DOI: 10.1002/ejoc.200900814

Resorcinarene Podand with Amine-Functionalized Side Arms – Synthesis, Structure, and Binding Properties of a Neutral Anion Receptor

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Keywords: Supramolecular chemistry / Host-guest systems / Anions / Receptors / Resorcinarene

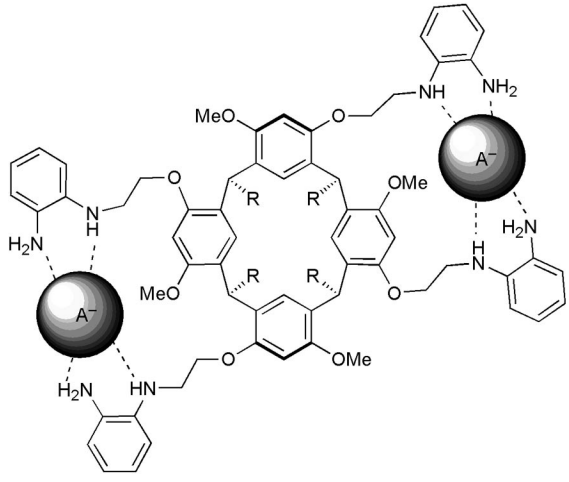
The synthesis and structure of a neutral resorcinarene host bearing four amine-functionalized side arms is described. The anion binding properties were investigated in solution by ^{1}H NMR spectroscopic titration and diffusion experiments and in the gas phase by mass spectrometric studies. It was observed that in solution 1:2 (host/guest) complexes were formed between the resorcinarene host and the basic fluoride and acetate anions, whereas in the gas phase 1:1 complexes with other anions (Cl^-, $HCOO^-$, NO_3^-, and BF_4^-) were detected additionally.

Introduction

The development and synthesis of anion receptors has gained a considerable amount of attention over the last decades.[1] The interest in anions arises from their importance in biological, environmental and chemical processes, which has induced a number of papers dealing with anion sensing, transport, and extraction as well as the use of anions in organic reactions.[2] The varying geometry and larger radii of anions compared to the most common cations greatly influences the binding, which again set the demands on the design of the receptor molecule in terms of host-guest complementarity and selectivity.[3] In addition, the solvent has a more pronounced role in anion binding in terms of solvation and desolvation effects, which are namely attributed to the protic, polar, or hydrogen-bonding nature of the solvent, and furthermore, the basicity of certain anions may vary drastically depending on the solvent used.[1,3]

Calixarenes have been extensively utilized in the design of anion receptors.[1c] The calixarene core provides a preorganized three-dimensional structure, which is easily modified by incorporation of anion binding ligands in the form of bridges or pendant side chains at the upper or lower rim of the calixarene framework.[1c] In neutral anion receptors, anion recognition is mainly based on hydrogen bonding interactions, which are generally provided in the binding site through amine, amide, urea, or thiourea moieties.[1c,4] Although hydrogen bonding interactions are not as strong as electrostatic interactions, they are directional, which contributes to the recognition and selectivity of certain anion geometries.

Our approach utilizes tetramethoxyresorcinarene[5] as the platform, which has a well-defined macrocyclic structure yet enough freedom to reorganize in order to best accommodate the guest molecule. Thus, four amine-functionalized side arms were attached on the upper rim of the resorcinarene bowl to create a neutral tetrapodal structure, in which the resorcinarene core adopts a boat conformation. Two binding sites are formed between the neighboring outstretched side arms at both ends of the resorcinarene cavity, the amine groups offering hydrogen bonding interactions with the anion (Scheme 1). The anion binding properties were investigated in solution and in the gas phase. In solution, binding was observed only between the more basic F^-



Scheme 1. A schematic presentation of the suggested anion binding mode for the tetrapodal resorcinarene receptor.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900814.

and AcO^- anions and the resorcinarene host, whereas in the gas phase complexes were detected with other anions (Cl^-, $HCOO^-$, NO_3^- and BF_4^-) as well.

Results and Discussion

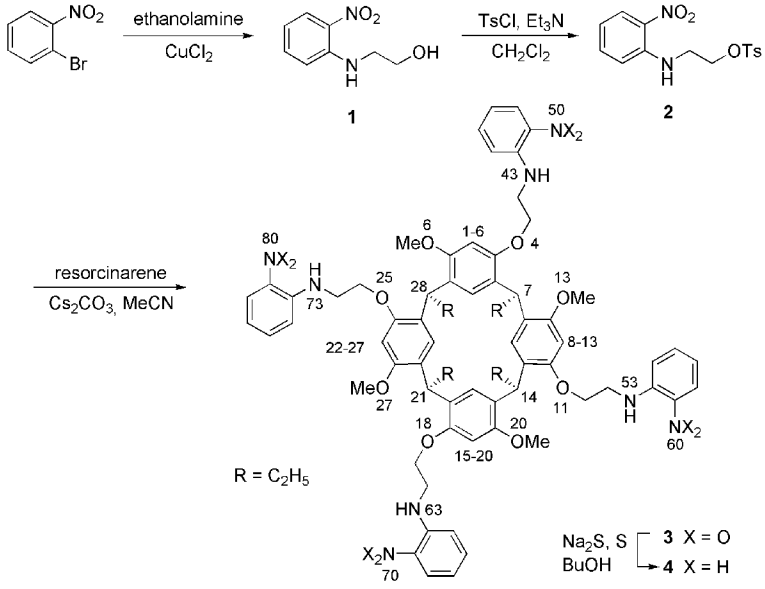
Synthesis

The synthesis of tetramethoxy resorcinarene host **4**, bearing four amine-functionalized side arms, was achieved by incorporating four *o*-nitro-*N*-(2-hydroxyethyl)aniline units into the tetramethoxy resorcinarene[5] platform (Scheme 2). *o*-Nitro-*N*-(2-hydroxyethyl)aniline (**1**) was prepared according to a slightly modified literature method[6] by treatment of *o*-bromonitrobenzene with ethanolamine in the presence of anhydrous copper(II) chloride in almost quantitative yield. Tosylation of the hydroxy group with *p*-toluenesulfonyl chloride in the presence of triethylamine in dichloromethane afforded the tosylated species **2** with 75% yield, which could then be attached to the resorcinarene scaffold by nucleophilic substitution reaction using anhydrous Cs_2CO_3 as the base and dibenzo-18-crown-6 as the phase-transfer-catalyst in refluxing acetonitrile, giving resorcinarene derivative **3** with 80% yield. The reduction of the nitro group into an amino group proved unsuccessful with hydrazine/Raney-Ni and tin(II) chloride, but was finally accomplished after several attempts using sodium sulfide and sulfur in refluxing butanol, which afforded resorcinarene host **4** in 70% yield. The structures of **4** and its intermediates were characterized by means of NMR spectroscopy and mass spectrometry, X-ray crystallography, and elemental analysis, which all confirmed the success of the reactions.

Structural Properties

The structural properties of **4** were investigated in solution by ^1H NMR spectroscopy and in the solid state by X-ray crystallography. As a result of substituting the four hydroxy groups of tetramethoxy resorcinarene with four amine-functionalized side arms, there no longer exists a hydrogen bonding network on the upper rim of the resorcinarene bowl to keep the molecule in a crown conformation, but it has to adopt a more favorable boat conformation instead. This is seen in the ^1H NMR spectra of **4** at room temperature as a set of averaged signals for all the protons belonging to the resorcinarene core due to fast boat-to-boat interconversion.[7] As the temperature is decreased, the core resorcinarene resonances start to broaden and finally give a set of doublets as –60 °C is reached corresponding to the reduced C_2 symmetry of the boat conformation. Due to overlapping signals this was most clearly observed with the aromatic and methoxy protons of the resorcinarene core.

Resorcinarene host **4** forms co-crystals by slow evaporation from acetonitrile (**Ia**), acetonitrile/ethanol (**Ib**), acetonitrile/TBACl (**II**) and pyridine (**III**) solutions. The crystal structures **Ia** and **Ib** are isomorphous with nearly identical unit cell parameters. In all of the structures, both the left- and right-handed isomers[7] of the host molecule are present in the unit cell and the resorcinarene host **4** adopts a boat conformation, in which the resorcinarene skeleton is somewhat twisted (Figure 1). In the structures **Ia/Ib** the resorcinarene cavity is slightly more opened than in the structures **II** and **III** with an angle of 40.3(1)° between the upright aromatic rings and an angle of 145.8(1)° between the aromatic rings in the horizontal plane, whereas the respective angles in the structures **II** and **III** are 31.6(1)° and 166.1(1)° (average values of the two structures).



Scheme 2. Synthesis of the amine-functionalized resorcinarene host **4** with crystallographic numbering.

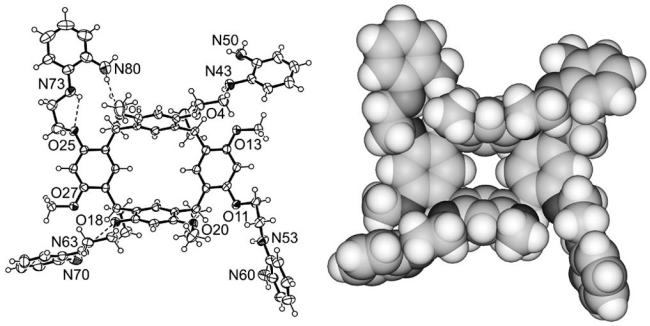


Figure 1. ORTEP plot (at 50% probability level) and CPK model of the crystal structure **Ib** of **4** (top views). The dashed lines indicate intramolecular hydrogen bonds. Solvent molecules have been omitted for clarity.

Table 1. Selected torsion angles [°] of **4**.

	Ia[a]/**Ib**[b]	**II**[a]	**III**[b]
O4/6–C41–C42–N43	–65.6(3)	–62.9(2)	65.8(3)
O11/13–C51–C52–N53	57.9(5)	–65.0(2)	65.7(4)
O18/20–C61–C62–N63	–59.6(3)	–67.0(2)	61.8(3)
O25/27–C71–C72–N73	–63.6(3)	62.3(3)	75.1(4)

[a] Left-handed isomer (O6). [b] Right-handed isomer (O4) in the asymmetric unit.

The amine-functionalized side arms fan out on the side of the resorcinarene core with the -OCH_2CH_2NH- torsion angles of each side arm close to 60° corresponding to a gauche conformation (Table 1). In the structures **Ia/Ib** the side arms lie above the plane formed by the methine bridges (C7–C14–C21–C28) with the amine groups facing the outer surface of the resorcinarene core (Figure 2). In structure **III**, on the other hand, two opposite side arms are bent below the plane and face the lower rim ethyl chains, whereas, in structure **II** only one side arm is bent below the plane and the amine groups of the opposite side arm point toward the resorcinarene cavity (Figure 2). The amine groups, in the structures **Ia/Ib** and **III**, form intra- and intermolecular hydrogen bonds with the phenolic oxygen atoms and/or the amine groups of the parent or neighboring resorcinarene unit [2.758(3)–3.358(4) Å for the intra- and 3.002(4) – 3.513(4) Å for the intermolecular N···O and N···N distances].

In both of the structures **Ia/Ib** and **III**, hydrogen bonded pairs are formed between the left- and right-handed isomers. The difference between the two structures lies in the position of the isomers relative to one another, which also

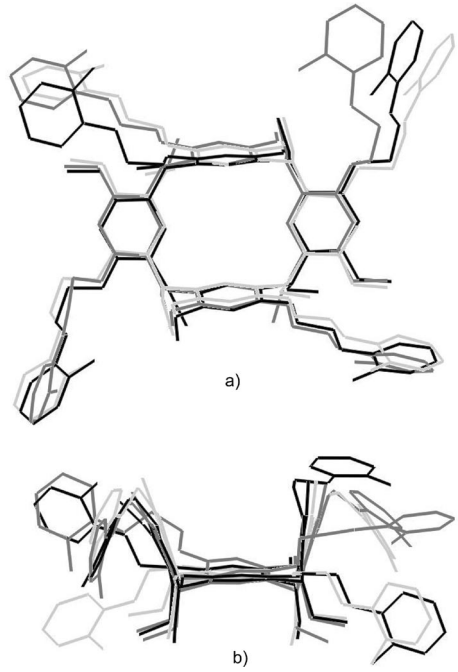


Figure 2. (a) Top and (b) side views of the structures **Ia/Ib** (dark gray), **II** (black) and **III** (light gray) as a superposition drawing showing the different geometries of the amine-functionalized side arms. Hydrogen atoms and solvent molecules have been omitted for clarity.

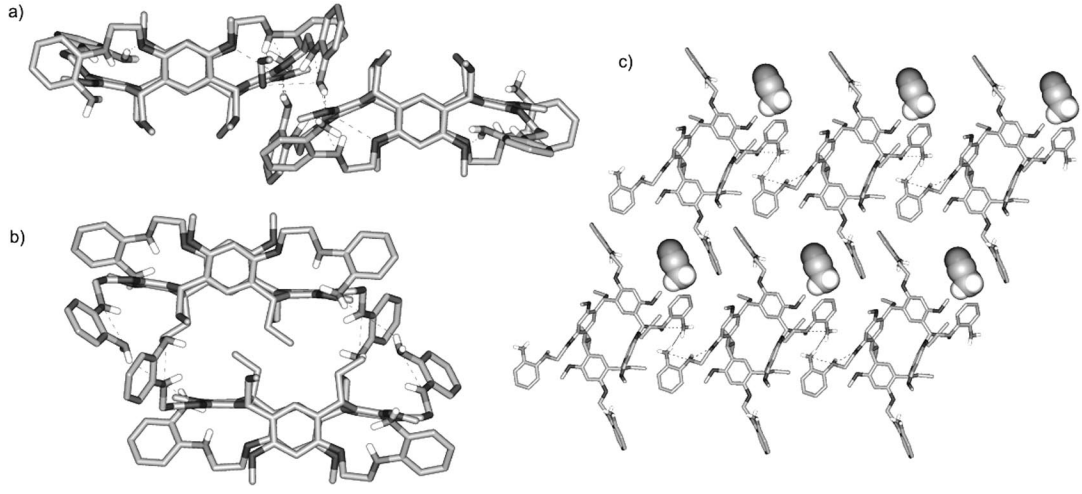


Figure 3. The hydrogen bonded pairs formed between the left- and right-handed isomers (a) in structure **Ia/Ib** and (b) in structure **III** excluding the solvent molecules for clarity. (c) The chains formed by the intermolecular hydrogen bonds between the neighboring resorcinarene molecules in structure **II**. Hydrogen bonds are shown by the dashed lines and only amine hydrogen atoms are shown for clarity.

explains the placement of the side arms above or below the plane. In structures **Ia/Ib** the pairs are interconnected to one another through the horizontal aromatic rings of the opposite facing resorcinarene molecules, and the amine-functionalized side arms thus settle above the plane (Figure 3, a). In structure **III**, on the other hand, the pairs are composed of two opposite facing resorcinarene molecules interlinked together by the ethyl chains, and therefore, in order to form the intermolecular hydrogen bonds between the neighboring molecules, the side arms are forced to bend below the plane (Figure 3, b).

In structure **II**, however, only intermolecular hydrogen bonds are formed between the amine groups of two neighboring resorcinarene molecules [average N···O distance of 3.398(4) Å] which results in a formation of chains in the crystal packing. The acetonitrile solvent molecules in the crystal lattice act as linkers between the parallel chains, which form uniform layers (Figure 3, c).

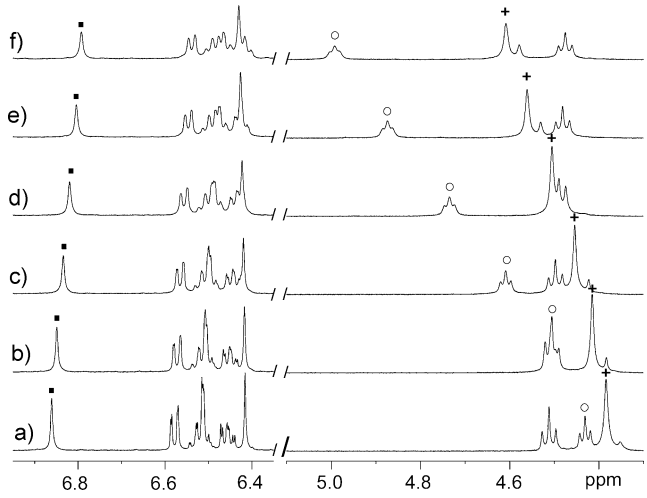


Figure 4. ^{1}H NMR titration spectra of **4** with F^- in [D_6]DMSO at 30 °C showing the changes in the chemical shifts of the aromatic and amine protons upon the addition of guest as a TBA salt. (a) Free host, (b) 0.5, (c) 1.0, (d) 1.6, (e) 2.5 and (f) 4.0 equiv. of guest added in [D_6]DMSO. (■ = ArH, ○ = NH and + = NH_2).

Solution Binding Studies

Anion binding studies were performed by ^{1}H NMR spectroscopic titration experiments with various anions in [D_6]-DMSO, which was chosen as the solvent due to solubility considerations, and because the amine resonances could only be seen in [D_6]DMSO as opposed to other available solvents (i.e. $CDCl_3$). The anions were added as their tetrabutylammonium (TBA) salts, since the larger cation was thought to be less susceptible to interact with the host molecule compared to the smaller tetramethylammonium counter cation.[8]

With Cl^-, Br^-, I^-, NO_3^-, PF_6^- and BF_4^- anions the addition of ten equivalents of the anion caused no changes in the ^{1}H NMR spectra of **4**, which suggested that very weak or no binding was taking place with these anions in solution. However, upon the addition of F^- anions significant changes were observed in the ^{1}H NMR spectrum of **4** as both the -NH and -NH_2 amine resonances shifted downfield, which was attributed to anion binding taking place (Figure 4). Changes in the chemical shifts of the aromatic and the methine protons of the resorcinarene core were also observed, which suggest alteration in the host conformation upon binding, and also, possible CH···anion interaction[9] between the host and the F^- anion. However, there were no changes observed in the chemical shifts belonging to the TBA^+ counter cation, which indicated that the TBA^+ cation was not interacting with the host molecule, and that the changes observed for the resorcinarene host **4** were solely caused by the anion alone.

The behavior of the F^- anion and its ability to act as a strong base in [D_6]DMSO[10] and deprotonate the -NH hydrogen of the receptor molecule has been reported in the literature by Fabbrizzi and others.[11] It has been postulated that there is a two-step process that involves a formation of genuine hydrogen-bonded complex between the neutral host and the F^- anion in the first binding equilibrium while in the next step a second F^- anion abstracts the HF fragment to form a bifluoride HF_2^- anion. In fact, a closer look at the spectrum of **4** with 2 equiv. of F^- anions showed a triplet further downfield at δ = 16.2 ppm, which was denoted to HF_2^- anion.[11,12] The free HF_2^- anion, as its TBA salt, has been reported[12] to show up at δ = 15.4 ppm in [D_6]DMSO, which would imply that the F^- anion was actually bound to the receptor **4** as HF_2^- anion. This has also been described as a "frozen" proton release or an incipient proton transfer reaction in a recent review.[13] With acidic -NH hydrogen atoms complete deprotonation is also possible, which results in a release of HF. This, however, was ruled out as the amine resonances did not disappear even after a large excess of F^- anion had been added, and furthermore, inspection of the DMSO pK_a values[10] of aniline (30.6) as a model for the receptor and HF (15) clearly shows that the fluoride alone is not basic enough to deprotonate a significant fraction of the receptor.

The stoichiometry was confirmed by a modified Job plot analysis,[14] which gave a maximum corresponding to a 1:2 host-guest complex formation, and the stability constants were calculated by the EQNMR[15] computer program for the two step binding equilibrium according to the equations (1) and (2), where G denotes F^- and G_2 becomes F_2^- in the second equilibrium with an overall binding constant of $\beta_{12} = K_{11}K_{12}$ (Table 2). The chemical shift of the aromatic proton of the resorcinarene core was followed since both the -NH and -NH_2 amine resonances would broaden and finally disappear[16] in the course of the titration experiment.

$$H + G \rightarrow HG \quad (1)$$

$$HG + G \rightarrow HG_2 \quad (2)$$

The addition of AcO^- anion also caused similar changes in the spectrum of **4**, although, at higher guest concentration. Host **4** appears to readily form hydrogen bonds with the more electronegative F^- and AcO^- anions compared to the other anions investigated, and that the basicity of the

Table 2. Diffusion coefficients[a] (10^{-5} $cm^2 s^{-1}$) and binding constants[b] (M^{-1}) of **4** with selected anions in [D_6]DMSO at 303 K.

	D_{DMSO}	D_{Host}	D_{TBA+}	K
4	0.89 ± 0.01	0.258 ± 0.006	–	–
F^-	1.05 ± 0.01	–	0.572 ± 0.002	–
4 + F^-	0.97 ± 0.01	0.262 ± 0.004	0.414 ± 0.001	K_{11} = 360 K_{12} = 37
4+ AcO^-	–	–	–	K_{11} = 40 K_{12} = 11

[a] Values are average ± standard deviation of three experiments. The solutions studied were 5 mM in **4** and 10 mM in anion as its TBA salt. [b] Binding constants were calculated from ^{1}H NMR spectroscopic titration data fitted to a 1:2 (host/guest) binding model using EQNMR;[15] errors less than 15%. Anions were added as their TBA salts.

anions in [D_6]DMSO determines the binding strength, which was the strongest with F^- anion (Table 2). Moreover, the lack of binding observed with the other anions could additionally result from the solvation effects induced by [D_6]DMSO, as it is able to form strong hydrogen bonds with the host molecule, and therefore, only the more strongly binding anions will be able to overcome this competition at the binding site.

^{1}H NMR spectroscopic diffusion measurements were additionally carried out with F^- anion in [D_6]DMSO, in order to substantiate whether the changes in the chemical shifts of **4** during titration experiments were rightfully attributed to anion binding interactions taking place instead of just deprotonation, since diffusion is less sensitive to proton transfer than chemical shifts.[17] A 1:2 host-guest solution in [D_6]DMSO was substantiated, and, although the HF_2^- anion was also identified in the spectra, the diffusion coefficient could not be accurately determined from the HF_2^- chemical shift due to the low intensity and broadness of the resonance. However, it seems reasonable to presume that the formed HF_2^- anion forms an ion pair with its counter cation, TBA^+, which was conveniently visible in the ^{1}H NMR spectra and was therefore examined. It was found that the diffusion coefficient of TBA^+ cation in the complex was lower than that of the "free" TBA^+ cation, which indicates that host **4** and TBA[HF_2] ion pair forms a moderately bound entity that is comparable with the binding strength determined by ^{1}H NMR spectroscopic titration experiment (Figure 5, Table 2).

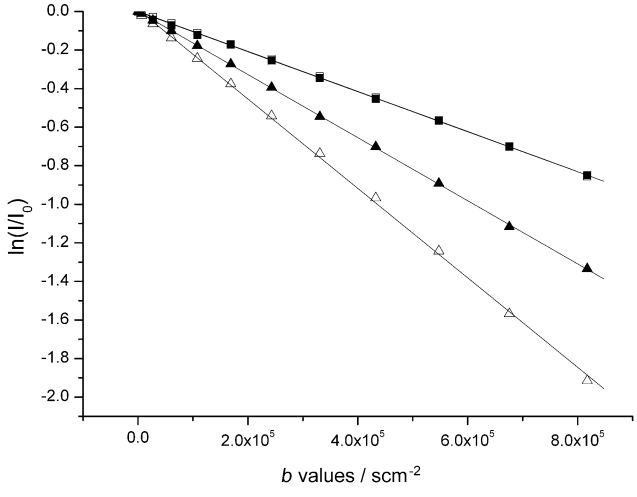


Figure 5. Normalized signal decay $\ln(I/I_0)$ as a function of b values for **4** (■) and TBAF (Δ) in the free state and for the TBA^+ cation (▲) in a 1:2 host-guest solution of **4** and TBAF, respectively, in [D_6]DMSO at 303 K.

Although solid-state investigations would reveal more information about anion binding mode in host **4**, unfortunately, all attempts to obtain good quality crystals of the anion complexes of **4** for crystal structure determination have so far failed.

Gas-Phase Binding Studies

In order to provide additional evidence for the binding of anions to the *neutral* receptor and to gain insight into similarities or solvation-induced differences between the situation in solution and the gas-phase, negative-mode electrospray-ionization mass spectrometric (ESI-MS) experiments were performed. For this purpose, an equimolar solution of **4** and each anion (or a combination of two different anions in the case of fluoride and acetate, respectively) was electrosprayed, and the formation of complexes was monitored by high-resolution Fourier-transform ion-cyclotron-resonance (FTICR) mass spectra.

Figure 6 shows the ESI-FTICR mass spectrum obtained from a 50 μM acetonitrile solution of **4**, acetate, and fluoride. In addition to the expected complexes of **4** with fluoride and acetate, the complexes with chloride and formate are also formed from background anions. Chloride is almost omnipresent in the negative mode and the formate anion is due to a hard-to-remove memory effect from previous experiments in the positive mode, in which formic acid was used. It is advantageous to use AgOAc to generate the acetate complexes, because the silver ions help to scavenge background chloride. Irrespective of the ionization conditions, 1:2 complexes of the receptor and the anion have not been observed – a finding which can be attributed to the significantly stronger repulsion between the two charges in the desolvated complex. Instead, 2:1 complexes are observed, which however are likely due to "unspecific" binding. An HF_2^- complex of receptor **4** is not observed in the gas phase. This is not unexpected, because it would easily lose HF during the ionization/desolvation process, even when initially formed in solution. Consequently, these findings already show that there are differences between the solution situation and that in the gas-phase.

The most remarkable difference between solution and gas-phase binding behavior of **4** is that not only fluoride and acetate complexes are observed in the mass spectra. The gas-phase experiments furthermore provide evidence for chloride, nitrate, tetrafluoroborate, and formate to form 1:1 complexes. Likewise, many other anions will certainly bind. Consequently, a number of anions – among them even the weakly binding ones such as BF_4^- – experience attractive interactions with the receptor, although no bind-

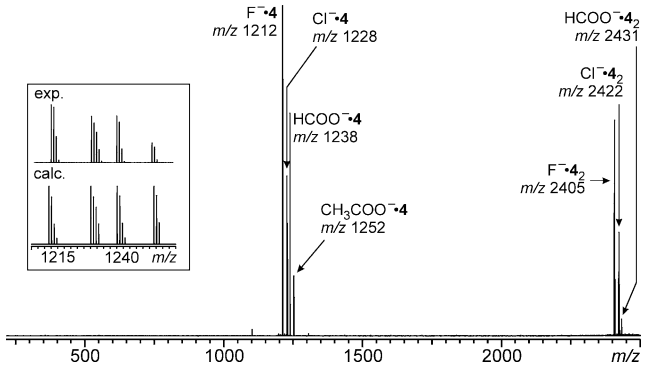


Figure 6. Negative mode ESI-FT-ICR mass spectrum of an equimolar solution of **4**, AgOAc, and TBAF (50 μM).

ing is observed in solution. This finding can be easily traced back to the competition with the solvent. In the solution studies, DMSO was used, which is quite a strong hydrogen-bond acceptor and present in large excess. Consequently, weakly hydrogen-bonding anions cannot compete with the solvent. In the gas phase, however, the competition does not exist and the intrinsic attractive forces are seen that hold the complex together. It should be briefly noted that we do not use the mass spectroscopic data to monitor solution concentrations of the complexes, but simply refer to the fact that the mere existence of a complex in the gas phase provides evidence for an attractive binding interaction. In that sense, the spray solvent (acetonitrile or methanol in our experiments) does not play a role.

Furthermore, electrostatic interactions are significantly increased in the gas phase as compared to solution due to the change in permittivity of the medium as expressed in the dielectric constants. The vacuum dielectric constant is 1 by definition, while that of DMSO is 48. Consequently, any electrostatic interaction between the anion and the dipoles of the receptor should increase in strength by a factor of approximately 48 upon the transition into the gas phase.

In a tandem mass spectrometric experiment, the complex ions of interest can be mass-selected and subjected to gas-phase chemical experiments. After isolation of the parent ions, a 25 W CO_2 laser (10.6 μm wavelength) was used to fragment the ions in the FTICR cell in an infrared radiative multiphoton dissociation (IRMPD) experiment. The corresponding spectra for three selected anions, i.e. the formate, chloride, and fluoride complexes of **4**, are shown in Figure 7. These complexes show interesting differences in their fragmentation behavior (Scheme 3):

(a) The fragmentation spectrum of the formate complex is very simple. The only dominating fragmentation channel is the loss of the complete neutral receptor (Scheme 3, channel A).

(b) For the chloride complex, the complete receptor loss is again by far the most abundant fragmentation channel, but in addition a quite low-intensity fragment is observed at *m*/*z* 1057. It can be attributed to a nucleophilic attack of the almost naked chloride at the spacer connecting one of the branches to the resorcinarene scaffold (Scheme 3, channel B).

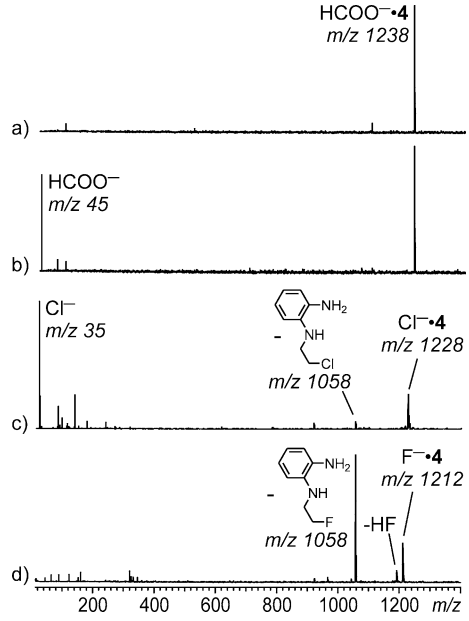
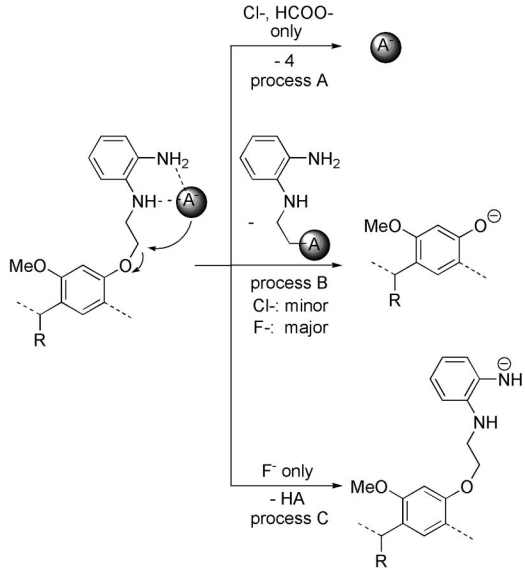


Figure 7. (a) ESI-FTICR mass spectrum of $HCOO^-$•**4** after mass selection. The small signal at *m*/*z* 1102 corresponds to stray radiation. (b) IRMPD experiment with 500 ms irradiation time of a 25 W IR laser. (c) IRMPD experiment conducted with Cl^-•**4** under the same conditions. (d) Analogous IRMPD experiment with F^-•**4**.



Scheme 3. Fragmentation reactions observed in the tandem MS spectra shown in Figure 7.

(c) For the fluoride complex, no loss of the complete receptor is observed anymore. Instead, the anion is so nucleophilic in the absence of solvent that channel B becomes by far the major one. The fact that the fragment appears at the same *m*/*z* as that observed in the MS/MS spectrum of the chloride complex also confirms that the halide is incorporated in the neutral fragment in both cases. This reaction is already quite remarkable in that a reaction involving covalent bonds smoothly proceeds as the major reaction pathway within a noncovalent complex.[18] Noncovalent bond frag-

mentation cannot efficiently compete indicating how strongly bound the fluoride indeed is. But a second aspect is also important to note: As a minor fragment, a loss of HF is observed at *m*/*z* 1191. In view of the proton affinities of fluoride (1529 kJ/mol)[19] and anilide (1502 kJ/mol)[20] as a model compound for the receptor for which the gas-phase thermochemical data is known, fluoride is capable of deprotonating the receptor in the gas phase. This aspect nicely closes the cycle back to the above discussed solution-phase binding of the HF_2^- anion. These fragmentation spectra clearly reflect the properties of the different anions, for example the much higher nucleophilicity and basicity of fluoride.

Conclusions

In conclusion, the synthesis and structural properties of a neutral resorcinarene host **4**, bearing four amine-functionalized side arms, is reported. The complexation properties of **4** toward various anions (halides, AcO^-, $HCOO^-$, NO_3^-, PF_6^-, and BF_4^-) were investigated both in solution and in the gas phase. In solution, resorcinarene host **4** readily formed 1:2 host-guest complexes with fluoride and acetate anions, and the basicity of these anions seemed to be the driving force in the formation of hydrogen-bonding interactions with receptor **4**. With fluoride, in particular, the binding was identified as a two step process, which involved the formation of a bifluoride, HF_2^- anion in the second stage of the binding. Fluoride also represents a special case in the gas phase. Its high basicity leads to HF losses, while no HA losses have been observed for any of the other anions. In addition, fluoride is also the most nucleophilic anion under study. It is interesting to see how the high hydrogen-bond energies lead to nucleophilic substitution reactions rather than the cleavage of the noncovalent bonds. The strong effects of the surrounding environment become again clearly visible.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX 500 spectrometer and chemical shifts were calibrated to the residual proton and carbon resonance of the solvent. Routine ESI mass spectra were measured with Micromass LCT ESI-TOF instrument. Elemental analyses were determined with Vario EL III instrument. Melting points were measured in open capillaries with a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Tetramethoxy resorcinarene[5] and **1**[6] were prepared according to literature procedures. All other reagents used were commercial unless otherwise noted. Dichloromethane and acetonitrile were distilled from $CaCl_2$ and stored over 3 Å molecular sieves under N_2 atmosphere.

***o*-Nitro-*N*-(2-tolylsulfonyloxyethyl)aniline (2):** A mixture of **1** (4.1 g, 22.5 mmol) and *p*-toluenesulfonyl chloride (5.0 g, 26.2 mmol) was dissolved in dry dichloromethane (50 mL) under nitrogen with stirring. Triethylamine (3.6 mL, 26.0 mmol) in dichloromethane was added dropwise and the reaction mixture was stirred at room temperature for two days. Water was added to the reaction mixture and neutralized by the addition of 2 N HCl solution. The organic layer was separated and washed two times with water, dried with $MgSO_4$ and the solvents evaporated to dryness under vacuum. Recrystallization from hot chloroform/hexane afforded 5.6 g (75%) of orange powdery solid; m.p. 122–124 °C. ^1H NMR ($CDCl_3$): δ = 8.13 (dd, ^3J = 1.5, ^3J = 7.0 Hz, 1 H, ArH), 7.98 (br. s, 1 H, NH), 7.73 (m, 2 H, ArTs), 7.41 (m, 1 H, ArH), 7.25 (m, 2 H, ArTs), 6.75 (dd, ^3J = 0.9 and ^3J = 7.8 Hz, 1 H, ArH), 6.69 (m, 1 H, ArH), 4.27 (t, ^3J = 5.5 Hz, 2 H, CH_2), 3.63 (q, ^3J = 5.7 Hz, 2 H, CH_2), 2.40 (s, 3 H, $TsCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 145.2, 144.4, 136.2, 132.6, 132.5, 129.8, 127.8, 127.0, 116.1, 113.2, 67.3, 41.5, 21.6 ppm. MS (ESI-TOF): *m*/*z* = 359.03 $[M + Na]^+$. $C_{15}H_{16}N_2O_5S$ (336.37): calcd. C 53.56, H 4.79, N 8.33; found C 53.46, H 4.66, N 8.17.

Tetramethoxy-tetrakis{[2-(2-nitrophenyl)amino]ethoxy}resorcinarene (3): A mixture of tetramethoxyresorcinarene[5] (1.0 g, 1.5 mmol), Cs_2CO_3 (4.1 g, 12.6 mmol) and dibenzo-18-crown-6 (0.41 g, 1.1 mmol) was suspended in dry acetonitrile (60 mL) under nitrogen and refluxed for 15 min before the dropwise addition of **2** (2.2 g, 6.5 mmol) in acetonitrile (40 mL) with vigorous stirring. The resulting yellow suspension was refluxed overnight. After cooling to room temperature the reaction mixture was filtered by suction and solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and washed with water. The organic layer was separated, dried with $MgSO_4$ and the solvents evaporated to dryness under vacuum. Recrystallization from methanol/chloroform afforded 1.6 g (80%) of orange crystalline solid; m.p. 195–198 °C. ^1H NMR ($CDCl_3$): δ = 8.23 (br. t, ^3J = 5.3 Hz, 4 H, NH), 8.17 (dd, ^3J = 1.6, ^3J = 7.0 Hz, 4 H, ArH), 7.42 (m, 4 H, ArH), 6.88 (d, ^3J = 8.0 Hz, 4 H, ArH), 6.68 (s, 4 H, ArH_{reso}), 6.65 (m, 4 H, ArH), 6.25 (s, 4 H, ArH_{reso}), 4.43 (t, ^3J = 7.6 Hz, 4 H, CH), 4.07 (m, 4 H, CH_2CH_2), 4.83 (m, 4 H, CH_2CH_2) 3.51–3.46 (overlapping s and m, 20 H, OCH_3 and CH_2CH_2), 1.86 (m, 8 H, CH_2CH_3), 0.89 (t, ^3J = 7.3 Hz, 12 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 155.8, 154.8, 145.3, 136.1, 132.3, 127.0, 126.9, 126.7, 126.3, 115.5, 113.7, 97.9, 67.5, 55.8, 42.6, 37.0, 27.8, 12.6 ppm. MS (ESI-TOF): *m*/*z* = 1335.54 $[M + Na]^+$. $C_{72}H_{80}N_8O_{16}\cdot 0.5CHCl_3$ (1373.17): calcd. C 63.40, H 5.91, N 8.16; found C 63.39, H 5.71, N 8.03.

Tetrakis{[2-(2-aminophenyl)amino]ethoxy}-tetramethoxyresorcinarene (4): A mixture of **3** (1.6 g, 1.2 mmol), 60% sodium sulfide (5.9 g, 75.6 mmol) and sulfur (1.3 g, 40.5 mmol) were suspended in 1-butanol (150 mL) and refluxed overnight. After cooling to room temperature, water (100 mL) was added in the reaction mixture with vigorous stirring. The organic layer was separated, washed repeatedly with water and finally treated with hexane. The precipitate formed was separated by suction filtration, washed with methanol and dried in vacuo. Yield 1.0 g (70%) of beige powdery solid; m.p. 186–188 °C. ^1H NMR ($CDCl_3$): δ = 6.78 (m, 4 H, ArH) 6.73 (s, 4 H, ArH_{reso}), 6.72–6.64 (m, 12 H, ArH), 6.22 (s, 4 H, ArH_{reso}), 4.47 (t, ^3J = 7.6 Hz, 4 H, CH), 4.09 (m, 4 H, CH_2CH_2), 3.87 (m, 4 H, CH_2CH_2), 3.48 (s, 12 H, OCH_3), 3.38 (m, 4 H, CH_2CH_2), 3.29 (m, 4 H, CH_2CH_2), 1.88 (m, 8 H, CH_2CH_3), 0.92 (t, ^3J = 7.2 Hz, 12 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 155.7, 154.8, 136.7, 135.6, 126.2, 126.1, 126.0, 119.9, 119.4, 116.0, 112.9, 96.9, 67.2, 56.0, 44.0, 36.9, 27.9, 12.7 ppm. MS (ESI-TOF): *m*/*z* = 1193.69 $[M]^+$. $C_{72}H_{88}N_8O_8$ (1193.54): calcd. C 72.46, H 7.43, N 9.39; found C 72.13, H 7.47, N 9.00.

NMR Spectroscopic Methods: ^1H NMR titrations were done by subsequently adding increasing aliquots of the F^- and AcO^- anions as their TBA salts in [D$_6$]DMSO in the solution of the host in [D$_6$]-DMSO and recording the spectra at 303 K with Bruker Avance

DRX 500 spectrometer. The obtained titration data was analyzed by the computer program EQNMR.[15] For the other investigated anions (Cl^-, Br^-, I^-, NO_3^-, BF_4^- and PF_6^-) a 10 fold excess of the salt (added as TBA salts) confirmed there was no interaction between the host and the guest species. Job plot samples were prepared with 0.3, 0.5, 1, 2, and 3 equiv. of the salt while keeping the sum of host and guest concentration equal.

NMR diffusion measurements were performed by using Bruker Avance 400 MHz spectrometer equipped with a Great 1/10 pulsed gradient unit and a direct probe at 303 K. A LED[21] pulse sequence was used for the diffusion measurements with a sine-shape pulsed gradient duration δ of 2.5 ms incremented from 0 to 27.0 G cm^{-1} in twelve steps. The pulsed gradient separation Δ was 100 ms and the eddy current delay was 5 ms. The reported diffusion coefficients are the average ± standard deviation of at least three different measurements. The samples were prepared 5 mM in **4** and 10 mM in the anion as its TBA salt.

Gas-Phase Binding Studies: All gas-phase experiments described herein were conducted with an Ionspec QFT-7 FT-ICR mass spectrometer (Varian Inc., Lake Forest, CA), equipped with a 7 T superconducting magnet and a Micromass Z-Spray electrospray ionization (ESI) source (Waters Co., Saint-Quentin, France). The samples were introduced into the source as 50 μM solutions of **4** and the corresponding anion in acetonitrile (or methanol) at flow rates of 1–2 μL/min. A constant spray and highest intensities were achieved with a capillary voltage of 3800 V at a source temperature of 40 °C. The parameters for sample cone and extractor cone voltage were optimized for maximum intensitites of the desired complexes. Multiple scans (10–20) were recorded and averaged for each spectrum in order to improve the signal-to-noise ratio. After accumulation and transfer into the instrument's FTICR analyzer cell, the ions were detected by a standard excitation and detection sequence.

For the fragmentation experiments, the ions of interest were mass selected in the ICR cell and irradiated with a 25 W CO_2 laser in the IR region [infrared multiphoton dissociation (IRMPD), 10.6 μm wavelength] to induce fragmentation.

Crystal Structure Determination: Data were recorded by using a Nonius Kappa CCD diffractometer having an Apex II detector with graphite-monochromatized Cu-K_α [λ(Cu-K_α) = 1.54178 Å] radiation at temperature of 173.0 K. The data were processed with Denzo-SMN v0.97.638.[22] The structures were solved by direct methods (SHELXS-97[23]) and refinements based on F^2 were made by full-matrix least-squares techniques (SHELXL-97[24]). The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms, except for the amine hydrogen atoms, which were located from the difference Fourier map. Absorption correction[25] was made to all structures, but used only in the structure Ib since it worsened the R-value with all the other structures.

CCDC-705756 (for **Ia**), -705757 (for **Ib**), -735535 (for **II**) and -735536 (for **III**) contain 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.

Ia: Colorless block crystals ($0.30 \times 0.15 \times 0.05$ mm^3) were grown by slow evaporation from acetonitrile solution of **4**. Crystal data: $C_{72}H_{88}N_8O_8 \cdot 2CH_3CN$; M_r = 1275.61; triclinic; space group $P\bar{1}$; a = 15.3148(5), b = 15.8823(5), c = 16.3810(5) Å; α = 74.421(1), β = 82.453(1), γ = 63.744(1)°; V = 3441.7(2) Å^3; Z = 2; $\rho_{calcd.}$ = 1.231 Mg m^{-3}; 2θ range = 3.19–67.29°; 17646 reflections collected; 11837 independent reflections (R_{int} = 0.237); 912 parameters; R_1 = 0.059, wR_2 = 0.130 for observed data [$I > 2\sigma(I)$]; R_1 = 0.092, wR_2 = 0.150 for all data; GOF = 1.062. Disordered solvent acetonitrile over two positions with site occupancy of 0.6:0.4. The bonding distances are restrained to be equal (SADI). DFIX used for amine hydrogen atoms H53, H70B, H80A and H80B.

Ib: Colorless block crystals ($0.10 \times 0.10 \times 0.05$ mm^3) were grown by slow evaporation from acetonitrile/ethanol solution of **4**. Crystal data: $C_{72}H_{88}N_8O_8 \cdot CH_3CN \cdot CH_3CH_2OH$; M_r = 1280.63; triclinic; space group $P\bar{1}$; a = 15.2189(5), b = 15.8530(5), c = 16.5455(5) Å; α = 74.357(3), β = 83.113(2), γ = 64.094(2)°; V = 3457.7(2) Å^3; Z = 2; $\rho_{calcd.}$ = 1.230 Mg m^{-3}; 2θ range = 3.19–67.02°; 14508 reflections collected; 11223 independent reflections (R_{int} = 0.136); 912 parameters; R_1 = 0.083, wR_2 = 0.199 for observed data [$I > 2\sigma(I)$]; R_1 = 0.142, wR_2 = 0.240 for all data; GOF = 1.033; Disordered solvent acetonitrile over two positions with site occupancy of 0.2:0.8.

II: Colorless block crystals ($0.30 \times 0.25 \times 0.10$ mm^3) were grown by slow evaporation from acetonitrile/TBACl solution of **4**. Crystal data: $C_{72}H_{88}N_8O_8 \cdot CH_3CN$; M_r = 1234.56; triclinic; space group $P\bar{1}$; a = 14.9523(3), b = 14.9859(4), c = 17.0271(4) Å; α = 109.464(2), β = 100.650(2), γ = 104.694(2)°; V = 3324.4(1) Å^3; Z = 2; $\rho_{calcd.}$ = 1.233 Mg m^{-3}; 2θ range = 2.88–63.45°; 16387 reflections collected; 10787 independent reflections (R_{int} = 0.045); 910 parameters; R_1 = 0.049, wR_2 = 0.119 for observed data [$I > 2\sigma(I)$]; R_1 = 0.071, wR_2 = 0.133 for all data; GOF = 1.017; disordered ethyl chain C35-**C36** and methoxy group O11–**C38** over two positions with the site occupancies of 0.6:0.4 and 0.7:0.3, respectively. Disordered solvent acetonitrile over two positions with site occupancy of 0.7:0.3 and the bonding distances are restrained to be equal (SADI).

III: Colorless block crystals ($0.15 \times 0.15 \times 0.10$ mm^3) were grown by slow evaporation from pyridine solution of **4**. Crystal data: $C_{72}H_{88}N_8O_8 \cdot 3C_5H_5N$; M_r = 1430.80; monoclinic; space group $P2_1/c$; a = 13.6942(3), b = 22.2544(4), c = 25.7929(5) Å; β = 96.985(1)°; V = 7802.2(3) Å^3; Z = 4; $\rho_{calcd.}$ = 1.218 Mg m^{-3}; 2θ range = 2.63–67.09°; 23691 reflections collected; 13318 independent reflections (R_{int} = 0.061); 1025 parameters; R_1 = 0.066, wR_2 = 0.154 for observed data [$I > 2\sigma(I)$]; R_1 = 0.114, wR_2 = 0.185 for all data; GOF = 1.026; Disordered solvent pyridine over two positions with site occupancy of 0.8:0.2. Restraints SAME and EADP used for the disordered part.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of **2**, **3**, and **4**; crystal structure of **3**; Job plot and NMR titration data; gas-phase binding data.

Acknowledgments

K. S. wishes to thank the Academy of Finland for funding (project 116503), Mr. Reijo Kauppinen for his help with the NMR measurements and B. Sc. Katri Moilanen for her help with the synthesis.

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Received: July 20, 2009
Published Online: October 27, 2009

