CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201200428

A Series of Amino Acid Functionalized Tripodal Hexaamide Anion Receptors: Ion-Pair-Assisted Capped-Cleft Formation by a Pentafluorophenyl-Functionalized Amide

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Abstract: A new series of tris(2-aminoethyl)amine (tren)-based L-alanine amino acid backboned tripodal hexaamide receptors (L1–L5) with various attached moieties based on electron-withdrawing fluoro groups and lipophilicity have been synthesized and characterized. Detailed binding studies of L1–L5 with different anions, such as halides (F^-, Cl^-, Br^-, and I^-) and oxyanions (AcO^-, BzO^- (Bz = benzoyl), NO_3^-, $H_2PO_4^-$, and HSO_4^-), have been carried out by isothermal titration calorimetric (ITC) experiments in acetonitrile/dimethylsulfoxide (99.5:0.5 v/v) at 298 K. ITC titration experiments have clearly shown that receptors L1–L4 invariably form 1:1 complexes with Cl^-, AcO^-, BzO^-, and HSO_4^-, whereas L5 forms a 1:1 complex only with AcO^-. In the case of Br^-, I^-, and NO_3^-, no appreciable heat change is observed owing to weak interactions between these anions and receptors; this is further confirmed by ^1H NMR spectroscopy. The ITC binding studies of F^- and $H_2PO_4^-$ do not fit well for a 1:1 binding model. Furthermore, ITC binding studies also revealed slightly higher selectivity of this series of receptors towards AcO^- over Cl^-, BzO^-, and HSO_4^-. Solid-state structural evidence for the recognition of Cl^- by this new category of receptor was confirmed by single-crystal X-ray structural analysis of the complex of tetrabutylammonium chloride (TBACl) and L1. Single-crystal X-ray diffraction clearly showed that the pentafluorophenyl-functionalized amide receptor (L1) encapsulated Cl^- in its cavity by hydrogen bonds from amides, and the cavity of L1 was capped with a TBA cation through hydrogen bonding and ion-pair interactions to form a capped-cleft orientation. To understand the role of the cationic counterpart in solution-state Cl^- binding processes with this series of receptors (L1–L4), a detailed Cl^- binding study was carried out with three different tetraalkylammonium (Me_4N^+, Et_4N^+, and Bu_4N^+) salts of Cl^-. The binding affinities of these receptors with different tetralkylammonium salts of Cl^- gave binding constants with the TBA cation in the following order: butyl > ethyl > methyl. This study further supports the role of the TBA countercation in ion-pair recognition by this series of receptors.

Keywords: host–guest systems · ion pairs · receptors · thermodynamics · X-ray diffraction

Introduction

In recent years, one of the most interesting topics in host–guest chemistry is the design and synthesis of receptors able to recognize anions and ion pairs efficiently and selectively.[1] Selective anions and ion-pair receptors are important because of their decisive role in biological, environmental, and industrial applications.[2–32] Specifically, Cl^- plays a pivotal role in biological processes, for example, in signal transduction, pH regulation, transportation of organic solutes through the cell membrane, cell migration, and cell proliferation. In particular, the active site of the narrowest pore region of the Cl^- ion channel consists of an amino acid containing backbone, in which Cl^- interacts through hydrogen bonds to two amide −NH protons of a phenylalanine residue and two hydroxy groups of serine and tyrosine residues in the protein chains.[33] During our search for a new type of synthetic receptor of biological relevance, we have chosen an amino acid as the backbone to design a tris(2-aminoethyl)amine (tren)-based tripodal amide[5a,23–25] scaffold decorated with terminal aromatic moieties (Scheme 1). Herein, we have designed and synthesized a new series of tren-based tripodal hexaamide receptors with L-alanine amino acid backbones functionalized with pentafluorophenyl (L1), tetrafluorophenyl (L2), trifluorophenyl (L3), 3,5-bis(trifluoromethyl)phenyl (L4), and phenyl (L5) terminal groups for anion binding and selectivity studies. We have also structurally demonstrated the formation of a capped-cleft arrangement by receptor L1 through ion-pair recognition, in which the receptor and tetrabutylammonium (TBA) group are in contact through hydrogen-bonding interactions and Cl^- is buried in the cavity of the ternary complex. To the best of our knowledge, this represents a new example of a tripodal

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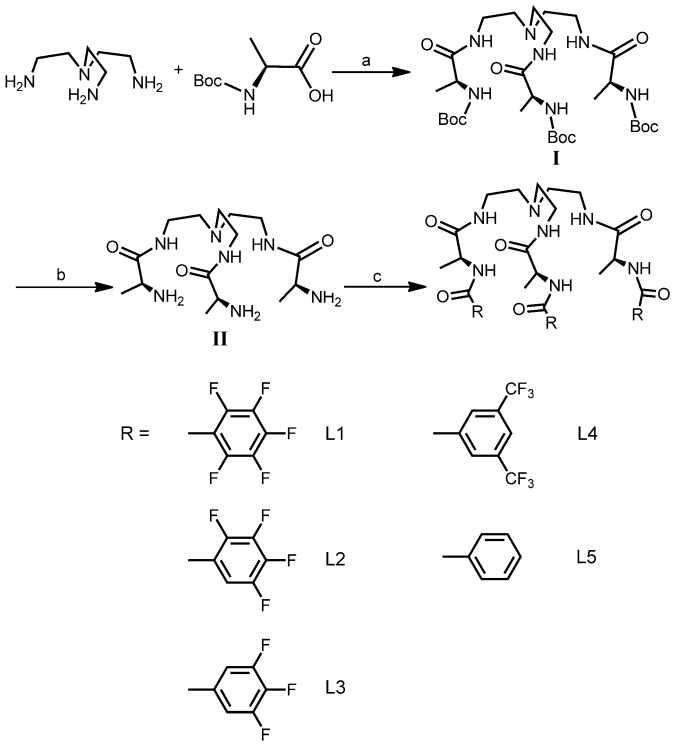
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201200428.



Scheme 1. Schematic representation of receptors L1–L5. Reagents and conditions: a) DCC, HOBT, THF; 0–5 °C, 3 h; RT, 3 days; b) TFA, DCM; RT, 12 h; c) RCOCl, NEt_3, DCM; 0–5 °C, 1 h; RT, 24 h.

hexaamide receptor with an amino acid backbone capable of recognizing an ion pair through the capping of a TBA countercation over a chloride-encapusulated hexaamide complex, as evidenced by single-crystal X-ray crystallography. Furthermore, we have also demonstrated the effect of the tetraalkylammonium countercation in anion-binding processes.

Results and Discussion

Syntheses

Receptors L1–L5 were synthesized in good yield following a three-step synthetic process (Scheme 1). To develop tripodal anion receptors with biologically relevant components and higher flexibility, the L-alanine moiety was chosen and incorporated in the design of a series of tren-based hexaamide receptors. To investigate the anion-binding properties of these tripodal receptors with different types of spherical anions (F^-, Cl^-, Br^- and I^-), planar oxyanions (AcO^-, BzO^- (Bz = benzoyl), and NO_3^-), and tetrahedral oxyanions ($H_2PO_4^-$ and HSO_4^-), the tetralkylammonium salts were used. Several attempts have been made to obtain single crystals of complexes, but we were only able to isolate single crystals for L1 with TBACl. Complex **1** [L1(Cl^-)(Bu_4N^+)] was isolated in moderate yield. Detailed crystallographic information for complex **1** is given in Table S1 in the Supporting Information.

Anion Binding and Selectivity Studies

Attempts have been made to study the binding properties of L1 with various anions in the solution state by ^{1}H NMR spectroscopy experiments in [D_6]DMSO (DMSO = dimethylsulfoxide) at 298 K. Qualitative ^{1}H NMR spectroscopy studies show that there is a shift in the signal for the −NH protons of L1 with F^-, AcO^-, and $H_2PO_4^-$, whereas other anions Cl^-, Br^-, I^-, NO_3^-, and HSO_4^- do not show any such appreciable shift in [D_6]DMSO (see Figures S30–S38 in the Supporting Information). On the other hand, titration curves of F^-, AcO^-, and $H_2PO_4^-$ are inconclusive because they do not show the saturation point of the chemical shift of the −NH protons, even after the addition of several equivalents of the anions with respect to L1 (see Figure S67 in the Supporting Information). Thus, we have undertaken isothermal titration calorimetry (ITC) experiments in acetonitrile (ACN)/DMSO (99.5:0.5 v/v) to evaluate the detailed thermodynamic and kinetic signatures of different anions with this receptor. Our choice of solvent system is based on the fact that L1 is insoluble in ACN and negligible heat changes for L1 are observed with various anions in DMSO. The detailed energetic signature of receptors L1–L5 with various anions (F^-, Cl^-, Br^-, I^-, AcO^-, BzO^-, NO_3^-, $H_2PO_4^-$, and HSO_4^-) is explored by using ITC experiments in ACN/DMSO (99.5:0.5 v/v) at 298 K (Figure 1 and Figures S40–S66 in the Supporting Information). For Br^-, I^-, and NO_3^-, no appreciable heat change is observed during ITC experiments, that is, these anions do not show 1:1 complexation in the solution state (see Figure S40 in the Supporting Information). The ^{1}H NMR spectroscopy experiments for L1 in the presence of excess Br^-/I^-/NO_3^- do not show any shift of amide −NH protons with respect to L1; this clearly supports the nonbinding nature of these anions towards L1 in ITC experiments (see Figures S32, S33, and S36 in the Supporting Information). The ITC profile of F^- binding with L1 does not show a good fit for the 1:1 binding model (see Figure S40 in the Supporting Information); this is probably as a result of deprotonation of amide −NH protons in the presence of F^-, which is supported by the disappearance of the signal for L1 amide −NH protons in the presence of excess F^- in the ^{1}H NMR spectroscopy experiment (see Figure S30 in the Supporting Information). $H_2PO_4^-$ also does not exhibit a good fit to the 1:1 binding model in ITC experiments, although we observed a shift in the amide −NH protons in the ^{1}H NMR spectroscopy experiment (see Figure S38 in the Supporting Information). The upper panels of the ITC titration profiles for L1 with the Cl^-, AcO^-, BzO^- and HSO_4^- in Figure 1 show the heat pulses experimentally observed in each titration step. The lower panels report the respective time integrals, which translates to the heat absorbed for each aliquot and its coherence to a 1:1 binding model. The ITC titration profiles of receptor L1 with the interacting anions indicates 1:1 binding ($n = 1.01$ to 1.12) of the host–guest complexes (Table 1). The binding of Cl^- is influenced by both enthalpic and entropic contributions; this is evident from the comparable values of these two thermo-

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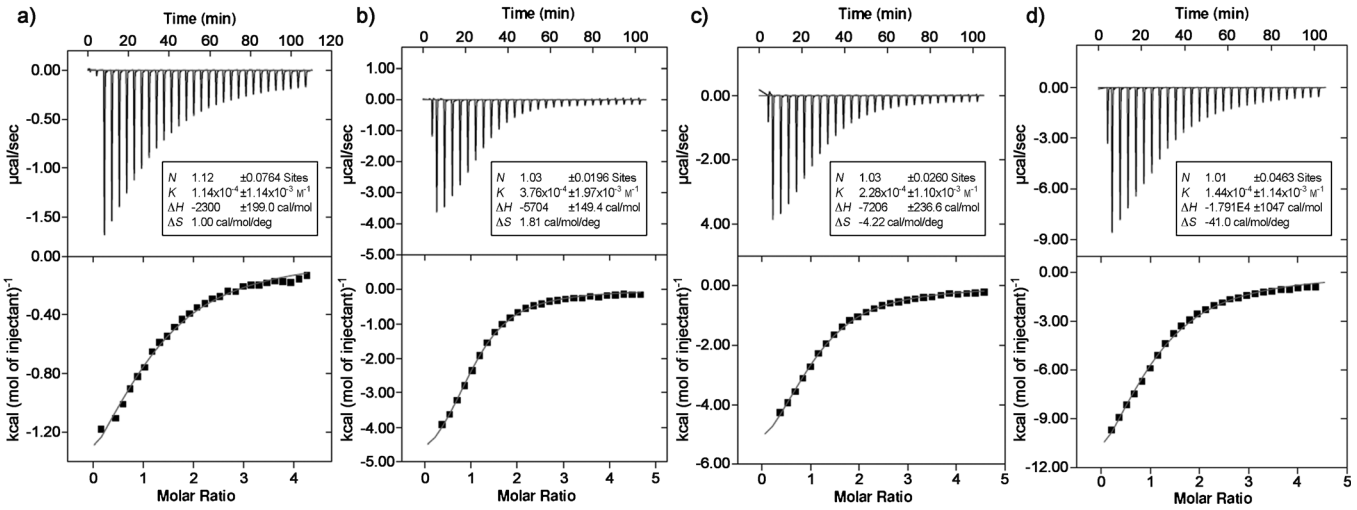

Figure 1. ITC titration profiles in ACN/DMSO (99.5:0.5 v/v) at 298 K of a) TBACl (2.82 mM); b) TBAOAc (2.26 mM); c) TBAOBz (2.21 mM), and d) $TBAHSO_4$ (2.20 mM) added to a 0.10 mM solution of host L1.

Table 1. ITC titrations of various TBA anion salts with L1–L5 carried out in ACN/DMSO (99.5:0.5 v/v) at 298 K.

Host	Guest	n	$T\Delta S$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]	log K_a
L1	TBACl	1.12	+3.24	−2.30	−5.55	4.05
	TBAOAc	1.03	+0.54	−5.70	−6.24	4.57
	TBAOBz	1.03	−1.26	−7.21	−5.95	4.36
	$TBAHSO_4$	1.01	−12.22	−17.91	−5.69	4.16
L2	TBACl	1.18	+2.61	−2.78	−5.50	3.95
	TBAOAc	1.17	+1.26	−4.99	−6.25	4.58
	TBAOBz	1.13	+0.83	−4.63	−5.46	4.00
	$TBAHSO_4$	1.00	−8.43	−12.96	−4.53	3.32
L3	TBACl	0.94	+1.97	−4.12	−6.09	4.22
	TBAOAc	1.11	+1.45	−4.77	−6.22	4.56
	TBAOBz	1.01	+0.09	−5.28	−5.19	3.94
	$TBAHSO_4$	1.13	−7.84	−13.62	−5.78	4.23
L4	TBACl	1.04	+1.87	−4.00	−5.87	4.09
	TBAOAc	1.01	−1.38	−6.96	−5.58	4.08
	TBAOBz	1.00	−0.14	−5.37	−5.23	3.83
	$TBAHSO_4$	0.94	−10.54	−15.52	−4.98	3.63
L5	TBAOAc	1.05	+0.79	−4.39	−5.18	3.79

dynamic parameters, that is, the Cl^- complex is formed with a ΔH contribution of about 41% of the interaction energy. In combination with a comparable entropic term, this gives rise to a favorable (negative) ΔG and a log K_a value of 4.05 in this solvent system. Interestingly, the interaction of L1 with AcO^- is almost driven by enthalpy. The AcO^- complex is formed with a ΔH contribution of >91% to the overall interaction energy. It is also observed that, for the combination of entropy and enthalpy, this gives rise to the highest favorable ΔG value of all investigated anions. The highest binding constant value, log K_a of 4.57 for the AcO^-–L1 adduct also provides justification for the highest negative ΔG value (Table 1). For BzO^- and HSO_4^-, the energetic signatures of these interactions are characterized by high exothermicities (large negative ΔH values) with opposing entropies (negative $T\Delta S$ values). After considering all of the thermodynamic and kinetic parameters for receptor L1 towards anion binding, it can be clearly stated that AcO^- has the highest selectivity of the anions investigated. The anion binding order for receptor L1 can be written as $AcO^- > BzO^- > HSO_4^- \approx Cl^-$. To generalize this new series of tripodal hexaamide anion receptors with amino acid backbones, we synthesized five receptors (L1–L5) with various aryl group attachments with a variety of electron withdrawing and lipophilic natures. Table 1 clearly shows that the binding processes for AcO^- and Cl^- with receptors L2–L5 are entropy and enthalpy driven; this is evident from the positive entropy and negative enthalpy values, similar to those observed for L1. Favorable entropy-driven association probably results from their willingness to enter and fit into the host cavity with suitable hydrogen-bonding interactions. On the other hand, the binding of BzO^- is almost entirely enthalpy driven throughout the series of receptors; no appreciable contributions come from the entropy value. This phenomenon can be attributed to the larger size of BzO^- relative to that of AcO^- and Cl^-, which restricts the guest from entering or fitting into the tripodal receptor cavity. For HSO_4^-, high negative enthalpy values for the receptors in the series easily compensate for the moderate unfavorable negative entropy values in the binding processes; this probably arises from the larger size and higher solvation of HSO_4^- under the experimental conditions. For receptor L5, we were only able to evaluate the binding constant with AcO^- (Table 1). All of the anions under investigation in our experimental conditions were unable to produce a one-site binding model with L5, except for AcO^-. The amide −NH in L5 was the least acidic of the receptors in the series. Thus, in general, L5 should show minimum interactions with the anions. For AcO^-, the overall shape, size, and basicity of the ion might play a role in 1:1 complex formation with L5 under our experimental conditions. It has been shown that, for low binding constants (<

10^2), ITC does not provide any reliable values for 1:1 binding; this is probably the case for L5.[32] Detailed analysis of the results given in Table 1 shows that all of the receptors (L1–L5) have slightly higher selectivity toward AcO^- than the other investigated anions, although for receptor L4, AcO^- and Cl^- have comparable binding constant values. Figure S41 in the Supporting Information shows ITC titration profiles for AcO^- with receptors L1–L5. The ITC titration profiles of receptors L1–L5 with AcO^- show a good fit for the 1:1 binding model with stoichiometry (n) ranging from 1.03 to 1.17 for the host–guest complex (Table 1 and Figure S41 in the Supporting Information).

Effect of Countercations on Anion Recognition and Ion-Pair-Assisted Capped-Cleft Formation

After several attempts to obtain solid-state evidence of anion complexes with the receptors, we were able to isolate a single crystal for L1 with TBACl. Complex **1** crystallized in a monoclinic crystal system with the $P2(1)$ space group. The asymmetric unit of **1** has a distorted C_{3v} symmetric cavity, which is evident from the difference in basal N···N distances (N2···N4 = 4.188, N4···N6 = 4.516, and N6···N2 = 4.208 Å). Single crystals of complex **1** as $[L1(Cl^-)(Bu_4N^+)]$ were grown from the ACN/diisopropyl ether binary solvent system in moderate yield upon very slow evaporation of a solution of L1 in the presence of TBACl. Along with receptor L1, the asymmetric unit of complex **1** contains one encapsulated Cl^- and one TBA countercation to balance the overall charge. Evidence for the recognition of TBACl by L1 as an ion pair was obtained from single-crystal X-ray structural analysis of **1**. In the solid-state structure of **1**, receptor L1 completely engulfed Cl^- in its three extended arms through three strong N–H···Cl hydrogen-bonding interactions; two from tren amide –NH protons and one from the –NH proton of the amide linkage of the L-alanine moiety (Figure 2 and Table S1 in the Supporting Information). Interestingly, the Cl^--encapsulated expanded tripodal receptor L1 has adequate space to interact with the TBA countercation, thus resulting in partial engulfment of the respective cation through two strong C–H···O interactions and one C–H···F interaction with the acidic $-CH_2$ group adjacent to the cationic bridgehead nitrogen (Figure 2 and Table S1 in the Supporting Information). The distance measured between the bridgehead nitrogen atoms of L1 and the TBA countercation is 8.140 Å. This hydrogen-bonded attachment of the TBA group to the extended arms of L1 makes a close molecular arrangement that can be regarded as a capped-cleft obtained by ion-pair interactions, in which the bridgehead nitrogen of receptor L1 and the quaternary nitrogen of the TBA cation form two terminals of the ternary complex. It is important to note that our previous studies on tren-based pentafluorophenyl-substituted tripodal amine[22] and amide[23] systems show that the Cl^- guest is encapsulated inside the C_{3v} symmetric cavity of the respective receptor without any interactions with the countercation (Figure 3a and b). The present design of tripodal amide receptors L1–L5 have extended amino acid based arms, and thus, in case of L1, upon recognition of Cl^- in complex **1**, there is enough space to accommodate another guest (Figure 3c). In fact, in complex **1** this space is occupied by the TBA countercation, which directly interacts with L1 through multiple hydrogen-bonding interactions (Figure 3d). Thus, this category of tripodal amide receptor recognizes an ion pair and results in a pseudo-closed assembly of a ternary complex formed by L1 and TBACl. Similar tetramethylammonium (TMA) versus TBA ion-pair recognition has been demonstrated by uranyl–salophen-based ditopic receptors. Ion-pair recognition of TMA salts by halogenated resorcinarenes have also been reported very recently.[34] Solid-state X-ray structural evidence of TBA-capped Cl^- encapsulation led us to investigate the effect of the countercation in the capping process for Cl^- binding with receptors L1–L4. Detailed Cl^- binding studies of the receptors with different tetraalkylammonium salts (TBA, tetraethylammonium (TEA), TMA) were performed by ITC. From these studies it becomes clear that, in the above-mentioned solvent system, the values of kinetic and thermodynamic parameters obtained by ITC experiments depend on the size of the alkyl group of the countercation (Table 2). The Cl^- binding constant, log K_a, for L1 was 4.05 (Figure 4 and Table 2) when TBA was used as the countercation. Surprisingly, when the alkyl group is methyl (i.e., TMACl) rather than butyl, the Cl^- binding affinity is reduced to a value of 3.59 (Figure 4), whereas for TEACl, which is a moderate volume countercation, the Cl^- binding

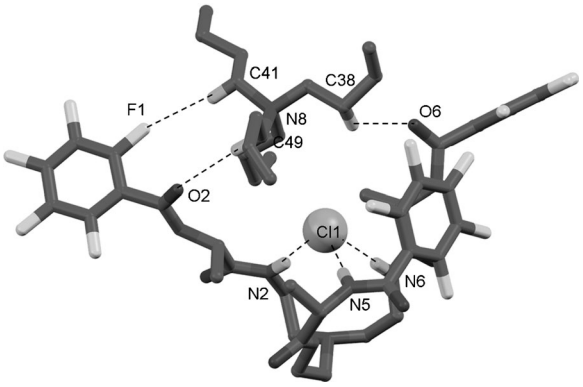

Figure 2. a) Ball and stick model depicting ion-pair recognition in complex **1** (non-acidic hydrogen atoms are omitted for clarity).

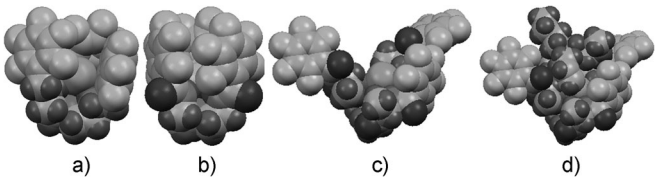

Figure 3. Space-filling model depicting a) the Cl^- complex of tren-based pentafluoroammonium salt; b) the Cl^- complex of tren-based pentafluoroamide; c) Cl^-–L1 recognition in complex **1** (the TBA group is omitted to show the space available after chloride recognition); and d) a space-filling model of **1**.

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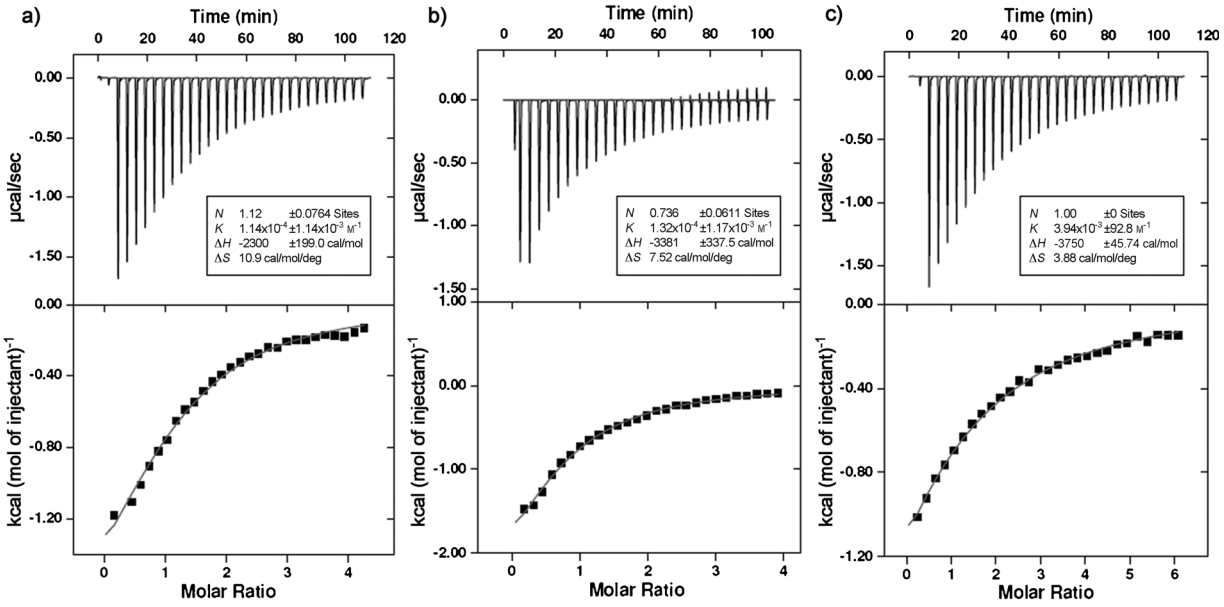

Figure 4. ITC titration profiles in ACN/DMSO (99.5:0.5 v/v) at 298 K of a) TBACl (2.82 mM), b) TEACl (2.32 mM), and c) TMACl (3.71 mM) added to a 0.10 mM solution of host L1.

Table 2. ITC titrations of various tetraalkylammonium chloride salts with L1–L4 carried out in ACN/DMSO (99.5:0.5 v/v) at 298 K.

Host	Guest	n	$T\Delta S$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]	log K_a
L1	TBACl	1.12	+3.24	−2.30	−5.55	4.05
	TEACl	1.00	+1.75	−3.67	−5.42	3.97
	TMACl	1.00	+1.16	−3.75	−4.91	3.59
L2	TBACl	1.18	+2.61	−2.78	−5.50	3.95
	TEACl	0.90	+1.33	−4.04	−5.37	3.94
	TMACl	0.95	+1.22	−3.92	−5.14	3.76
L3	TBACl	0.94	+1.97	−4.12	−6.09	4.22
	TEACl	0.74	−0.78	−6.31	−5.53	4.05
	TMACl	0.73	−0.08	−5.56	−5.48	4.02
L4	TBACl	1.04	+1.87	−4.00	−5.87	4.09
	TEACl	1.18	+2.15	−3.36	−5.51	4.04
	TMACl	1.05	+1.35	−4.10	−5.45	3.99

affinity of receptor L1 lies between these values (3.97). Further evidence was obtained by solid-state single-crystal X-ray structural investigations into complex **1**, for which both Cl^- and the TBA countercation were strongly hydrogen bonded to receptor L1. Therefore, the effect of the countercation in the capping process follows the order TBA ≈ TEA > TMA; this is evident from the decreasing trends in free energy change (ΔG) for this particular process (Table 2). The other receptors (L2–L4) follow almost the same binding trend as that observed for L1.

Conclusion

We have designed and synthesized a new series of hexaamide tripodal receptors with amino acid backbones and determined their solution-state anion-binding capabilities through ITC experiments. From the solution-state binding of the receptors, it was found that AcO^- had the highest selectivity of the anions investigated. The anion selectivity was systematically justified from the thermodynamic and kinetic parameters. Single-crystal X-ray structural evidence showed that one of the receptors could bind an ion pair in its cavity thanks to the extended tripodal arms, which result in the formation of a capped-cleft-like molecular assembly. We have also shown the effect of the countercation on anion binding by using a solution-state study. ITC studies indicated that TBA would be a better choice of cap to favor anion-recognition processes.

Experimental Section

Materials and Methods

Boc-Ala-OH (Boc = *tert*-butyloxycarbonyl); tren; pentafluorobenzoyl chloride; 2,3,4,5-tetrafluorobenzoyl chloride; 3,4,5-trifluorobenzoyl chloride; 3,5-bis(trifluoromethyl)benzoyl chloride; benzoyl chloride; and TBA, TEA, and TMA salts of F^-, Cl^-, Br^-, I^-, AcO^-, BzO^-, NO_3^-, $H_2PO_4^-$, and HSO_4^- were purchased and used without further purifications. *N,N'*-Dicyclohexylcarbodiimide (DCC), 1-hydroxybenztriazole (HOBT), and trifluoroacetic acid (TFA) were purchased from Sigma–Aldrich and Cyno-chem, India. All NMR spectra were recorded on 300 and 500 MHz FT-NMR spectrometers in $CDCl_3$, [D_7]DMF (DMF = *N,N*-dimethylformamide), and [D_6]DMSO at 25 °C. Chemical shifts for ^1H and ^{13}C NMR spectra were reported in ppm, calibrated to the residual solvent peak set, with coupling constants reported in Hz.

*Synthesis of Compound **I***

Boc-Ala-OH (2.0 g, 10.57 mmol) was added to a 250 mL two-necked round-bottomed flask, dissolved in dry THF (50 mL), and cooled to 0 °C in an ice bath. DCC (2.18 g, 10.57 mmol) was added to the reaction mix-

ture. The reaction mixture was allowed to stir at 0 °C for 15 min. Then, HOBT (1.65 g, 10.57 mmol) was added to the stirring mixture. The suspension formed was stirred for another 30 min at same temperature. Thereafter, tren (0.53 mL, 3.54 mmol) in dry THF (50 mL) was added to a pressure-equalizing funnel and added slowly over a period of 1–2 h to the reaction mixture at 0 °C. The reaction mixture was allowed to stir at 0–5 °C for 3 h and at RT for 3 days under nitrogen atmosphere. The precipitate formed was filtered off and washed with cold THF (5×5 mL). The filtrate was evaporated to dryness under reduced pressure. The crude semisolid product obtained was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with water (3×50 mL), 5% $NaHCO_3$ (1×100 mL), and brine solution (2×50 mL). The organic layer was collected and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to yield a crude off-white solid. Compound **I** was isolated as a white solid (1.75 g, 75%) by column chromatography (60–120 mesh silica gel: methanol/$CHCl_3$ (0.03:1 v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 27H), 2.55 (t, 6H), 2.88–2.94 (m, 3H), 3.35–3.41 (m, 3H), 4.31 (s, 3H), 5.63 (d, 3H), 7.69 ppm (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 18.8, 28.4, 38.7, 50.1, 54.8, 79.8, 156.0, 174.2 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{30}H_{57}N_7O_9$: 659.4218 [M^+]; found: 660.2113; elemental analysis calcd (%) for $C_{30}H_{57}N_7O_9$: C 54.6, H 8.71, N 14.86; found: C 54.52, H 8.65, N 14.80.

*Synthesis of Compound **II***

Compound **I** (500 mg, 0.76 mmol) was dissolved in dry CH_2Cl_2 (30 mL) in a 100 mL round-bottomed flask and allowed to stir at room temperature under a nitrogen atmosphere for 30 min. Trifluoroacetic acid (TFA; ≈5 mL) was dissolved in dry CH_2Cl_2 (20 mL) and added to a 50 mL pressure-equalizing funnel. This acid solution was added dropwise over a period of 1 h with constant stirring at room temperature. The reaction mixture was then stirred overnight at RT under an inert atmosphere. The solution turned brown at the end of the reaction. The solvent was evaporated and dried under high vacuum to give a highly viscous sticky mass. The deprotected amine (as a triflate salt) was used for subsequent steps without further purification.

General Synthetic Procedure of Compound L1–L5

Triamine (500 mg, 0.71 mmol) was added to a 100 mL round-bottomed flask and dissolved in dry CH_2Cl_2 (50 mL). Excess TEA (1.0 mL, 10 mmol) was added to this solution and the reaction mixture was allowed to stir at RT under a nitrogen atmosphere for 15 min for complete dissolution. Thereafter, the corresponding acid chloride (0.31 mL, 2.13 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and added to a 100 mL pressure-equalizing funnel. This solution was added dropwise over a period of 1 h with constant stirring at room temperature. After complete addition, the reaction mixture was allowed to stir at room temperature in an inert atmosphere for 1 day. The white precipitate formed was filtered off and washed several times with CH_2Cl_2 and water to remove excess TEA and TEACl. The colorless solid was washed finally with diethyl ether and dried in air to yield the desired product as a white solid for L1. For ligands L2–L5, the organic layer was washed with a saturated solution of $NaHCO_3$ (2×50 mL) and brine (2×50 mL). The resulting organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the desired product as a solid.

Ligand L1

White solid; yield 80%; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 1.41 (d, *J* = 7.5 Hz, 9H), 2.62 (t, *J* = 6.5 Hz, 6H), 3.26–3.29 (m, 6H), 4.67–4.69 (m, 3H), 8.03 (s, 3H), 9.05 ppm (d, *J* = 7.5 Hz, 3H); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.27 (d, *J* = 7.0 Hz, 9H), 2.54 (t, *J* = 6.5 Hz, 6H), 3.13–3.09 (m, 3H), 3.20–3.17 (m, 3H), 4.48–4.51 (m, 3H), 7.99 (br, 3H), 9.10 ppm (br, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 18.9, 37.6, 49.6, 53.7, 113.0, 136.4, 138.4, 142.7, 144.7, 156.7, 171.7, 188.5 ppm; ^{19}F NMR (500 MHz, [D$_6$]DMSO): δ = −164.29, −155.96, −144.27 ppm; HRMS (ESI −): *m/z* calcd for $C_{36}H_{30}F_{15}N_7O_6$: 941.2018 [M^+]; found: 940.9461; HRMS (ESI$^+$) Calcd for $C_{36}H_{30}F_{15}N_7O_6$ 941.2018 [M^+]; found: 942.1697; elemental analysis calcd (%) for $C_{36}H_{30}F_{15}N_7O_6$: C 45.92, H 3.21, N 10.41; found: C 45.90, H 3.18, N 10.36.

Ligand L2

Brown solid; yield: 72%; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 1.59 (d, *J* = 7.5 Hz, 9H), 2.70–2.75 (m, 6H), 3.34–3.42 (m, 6H), 4.75–4.78 (m, 3H), 8.04–8.09 (m, 3H), 8.12–8.14 (t, *J* = 5.5 Hz, 3H), 8.93 ppm (d, *J* = 7 Hz, 3H); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.29 (d, *J* = 6.5 Hz, 9H), 3.11–3.17 (m, 6H), 4.42–4.45 (m, 3H), 7.59–7.62 (m, 3H), 7.92 (br, 3H), 8.59 ppm (br, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 18.7, 37.7, 49.7, 53.8, 112.4, 139.5, 142.4, 144.6, 145.5, 146.6, 147.5, 161.0, 172.1 ppm; ^{19}F NMR (500 MHz, [D$_6$]DMSO): δ = −157.93, −155.50, −141.70 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{36}H_{33}F_{12}N_7O_6$: 888.2301 [M^+]; found: 888.3749; elemental analysis calcd (%) for $C_{36}H_{33}F_{12}N_7O_6$: C 48.71, H 3.75, N 11.05; found: C 48.70, H 3.72, N 11.01.

Ligand L3

White solid, yield: 75%; ^{1}H NMR (500 MHz, [D$_7$]DMF): δ = 1.59 (d, *J* = 7.0 Hz, 9H), 2.76 (s, 6H), 3.07–3.09 (m, 6H), 4.77–4.80 (m, 3H), 7.82–7.86 (m, 3H), 8.22 (s, 6H), 8.69 ppm (d, *J* = 5.5 Hz, 3H); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.31 (d, *J* = 7.0 Hz, 9H), 3.10 (s, 6H), 4.39–4.422 (m, 3H), 7.80–7.86 (m, 9H), 8.68 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 17.7, 37.1, 49.4, 53.2, 112.6, 130.3, 139.7, 148.9, 150.9, 162.8, 171.9 ppm; ^{19}F NMR (500 MHz, [D$_6$]DMSO): δ = −159.62, −136.83 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{36}H_{36}F_9N_7O_6Na$: 856.2481 [M^++Na]; found: 856.0809; elemental analysis calcd (%) for $C_{36}H_{36}F_9N_7O_6$: C 51.86, H 4.35, N 11.76; found: C 51.85, H 4.28, N 11.73.

Ligand L4

White solid; yield: 60%; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.35 (d, *J* = 6.5 Hz, 9H), 3.13 (s, 6H), 4.47–4.49 (m, 3H), 7.93 (s, 3H), 8.23 (s, 3H), 8.49 (s, 6H), 7.93 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 18.3, 37.8, 50.0, 53.9, 122.6, 124.8, 128.9, 130.1, 131.0, 136.7, 163.7, 172.4 ppm; ^{19}F NMR (500 MHz, [D$_6$]DMSO): δ = −62.80 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{42}H_{39}F_{18}N_7O_6$: 1079.2674 [M^+]; found: 1080.0648; elemental analysis calcd (%) for $C_{42}H_{39}F_{18}N_7O_6$: C 46.72, H 3.64, N 9.08; found: C 46.72, H 3.62, N 9.01.

Ligand L5

Off-white solid; yield: 70%; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.32 (d, *J* = 7.2 Hz, 9H), 3.10 (d, *J* = 5.5 Hz, 6H), 4.45–4.49 (m, 3H), 7.41–7.48 (m, 6H), 7.50 (s, 3H), 7.84–7.90 (m, 9H), 8.46 ppm (s, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.0, 37.1, 48.9, 53.2, 64.9, 127.4, 127.4, 127.5, 128.1, 134.0, 166.0, 172.3 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{36}H_{45}N_7O_6$: 671.3431 [M^+]; found: 672.4031; elemental analysis calcd (%) for $C_{36}H_{45}N_7O_6$: C 64.36, H 6.75, N 14.59; found: C 64.32, H 6.68, N 14.72.

*Synthesis of Complex **1***

L1 (40 mg, 0.042 mmol) was suspended in ACN (4 mL) and then TBACl (23 mg, 0.02 mmol) was added to the solution. The solution became clear after sonication and the mixture was stirred at room temperature for 10 min. A large amount of diisopropyl ether was then added and the solution was allowed to slowly evaporate to allow crystallization. After a week, colorless crystals of complex **1** suitable for X-ray diffraction studies were obtained (40%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.91–0.96 (m, 12H), 1.27–1.35 (m, 8H), 1.54–1.57 (m, 8H), 3.19–3.07 (m, 14H), 4.49–4.54 (m, 3H), 8.07 (s, 3H), 9.13 ppm (d, *J* = 12.0 Hz, 3H); HRMS (ESI$^-$): *m/z* calcd for $C_{52}H_{66}ClF_{15}N_8O_6$: 976.1707 [$M^+$]; found: 976.8221; elemental analysis calcd (%) for $C_{52}H_{66}ClF_{15}N_8O_6$: C 51.21, H 5.45, N 9.19; found: C 51.14, H 5.42, N 9.20.

ITC Studies

The ITC experiments were performed on a MicroCal VP-ITC instrument. All titrations were carried out at 298 K in ACN/DMSO (99.5:0.5 v/v). Approximately 0.1 mM solutions of receptors L1–L5 were prepared in ACN/DMSO (99.5:0.5 v/v) and loaded into the measuring cell. This solution was titrated with 30 injections (10 μL) of approximately 3.0 mM solutions of tetraalkylammonium salts of halides (F^-, Cl^-, Br^- and I^-) and oxyanions (AcO^-, BzO^-, NO_3^-, $H_2PO_4^-$ and HSO_4^-) prepared in ACN. In all cases the anion under study was titrated into the host solution. An

interval of 220 s was allowed between each injection and the stirring speed was set at 329 rpm. The obtained data was processed by using Origin 7.0 software supplied with the instrument and fitted to a one-site binding model. The initial study of the effect of the various salts was repeated three times with the receptors and showed good reproducibility. Blank titrations of tetraalkylammonium salts into plain solvent were also performed and subtracted from the corresponding titration to remove any effect from the heats of dilution from the titrant. In general, the stoichiometry (n), association constants (K_a), change in entropy (ΔS), and change in enthalpy (ΔH) values determined from these experiments were within experimental error limits.

X-ray Crystallographic Analyses

The crystallographic data, details of data collection, and refinement parameter for complex **1** are summarized in Table S1 in the Supporting Information. A suitably sized single crystal was selected from the mother liquor, immersed in paratone oil, mounted on the tip of a glass fiber, and cemented with epoxy resin. Intensity data for these crystals were collected by using $Mo_{K\alpha}$ ($\lambda = 0.7107$ Å) radiation on a Bruker SMART APEX II diffractometer equipped with charge-coupled device (CCD) area detector at 100 K.

Reflections were measured from a hemisphere of data collected with each frame covering 0.5° in ω. Data integration and reduction were processed with SAINT[35] software provided with the software package of SMART APEX II. An empirical absorption correction was applied to the collected reflections with SADABS.[36] The structures were solved by direct methods using SHELXTL[37] and were refined on F^2 by the full-matrix least-squares technique using the SHELXL-97[38] program package. Graphics were generated by using PLATON[39] and MERCURY 2.3.[40] In all cases, the non-hydrogen atoms were refined anisotropically until convergence. All of the hydrogen atoms were geometrically positioned and treated as riding atoms.

*Crystallographic data for complex **1***

$C_{52}H_{64}N_8O_6F_{15}Cl$; $M_r = 1217.56$; monoclinic; space group $P2(1)$; $a = 11.924(5)$, $b = 19.531(8)$, $c = 13.402(5)$ Å; $\alpha = 90.00$, $\beta = 108.455(6)$, $\gamma = 90.00°$; $V = 2961(2)$ Å^3; $\rho_{calcd} = 1.366$ g cm^{-3}; $Z = 2$; $\lambda = 0.71073$ Å; $T = 293(2)$ K; 15625 reflections; 5161 independent ($R_{int} = 0.0992$) and 6916 observed reflections [$I \geq 2\sigma(I)$]; 745 refined parameters; $R_1 = 0.0582$; $wR_2 = 0.1354$; GOF = 1.068. CCDC 842426 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

P.G. gratefully acknowledges the Department of Science and Technology (DST), New Delhi, India, for financial support through a Swarnajayanti Fellowship. P.B. and B.A. would like to acknowledge the CSIR, New Delhi, India, for Senior Research Fellowships. X-ray crystallography studies were performed at the DST-funded National Single-Crystal X-ray Diffraction Facility at the Department of Inorganic Chemistry, IACS.

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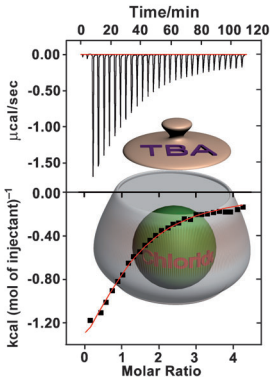
Received: May 11, 2012
Revised: June 11, 2012
Published online: ■■ ▮▮, 0000

FULL PAPER

In a bind: Ion-pair recognition and anion binding studies of a series of tripodal amide receptors with L-alanine amino acid backbones, in which tetrabutylammonium acts as a cap for the chloride-encapsulated tripodal cleft (see picture).



Host–Guest Systems

*Purnandhu Bose, Iyyamperumal Ravikumar, Bidyut Akhuli, Pradyut Ghosh** _____ ▮▮▮▮–▮▮▮▮

A Series of Amino Acid Functionalized Tripodal Hexaamide Anion Receptors: Ion-Pair-Assisted Capped-Cleft Formation by a Pentafluorophenyl-Functionalized Amide