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Novel Concave Building Block for the Synthesis of Organic Hosts

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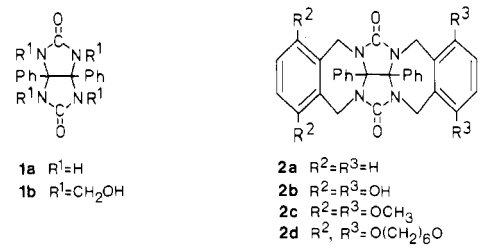
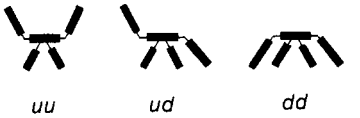
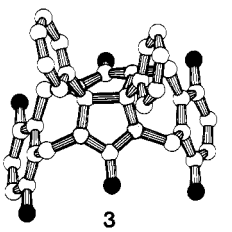
Natural hosts frequently contain a cavity or cleft whose inner concave surface matches the convex surface of a guest.[2] Recently, synthetic hosts that mimic this feature (cavitands[3a]) have been designed.[3,4] If new and more elaborate host-guest systems are to be developed, versatile and readily accessible building blocks must be available. Here, we describe a novel building block, **2**, that meets these requirements. Compound **2** contains two fused 2-imidazolidone rings, which are flanked by two *o*-xylylene units. Its overall shape is concave and its convex side is shielded by two phenyl substituents. The use of **2** in the synthesis of three new cavitands is demonstrated.[4]

Diphenylglycoluril (**1a**)[5a] was treated with paraformaldehyde and NaOH in Me_2SO to yield the tetrakis(hydroxymethyl) derivative **1b** (85%).[5b] Refluxing **1b** in benzene with 4 equiv of *p*-toluenesulfonic acid gave **2a** in 35% yield. Similarly, treatment of **1b** with an excess of hydroquinone or 1,4-dimethoxybenzene in 1,2-dichloroethane gave **2b** (75%) and **2c** (50%), respectively. Molecular models indicate that the *o*-xylylene units of **2** can have upward (*u*) or downward (*d*) orientations, leading to three possible conformers: *uu*, *ud*, or *dd*. Molecular mechanics calculations reveal that conformer *uu* has the lowest energy.[6] For compound **2b** an X-ray structure determination was performed.[7,8] This structure determination (**3**) confirms the *uu* conformation of **2** in the solid state.



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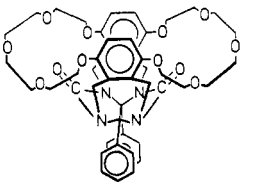
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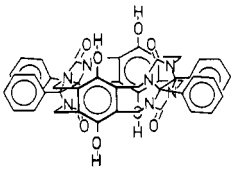
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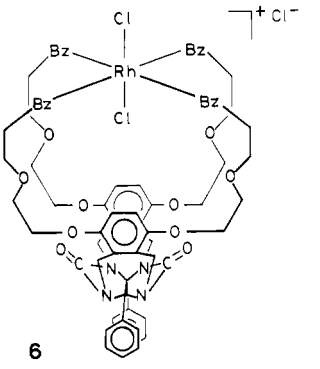

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The ^1H NMR spectrum of fully acetylated **2b** in CD_2Cl_2 and in Me_2SO-d_6 displays one pair of well-defined doublets for the CH_2 protons at δ 5.05 and 3.85 (J = 16 Hz). The position and splitting pattern of the doublets did not change over a temperature range as large as −95 to 150 °C. This led us to believe that either one conformer (*uu* or *dd*) is present or that all three conformers interconvert rapidly. To solve this question we synthesized compound **2d**. The $(CH_2)_6$ bridges of this compound do not allow for any other conformation than *uu*. As the ^1H NMR spectra of **2d** and its nonbridged analogue **2c** show identical pairs of doublets for the CH_2N protons (±0.05 ppm), we conclude that compounds **2** also adopt the *uu* conformation in solution.

Basket-shaped cavitand **4** was prepared (75%) by treating **2b** with 2 equiv of 1,11-dichloro-3,6,9-trioxaundecane and K_2CO_3 in Me_2SO.[8] The oxygen atoms of the urea units and the oxyethylene bridges form two receptor sites at the far ends of the molecule. These receptor sites bind alkali metal ions with affinities peaking for K^+.[9] Cavitand **4** forms strong 1:1 complexes with protonated diamines e.g., $\{H_3N(CH_2)_6NH_3\}^{2+}$.[9] In these complexes the guest is wedged in between the *o*-xylylene rings as is concluded from the observed upfield shifts (up to 1.5 ppm) of the guest CH_2 protons in the ^1H NMR spectrum.

Refluxing **1b** and hydroquinone (molar ratio 1:1) in 1,2-dichloroethane in the presence of 4 equiv of *p*-toluenesulfonic acid produced cavitand **5** (3%, yield not optimized).[10] Compound **5**

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(7) Crystal data for **2b**: $C_{32}H_{26}N_4O_6 \cdot 5Me_2SO$, $P\bar{1}$, Z = 2, a = 9.129 (1) Å, b = 16.097 (1) Å, c = 16.218 (1) Å, α = 101.52 (1)°, β = 96.83 (1)°, γ = 90.57 (1)°, current R = 0.16. Details will be published elsewhere.

(8) Compound **2b**: IR (KBr) 3350, 2900, 1720, 1690, 1475, 1450 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.67 (s, 4 H, OH), 7.10 (s, 10 H, Ar H), 6.47 (s, 4 H, Ar H), 5.37 and 3.57 (2 d, 8 H, CH_2, J = 16 Hz); FAB MS (glycerol, thioglycerol, acetic acid), m/e 563 $(M + H)^+$. Fully acetylated **2b**: ^1H NMR (CD_2Cl_2) δ 7.09 (s, 10 H, Ar H), 6.92 (s, 4 H, Ar H), 5.05 and 3.85 (2 d, 8 H, CH_2, J = 16 Hz), 2.34 (s, 12 H, CH_3CO); FAB MS (triethyl citrate), m/e 731 $(M + H)^+$. Compound **4**: IR (KBr) 2910, 2860, 1715, 1475, 1450, 1130, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (s, 10 H, Ar H), 6.65 (s, 4 H, Ar H), 5.65 (d, 4 H, NC*H*HAr, J = 16 Hz), 3.50-4.35 (m, 36 H, NCH*H*Ar and OCH_2CH_2); FAB MS (triethyl citrate), m/e 879 $(M + H)^+$. Compound **5**: FAB MS (glycerol, H_2SO_4), m/e 905 $(M + H)^+$. Fully acetylated **5**: IR (KBr) 3605 and 3555 (bound H_2O), 3940, 1760, 1730, 1645, 1465, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (s, 20 H, Ar H), 4.93 and 3.82 (2 d, 16 H, CH_2, J = 16 Hz), 2.54 (s, 12 H, CH_3CO); FAB MS (triethyl citrate), m/e 1073 $(M + H)^+$. Compound **6**: UV-vis (Me_2SO) 413 nm (ϵ 223); ^1H NMR (Me_2SO-d_6) δ 8.45 (s, 4 H, NCHN), 7.65 and 7.10 (2 m, 26 H, ArH), 6.60 (s, 4 H, Ar H), 5.40 (d, 4 H, NC*H*HAr, J = 16 Hz), 4.40 (m, 8 H, OCH_2CH_2N), 3.5-4.0 (m, 28 H, NCH*H*Ar and $OCH_2CH_2OCH_2$); FAB MS (glycerol, thioglycerol), m/e 1522 M^+, 1487 $(M - Cl)^+$, 1452 $(M - 2Cl)^+$, 1418 $(M - 3Cl + H)^+$, 1316 $(M - RhCl_3 + H)^+$; conductivity measurements (Me_2SO, 10^{-3} M): 1:1 electrolyte, Λ 34 Ω^{-1} cm^2 mol^{-1}. All compounds gave C, H, and N analyses within 0.3% of theory.

(9) Binding free energies of picrate salt guests of **4** at 25 °C in $CHCl_3$ ($-\Delta G°$/kcal mol^{-1} for 1:1 complex): Li^+, 8.45; Na^+, 8.95; K^+, 11.45; Rb^+, 10.50; Cs^+, 9.25; NH_4^+, 9.50; $\{H_3N(CH_2)_5NH_3\}^{2+}$, 15.0; $\{H_3N(CH_2)_6NH_3\}^{2+}$, 16.0.

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contains two diphenylglycoluril and two hydroquinone rings linked through eight methylene bridges. The void in **5** (2.5 × 2.0 Å) is not large enough to hold an organic guest. However, higher homologues of **5**, e.g., those containing additional diphenylglycoluril and hydroquinone rings, do have large enough voids.[10]

Starting from **2**, hosts that have a metal center next to a cavity are readily accessible. As an example, we prepared **6** by reacting **2b** successively with: excess of $Tos(OCH_2CH_2)_2Cl$ and base in Me_2SO, excess of benzimidazole (Bz) and NaH in DMF, and 1 equiv of $RhCl_3$ in Me_2SO (overall yield 70%). Compound **6** has two trans-coordinated Cl ligands, one being inside the cavity, the other outside. The binding and catalytic properties of hosts **4-6** are currently being investigated and will be published in forthcoming papers.

Acknowledgment. We thank Prof. Wiendelt Drenth for stimulating discussions.

(10) In addition to **5** a compound is isolated which contains three diphenylglycoluril and three hydroquinone rings, linked through 12 methylene bridges (symmetry D_{3h}). The cavity of this cavitand has a diameter of ~5 Å. Sijbesma, R. P.; Smeets, J. W. H.; Nolte, R. J. M., unpublished results.

Observation of a Nonconcerted Double Proton Transfer in the Solid State by ^{15}N CPMAS NMR

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We present here for the first time NMR spectroscopic evidence of a nonconcerted double proton transfer. The double proton motion studied occurs along slightly asymmetric double-minimum potentials in solid TTAA[2] according to Scheme I. For H-chelates of the malonaldehyde type like TTAA, it has been very difficult to establish the double-minimum character of the proton potential using different spectroscopic techniques[3] including NMR.[4] Goedken et al.[5] have performed an X-ray crystallographic analysis of solid TTAA, have postulated the "diagonal" tautomerism **1** ⇌ **3** shown in Scheme I, and have further suggested that the degeneracy of this process is lifted due to a rhombic distortion of the unit cell. However, the X-ray method cannot reveal details such as the nonconcerted character of the double proton motion in TTAA or if the tautomerism is static or dynamic.

Since solid-state proton transfers between nitrogen atoms are most directly probed by ^{15}N CPMAS NMR,[6,7] we have performed such experiments on 95% ^{15}N-enriched TTAA.[8] Figure 1 shows some of the ^{15}N CPMAS spectra obtained with an apparatus described previously.[9] We observe four lines, a-d, of equal intensity. Between 100 and 80 K, the lowest temperature where experiments were performed, no spectral changes occur, indicating that the chemical shifts are temperature independent within experimental error. Taking into account ^{15}N solution NMR data,[10] we assign the overlapping lines a and d to NH atoms and the two resolved lines b and c to two inequivalent =N— atoms in solid TTAA. As the temperature is increased, lines d and c move toward each other without coalescing, as do lines a and b. The low-field shift of line a from 96 to 288 K matches the high-field shift of line b over the same temperature range. The same is true for lines d and c. Since the intrinsic chemical shifts are temperature independent, these changes can only be explained by fast proton transfer from atom a to b and from atom d to c. In other words, the position of line n depends on the average proton density p_n on atom n. The observed chemical shift difference $\delta_{mn} = \delta_m$

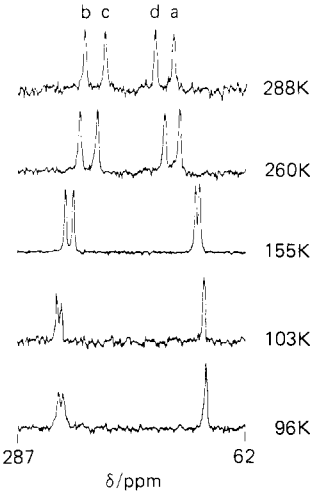
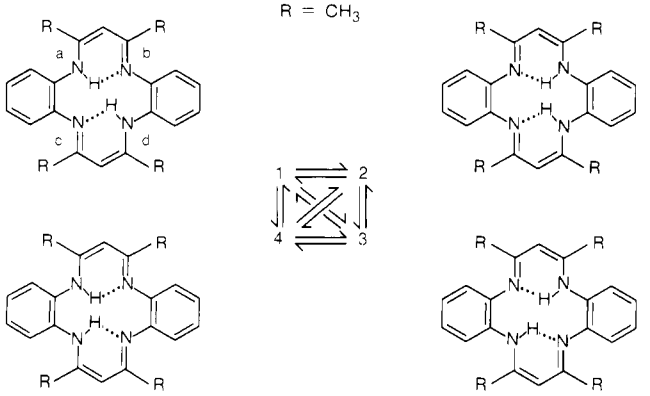


Figure 1. ^{15}N CPMAS NMR spectra of 95% ^{15}N-enriched TTAA at 6.082 MHz as a function of temperature: 10-Hz line broadening, 1K-4K zero filling, 25-ms cross-polarization time, 4000-Hz sweep width, 1.5-s repetition time, 9-μs $^1H-\pi/2$ pulses, quadrature detection, 1000 scans on the average; reference, external $^{15}NH_4NO_3$.

Scheme I



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(2) TTAA = 1,8-dihydro-5,7,12,14-tetramethyldibenzo[*b,i*]-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene-$^{15}N_4$ (tetramethyldibenzotetraaza(14)annulene).

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