Rim, side-arms and cavity: three sites for the recognition of anions with tetra-azolium-resorcinarene cavitands

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We would like to dedicate this article to the memory of Roberto Sánchez-Delgado

Abstract: Two tetrabenzoimidazolium-resorcinarene cavitands were prepared and used for the recognition of chloride, bromide, iodide, cyanide, nitrate, perchlorate, hexanoate, phenylsulfonate and *p*-tolylsulfonate. Binding affinities of the two cavitands were determined by ^{1}H NMR titrations 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 cavitand, although chloride and bromide also interacted with the aromatic C-H bonds placed between adjacent arms of the cavitand. By way of contrast, the recognition of the two anions with an aromatic ring (phenylsulfonate and *p*-tolylsulfonate) is produced by the encapsulation of the aromatic part of the anions inside the hydrophobic cavity of the host. In the case of the C2-Me tetrabenzoimizazolium-resorcinarene receptor, the ability of the molecule to bind all inorganic anions and hexanoate was suppressed, while the receptor maintained its ability to strongly bind phenylsulfonate and *p*-tolylsulfonate. This is interpreted by the suppression of the ability of the cavitand to form hydrogen bonds at the rim of the molecule, by the 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 within 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,[3] Alcalde,[4] Kim[5] and Fabbrizzi.[6] Due to their cationic nature, for this type of receptors it is now well accepted that the recognition of anions is dominated by a combination of electrostatic interactions and hydrogen bonding [(C-H)$^{+\cdots}$A$^-$]. In most cases, the reported imidazolium-based receptors have one to four imidazoliums in the form of tweezers, dipodal, tripodal or other open forms, while less attention has been given to the preparation of imidazolium-based macrocycles with closed conformations. The preparation of receptors combining an array of positively charged imidazoliums 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 the case of anions, due to their larger variation in size and geometry compared with cations. The idea of combining imidazoliums with cavities was first proposed by Yoon and co-workers one decade ago,[8] by preparing a calixarene-based cavitand bearing four imidazolium rings as receptors for anions. Since then, only very few examples of the incorporation of imidazoliums in organized architectures, such as calixarenes or resorcinarenes,[9] have been described, most probably due to the difficult synthetic procedures involved.

Tetrabenzoimidazole-resorcinarene cavitands 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 a 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 cavitands, to prepare a highly versatile molecule 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 cavitands, whose recognition properties are evaluated. In contrast with all other calixarenes or resorcinarene molecules containing imidazoliums described so far,[9] our new molecules contain four benzoimidazolium fragments, which are directly embedded into the rigid structure of the cavitand, therefore limiting the flexibility of the azoliums and providing an organized macromolecule for the encapsulation of inorganic and organic anions.

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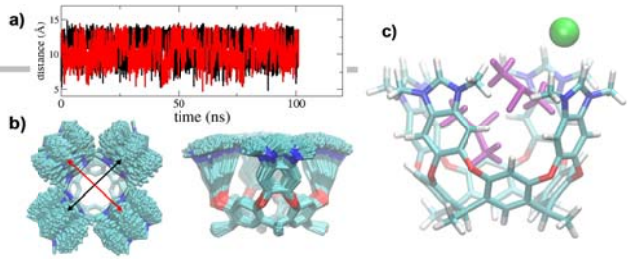
Results and Discussion

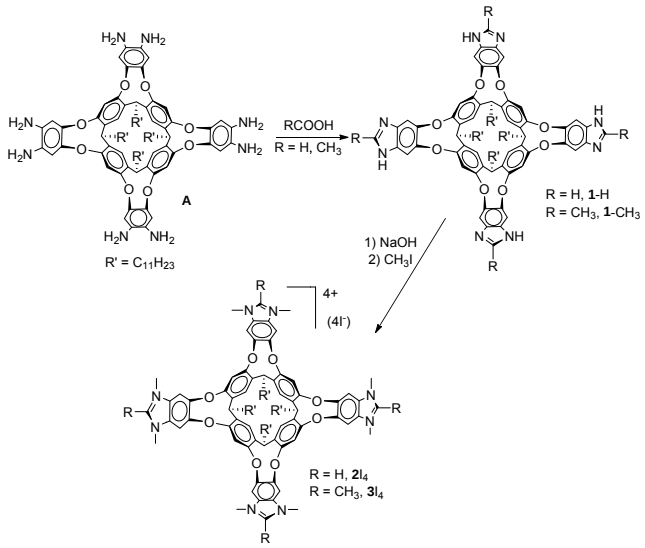
Results are presented in three sections devoted first to the preparation of the cavitands and then to the analysis of their recognition abilities for anions.

a) Preparation of the imidazolium-based cavitands

We first prepared the tetrabenzoimidazolium iodide **2I$_4$** by reaction of the tetrabenzoimidazole cavitand **1**-H[10a] with NaOH



in dimethylsulfoxide (DMSO), followed by the addition of CH_3I (yield 44 %). For the preparation of the methyl-substituted cavitand **3I$_4$**, we started by the tetra-cyclization of the octa-aminocavitand **A** in the presence of acetic acid, which afforded the methyl-substituted resorcinarene-based tetrabenzoimidazole cavitand **1**-CH_3. The octa-N-methylation of **1**-CH_3 to afford the tetrabenzoimidazolium compound **3I$_4$** was performed by reaction of **1**-CH_3 with NaOH in dimethylsulfoxide (DMSO), followed by the addition of CH_3I (yield 70 %). The related hexafluorophosphate salts, **2(PF$_6$)$_4$** and **3(PF$_6$)$_4$** were readily prepared by anion exchange of **2I$_4$** and **3I$_4$** with $[NH_4](PF_6)$ in CH_3OH. All salts were characterized by NMR spectroscopy and ESI mass spectrometry.



Scheme 1. Preparation of cavitands **2I$_4$** and **3I$_4$**

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 ESI for the full spectra of all new species). The signal due to the acidic proton at the benzoimidazolium appears at 9.69 ppm (for **2I$_4$**). This signal does not appear in the spectrum of **3I$_4$**, but instead the 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 ^{1}H NMR signal due to the proton of the resorcinarene methine group at 5.70 and 5. 65 ppm (for **2I$_4$** and **3I$_4$**, respectively).[12] Similar spectroscopic features are observed for **2(PF$_6$)$_4$** and **3(PF$_6$)$_4$**.

The vase conformation of the cavitands is also supported by molecular dynamics (MD) simulations of **2I$_4$** and **3I$_4$**, which we carried out in explicit DMSO (see ESI 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 may be described as an antisymmetric stretch, in which the distances between adjacent arms are maintained, whereas the distances between opposing arms are anticorrelated (Figure 1). Simulations show that the cavitands' cavities are 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 deeper DMSO molecule inside the cavitand exchanges with bulk solvent molecules on a slower timescale than the molecules at the rim (Figure S51). In line with Rebek's rule,[14] the packing coefficient is around 50% for both cavitands (see Supplementary Information for details and corresponding movie showing the flexibility of the cavitand: movie_cavity_2I4_slice.mpg).

Figure 1. MD simulation of **2I$_4$**. (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 (green sphere) interacting with an arm's tip at the rim

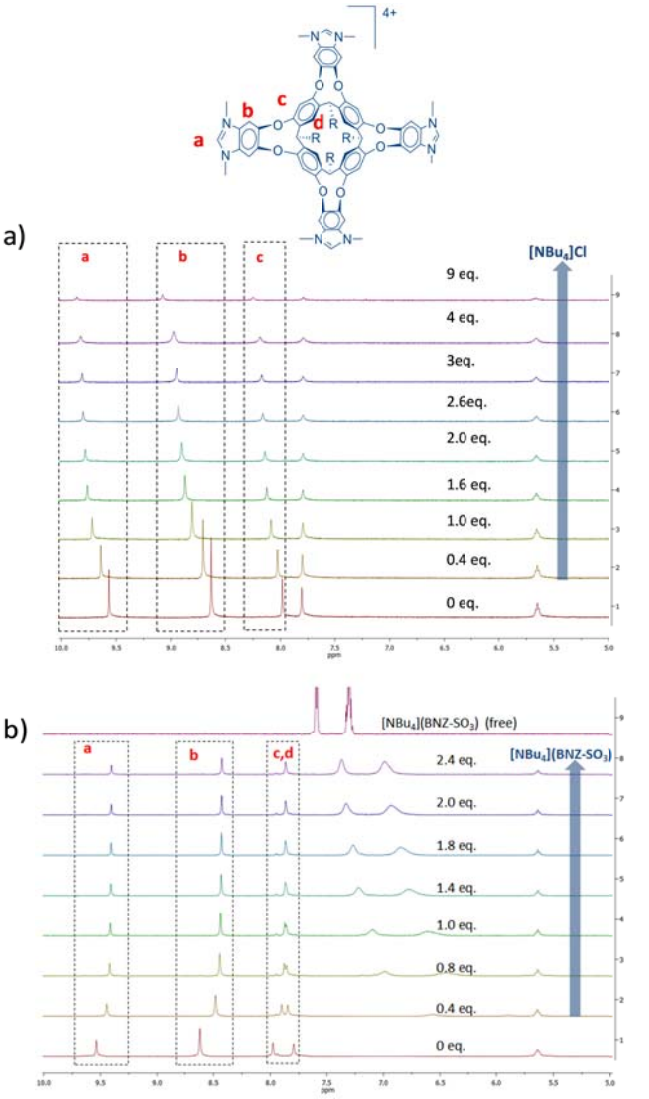
b) Anion recognition

We first studied the recognition scope of **2(PF$_6$)$_4$** with a variety of anions, which were added as tetrabutylammoium salts. The binding affinities were studied by ^{1}H NMR spectroscopic methods in DMSO. The anions chosen for this study (chloride, bromide, iodide, perchlorate, nitrate, cyanide, hexanoate, phenylsulfonate and *p*-tolylsulfonate) 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 the oxidation of the benzoimidazoliums to benzoimidazolidones (detected by mass spectrometry), as a consequence of the deprotonation of the azoliums 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 imidazoliums 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, therefore indicating that the anion is not only interacting with the rim of the molecule, where the more acidic C-H bonds are located. This observation is particularly relevant for the case of the titrations with Cl^-, for which the shifts in the resonances of the phenylene protons (b, in Figure 2a) are downfield shifted by 0.56 ppm, compared to the shifts in the resonances of the imidazolium protons, which are 0.4 ppm. All other inorganic anions such as nitrate, cyanide, perchlorate or iodide, and also hexanoate, only shifted the resonance of the more acidic imidazolium proton.

In contrast to these anions, addition of phenyl-sulfonate (BNZ-SO_3^-) or *p*-tolylsulfonate (PT-SO_3^-) results in the upfield shift of the signals of both the phenylene protons of the cavitand, and of the signals due to the aromatic protons of the anions (see ESI). This result is strongly suggestive of a situation in which the anion is encapsulated inside the cavity of the tetrabenzoimidazolium 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 the anion added, thus indicating a dynamic situation in which free and encapsulated guests are in fast exchange on the NMR timescale. Similar features were observed in the spectra of **3(PF$_6$)$_4$** treated with chloride, bromide, benzene- and toluene-sulfonates (see ESI).

MD simulations of **2I$_4$**, **2Cl$_4$** and **2(BNZ-SO$_3$)$_4$**, and of **3I$_4$**, **3Cl$_4$** and **3(BNZ-O$_3$)$_4$** in explicit DMSO solvent were carried out to investigate anion-cavitand interactions. A 100 ns simulation was performed for each system, providing 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 thee simulations are provided as supplementary material in order to afford a clearer picture of this description. Figure 3a,b shows the most visited regions of iodides and benzeneulphonate around the positively charged cavitand **2**$^{4+}$ (see also Figures S52-55).

For halides, two favorable binding regions may be recognized, in agreement with the experimental evidences obtained by the ^{1}H NMR titrations. One is at the rim of the cavity, with the acidic C-H bonds of the azoliums. The other is on the side of the cavitand, with the anions simultaneously interacting with the phenylene C-H bonds of adjacent benzoimidazolium fragments and with the resorcinarene aromatic CH bond which is pointing 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). For cavitand **3**$^{4+}$ (see Figures S53-55 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 -CH_3 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 an anion (either chloride or iodide) inside the cavitand's pocket shows the anion moving out of the cavity in the early stage of the simulation. Based on the residence times (Figure S52) and occupancies (Figures S53 and



S54), the interactions of chloride with the arms of the cavitand appear stronger that with the rim atoms, whereas for iodide specific interactions are short lived and thus weaker.

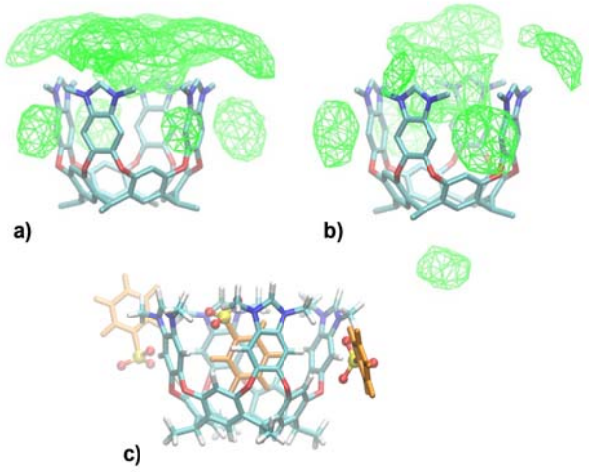


Figure 2. Representative region of the ^{1}H NMR (500 MHz) spectra of the titration of **2(PF$_6$)$_4$** with, a) [NBu$_4$]Cl and b) [NBu$_4$](BZN-SO$_3$), both in DMSO-d$_6$. In both cases, the lower case spectrum corresponds to free **2(PF$_6$)$_4$**. The upper spectrum of series b, corresponds to free [NBu$_4$](BZN-SO$_3$).

For the case of **2(BNZ-SO$_3$)$_4$** and **3(BNZ-SO$_3$)$_4$**, simulations show a different behavior than for halides. In this case one anion persistently occupies the interior of the cavitand (Figure 3b, for **2(BNZ-SO$_3$)$_4$**), 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 Supplementary Information). The substrate shows π-staking interactions with two opposing arms, occasionally reorienting by 90 degrees along its axis, thus exchanging interacting arms (see Figure S52). In line with Rebek's rule,[14] the packing coefficient is around 50% (worth noting is that compared to **2I$_4$** and **3I$_4$**, the cavity shrinks about the guest, thus the volume of the host is adapted to the size of the guest). For **2(BNZ-SO$_3$)$_4$**, we observed that the substrate shortly left the cavity once during the simulation, suggesting some degree of fluctuation. These interactions of the substrate with the cavitand are reflected in the ^{1}H NMR titration experiment showing the shift of the signals corresponding to the aromatic protons of both the cavitand and the ligand. Based on the residence times (Figure S52) and occupancies (Figures S55), we estimate the strength of interactions of benzenesulfonate with the sites at cavitands **2** and **3** as: cavity interior > arms > rim.

Figure 3. MD simulations of **2Cl$_4$** (a) and **2(BNZ-SO$_3$)$_4$** (b,c). In a) and b) the occupancy of anions around the cavitands: green isosurface at 1‰ probability. In c), snapshot of the cavitand showing the phenylsulfonate molecules in orange sticks, with oxygen atoms as red balls.

c) Determination of affinity constants

Analysis of the ^{1}H NMR titrations allowed determining the stoichiometry of the host:guest complexes formed and their association constants (K_a).[17] We determined that the stoichiometry of the complexes formed was 1:1 related to **2**$^{4+}$:X$^-$, for all anions (X$^-$) used based on the binding isotherms resulting from the ^{1}H 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 analyse the residual distribution of the titration data fitting.[19] In all cases the 1:1 stoichiometry gave the lowest residuals compared to a potential 1:2 stoichiometry (selected examples are shown in the Supplementary Information). The experiments carried out using ESI mass spectrometry also supported this stoichiometry, because the m/z peaks due to the tricationic complexes formed by the association of **2**$^{4+}$ with one equivalent of anion (see SI for more details) were the only ones revealed. 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$^-$ > Br$^-$ > I$^-$, in agreement with the basicity trend of the anions. In general, all inorganic anions showed association constants ranging between 100-500 M^{-1}. Since all these anions have in common that they all interact with the periphery of the cavitand by essentially H-bonding interactions, it may be assumed that this is the range of binding affinities associated to the presence of the acidic C-H 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*-tolylsulfonate and phenylsulfonate), whose K_{11} values are 2-3 orders of magnitude higher. Thus, for these molecules the encapsulation in the pocket of the cavitand produces a much more stable host-guest complex, than those formed with the rest of the inorganic anions, hence indicating 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 to a high uncertainty, due to the well-accepted limitations in the determiniation of high affinity constants (> 10^4 M^{-1}) by ^{1}H NMR titrations.[17a, 20]

A very interesting consequence of the recognition properties of **2**$^{4+}$ may be inferred from comparing the binding affinities of **3**$^{4+}$ with the same anions. It may be worth recalling that **3**$^{4+}$ differs from **2**$^{4+}$ by the presence of four methyl groups instead of the four protic hydrogens 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 shown in Table 1, the presence of the methyl groups at the rim of **3**$^{4+}$ produces the practical inhibition of the affinity of the cavitand for all inorganic anions and hexanoate (only the chloride and bromide maintain small binding constants ranging between 6-13 M^{-1}), while maintaining a high affinity for the anions with the aromatic functionalities. The observation that chloride and bromide still show some measurable binding constants with **3**$^{4+}$

is a direct consequence that these two anions are able to bind to the aromatic C-H binds located at the arms of the cavitand. These findings have important implications in the design of these and future cavitands, because they reflect how subtle changes in the design of the receptor may have very important consequences in the selectivity of the resulting sensor.

Table 1. Binding constants of **2(PF$_6$)$_4$** and **3(PF$_6$)$_4$** with [NBu$_4$]X (DMSO, 25ºC).[a]

		Host K_{11}, M^{-1}	
Entry	Anion	**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	*p*-tolylsulfonate	>10^4	>10^4
9	phenylsulfonate	8677 (8.6%)	3720 (49%)

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

Conclusions

In summary, we prepared two new tetrabenzoimidazolium-resorcinarene cavitands for the recognition of anions. The C2-H tetrabenzoimidazolium 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 used. The recognition abilities of **2(PF$_6$)$_4$** exceeded all of our initial expectations in the sense that it showed three clear recognition sites, which were selectively operating depending on the nature of the anions used. Larger-sized inorganic anions, such as iodide, perchlorate, cyanide, nitrate and hexanoate are predominantly recognized at the rim of the molecule, by the hydrogen bonding interaction with the acidic C-H proton of the benzoimidazolium. Smaller-sized inorganic anions, such as chloride and bromide are also interacting with the adjacent arms of the molecule, by the hydrogen-bonding interactions with the C-H bonds of the phenylene rings of the benzoimidazoliums and those from the resorcinarene. Finally, anions with an aromatic functionality such as phenylsulfonate and *p*-tolylsulfonate are recognized by the 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 ^{1}H NMR spectroscopy, which shows clearly distinctive situations depending on the anion used in the titration. The combination of both, the presence of the imidazoliums and the pre-organized 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, for which the acidic C-H bond of the azolium is expected to undergo fast H/D exchange (we are currently working in 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 of 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 H-bonding abilities of the cavitand, and for this reason the receptor is now unable to complex all those anions that showed affinity by the protons at the rim of **2^{4+}**, thus being converted into a highly selective receptor. Only chloride and bromide, displayed 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 functionalities, phenylsulfonate and *p*-tolylsulfonate, 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 using standard Schlenk techniques and high vacuum. Anhydrous solvents were either 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 supliers. NMR spectra were recorded on spectrometers operating 500 MHz (^{1}H NMR) and 126 MHz (^{13}C NMR). NMR spectra were recorded at room temperature with CD_2Cl_2 or DMSO-d_6 as solvents.

A Q-TOF mass spectrometer with an electrospray source operating in the V-mode was used. The drying gas as well as the cone gas was nitrogen at a flow of 300 Lh^{-1} and 30 Lh^{-1}, respectively. The temperature of the source block was set to 100 °C and the desolvation temperature was set to 150 °C. A capillary voltage of 3.5 kV or 3.3 kV was used in the positive or negative scan mode, respectively and the cone voltage was adjusted typically to *U*c= 50 V. Mass calibration was performed by using NaI solutions in isopropanol:water (1:1) from m/z 50–3000.

Synthesis of compounds

Compound 2I$_4$: A mixture of tetrabenzimidazolecavitand **1** (480.0 mg, 0.31 mmol) and NaOH (62.5 mg, 1.56 mmol) was stirred in 2ml of DMSO at room temperature for 2h. After this time CH_3I (86µl, 1.24mmol) was added and the mixture was stirred at 37ºC for 8h. Then, CH_3I (860µl, 12.4mmol) was added and the mixture was stirred at 100ºC for 8h. The final suspension was cooled to room temperature and the crude salt was precipitated in methanol (50ml). 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 **[2][I]$_4$** was obtained as a brown-red solid in a 44% yield (300mg). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (s, 4H CH_{NHC}), 8.63 (s, 8H, C$H_{aromatic}$), 7.98 (s, 4H, C$H_{aromatic}$), 7.81 (s, 4H, C$H_{aromatic}$), 5.65 (t, *J* = 7.8 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 Hz, 12H, CH_3). HRMS ESI-TOF-MS (positive mode): 419.5 [M-4I]$^+$, 601.7 [M-3I]$^{3+}$, 966.0 [M-2I]$^{2+}$.

Compound [2][PF$_6$]$_4$: A mixture of compound **2I$_4$** (90.5 mg, 0.041mmol)was dissolved in acetone (30ml) and mixed with a solution of NH_4PF_6 (35.2mg, 0.22mmol) in CH_3OH(10ml). The reaction was stirred at 40 ºC for 24h. The final suspension was cooled to room temperature and a white precipitate appears after few minutes. This precipitate was filtered, washed with CH_3OH and dried. This compound was obtained in 86% of yield (80mg). 1H NMR (500 MHz, DMSO-d6): δ 9.57 (s, 4H CH_{NHC}), 8.63 (s, 8H, C$H_{aromatic}$), 7.99(s, 4H, C$H_{aromatic}$), 7.80(s, 4H, C$H_{aromatic}$), 5.66(t, J = 7.8 Hz, 4H,CH), 3.91 (s, 24H, CH_3), 2.42(m, 8H,CH_2), 1.44(m, 8H,CH_2), 1.25(m, 64H,CH_2), 0.86(m, 12H,CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ 154.8, 151.7, 144.8, 136.4, 129.4, 126.0, 115.8, 109.9, 49.1, 34.0, 31.8, 31.7, 29.7, 29.6, 29.5, 29.2, 28.2, 22.6, 14.4. Electrospray MS (Cone 20V)(m/z, fragment):419.7 [M-4PF$_6$]$^+$, 607.8 [M-3PF$_6$]$^{3+}$.

Compound 1-CH$_3$:A mixture of octaaminocavitand (418mg, 0.275mmol) and acetic acid (10ml) was stirred at 100ºC for 48h. After this time the reaction was cooled to room temperature. A saturate solution of K_2CO_3 (aq) was added to the mixture in an ice-water bath until pH=8. A white precipitate appears after few minutes. The precipitate was filtered, 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 a mixture of methanol. Compound **1**-CH_3 was obtained in 68% yield (303.8mg, 0.187mmol). ^{1}H NMR (500 MHz, CD_2Cl_2-CD_3OD):δ 7.45 (s, 8H, C$H_{aromatic}$), 7.44 (s, 4H, C$H_{aromatic}$), 7.19 (s, 4H, CH_{NHC}), 5.65 (m, 4H, CH), 2.37 (s, 12H, CH_3), 2.19 (m 8H, CH_2), 1.40 (m, 8H, CH_2), 1.22 (m, 64H, CH_2), 0.83 (t, 12H, CH_3).^{13}C 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. HRMS ESI-TOF-MS (positive mode): 1619 [M-H]$^+$.

Compound 3I$_4$: A mixture of compound **1**-CH_3 (200.0 mg, 0.12 mmol) and NaOH (29.7 mg, 1.56 mmol) was stirred in 2ml of DMSO at room temperature for 2h. After this time CH_3I (31µl, 0.48mmol) was added and the mixture was stirred at 37ºC for 8h. Then, CH_3I (310µl, 4.8mmol) was added and the mixture was stirred at 100ºC for 8h. The final suspension was cooled to room temperature and the crude salt was precipitated in methanol (20ml). 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 **3I$_4$**was obtained in 70% yield (193.9mg, 0.09mmol) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 8H, C$H_{aromatic}$), 7.96 (s, 4H, C$H_{aromatic}$), 7.80 (s, 4H, C$H_{aromatic}$), 5.65 (m, 4H, CH), 3.87 (s, 24H, CH_3), 2.76 (s, 12H, C$H_{3,NHC}$), 2.42 (m, 8H, CH_2), 1.43 (m, 8H, CH_2), 1.26 (m, 64H, CH_2), 0.85 (t, 12H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): 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. HRMS ESI-TOF-MS (positive mode): [M]$^{4+}$ 953.5.

Compound [3][PF$_6$]$_4$: Compound **[3][I]$_4$** (356.3 mg, 0.161mmol) was dissolved in acetonitrile (20ml) and mixed with NH_4PF_6 (138mg, 0.86mmol). The reaction was stirred at room temperature for 1h. The final suspension was cooled to room temperature and the solvent was removed. The solid was suspended in CH_3OH, filtered, washed with CH_3OH and dried. This compound was obtained in 90% of yield (300mg, 0.144mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 8H, C$H_{aromatic}$), 7.95 (s, 4H, C$H_{aromatic}$), 7.80 (s, 4H, C$H_{aromatic}$), 5.67 (m, 4H, CH), 3.84 (s, 24H, CH_3), 2.69 (s, 12H, C$H_{3,NHC}$), 2.43 (m, 8H, CH_2), 1.45 (m, 8H, CH_2), 1.26 (m, 64H, CH_2), 0.85 (t, 12H, CH_3).^{13}C NMR (101 MHz, DMSO-d_6): 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. HRMS ESI-TOF-MS (positive mode): 433.3 [M]$^{4+}$.

Computational Studies

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 $C_{11}H_{23}$ chains. The cavitand was considered as build from 8 residues, 4 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 4 counterions (either Cl^-, I^-, benzenesulfonate) to neutralize the simulation cell and ~1000 DMSO molecules in a cubic cell of ~47 Å edge. Counterions were placed the most favorable interacting sites of the cavitand's electrostatic potential. Force field parameters for DMSO were 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 2 MD step, and a full electrostatic evaluation was performed every 4 MD steps using the particle mesh Ewald method[26] on a 64 x 64 x 64 grid. All bonds involving hydrogen atoms were constrained.[27] A cutoff distance of 12 Å was used for non-bonded interactions.

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Keywords: anion recognition • cavitand • resorcinarene • imidazolium • computational calculations

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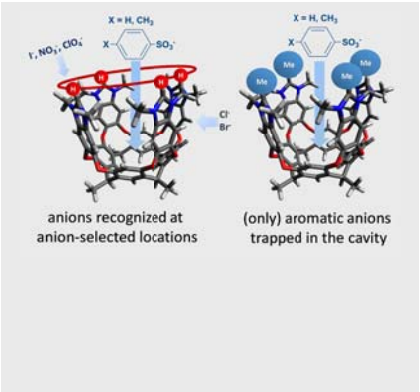
Entry for the Table of Contents

FULL PAPER

Two resorcinarene-tetraimidazolium cavitands combine hydrogen-bonding C-H···π interactions to modulate the selectivity towards the recognition of anions.



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Rim, side-arms and cavity: three sites for the recognition of anions with tetra-azolium-resorcinarene cavitands