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High-Affinity Binding

N-Alkyl Ammonium Resorcinarene Salts as High-Affinity Tetravalent Chloride Receptors

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Abstract: *N*-Alkyl ammonium resorcinarene salts (NARYs, Y = triflate, picrate, nitrate, trifluoroacetates and NARBr) as tetravalent receptors, are shown to have a strong affinity for chlorides. The high affinity for chlorides was confirmed from a multitude of exchange experiments in solution (NMR and UV/Vis), gas phase (mass spectrometry), and solid-state (X-ray crystallography). A new tetra-iodide resorcinarene salt (NARI) was isolated and fully characterized from exchange experiments in the solid-state. Competition experiments with a known monovalent bis-urea receptor (**5**) with strong affinity for chloride, reveals these receptors to have a much higher affinity for the first two chlorides, a similar affinity as **5** for the third chloride, and lower affinity for the fourth chloride. The receptors affinity toward chloride follows the trend $K_1 \gg K_2 \gg K_3 \approx \mathbf{5} > K_4$, with $K_a = 5011\ M^{-1}$ for **5** in 9:1 $CDCl_3/[D_6]DMSO$.

Introduction

Weak interactions are widely utilized in the design of functional assemblies with a multitude of applications.[1] The design and control of weak interactions is a paramount challenge to researchers both in the fundamental and application level.[2] Given that these interactions form the basis for the molecular recognition of structurally and chemically different species, it is of crucial importance that these interactions are well understood. Anions are perhaps the most important biological entities considering their critical impact on all forms of life.[3,4] Cofactors, most enzyme substrates, and DNA are anionic in nature.[5] Halides are one of the most abundant anions in living systems. It is known that chloride is present in high concentrations in extracellular fluids,[6] iodide is critical for the biosynthesis of hormones by the thyroid gland,[7] and fluoride is essential for healthy bone and teeth growth.[8]

In the past, research has mostly concentrated on cation recognition, and limited attention has been given to anions.[9] This limitation has been, in part, due to the intrinsic and very challenging properties of anions when compared with their isoelectric cations. For example, anions have higher sensitivity to pH, wider range of geometry modulation (spherical, linear, tetrahedral, ellipsoidal etc.), and higher free energies of hydration compared with cations.[10] Despite these challenges, research on the recognition and coordination of anions is ongoing. The key factors in the design for anion receptors include (but are not limited to) electrostatic and hydrogen-bond interaction sites in the receptor. This has led to the design of receptors that can bind multiple anions, and these have been used as sensors and in separations.[10] Positively charged protic anion receptors have the advantage of having both electrostatic and hydrogen-bonding sites, but they usually suffer from low solubility in nonpolar media. These issues have meant that increasing attention is being paid to electroneutral anion receptors[10] that can function in nonpolar media, and thus exhibit useful properties for "phase-transfer" applications.[11] However, the development of an anion receptor having both electrostatic and hydrogen-bonding sites that could still function in nonpolar media, would have outstanding potential as a sequestering agent.

The *N*-alkyl ammonium resorcinarene halides,[12] NARXs (X = Cl, Br, or I) obtained from ring opening of the corresponding tetrabenzoxazines[13] in the presence of mineral acids under reflux conditions, are stabilized by a strong circular hydrogen bonded cation-anion seam $(\cdots NR'R''H_2^+\cdots X^-\cdots)_4$ as shown in Scheme 1.[12] These hydrogen bonded analogues of covalent cavitands are a subset of the resorcinarene family. They possess four spatially fixed halide anions (Scheme 1) with deep cavities for guest binding. Reports have shown the *N*-alkyl ammonium resorcinarene salts to be suitable receptors for a variety of neutral guests[14] and recently anions[15] through several simultaneous weak interactions utilizing the electron-rich resorcinarene cavity and the hydrogen bonded cation-anion seam. Furthermore, the four spatially fixed anions can act as halogen-bond acceptors, and, through concerted halogen bonds, result in molecular architectures with guest binding

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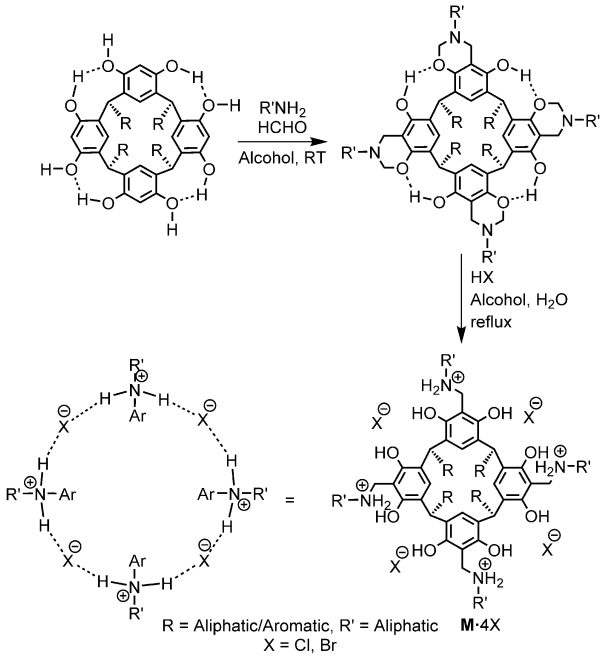

Scheme 1. *N*-Alkyl ammonium resorcinarene halides (NARXs, X = Cl or Br) with a strong circular hydrogen-bond seam.

properties such as deep cavity cavitands,[16] capsular,[17] and dumbbell-like dimeric assemblies.[18]

Small and spherical anions such as chloride or bromide are strongly bound into the *N*-alkyl ammonium resorcinarene skeleton as a result of their suitable size and strong hydrogen-bond acceptor character (Figure 1).[12] The chloride and bromide anions are optimal in size as seen from the symmetrical conformations of the X-ray structures of the *N*-alkyl ammonium resorcinarene halides (Figure 1a and b).[12] Larger and non-spherical anions such as nitrate (trigonal planar), picrate (aromatic planar), and triflate (ellipsoidal), possessing multiple hydrogen bond acceptor sites, manifest a complex array of intra- and intermolecular hydrogen bonds, resulting in less-symmetrical cavitand-like structures (Figure 1c and d).[12c] Our hypothesis is that the more suitably sized chloride and bromide will replace the larger and spatially ill-fitting nonspherical anions within the cation-anion seam. Additionally, the stronger hydrogen-bonding acceptor character of the chloride anion would make it the perfect target for anion binding studies. Thus, the NARYs (Y = triflate, picrate, nitrate and trifluoroacetates) and NARBr could be utilized as high affinity, tetravalent chloride receptors. In this contribution, a set of experiments conducted in solution (NMR and UV/Vis), in the solid-state (X-ray crystallography), and in the gas phase (mass spectrometry) were performed to probe the anion-binding properties of the NARYs **1**·4Y–**4**·4Y, and NARBr (Figure 2), with results showing high affinity for chloride. The binding stoichiometry was investigated through Job plot analysis.[19] During the course of the crystallization experiments, a new *N*-alkyl ammonium resorcinarene halide, the tetra-iodide, NARI, was isolated and fully characterized. Competition experiments with a known[20] bis-urea based

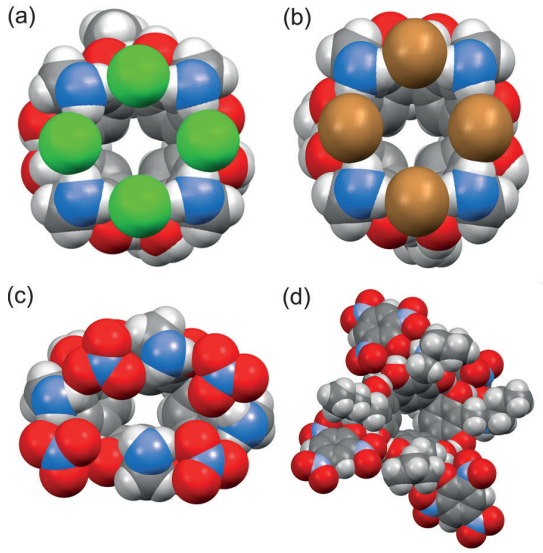

Figure 1. CPK plots of A) NARCl, B) NARBr, and two NARYs in which Y is: C) nitrate and D) picrate (D). The upper rim groups are omitted to show the position of the anion in the cation–anion seam, and how it affects the conformation of the resorcinarenes.[12c]

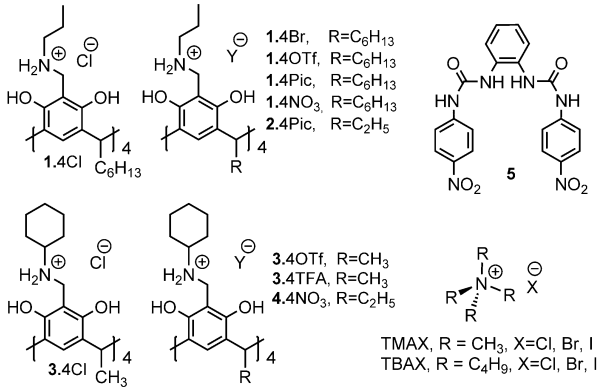

Figure 2. The chemical structures of the NARCls (**1**·4Cl and **3**·4Cl), NARBr (**1**·4Br), and the NARYs (**1**·4Y–**4**·4Y in which Y = triflate, picrate, nitrate and trifluoroacetate), the chloride receptor **5**, tetramethyl ammonium (TMA), and tetrabutyl ammonium (TBA) halides.

chloride receptor **5**, that binds chloride with a binding constant of 5×10^3 (Figure 2) in 9:1 $CDCl_3/[D_6]DMSO$, was challenged against the NARYs to quantify the chloride affinity of the receptors.

Results and Discussion

The Mannich condensation reaction[13] between aliphatic amines and resorcinarenes in the presence of excess formaldehyde results in tetrabenzoxazines (Scheme 1).[13] Ring-opening of the six-membered tetrabenzoxazine ring in the presence of an acid (HCl, HBr, picric acid, triflic acid, and trifluoroacetic acid) under reflux conditions gives NARXs **1**·4X–**3**·4X and NARYs **1**·4Y–**4**·4Y (Figure 2) in 50–85% yields.[12] The nitrate

salt **4**·4NO_3 was obtained through anion exchange between the chloride salt and silver nitrate.[12c]

NMR Analyses

The -OH and -NH_2 protons are involved in intramolecular hydrogen bonding and complete the cation–anion seam (Scheme 1). Changing the anions will have a direct effect on the chemical environment of the -OH and -NH_2 groups. In a typical exchange experiment in solution, tetrabutyl ammonium halides, TBAXs (X = Cl or Br), were utilized as the halide source. An increasing amount of TBAX was added to a solution of NARYs **1**·4Y–**4**·4Y, NARBr, and the resulting ^{1}H NMR spectra were compared with those of the corresponding NARCl or NARBr. Taking the exchange experiment between **1**·4OTf and TBACl as an example, the results show that the -OH and -NH_2 signals of the **1**·4OTf move toward those of the pure **1**·4Cl. This clearly suggests that the triflate anions are being replaced by the chloride anions (Figure 3, **I**). After the addition of four equivalents of chloride, saturation of the -NH_2 is observed. Exchange experiments between **1**·4Br and TBACl as well as **1**·4Pic with TBACl show that the chloride will replace the bromide (Figure 3, **II**) and picrate anions (see the Supporting Information, Figure S1).

Exchange experiments between **1**·4Y–**4**·4Y and TBABr, confirm that the receptor binds the bromide anion (Figure 4, **I** and Figure S3 in the Supporting Information) when chloride is not present. Although the hydrogen-bonding affinity of chloride is higher than that of the bromide anion, crystal structures show both anions to be of suitable size for a snug fit into the cation–anion seam. A simple control experiment was performed to further confirm the relative affinities. When TBABr was used as the bromide source and titrated against **1**·4Cl, it was evident that the bromide could not replace the chloride, thus confirming the higher affinity of chloride over bromide (Figure 4, **II**).

The ^{1}H NMR spectroscopic exchange experiments presented above clearly show that NARYs tend to bind chlorides in preference to any other anions in chloroform. Job plot analysis is a technique that can be used to determine the binding stoichiometry in host–guest systems.[19] However, the scope of such

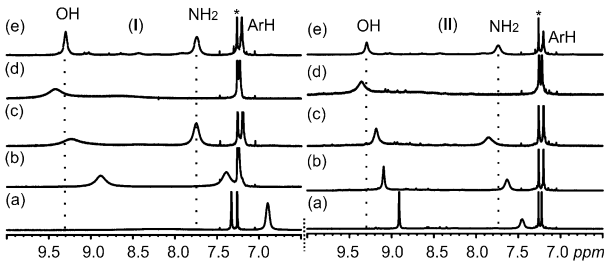

Figure 3. Selected region of the ^{1}H NMR spectra recorded in $CDCl_3$ (500 MHz, 303 K) after the addition of up to 10 equivalents of TBACl to: (**I**) **1**·4OTf: a) 0.0, b) 2.0, c) 4.0, d) 10.0 equiv, and e) **1**·4Cl; (**II**) **1**·4Br: a) 0.0, b) 2.0, c) 4.0, d) 10.0 equiv, and e) **1**·4Cl. Stars represent the residual $CDCl_3$, and the dotted lines give an indication of the shift changes.

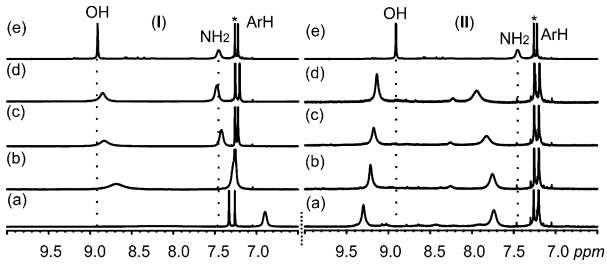

Figure 4. Selected region of the ^{1}H NMR spectra in $CDCl_3$ (500 MHz, 303 K) after the addition of up to 10 equivalents of TBABr to: (**I**) **1**·4OTf: a) 0.0, b) 2.0, c) 4.0, d) 10.0 equiv, and e) **1**·4Br; (**II**) **1**·4Cl: a) 0.0, b) 2.0, c) 4.0, d) 10.0 equiv, and e) **1**·4Br. The minor changes in the -OH and -NH_2 signals result from higher salt concentrations. Stars represent the residual $CDCl_3$, and the dotted lines give an indication of the shift changes.

analysis can be seriously limited in complex systems with binding stoichiometry other than 1:1.[19] Despite this limitation, Job plot analysis was employed to determine the stoichiometry of the anion exchange process. Taking the anion exchange between the receptor **1**·4OTf and TBACl under investigation, the results clearly show the 1:4 binding stoichiometry (Figure 5).

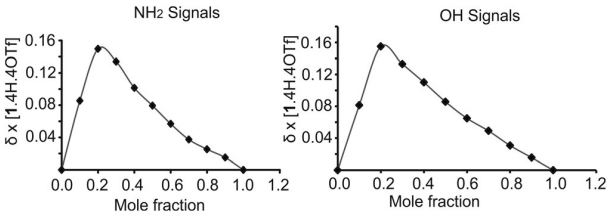

Figure 5. Job plot analysis of a mixture of **1**·4OTf and TBACl in $CDCl_3$ at 303 K revealing a 1:4 binding stoichiometry.

UV/Vis Analyses

UV/Vis spectroscopic analyses were carried out to gain further insight into the relative affinities of NARYs toward halides. For this purpose, absorption spectra of the picrate chromophore of the corresponding **2**·4Pic were monitored during titrations with TBAX (X = Cl, Br, I). As anticipated, the addition of halides to **2**·4Pic in $CHCl_3$ resulted in a bathochromic shift of the picrate absorbance from 334 to 370 nm (Figure 6a), indicating a transition from TBACl/Br/I to TBA picrate,[21] and formation of the corresponding NARCl, NARBr, and NARI. The presence of a clear isosbestic point at 349 nm suggests that the two species are in equilibrium. The titration profiles for different halides clearly demonstrate the highest binding affinity for chloride, and the lowest for iodide (Figure 6 and Figures S10 and S11 in the Supporting Information).

Mass Spectrometry

Electrospray ionization (ESI) mass spectrometry is a soft ionization technique that has been used extensively for structure determinations and for analyses of complex species in the gas phase.[22] The NARYs and NARBr are held together by several

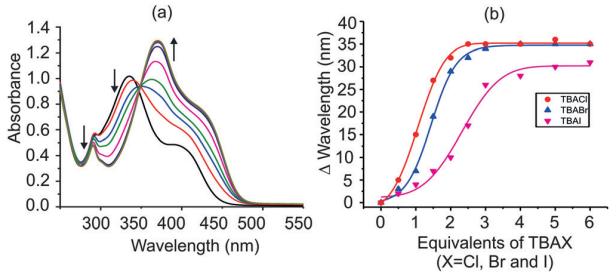

Figure 6. a) UV/Vis spectra of **2**·4 Pic (25 μM in $CHCl_3$) with increasing concentrations of TBACl (12.5 μM steps to 75 μM, 25 μM steps to 150 μM); b) UV/Vis titration plots for **2**·4 Pic (25 μM in $CHCl_3$) with different TBA halides.

weak interactions, emphasized by the many species usually seen in the mass spectrum.[12,14] The loss of multiple hydrogen chloride (HCl) molecules from the host is a common phenomenon with these large organic salts. Even at soft ionization parameter values, it is generally observed that these salts will not survive the high vacuum of a mass spectrometer, and thus cannot be seen as intact molecular ions. Nonetheless, ESI mass spectrometry was utilized to study the anion exchange and the high chloride affinity of the NARYs and NARBr in the gas phase. In a typical experiment, the ESI mass spectra of **1**·4 Y–**4**·4 Y or NARBr was recorded and analyzed. Potassium chloride (KCl) as a chloride source was added to the sample and the ESI mass spectrum was recorded again and analyzed. A $CHCl_3$/acetonitrile mixture was used as the spray solvent.

Taking **1**·4 OTf as an example, in the positive ion mode, progressive loss of HOTf resulted in signals corresponding to $[(\mathbf{1})\text{-}3H]^+$ (*m/z* 1109), $[(\mathbf{1}\cdot OTf)-2H]^+$ (*m/z* 1259), $[(\mathbf{1}\cdot 2OTf)-H]^+$ (*m/z* 1409), $[\mathbf{1}\cdot 3OTf]^+$ (*m/z* 1559), and the sodium adduct $[\mathbf{1}\cdot 4OTf+Na]^+$ (*m/z* 1731) (Figure 7 a). Up to five equivalents of KCl were added to this sample, and the ESI mass spectrum was recorded. The results show that the chlorides replace all the triflates.

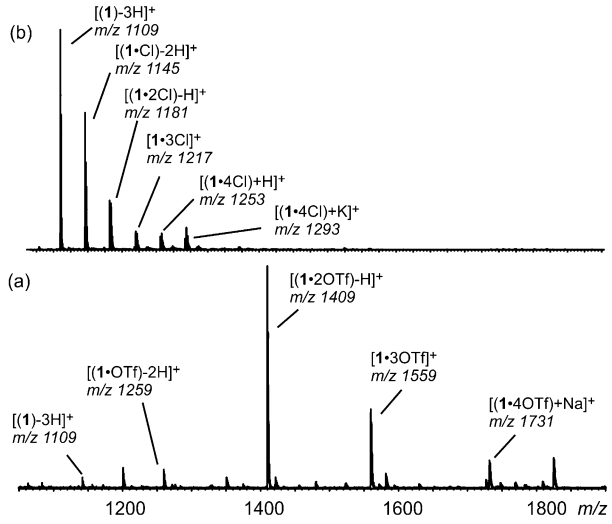

Figure 7. Positive ESI mass spectra: a) **1**·4 OTf and b) after the addition of KCl. All the triflate anions are replaced by the chloride anions.

In the spectrum, signals corresponding to $[(\mathbf{1})-3H]^+$ (*m/z* 1109), $[(\mathbf{1}\cdot Cl)-2H]^+$ (*m/z* 1145), $[(\mathbf{1}\cdot 2Cl)-H]^+$ (*m/z* 1181), $[\mathbf{1}\cdot 3Cl]^+$ (*m/z* 1217), the protonated $[\mathbf{1}\cdot 4Cl+H]^+$ (*m/z* 1253), and the potassium adduct $[\mathbf{1}\cdot 4Cl+K]^+$ (*m/z* 1293) were observed (Figure 7 b). The isotope patterns obtained by experiment were consistent with those simulated on the basis of natural abundances. Similar experiments were performed with **1**·4 Br and **1**·4 Pic, with results showing similar patterns, as shown in Figure 7 (see the Supporting Information, Figures S12 and S13).

X-ray Analyses

The anion exchange processes were also monitored in the solid-state by conducting numerous crystallization experiments and detailed X-ray crystallographic analyses. In a typical crystallization experiment, the TBAX (X = Cl, Br, or I) was chosen as the halide source, and four equivalents of TBAX was added to a $CHCl_3$/MeOH mixture containing NARYs with different anions, and the sample was allowed to concentrate by slow evaporation. Crystallization experiments were performed with and without 1,4-dioxane as a guest molecule at room temperature to facilitate the crystallization process.

Crystals of **3**·4 Br were isolated from the crystallization of **3**·4 OTf and TBABr in $CHCl_3$/MeOH solution in the presence of 1,4-dioxane. As shown in Figure 8, instead of the triflate, four bromides are present in the structure, and they are tightly held by -NH···Br and -OH···Br hydrogen bonds. All the bromide anions in dioxane@**3**·4 Br structure are well ordered, implying the space between the *N*-cyclohexyl ammonium rims is very suitable for bromide anion.

Interestingly, by substituting the triflate anions from **3**·4 OTf with TBAI in $CHCl_3$/MeOH mixture, suitable crystals of **3**·4 I (Figure 9) were obtained. The direct synthesis of **3**·4 I was never achieved because of the weakness of HI as an acid. The opening of the cavity in this $CHCl_3$@**3**·4 I structure is much larger than that in $CHCl_3$@NARCl,[14a] reflecting the significantly larger N···N distance (6.581 Å, Table S2) in the resorcinarene skeleton when compared with the chloride complex (6.187 Å).[14a]

In solution, the replacement of bromide by chloride was observed through ^1H NMR analysis. We tested this possibility in the solid-state by mixing **3**·4 Br and TBACl in $CHCl_3$/MeOH mixture with a few drops of 1,4-dioxane. Fortunately, crystalline

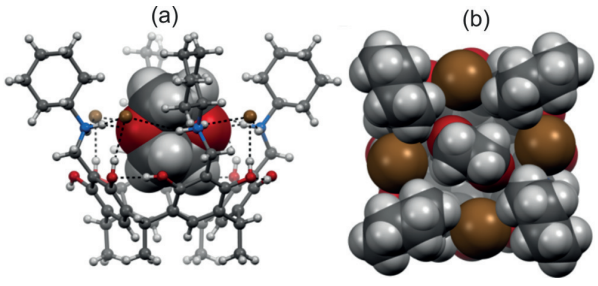

Figure 8. a) Side view and b) top view of the X-ray structure of **3**·4 Br with encapsulated 1,4-dioxane.

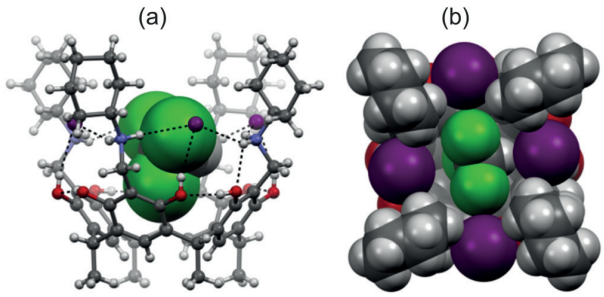

Figure 9. a) Side view and b) top view of the X-ray structure of **3**·4I with encapsulated $CHCl_3$.

plates were obtained upon slow evaporation. The structural analysis of the crystals by X-ray crystallography showed similar unit cell parameters to those in dioxane@**3**·4Br. However, careful investigation of the electron densities in the anion positions indicated some discrepancies, and the positions were better assigned as mixtures of bromide and chloride (Figure 10). The refinement obtained by constraining the unit occupancy for the sum of bromide and chloride gave a ratio of 0.8:0.2 (Br^-/Cl^-). However, the limited quality of the crystal implies that the refinement results are not fully reliable.

Tetramethyl ammonium halides (TMAXs) were also utilized as the halide source in exchange crystallization experiments. Mixing of TMACl and **4**·4NO_3 in $CHCl_3$/MeOH mixture gave diffraction quality crystals; X-ray analysis of the crystals revealed the structure to be CH_3OH@**4**·4Cl (Figure 11). The structure

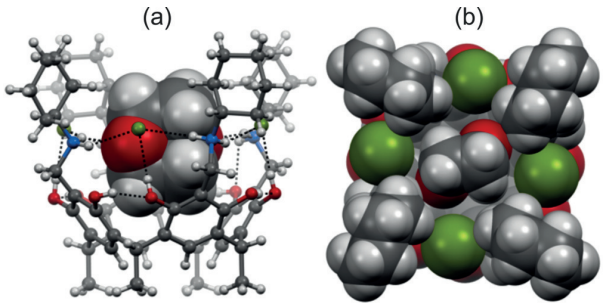

Figure 10. a) Side view and b) top view of the X-ray structure of **3**·3.2Br·0.8Cl with encapsulated 1,4-dioxane.

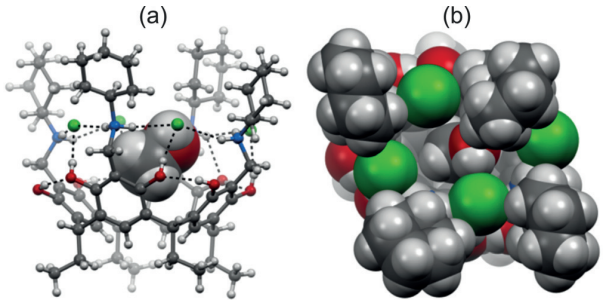

Figure 11. a) Side view and b) top view of the X-ray structure of **4**·4Cl with encapsulated MeOH.

clearly shows that all four nitrate anions are completely replaced by chlorides. The four chloride anions fit well between the *N*-cyclohexyl ammonium groups with -NH···Cl and -OH···Cl hydrogen bonds. Notably, one of the chlorides in this structure is disordered over two positions.

Competition Experiments and ^{1}H NMR Titrations

NMR Competition Experiments: The results presented above show the NARYs to have high affinity for spherical halides, especially chlorides, over large nonspherical anions. The binding of the chloride anions by the NARY and NARBr receptors is fast on the NMR timescale. Considering there are four binding sites for the chloride anions, combined with the fast exchange process, quantifying the binding process by measuring association constants would be extremely difficult. However, utilizing a known chloride receptor in competition experiments with the NARY and NARBr receptors could give indirect information on the comparative binding strength. In the process, a bis-urea receptor **5** (Figure 2), which is known to have high affinity for halides, especially chloride,[20] was utilized in a series of competition experiments. Different equivalents of TBACl (200 mM) were added to a solution ($CDCl_3$/[D_6]DMSO, 9:1 v/v) of the chloride receptor **5** (20 mM), and the ^{1}H NMR spectrum was recorded. The solvent system was chosen because of the limited solubility of **5** in pure chloroform, and to reduce the binding affinity of **5** toward chloride in more competitive solvent to obtain a more reliable binding constant. Changes in the signals of receptor **5**, especially the urea protons, clearly show complexation of the chloride upon stepwise addition of TBACl (Figure 12). In this solvent mixture ($CDCl_3$/[D_6]DMSO, 9:1 v/v) the addition of TBACl to **1**·4OTf–**4**·4OTf gave similar results to those measured in pure $CDCl_3$ (see the Supporting Information, Figure S2).

In the competition experiment, different equivalents of TBACl were added to an equimolar mixture of **5** and **3**·4OTf, and the ^{1}H NMR spectrum was recorded. Upon the addition of up to two equivalents of TBACl, no changes were observed in the protons of the receptor **5**, whereas changes in the -OH and -NH_2 signals of **3**·4OTf were observed (Figure 13). Changes in the signals of both receptors **5** and **3**·4OTf were observed from addition of the third equivalent of TBACl, with saturation of both receptors after addition of the fifth equivalent. These results unambiguously show receptor **3**·4OTf to be a much stronger receptor for the first two chlorides, and to be of comparable strength to **5** for the subsequent chlorides (Figure 13). Exchange experiments with **1**·4OTf gave similar results (see the Supporting Information, Figure S9).

Other experiments were performed to further probe the chloride complexation dynamics with both receptors. For example, the addition of receptor **5** to **3**·4Cl showed changes in the protons of both receptors, which supports the competition for the third and fourth chlorides (see the Supporting Information, Figure S4). Furthermore, the addition of **1**·4OTf to an equimolar mixture of **5** and TBACl also show that **1**·4OTf can extract chlorides from the Cl@**5** complex (see the Supporting Information, Figure S5).

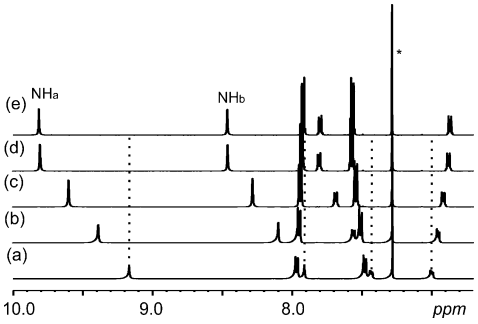

Figure 12. Selected region of the ^{1}H NMR ($CDCl_3$/DMSO, 9:1 v/v, 298 K) spectra observed upon the addition of TBACl (200 mM) to the receptor **5** (20 mM): a) 0.0, b) 0.5, c) 1.0, d) 2.0 and e) 4.0 equiv. Stars represent the residual $CDCl_3$, and the dotted lines give an indication of the shift changes.

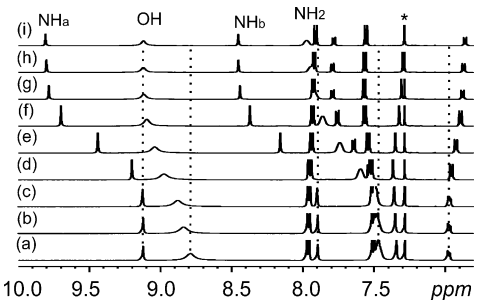

Figure 13. Selected region of the ^{1}H NMR ($CDCl_3$/DMSO, 9:1 v/v, 298 K) spectra observed upon the addition of TBACl (200 mM) to an equimolar mixture of **5** and **3**·4 OTf (10 mM): a) 0.0, b) 0.5, c) 1.0, d) 2.0, e) 3.0, f) 4.0, g) 5.0, h) 6.0, and i) 9.0 equiv. Stars represent the residual $CDCl_3$, and the dotted lines give an indication of the shift changes.

^{1}H NMR titrations: A series of titration experiments with **3**·4 OTf and **5** were carried out in 9:1 $CDCl_3$/DMSO solvent mixture to compare the binding efficiency of the two receptors. In a typical titration experiment, an increasing amount of TBACl (500 mM) was added to a solution of receptor (10 mM). In a reference titration, the K_a value for Cl^-@**5** (9:1 $CDCl_3$/DMSO) was measured to be 5011 M^{-1} (Figure 12 and Figure S7 in the Supporting Information), based on a 1:1 binding model, using the HypNMR2008 computer program utilizing a nonlinear least square fitting procedure.[23] When a sample with equimolar amounts of **3**·4 OTf and **5** (10 mM) was titrated with TBACl, the -OH and -NH_2 protons of **3**·4 OTf showed clear downfield shifts, supporting the conclusion that hydrogen-bond interactions form between chlorides and the NARY receptor (Figure 14). Complexation induced changes of the urea protons H_a and H_b of **5** were only observed after the addition of two equivalents of chloride. These results clearly indicate a stronger interaction between **3**·4 OTf and the first two equivalents of the added chloride. Upon further chloride addition, **3**·4 OTf and **5** compete for the third chloride, and the reference receptor **5** has stronger affinity toward the fourth chloride (Figures 13 and 14). From these observations it is clear that the binding constants for 1:1 and 1:2 complex formation between **3**·4 OTf and chloride exceeds the binding constant measured for **5**, *viz.*

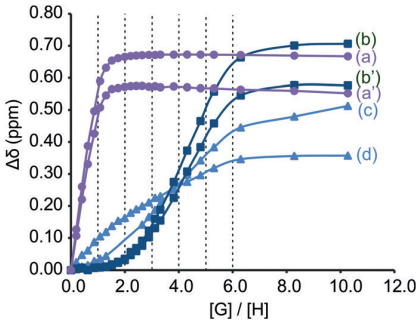

Figure 14. The chemical shift differences observed after the titration of TBACl to the reference receptor **5** (H_a/H_b = a/a'), and to an equimolar mixture of **5** (H_a/H_b = b/b') and **3**·4 OTf (c = NH_2, d = OH).

$K_a \gg 5000$, and the binding constant of **3**·4 OTf for the 1:3 complex is in the same range as with the reference receptor **5** (Figure 14). This is logical because the electrostatic repulsions between the chloride anions in the **3**·2 OTf·2 Cl complex makes the further binding of chloride thermodynamically unfavorable. The **3**·4 OTf also has an entropic advantage because of its preorganized nature. Likewise, from a statistical point of view, the four binding sites have an extra advantage over the single binding site of receptor **5**. The behavior of the -OH and -NH_2 protons in the titration experiment is similar to the changes observed in the titration experiment between **3**·4 OTf and TBACl (Figures S2 and S8). From these results, the binding affinity of the **3**·4 OTf toward the four chlorides can be ordered: $K_1 \gg K_2 \gg K_3 \approx \mathbf{5} > K_4$, with $K_a = 5011\ M^{-1}$ for **5**.

Conclusion

The present work describes the binding properties of anions by the *N*-alkyl ammonium resorcinarene salts, NARYs. The results of a series of exchange experiments show the NARYs and NARBr to have a particularly high affinity for chloride. Electrostatic interactions and hydrogen bonds are the main interactions involved in the binding process. The high affinity for chloride can be attributed to its spherical shape, suitable size, and strong hydrogen-bond acceptor nature, with a perfect fit between the spatially separated -NH_2^+-R groups. The anion exchange processes were confirmed in solution at the micromolar and millimolar concentration range through UV/Vis and NMR spectroscopic studies, respectively. Despite the harsh conditions and general instability of salts in the high vacuum of a mass spectrometer, gas-phase studies also revealed strong affinity of the NARYs and NARBr toward chloride anions. Several single-crystal X-ray structures were obtained from the anion exchange and competition experiments, which further established the high affinity for chloride over other anions. In the process, the first tetraiodide salt **3**·4 I, NARI, was obtained and analyzed, revealing a striking similarity to the tetrabromide salt. Competition experiments in solution were conducted with a known bis-urea receptor, having high affinity for chloride, to give an estimation of the binding affinity of the NARYs toward chloride. These results show the NARYs to have higher affinity

for the first two chloride anions, comparable affinity with **5** for the third chloride, and lower affinity for the fourth chloride in the order of $K_1 \gg K_2 \gg K_3 \approx \mathbf{5} > K_4$. We have shown that NARYs and NARBr, which incorporate both electrostatic and hydrogen bond interactions, work efficiently in nonpolar media, and act as robust chloride receptors. The covalently bound -NH_2^+-R groups at the upper rim of the resorcinarene skeleton are spatially perfectly oriented to form a strong circular cation–anion seam through hydrogen bonding, providing four pockets for the perfectly sized anion (chloride). This work highlights the benefits of utilizing the strengths of different weak interactions working cooperatively, incorporated in a single receptor to effectively target a substrate. Such a receptor could be useful for "phase-transfer" applications.

Experimental Section

The tetramethylammonium salts, tetrabutylammonium salts, and potassium chloride were purchased and used as received. *N*-Alkyl ammonium resorcinarene chlorides **1**·4 Cl, **3**·4 Cl and other salts, NARYs, **1**·4 Y–**4**·4 Y, and the reference receptor **5** were synthesized according to reported procedures.[14,15,20] NMR measurements were performed with a Bruker Avance 500 MHz spectrometer. Mass spectrometric experiments were performed with a micromass LCT ESI-TOF instrument equipped with a Z geometry ion source. Details of the NMR, UV/Vis, and mass spectrometric measurements are presented in the Supporting Information. For X-ray crystallographic analysis, the data were collected with an Agilent Super-Nova diffractometer with mirror-monochromatized Mo-Kα ($\lambda = 0.71073$ Å) radiation. Details of data collection and reduction, as well as structure solution and refinement are given in the Supporting Information. CCDC 1429821 (dioxane@**3**·4 Br), 1429822 (**3**·4 Br), 1429823 (**3**·4 I), and 1429824 (CH_3OH@**4**·4 Cl) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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