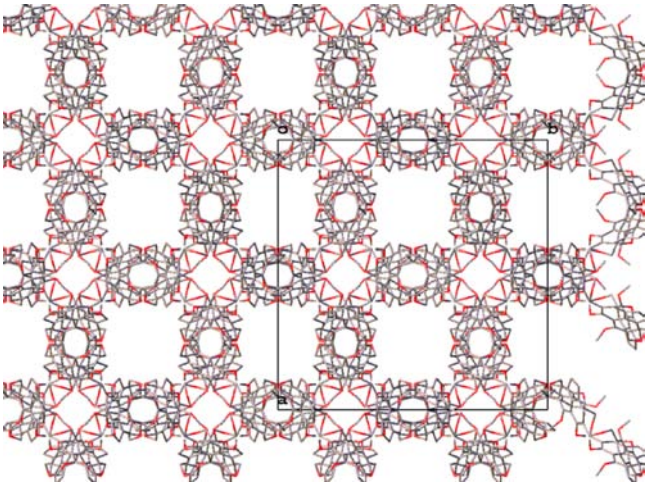


Figure 3. Extended packing diagram from the X-ray structure determination of **13**, viewed down the *c*-axis, showing significant solvent-accessible regions. H-atoms omitted for clarity.

Molecular modeling[20] suggested that **13** could have a similar well-defined bowl structure to that of **4** (or **4a**) which could accommodate a C_{60} fullerene molecule (Figure 4), and

(20) Molecular modeling was conducted using the MMFF force field with Spartan'10 software by Wavefunction Inc., Irvine, CA.

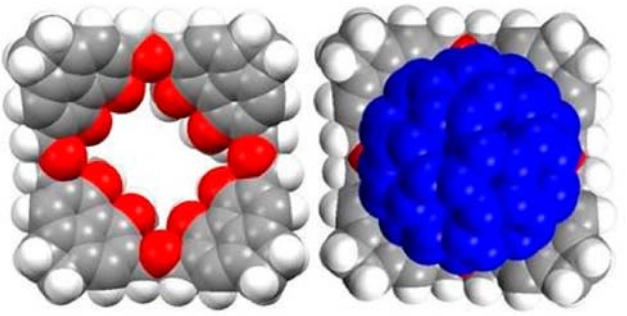


Figure 4. Molecular modeling structures (MMFF minimized) showing **13** (left) and its supramolecular complex with C_{60} (right).

this was a primary objective for undertaking the synthesis of these macrocyclic hosts.

Experiments were undertaken to determine if the molecular modeling prediction of C_{60} binding as a guest molecule to **13** could be realized. Equimolar amounts of the host and guest compounds were dissolved in several solvent systems. Upon standing and slow evaporation, dark microcrystalline materials separated from the toluene solution, but these were too small and unsuitable for X-ray analysis. However, when the residue obtained after all of the solvent had evaporated was redissolved in toluene-d_8 and its ^{1}H NMR spectrum was measured, significant chemical shift changes could be noted. A titration experiment was therefore undertaken with a fresh sample of **13**. The chemical shifts of the OCH_3, the bridging ($-CH_2CH_2-$) groups, and also of the aromatic singlet proton signals were all affected by supramolecular complexation with C_{60} (Figure 5). These different chemical shift changes are likely due to the different contact effects that the "nesting" of the C_{60} has on these three sets of protons.

An average K_{assoc} value of 616 ± 102 M^{-1} for the complexation between **13** and C_{60} was obtained. This value is based upon the corresponding K_{assoc} values determined using nonlinear 1:1 binding isotherms[21] for the chemical shift changes of each of the three sets of proton signals most affected.

(21) (a) Connors, K. A. *Binding Constants*; Wiley: New York, 1987. (b) Association constants were calculated using nonlinear curve fitting using the program ORIGINPro 7.5 from OriginLab Corporation.

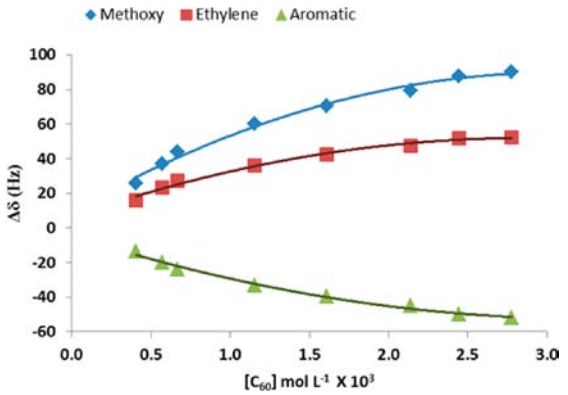


Figure 5. Graph showing the changes in ^{1}H NMR chemical shifts ($\Delta\delta$) in Hz for the protons in **13** from titration experiments with C_{60} in toluene-d_8.

In conclusion, we have reported a series of new derivatives for acenaphthene which have been synthesized for the first time via a modified Ullmann coupling methodology. These compounds served as starting compounds toward the further functionalization of the acenaphthenes which, using a Williamson-ether type coupling, formed the new macrocyclic oxacalixarene analogue **13** for which the X-ray crystal structure revealed it to be in a 1,3-alternate conformation. ^{1}H NMR solution complexation experiments showed that this macrocycle formed a 1:1 complex with C_{60} fullerene in toluene-d_8. Further studies with this new bowl-shaped macrocycle are ongoing.

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Supporting Information Available. General experimental methods and the ^{1}H and ^{13}C NMR spectra of all new compounds as well as the crystallographic information files (CIF) of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.