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Facile, high yielding synthesis of deepened cavitands. A synthetic and theoretical study.

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Facile, high yielding synthesis of deepened cavitands.

A synthetic and theoretical study.

Abstract

A wide variety of 2-methyl-resorcinol-based deepened cavitands were synthesized from readily available reagents in a four-step procedure with overall yields of up to 62 %. A systematic variation of the rim was carried out by building-up a flexible upper aromatic wall on the rigid cavitand platform through CH₂, CH₂O and CH₂OCH₂ spacers. These aromatic walls were further extended by a Suzuki cross-coupling reaction. Full characterization of the synthesized cavitands was carried out. The solid state structure of tetrakis(phenoxyethyl)cavitand was determined by X-ray crystallography. Gas phase theoretical calculations for this molecule predict the presence of weak T-shaped interactions between the upper phenyl rings. The host-guest complex formation ability of two deepened cavitand hosts towards 4-chloro-benzotrifluoride was proved by photoluminescence method.

Keywords: Supramolecular chemistry; Host-guest systems; Cavitands; Pi interactions

1. Introduction

The “molecule within a molecule” concept was first introduced by Donald J. Cram.^[1] Since then, there has been an ever growing interest in molecular containers having expanded inner cavities capable of housing sizable or multiple guests. Molecular containers are of particular interest in separation science, drug delivery systems, and molecular sensing and recognition.^[2] Host molecules are able to shield their guests from the exterior solution, which might cause radical changes in their physical and/or chemical properties. This phenomenon was nicely demonstrated *e.g.* in the stabilization of short-lived reaction species such as cyclobutadiene.^[3] Furthermore, the encapsulation of guest molecules within an extended cage and subsequent release of the products may result in their use as nanosized reactor chambers.^[4]

Several synthetic methodologies were developed in order to increase the inner volume of molecular containers. The covalent synthesis of the first closed-surface carcerand and its carceplex^[5] has inspired a number of researchers to prepare structurally well-defined container compounds and determine their host-guest binding properties.^[6] However, these synthetic procedures mostly involve intricate reaction routes that are frequently combined with low isolated yields, which make their application rather limited. Recently, dynamic covalent chemistry has been effectively utilized to overcome such difficulties.^[7] Self-

assembly through metal-ligand interactions, van der Waals forces and, mainly, hydrogen bonding also plays an important part in constructing large molecular capsules with increased internal cavities.^[8] On the other hand, these non-covalent systems often suffer from relative instability, functional group intolerance and insolubility in organic solvents.

First-generation cavitands^[9] based on resorcin[4]arenes^[10] are conformationally rigid, bowl-shaped molecules, and thus, are ideal platforms for accommodating small molecules, ions or both. Various synthetic strategies have been developed to produce deepened cavitands with an open-end. The depth of the cavitands was increased either by Suzuki cross-coupling reactions^[11] or by bridging the resorcinarene hydroxyl groups with 1,4-diazine derivatives.^[12] This latter family of cavitands was developed further into one of the largest synthetic hosts, which are able to complex extended adamantane and pyridine derivatives of up to 19 Å in length.^[13] Surprisingly, only a few studies utilize the convenient Williamson etherification on the rim of the cavitand skeleton.^[14] Herein, we report a facile, high yielding synthetic procedure and full characterization of a novel family of deepened cavitands.

2. Results and discussion

2.1. Synthetic studies

This series of deepened cavitands was synthesized in four simple, high yielding steps; starting from 2-methylresorcinol and acetaldehyde (Scheme 1). The obtained tetrakis(methyl)resorcin[4]arene^[15] (**1**) was bridged by BrCH₂Cl (**2**),^[16] and selectively brominated according to Sorrell and Pigge^[17] using azobisisobutyronitrile (AIBN) as a catalyst to afford tetrakis(bromomethyl)cavitand (**3**) in 80% combined yield. Cavitand **3** was then reacted with an excess of various aliphatic alcohols and phenols in the presence of an adequate base to give the corresponding tetrakis(alkoxymethyl) (**5**, **6**, **10**) and tetrakis(aryloxymethyl) cavitands (**7-9**) in high (60-78 %) isolated yields. These reactions proceeded well at room temperature; however, full etherification was only seen at 70 °C after 16 hours. Sodium hydroxide was used to deprotonate phenol derivatives, while K₂CO₃ was sufficient to carry out the reaction with methanol. Sodium hydride was employed for the preparation of **10**. All these cavitands turned out to be pure after performing a simple work-up procedure, except for compound **8** that required further purification. Cavitand **3** was also reacted with PhB(OH)₂ under typical Suzuki-reaction conditions to yield tetrabenzylcavitand (**11**). The presence of an unidentified minor component made purification by column chromatography inevitable, which dramatically decreased the yield to 24% in this coupling

reaction. Compound **9**, bearing four aryl iodide moieties, was used to further extend the aromatic walls of the cavity in a Suzuki cross-coupling reaction (Scheme 2). This reaction provided cavitand **12** with a considerably large, hydrophobic pocket in good yield (59%).

We also describe a simple method for the synthesis of tetrakis(hydroxymethyl)cavitand (**4**). This key intermediate was previously prepared either by LiAlH_4 reduction of tetraesters^[5, 18] or by hydrolysis of the tetra(acetoxymethyl)cavitand.^[19] Here, we propose NaOH hydrolysis of **3** that affords **4** in excellent yield (81%). Tetrol **4** was employed to synthesize **10** using the easily available benzyl bromide derivative (see Experimental Section, Method B.).

All compounds possess a high degree of symmetry (C_4) due to the complete, four-fold etherification, which is reflected in their simple ^1H -NMR spectra. The formation of the alkyl(aryl)oxymethyl cavitands was best followed by the unique downfield shifts of the methylene-spacer (ArCH_2O) protons (Figure 1). Upon performing the Suzuki cross-coupling reaction, this singlet resonance was upfield shifted to 3.71 ppm in cavitand **11**. The chemical shifts of the methyleneoxy-bridge (OCH_2O) protons are also characteristic; they appear as a sharp pair of doublets indicating the inherent rigidity of the cavitand framework. All signals of the “parent” cavitand skeleton are broadened in CDCl_3 in the ^1H -NMR spectrum of compound **6**, while the resonances of the C_{12} alkyl chain remain sharp (Figure 1). However, the observed line broadening disappears upon changing the NMR solvent to dmsO-d_6 . Compound **6** bearing long alkyl chains resembles the cavitand obtained by ROMP of caprolactam.^[20] The structural assignments of this cavitand family were also confirmed by ^{13}C -NMR and MALDI-TOF MS measurements. The matrix (2,5-dihydroxybenzoic acid (DHB)) and the solvents used contain sodium ions, thus sodium adducts are commonly detected by MALDI-TOF MS. The mass shifts were only $[\text{M}+22]^+$ instead of the expected $[\text{M}+23]^+$ due to the difference in the average mass that is always higher than monoisotopic mass, and because of the inhomogeneous matrix/sample mixture layer, which is quite usual with DHB. In these cases, a mass shift of 0.2-0.3 Da was obtained according to the appeared double peaks.

Colourless single crystals of **7** suitable for X-ray crystallography were obtained from a $\text{CHCl}_3/\text{MeOH}$ recrystallization chamber. The molecular structure of **7** is shown in Fig. 2. Dihedral angles formed by the planes of the $\text{C1}...\text{C6}$ rings are 76.6° (A/B, A/C, B/D, C/D) and 57.5° (A/D, B/C). Each ring forms two different dihedral angles with its neighbours, *i.e.*, the dihedral angles alternate. The $\text{C8}...\text{C13}$ ring planes behave differently. They form identical dihedral angles with their neighbours (83.6°) and a different one across the macrocycle

(38.9°). Characteristic torsion angles of the linkers joining the structural units range from 91.4° to 100.9° (Table 1).

2.2 Theoretical studies

The geometry of compound **7** was optimized at the PBE/PBE/6-31G(d,p) level of theory and the resulting structure is shown in Figure 3. The minimum-energy structure exhibits symmetry very close to C_4 . Most of the computed structural parameters (bond length, bond angles and torsion angles) are in reasonable agreement with the X-ray structure of **7**. The deviation from C_{4v} symmetry to C_4 is a consequence of the deviation of dihedral angle (C6-C1-C7-O4) from -90° to -77.8° (-76.4° in the X-ray structure). The rotation of the phenoxy groups around the C1-C7 axis (and the analogous carbon-carbon bonds) results in a subtle change in the bond lengths as well as in the natural (NPA) charges of the aromatic rings and the OCH₂O bridges of the cavitand skeleton. The C-C distances in the aromatic rings are somewhat elongated compared to 1.403 Å in benzene, optimized at the same level of theory as **7**.

The main difference between the computed and the experimental structures is the significantly closer arrangement of the four phenoxymethyl groups which can be attributed to weak interactions of the neighbouring rings causing a slight contraction of the C12-C13 bond. In contrast to the T-shaped π - π interactions described in the literature,^[21] where the first ring is oriented towards the center of the second one, these intramolecular interactions can be attributed mainly to the interactions between the inner ortho(or meta)-positioned hydrogen and the ortho (or meta) carbon of the perpendicularly orientated neighbouring ring (see Figure 3). These non-contact distances are estimated to be 3.522 Å and 3.141 Å, respectively.

The molecular graph of **7** (Figure 4) obtained within the framework of the Quantum Theory of Atoms In Molecules (QTAIM) analysis exhibits a cage critical point (CCP) revealing a cage formed by the aromatic rings of the phenoxymethyl substituents. This cage is outlined by the H...C interactions between the perpendicular rings forming a four-sided wall, and additionally, an upper and a lower plane having one ring critical point (RCP) for each. Figure 5 shows the Laplacian distribution $\nabla^2\rho(\mathbf{r})$ in the plane of the T-shaped interaction. Several other ring structures are predicted within **7** with another CCP in the center of the cavitand backbone.

Espinosa and co-workers proposed a simple formula expressing the relationship between the hydrogen bond energy and the local potential energy density $V(\mathbf{r})$ in the bond critical point^[22] with the proportionality factor being in volume atomic units:

$$E_{HB} = \frac{1}{2}V(\mathbf{r}_{CP}) \quad (1)$$

The local potential energy density $V(\mathbf{r}_{CP})$ can be obtained from the topological parameters using the local form of the virial equation:

$$V(\mathbf{r}_{CP}) = \frac{\hbar^2}{4m} \nabla^2 \rho(\mathbf{r}_{CP}) - 2G(\mathbf{r}_{CP}) \quad (2)$$

where G is the local electronic kinetic energy density.

Using Eq. 1 the interaction energy is estimated to be 0.7 kcal/mol and 1.5 kcal/mol for the C...H interactions with distances 3.522 Å and 3.141 Å, respectively. Thus, the overall stabilization energy for the T-shaped interactions of the upper aromatic walls is less than 10 kcal/mol; suggesting that an incoming, appropriate guest molecule can enter the cavity with a low activation barrier.

2.3. Host-guest complexation studies

As preliminary studies, the host-guest complex formation ability of two deepened cavitand molecules (**7** and **8**) towards 4-chloro-benzotrifluoride (**13**) was investigated with photoluminescence (PL) method in chloroform (see Experimental). The Benesi-Hildebrand method combined with the van't Hoff theory was applied to calculate the thermodynamic parameters of the molecular association. The results justified the presence of the host-guest complexes in solution with considerable concentration and possessing 1:1 stoichiometry. Figure 6 shows the Job's plot of the interaction of host **8** with **13**. However, our experiments show significantly different thermodynamics for the complex formation. Although these host – guest interactions associated with almost the same Gibbs free energy changes at room temperature ($\Delta G = -26.8$ kJ/mol for **7:13** and $\Delta G = -27.2$ kJ/mol for **8:13**, respectively), the enthalpy change is much higher when the complex of **7** is formed ($\Delta H = -36.8$ kJ/mol for **7:13** and $\Delta H = -29.2$ kJ/mol for **8:13**, respectively). The entropy changes were found to be considerably different ($\Delta S = -33.5$ J/K·mol for **7:13** and $\Delta S = -6.7$ J/K·mol for **8:13**, respectively). The well-known enthalpy-entropy compensation may be responsible for this unexpected phenomenon, which is probably due to the steric hindrance of the methyl groups located on the upper phenyl rings of compound **8**. The stability constants K_{ass} at room-

temperature were determined to be $4.9 \times 10^5 \text{ dm}^3/\text{mol}$ for **7:13**, and $5.8 \times 10^5 \text{ dm}^3/\text{mol}$ for **8:13** complexes, respectively.

3. Conclusions

In sum, Williamson etherification provides easy access to a wide variety of deepened cavitands from readily available, inexpensive alcohols. The synthesized cavitands exhibit great stability and good solubility in most organic solvents. The upper aromatic walls are attached to a rigid cavitand platform through CH_2 , CH_2O and CH_2OCH_2 spacers. Hence, this “upper cavity” of the molecule possesses some flexibility, which allows potential guest molecules to enter and to be more or less surrounded by the walls of the host. In this way, the entrapment of guest molecules and their isolation from the bulk medium can be more effective. Theoretical calculations suggest that the formation of a host-guest complex might take place via a small activation barrier. This novel series of deepened cavitands may be useful for complexing electron-poor aromatics, such as nitroaromatics, benzotrifluorides, *etc.* due to the presence of a flexible binding pocket with tunable electron-density. Indeed, two of these deepened cavitands (**7** and **8**) behave as hosts and show the formation of 1:1 complexes with 4-chloro-benzotrifluoride as a guest. Furthermore, cavitand **9**, bearing four aryl iodide moieties, may serve as a potential intermediate for further functionalization of this cavitand family, as demonstrated in the synthesis of cavitand **12**.

4. Experimental Section

4.1. General procedures and materials

All reagents and solvents were purchased from Aldrich. For the synthesis of **10**, THF was distilled from sodium/benzophenone under argon atmosphere, and the reaction was carried out under Ar by using standard Schlenk-techniques. General work-up procedure is as follows: the reaction mixture was partitioned between CH_2Cl_2 (30 ml) and water (30 ml). The organic phase was separated, and the aqueous phase was extracted with another portion of CH_2Cl_2 (30 ml). The combined organic phases were washed with water (2x30 ml), dried over MgSO_4 , and evaporated to dryness. The residue was treated with MeOH, and the resulting precipitate was collected by filtration. ^1H and ^{13}C -NMR spectra were recorded at 25°C in CDCl_3 on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. The ^1H and ^{13}C chemical shifts (δ), reported in parts per million (ppm) downfield, are referenced to residual CHCl_3 (7.26 ppm) and to the carbon resonance of CDCl_3 (77.00 ppm), respectively. MALDI-TOF spectra were obtained on an Autoflex II TOF/TOF spectrometer

(Bruker Daltonics) in positive ion modes, using a 337 nm pulsed nitrogen laser (accelerating voltage: 20.0 kV, matrix: 2,5-dihydroxybenzoic acid).

4.2. Crystallography

CCDC-795580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data: $C_{64}H_{56}O_{12}$; MW: 1017.09; colourless; block size: 0.37x0.35x0.35 mm; tetragonal space group $P4/ncc$ (No. 130); $a = 15.4744(13)$ Å; $c = 25.423(2)$ Å; $V = 6087.7(9)$ Å³; $Z = 4$; $D_x = 1.110$ gcm⁻³; $\mu = 0.076$ mm⁻¹; $F(000) = 2144$.

Data collection: Intensity data were collected on a Rigaku R-Axis Rapid diffractometer with Mo-K_a radiation ($\lambda = 0.71075$ Å) at room temperature. 46012 reflections were collected of which 1602 were unique, $R_{\text{int}} = 0.067$. Numerical absorption correction^[23] was applied to the data (the minimum and maximum transmission factors were 0.975 and 0.986). The crystals diffract poorly, the resolution of the data is limited to 1 Å.

Structure solution and refinement: The structure was solved with direct methods and refined by anisotropic full-matrix least-squares refinement^[24] on F^2 . Hydrogen positional coordinates were calculated from assumed geometries and were not refined. Difference electron density maps indicate the presence of highly disordered solvent molecules. The SQUEEZE procedure of program PLATON^[25] was applied and the solvent-free data were used in further refinement cycles (solvent accessible volume 1309.0 Å³, total electron count 162 e). Atoms of the C8...C13 phenyl ring were fitted to a regular hexagon and treated as a rigid group throughout the refinement. 1602 reflections were used for the refinement of 158 parameters ($R = 0.1043$, $wR2 = 0.2403$ for all intensity data; $R = 0.0798$, $wR2 = 0.2189$ for 1332 $[I > 2s(I)]$, $GOOF = 1.10$). The minimum and maximum final residual electron density was -0.23, 0.18 eÅ⁻³. A cavity of 2.34 Å radius is inside the cavitand moiety (the centre of the sphere is at 0.250, 0.250, 0.400). The whole molecule was generated by the $1/2-y, x, z$; $1/2-x, 1/2-y, z$ and $y, 1/2-x, z$ symmetry operations (Fig. 2).

4.3. Synthetic Procedures

4.3.1. Tetrakis(hydroxymethyl)cavitand (**4**).

To the THF (30 ml) solution of 1 g (1.04 mmol) of **3** 30 ml of 1M aqueous NaOH solution was added. The reaction mixture was stirred at 70 °C for 48 hours. The reaction mixture was partitioned between CH₂Cl₂ (60 ml) and water (30 ml). The organic phase was

separated, and the aqueous phase was extracted with another portion of CH₂Cl₂ (30 ml). The combined organic phases were washed with 0.5% aq. HCl solution (30 ml), water (60 ml) and dried over MgSO₄. Evaporation of the solvent yielded a light yellow solid (m=600 mg, 81%).

¹H-NMR (CDCl₃): 1.77 (d, J=6.9 Hz, 12H, CH₃CH); 4.44 (d, J=6.8 Hz, 4H, inner of OCH₂O); 4.54 (s, 8H, ArCH₂O); 5.03 (q, J=6.9 Hz, 4H, CHCH₃); 5.91 (d, J=6.8 Hz, 4H, outer of OCH₂O); 7.26 (s, 4H, Ar). ¹³C-NMR (CDCl₃): 16.02 (CH₃CH); 31.09 (CH₃CH); 55.36 (CH₂OH); 99.67 (OCH₂O); 119.61; 126.25; 139.03; 153.10. MS: 735.17 [M+22]⁺.

4.3.2. Tetrakis(methoxymethyl)cavitand (**5**).

To the THF (15 ml) solution of 300 mg (0.31 mmol) of **3** 10 ml of MeOH and 689 mg (4.96 mmol) of K₂CO₃ was added. The reaction mixture was stirred at 70 °C for 16 hours.

General work-up procedure, white solid (m=185 mg, 78%).

¹H-NMR (CDCl₃): 1.75 (d, J=7.5 Hz, 12H, CH₃CH); 3.32 (s, 12H, OCH₃); 4.27 (s, 8H, ArCH₂O); 4.39 (d, J=7.2 Hz, 4H, inner of OCH₂O); 5.02 (q, J=7.5 Hz, 4H, CHCH₃); 5.85 (d, J=7.2 Hz, 4H, outer of OCH₂O); 7.25 (s, 4H, Ar). ¹³C-NMR (CDCl₃): 16.04 (CH₃CH); 31.06 (CH₃CH); 58.45 (OCH₃); 64.38 (ArCH₂O); 99.52 (OCH₂O); 119.86; 123.89; 138.70; 153.54. MS: 791.24 [M+22]⁺.

4.3.3. Tetrakis(dodecanoxymethyl)cavitand (**6**).

To the THF (10 ml) solution of 881 mg (4.73 mmol) of 1-dodecanol 5 ml of 0.95 M aqueous NaOH solution was added, and was left stirring for 30 min. This solution was then slowly added to the THF (10 ml) solution of 285 mg (0.3 mmol) of **3**. The reaction mixture was stirred at 70 °C for 16 hours. General work-up procedure, white solid (m=249 mg, 60%).

¹H-NMR (CDCl₃): 0.88 (t, J=6.8 Hz, 12H); 1.26 (br.m., 72H); 1.56 (quint., J=6.8 Hz, 8H); 1.76 (d, J=6.8 Hz, 12H, CH₃CH); 3.63 (t, J=6.8 Hz, 8H, OCH₂R); 4.56 (br.m., 12H, outer of OCH₂O overlapping with ArCH₂O); 5.03 (br.s., 4H, CHCH₃); 5.91 (br.s., 4H, outer of OCH₂O); 7.25 (s, 4H, Ar). ¹³C-NMR (CDCl₃): 14.08; 16.04 (CH₃CH); 22.67; 25.74; 29.33; 29.42; 29.60 (triple intensity); 29.70; 31.13 (CH₃CH); 31.90; 32.81; 55.37 (ArCH₂O); 63.09; 99.74 (OCH₂O); 119.62; 126.35; 139.05; 153.21.

4.3.4. Tetrakis(phenoxymethyl)cavitand (**7**).

To the THF (10 ml) solution of 200 mg (0.21 mmol) of **3** 2 ml of 1M aqueous solution of NaOPh (freshly prepared from phenol and NaOH) was added. The reaction mixture was stirred at 70 °C for 16 hours. General work-up procedure, white solid (m=160 mg, 75%).

¹H-NMR (CDCl₃): 1.83 (d, J=7.4 Hz, 12H, CH₃CH); 4.69 (d, J=7.3 Hz, 4H, inner of OCH₂O); 4.91 (s, 8H, ArCH₂O); 5.10 (q, J=7.4 Hz, 4H, CHCH₃); 5.77 (d, J=7.3 Hz, 4H, outer of OCH₂O); 6.94 (m, 12H, Ph); 7.25 (m, 8H, Ph); 7.40 (s, 4H, Ar). ¹³C-NMR (CDCl₃): 16.19 (CH₃CH); 31.22 (CH₃CH); 60.45 (ArCH₂O); 100.10 (OCH₂O); 114.58; 120.50; 121.01; 122.77; 129.51; 138.90; 154.04; 158.71. MS: 1039.20 [M+22]⁺.

4.3.5. Tetrakis(mesytoxymethyl)cavitand (**8**).

To the THF (10 ml) solution of 920 mg (6.76 mmol) of 2,4,6-trimethylphenol 10 ml of 0.68 M aqueous NaOH solution was added, and was left stirring for 30 min. This light-violet solution was then slowly added to the THF (10 ml) solution of 400 mg (0.41 mmol) of **3**. The reaction mixture was stirred at 70 °C for 16 hours. General work-up procedure, white solid (m=350 mg, 72%). An analytically pure sample was obtained by column chromatography (silica gel; eluent: benzene, R_f=0.51).

¹H-NMR (CDCl₃): 1.85 (d, J=7.4 Hz, 12H, CH₃CH); 2.22 (s, 12H, ArCH₃); 2.27 (s, 24H, ArCH₃); 4.50 (d, J=7.2 Hz, 4H, inner of OCH₂O); 4.61 (s, 8H, ArOCH₂); 5.18 (q, J=7.4 Hz, 4H, CHCH₃); 6.00 (d, J=7.2 Hz, 4H, outer of OCH₂O); 6.81 (s, 8H, Ar); 7.42 (s, 4H, Ar). ¹³C-NMR (CDCl₃): 16.17 (CH₃CH); 16.24 (ArCH₃); 20.57 (ArCH₃); 31.31 (CH₃CH); 64.19 (OCH₂); 100.20 (OCH₂O); 120.49; 122.96; 129.54; 130.74; 133.47; 139.24; 153.29; 153.98. MS: 1207.68 [M+22]⁺.

4.3.6. Tetrakis(4-iodo-phenoxy)methyl)cavitand (**9**).

To the THF (10 ml) solution of 740 mg (3.36 mmol) of 4-iodophenol 10 ml of 0.34 M aqueous NaOH solution was added, and was left stirring for 30 min. This solution was then slowly added to the THF (10 ml) solution of 200 mg (0.21 mmol). The reaction mixture was stirred at 70 °C for 16 hours. General work-up procedure, white solid (m=215 mg, 67%).

¹H-NMR (CDCl₃): 1.81 (d, J=7.4 Hz, 12H, CH₃CH); 4.59 (d, J=7.3 Hz, 4H, inner of OCH₂O); 4.86 (s, 8H, ArCH₂O); 5.07 (q, J=7.4 Hz, 4H, CHCH₃); 5.73 (d, J=7.3 Hz, 4H, outer of OCH₂O); 6.66 (d, J=8.7 Hz, 8H, Ar); 7.38 (s, 4H, Ar); 7.54 (d, J=8.7 Hz, 8H, Ar). ¹³C-NMR (CDCl₃): 16.13 (CH₃CH); 31.20 (CH₃CH); 60.62 (OCH₂); 83.30; 99.95 (OCH₂O); 116.84; 120.71; 122.31; 138.39; 138.95; 153.93; 158.44. MS: 1542.77 [M+22]⁺.

4.3.7. Tetrakis(benzyloxymethyl)cavitand (**10**).

Method A: To the THF (10 ml) solution of 0.26 ml (2.5 mmol) of benzyl alcohol 100 mg (2.5 mmol) of 60% NaH was added, and the mixture was left stirring for 30 min. Then, THF (10 ml) solution of 300 mg (0.31 mmol) of **3** was slowly added. The reaction mixture

was stirred at 70 °C for 16 hours, and it was poured into 30 ml 0.1 N HCl. 30 ml of CH₂Cl₂ was added, the organic phase was separated, and the aqueous phase was extracted with another portion of CH₂Cl₂ (30 ml). The combined organic phases were washed with water (2x30 ml), dried over MgSO₄, and evaporated to dryness. The residue was treated with MeOH, and the resulting precipitate was collected by filtration. White solid, m=230 mg (69%).

Method B: To the THF (10 ml) solution of 200 mg (0.28 mmol) of **4** 90 mg (2.24 mmol) of 60% NaH was added, and the mixture was left stirring for 30 min. Then 0.27 ml (2.24 mmol) of benzyl bromide was slowly added. The reaction mixture was stirred at 70 °C for 16 hours. Work-up as described in *Method A*. White solid, m=160 mg (53%).

¹H-NMR (CDCl₃): 1.74 (d, J=7.3 Hz, 12H, CH₃CH); 4.28 (m, 12H, ArCH₂O overlapped with inner of OCH₂O); 4.47 (s, 8H, OCH₂Ph); 5.00 (q, J=7.3 Hz, 4H, CHCH₃); 5.60 (d, J=7.1 Hz, 4H, outer of OCH₂O); 7.20-7.40 (m, 24H, Ar and Ph). ¹³C-NMR (CDCl₃): 16.10 (CH₃CH); 31.11 (CH₃CH); 61.72 (ArCH₂O), 72.85 (OCH₂Ph), 99.53 (OCH₂O); 119.88; 123.84; 127.76; 128.32 (double intensity); 130.09; 138.71; 153.72. MS: 1095.53 [M+22]⁺.

4.3.8. Tetrabenzylcavitand (**11**).

To the toluene (60 ml) solution of 1.04 g (1 mmol) of **3**, under Ar atmosphere 12 mg (0.05 mmol) of Pd(OAc)₂, 28 mg (0.1 mmol) of PPh₃, 1.15 g (8.3 mmol) of K₂CO₃ and 760 mg (6.2 mmol) of PhB(OH)₂ was added. The reaction mixture was vigorously stirred at 100°C for 16 hours. After cooling, it was filtered through a layer of Celite, and evaporated to dryness. Column chromatography (silica gel; eluent: benzene/n-hexane=4:1, R_f=0.64) yielded the product as white solid (229 mg, 24%).

¹H-NMR (CDCl₃): 1.72 (d, J=7.4 Hz, 12H, CH₃CH); 3.71 (s, 8H, ArCH₂Ph); 4.29 (d, J=6.9 Hz, 4H, inner of OCH₂O); 4.98 (q, J=7.4 Hz, 4H, CHCH₃); 5.90 (d, J=6.9 Hz, 4H, outer of OCH₂O); 7.15-7.26 (m, 24H, Ar and Ph). ¹³C-NMR (CD₂Cl₂): 19.66 (CH₃CH); 31.66 (ArCH₂Ar); 32.14 (CH₃CH); 99.86 (OCH₂O); 119.33; 126.67; 127.35; 128.85; 129.19; 139.74; 141.01; 153.49. MS: 975.50 [M+22]⁺; 953.44 [M]⁺.

4.3.9. Tetrakis(4-phenyl-phenoxy)methyl)cavitand (**12**).

To the toluene (20 ml) solution of 380 mg (0.25 mmol) of **9**, under Ar atmosphere 2.9 mg (0.013 mmol) of Pd(OAc)₂, 6.8 mg (0.026 mmol) of PPh₃, 276 mg (2 mmol) of K₂CO₃ and 183 mg (1.5 mmol) of PhB(OH)₂ was added. The reaction mixture was vigorously stirred

at 80 °C for 2 days. After cooling, it was filtered through a layer of Celite, and evaporated to dryness. The residue was treated with MeOH, and the resulting precipitate was collected by filtration (195 mg, 59%).

¹H-NMR (CDCl₃): 1.85 (d, J=7.4 Hz, 12H, CH₃CH); 4.73 (d, J=7.3 Hz, 4H, inner of OCH₂O); 4.97 (s, 8H, ArCH₂Ph); 5.12 (q, J=7.4 Hz, 4H, CHCH₃); 5.82 (d, J=7.3 Hz, 4H, outer of OCH₂O); 6.99 (d, J=8.5 Hz, 8H, Ph); 7.27-7.53 (m, 32H, Ar and Ph). ¹³C-NMR (CD₂Cl₂): 16.20 (CH₃CH); 31.26 (CH₃CH); 60.66 (ArCH₂O); 100.17 (OCH₂O); 114.89; 120.62; 122.78; 126.65; 128.17; 128.70; 134.12; 138.95; 140.55; 154.08; 158.25. MS: 1343.41 [M+22]⁺.

4.4. Computational details

The geometry of **7** was calculated without any symmetry constraints using the gradient-corrected exchange functional developed by Perdew, Burke and Ernzerhof in combination with a correlation functional, developed also by the same authors, and denoted as PBE/PBE.^[26] The 6-31G(d,p) basis set^[27] was employed throughout this study. For the stationary point, the Hessian was evaluated in order to characterize the genuine minima (no imaginary frequency). Natural population analysis (NPA) and natural bond orbital (NBO) analysis^[28] were performed at the same level of theory as the one used for geometry optimization. For the calculations, the Gaussian 03 suite of programs was used^[29]. QTAIM (Quantum Theory of Atoms In Molecules) analysis of the wave function was carried out with the AIM2000 software^[30] to investigate the electron density of the optimized structure.

4.5. Host-guest complexation experiments

The host-guest complex formation ability of two deepened cavitands (**7** and **8**) towards 4-chloro-benzotrifluoride (**13**) was investigated with photoluminescence (PL) method in chloroform. Samples containing 10⁻⁴ M of **7** or **8** were prepared for these experiments, and the PL spectra of the host molecules were recorded both in the absence and in the presence of 4-chloro-benzotrifluoride as a guest. The concentration of the guest was varied from 1x10⁻⁴ M up to 9x10⁻⁴ M through 1x10⁻⁴ M steps. The samples were excited at 395 nm and the PL peak of the host obtained at 430 nm was used for data evaluation. A highly sensitive Fluorolog τ3 spectrofluorometric system (Jobin-Yvon/SPEX) was used, for data collection; a photon counting method with 0.2 s integration time was applied. Excitation and emission bandwidths were set to 1 nm. 1 mm layer thickness of the fluorescent probes with front face detection was used to eliminate the inner filter effect. The stoichiometry of the formed complexes was

checked by the Job's method. The Benesi – Hildebrand method was employed to determine the stability constants at all temperatures.^[31] The van't Hoff theory was applied to calculate the thermodynamic parameters of the interactions.

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References

- [1] D.J. Cram, *Nature* **1992**, 356, 29-36.
- [2] D.J. Cram, J.M. Cram, *Container Molecules and their Guests*; Royal Society of Chemistry: Cambridge, 1994.
- [3] D.J. Cram, M.E. Tanner, R. Thomas, *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1024-1027.
- [4] D.M. Vriezema, M.C. Aragoes, J.A.A.W. Elemans, J.J.L.M. Cornelissen, A.E. Rowan, R.J.M. Nolte, *Chem. Rev.* **2005**, 105, 1445-1489.
- [5] a) D.J. Cram, S. Karbach, Y.H. Kim, L. Baczynskyj, G.W. Kallemeyn, *J. Am. Chem. Soc.* **1985**, 107, 2575-2576; b) D.J. Cram, S. Karbach, Y.H. Kim, L. Baczynskyj, K. Marti, R.M. Sampson, G.W. Kallemeyn, *J. Am. Chem. Soc.* **1988**, 110, 2554-2560.
- [6] a) R. Warmuth, J. Yoon, *Acc. Chem. Res.* **2001**, 34, 95-105; b) A. Jasat, J.C. Sherman, *Chem. Rev.* **1999**, 99, 931-967.
- [7] X. Liu, R. Warmuth, *J. Am. Chem. Soc.* **2006**, 128, 14120-14127.
- [8] a) T. Heinz, D.M. Rudkevich, J. Rebek, Jr., *Angew. Chem. Int. Ed. Eng.* **1999**, 38, 1136-1139; b) L.R. MacGillivray, J.L. Atwood, *Nature* **1997**, 389, 469-472; c) G.W.V. Cave, M.C. Ferrarelli, J.L. Atwood, *Chem. Commun.* **2005**, 2787-2789; d) L.R. MacGillivray, P.R. Diamante, J.L. Reid, J.A. Rippmeester, *Chem. Commun.* **2000**, 359-360; e) B. Botta, M. Cassani, I. D'Acquarica, D. Subissati, G. Zappia, G. Delle Monache, *Curr. Org. Chem.* **2005**, 9, 1167-1202.
- [9] a) J.R. Moran, S. Karbach, D.J. Cram, *J. Am. Chem. Soc.* **1982**, 104, 5826-5828; b) D.J. Cram, S. Karbach, H.E. Kim, C.B. Knobler, E.F. Maverick, J.L. Ericson, R.C. Helgeson, *J. Am. Chem. Soc.* **1988**, 110, 2229-2237.
- [10] P. Timmerman, W. Verboom, D.N. Reinhoudt, *Tetrahedron* **1996**, 52, 2663-2704.

- [11] a) S. Ma, D.M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 4977-4981, b) C.B. Aakeröy, N. Schultheiss, J. Desper, *Org. Lett.* **2006**, *12*, 2607-2610.
- [12] a) J.R. Moran, J.L. Ericson, E. Dalcanale, J.A. Bryant, C.B. Knobler, D.J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 5707-5714; b) F.C. Tucci, D.M. Rudkevich, J. Rebek, Jr. *J. Org. Chem.* **1999**, *64*, 4555-4559.
- [13] a) S.D. Starnes, D.M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.*, **2001**, *123*, 4659-4669; b) F.C. Tucci, A.R. Renslo, D.M. Rudkevich, J. Rebek, Jr. *Angew. Chem. Int. Ed.* **2000**, *39*, 1076-1079.
- [14] a) E.S. Barrett, J.L. Irwin, K. Picker, M.S. Sherburn, *Aust. J. Chem.* **2002**, *55*, 319-325; b) H. Boerrigter, W. Verboom, G.J. van Hummel, S. Harkema, D.N. Reinhoudt, *Tetrahedron Lett.* **1996**, *37*, 5167-5170.
- [15] L.M. Tunstad, J.A. Tucker, E. Dalcanale, J. Weiser, J.A. Bryant, J.C. Sherman, R.C. Helgeson, C.B. Knobler, D.J. Cram, *J. Org. Chem.* **1989**, *54*, 1305-1312.
- [16] E. Roman, C. Peinador, S. Mendoza, A.E. Kaifer, *J. Org. Chem.* **1999**, *64*, 2577-2578.
- [17] T.N. Sorrell, F.C. Pigge, *J. Org. Chem.* **1993**, *58*, 784-785.
- [18] E.E. Dueno, K.S. Bisht, *Tetrahedron* **2004**, *60*, 10859-10868.
- [19] S. Pellet-Rostaing, L. Nicod, F. Chitry, M. Lemaire, *Tetrahedron Lett.* **1999**, *40*, 8793-8796.
- [20] R. Wu, T.F. Al-Azemi, K.S. Bisht, *Chem. Commun.* **2009**, 1822-1824.
- [21] P. Hobza, H.L. Selzle, E.W. Schlag, *J. Am. Chem. Soc.* **1994**, *116*, 3500-3506.
- [22] E. Espinosa, E. Molins, C. Lecomte, *Chem. Phys. Lett.* **1998**, *285*, 170-173.
- [23] T. Higashi (1998), NUMABS, rev. **2002** (Rigaku/MSI Inc.).
- [24] G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112-122.
- [25] A.L. Spek, *J. Appl. Cryst.* **2003**, *36*, 7-13.
- [26] J.P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865-3868.
- [27] W.J. Hehre, R. Ditchfield, J.A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257-2261.
- [28] NBO Version 3.1, E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold.
- [29] *Gaussian 03, Revision B.05*, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P.

1
2
3 Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O.
4 Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G.
5 Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I.
6 Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M.
7 Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, and J.A. Pople,
8 Gaussian, Inc., Pittsburgh PA, **2003**.
9
10 [30] F.W. Biegler-König, J. Schönbohm, AIM2000, 2.0 ed.; Büro für Innovative Software:
11 Bielefeld, Germany, **2002**.
12
13 [31] H. Benesi, J. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703-2707.
14
15
16
17
18
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20
21
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Tables

Table 1. Characteristic bond distances (Å) and torsion angles (°). Atoms marked with *a* indicate neighbouring structural units.

C1-C2	1.399(7)	C1-C6	1.400(7)
C2-C3	1.376(7)	C5-C6	1.388(7)
C3-C4	1.399(7)	C4-C5	1.398(7)
C2-O1	1.398(6)	C6-O3	1.405(6)
C3-C15	1.536(7)	C15-C16	1.531(7)
O1-C14	1.418(6)	C1-C7	1.509(6)
C7-O4	1.438(5)	O4-C8	1.344
C8-C13	1.390	C13-C12	1.390
C12-C11	1.390	C11-C10	1.390
C10-C9	1.390	C9-C8	1.390
C4-C3-C15-C6 ^a	92.5(5)	C4-C5-C15 ^a -C3 ^a	93.3(5)
C1-C2-O1-C14	98.8(5)	C2-O1-C14-O3 ^a	-92.0(5)
O1-C14-O3 ^a -C6 ^a	91.4(5)	C14-O3 ^a -C6 ^a -C1 ^a	100.9(5)

Captions

Scheme 1. Synthetic route for the deepened cavitands.

Scheme 2. Synthesis of tetrakis(4-phenyl-phenoxy)methylcavitand (**12**).

Figure 1. Partial ^1H -NMR spectra of **5-9** and **11**, **o** and **x** denote the spacer methylene and CHCH_3 protons, respectively (* stands for the residual protons of CH_2Cl_2).

Figure 2. a.) Molecular diagram of **7** with the atomic numbering (hydrogen atoms are omitted for clarity). Atomic displacement ellipsoids represent 40% probabilities.

b.) Top-view of the molecule. Symmetry generated parts are drawn in green, blue and red colours. Carbon atoms are denoted by bare numbers.

Figure 3. Structure of **7** computed at the PBE/PBE/6-31G(d,p) level of theory.

Selected bond distances are in Å. NPA charges are written in italics.

Figure 4. Molecular graph of **7** (top view). The color scheme identifying the critical points is as follows: red for bond critical points (BCPs); yellow for ring critical points (RCPs) and green for cage critical points (CCPs). The nuclear maxima are denoted by larger spheres.

Figure 5. Laplacian distribution of **7** illustrating the “T-shaped” interaction between two phenyl rings. Solid lines indicate charge concentrations ($\nabla^2\rho(\mathbf{r}) < 0$) whereas dashed lines ($\nabla^2\rho(\mathbf{r}) > 0$) show charge depletions. Bond critical points are indicated with dark grey, whereas the ring critical point is light grey. Bond paths (lines of maximum electron density) linking nuclei and zero-flux surfaces (which partition the molecule into its constituent atoms) are designated with solid lines.

Figure 6. Job's plot of the interaction of host **8** with 4-chloro-benzotrifluoride (**13**).

Scheme 1. Synthetic route for the deepened cavitands.

Scheme 2. Synthesis of tetrakis(4-phenyl-phenoxy)methylcavitand (12).

Figure 1. Partial ^1H -NMR spectra of 5-9 and 11, o and x denote the spacer methylene and CHCH_3 protons, respectively (* stands for the residual protons of CH_2Cl_2).

Figure 2. a.) Molecular diagram of 7 with the atomic numbering (hydrogen atoms are omitted for clarity). Atomic displacement ellipsoids represent 40% probabilities.
b.) Top-view of the molecule. Symmetry generated parts are drawn in green, blue and red colours. Carbon atoms are denoted by bare numbers.
138x75mm (600 x 600 DPI)

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80x79mm (300 x 300 DPI)

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81x48mm (600 x 600 DPI)

Figure 6. Job's plot of the interaction of host 8 with 4-chloro-benzotrifluoride (13).
292x204mm (150 x 150 DPI)