

Anion Recognition

Rim, Side Arms, and Cavity: Three Sites for the Recognition of Anions by Tetraazolium Resorcinarene Cavitannds

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Abstract: Two tetrabenzoimidazolium-resorcinarene cavitannds were prepared and used for the recognition of chloride, bromide, iodide, cyanide, nitrate, perchlorate, hexanoate, benzenesulfonate, and *p*-toluenesulfonate. Binding affinities of the two cavitannds were determined by ¹H NMR titration and computational analysis. The observed spectral changes were related to specific interaction sites, which were supported by the computational studies. In the case of the C2–H tetrabenzoimidazolium-resorcinarene, the recognition region of the inorganic anions and hexanoate was located at the rim of the cavitannd, although chloride and bromide also interacted with the aromatic C–H bonds located between adjacent arms of the cavitannd. By contrast, the rec-

ognition of the two anions with an aromatic ring (benzenesulfonate and *p*-toluenesulfonate) results from encapsulation of the aromatic part of the anions inside the hydrophobic cavity of the host. In the case of the C2–Me tetrabenzoimidazolium-resorcinarene receptor, the ability of the molecule to bind all inorganic anions and hexanoate was suppressed, but the receptor maintained its ability to strongly bind benzenesulfonate and *p*-toluenesulfonate. This is interpreted in terms of suppression of the ability of the cavitannd to form hydrogen bonds at the rim of the molecule due to replacement of the C2–H proton by a methyl group, while the hydrophobic pocket of the molecule maintains its binding abilities.

Introduction

Given the importance of anions in the context of environmental chemistry, the design of anion-selective receptors continues to attract great interest in the supramolecular community.^[1] Among the various types of these receptors, imidazolium-based supramolecules have been extensively investigated^[1a,2] since the pioneering works by Sato et al.,^[3] Alcalde et al.,^[4] Kim et al.,^[5] and Fabbrizzi et al.^[6] Due to their cationic nature, it is now well accepted that the recognition of anions by this type of receptors is dominated by a combination of electrostatic interactions and hydrogen bonding [(C–H)⁺... A⁻]. In most cases, the reported imidazolium-based receptors have one to four imidazolium units in the form of tweezer, dipodal, tripodal, or other open forms, whereas less attention has been paid to the preparation of imidazolium-based macrocycles with closed conformations. Receptors combining an array of positively

charged imidazolium units and a cavity may enhance the binding affinity and selectivity toward anions, depending on the adaptability of the cavity to the steric and electronic requirements of the guest.^[7] This is particularly important for anions, due to their larger variation in size and geometry compared with cations. The idea of combining imidazolium units with cavities was first proposed by Yoon and co-workers a decade ago,^[8] by preparing a calixarene-based cavitannd bearing four imidazolium rings as receptors for anions. Since then, only very few examples of the incorporation of imidazolium units in organized architectures, such as calixarenes or resorcinarenes,^[9] have been described, most probably due to the difficult synthetic procedures involved.

Tetrabenzoimidazole-resorcinarene cavitannds are known to be effective receptors for hosting and selectively recognizing small neutral molecules and cations.^[10] On the other hand, anion– π contacts, defined as the favorable electrostatic complementarity between negatively charged entities and electron-deficient π systems, are emerging as a new branch in supramolecular chemistry.^[11] Taking all this into account, we envisaged combining imidazolium salts with the presence of an electron-deficient pocket in resorcinarene cavitannds to prepare a highly versatile receptor for the recognition of a wide variety of anions of different natures, shapes, and sizes. In this work, we describe the preparation of two tetrabenzoimidazolium-resorcinarene cavitannds and the evaluation of their recognition properties. In contrast to all other calixarenes or resorcinarene molecules containing imidazolium units described so

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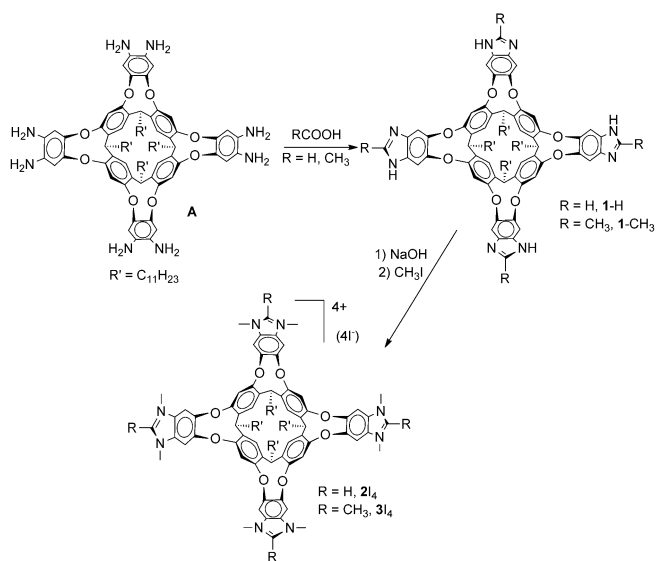
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far,^[9] our new compounds contain four benzoimidazolium fragments, which are directly embedded into the rigid structure of the cavitand and thus limit the flexibility of the azolium moieties and provide an organized macromolecule for the encapsulation of inorganic and organic anions.

Results and Discussion

Preparation of the imidazolium-based cavitands

We first prepared the tetrabenzoimidazolium iodide **2I₄** (Scheme 1) by reaction of tetrabenzoimidazole cavitand **1-H**^[10a]



Scheme 1. Preparation of cavitands **2I₄** and **3I₄**.

with $NaOH$ in DMSO, followed by addition of CH_3I (44% yield). For the preparation of methyl-substituted cavitand **3I₄**, we started with the tetracyclization of octa-amino cavitand **A** in the presence of acetic acid, which afforded methyl-substituted resorcinarene-based tetrabenzoimidazole cavitand **1-CH₃**. Octa-*N*-methylation of **1-CH₃** to afford tetrabenzoimidazolium compound **3I₄** was performed by reaction of **1-CH₃** with $NaOH$ in DMSO, followed by the addition of CH_3I (70% yield). The related hexafluorophosphate salts **2(PF₆)₄** and **3(PF₆)₄** were readily prepared by anion exchange of **2I₄** and **3I₄** with NH_4PF_6 in CH_3OH . All salts were characterized by NMR spectroscopy and ESI mass spectrometry.

The NMR spectra of the tetrabenzoimidazolium salts reveal highly symmetric systems, as illustrated by the appearance of one set of signals due to each of the four branches of the molecules (see Supporting Information for the full spectra of all new species). The signal due to the acidic proton at the benzoimidazolium group appears at 9.69 ppm for **2I₄**. This signal does not appear in the spectrum of **3I₄**, and instead a singlet due to the presence of the four $NC(CH_3)N$ groups appears at 2.76 ppm. The two molecules adopt a vase-type conformation, as indicated by the 1H NMR signal due to the proton of the re-

sorcinarene methine group at 5.70 and 5.65 ppm for **2I₄** and **3I₄**, respectively.^[12] Similar spectroscopic features are observed for **2(PF₆)₄** and **3(PF₆)₄**.

The vase conformation of the cavitands is also supported by molecular dynamics (MD) simulations of **2I₄** and **3I₄**, which we carried out in explicit DMSO (see Supporting Information for parameters development and simulation details; note that, in order to simplify the calculations, methyl groups were used instead of the full $C_{11}H_{23}$ chains). Reports on MD simulations of supramolecular systems are rare, especially those regarding resorcinarene-based cavitands.^[13] The conformational dynamics of the cavitand can be described as an antisymmetric stretch in which the distances between adjacent arms are maintained, whereas the distances between opposing arms are anti-correlated (Figure 1). Simulations show that the cavitand cavities are

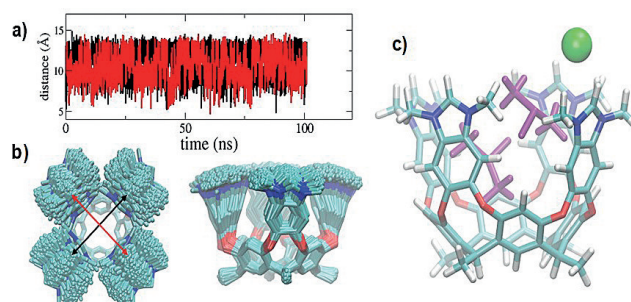


Figure 1. MD simulation of **2I₄**. a) The variation in time of the distances between opposing arms of the cavitand. b) A set of 500 equally spaced conformations along the simulation were overlapped to show the movements of the arms (top and side views). c) Representative snapshot showing two DMSO solvent molecules (purple sticks) occupying the cavity and an iodide ion (green sphere) interacting with the tip of an arm at the rim.

occupied by DMSO molecules: one molecule is found at the bottom of the cavity, and one or two other molecules occupy the rim region (Figure 1). The DMSO molecule deeper inside the cavitand exchanges with bulk solvent molecules on a slower timescale than the molecules at the rim (Figure S51 in the Supporting Information). According to Rebek's rule,^[14] the packing coefficient is around 50% for both cavitands (see Supporting Information for details and a movie showing the flexibility of the cavitand).

Anion recognition

We first studied the recognition scope of **2(PF₆)₄** with a variety of anions, which were added as tetrabutylammonium salts. The binding affinities were studied by 1H NMR spectroscopic methods in DMSO. The anions chosen for this study (chloride, bromide, iodide, perchlorate, nitrate, cyanide, hexanoate, benzenesulfonate, and *p*-toluenesulfonate) are of contrasting geometries and charge densities. Other anions, such as fluoride and acetate were also tested, but in the course of the titrations we observed oxidation of benzoimidazolium to benzoimidazolidone (detected by mass spectrometry), as a consequence of the deprotonation of the azolium groups by the basic anions

and the subsequent oxidation of the resulting N-heterocyclic carbenes. In general, addition of the anions caused downfield shifts in the imidazolium proton resonance, in agreement with previous works regarding the use of imidazolium compounds for anion recognition.^[1a,2] However, in the case of the titrations with chloride and bromide, the signals due to the protons at the arms of the cavity showed significant downfield shifts, which indicate that the anion does not interact only with the rim of the molecule, where the more acidic C–H bonds are located. This observation is particularly relevant to the titrations with Cl[−], for which the downfield shift of the resonance of the phenylene protons (b in Figure 2a) of 0.56 ppm is comparable to that of the imidazolium protons (0.4 ppm). All other inorganic anions, such as nitrate, cyanide, perchlorate, and iodide,

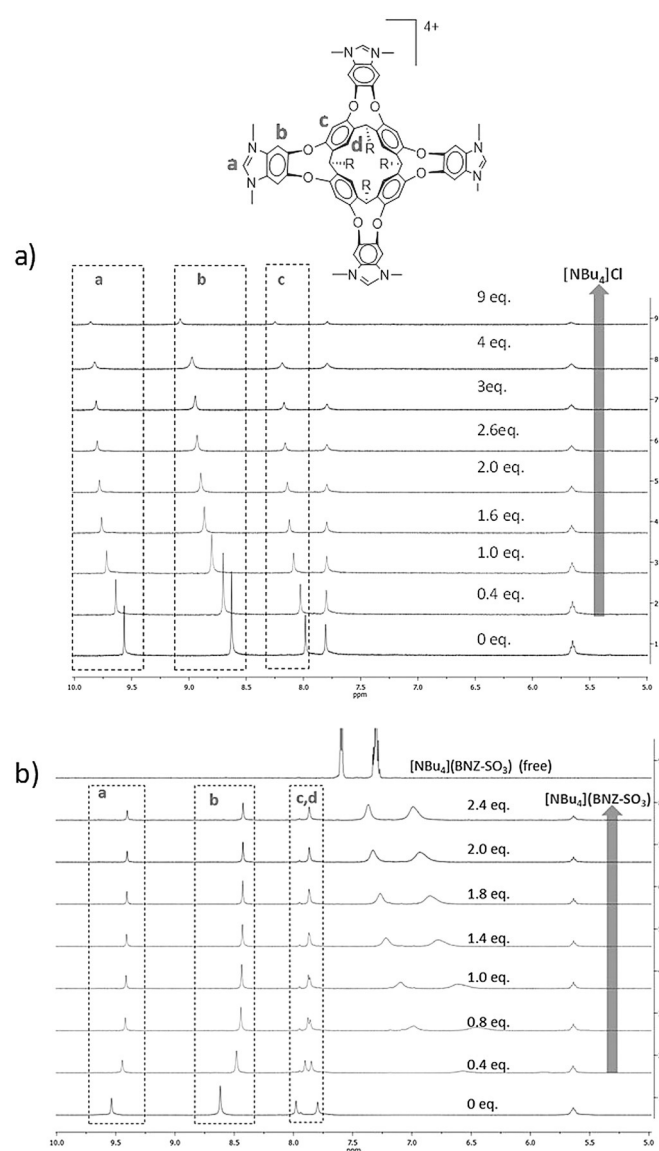


Figure 2. Representative region of the ¹H NMR (500 MHz) spectra of the titration of **2**(PF₆)₄ with a) [NBu₄]Cl and b) [NBu₄](BNZ-SO₃), both in [D₆]DMSO. In both cases, the lowermost spectrum corresponds to free **2**(PF₆)₄. The uppermost spectrum of series b) corresponds to free [NBu₄](BNZ-SO₃).

as well as hexanoate, only shifted the resonance of the more acidic imidazolium proton.

In contrast to these anions, addition of benzenesulfonate (BNZ-SO₃[−]) or *p*-toluenesulfonate (PTSO₃[−]) results in upfield shifts of the signals of both the phenylene protons of the cavitand and the signals due to the aromatic protons of the anions (see Supporting Information). This result is strongly suggestive of a situation in which the anion is encapsulated inside the cavity of the tetrabenzimidazolium cavitand, most likely due to C–H⋯π interactions. The signals due to the protons of these two guests are broad and, despite being strongly upfield shifted with respect to the resonances of the free anions, their chemical shifts are dependent on the amount of anion added, and thus indicative of a dynamic situation in which free and encapsulated guests are in fast exchange on the NMR time-scale. Similar features were observed in the spectra of **3**(PF₆)₄ treated with chloride, bromide, benzenesulfonate, and toluenesulfonate (see Supporting Information).

MD simulations of **2I**₄, **2I**₄, **2**(BNZ-SO₃)₄, **3I**₄, **3I**₄, and **3**(PTSO₃)₄ in explicit DMSO solvent were carried out to investigate anion–cavitand interactions. A 100 ns simulation was performed for each system to provide a picture of the preferred interaction modes between the cavitands and the anions, and a qualitative estimation of their relative strength. The movies of these simulations are provided as Supporting Information to afford a clearer picture of this description. Figure 3a and b show the most visited regions of iodide and benzenesulfo-

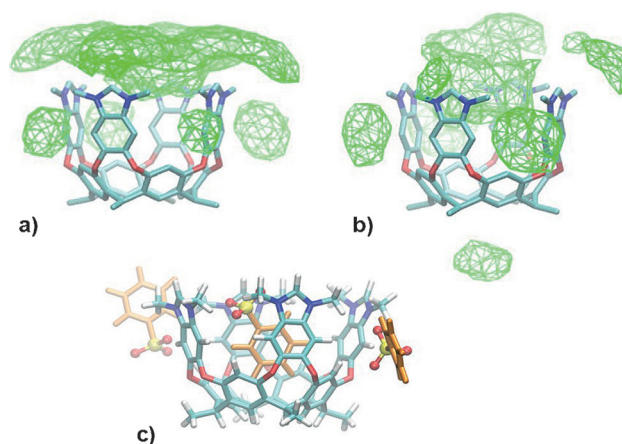


Figure 3. MD simulations of **2I**₄ (a) and **2**(BNZ-SO₃)₄ (b, c). a), b) Occupancy of anions around the cavitands: green isosurface at 1% probability. c) Snapshot of the cavitand showing the benzenesulfonate molecules as orange sticks and oxygen atoms as red balls.

nate anions around the positively charged cavitand **2**⁴⁺ (see also Figures S52–S55).

For halides, two favorable binding regions can be recognized, in agreement with the experimental evidence obtained by ¹H NMR titration. One is at the rim of the cavity, with the acidic C–H bonds of the azolium units. The other is on the side of the cavitand, where the anions simultaneously interact with the phenylene C–H bonds of adjacent benzoimidazolium fragments and with the resorcinarene aromatic C–H bond,

which points toward the cationic side of the molecule. The participation of aryl C–H bonds in the recognition of anions is rather unusual,^[15] although the earliest examples were reported in 2002.^[16] In line with this finding, the molecular electrostatic potential of the cavitand shows that the positive charge of the molecule is widely distributed through the arms of the cavitand (Figure S56 in the Supporting Information). For cavitand **3**⁴⁺ (see Figures S53–S55 and the movies provided in the Supplementary Information), chloride interacts with the side-arm region, whereas the interaction at the rim occasionally takes place with the CH₃ substituents of two adjacent arms. For both cavitands **2**⁴⁺ and **3**⁴⁺, the simulations show that chloride and iodide do not visit the interior of the cavity. Indeed, MD simulations that started with a chloride or iodide anion inside the cavitand pocket showed the anion moving out of the cavity in the early stage of the simulation. From the residence times (Figure S52 in the Supporting Information) and occupancies (Figures S53 and S54 in the Supporting Information), the interactions of chloride with the arms of the cavitand appear stronger than those with the rim atoms, whereas for iodide specific interactions are short-lived and thus weaker.

In the case of **2**(BNZ-SO₃)₄ and **3**(BNZ-SO₃)₄, simulations show a different behavior than for halides. In this case one anion persistently occupies the interior of the cavitand (Figure 3b), while all other three are about the rim. The anion is oriented with the aromatic moiety inside the cavitand and the sulfonate group towards the rim (see Figure 3c and movies in the Supporting Information). The substrate shows π -stacking interactions with two opposing arms with occasional reorientation by 90° along its axis and thus exchange of interacting arms (see Figure S52 in the Supporting Information). In line with Rebek's rule,^[14] the packing coefficient is around 50% (it is noteworthy that compared to **2I**₄ and **3I**₄, the cavity shrinks about the guest, and thus the volume of the host is adapted to the size of the guest). For **2**(BNZ-SO₃)₄, we observed that the substrate briefly left the cavity once during the simulation, and this suggests some degree of fluctuation. These interactions of the substrate with the cavitand are reflected in the ¹H NMR titration experiment showing the shift of the signals corresponding to the aromatic protons of both the cavitand and the ligand. On the basis of the residence times (Figure S52 in the Supporting Information) and occupancies (Figure S55 in the Supporting Information), we estimate the strength of interactions of benzenesulfonate with the sites at cavitands **2** and **3** as cavity interior > arms > rim.

Determination of affinity constants

Analysis of the ¹H NMR titrations allowed the stoichiometry of the host:guest complexes formed and their association constants K_a to be determined.^[17] We determined that the stoichiometry of the complexes formed was 1:1 for **2**⁴⁺:X⁻ for all anions X⁻ on the basis of the binding isotherms resulting from the ¹H NMR titrations, which in all cases were best fitted to the formation of 1:1 complexes. Job plots also supported this stoichiometry,^[18] but their limited applicability prompted us to also analyze the residual distribution of the titration-data fit-

ting.^[19] In all cases the 1:1 stoichiometry gave the smallest residuals compared to a potential 1:2 stoichiometry (selected examples are shown in the Supporting Information). The ESI mass spectrometric experiments also supported this stoichiometry, because only the m/z peaks due to the tricationic complexes formed by the association of **2**⁴⁺ with one equivalent of anion (see Supporting Information for more details) were observed. The 1:1 association constants K_{11} were calculated by global nonlinear regression analysis by simultaneously including all protons showing chemical-shift variations.^[17a,20] As can be seen in Table 1, K_{11} values for **2**⁴⁺ follow the trend Cl⁻ >

Table 1. Binding constants of **2**(PF₆)₄ and **3**(PF₆)₄ with [NBu₄]X (DMSO, 25 °C).^[a]

Entry	Anion	Host K_{11} [M ⁻¹]	
		2 (PF ₆) ₄ ^[b]	3 (PF ₆) ₄ ^[b]
1	Cl ⁻	470 (3.3%)	6.9 (3%)
2	Br ⁻	215 (9.7)	13.2 (2%)
3	I ⁻	71 (4%)	≈ 0
4	ClO ₄ ⁻	370 (4%)	≈ 0
5	NO ₃ ⁻	100 (4%)	≈ 0
6	CN ⁻	93 (4%)	≈ 0
7	hexanoate	106 (5%)	≈ 0
8	<i>p</i> -toluenesulfonate	> 10 ⁴	> 10 ⁴
9	benzenesulfonate	8677 (8.6%)	3720 (49%)

[a] K_{11} values calculated by global nonlinear regression analysis.^[17a,20]
[b] Errors are given in parentheses.

Br⁻ > I⁻, in agreement with the basicity trend of the anions. In general, all inorganic anions showed association constants ranging between 100 and 500 M⁻¹. Since all these anions have in common that they interact with the periphery of the cavitand by essentially hydrogen-bonding interactions, it can be assumed that this is the range of binding affinities associated with the presence of acidic CH protons at the rim of the receptor. A clearly distinct situation arises from the observation of the affinities shown for the two aryl-substituted anions (*p*-toluenesulfonate and benzenesulfonate), the K_{11} values of which are 2–3 orders of magnitude larger. Thus, for these molecules encapsulation in the pocket of the cavitand produces a host-guest complex that is much more stable than those formed with the rest of the inorganic anions, and this indicates a very high degree of selectivity of the receptor. In the case of the association constant of **2**⁴⁺ with *p*-toluenesulfonate, the estimated value of K_{11} is associated with a high degree of uncertainty, due to the well-accepted limitations in the determination of large affinity constants (> 10⁴ M⁻¹) by ¹H NMR titrations.^[17a,20]

An interesting consequence of the recognition properties of **2**⁴⁺ can be inferred by comparing the binding affinities of **3**⁴⁺ with the same anions. Receptor **3**⁴⁺ differs from **2**⁴⁺ by the presence of four methyl groups instead of the four protic hydrogen atoms at the rim of the molecule; hence, in principle, it can be considered that the hydrogen-bonding abilities of the molecule are suppressed, while the positive charges and the pocket are maintained. This gives a good opportunity to compare the recognition properties of two equally charged and

topologically similar molecules, but with different recognition functions. As can be seen from the results listed in Table 1, the presence of the methyl groups at the rim of 3^{4+} inhibits the affinity of the cavitand for all inorganic anions and hexanoate (only chloride and bromide maintain small binding constants ranging between 6 and 13 M^{-1}), while maintaining a high affinity for the anions with aromatic functionality. The observation that chloride and bromide still show some measurable binding constants with 3^{4+} is a direct consequence of the fact that these two anions are able to bind to the aromatic CH groups located at the arms of the cavitand. These findings have important implications for the design of these and future cavitands, because they reflect how subtle changes in the design of the receptor may have very important consequences for the selectivity of the resulting sensor.

Conclusion

We prepared two new tetrabenzimidazolium-resorcinarene cavitands for the recognition of anions. The C2–H tetrabenzimidazolium cavitand is able to recognize a variety of anions with contrasting geometries and charge densities, but the type of recognition and the binding affinity are clearly dependent on the nature of the anions. The recognition abilities of $2(\text{PF}_6)_4$ exceeded all of our initial expectations in the sense that it showed three clear recognition sites, which were selectively operative depending on the nature of the anions used. Larger inorganic anions, such as iodide, perchlorate, cyanide, and nitrate, as well as hexanoate, are predominantly recognized at the rim of the molecule, through the hydrogen-bonding interaction with the acidic CH proton of the benzoimidazolium unit. Smaller inorganic anions, such as chloride and bromide, also interact with the adjacent arms of the molecule, through hydrogen-bonding interactions with the C–H bonds of the phenylene rings of the benzoimidazolium units and those of the resorcinarene moiety. Finally, anions with aromatic functionality, such as benzenesulfonate and *p*-toluenesulfonate, are recognized by encapsulation of the aromatic part of the anion inside the cavity of the host. This situation has a clear consequence in the titration of the different anions by ^1H NMR spectroscopy, which shows clearly distinctive situations depending on the anion used in the titration. The combination of both the presence of the imidazolium groups and the preorganized structure provides a clear enhancement in the recognition abilities of the molecule. This may have a clear advantage in the recognition of anions in D_2O , in which the acidic C–H bond of the azolium moiety is expected to undergo fast H/D exchange (we are currently working on making a water-soluble analogue of 2^{4+}).^[21] This can be especially useful for the detection of potentially toxic (cyanide) or environmentally deleterious (nitrate) anions.

The study on the binding affinities of 3^{4+} , in which the protons at the rim of the molecule are substituted by four methyl groups, revealed that the sensing properties of the molecule are strongly modified. The presence of the C2–Me groups at the rim of the molecule suppresses the hydrogen-bonding ability of the cavitand, and for this reason the receptor is now

unable to complex all those anions that showed affinity to the protons at the rim of 2^{4+} , and thus 3^{4+} is a highly selective receptor. Only chloride and bromide showed small yet measurable association constants with 3^{4+} , because they are also able to bind to the aromatic C–H bonds located at the side arms of the molecule. The ability of 3^{4+} to complex the anions with aromatic functionality, namely, benzenesulfonate and *p*-toluenesulfonate, remained practically unchanged compared to that shown by 2^{4+} . Both hydrogen-bonding and C–H $\cdots\pi$ interactions are at play in the binding affinities of 2^{4+} and 3^{4+} , and their interplay may inspire future research aiming to design new highly selective anion receptors.

Experimental Section

General comments

All manipulations were carried out under nitrogen by using standard Schlenk techniques and high vacuum. Anhydrous solvents were distilled from appropriate drying agents (SPS) or purchased from Aldrich and degassed prior to use by purging with dry nitrogen and kept over molecular sieves. The resorcinarene-imidazole-cavitand **1-H**^[10a] and the octaamino resorcinarene **A**^[22] were obtained according to literature procedures. All other reagents were used as received from commercial suppliers. NMR spectra were recorded with spectrometers operating at 500 MHz (^1H NMR) and 126 MHz (^{13}C NMR). NMR spectra were recorded at room temperature with CD_2Cl_2 or $[\text{D}_6]\text{DMSO}$ as solvents.

A Q-TOF mass spectrometer with an electrospray source operating in the V-mode was used. The drying gas and cone gas were both nitrogen at a flow rate of 300 and 30 L h^{-1} , respectively. The temperature of the source block was set to 100°C and the desolvation temperature was set to 150°C . Capillary voltages of 3.5 and 3.3 kV were used in the positive and negative scan modes, respectively, and the cone voltage was adjusted typically to $U_c = 50 \text{ V}$. Mass calibration was performed by using solutions of NaI in propan-2-ol:water (1:1) in the range m/z 50–3000.

Synthesis of compounds

Compound 2I₄: A mixture of tetrabenzimidazole cavitand **1-H** (480.0 mg, 0.31 mmol) and NaOH (62.5 mg, 1.56 mmol) was stirred in 2 mL of DMSO at room temperature for 2 h. After this time CH_3I (86 μL , 1.24 mmol) was added and the mixture was stirred at 37°C for 8 h. Then, CH_3I (860 μL , 12.4 mmol) was added and the mixture was stirred at 100°C for 8 h. The final suspension was cooled to room temperature and the crude salt was precipitated in methanol (50 mL). The resulting brown precipitate was collected by filtration, washed with methanol, and dissolved in acetone. The solvent was removed under vacuum and the solid was precipitated in methanol and collected by filtration. Compound **2I₄** was obtained as a brown-red solid in a 44% yield (300 mg). ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 9.60$ (s, 4H, $\text{CH}_{\text{NH(C)}}$), 8.63 (s, 8H, $\text{CH}_{\text{aromatic}}$), 7.98 (s, 4H, $\text{CH}_{\text{aromatic}}$), 7.81 (s, 4H, $\text{CH}_{\text{aromatic}}$), 5.65 (t, $J = 7.8 \text{ Hz}$, 4H, CH), 3.92 (s, 24H, CH_3), 2.43 (m, 8H, CH_2), 1.45 (m, 8H, CH_2), 1.26 (m, 64H, CH_2), 0.87 (t, $J = 6.7 \text{ Hz}$, 12H, CH_3); HRMS ESI-TOF-MS (positive mode): m/z 419.5 $[\text{M}-4\text{I}]^+$, 601.7 $[\text{M}-3\text{I}]^{3+}$, 966.0 $[\text{M}-2\text{I}]^{2+}$.

Compound 2[PF₆]₄: Compound **2I₄** (90.5 mg, 0.041 mmol) was dissolved in acetone (30 mL) and the solution mixed with a solution of NH_4PF_6 (35.2 mg, 0.22 mmol) in CH_3OH (10 mL). The reaction mixture was stirred at 40°C for 24 h. The final suspension was cooled to room temperature and a white precipitate appeared

after few minutes. This precipitate was collected by filtration, washed with CH₃OH, and dried (80 mg, 86% yield). ¹H NMR (500 MHz, [D₆]DMSO): δ = 9.57 (s, 4H, CH_{NHC}), 8.63 (s, 8H, CH_{aromatic}), 7.99 (s, 4H, CH_{aromatic}), 7.80 (s, 4H, CH_{aromatic}), 5.66 (t, J = 7.8 Hz, 4H, CH), 3.91 (s, 24H, CH₃), 2.42 (m, 8H, CH₂), 1.44 (m, 8H, CH₂), 1.25 (m, 64H, CH₂), 0.86 (m, 12H, CH₃); ¹³C NMR (126 MHz, [D₆]DMSO): δ = 154.8, 151.7, 144.8, 136.4, 129.4, 126.0, 115.8, 109.9, 49.1, 34.0, 31.8, 29.7, 29.6, 29.5, 29.2, 28.2, 22.6, 14.4; electrospray MS (U_c = 20 V): m/z 419.7 [M-4PF₆]⁺, 607.8 [M-3PF₆]³⁺.

Compound 1-CH₃: A mixture of octaamino cavitand (418 mg, 0.275 mmol) and acetic acid (10 mL) was stirred at 100 °C for 48 h. After this time the reaction mixture was cooled to room temperature. A saturated aqueous solution of K₂CO₃ was added to the mixture in an ice/water bath until pH 8. A white precipitate appeared after few minutes. The precipitate was collected by filtration, washed with water, and dried. The crude product was purified by column chromatography. The pure compound was eluted with dichloromethane: methanol (9:1) and precipitated in methanol. Compound 1-CH₃ was obtained in 68% yield (303.8 mg, 0.187 mmol). ¹H NMR (500 MHz, CD₂Cl₂/CD₃OD): δ = 7.45 (s, 8H, CH_{aromatic}), 7.44 (s, 4H, CH_{aromatic}), 7.19 (s, 4H, CH_{NHC}), 5.65 (m, 4H, CH), 2.37 (s, 12H, CH₃), 2.19 (m, 8H, CH₂), 1.40 (m, 8H, CH₂), 1.22 (m, 64H, CH₂), 0.83 (t, 12H, CH₃); ¹³C NMR (75 MHz, DMSO): δ = 149.13, 130.76, 127.86, 122.46, 40.79, 40.52, 40.24, 39.96, 39.68, 39.40, 39.13, 35.49, 32.19, 31.83, 29.57, 29.27, 26.46, 22.60, 14.41; ESI-TOF-MS (positive mode): m/z 1619 [M-H]⁺.

Compound 3I₄: A mixture of 1-CH₃ (200.0 mg, 0.12 mmol) and NaOH (29.7 mg, 1.56 mmol) was stirred in 2 mL of DMSO at room temperature for 2 h. After this time CH₃I (31 μL, 0.48 mmol) was added and the mixture was stirred at 37 °C for 8 h. Then, CH₃I (310 μL, 4.8 mmol) was added and the mixture was stirred at 100 °C for 8 h. The final suspension was cooled to room temperature and the crude salt was precipitated in methanol (20 mL). The resulting brown precipitate was collected by filtration, washed with methanol, and dissolved in acetone. The solvent was removed under vacuum and the solid was precipitated in methanol and collected by filtration. Compound 3I₄ was obtained in 70% yield (193.9 mg, 0.09 mmol) as a brown solid. ¹H NMR (500 MHz, [D₆]DMSO) δ = 8.56 (s, 8H, CH_{aromatic}), 7.96 (s, 4H, CH_{aromatic}), 7.80 (s, 4H, CH_{aromatic}), 5.65 (m, 4H, CH), 3.87 (s, 24H, CH₃), 2.76 (s, 12H, CH_{3,NHC}), 2.42 (m, 8H, CH₂), 1.43 (m, 8H, CH₂), 1.26 (m, 64H, CH₂), 0.85 (t, 12H, CH₃); ¹³C NMR (126 MHz, [D₆]DMSO): δ = 154.20, 153.07, 150.51, 135.60, 128.32, 115.16, 108.58, 33.25, 31.14, 29.00, 28.87, 28.79, 28.54, 27.56, 21.89, 13.70; ESI-TOF-MS (positive mode): m/z 953.5 [M]⁴⁺.

Compound [3][PF₆]₄: Compound [3][I]₄ (356.3 mg, 0.161 mmol) was dissolved in acetonitrile (20 mL) and the solution mixed with NH₄PF₆ (138 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 1 h. The final suspension was cooled to room temperature and the solvent was removed. The solid was suspended in CH₃OH, collected by filtration, washed with CH₃OH, and dried. This compound was obtained in 90% yield (300 mg, 0.144 mmol). ¹H NMR (500 MHz, [D₆]DMSO) δ = 8.55 (s, 8H, CH_{aromatic}), 7.95 (s, 4H, CH_{aromatic}), 7.80 (s, 4H, CH_{aromatic}), 5.67 (m, 4H, CH), 3.84 (s, 24H, CH₃), 2.69 (s, 12H, CH_{3,NHC}), 2.43 (m, 8H, CH₂), 1.45 (m, 8H, CH₂), 1.26 (m, 64H, CH₂), 0.85 (t, 12H, CH₃); ¹³C NMR (101 MHz, [D₆]DMSO): δ = 154.60, 153.49, 150.94, 135.97, 128.70, 125.91, 108.94, 33.68, 31.93, 31.57, 29.44, 29.31, 29.23, 28.98, 27.99, 22.33, 14.14, 10.69; ESI-TOF-MS (positive mode): 433.3 [M]⁴⁺.

Classical MD simulations

Model System and force-field parameters: A simplified model of the cavitand was considered, in which methyl groups were used

instead of the full C₁₁H₂₃ chains. The cavitand was considered to be built from eight residues: four for the scaffold and one for each arm. Atomic point charges were computed for each fragment independently according to the RESP methodology.^[23] Amber GAFF parameters were used for bonding and van der Waals interactions.^[24] A model for the solvated cavitand was built with the xleap program from the Amber distribution (www.ambermd.org), including four counterions (Cl⁻, I⁻, or benzenesulfonate) to neutralize the simulation cell and about 1000 DMSO molecules in a cubic cell of about 47 Å edge length. Counterions were placed in the most favorable interacting sites of the electrostatic potential of the cavitand. Force-field parameters for DMSO are available from the Amber parameters database (www.ambermd.org).

Molecular dynamics simulations: Classical MD simulations were performed with the NAMD code (http://www.ks.uiuc.edu/Research/namd)^[25] at constant temperature (300 K) and pressure (1 atm) under periodic boundary conditions. A 1 fs time step was used to integrate the equations of motion. Short-range nonbonded interactions were computed every two MD steps, and a full electrostatic evaluation was performed every four MD steps by using the particle mesh Ewald method^[26] on a 64 × 64 × 64 grid. All bonds involving hydrogen atoms were constrained.^[27] A cutoff distance of 12 Å was used for nonbonded interactions.

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