A Convenient Synthesis of Functionalized Cavitands via Free-Radical Bromination

Thomas N. Sorrell* and F. Christopher Pigge

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

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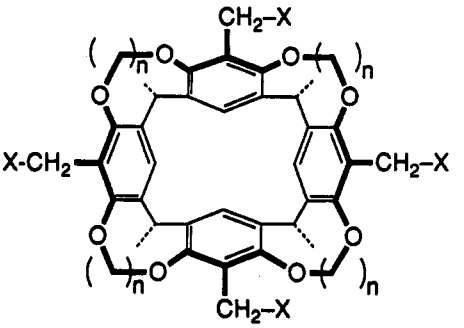
The selective complexation of neutral organic molecules by synthetic hosts has long been a goal of molecular recognition studies. Synthetic hosts employed in recent years have included cyclotriveratrylenes,[1] cyclodextrins,[2] and calix[*n*]arenes derived from the acid-catalyzed condensation of phenols with aldehydes.[3] A subclass of calixarenes known as cavitands are formed by condensing resorcinols with aldehydes, and Cram and co-workers have fashioned these rigid, bowl-shaped molecules to form inclusion complexes with a variety of organic guests such as $CHCl_3$, CH_2Cl_2, and CH_3CN.[4] Additionally, carcerands, comprising two cavitands linked by four covalent bridges, have been found to complex guests irreversibly during shell closure[5-7] while hemicarcerands, linked by three covalent bridges, reversibly bind a number of solvents and gases.[8]

While the cavitands have already provided valuable insight into factors governing host–guest chemistry, the full potential of these unique compounds with regard to metal complexation and catalysis has been largely unexplored. A possible explanation for this lack of attention resides with the cumbersome multistep syntheses involved in obtaining versatile intermediates such as **1** (Scheme I). The reported synthesis of **1** requires five steps starting from resorcinol and acetaldehyde and proceeds in a modest 7.5% overall yield.[4,5] Other drawbacks to this established route include long reaction times, the use of large amounts of solvents, and intermediates which require prolonged heating under vacuum to dry adequately.

In connection with a project aimed at the preparation of selectively functionalized cavitands,[9] we were intrigued by a recent report detailing the direct free-radical bromination of tri-*o*-thymotide to yield bromomethyl derivatives. The novelty of the reaction lies in the selective functionalization of the methyl groups while the theoretically more reactive isopropyl substituents are unaffected.[10] It is thought that geometric constraints inhibit

Scheme I



1 X = Cl, n = 1

2 X = H, n = 1
3 X = Br, n = 1 — NBS, $(PhCOO)_2$ 67%

4 X = H, n = 2
5 X = Br, n = 2 — NBS, $(PhCOO)_2$ 61%

resonance stabilization of the necessary tertiary, benzylic radical intermediate, resulting in a reversal of the normal selectivity observed in free radical halogenations (i.e., tertiary > secondary > primary).[11] While the formation of secondary radicals in preference to tertiary radicals in strained polycyclic hydrocarbons like norbornane is well documented,[12] it appears that the radical chemistry of rigid aromatic systems such as tri-*o*-thymotide has received little attention. Cavitands **2** and **4** are structurally similar to tri-*o*-thymotide in that geometric constraints should prevent resonance stabilization of a radical intermediate at the tertiary bridge positions, resulting in halogenation of the methyl groups.[13]

To test this hypothesis, cavitands **2** and **4** were readily prepared by the acid-catalyzed condensation of 2-methylresorcinol and acetaldehyde followed by treatment of the resulting octol with either $BrCH_2Cl$ or $TsO(CH_2)_2OTs$.[4] Conversion to the corresponding bromomethyl cavitands **3** and **5** was accomplished by heating a mixture of either **2** or **4** with 4 equiv of NBS and a catalytic amount of benzoyl peroxide in refluxing CCl_4. Thin-layer chromatography conducted during the course of the reaction revealed the presence of the final product as well as three additional mobile spots, presumably corresponding to mono-, bis-, and tris(bromomethyl) cavitands, which disappeared as the reaction progressed. In this manner, **3** and **5** were obtained in 67% and 61% yield, respectively, by simply triturating the crude product with methylene chloride. This unoptimized yield is excellent in terms of ease of isolation of analytically pure product.[14]

In summary, we have prepared the previously unknown bromomethyl cavitands **3** and **5** in three steps from

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(13) NBS is frequently employed in cavitand chemistry to brominate the position between the two phenolic groups of each ring of the resorcinol/aldehyde condensation product (cf. ref 6). That reaction presumably proceeds by an electrophilic mechanism, however, and not by a radical process.
(14) The reaction is very clean, the only other major product (by TLC) being succinimide. We utilized the trituration method because of its ease to obtain analytically pure material. Additional product may be isolated by chromatography of the methylene chloride extracts, but the low solubility of **3** and **5** makes this process somewhat tedious.

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commercially available 2-methylresorcinol in overall yields of 32% and 20%, respectively. The key transformation in this scheme involves the preferential, free-radical bromination of cavitands 2 and 4 at the formally less reactive primary, benzylic positions. This process leads to synthetically versatile cavitands with minimum effort and in significantly greater yields than the previously established route for the analogous tetrakis(chloromethyl) compound 1.

Experimental Section

All solvents and reagents are commercially available and were used without further purification. Cavitands 2 and 4 were prepared according to the literature procedure.[4] ^{1}H NMR spectra were recorded at 200 MHz. TLC was performed using Analtech silica gel GF plates (250 microns) and visualized with use of a UV lamp or iodine staining. Melting points are uncorrected.

7,11,15,28-Tetrakis(bromomethyl)-1,21,23,25-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*f*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocin Stereoisomer (3). Under an argon atmosphere, NBS (1.1 g, 6.31 mmol) and a catalytic amount of benzoyl peroxide were added to a solution of 2 (1.0 g, 1.54 mmol) in 100 mL of CCl_4. The mixture was allowed to reflux for 4 h. During this time, the NBS gradually dissolved to give a light orange solution. The color was slowly discharged with concomitant coprecipitation of succinimide and a portion of the product. After the mixture was cooled to rt, the precipitate was collected by filtration, and the filtrate was evaporated to afford a light yellow solid. Trituration of the combined solids with cold (−20 °C) CH_2Cl_2 followed by suction filtration yielded 1.0 g (67%) of a white solid, R_f(2:1 $CHCl_3$–hexanes) = 0.48, mp > 300 °C: ^{1}H-NMR ($CDCl_3$) δ 1.75 (d, 12 H, J = 7.4 Hz, CH_3), 4.42 (s, 8 H, CH_2Br), 4.57 (d, 4 H, J = 7.0 Hz, inner OCH_2O), 5.02 (q, 4 H, J = 7.4 Hz, CH), 6.04 (d, 4 H, J = 7.0 Hz, outer OCH_2O), 7.26 (s, 4 H, ArH). Anal. Calcd for $C_{40}H_{36}Br_4O_8$: C, 49.82; H, 3.76; Br, 33.15. Found: C, 49.63; H, 3.77; Br, 33.09.

8,13,18,32-Tetrakis(bromomethyl)-1,25,27,29-tetramethyl-5,6,10,11,15,16,20,21-octahydro-2,24:3,23-dimetheno-1*H*,25*H*,27*H*,29*H*-bis[1,4]dioxocino[6,5-*j*:6′,5′-*j*′]benzo[1,2-*e*:5,4-*e*′]bis[1,4]benzodioxonin Stereoisomer (5). This compound was prepared from 1.5 g (2.1 mmol) of 4 as described above except that the product does not precipitate from the reaction mixture. Thus, after being cooled to rt, the solution was filtered from succinimide and evaporated to afford a light yellow solid. Trituration of the resulting solid with cold (−20 °C) CH_2Cl_2 followed by suction filtration yielded 1.3 g (61%) of a white solid, R_f($CHCl_3$) = 0.83, mp > 300 °C: ^{1}H-NMR ($CDCl_3$) δ 1.64 (d, 12 H, J = 7.5 Hz, CH_3), 4.10–4.20 (m, 8 H, inner OCH_2CH_2O), 4.58–4.70 (m, 8 H, outer OCH_2CH_2O), 4.74 (s, 8 H, CH_2Br), 5.43 (q, 4 H, J = 7.5 Hz, CH), 7.55 (s, 4 H, ArH). Anal. Calcd for $C_{44}H_{44}Br_4O_8$: C, 51.79; H, 4.35; Br, 31.32. Found: C, 51.86; H, 4.41; Br, 31.21.

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