Design and Synthesis of a New Kind of Cavitand: Tetrapyrazolylcalix[4]arenes and Their Supramolecular Assemblies

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Abstract: Two novel calix[4]arene-based tetrapyrazolyl cavitands with different cavity size were synthesized by multistep reactions. In the solid state, one of the cavitands forms an infinite chain by intermolecular hydrogen bonding. The other cavitand undergoes coordination self-assembly with dimetal corners to form a supramolecular cage.

Key words: cavitands, calixarenes, hydrogen bonding, self-assembly, macrocycles

Over the past 30 years, the chemistry of container molecules has become one of the most exciting and challenging fields of research in organic chemistry.[1] In 1983, Cram introduced the concept of a closed-surface binding host, and synthesized the first examples of organic container molecules, which were named 'carcerands'. Carcerands are defined by the size of their inner cavities and they have various applications in supramolecular chemistry.[1] There is considerable demand for easily available and synthetically versatile building blocks for the construction of receptor molecules with high degrees of complexity and specific supramolecular functions.[2] As a new class of useful building blocks, the calixarenes have been recognized as promising candidates for the construction of molecular receptors, molecular devices, molecular switch systems, supramolecular materials, and the like.[3,4] Calixarenes can be easily prepared by a one-pot reaction of phenol with formaldehyde, and they can be selectively functionalized on the upper and/or lower rim.

Among various functional building blocks, pyrazoles have found a wide range of applications in the pharmaceutical and agrochemical industries, in nonlinear optical materials, in photography, and in host–guest chemistry.[5] Because of their varied coordination modes, pyrazoles play important roles in inorganic, organometallic, and materials chemistry,[6] and they can be used to construct pyrazolate-bridged multimetal and metal–metal bonding coordination systems.[5,6] In view of the potential applications of pyrazolate-bridged multimetal-coordination macrocyclic and cage-like hosts,[7] we have devoted great efforts to the design and synthesis of novel polypyrazolate-functionalized calixarenes that can be used to build new types of metal–organic functional supramolecular architectures, including metallo-macrocycles, molecular capsules, and metallo-cages.[6]

Important methods for the synthesis of polypyrazolate heterocycles included approaches based on the condensation of hydrazines with β-difunctional compounds or 1,3-dipolar cycloaddition reactions of diazo compounds.[5] For example, Ramirez et al.[6b] developed a strategy for preparing β-diketones and their derivatives through the reaction of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2λ^5-dioxaphospholе with aromatic aldehydes, followed by a molecular rearrangement in methanol.

Here, we report the synthesis of two upper-rim functionalized pyrazolylcalix[4]arenes **1** and **2** (Figure 1) with an all-*cone* conformation through multistep reactions. Cavitand **1** forms an infinite chain in the solid state by intermolecular hydrogen bonding. Coordination self-assembly of cavitand **2** with a dimetal motif results in the formation of a supramolecular cage.

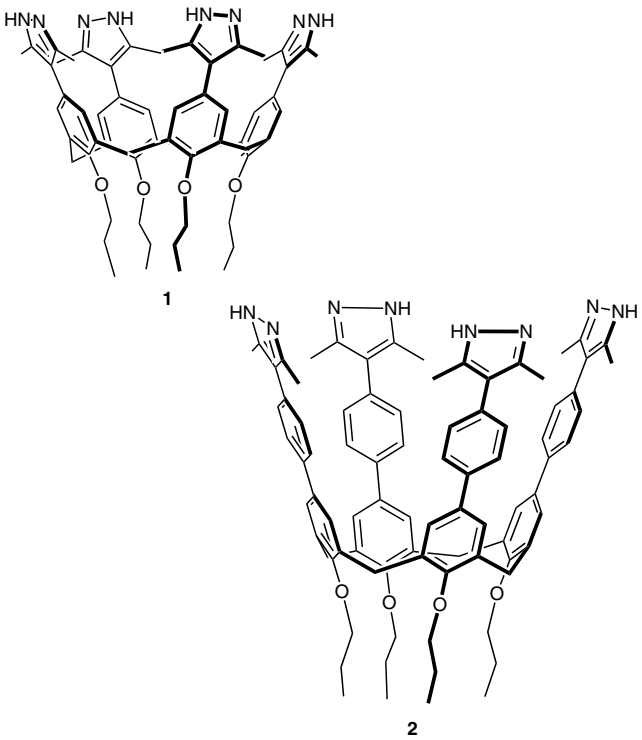

Figure 1 The structures of the *cone*-tetrapyrazolylcalix[4]arene cavitands **1** and **2**

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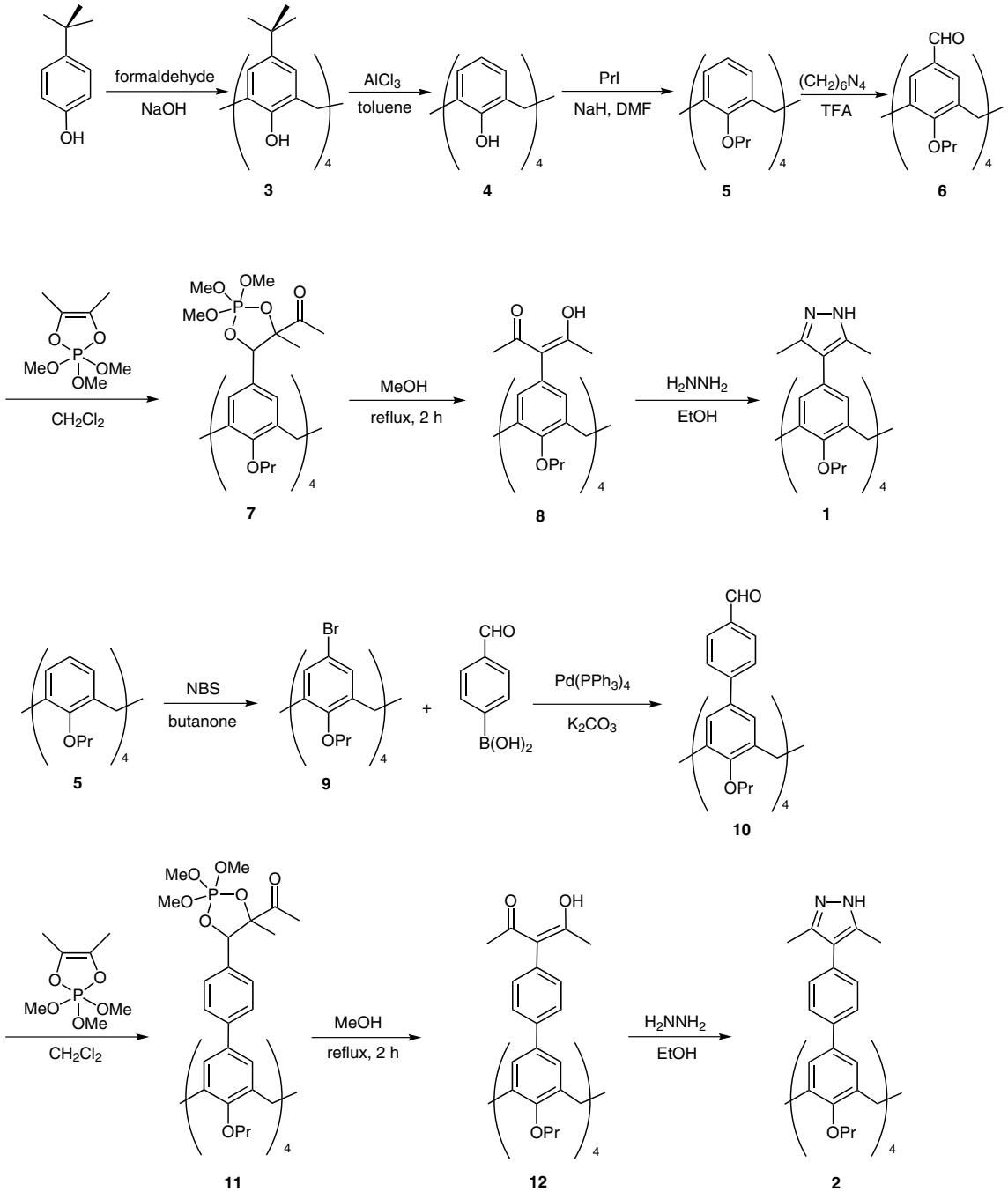
The synthesis of compounds **1** and **2** is shown in Scheme 1. Compounds **3**–**6** were prepared according to reported procedures.[2,8] The tetraformylated calix[4]arene **6** reacted with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2λ^5-dioxaphosphole in dichloromethane at room temperature to give the polyphosphorane **7**. The use of a tenfold excess of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2λ^5-dioxaphosphole and a relatively higher temperature (60 °C) promoted the reaction toward compound **7**, which could be further transformed into the desired tetraenol tetraketone **8** in 40% yield in a similar manner to that described in the literature.[6] The key intermediate **8** was treated with hydrazine hydrate in ethanol at room temperature to give 5,11,17,23-tetrakis(3,5-dimethyl-1*H*-pyrazol-4-yl)-25,26,27,28-tetrapropoxycalix[4]arene (**1**) as a white powder in 89% yield.

A new cavitand **2** with a deeper cavity was prepared by a route based on the optimized procedure for the synthesis of cavitand **1**. To expand the internal cavity, four phenyl rings were introduced as spacers on the upper rim of the calix[4]arene backbone through a Suzuki cross-coupling reaction of (4-formylphenyl)boronic acid with *cone*-5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene (**9**) in the presence of tetrakis(triphenylphosphine)palladium as a catalyst in toluene at 80 °C to give the desired compound **10** with *cone*-conformation in 65% yield.



Scheme 1 The synthesis of tetrakis(3,5-dimethyl-1*H*-pyrazol-4-yl)calix[4]arene-based compounds **1** and **2**

Compound **11** was synthesized by a similar route to compound **7**. Subsequent methanolysis provided a mixture of mono-, di-, tri-, and tetra-β-diketone derivatives of calix[4]arenes. Column chromatography on silica gel and subsequent recrystallization separated and purified the tetraenol tetraketo calixarene **12** in a low yield. Condensation of compound **12** with hydrazine hydrate in ethanol at room temperature gave 5,11,17,23-tetrakis[4-(3,5-dimethyl-1*H*-pyrazol-4-yl)phenyl]-25,26,27,28-tetrapropoxycalix[4]arene as a white powder. Calixarenes **1** and **2** were characterized by means of ^{1}H and ^{13}C NMR spectroscopy, MALDI-TOF mass spectroscopy, X-ray single-crystal diffraction, and elemental analysis.[9]

Small pyrazoles are widely used in the construction of supramolecular oligomers with multiple protons transfers through kinetic hydrogen bonds in various interaction modes.[5] In this work, the two tetrapyrazolylcalixarenes-based cavitands of different size were used as independent hydrogen-bonding units for the self-assembly of supramolecular architectures in solution. Suitable single crystals of compound **1** were obtained by vapor diffusion of ethyl acetate into a solution of **1** in dimethyl sulfoxide–acetonitrile at room temperature. Synchrotron X-ray structural analysis revealed that compound **1** crystallized in the monoclinic space group C2/c and exhibited an interesting linear chain structure with multiple intermolecular hydrogen bonds.[10] A ball-and-stick diagram of **1** is shown in Figure 2 and in the Supporting Information (Figure S14); two neighboring chains were arranged a crosswise manner in the two-dimensional sheet-like structure by a self-complementary effect in the solid state (Supporting Information; Figure S15).

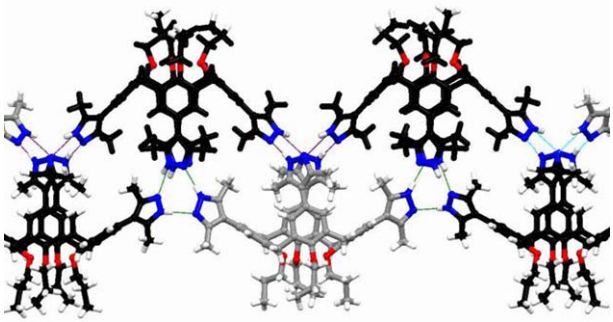


Figure 2 The crystal structure of tetrapyrazolylcalix[4]arene **1** containing multiple hydrogen bonds; light gray and black: carbon; blue: nitrogen; red: oxygen; white: hydrogen

The separation of the two opposite pyrazolyl groups (centroid to centroid) in the 1- and 3-positions (4.199 Å) is markedly different from those in the 2- and 4-positions (13.39 Å), indicating that the calix[4]arene-based linker adopts a 1,3-contracted 2,4-expanded conformation. Furthermore, three tetrapyrazolylcalixarene moieties in the asymmetric unit of **1** are held together by triple and quadruple cyclic hydrogen bonds, leading to the formation of triangular and saddle-shaped N′–H–N donor–acceptor hydrogen bonding motifs (Figure 3). The average $N'_D \cdots N_A$ distance of about 2.75 Å is shorter than the sum of their van der Waals radii, which suggests the presence of strong intermolecular hydrogen-bonding interactions. As a result of the flexibility of the calix[4]arene backbone, a pinch-cone configuration is favorably adopted in the self-assembly of the one-dimensional chains.

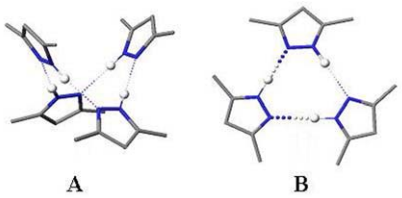


Figure 3 Hydrogen-bonding motifs in the tetrapyrazolylcalix[4]arene cavitand **1**

Besides the hydrogen-bonding self-assembly of compound **1** in solution, the larger cavitand **2** was initially used as a functional organic ligand to prepare complex **13**.[8] As shown in the Supporting Information (Scheme S1), the dimetal corner $[(bpy)_2Pd_2(NO_3)_2](NO_3)_2$ (38.5 mg, 0.05 mmol) was added to a suspension of compound **2** (32.1 mg, 0.025 mmol) in water (10 mL), and the mixture was stirred for four hours at room temperature. Acetone (3 mL) was then added and the mixture was stirred for 72 hours at 90 °C. The resulting clear solution was evaporated to dryness to give yellow microcrystals. The hexafluorophosphate salt of complex **13** was quantitatively prepared by exchange with a tenfold excess of potassium hexafluorophosphate in aqueous solution at 60 °C. Pure **13**·$8PF_6^-$ was obtained as a yellow microcrystalline solid by the vapor diffusion of diethyl ether into a solution of **13** in acetonitrile at room temperature. NMR spectroscopy indicated the formation of a single product. As shown in the temperature-dependent ^{1}H NMR spectrum of **13**·$8PF_6^-$ (Supporting Information; Figures S10 and S11), the signals at 3.27 to 4.63 ppm were assigned to methylene hydrogen atoms from the calix[4]arene ligands, whereas the protons of the bipyridyl ligand presented four sets of signals at 8.0–9.0 ppm in the downfield region. The corresponding resonances observed at 6.61, 7.32, and 8.18 ppm were ascribed to the protons of aromatic groups of the calix[4]arene backbone. Further evidence for the formation of cage **13**·$8PF_6^-$ was given by the CSI–TOF mass spectrum (Supporting Information; Figure S13), in which the featured peaks corresponding to the fragments with a general formula of $[M - (bpy)_2Pd_2 - n(PF_6^-) + 2H_2O + MeCN]^{n+}$ (n = 3, 4, 5, 6; M = **13**·$8PF_6^-$). The correlated ion peaks were observed at m/z = 1542.02 $[M - 3(PF_6^-)]^{3+}$ (calcd: 1542.28), 1120.03 $[M - 4(PF_6^-)]^{4+}$ (1120.46), 867.04 $[M - 5(PF_6^-)]^{5+}$ (867.38), and 698.53 $[M - 6(PF_6^-)]^{6+}$ (698.93).

On the basis of the results of the NMR spectroscopy and the CSI–TOF mass spectrometric analyses of **13**·$8PF_6^-$ in solution, we tentatively proposed a possible conformation of a dimeric metallo-capsule $\{[(bpy)Pd]_8L_4\}(PF_6^-)_8$ (where L is the deprotonated compound **2**) with a deep

cavity built through a metal-directed self-assembly, involving spontaneous deprotonation of the 1*H*-tetrapyrazolyl ligands. Therefore, by using the CAChe 6.1.1 program, we constructed a visual model of the molecular structure to evaluate the size and shape of **13**. Cage **13** has a molecular dimension of 22.9 × 19.4 × 19.2 Å and an interior void volume of 4331 Å^3, as shown in Figure 4.

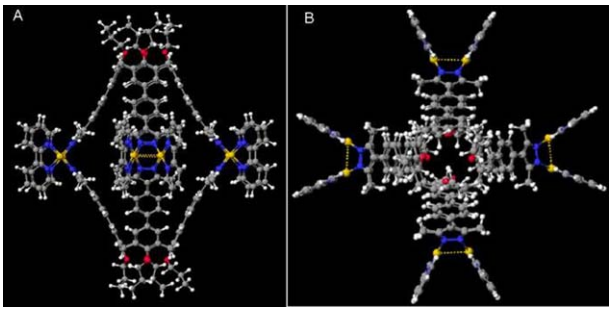


Figure 4 The modeled structure of the organometallic supramolecular cage **13**·8PF_6^- produced by using the CaChe 6.1.1 program. The model is constructed from the deprotonated cavitand **2** and the dimetal coordination corners, and is drawn as a ball-and-stick model. (A: side view; B: top view; light gray and black: carbon; blue: nitrogen; red: oxygen; white: hydrogen; yellow: palladium).

In conclusion, we synthesized several novel *cone*-tetra-β-diketone and tetrapyrazolyl calix[4]arenes compounds **8**, **1**, **12**, and **2** from simple starting materials. All new compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and CSI–TOF and MALDI–TOF mass spectrometry. Compound **1** self-assembled to form a one-dimensional chain through multiple intermolecular hydrogen bonds in the solid state. Compound **2** was used to construct a metallo-cage compound with a proposed [Pd_8L_2]-type structure containing a deep cavity with dimetal corners. These cage-shaped compounds and complexes with deep cavities might serve as hosts for small guest molecules and anions. The self-assembly and related function of tetrapyrazolyl compounds as bridging ligands in metal-directed self-assembly are currently under investigation.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **5,11,17,23-Tetrakis(3,5-dimethyl-1*H*-pyrazol-4-yl)-25,26,27,28-tetrapropoxycalix[4]arene (1)**
White powder; yield: 546 mg (85%); mp 285–289 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C): δ = 11.86 (s, 4 H, HN-pyrazole), 6.64 (s, 8 H, H-Ar), 4.44 and 3.24 (d, *J* = 12.1 Hz, 8 H, Ar-CH_2-Ar), 3.82 (t, *J* = 8.6 Hz, 8 H, ArO$CH_2CH_2CH_3$), 2.03 and 1.62 (s, 24 H, pyrazole-CH_3), 1.96 (ψ-sextet, 8 H, $ArOCH_2CH_2CH_3$), 0.98 (t, *J* = 8.4 Hz, 12 H, $ArOCH_2CH_2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 135.6, 134.3, 128.9, 118.41, 79.26, 56.59, 23.31, 18.63, 10.52; MS (MALDI–TOF, MeOH): *m/z*: calcd for [M + Na]$^+$ 991.56; found 991.6.
5,11,17,23-Tetrakis[4-(3,5-dimethyl-1*H*-pyrazol-4-yl)phenyl]-25,26,27,28-tetrapropoxycalix[4]arene (2)
White power; yield: 55 mg (75%); mp 233–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 12.19 (s, 4 H, HN-pyrazole), 7.34 (s, *J* = 8.8 Hz, 8 H, phenyl-H), 7.01–7.08 (d, *J* = 8.4 Hz, 8 H, phenyl-H), 6.98 (s, 8 H, calixarene-Ar-H), 4.51 and 3.43 (d, *J* = 7.8 Hz, 8 H, ArCH_2Ar), 3.98 (d, *J* = 12.8 Hz, 8 H, ArO$CH_2CH_2CH_3$), 2.17 (s, 24 H, pyrazole-CH_3), 1.97–2.01 (4-sextet, *J* = 8.0 Hz, 8 H, $ArOCH_2CH_2CH_3$), 1.00 (t, *J* = 7.4 Hz, 12 H, $ArOCH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.32, 146.72, 135.55, 134.46, 133.56, 129.92, 127.26, 126.74, 31.33, 23.34, 10.38. MS (MALDI–TOF, MeOH–DMSO): *m/z*: calcd for [M + H_2O + H^+]: 1291.7; found: 1290.1. Anal Calcd for $C_{84}H_{88}N_8O_4·2H_2O$: C, 77.03; H, 7.08; N, 8.56. Found: C, 77.11, H, 7.06; N, 8.52.

(10) Crystallographic data for compound **1** have been deposited with the accession number CCDC 928591, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.