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Synthesis of a Preorganized Hybrid Macrobicycle with Distinct Amide and Amine Clefts: Tetrahedral versus Spherical Anions Binding Studies

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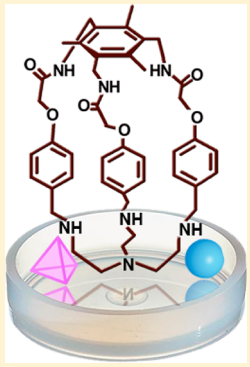
Supporting Information

ABSTRACT: A new C_{3v} symmetric amido-amine hybrid macrobicycle, **L** is synthesized toward anion recognition in its protonated states. **L** contains tri-amide and tetra-amine clefts separated by *p*-phenylene spacers. The solid-state structure of methanol-encapsulated **L** exhibits an overall cavity length of ~12.0 Å where the amide and amine -NH protons are converged toward the center of the respective cavities. Conformational analysis of **L** in solution is established by NOESY NMR. Anion binding of $[H_3L]^{3+}$ with spherical (Cl^-, Br^-, I^-) and tetrahedral (ClO_4^-, SO_4^{2-}) anions are carried out by isothermal titration calorimeter in dimethylsulfoxide. The association of halides with $[H_3L]^{3+}$ is endothermic and entropy driven. However, association of tetrahedral anions is exothermic in nature and both entropy- and enthalpy-driven. The overall association constants show the following order: HSO_4^- > Br^-> Cl^- ≈ ClO_4^-. Single crystal X-ray structures of ClO_4^- and Br^- complexes of protonated **L** show encapsulation of ClO_4^- in the amide cleft of $[H_2L]^{2+}$ (complex **1**) and encapsulation of Br^- in the ammonium cleft of $[H_3L]^{3+}$ (complex **2**). Further, preorganization of **L** toward encapsulation of spherical and tetrahedral anions is established by comparing its amide, amine, and overall cavity dimensions with **1** and **2**.



INTRODUCTION

Recognition of anions by synthetic receptors has been one of the most rapidly growing fields of supramolecular chemistry in the past decade.[1−7] Anions play various essential roles in the chemical and biological processes that encourage synthetic chemists to develop new classes of receptors.[8,9] Receptor-substrate binding site complementarity and solvation effects are important factors that must be considered in the designing aspects of any new receptor. The preorganization of the receptor is an essential feature to address the guest binding selectivity. Since the discovery of katapinands for halide recognition, a large number of macrobicyclic systems have been studied for recognition of anions and their various chemistries.[10−17] Most popular in this series is anion recognition by polyammonium cryptands.[18−30] Later on, polyamide-based macrobicyclic neutral receptors have shown different new features in this area.[31−37] One of the most interesting properties of macrobicyclic receptors is the recognition of multiple anions such as HF_2^-, HCl_2^-, etc. within a polyammonium cage.[38,39] A few examples of recognition of a cation and an anion in the heteroditopic macrobicyclic hosts are also known in the literature.[40−45] Thus most of the cryptands studied for anionic guests are accompanied by a polyamine/polyammonium cavity or polyamide environment. However, the incorporation of polyamine and polyamide functionalities into a suitable macrobicyclic ligand make them attractive receptors mainly because of the balanced combinations of both electrostatic and hydrogen-bonding interactions with significantly higher anion affinities. Herein we report a new amido-amine hybrid preorganized macrobicyclic C_{3v} symmetric host (**L**, Figure 1)

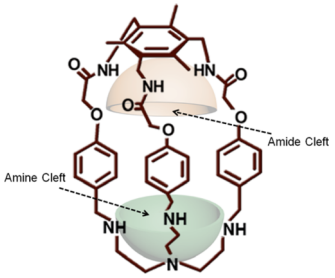


Figure 1. Cartoon picture of the hybrid macrobicycle **L** with distinct amide and amine clefts.

having two distinct clefts, one polyamide and another polyamine, in good yield. Further attempt is made to understand the binding of anions with spherical size such as chloride, bromide, and iodide and tetrahedral anions such as perchlorate and sulfate. Importantly, solid-state structural analysis shows preferential encapsulation of perchlorate (tetrahedral) in the polyamide cleft of $[H_2L]^{2+}$ and bromide (spherical) in the polyammonium pocket of $[H_3L]^{3+}$. To the best of our knowledge this represents the first example of a hybrid macrobicycle with distinct amide and amine clefts that

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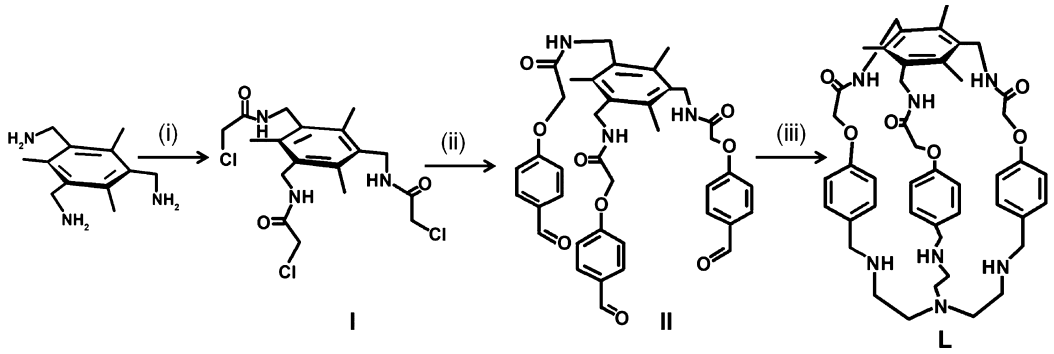
Scheme 1[a]



[a](i) Chloroacetyl chloride, CH_2Cl_2, NEt_3, 81%; (ii) 4-hydroxy-benzaldehyde, CH_3CN, K_2CO_3, 78%; (iii) tren, CH_3OH, CH_2Cl_2, $NaBH_4$, 65%.

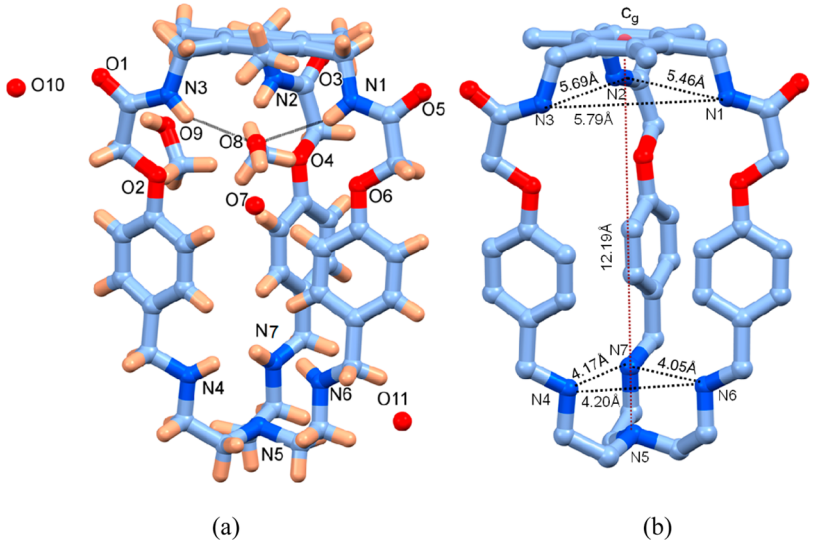


Figure 2. Single crystal X-ray structure of **L** shows (a) encapsulation of one methanol molecule having hydrogen bonding interactions with the amide protons of **L** and (b) cavity dimension of **L** (H atoms along with lattice water molecules are omitted for clarity).

shows compartmental binding of tetrahedral versus spherical anions in its protonated states.

RESULTS AND DISCUSSION

Ligand Design. Design of the amine- and amide-based heteroditopic macrobicylic cage arose from our curiosity to develop receptors for compartmental recognition of different anions. We have chosen ammonium and amide as recognition elements in our design to segregate the cage of the macrobicyclic receptor for anions of different basicity. Tris(2-aminoethyl)amine, tren-based polyammonium, and mesitylene-based tripodal acyclic amide receptors have shown enormous potential toward recognition of various anions in their clefts.[46−51] Thus it would be interesting to have a hybrid new generation cage receptor with mesitylene-based tri-amides and tren-based ammonium recognition clefts that are well separated by suitable spacers for the recognition of anion. It is also expected that the presence of the aromatic spacers in the receptor architecture would contribute to its rigidity, which can favor the preorganization and also can decrease the solvation effect of the receptor.

Synthesis. The new amido-amine-based macrobicycle, **L** is synthesized according to Scheme 1 in three steps. Reaction of chloroacetyl chloride with the tri-amine 1,3,5-tris-(aminomethyl)-2,4,6-trimethylbenzene in dichloromethane in the presence of triethylamine gives **I** in good yield. Compound **II** is obtained upon reaction between **I** and 4-hydroxybenzaldehyde in acetonitrile in the presence of anhydrous K_2CO_3. High dilution reaction between tris(2-aminoethyl)amine (tren) and **II** in dichloromethane/methanol (dropwise addition) at room temperature resulted the desired heteroditopic host, **L**, in good yield (∼65%).

Conformational Analysis. The structural information and conformational geometry of **L** was determined by solid-state structural analysis and solution-state NOESY NMR study. Single crystals of **L** suitable for X-ray diffraction studies were obtained by slow evaporation of a methanol/dichloromethane solution at room temperature. The asymmetric unit contains **L** with three water molecules and two methanol as solvent of crystallization. The crystal structure of **L** shows that all of the amide and amine moieties are orientated in such a way that the attached hydrogen atoms are pointed inside the cavity of the macrobicycle (Figure 2a). This type of arrangement of all of the hydrogen bond donor atoms could facilitate better interaction with the anionic guest by encapsulating it within the cavity. Therefore these groups are well preorganized for the interaction with an anionic guest. The three amide groups are apart from each other with an average N···N distance of 5.65 Å (Table 6S in Supporting Information). One methanol is occupied in the amide cleft, whereas the other solvent

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molecules are located outside the macrobicyclic host. The amide groups are oriented in such a way that amide hydrogen atoms are directed toward its cavity and hydrogen bonded to the encapsulated methanol with bond distances of N1···O8 = 3.291 Å and N3···O8 = 3.173 Å. The distance between the centroid of the mesitylene moiety (C_g) to the bridge head nitrogen atom (N5) of **L** is 12.19 Å, which indicates a large cavity of **L** for accommodation of guest species (Figure 2b). Further, the secondary amines of the tren subunit are separated from each other with an average distance of 4.14 Å, which makes the amine clefts slightly smaller compared to that of the amide clefts. Structural analysis further reveals that the three *p*-phenylene moieties of **L** impose a conformational rigidity and also work as spacers to segregate the amide and amine clefts distinctly.

The ^{1}H NMR spectroscopic studies are performed to obtain the information about the conformational behavior of **L** in solution. The ^{1}H NMR spectra of **L** in $CDCl_3$ and DMSO-d_6 show different chemical shifts for amide -NH protons and some other spectral features (Figures 8S and 9S in Supporting Information). Down field shift of 0.98 ppm of the amide -NH proton in DMSO-d_6 compared to that in $CDCl_3$ indicates a higher degree of solvation for **L** in DMSO-d_6. The NOESY spectrum of **L** in $CDCl_3$ (Figure 3) clearly shows five cross

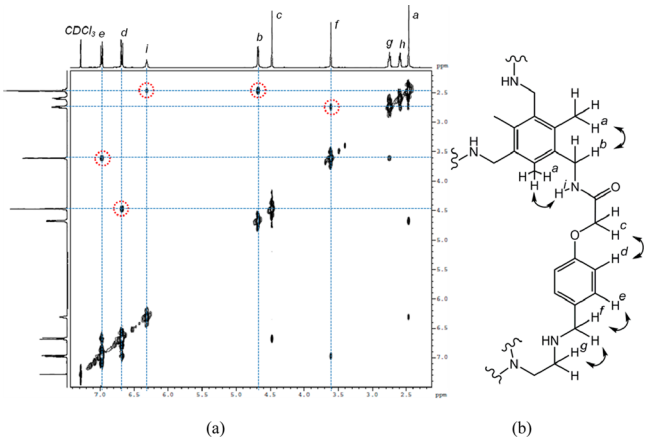

Figure 3. (a) 2D NOESY spectrum shows five spatial ^{1}H−^{1}H coupling of **L**. (b) Chemical structure of one of the arm of **L** showing the interactions between the labeled protons.

peaks that correspond to the following interactions: H^a−H^b, H^c−H^d, H^e−H^f, H^f−H^g, and H^i−H^a. All five cross-peaks in solution are consistent with the solid-state conformation of **L** in which similar spatial arrangement for the corresponding proton pairs are observed (Figure 2).

Solution-State Anion Binding Studies. Receptor **L** in its protonated state, $[H_3\mathbf{L}](PF_6)_3$, is explored for binding of spherical and tetrahedral anions such as Cl^-, Br^-, I^-, HSO_4^-, and ClO_4^- as their tetrabutylammonium salts by isothermal titration calorimeter (ITC) in dry DMSO. Hexafluorophosphate (PF_6^-) salt of the protonated **L** is used as host in this investigation. PF_6^- has been chosen as counteranion because of its poor hydrogen bond acceptor ability; it would not bind to the host significantly. Figure 4 shows two representative binding isotherms obtained by titrating $[H_3\mathbf{L}](PF_6)_3$ with the solution of TBABr and $TBAClO_4$, respectively.

Binding studies of chloride and hydrogen sulfate with $[H_3\mathbf{L}](PF_6)_3$ using TBACl and $TBAHSO_4$ are also carried out similarly (Figures 22S and 24S in Supporting Information). However, complexation of TBAI with $[H_3\mathbf{L}](PF_6)_3$ turns out to be very weak to be reliably quantified by an ITC titration.[52] Thermodynamic parameters for the complexation of $[H_3\mathbf{L}](PF_6)_3$ with different anions are summarized in Table 1. The overall association constants K_T are calculated from stepwise binding constants K_1, K_2, and K_3, which are evaluated on the basis of the sequential binding model.[53] The calculated overall association constants follow the order as $HSO_4^- > Br^- > Cl^- \approx ClO_4^-$.

The higher overall association constant for Br^- compared to that of the Cl^- could be due to better fitting of Br^- into the ammonium cleft of the host (as obtained from the solid-state structure of the bromide complex, which is discussed later). In cases of Cl^- and Br^- an endothermic binding pattern is observed along with very high positive entropy values, indicating an entropy-driven association of spherical anion with $[H_3\mathbf{L}]^{3+}$ in DMSO. On the other hand, binding of ClO_4^- and HSO_4^- in DMSO are exothermic in nature. However, the binding of these tetrahedral anionic guests to the $[H_3\mathbf{L}]^{3+}$ is found to be both entropy- and enthalpy-driven (Table 1). A relatively high entropic contribution, $T\Delta S$, in all of the cases suggests a better fitting of the anionic guests somewhere in the amido-ammonium hybrid host cavity, which eventually releases host/guest-associated solvent molecules to the system during complexation.

Structural Analysis. Single crystals of perchlorate complex of **L** and **1** suitable for X-ray diffraction studies were obtained upon protonation of **L** with perchloric acid in an acetonitrile/water mixture by slow evaporation. The complex **1** crystallized in an orthorhombic space group *Pbca*. The structure shows that the asymmetric unit of **1** contains a protonated macrobicycle, $[H_2\mathbf{L}]^{2+}$, two perchlorate ions, two water molecules, and one acetonitrile as solvent of crystallization (Figure 5a). Structural analysis of **1** shows bis-protonation of **L** with one encapsulated perchlorate ion in the amide compartment, and the ammonium pocket is occupied by one water molecule (Figure 5a). An imaginary plane passing through the three *p*-phenylene spacers of **L** separates the receptor into two distinct hydrogen bonding clefts, mesitylene-based tri-amide (N1, N2, N3) and tren-based ammonium/amine (N4, N6, N7) pockets (Figure 20S in Supporting Information). It is clearly evident from the single crystal X-ray structure of **1** that perchlorate resides in the amide pocket, 2.48 Å above the imaginary plane, whereas the water molecule resides in the ammonium pocket 1.86 Å below the imaginary plane (Figure 20S in Supporting Information).

The encapsulated perchlorate ion is involved in two N−H···O hydrogen bonding interactions with amide proton centers (N2 and N3). Two oxygen atoms (O14, O13) of the perchlorate are hydrogen bonded with N−H···O bond distances of 2.26 and 2.35 Å, respectively (Table 4S in Supporting Information). Oxygen atom (O19) of the encapsulated water molecule is in three strong hydrogen bonding interactions with the ammoninum/amine centers with N−H···O bond distances in the range of 1.83−2.11 Å. In the complex **1** the distance between the centroid of the mesitylene moiety and the bridge head nitrogen atom is 11.31 Å, which is quite similar as observed in case of free receptor **L** (12.19 Å).

Single crystals of bromide complex of **L** and **2** are grown upon protonation of **L** with hydrobromic acid in an acetonitrile−water mixture on slow evaporation. Complex **2** crystallizes in a monoclinic system in the $P2_1/c$ space group having a protonated macrobicycle $[H_3\mathbf{L}]^{3+}$, three bromide ions,

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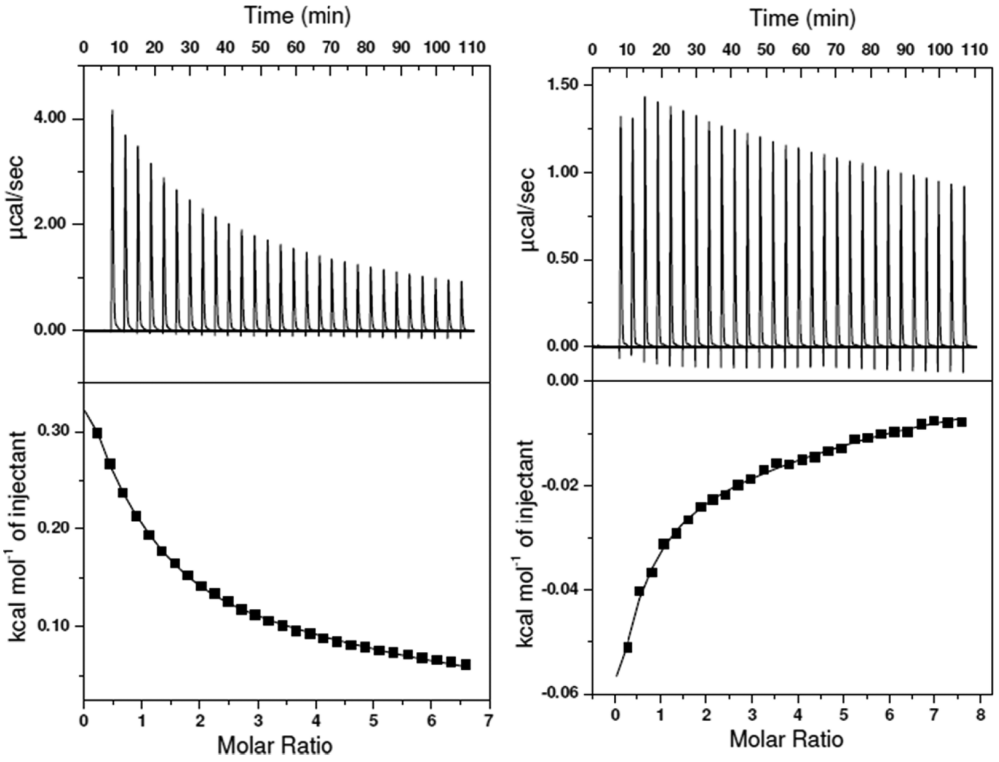

Figure 4. ITC traces and binding isotherms for (a) titrations of receptor $[H_3L]^{3+}$ (1 mM) with TBABr (38 mM) and (b) titrations of receptor $[H_3L](PF_6)_3$ (0.98 mM) with $TBAClO_4$ (44.4 mM) in dry DMSO at 298 K. The upper panel shows the heat pulses experimentally observed in each titration step. The lower panel reports the respective time integrals translating as the heat changed for each aliquot and its coherence to a sequential binding model.

Table 1. Association Constants K_a, Gibbs Energies ΔG, Enthalpies ΔH, and Entropies $T\Delta S$ Associated with the Complexation of TBACl, TBABr, $TBAClO_4$, and $TBAHSO_4$ with Receptor $[H_3L](PF_6)_3$ in Dry DMSO at 298 K

guests	assoc constants K_a (M^{-1})	ΔH (cal/mol)	$T\Delta S$ (cal/mol/deg)	ΔG (cal/mol)
TBACl	K_1 = 6.69E2 ± 12	ΔH_1 = 3447 ± 40.8	$T\Delta S_1$ = 7301	ΔG_1 = −3854
	K_2 = 1.54E3 ± 34	ΔH_2 = −2490 ± 51.2	$T\Delta S_2$ = 1859.5	ΔG_2 = −4349.5
	K_3 = 3.7E2 ± 6.7	ΔH_3 = 1826 ± 18.4	$T\Delta S_3$ = 5334.2	ΔG_3 = −3508.2
	K_T = 3.81E8 ± 11.82			
TBABr	K_1 = 3.13E3 ± 80	ΔH_1 = 427.3 ± 4.47	$T\Delta S_1$ = 5185.2	ΔG_1 = −4757.9
	K_2 = 1.39E3 ± 44	ΔH_2 = 52.42 ± 8.10	$T\Delta S_2$ = 4350.8	ΔG_2 = −4298.4
	K_3 = 1.29E2 ± 2.6	ΔH_3 = 1233 ± 19.2	$T\Delta S_3$ = 4112.4	ΔG_3 = −2879.4
	K_T = 5.61E8 ± 31.62			
$TBAClO_4$	K_1 = 1.22E3 ± 66	ΔH_1= −105.4 ± 3.39	$T\Delta S_1$ = 4112.4	ΔG_1 = −4217.8
	K_2 = 1.10E3 ± 90	ΔH_2 = 40.91 ± 5.24	$T\Delta S_2$ = 4172.0	ΔG_2 = −4131.1
	K_3 = 2.76E2 ± 13	ΔH_3 = −151.0 ± 4.14	$T\Delta S_3$ = 3188.6	ΔG_3 = −3339.6
	K_T = 3.7E8 ± 32.17			
$TBAHSO_4$	K_1 = 1.11E4 ± 340	ΔH_1 = −661.0 ± 2.98	$T\Delta S_1$ = 4857.4	ΔG_1 = −5518.4
	K_2 = 5.16E2 ± 12	ΔH_2 = −1323 ± 21	$T\Delta S_2$ = 2378.0	ΔG_2 = −3701.0
	K_3 = 1.27E2 ± 2.4	ΔH_3 = 117.1 ± 43.8	$T\Delta S_3$ = 2980	ΔG_3 = −2862.9
	K_T = 7.27E8 ± 156.93			

one water molecule, and one acetonitrile (Figure 5b). In complex **2**, **L** is in the triprotonated $[H_3L]^{3+}$ state. The receptor $[H_3L]^{3+}$ encapsulates one bromide ion and an acetonitrile in its compartments. Interestingly, a reverse order in anion and solvent encapsulation is observed in case of **2** when compared with the single crystal X-ray of **1**. The encapsulated bromide ion in $[H_3L]^{3+}$ occupies the ammonium compartment, whereas the amide pocket is engaged with one acetonitrile molecule. The encapsulated bromide (Br3) resides in the ammonium pocket, 1.50 Å below the imaginary plane, whereas water molecule resides in amide pocket 2.71 Å above the imaginary plane (Figure 20S in Supporting Information). The bromide ion (Br3) is in H-bonding interactions with three protonated ammonium centers (N4, N6, N7) with N−H···Br distances in the range of 2.36−2.62 Å (Table 5S in Supporting Information). The distance between centroid of the bridge head mesitylene to bridge head nitrogen atom is measured as 11.96 Å, which is pretty close to the values obtained in cases of

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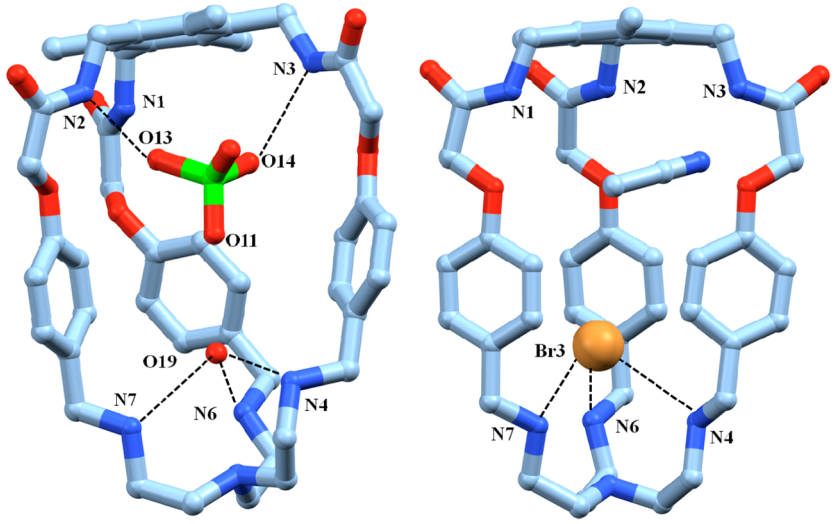

(a) (b)

Figure 5. Single crystal X-ray structure of (a) complex **1**; perchlorate is in the amide compartment of $[H_2L]^{2+}$, and water is in ammonium pocket. (b) Complex **2**; bromide is in the ammonium compartment of $[H_3L]^{3+}$, whereas acetonitrile is in ammonium pocket. (H atoms and counteranions along with lattice water molecules are omitted for clarity.)

L and **1**. It is important to mention that the cleft size of the amide and amine/ammonium of the macrobicycle after encapsulation of the anionic guest into the corresponding clefts remains almost the same compared to that of the methanol encapsulated **L** (Table 6S in Supporting Information). This indeed suggests the preorganization of the receptor design toward anion recognition.

CONCLUSION

A new hybrid macrobicylic host with two distinct cavities consisting of amine and amide as potential recognition elements for anionic guests is synthesized for the first time. The overall cavity dimension of this hybrid macrobicycle is relatively large, having two distinct compartments of different environments that have potential for guest encapsulation. The solid-state conformation of **L** matches well with the solution-state conformation obtained from NOESY NMR. Both solution-state ITC and single crystal X-ray study confirm binding of anions of different dimensionalities with the protonated host. The ITC study demonstrates selectivity toward hydrogen sulfate over other anions studied in DMSO. Exothermic versus endothermic processes are observed in cases of tetrahedral and spherical anions, respectively. Preorganization and compartmental recognition of anions with different dimensionalities are established with the newly designed hybrid amido-amine receptor. This type of host with new anion recognition property could be useful in the development of hetero multianionic receptors that can recognize anions of different dimensions in a single molecular entity.

EXPERIMENTAL SECTION

General Details. The reagents were obtained from commercial suppliers and used as received without further purification unless otherwise indicated. 1,3,5-Tris(aminomethyl)-2,4,6-trimethylbenzene was synthesized using a previously reported procedure.[54] Peak assignments in the ^{1}H NMR spectra were confirmed by using H,H-COSY spectra of selected compounds. DEPT spectra were used to interpret the ^{13}C NMR spectra. The special interactions between the protons of the macrobicyclic host were interpreted by NOESY NMR spectroscopy in $CDCl_3$.

Isothermal Titration Calorimetric (ITC) Studies. Titration experiments were carried out at 298 K in dry dimethylsulfoxide (DMSO). A solution of $[H_3L](PF_6)_3$ in DMSO was taken in the cell. This solution was then titrated with 30 injections of 10 μL of anion solutions prepared in DMSO. An interval of 220 s was allowed between each injection, and the stirring speed was set at 329 rpm. The obtained data was processed using Origin 7.0 software supplied with the instrument and fitted to a sequential binding model. Blank titration of anion into solvent was also performed and subtracted from the corresponding titration to remove any effect from the heats of dilution from the titrant. The studies of the effect of both the anions were repeated twice with two different batches of $[H_3L](PF_6)_3$ and showed good reproducibility.

X-ray Crystallography. Crystals suitable for single crystal X-ray diffraction studies were selected from the mother liquor and immersed in paratone oil, then mounted on the tip of a glass fiber, and cemented using epoxy resin. Intensity data for the crystals **L**, **1**, and **2** were collected using Mo Kα (λ = 0.7107 Å) radiation on a single crystal X-ray diffractometer equipped with CCD area detector at 298/150 K. The data integration and reduction were processed with SAINT[55] software. An empirical absorption correction was applied to the collected reflections with SADABS.[56] The structures were solved by direct methods using SHELXTL[57] and were refined on F^2 by the full-matrix least-squares technique using the SHELXL-97[58] program package. Graphics were generated using PLATON[59] and MERCURY 2.3.[60] The non-hydrogen atoms were refined anisotropically till convergence. In the cases of complexes **L**, **1**, and **2** the hydrogen atoms were geometrically fixed at idealized positions. In the cases of complexes **1** and **2**, even though the data were collected at 150 K, the hydrogen atoms attached to the lattice water molecule could not be located from the difference Fourier map. In case of complex **1**, one of the oxygen atoms (O13) of the encapsulated perchlorate ion was disordered at two sites, and the occupancy factors were refined using the FVAR command of the SHELXTL program and isotropically refined. In the case of complexes **2**, even though the data was collected at 150 K several times, we were unable to assign electron density for solvent molecules in the unit cell. The routine SQUEEZE[61] was applied to intensities data of complexes **2** to take into account the disordered solvent molecules. The number of electrons found in the

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solvent-accessible void is close to that expected for one CH_3CN molecule in the unit cell.

CCDC-903584(**L**), CCDC-903583 (**1**), and CCDC-903582 (**2**) contain the supplementary crystallographic data for this paper.

Compound I. In a 100-mL round bottomed flask was dissolved 0.6 g (2.9 mmol) of 1,3,5-tris(aminomethyl)-2,4,6-trimethylbenzene in 50 mL of dry dichloromethane. About 1.4 mL (10 mmol) of dry triethylamine was added to the above solution. The mixture was allowed to stir at 0 °C temperature in a nitrogen atmosphere for 15 min. Then 0.716 mL (9 mmol) of chloroacetyl chloride in 25 mL of dry dichloromethane was taken in a 50-mL pressure equalizer funnel. This solution was added dropwise for a period of 1 h with constant stirring 0 °C temperature. After the addition, the reaction mixture was allowed to stir at room temperature in a nitrogen atmosphere for another 7 h. The precipitate was filtered and washed three times with 2 M HCl, saturated $NaHCO_3$ solution and saturated NaCl solution. The off white solid was isolated and dried over vacuum to yield the desired product **I**. Yield: 1.025 g (81%). HRMS (ESI): *m*/*z* calcd for $C_{18}H_{24}Cl_3N_3O_3Na$ $[M + Na]^+$ 458.0781, found 458.0781. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.29 (s, 9H, Ar-CH_3), 4.03 (s, 6H, -CH_2Cl), 4.35 (d, 6H, *J* = 5 Hz, Ar-CH_2), 8.20 (br, 3H, CONH). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.31(CH_3), 38.94 (CH_2), 42.99 (CH_2), 132.92 (Ar-C), 137.16 (Ar-C), 166.15 (CO).

Compound II. In a 250-mL round-bottomed flask was dissolved 0.873 g (2 mmol) of **I** in 100 mL of acetonitrile. K_2CO_3 (2 g, 15 mmol) and 4-hydroxybenzaldehyde (0.85 g, 7 mmol) were added to that solution at room temperature. The reaction mixture was allowed to stir at 80 °C in nitrogen atmosphere for 24 h. The precipitate was filtered and repeatedly washed with water. This off-white solid, compound **II** was dried and was used in the next step without further purification. Yield: 1.08 g (78%). HRMS (ESI): *m*/*z* calcd for $C_{39}H_{39}N_3O_9Na$ $[M + Na]^+$ 716.2584, found 716.2584. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.32 (s, 9H, Ar-CH_3), 4.41 (d, 6H, *J* = 5 Hz, Ar-CH_2), 4.65 (s, 6H, COCH_2O), 7.09 (d, 6H, *J* = 10 Hz, Ar-CH), 7.85 (d, 6H, *J* = 10 Hz, Ar-CH), 8.13 (t, 3H, *J* = 5 Hz, NH), 9.85 (s, 3H, -CHO). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.33 (CH_3), 38.44 (CH_2), 67.18 (CH_2), 115.56 (Ar-C), 130.49 (Ar-C), 132.15 (Ar-C), 132.97 (Ar-C), 137.13 (Ar-C), 163.26 (Ar-C), 167.10 (CO), 191.79 (-CHO).

Macrobicycle L. In a 500-mL three-neck round-bottom flask, two necks were fitted with 100 mL pressure equalizers and another for nitrogen atmosphere. Compound **II** (0.3 g, 0.43 mmol) in 50 mL of dichloromethane in one pressure equalizer and tris(2-aminoethyl)-amine (tren, 0.065 mL, 0.43 mmol) dissolved in 50 mL of methanol in another pressure equalizer were added drop by drop to 100 mL of methanol with stirring. After complete addition, the reaction mixture was stirred for another 24 h. Sodium borohydride 0.95g (2.6 mmol) was added to the reaction mixture and stirred for 6 h. The reaction mixture was filtered, and the filtrate was evaporated at low pressure. The solid was dissolved in 100 mL of water, and the precipitate was filtered and dried to yield the desired product **L** as white solid. Yield: 0.22 g (65%). HRMS (ESI): *m*/*z* calcd for $C_{45}H_{58}N_7O_6$ $[M + H]^+$ 792.4449, found 792.4443. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 9H, Ar-CH_3), 2.57 (t, 6H, *J* = 5.4 Hz, NCH_2CH$_2$NH), 2.72 (t, 6H, *J* = 5.4 Hz, NCH$_2$CH_2NH), 3.59 (s, 6H, Ar-CH_2NHCH$_2$), 4.45 (s, 6H, COCH_2O), 4.65 (d, 6H, *J* = 4.2 Hz, ArCH_2NHCO), 6.28 (br, 3H, NHCO), 6.66 (d, 6H, *J* = 8.7 Hz, Ar-H), 6.96 (d, 6H, *J* = 8.7 Hz, Ar-H). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.36 (s, 9H, Ar-CH_3), 2.40 (br, 12H, NCH_2CH_2NH), 3.53 (s, 6H, Ar-CH_2NHCH$_2$), 4.42 (s, 6H, COCH_2O), 4.50 (d, 6H, *J* = 6 Hz, ArCH_2NHCO), 6.82 (d, 6H, *J* = 9 Hz, Ar-H), 7.11 (d, 6H, *J* = 9 Hz, Ar-H), 7.26 (t, 3H, *J* = 6 Hz, NHCO). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.24 (CH_3), 37.85 (CH_2), 47.27 (CH_2), 52.79 (CH_2), 54.78 (CH_2), 67.74 (CH_2), 115.00 (Ar-C), 129.41 (Ar-C), 133.25 (Ar-C), 134.28 (Ar-C), 136.97 (Ar-C), 156.39 (Ar-C), 167.32 (CO).

Complex 1. Compound **L** (0.1 mmol, 0.079 g) was dissolved in 10 mL of CH_3OH/CH_2Cl_2 (1:1), and few drops of perchloric acid were added to the stirring solution. The reaction mixture was stirred for another 6 h. A precipitate developed, which was filtered and collected after repeated washing with diethyl ether. The off-white solid was obtained as pure product. Yield: ~0.064g (64%). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.38 (s, 9H, Ar-CH_3), 2.60 (br, 6H, NCH_2CH$_2$NH), 4.11 (s, 6H, Ar-CH_2), 4.50 (m, 12H), 7.04 (d, 6H, *J* = 9 Hz), 7.31 (d, 6H, *J* = 9 Hz), 7.37(t, 3H, *J* = 6 Hz), 8.48 (br, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.39 (CH_3), 37.94 (CH_2), 42.74 (CH_2), 49.27 (CH_2), 49.43 (CH_2), 67.50 (CH_2), 115.73(Ar-C), 124.19 (Ar-C), 131.95 (Ar-C), 133.14 (Ar-C), 137.09 (Ar-C), 158.29 (Ar-C), 167.11 (CO). ESI-MS of **1** at *m*/*z* 992.0, 892.1, and 792.2 and 396.6 corresponded to $[H_3L.2ClO_4]^+$, $[H_2L.ClO_4]^+$, $[HL]^+$, $[H_2L]^{2+}$/2 respectively. Anal. Calcd for $C_{45}H_{59}N_7O_{14}Cl_2$: C, 54.43; H, 5.99; N, 9.87. Found: C, 54.32; H, 6.12; N, 9.75.

Complex 2. Compound **L** (0.1 mmol, 0.079 g) was dissolved in 10 mL of CH_3OH/CH_2Cl_2 (1:1), and a few drops of hydrobromic acid were added to the stirring solution. The reaction mixture was stirred for another 4 h. A precipitate developed which was filtered and collected after repeated washing with diethyl ether. The off-white solid was crystallized in an acetonitrile/water mixture, and the crystals were isolated as product. Yield: 0.071 g (68%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.38 (s, 9H, Ar-CH_3), 2.65 (br, 6H, NCH_2CH$_2$NH), 2.80 (br, 6H, NCH$_2$CH_2NH), 4.16 (s, 6H, Ar-CH_2NHCH$_2$), 4.51 (s, 12H, COCH_2O, ArCH_2NHCO), 7.01 (d, 6H, *J* = 10 Hz, Ar-H), 7.41 (s, 3H, NHCO), 7.47 (d, 6H, *J* = 10 Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.41 (CH_3), 34.80 (CH_2), 37.90 (CH_2), 43.17 (CH_2), 49.32 (CH_2), 67.61 (CH_2), 115.44(Ar-C), 124.42 (Ar-C), 132.23 (Ar-C), 133.12 (Ar-C), 137.08 (Ar-C), 158.15 (Ar-C), 167.08 (CO). ESI-MS of **2** at *m*/*z* 792.2 and 396.6 corresponded to $[HL]^+$and $[H_2L]^{2+}$/2 respectively. However, no peak was found along with the counteranion, bromide. Anal. Calcd for $C_{45}H_{60}N_7O_6Br_3$: C, 52.23; H, 5.84; N, 9.48. Found: C, 52.18; H, 5.91; N, 9.37.

$[H_3L](PF_6)_3$. Complex **2** (100 mg, 0.1 mmol) was dissolved in CH_3OH/H_2O (1:1) (10 mL). Then, 100 mg of potassium hexafluorophosphate dissolved in water (5 mL) was added into the above solution and stirred for 4 h. The white precipitate was filtered, washed with wate,r and dried in vacuo to isolate the product. Yield: 61 mg (50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 9H, Ar-CH_3), 2.56 (br, 6H, NCH_2CH$_2$NH), 2.85 (br, 6H, NCH$_2$CH_2NH), 4.10 (s, 6H, Ar-CH_2NHCH$_2$), 4.50 (s, 12H, COCH_2O, ArCH_2NHCO), 6.98 (d, 6H, *J* = 8.7 Hz, Ar-H), 7.35 (d, 6H, *J* = 8.7 Hz, Ar-H), 7.41 (s, 3H, NHCO); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 16.35 (CH_3), 37.84 (CH_2), 42.93 (CH_2), 49.48 (CH_2), 49.82 (CH_2), 67.55 (CH_2), 115.52 (Ar-C), 124.55 (Ar-C), 132.10 (Ar-C), 133.16 (Ar-C), 137.08 (Ar-C), 158.09 (Ar-C), 167.06 (CO). ESI-MS of $[H_3L](PF_6)_3$ at *m*/*z* 792.1 and 396.6 corresponded to $[HL]^+$and $[HL]^{2+}$/2, respectively. However, no peak was found along with counteranion, hexafluorophosphate. Anal. Calcd for $C_{45}H_{60}N_7O_6P_3F_{18}$: C, 43.95; H, 4.92; N, 7.97. Found: C, 44.11; H, 4.81; N, 8.12.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, synthesis, ITC, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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