

Selective Functionalization of Cavitands: Synthesis of a New Hemicarcerand

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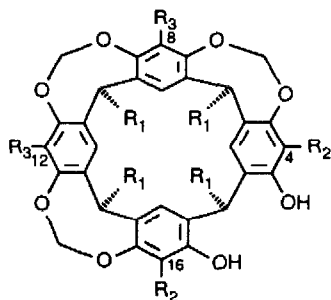
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Abstract: Partly bridged cavitands **2** and **4** can be selectively debrominated in one step by treatment with 5 equiv of *n*-BuLi in THF to afford the corresponding dibromo derivatives **5** and **6** in 90% and 77% yield, respectively. After incorporation of the fourth bridge, the remaining two bromines can be replaced by CN to give **9** (>95%), C(O)OMe to give **10** (60%) or OH to give **11** (62%). Two molecules of **11** were coupled with CH₂BrCl in DMSO/THF under high dilution conditions to give new hemicarcerand **12** in 71% yield.

In supramolecular chemistry,¹ a number of building blocks, like cyclodextrins² and calixarenes,³ have been extensively studied. Resorcinol-based calixarenes, introduced by Högberg,⁴ are especially interesting since they complex neutral guests, e.g. sugars with some degree of selectivity.⁵ Moreover, Cram has shown that cavitands⁶ and carcerands⁷ complex different kinds of neutral molecules. In our group, we are currently exploring an approach to use these medium-sized molecules as frameworks or platforms to which functional groups for intermolecular interactions can be attached. In a later stage, several of these platforms can be connected to build up larger structures.

In comparison with calix[4]arenes,⁸ little attention has been paid to selective functionalization of octols⁹ and cavitands. Only very recently, an octol derivative containing two bromines and two allyl groups at the upper rim was described.¹⁰ This prompts us to report our preliminary results on the selective functionalization of cavitands, using partly bridged cavitands as a key intermediate.

Partly bridged cavitand **1** was first reported by Cram *et al.*^{6a} as a by-product (11%) in the synthesis of completely bridged cavitands. We were able to optimize the reaction conditions and to obtain partly bridged cavitand **2**¹¹ in 53% yield by reaction of the corresponding tetrabromooctol¹² with K₂CO₃ (10 equiv)/CH₂BrCl (4 equiv)/DMF at 70 °C for 4 days. In comparison with completely bridged cavitands, the partly bridged cavitands have a lower degree of symmetry, because the four aromatic rings bearing the bromines are no longer equivalent. After debromination, this may give the possibility of selective functionalization at the 4- and 16-positions.



- 1 $R_1 = \text{CH}_3$, $R_2 = R_3 = \text{Br}$
- 2 $R_1 = \text{CH}_2(\text{CH}_2)_9\text{CH}_3$, $R_2 = R_3 = \text{Br}$
- 3 $R_1 = \text{CH}_2(\text{CH}_2)_9\text{CH}_3$, $R_2 = R_3 = \text{H}$
- 4 $R_1 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $R_2 = R_3 = \text{Br}$
- 5 $R_1 = \text{CH}_2(\text{CH}_2)_9\text{CH}_3$, $R_2 = \text{Br}$, $R_3 = \text{H}$
- 6 $R_1 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $R_2 = \text{Br}$, $R_3 = \text{H}$
- 7 $R_1 = \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $R_2 = \text{Br}$, $R_3 = \text{SCH}_3$

Upon treatment of **2** with excess of *n*-BuLi in THF at $-78\text{ }^\circ\text{C}$ for 45 min followed by hydrolysis, we isolated, beside the fully debrominated product **3**, considerable amounts of mono- and dibromo derivatives, indicating that removal of the bromines was not equally fast at all four positions. Reducing the amount of metallating agent to 5 equiv and the reaction time to 1 min, yielded the dibromo derivative **5** in 90% yield after column chromatography. In a similar way, **6** was synthesized in 77% yield.

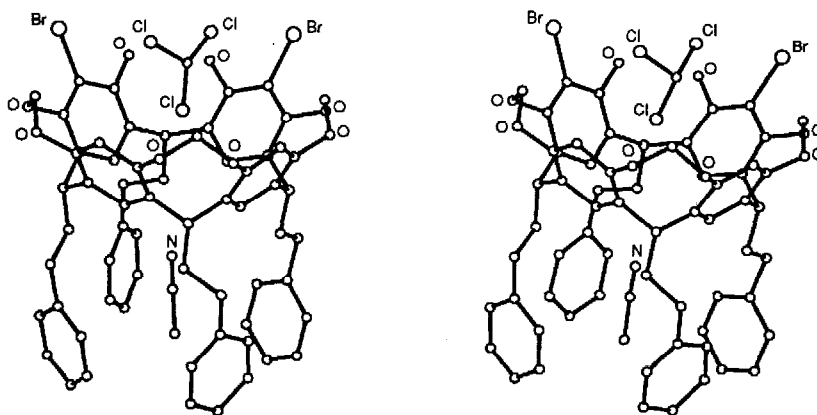
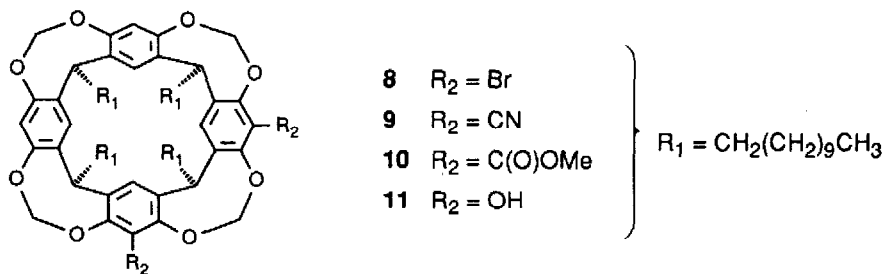


Fig. 1. The two independent molecules in the unit cell of the X-ray structure of compound **6** (crystallized from $\text{CHCl}_3/\text{CH}_3\text{CN}$).

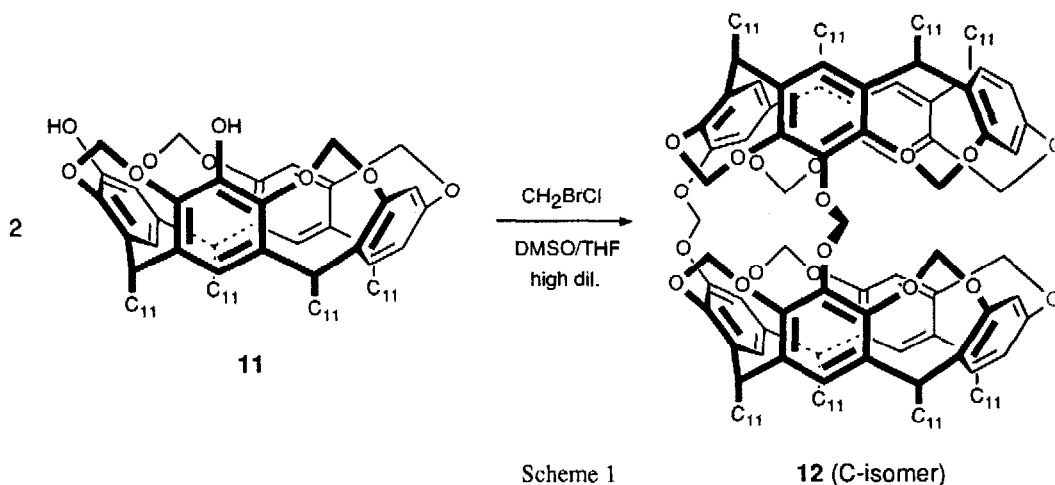
The ^1H NMR spectrum of **6** exhibits a characteristic singlet at 6.57 ppm for the two incorporated hydrogens. Evidence for the regiochemistry of the reaction was given by a single crystal X-ray analysis (Fig. 1),¹³ which showed that the remaining bromines are adjacent to the free hydroxyl groups. The regioselectivity of the reaction may be due to deprotonation of the free hydroxyl groups, which deactivate the aromatic ring for metal-halogen exchange because of the enhanced electron density in the aromatic rings. A similar inhibition of metal-halogen exchange has been previously observed in the case of bromoanilines and cyanomethylphenyl bromides.¹⁵

When the reaction mixture is quenched with electrophiles other than H^+ , the 8- and 12-positions can be functionalized selectively. This is illustrated by the reaction with CH_3SSCH_3 to give **7**.

The partly bridged cavitand **5** was converted quantitatively into the completely bridged cavitand **8** using excess of CH_2BrCl and K_2CO_3 in refluxing CH_3CN for 24 h. After this, the two bromines could be easily



substituted by a variety of functional groups, leaving the free 8- and 12-positions unaffected. Heating **8** with CuCN in refluxing N-methylpyrrolidone for several hours gave **9** in almost quantitative (>95%) yield. Treatment of **8** with n-BuLi in THF at $-100\text{ }^\circ\text{C}$ followed by quenching with ClC(O)OMe produced **10** in 60% yield. Quenching of the lithiated product at $-78\text{ }^\circ\text{C}$ with B(OMe)₃ followed by oxidation with basic H₂O₂ afforded **11** in 62% yield. A similar diol with 2-phenylethyl side chains was reported before by Cram *et al.*¹⁵ in an overall yield of 0.7%.¹⁷



To illustrate the utility of the selectively functionalized cavitands, we subjected diol **11** to a coupling reaction with CH₂BrCl in order to synthesize the new hemicarcerand **12** (Scheme 1). The reaction was performed under Cram's high dilution conditions¹⁶ in DMSO/THF to give, after a reaction time of 4 days, a colorless compound in 71% yield, identified by FAB MS to be the expected coupled product ($M^+ = 2395$). Two diastereomers, denoted C and Z analogously to recently published related hemicarcerands,¹⁸ can be formed, but ¹H NMR spectroscopy strongly suggests that only one isomer is formed. The spectrum is broad when recorded in CDCl₃ at room temperature, but sharpens up when measured in CDCl₂CDCl₂ at 90 °C. Most significant is the upfield shift for half of the inner and outer protons of the methylene bridges shifting from 4.4 to 3.5 ppm and 5.8 to 5.1 ppm, respectively. This leads us to conclude that **12** (isomer C) is formed, since only in this structure are the methylene bridges able to enter in the molecular cavity of the opposite octol fragment and this will cause an upfield shift.

Supplementary Material. Figure of the numbering of atom positions and tables of positional parameters, bond distances and bond angles of the X-ray structure of compound **6** (16 pages).

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11. All new compounds were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy, FAB MS and elemental analyses.
12. Prepared in a similar way as reported for analogous compounds.^{6a}
13. Crystal data: $\text{C}_{63}\text{H}_{54}\text{Br}_2\text{O}_8 \cdot \text{CHCl}_3 \cdot 3 \text{CH}_3\text{CN}$, triclinic, *P*-1, $a = 10.629$ (3), $b = 20.719$ (4), $c = 28.514$ (6) Å, $\alpha = 82.08$ (2), $\beta = 87.23$ (2), $\gamma = 85.58$ (2)°, $V = 6197$ (7) Å³, $D_c = 1.438$ g cm⁻³, $Z = 4$, $T = 138$ K, Mo K_α radiation, ω -2 θ scan mode, $2.5 < \theta < 20^\circ$. Refinement of 7163 observed reflections ($F_0^2 > 3\sigma(F_0^2)$) gave an *R*-factor of 8.7%. The crystal structure contains two independent molecules. Hydrogen atoms were not resolved. The Br atoms and the atoms of the CHCl_3 guest molecules were refined anisotropically. The total number of parameters refined was 749. All calculations were done with SDP.¹⁴
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17. This yield is based on the corresponding tetrabromooctol; in our case the overall yield is 32%.
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