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Anion Binding by a Tetradipicolylamine-Substituted Resorcinarene Cavitand

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Anion binding has been achieved with a resorcinarene substituted with four 2,2′-dipicolylamine moieties on the upper rim. The four dipicolylamine groups reside in proximity on one rim of the cavitand. The dipicolylamine groups were protonated with triflic acid to provide the cationic ammonium sites for anion binding. This anion receptor binds strongly to anions of different geometries, such as $H_2PO_4^-$, Cl^-, F^-, $CH_3CO_2^-$, HSO_4^-, and NO_3^-. The association constants for binding these anions are large, on the order of log $K = 5$ in CD_3CN, a solvent of intermediate dielectric constant. These values represent significant binding compared to other cavitands with nitrogen pendant groups. Evidence suggests that the cavitand provides two identical receptor sites formed by two dipicolylamine groups, facilitating the simultaneous binding of two anions. Intramolecular binding of anions between two protonated dipicolylamine groups is indicated on the basis of the comparison to a structurally similar monomeric analogue and by semiempirical PM3 molecular modeling. Titrations with the analogue result in much weaker anion association, even at high concentrations, indicating the importance of proximity and preorganization of sites on the cavitand upper rim.

Introduction

Anion binding compounds are desirable for a variety of applications. In nature, proteins use multiple hydrogen bonds for selective binding of anions.[1] Anion binding compounds could be used to stabilize and increase the bioavailability of anionic drugs, along similar lines to those already applied to cyclodextrin neutral drug inclusion complexes.[2] Selective binding of anionic species is of environmental interest with respect to developing new waste remediation methods for toxic anions, such as selenate or radioactive pertechnetate. There is interest in producing sulfate selective hosts for removing sulfate from nitrate-rich radioactive waste, because vitrification of low-activity nuclear waste performed by producing glass logs from evaporated waste solutions is adversely affected by the presence of sulfate.[3]

Anions have larger radii and a greater variety of geometries than common cations. This characteristic requires complexity in the three-dimensional structure of anion receptors. Recent reviews describe anion recognition,[1] some with specific emphasis on the use of amine,[1d] amide,[1c] urea,[1c] thiourea,[1c] pyrrole,[1e] guanidinium,[1f] and metal coordination−Lewis acid groups.[1g] Also, current books on supramolecular chemistry contain summaries of research in this field.[4]

Some of the most well studied types of synthetic anion hosts are cyclic and bicyclic hydrogen-bonding compounds. For example, macrocyclic hosts that contain hydrogens bound

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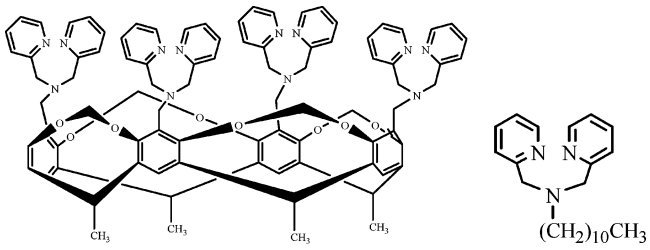
to nitrogens prove to be good anion receptors.[5] Several anion binding sites are usually combined in a receptor to provide stronger anion binding than could be possible with a single site. Molecules are also often prepared with mixed types of anion receptor moieties. One recent example has a molecular cleft,[6] where a metal center directs the orientation of several arms containing hydrogen-bonding groups. The amine or quanidinium groups on the arms of the receptors provide electrostatic and hydrogen bonding or strong dipole−dipole interactions to an anion guest.

Concave molecular structures referred to as cavitands have been of interest in host−guest chemistry because of their ability to bind small molecules within a central hydrophobic cavity.[7,8] One widely used and versatile family of cavitands comprises the resorcinarenes.[9] When resorcinarene cavitands were first elucidated by Cram and co-workers, they reported that resorcinarenes could be made less flexible by bridging the upper rim with methylene groups.[10] Resorcinarene-based cavitands are versatile hosts because a variety of functional groups can be attached to their upper and lower rims. For example, hydrogen-bonding functionalities can be appended to the upper rim and used to control structure conformation as well as guest binding affinity.[11−20] However, using hydrogen-bonding groups on resorcinarenes to assist in anion binding is still in its early stages.[18−19,21] It has been demonstrated that a derivatized resorcinarene can provide a framework for complex ion-pair recognition, where the cavity provides a good receptor for a tetramethylammonium cation, while groups on the upper rim provide for anion binding.[22] Of the resorcinarene-based anion receptors, association constants for only a few are known.[19]

Previously, we reported attaching 2,2′-dipicolylamine (dpa) to the upper rim of resorcinarene to produce **1** to investigate the metal coordination chemistry of this structure.[23] When the pyridine and amine groups on this molecule are protonated, there is potential for cooperative binding of anions. In this paper we focus on the protonated cavitand **1**, in which converging hydrogen bonding from multiple dpa moieties to a guest species, such as an anion, can occur. We report on the anion-binding capabilities of the protonated **1**, H_{12}**1**, and give the anion-binding constants for this receptor.



1 dpa-undecyl

Experimental Section

General information. All commercial reagents were used as supplied from Cambridge Isotopes Laboratories and Aldrich Chemical Inc, unless otherwise noted. Cavitand **1** was prepared in the manner described previously by our group.[23] ^{1}H NMR studies were performed on a Varian INOVA 300 MHz multinuclear FT-NMR or VXR 500-MHz multinuclear FT-NMR spectrometers. Titrations were performed using the Varian INOVA 300 MHz instrument. NMR chemical shifts are reported in ppm, and NMR studies were performed at 22.8 ± 0.5 °C.

Synthesis of dpa-undecyl. To understand the interaction with anions of a single isolated dpa ligand, a compound with a dpa binding site similar to that found in **1** was synthesized by the following method. To a solution of 1-bromoundecane (1.27 g, 5.40 mmol) in 16 mL of benzene was added 2,2′-dipicolylamine (1.07 g, 5.37 mmol) and triethylamine (0.300 g, 2.96 mmol). This solution was heated at 90 °C for 48 h while stirring, after which the benzene was removed under rotoevaporation and the crude product was extracted into chloroform and washed with water. The chloroform solution was then concentrated and the product separated on a silica gel column using chloroform as eluent until the first band separated from the bulk and then 92% chloroform/8% methanol as eluent. The first band, which contained the product, was evaporated to

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dryness and dried under vacuum to produce dpa-undecyl (1.46 g, 77%): MS (FAB^+) m/z = 354; ^1H NMR (200 MHz, CD_3Cl) δ 0.877 (t, 3 H, CH_3), 1.218 (m, 18 H, CH_2) 2.578 (t, 2 H, CH_2), 3.809 (s, 4 H, NCH_2), 7.156 (t, 2 H, Ar CH), 7.558 (d, 2 H, Ar CH) 7.647 (t, 2 H, Ar CH), 8.511(d, 2 H, Ar CH).

Acid Titration of 1. Compound **1** (10 mg, 7.0 μmol) was placed in an NMR tube, dissolved in 650 μL of CD_3CN, and titrated (4 μL additions) with a 0.8799 M CD_3CN solution of trifluoromethanesulfonic (triflic) acid. To avoid decomposition from heat of dilution, the triflic acid solution was prepared by adding triflic acid to liquid-N_2-cooled CD_3CN. Before protonation, the NMR chemical shifts for **1** are as follows: ^1H (300 MHz, CD_3CN) δ 1.705 (d, 12 H, CH_3), 3.399 (s, 8 H, $ArCH_2$), 3.713 (s, 16 H, NCH_2), 3.930 (d, 4 H, OCH_2O), 4.465 (q, 4 H, CH), 5.527 (d, 4 H, OCH_2O), 7.234 (t, 8 H, Ar H), 7.300 (s, 4 H, Ar H), 7.641 (d, 8 H, Ar H), 7.774 (t, 8 H, Ar H), 8.370 (t, 8 H, Ar H). After addition of 12 equiv of triflic acid the NMR chemical shifts for **1** are as follows: ^1H (300 MHz, CD_3CN) δ 1.644 (d,12 H, CH_3), 3.905 (d, 4 H, OCH_2O), 4.301 (s, 8 H, $ArCH_2$), 4.477 (q, 4 H, CH), 4.953 (s, 16 H, NCH_2), 5.664 (d, 4 H, OCH_2O), 7.319 (s, 4 H, Ar H), 8.164 (t, 8 H, Ar H), 8.220 (d, 8 H, Ar H), 8.636 (t, 8 H, Ar H), 8.842 (d, 8H, Ar H).

To verify protonated **1** could be returned to its deprotonated form, a base titration was performed on acidified **1** solution. A sample of **1** in 650 μL of CD_3CN (10 mg, 7.0 μmol) that had been acidified with 20 equiv of triflic acid was titrated with a 0.8699 M CD_3CN triethylamine solution (4 μL additions). As base was added, the chemical shifts of **1** returned to the shifts of the deprotonated cavitand, indicating that the protons were removed from all three of the dpa nitrogens.

Anion Titrations. Samples of **1** in CD_3CN (10 mg, 7.0 μmol) were protonated while in an NMR tube with either 12 or 18 equiv of triflic acid in preparation for the anion titration. The anion solutions were prepared by adding a sufficient quantity of the tetrabutylammonium (TBA) salt of each anion to CD_3CN to make a 0.696 M solution. The anion solutions were sonicated and stored at 4 °C. The NMR titrations were performed by adding 3 or 4 μL (0.3 or 0.4 equiv) aliquots of the anion solution to a solution of **1** and noting the chemical shift changes. Also, titrations were done with initial quantities of **1** of 3 mg (2.1 μmol) and 20 mg (14 μmol).

Determination of Anion Binding Constants. Binding constants were determined by nonlinear least-squares fitting of the NMR titration curves using Sigmaplot 2002 for Windows version 8.02 and Graphpad Prism 4 for Windows. The 1:1 binding isotherm used has been described by Connors.[24] All reported binding constants are with respect to TBA perchlorate, which was used to correct chemical shifts from changes in solution ionic strength and concentration of TBA cation. TBA perchlorate was used since the perchlorate anion was the weakest binding anion. In the case of excess acid (18 equiv), titration curves were fit after the consumption of excess acid and at the point where changes in chemical shifts of **1** began to occur.

The binding curves for the anion titrations with **1** when 12 equiv of acid are present show that chemical shift changes are complete after 2 equiv of anion. This result indicates an anion to **1** ratio of 2:1 and implies that two dpa arms are binding to each anion. Noting that the binding curves do not show two different slopes or discontinuity in anion binding, we can simplify the binding process and think of two binding sites/**1**, which binding sites bind anions independently of each other. Equilibrium equations can be written for anion binding to **1** ($\mathbf{1}_{12H}$ = protonated **1**, A = anion):

$$\mathbf{1}_{12H} + A \rightleftharpoons \mathbf{1}_{12H}A \quad K_1 = \frac{[\mathbf{1}_{12H}A]}{[\mathbf{1}_{12H}A][A]} \tag{1}$$

$$\mathbf{1}_{12H}A + A \rightleftharpoons \mathbf{1}_{12H}A_2 \quad K_2 = \frac{[\mathbf{1}_{12H}A_2]}{[\mathbf{1}_{12H}A][A]} \tag{2}$$

We make the simplifying assumption that the two binding sites on $\mathbf{1}_{12H}$ are independent of each other and $K_1 = K_2$. Thus, we use a 1:1 binding isotherm for anion binding to **1**. Specifically,

$$S + A \rightleftharpoons SA \quad K = \frac{[SA]}{[S][A]} \tag{3}$$

where S is a binding site consisting of two protonated dpa groups, A is an anion, and K is equal to K_1 and to K_2.

If there is only one type of binding site on **1**, the chemical shift, δ, produced by anion addition to each site will be equivalent. The change in chemical shift upon anion binding from the initial chemical shift, Δcs, is monitored by NMR and is proportional to the amount of bound anion. The ratio of bound anion or bound **1**, which are equal (SA), to total **1** (S_t) is proportional to the change in chemical shift divided by the total possible change in chemical shift, $\Delta cs/(cs_{final} - cs_{initial})$ and represented by the following equation in a fast exchange process:[24]

$$\Delta cs/(cs_{final} - cs_{initial}) = [SA]/[S_t] \tag{4}$$

Combining eqs 4 and 3 and using the mass balance equation

$$[S_t] = [SA] + [S] \tag{5}$$

gives a simple 1:1 binding isotherm for a single binding site on **1**

$$\Delta/\Delta_o = nK[A]/(1 + K[A]) \tag{6}$$

where $\Delta = \Delta cs$, $\Delta_o = cs_{final} - cs_{initial}$, and [A] is the free anion concentration. Here, n is the number of independent binding sites (2 in this case). This equation is dependent on free anion concentration and not on the ratio of ligand to anion, which is important for a fast exchange process where the concentration of free vs bound host cannot be determined. To put [A] in terms of total anion (A_t), we can use the mass balance equation

$$[A_t] = [SA] + [A] \tag{7}$$

Combining eq 7 with eq 6 gives

$$\Delta = \frac{\Delta_o 2K\left([A_t] - \left(\frac{\Delta}{\Delta_o}\right)[S_t]\right)}{1 + K\left([A_t] - \left(\frac{\Delta}{\Delta_o}\right)[S_t]\right)} \tag{8}$$

where $\Delta_o = \Delta_o$ multiplied by a constant which takes into account slope changes due to solution affects. The initial value of Δ_o in the fit was $cs_{final} - cs_{initial}$. By preparing a plot of Δ_o vs $([A_t] - (\Delta/\Delta_o)[S_t])$ for each anion titration and performing a nonlinear fit of these data using eq 8, where K and Δ_o are unknown, we can determine K for each anion.

Results and Discussion

The dpa-resorcinarene cavitand, **1**, has 12 nitrogens from pyridines and amines positioned on arms around its upper rim. When protonated, these nitrogens can form a positive

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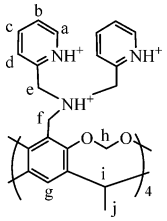

Figure 1. Hydrogen NMR assignments for **1**.

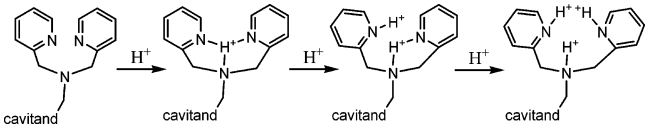

Figure 2. Protonation of the dpa groups. The first proton is shared by all of the nitrogen atoms resulting in NMR chemical shifts of protons next to the alkylamine and on the pyridines. Once two protons are bonded, one pyridine group has more flexibility. With the addition of the third proton, each nitrogen has a proton and the pyridine groups will have freedom to move away from each other to separate charges.

cavity and/or an array of flexible hydrogen-bonding sites for guest molecules such as anions. The protonation of **1** is accomplished by adding acid and can be monitored by the changes in the hydrogen NMR signals at various sites on **1** (Figure 1).

The hydrogen resonances closest to nitrogen atoms shift downfield by as much as 1 ppm. For example, the resonance of hydrogen **a** moves from 8.42 to 8.84 ppm, **c** from 7.68 to 8.65 ppm, **e** from 3.64 to 4.99 ppm, and **f** from 3.42 to 4.37 ppm. Even one of the resonances of hydrogen **h** moves downfield by 0.45 ppm. The other hydrogen **h** resonance, along with **i**, move upfield slightly by 0.2 and 0.4, respectively. After 12 equiv of acid is added to **1** (3 equiv/dpa group), hydrogen resonances cease to shift, indicating that all the nitrogens have been protonated. The aromatic hydrogens finish shifting before the other hydrogens and after 8 equiv of acid/**1** is added (2 equiv/dpa). The analogue dpa-undecyl compound also showed aromatic hydrogen shifts complete by 2 equiv of acid/dpa, and other hydrogen shifts complete at 3 equiv of acid/dpa. This indicates that the first and second protons reside not only on the amine nitrogen but are also shared by the pyridine nitrogens. Figure 2 gives possible protonated structures, which correlate to the chemical shift changes. The pyridine nitrogens are to some extent protonated through out the process, which results in the chemical shift changes of the aromatic hydrogens. The chemical shift changes in the benzylic and methylene hydrogens, **e** and **f**, are due to not only the protonation of the amine nitrogens but also to conformational changes of **1** when it enhances charge separation. Reversibility of the protonation process was observed by performing titrations with triethylamine and noting that the initial chemical shifts for **1** return. While the mechanism for stepwise protonation is interesting, the important point for our purposes here is that once 12 equiv of acid is added, clearly all sites are protonated.

With **1** fully protonated, hydrogen-bonding sites are available for anion binding. The tetrabutylammonium salts of various anions were added incrementally to the protonated cavitand and binding was monitored by ^{1}H NMR. After

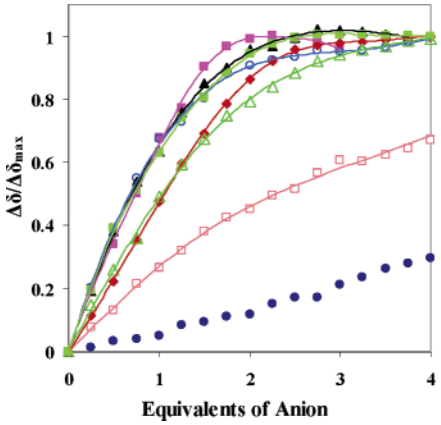

Figure 3. Binding saturation curves based on ^{1}H NMR titrations of acidified cavitand in acetonitrile with tetrabutylammonium anion salts. Anions: acetate (■); fluoride (▲); dihydrogen phosphate (■); chloride (○); nitrate (◆); hydrogen sulfate (△); perrhenate (□); perchlorate (●). $\Delta\delta$ is the chemical shift difference of the **f** proton after an aliquot of anion has been added compared to before any anion addition. $\Delta\delta/\Delta\delta_{max}$ is the change in chemical shift upon anion binding divided by the maximum change in chemical shift.

protonation of **1** with 12 equiv of triflic acid, one proton for each nitrogen, TBA anion salts were titrated into a solution of **1** and anion binding was monitored by changes in ^{1}H NMR chemical shifts. The largest chemical shifts, usually in the downfield direction, were from protons **e**, **f**, **h**, and the aromatic protons **a**−**d**. These hydrogen signals are from groups close to the protonated nitrogens, where anion binding is expected to occur. The changes occurring in the chemical shift of proton **h** indicate anion approach to or distortion of the upper rim of the cavitand.

Anion titration curves were generated by plotting the shifts in the hydrogen resonances. Figure 3 shows the titration curves for the **f** proton as a representative example. All the proton resonances gave nearly identical titrations curves. The gradual chemical shift changes that are observed in the NMR spectra are consistent with the formation of a complex in a fast exchange process. There are not two signals observed, one for unbound and one for bound cavitand. Plotting anion equivalents/**1** vs change in chemical shift/maximum change in chemical shift gives saturation curves and shows that most anion association is complete at 2 equiv of anion/**1** (Figure 3). The curves give good visual representation, based on their curvature, of the magnitude of binding of each anion. For example, chloride, acetate and dihydrogen phosphate associate more strongly with **1** than do perrhenate or perchlorate. From these curves, binding constants were calculated as described above. Table 1 lists the anion binding constants calculated. To test for a change in the binding mechanism, chloride binding constants were calculate at more than one concentration of **1**. The log K values for chloride at the different concentrations (4.2−28 mM) of **1** were all within experimental error, ±0.4. Thus, the binding species remains similar throughout the concentration range.

Protonated **1** in acetonitrile binds halides and oxoanions strongly, with log K values ranging from 4 to 5. The binding constants are fairly similar for the different anions, except for perrhenate and perchlorate which bind weakly. The values do not correlate uniquely to anion base strength, solvation

Table 1. Association Constants (log *K*) of **1** with Anions in CD_3CN at 23 °C As Determined by ^1H NMR Titration

anion[a]	log *K* (M^{-1})[b]	anion[a]	log *K* (M^{-1})[b]
Cl^-	5.58 ± 0.02	NO_3^-	4.91 ± 0.06
F^-	5.47 ± 0.03	ReO_4^-	4.29 ± 0.02
$H_2PO_4^-$	5.41 ± 0.03	ClO_4^-	<1
$CH_3CO_2^-$	5.29 ± 0.07	Br^-	na[c]
HSO_4^-	4.99 ± 0.03	I^-	na[c]

[a] Tetrabutylammonium salts of the anions were used. [b] Errors calculated from how well data fit saturation curves. [c] Precipitate formed during the titration.

energy, or ionic radius. Neither do they correlate to anion geometry—for example F^-, $H_2PO_4^-$, and $CH_3CO_2^-$ all bind with similar strength and yet have different geometries. The flexibility of the dpa arms most likely allows for binding to anions with various geometries. These binding constants in the relatively polar acetonitrile are on the same order of magnitude as those of a thiourea-substituted resorcinarene,[19c] where anionic isophthalates gave log *K* values on the order of 3.6−5.5 in polar protic solvents. The binding constants for **1** are much higher than a neutral resorcinarene, which yielded log *K* values in chloroform from 2.2 to 3.5.[19b] Comparing the binding constants of **1** to other protonated nitrogen anion receptors, which have *K* values ranging from 1 to 5, places **1** among the strongest binders.[1d] Compound **1** reinforces the concept that flexible receptors with large enough binding domains will accommodate anions of varying sizes and geometries. This concept is also shown by recent anion binders composed of polythioamide macrocycles and bicycles.[5g] Anion binding changes as the receptor is made more rigid and the binding domain decreased. Specifically, binding constants change from log $K = 5.0$ to 1.0 for a given anion depending on the size and rigidity of the binding domain.

Molecular modeling studies of **1** and bound anions show that two anions can be accommodated by **1**.[25] Figure 4 shows chloride ions bound in two identical sites by dpa sidearms. Modeling other anions (fluoride and dihydrogen sulfate) shows that the dpa arms of **1** can change position and bind other anions of nonspherical geometry. The model figures show that the bound anions are surrounded by aromatic residues and have little exposure to solvent. In essence, by surrounding the anions, **1** protects them from being pulled away from the binding site, which results in large binding constants. Other anion receptor molecules show how solvent exposure can result in the mode of binding changing from a guest-to-host ratio of 1:2 to 1:1[19c] or how greater *K* values are obtained when the anion is more fully encapsulate by residues on the receptor.[22]

Although anion binding to **1** is shown as a static structure with two dpa arms binding each anion, it is a complex process. In order for the anion to bind, the triflate anions associated with the protonated nitrogens must be displaced and the cationic dpa arms must approach each other. For this to happen several steps must occur which include anion−cation bond dissociation of the triflates and ammoniums, carbon−carbon bond rotations of the cavitand, compensation for coulumbic as well as steric repulsions between dpa arms, columbic attractions between the ammonium cations and anion, and solvation and desolvation of anions and cavitand. We favor dpa arms from each cavitand binding an anion instead of two different cavitands binding an anion in an intermolecular fashion because the noncavitand molecule, dpa-undecyl, showed very weak anion binding.

(25) Modeling of cavitand−anion complexes was performed using PC Spartan Pro and energy minimized using semiempirical PM3 calculations. The structure with two cavitands and four anions is also possible but has a higher calculated energy than the structure shown.

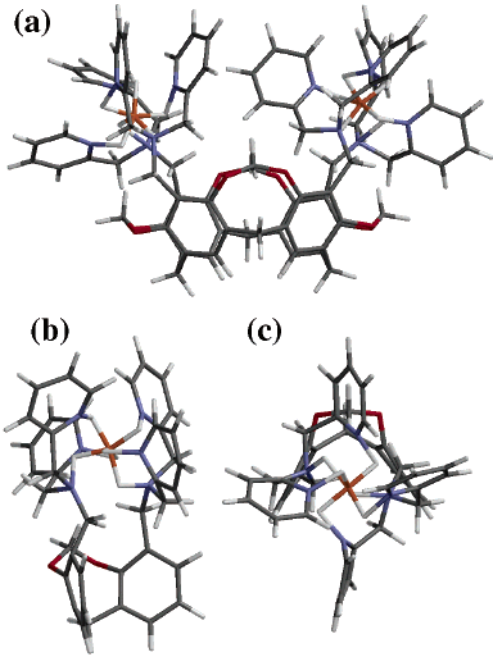

Figure 4. Semiempirical PM3 modeling of chloride ions (orange) binding to acidified **1**: (a) binding of two chlorides by identical binding sites formed by two dpa side arms; (b) cutaway side view of a chloride binding site from the interior of the cavitand; (c) top down view of a chloride bound by six hydrogens from one of the binding sites of the receptor.

The importance of the preorganized anion binding site in **1**, which has binding groups that can work cooperatively, is shown by the anion titration studies with the dpa-undecyl model compound. The protonated dpa-undecyl has the same dpa ammonium binding region as **1**. When titrated with anion, protonated dpa-undecyl showed very little change in ^1H NMR signals, less than 0.2 ppm, even when 5 equiv of anion had been added. In fact, the binding curves showed so little vertical rise that accurate binding constants could not be calculated. The stronger association between anions and protonated **1** is clearly due to cooperative binding of anions between dpa ligands. The lack of binding by dpa-undecyl indicates that preorganization around the upper rim of **1** aids in anion binding between two dpa ligands. It also discounts the likelihood of intermolecular binding with **1**, since the protonated dpa does not associate with anions when no preorganization has occurred.

Conclusions

The resorcinarene-based cavitand, **1**, containing four 2,2′-dipicolylamine moieties on its upper rim, was found to provide strong binding of anions such as Cl^-, F^-, $H_2PO_4^-$,

$CH_3CO_2^-$, HSO_4^-, and NO_3^- through multiple hydrogen bonds. Compound **1** provides two identical receptor sites formed by two dpa pendant groups, facilitating the simultaneous binding of two anions. Anions of various geometries are bound with large binding constants on the order of log $K = 4-5$ in acetonitrile. Intramolecular binding of anions between two dpa groups is shown on the basis of titration results, comparison to a model compound, and semi-empirical PM3 molecular modeling. Preorganization of flexible anion receptor sites is a key factor in favor of strong anion binding.

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