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Water-Soluble Resorcin[4]arene Based Cavitands

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Abstract: Water-soluble resorcin[4]arene based cavitands were obtained in good yields by reaction of bromomethylcavitands with pyridine. Their solubility was determined by conductometry. The behaviour in water depends on the alkyl chain length; the methylcavitand does not aggregate, whereas the pentyl- and undecylcavitands do, as was shown by ^{1}H NMR spectroscopy and Transmission Electron Microscopy.

Keywords: Supramolecular Chemistry; Pyridinium Salts; Aggregation; Complexation.

One of the objectives of supramolecular chemistry[1] is to mimic Nature in its development of specific receptor molecules. An impressive number of systems have been synthesized for this purpose, but often they are applied in organic solvents, whereas water is the solvent of utmost importance in Nature. For *in vivo* applications one could chose water-soluble building blocks such as cyclodextrins. Otherwise, the molecular platform to which functional groups are attached has to be made water-soluble. In our group we frequently use hydrophobic, appropriately functionalized calix[4]arenes and resorcin[4]arenes as receptors for cations, anions, and neutral molecules.

In contrast to the calix[4]arenes[2], there are only a few examples of water-soluble, resorcin[4]arene based cavitands. The very rigid cavitands[3],[4], which have as a main advantage over the calix[4]arenes that they contain a permanent cavity that can be used for complexation, are easily prepared by bridging of the hydroxyl groups of neighboring aromatic rings of parent resorcin[4]arene **1**[5],[6]. The most frequently used bridging reagent is bromochloromethane, leading to cavitands **2**. Sherman *et al.*[7] synthesized the tetrahydroxycavitands **3a** and **3b** that are water-soluble under alkaline conditions. However, in water they behave quite differently. The ^{1}H NMR spectrum of cavitand **3a** is sharp, well-resolved, and concentration independent, whereas the spectrum of cavitand **3b** is broad, suggesting that the pendant phenethyl groups induce aggregation in water. The only other water-soluble cavitand **4b** known so far, was prepared by coupling of cavitand **4a** with peptide chains[8]. In this communication we describe our preliminary results on a novel type of cavitand that is water-soluble over a broad pH range due to the presence of permanent charges, and its (complexation) behaviour.

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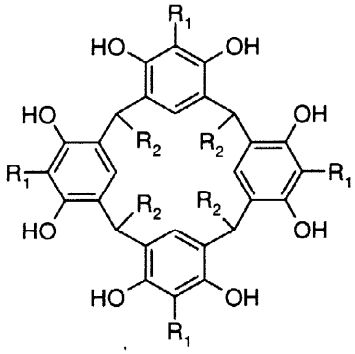
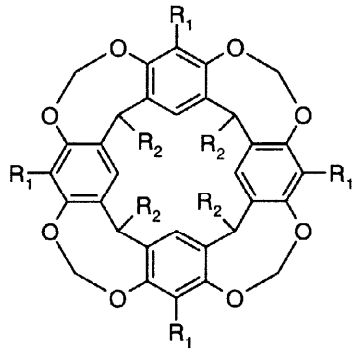
The bromomethylcavitands **5**, obtained by reaction of cavitands **2** (R_1 = CH_3) with *N*-bromosuccinimide[9],[10],[11], were chosen as suitable starting materials, because of their reactivity toward amines. Reaction with tertiary amines should give permanently charged compounds, which are thus water-soluble over a broad pH range. It was decided to use pyridine as an amine, which should afford cationic moieties with sp^2 hybridized nitrogen atoms as the cationic centers, because inspection of CPK-models indicated a strong steric hindrance when sp^3 hybridized nitrogen atoms are involved.

Reaction of bromomethylcavitands **5** with 50 equivalents of pyridine in ethanol led in very good yields to the cationic cavitands **6a-c**.[1] ^{1}H NMR spectroscopy, recorded in polar solvents, clearly indicated the full substitution of the bromo atoms by the presence of only one singlet for the methylene groups connecting the pyridine moieties and the cavitand.



1 R_1 = H, CH_3, OH; R_2 = alkyl, aryl



2 R_1 = H, CH_3, OH; R_2 = alkyl, aryl
3a R_1 = O^-Na^+; R_2 = CH_3
3b R_1 = O^-Na^+; R_2 = $CH_2CH_2C_6H_5$
4a R_1 = SH; R_2 = CH_3
4b R_1 = S-Protein; R_2 = CH_3
5 R_1 = CH_2Br; R_2 = CH_3 (**a**), C_5H_{11} (**b**), or $C_{11}H_{23}$ (**c**)

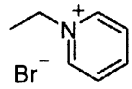
6 R_1 =  ; R_2 = CH_3 (**a**), C_5H_{11} (**b**), or $C_{11}H_{23}$ (**c**)

Chart 1

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[1] **7,11,15,28-Tetrakis(pyridinomethyl)-1,21,23,25-tetramethylcavitand tetrabromide (6a).** Yield 92%; mp > 270 °C (dec); ^{1}H NMR (D_2O) δ 8.87 (d, 8 H, *J* = 5.8 Hz, *o*-NPyrH), 8.53 (t, 4 H, *J* = 7.8 Hz, *p*-NPyrH), 8.05 (dd, *J* = 7.0 and 7.2 Hz, 8 H, *m*-NPyrH), 7.78 (s, 4 H, ArH), 6.35 [d, 4 H, *J* = 7.3 Hz, OCH_2O (outer)], 5.75 (s, 8 H, CH_2N), 4.92 (q, 4 H, *J* = 7.4 Hz, ArCHAr), 4.68 [d, 4 H, *J* = 7.4 Hz, OCH_2O (inner)], 1.80 (d, 12 H, *J* = 7.3 Hz, $CHCH_3$); ^{13}C NMR (CD_3OD) δ 154.6 (s, ArC-O), 147.3 and 146.2 (d, ArC-H), 141.4 (s, ArC), 129.6 and 126.1 (d, ArC-H), 121.4 (s, ArC), 101.6 (t, OCH_2O), 56.4 (t, $ArCH_2N$), 33.3 (d, ArCHAr), 17.0 (q, CH_3); FAB-MS *m/z* 1281.0 ($[M + H]^+$, calcd 1281.1); Anal. Calcd for $C_{60}H_{56}Br_4N_4O_8 \cdot 2H_2O$: C, 54.73; H, 4.59; N, 4.25. Found: C, 54.83; H, 4.94; N, 4.04.

7,11,15,28-Tetrakis(pyridinomethyl)-1,21,23,25-tetrapentylcavitand tetrabromide (6b). Yield 91%; mp 260-262 °C; ^{1}H NMR (CD_3OD) δ 9.03 (d, 8 H, *J* = 5.6 Hz, *o*-NPyrH), 8.60 (t, 4 H, *J* = 7.8 Hz, *p*-NPyrH), 8.13 (dd, *J* = 6.7 and 7.5 Hz, 8 H, *m*-NPyrH), 7.70 (s, 4 H, ArH), 6.32 [d, 4 H, *J* = 7.4 Hz, OCH_2O (outer)], 5.81 (s, 8 H, CH_2N), 4.80-4.70 [m, 8 H, ArCHAr and OCH_2O (inner)], 2.55-2.35 (m, 8 H, $CHCH_2$), 1.50-1.15 [m, 24 H, $(CH_2)_3Me$], 0.86 (t, 12 H, *J* = 6.9 Hz, $C_4H_8CH_3$); ^{13}C NMR (CD_3OD) δ 155.1 (s, ArC-O), 147.3 and 146.2 (d, ArC-H), 140.3 (s, ArC), 129.6 and 126.3 (d, ArC-H), 121.7 (s, ArC), 101.8 (t, OCH_2O), 56.3 (t, $ArCH_2N$), 38.8 (d, ArCHAr), 32.8, 30.8, 28.8, and 23.8 [t, $(CH_2)_4Me$], 14.5 (q, CH_3); FAB-MS *m/z* 1504.8 ($[M + H]^+$, calcd 1505.3); Anal. Calcd for $C_{76}H_{88}Br_4N_4O_8 \cdot 10H_2O$: C, 54.16; H, 6.46; N, 3.32. Found: C, 54.17; H, 6.09; N, 3.49.

7,11,15,28-Tetrakis(pyridinomethyl)-1,21,23,25-tetraundecylcavitand tetrabromide (6c). Yield 85%; mp 179-181 °C; ^{1}H NMR (CD_3OD) δ 9.04 (br d, 8 H, *o*-NPyrH), 8.61 (t, 4 H, *J* = 7.8 Hz, *p*-NPyrH), 8.15 (br dd, 8 H, *m*-NPyrH), 7.75 (s, 4 H, ArH), 6.34 [br d, 4 H, OCH_2O (outer)], 5.81 (s, 8 H, CH_2N), 4.76 [br d, 4 H, OCH_2O (inner)], 2.60-2.40 (m, 8 H, $CHCH_2$), 1.50-1.05 [m, 72 H, $(CH_2)_9Me$], 0.88 (t, 12 H, *J* = 6.7 Hz, $C_{10}H_{20}CH_3$); ^{13}C NMR (CD_3OD) δ 154.9 (s, ArC-O), 147.3 and 146.2 (d, ArC-H), 140.3 (s, ArC), 129.7 (d, ArC-H), 101.6 (t, OCH_2O), 56.8 (t, $ArCH_2N$), 33.1 (d, ArCHAr), 30.8, 30.5, 29.2, and 23.8 [t, $(CH_2)_{10}Me$], 14.5 (q, CH_3); FAB-MS *m/z* 1841.7 ($[M + H]^+$, calcd for $C_{100}H_{136}Br_4N_4O_8$ 1841.7).

Water-Solubility and Aggregational Behaviour. Conductometry was used as a method to determine the solubility of the cationic cavitands **6** in water. The solubilities were determined accurately by preparing dilution series of the cavitands, and measuring the conductivity, which was plotted against the concentration. Subsequently, a saturated solution was prepared, which was then, after filtration, diluted by a known factor. The conductance of this solution was measured and using the plot the concentration was found. With the dilution factor the concentration of the saturated solution was calculated. The solubilities of the cavitands are summarized in Table 1. It is found that the most hydrophobic cavitand exhibits the highest water-solubility, which is attributed to the formation of aggregates.

Table 1 Solubilities in Water of Charged Cavitands **6**.

Cavitand	*Water-Solubility at 20 °C (mM)*
6a	16
6b	53
6c	> 140

The ^{1}H NMR spectra in water of the undecyl- and pentylcavitands **6b** and **6c** show considerable peak broadening, indicating the presence of aggregates. Upon heating of the NMR samples the peaks sharpened. Peak broadening is not observed for the methylcavitand **6a**, indicating that this compound does not form aggregates at concentrations up to 10^{-2} M. These observations are comparable to the findings of Sherman *et al.*[7] for cavitands **3**.

The ionic water-soluble cavitands **6a-c** were studied by Transmission Electron Microscopy (TEM) to check for the formation of aggregates. In the case of undecylcavitand **6c** distinct, rod-shaped aggregates were observed (Figure 1). It is assumed that this cavitand forms bilayers by intercalation of the alkyl chains, as was observed in an X-ray crystal structure of resorcin[4]arene **1** (R_1 = H; R_2 = $C_{11}H_{23}$)[12]. These bilayers then rolled up to form the rod-like aggregates as presented in the left picture in Figure 1. Freeze fracturing of a solution of cavitand **6c** also confirmed the formation of aggregates in water (right picture in Figure 1).

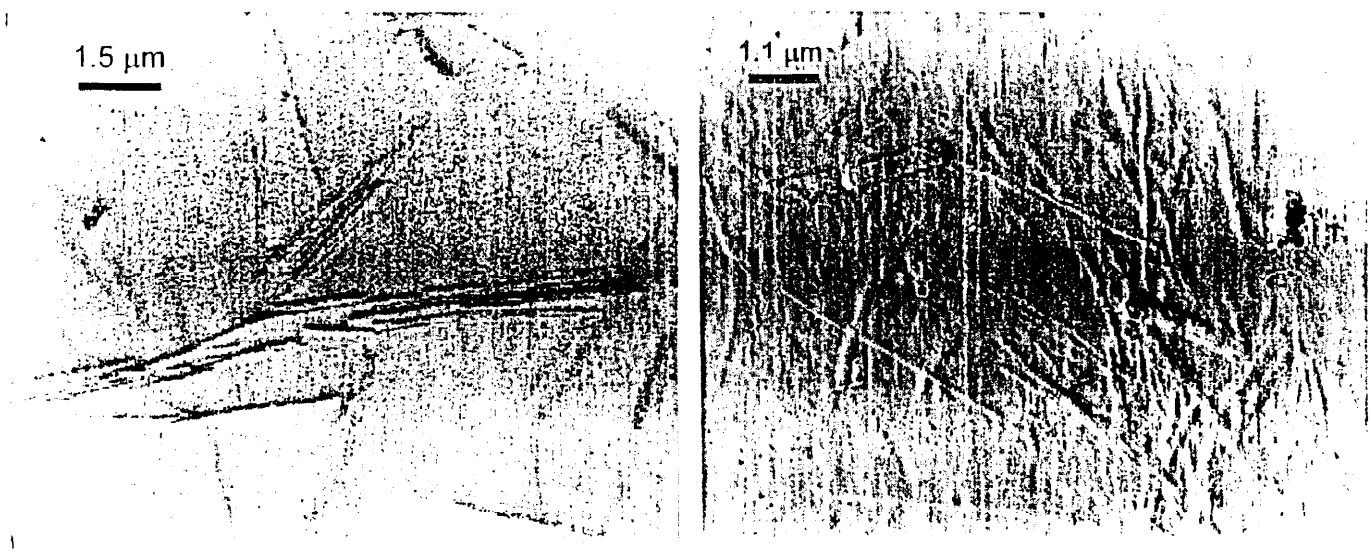

Figure 1 *TEM pictures of cavitand* **6c**. *Left: Pt shadowing technique; Right: freeze fracture technique.*

Complexation Studies. Because of its non-aggregating behaviour in water, methylcavitand **6a** was selected for complexation studies by ^{1}H NMR spectroscopy. Job plots of titration experiments with *p*-cresol and *p*-toluene sulfonate indicated the formation of 1 : 1 host : guest complexes. The association constants were calculated to be 1.1 x 10^2 and 5.2 x 10^2 M^{-1}, respectively. These values indicate that complexation is not inhibited by steric hindrance of the pyridinium moieties. In fact, the higher association constant for the complexation of *p*-toluene sulfonate indicates a positive effect of the presence of opposite charges.

Unfortunately, 2D-NMR spectroscopy with the *p*-cresol complex of cavitand **6a** did not reveal information about the position of the pyridinium moieties. With ROESY and NOESY spectroscopy no cross peaks between the pyridinium moieties and *p*-cresol were observed.

The development of these charged, non-peptide cavitands, which are all soluble in water over a broad pH range, may be a first step toward their *in vivo* application. Their behaviour in water is strongly influenced by the length of the alkyl chains. The non-aggregating methylcavitand **6a** is able to form 1 : 1 complexes with water-soluble methyl group containing aromatic compounds. The undecylcavitand **6c** clearly forms rod-like aggregates in aqueous solutions, as was evidenced by electron microscopy.

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