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Complexation of Small Molecules by Open-Ended Resorcarene Hosts

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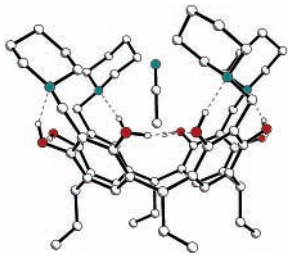
ABSTRACT



Sterically hindered tetraaminomethylated resorcarenes form inclusion complexes in $CDCl_3$ with acetonitrile and acetaldehyde, which are kinetically stable on the NMR time scale at 233 K.

Intramolecular hydrogen bonds have been widely used for preorganization of host molecules and self-assembled systems.[1] For example, resorcarene octols **1**, rigidified by four intramolecular hydrogen bonds, form in the solid state various open-ended inclusion complexes with small molecules,[2] as well as dimeric and hexameric capsular assemblies.[3] The cyclic array of hydrogen bonds is responsible for a high kinetic stability of inclusion complexes of self-folding octaamido cavitands with various adamantane derivatives and *N*-methylquinuclidinium cation.[4] It has been shown that readily available tetraaminomethylated resorcarene derivatives **2** and **3** adopt in the crystalline state a crown conformation stabilized by four intramolecular hydrogen bonds, while four pendant aminomethyl groups arranged in a chiral C_4-symmetrical fashion enlarge the intramolecular cavity of the resorcarene.[5] However, binding properties of compounds **2** and **3** in solution remain uncovered.

Herein we report on molecular recognition of acetonitrile and acetaldehyde by compounds **2** in $CDCl_3$.[6] It is shown that the kinetic stability of the 1:1 complexes is determined by the interplay of hydrogen bonding and steric effects.

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(1) For recent reviews on hydrogen bonding supramolecular systems, see: Prins, L.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382. Rudkevich, D. M. *Chem. Eur. J.* **2001**, *6*, 2679.

(2) MacGillivray, L. R.; Atwood, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6931. MacGillivray L. R.; Atwood, J. L. *Chem. Commun.* **1999**, 181. MacGillivray, L. R.; Spinney, H. I.; Reid, J. L.; Ripmeester, J. A. *Chem. Commun.* **2000**, 517.

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(6) For a recent review on the complexation of neutral molecules by calixarenes, see: Arduini, A.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Recognition of Neutral Molecules. Calixarene 2001.* Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer Academic Publisher: Dordrecht, Boston, London, 2001; pp 457−486.

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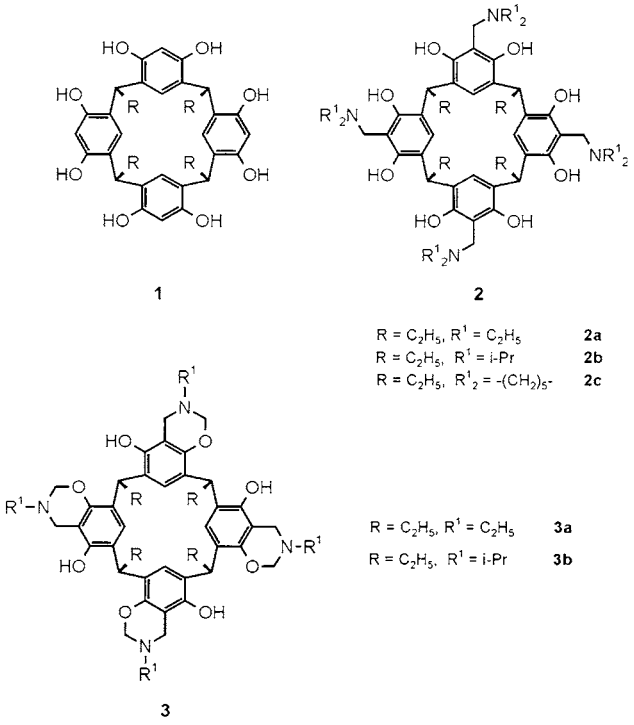

Aminomethylation of resorcarenes **1** with four molar equivalents of formaldehyde and secondary amines readily gives tetrasubstituted derivatives **2**,[7] which usually precipitate from the reaction mixture in analytically pure form. Slow crystallization of **2c** from the mixture of $CHCl_3$ and MeCN resulted in diffraction-quality single crystals.[8,9]

The molecule of **2c** adopts in the crystalline state a crown conformation stabilized by four intramolecular hydrogen bonds of length 2.66 Å (O−O distances) between neighboring hydroxyl groups (Figure 1). Four other hydroxy groups form intramolecular hydrogen bonds to the nitrogen atoms of the aminomethyl residues (O−N distances 2.52−2.59 Å). Such an arrangement makes the conformation inherently chiral and results in considerable enlargement of the cavity of the resorcarene. One acetonitrile molecule is included in this cavity with its methyl group pointing toward the π-basic socket of the resorcarene as a result of CH-π interactions with the resorcinol rings.

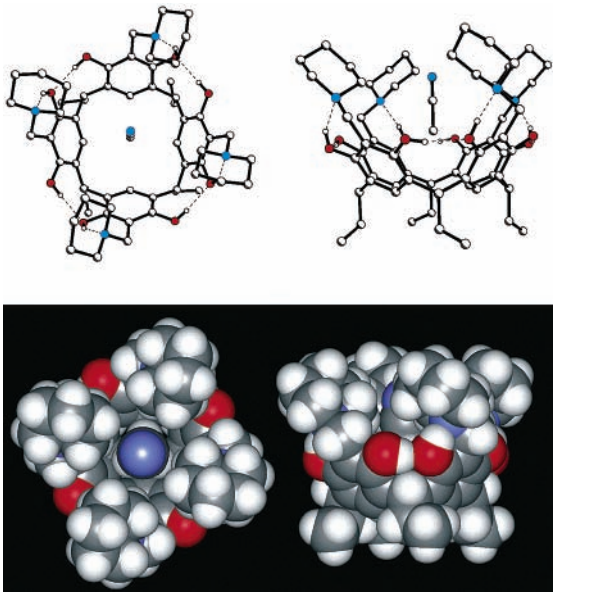

Figure 1. Crystal structure of **2c**·MeCN·2$CHCl_3$ in ball-and-stick and space filling presentation. Chloroform molecules are not shown. The hydrogen bonds are indicated in dotted lines. In the ball-and-stick presentation the CH-hydrogens are omitted for clarity.

The ^{1}H NMR spectrum of tetraamine **2b** measured in $CDCl_3$ at 303 K contains broadened resonances for the protons of hydroxyl groups centered at 10.0 and 16.0 ppm, respectively (Figure 2a). An AB quartet of the diastereotopic protons of the benzyl methylene groups and two sets of signals for the isopropyl protons characterize a C_4-symmetrical chiral conformation similar to that found in the crystalline state (Figure 1). Decrease of the temperature to 223 K does not change this pattern, whereas the OH protons emerge as sharp singlets at 16.0 and 9.7 ppm (Figure 2b). The former corresponds to the hydroxyls hydrogen bonded with amino groups, while the latter reflects the intramolecular hydrogen bonds between the resorcinol hydroxy groups.

Increase of the temperature to 330 K makes the rotation of the aminomethyl fragments fast on the NMR time scale. The ^{1}H NMR spectrum of **2b** at this temperature contains a singlet for the benzyl protons and one set of signals for the protons of the isopropyl protons in accordance with an average C_{4V}-symmetrical structucture. The barrier of the inversion could be determined on the basis of the signals

(7) **2a:** mp >300 °C; ^{1}H NMR ($CDCl_3$, 303 K, 250 MHz) δ 9.12 (br s, 8H), 7.10 (s, 4H), 4.22 (t, J = 7.0 Hz, 4H), 3.84 (m, 8H), 2.61 (m, 16H), 2.23 (m, 8H), 1.09 (t, J = 7.2 Hz, 24H), 0.95 (t, J = 7.0 Hz, 12H); ^{13}C NMR ($CDCl_3$, 303 K, 62.9 MHz) δ 153.3, 150.7, 123.9, 121.9, 107.9, 51.5, 46.5, 35.6, 26.6, 12.9, 11.1; MS (ESI-TOF) 942.18 $[M]^+$. **2b:** mp >300 °C; ^{1}H NMR ($CDCl_3$, 328 K, 250 MHz) δ 9.00 (br, 8H), 7.09 (s, 4H), 4.22 (t, J = 7.5 Hz, 4H), 3.90 (s, 8H), 3.16 (m, 8H), 2.22 (m, 8H), 1.11 (d, J = 7.4 Hz, 48H), 0.93 (t, J = 7.0 Hz, 12H); ^{13}C NMR ($CDCl_3$, 303 K, 62.9 MHz) δ 154.0, 151.6, 123.8, 121.7, 107.9, 48.4, 43.1, 35.5, 26.6, 19.3, 12.9; MS (ESI-TOF) 1053.60 $[M]^+$. **2c:** mp >300 °C; ^{1}H NMR ($CDCl_3$, 303 K, 250 MHz) δ 9.48 (br s, 8H), 7.07 (s, 4H), 4.17 (t, J = 7.3 Hz, 4H), 3.72 (s, 8H), 2.94 (br m, 16H), 2.19 (m, 8H), 1.59 (br m, 24H), 0.90 (t, J = 7.3 Hz, 12H); ^{13}C NMR ($CDCl_3$, 303 K, 62.9 MHz) δ 155.6, 123.9, 121.7, 107.5, 55.7, 53.6, 35.5, 26.4, 25.4, 23.7, 12.7; MS (ESI-TOF) 989.47 $[M]^+$. **3a:** mp >300 °C; ^{1}H NMR ($CDCl_3$, 303 K, 250 MHz) δ 7.73 (br, s, 4H), 7.11 (s, 4H), 4.94 (d, J = 9.8 Hz, 4H), 4.88 (d, J = 9.8 Hz, 4H), 4.10 (t, J = 7.8 Hz, 4H), 3.95 (d, J = 17.4 Hz, 4H), 3.79 (d, J = 17.4 Hz, 4H), 2.68 (m, 8H), 2.20 (m, 8H), 1.11 (t, J = 7.3 Hz, 12H), 0.91 (t, J = 7.2 Hz, 12H); ^{13}C NMR ($CDCl_3$, 303 K, 62.9 MHz) δ 149.8, 148.2, 124.2, 123.5, 121.1, 108.6, 82.7, 46.0, 45.7, 35.0, 26.7, 13.3, 12.7; MS (ESI-TOF) 877.36 $[M]^+$. **3b:** mp >300 °C; ^{1}H NMR ($CDCl_3$, 303 K, 250 MHz) δ 7.72 (s, 4H), 7.06 (s, 4 H), 5.00 (s, 8H), 4.07 (t, J = 7.9 Hz, 4H), 3.93 (d, J = 17.5 Hz, 4H), 3.88 (d, J = 17.5 Hz, 4H), 2.96 (m, 4H), 2.18 (m, 8H), 1.12 (d, J = 6.3 Hz, 12H), 1.07 (d, J = 6.3 Hz, 12H), 0.88 (t, J = 7.1 Hz, 12H); ^{13}C NMR ($CDCl_3$, 303 K, 62.9 MHz) δ 148.8, 148.4, 123.5, 123.0, 120.4, 109.0, 80.7, 49.6, 43.0, 34.4, 26.2, 21.1, 20.6, 12.2; MS (ESI-TOF) 933.50 $[M]^+$.

(8) Measurement on Enraf Nonius CAD4 diffractometer at 173.0 ± 0.1 K using graphite monochromatised Mo Kα radiation [λ (Mo Kα) = 0.71073 Å]. $C_{60}H_{84}N_4O_8$ (**2c**·CH_3CN·2$CHCl_3$, M_r = 1269.1, colorless crystal of size 0.5 × 0.3 × 0.25 mm^3, orthorhombic $C222_1$ (No. 20), a = 12.621(4) Å, b = 22.358(4) Å, c = 23.335(7) Å, V = 6585(3) Å^3, Z = 4, ρ_{calcd} = 1.280 g cm^{-3}, μ = 0.317 mm^{-1}, 393 parameters, R1 = 0.062, wR2 = 0.156 (for 1933 reflections $I > 2\sigma(I)$), R1 = 0.125, wR2 = 0.177 (for 3329 unique reflections), S = 1.052.

(9) Sheldrick, G.; *SHELXTL*; Siemens Industrial Automation, Inc.: Madison, 1993.

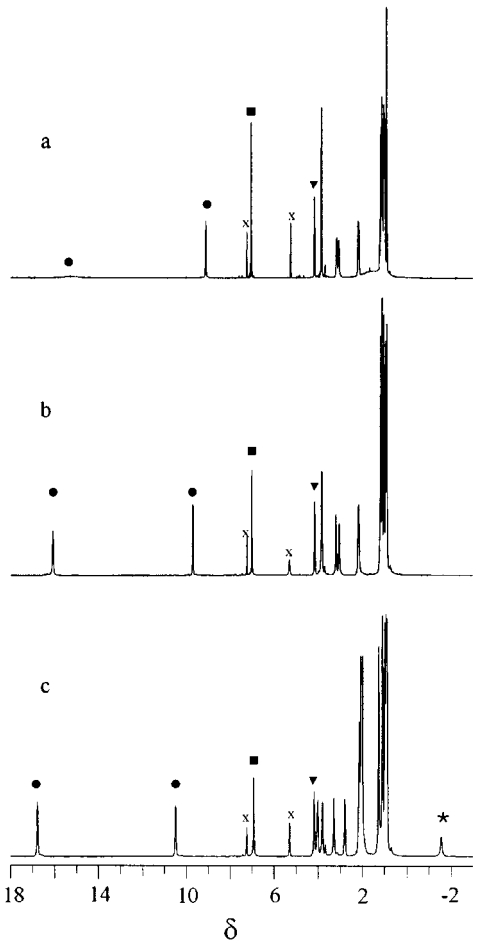

Figure 2. ^{1}H NMR (500 MHz, $CDCl_3$) spectra: (a) **2b** at 303 K; (b) **2b** at 233 K; (c) **2b** + 25 equiv of MeCN at 233 K. [**2b**] = 5 mM. Symbols designate the protons of (●) OH groups; (■) the resorcinol rings; (▼) methyne bridges; (∗) encapsulated acetonitrile; (x) $CHCl_3$ and CH_2Cl_2.

for methyne protons of the isopropyl groups. The coalescence of these two signals was detected at 312 K, which corresponds to $\Delta G^{\ddagger}$ of 15.5 kcal/mol.[10,11] The less bulky **2a** showed a comparable $\Delta G^{\ddagger}$ value of 15.9 kcal/mol at T_c = 328 K.[12] Unfortunately, no coalescence was detected for the signals of the hydroxy groups, most probably because of proton exchange with water.

The addition of 5 equiv of acetonitrile or acetaldehyde to the solution of **2b** in $CDCl_3$ at 303 K resulted in no significant changes in the ^{1}H NMR spectra of the components. Decreasing the temperature to 233 K led to the appearance of a new set of signals for the protons of **2b**, which increased at the expense of the original set upon further addition of the guest. This indicates the formation of a kinetically stable complex. After the addition of 25 equiv of acetonitrile the original set of signals of **2b** completely disappeared (Figure 2c). The signal at −1.56 ppm corresponds to the methyl protons of the acetonitrile molecule shielded by the π-electron clouds of the host **2b** ($\Delta\delta = -3.56$ ppm). The methyl protons of the complexed acetaldehyde emerged at −1.12 ppm, shifted upfield by 3.4 ppm. Integration of the spectra revealed a 1:1 stoichiometry for the inclusion complexes. The addition of methanol-d_4 (10%) or trifluoroacetic acid (trace amount) results in complete destruction of the acetonitrile complex as a result of the disruption of the hydrogen bonds in the host that destroys the intramolecular cavity. The rotation of the aminomethyl fragments becomes fast on the NMR time scale and the ^{1}H NMR signal of the benzyl protons transforms into a singlet.

Despite kinetic stability only moderate binding (K <10 M^{-1}) was estimated by a dilution experiment both for acetonitrile and acetaldehyde most probably because of the relatively weak C−H$\cdots\pi$ host−guest interactions. The ^{1}H NMR spectrum of **2b** in $CDCl_3$ in the presence of a 1:1 mixture of acetonitrile and acetaldehyde revealed that acetonitrile is bound about two times stronger than acetaldehyde. No kinetically stable complexes were observed with propionitrile, nitromethane, ethanol, *n*-butanol, and *tert*-butyl alcohol,[13] suggesting that the inclusion in the cavity of **2b** is selective to the size, shape, and electronic properties of a guest molecule. Essentially the same behavior was found for tetrapiperidine derivative **2c**. Surprisingly, tetradiethylamino resorcarene **2a** *does not form* kinetically stable complexes with acetonitrile and acetaldehyde between 303 and 233 K. This strongly suggests that the steric effect of isopropyl groups in **2b** and the higher conformational rigidity of piperidine rings in **2c** create a mechanical barrier for the guest release. Resorcarene tetrabenzoxazines **3**, which also exist in the crown conformation, do not form kinetically stable complexes with acetonitrile and acetaldehyde in $CDCl_3$ between 303 and 233 K, although 1:1 inclusion complexes are known in the crystalline state.[14] This is most probably caused by the flexibility of the benzoxazine rings of **3**, which destroys the intramolecular cavity in solution.

In conclusion, tetraaminomethylated resorcarenes **2b,c** possess extended π-basic cavities in which one molecule of acetonitrile or acetaldehyde can be included in $CDCl_3$. At 233 K these complexes proved to be stable on the NMR time scale. This stability is related to the self-folding of the host molecules through eight intramolecular hydrogen bonds, as well as to sterical effects and conformational rigidity of the aminomethyl fragments. The remarkable size selectivity of the complexation and the very simple synthesis of compounds **2** make them a new class of receptors for small organic guests. We are currently investigating the possibility of increasing the kinetic stability of the inclusion complexes

(10) Günther, H. *NMR Spectroscopy. An Introduction*; John Willey & Sons: Chichester, New York, Brisbane, Toronto, 1987; pp 242−243.

(11) At higher temperatures the signals of the isopropyl methyne protons emerged as two broadened singlets. The $\Delta\nu$ was calculated as distance between their centers. The small intensity of the sidebands of the AB quartet for the methylene benzyl protons prevented accurate determination of $\Delta G^{\ddagger}$.

(12) This was determined on the basis of coalescence data for the benzyl protons.

(13) Compare to: Shivanyuk, A.; Spaniol, T. P.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000,** *39,* 3497.

(14) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709.

through additional intramolecular hydrogen bonding between the pendant aminomethyl groups.

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Supporting Information Available: Details of crystal structure determination solution and refinement in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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