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ARTICLE TYPE

Design and Synthesis of Tröger's Base Ditopic Receptors: Host-Guest Interactions, a Combined Theoretical and Experimental Study

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Two flexible Tröger's base ditopic receptors **C4TB** and **C5TB** incorporating monoaza crown ether were designed and synthesized for bisammonium ion complexation. Comprehensive study of host-guest interactions were established by ^{1}H NMR spectroscopy and DFT calculations. Bisammonium chloride (**A1**) with shorter alkyl chain spacer showed highest affinity for the receptors. M06-2X/cc-pVTZ calculations including the solvent effects on host-guest complexes were employed to explain and rationalize the experimental trends. The short N-H···O or N-H···N hydrogen-bond distances observed in the range of 1.71-1.98 Å, indicate the existence of a strong charge assisted hydrogen bonding between host and guest. The unusual behaviour (higher binding constant) of **A5** in ^{1}H NMR titration is traced to the conformational folding of the guest.

Introduction

The quest for imitating the biological systems has led to the development of supramolecular chemistry which deals not only with synthesis of specific hosts for ligand binding but also molecular recognition and self assembly of molecular frameworks involving weak non-covalent interactions.[1] The earliest discovered supramolecular systems, crown ethers, have found several applications such as cation binders and phase transfer catalysts.[2] Designing specific receptors with capability of recognition of organic cations especially ammonium ions is a topic of outstanding importance and relevance because several bio-origin amines are being used as probes to measure the quality of food products of marine origin. Their widespread occurrence in the nature and many promising applications led to the development of effective receptors for amines. Crown ethers are desirable chemosensors or hosts for amines because of their ability to form strong complexes with organic cations. Recognition of bisammonium ions by specific receptors is an interesting challenge wherein selectivity depends on precise complementarity between bisammonium ion and receptor cavity size as well as the spacer chain length. The binding of these bidentate guests is best done by ditopic receptors. Since crown ethers are well known to form strong complexes with cation and NH_4^+ ions, they were chosen as ligands for the design of ditopic receptors for bisammonium ions as is exemplified by numerous literature examples.[3]

Among these receptors, a Tröger's base[4,5,6] bidentate receptor incorporating oxa crown ether reported by Wärnmark *et al*[7] is of particular interest. Tröger's base has a unique C_2-symmetric, V-shaped geometry and an inherent chirality due to two stereogenic nitrogen atoms which could be resolved into a chiral host.[8] The two crowns were directly built on the phenyl rings of the Tröger's base resulting in an excessively rigid host. Also since NH_4^+ is a highly directional guest (from solid state structures),[9] addition of certain amount of flexibility would make the host more dynamic. This leaves enough scope for designing a ditopic cation receptor containing Tröger's base that is flexible and dynamic showing good complementary face to face binding with ammonium ions. This can be achieved by adding a small alkyl linker between Tröger's base phenyl ring and the crown ether. Thus, new ditopic cation binding receptors **C4TB** and **C5TB** were designed (Figure 1). The current study involves the synthesis of Tröger's base bis(monoaza crown ethers) and their host-guest complexation with bisammonium ions, followed by ^{1}H NMR titrations and computational studies on host-guest interactions.

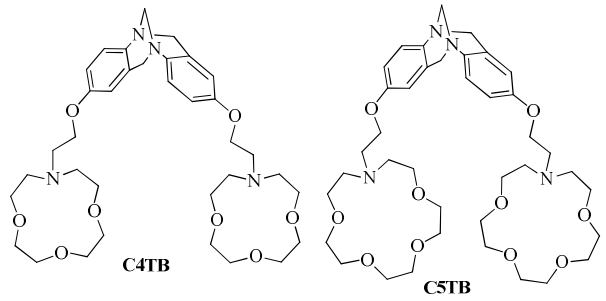

Figure 1. **C4TB** and **C5TB** receptors designed in this study for bisammonium ion recognition.

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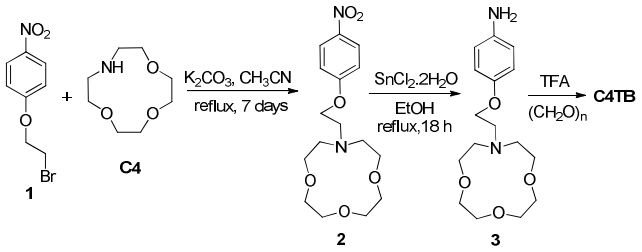
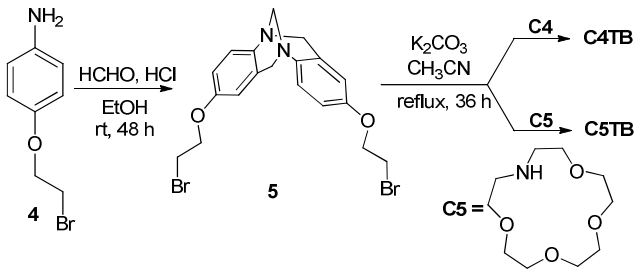
Results and Discussion

Synthesis of receptors C4TB and C5TB: The synthetic strategy for designed molecules involved a crucial precursor, 1-(2-bromoethoxy)-4-nitrobenzene **1**, which was prepared by the condensation of 4-nitrophenol and 2-chloroethanol followed by bromination (PBr_3) of hydroxyl group. Coupling of mono aza crown ether **C4** (synthesis of aza crowns from various ethylene glycols is done following reported protocols)[10] to 4-bromoethoxy nitrobenzene **1** followed by reduction of -NO_2 group in compound **2** to amine in compound **3** using $SnCl_2.2H_2O$ and condensation of resulting amine with paraformaldehyde in presence of TFA yields the desired ditopic receptor as shown in Scheme 1. But synthesis of **C4TB** by this approach was frustrating owing to very low yields as well as target compound could not be isolated in pure form.



Scheme 1. Synthetic route to receptor **C4TB**.

An alternative approach starting from 4-bromoethoxy nitrobenzene **1** is shown in Scheme 2. Reduction of nitro compound **1** to amine **4** was achieved using $SnCl_2.2H_2O$. 4-Bromoethoxy amino benzene **4** was subjected to Tröger's base formation reaction in formalin and HCl conditions. Tröger's base **5** was isolated in 27% yield after purification. This is the key intermediate for the synthesis of receptors. The corresponding aza crown ethers were directly coupled to the Tröger's base **5** in presence of K_2CO_3 and acetonitrile conditions. Two Tröger's base ditopic receptors **C4TB** and **C5TB** incorporating mono aza crown ether (two units) were synthesized as shown in Scheme 2 and they were isolated as foams in 68% and 74% yield, respectively. All new compounds were characterised by ^1H, ^{13}C NMR spectroscopy and mass spectrometry (NMR spectra of new compounds are provided in the Supporting Information).



Scheme 2. Synthetic route to receptors **C4TB** and **C5TB.**

NMR Titrations

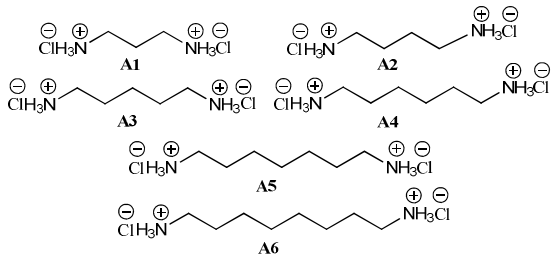


Figure 2. Bisammonium chlorides **Am**, **m = 1-6** used in the study as guest molecules.

Complexation studies of various primary bisammonium ions with two receptors were carried out using ^1H NMR titration method. A solution of host **C4TB/C5TB** was titrated by adding incremental amounts of guests **Am**, **m = 1-6** (Figure 2) until no further chemical shift changes were observed in CD_3OD. Low solubility of the bisammonium ions ruled out other solvents such as $CDCl_3$, CD_3CN and DMSO-d_6 solvents for this study.

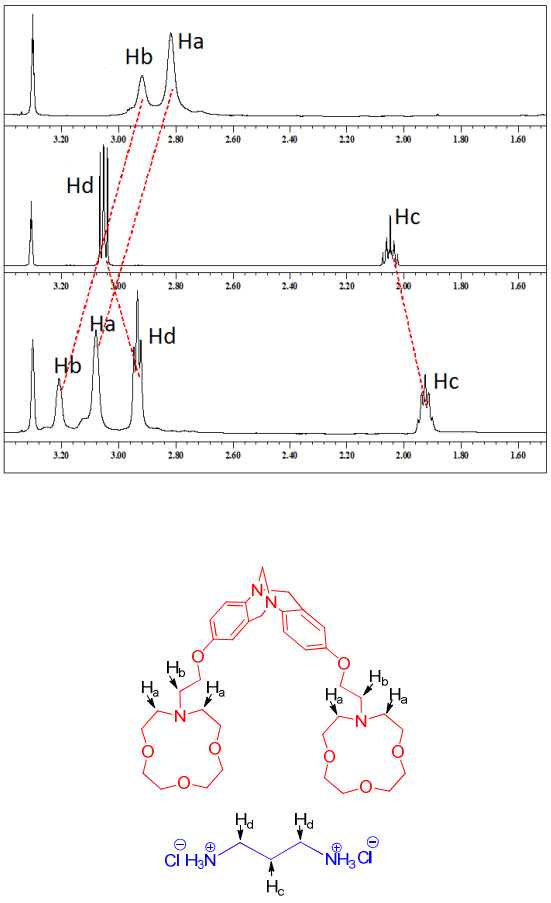


Figure 3. Partial ^1H NMR spectrum (600 MHz, CD_3OD at 293 K) of (a) free host **C4TB**, (b) free guest **A1**, (c) complex of **C4TB** and **A1** shows downfield shift of host –CH_2-N-CH_2 signal and upfield shift of guest signals indicates a strong complex formation.

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The free host crown ether signals and DMSO-d_6 signals merge making impossible to distinguish the chemical shift changes. In each case, a distinguishable proton was monitored as a function of substrate concentration (Figure 3). Chemical shift changes that were dependent on the substrate and receptor concentration ratio were taken as evidence for complexation. The aromatic and bridge protons are shifted downfield by 0.01-0.05 ppm and complexed aza crown ether -CH_2-N-CH_2- protons by 0.04-0.27 ppm compared to free receptor protons (Figure 3). Interestingly, the α-protons of the guest molecules moved upfield by 0.20-0.30 ppm. This indicates a strong complex formation.

A titration curve between Δδ and [G]/[H] was analyzed to determine the stoichiometry of the complex. A break in the titration curve (Δδ vs [G]/[H]) established a 1:1 stoichiometry for all the bisammonium ions with the receptor **C4TB**. The change in chemical shift values of the host protons in the complex spectrum as the function of increase in guest concentration are fitted by using equation 1 to determine the binding constants.[11] The calculated binding constants are listed in Table 1.

$$\Delta\delta = \frac{\Delta\delta_{max}}{2[H]}\left\{\left([H] + \frac{1}{K_a} + [G]\right) - \sqrt{\left([H] + \frac{1}{K_a} + [G]\right)^2 - 4[H][G]}\right\} \quad .. (1)$$

Where $\Delta\delta = \delta_{obs} - \delta_h$

Table 1. Association constants of host **C4TB** with bisammonium ions (**Am; m = 1-6**).

Bisammonium ion (**Am, m = 1-6**)	K_a (M^{-1})	$\Delta\delta_{max}$
1,3-propane bisammonium chloride (**A1**)	52±0.034	0.3332±0.03736
1,4-butane bisammonium chloride (**A2**)	40±0.011	0.2145±0.00452
1,5-pentane bisammonium chloride (**A3**)	27±0.012	0.1567±0.01563
1,6-hexane bisammonium chloride (**A4**)	20±0.010	0.1481±0.01781
1,7-heptane bisammonium chloride (**A5**)	44±0.004	0.1655±0.00344
1,8-octane bisammonium chloride (**A6**)	21±0.013	0.2824±0.04436

The binding constants are on the lower side probably due to solvent effects. It has been well documented in literature that the polarity of the solvent played an important role on complexation and binding constants are high in low polar solvents.[12] Herein, due to high polar nature and hydrogen bond-acceptor nature of CD_3OD used as solvent in ^{1}H NMR titrations, low binding constants were observed (CD_3OD can easily coordinate with NH_4^+ ion and weaken the complexation with crown ether hetero atoms). Binding constants for receptor **C4TB** show that K_a value for the protonated bisammonium ions decreases as the function of increase in chain length. From the summarized binding constant values, it is clear that the guest (**A1**) with shorter alkyl chain spacer was the best fit into the cavity of the receptor. Wärnmark's receptor[9] where the oxa crown ether was directly attached to the phenyl ring, showed 1,7-heptane bisammonium ion **A5** to be a better fit. Since the distance between the oxa crown ethers is higher, resulting in strong complex formation with longer chain bisammonium ion. On the other hand, **C4TB** is flexible with a chain linker, thus the aza crown ethers could bind stronger with short bisammonium ion (**A1**). Further the binding constants decrease as the function of chain length increases up to **A4**. Interestingly, the association constant of **A5** is found to be higher than **A4**. This could be attributed either due to both host flexibility and conformational folding of the guest **A5**.

Titrations were performed with monoammonium ion $CH_3NH_3^+Cl^-$, also. However, when compared to bisammonium ions, crown ether signals shifted to upfield (instead of downfield) upon incremental addition of guest. This indicates that ammonium ion was probably not bound inside the cavity of crown ethers but it was held in between both the crowns (sandwiched type) and methyl group stands out projecting into the concave cavity of Tröger's base. Upfield shifts of crown ether protons may be due to repulsions with methyl protons of guest. Chemical shift changes were very low which indicates weak interactions between host and guest. A perfect sigmoidal curve of Δδ vs [G] also indicates the 1:1 complexation (sandwich type complex; not 1_{host}:2_{guest} mode of binding as expected, see supporting information).

In case of complex formed between receptor **C5TB** and bisammonium ions, due to overlapping of crown ether -CH_2- and α-protons of bisammonium ion signals in ^{1}H NMR, the chemical shift changes were not distinguishable. Extremely small chemical shift changes were observed for aromatic and bridge protons. Due to non-availability of a clearly distinguishable proton in the host, the association constants could not be evaluated. Discouraged by the poor resolution of ^{1}H NMR signals and lack of distinguishable protons in **C5TB**-bisammonium ion complexes, synthesis of higher aza crown ether analogue of Tröger's base was not attempted (even though mono aza-18-crown-6 has been reported as best fit for ammonium ions).[13]

Computational studies

In order to rationalize the experimental investigations, quantum chemical calculations on complexes formed by **C4TB** and **C5TB** with six bisammonium ions (**Am**; **m = 1-6)** have been performed at PCM-M06-2X/cc-pVTZ//PCM-M06-2X/6-31G(d) level of theory. The **C4TB**···**Am** and **C5TB**···**Am** complexes were built as the bisammonium ions exist in their extended conformation between the crowns of **C4TB** and **C5TB**. The interaction of **C4TB** and **C5TB** with **Am** is mainly due to charge assisted hydrogen bonding (CAHB) between O/N atom (hydrogen bond acceptor) in the crown moiety and the N-H (hydrogen bond donor) bond of the bisammonium ion. The **C4TB**···**Am** and **C5TB**···**Am** host-guest complexes exhibit two different hydrogen bonding interactions such as N-H···O and N-H···N. The nitrogen and oxygen ratio of the crown ethers in the **C4TB** and **C5TB** systems are 2:6 and 2:8, respectively. Consequently, in any set of **C4TB**···**Am** or **C5TB**···**Am** complexes, the H···O type interactions were larger in number than H···N type of interactions. Among several hydrogen bonds exist in the host-guest complexes, the shorter hydrogen bond in **C4TB**···**Am** and **C5TB**···**Am** have been identified. The shortest hydrogen bond distances (H···N and H···O) of **C4TB**···**Am** and

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C5TB···Am complexes ranges from 1.71-1.98 Å and the corresponding N-H···O/N-H···N bond angles ranges from 152°-176°, respectively. Interestingly, the shortest hydrogen bond distances follow particular trend for **C4TB···Am** and **C5TB···Am** complexes. That is, the shortest H···N hydrogen bond distance found to be smaller compared to the shortest H···O hydrogen bond in **C4TB···Am** complexes; however, such trend has been reversed in cases of **C5TB···Am** complexes (see Table S2). The shorter hydrogen bonding distances (H···O/H···N) correlate well with the corresponding hydrogen bond donor (N-H) bond lengths. The obtained computational results underpin the criteria of hydrogen bond i.e., stronger the hydrogen bond weaker the H-bond donor bond length (N-H).[14] Various orientations of $CH_3NH_3^+$ in **C4TB···**$CH_3NH_3^+$ complex have been studied. The lowest energy structure of (BE =34.43 kcal/mol) shows $CH_3NH_3^+$ sandwiched between the crowns of **C4TB** (see SI).

Host-guest binding energy

This section describes the binding energies (BEs) of host-guest complexes in gas-phase (gas) as well as in solvent phase (sol) obtained at M06-2X/cc-pVTZ//M06-2X/6-31G* level and the results are shown in Figure 4. The calculated gas-phase binding energies are approximately two and a half times higher than the solvent-phase BEs (Table S3). It is apparently clear that in gas-phase the charge transfer between host and guest, found to be higher due to the absence of solvent effects and thus the higher binding energy is observed in gas-phase calculations. Comparing the BEs of **C4TB···Am** and **C5TB···Am** complexes, higher BEs were observed for **C5TB···Am** complexes.

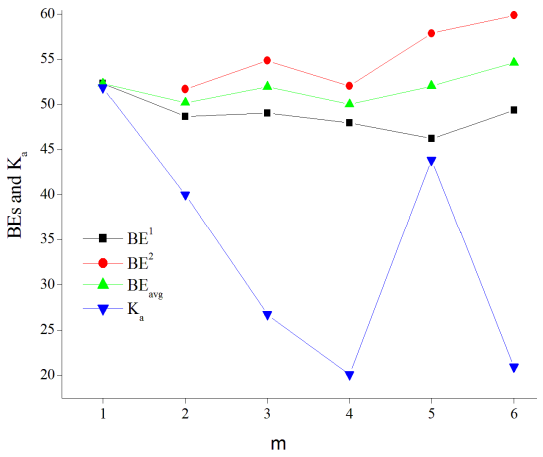

Figure 4. The solvent-phase binding energies (kcal/mol) of **C4TB···Am** and **C4TB···Am*** complexes and the association constant, K_a (M^{-1}).

It can be stated that 'bigger the crown size, higher the BE' a results similar to that observed in cation-π interaction.[15] The modulation of host-guest BEs are not systematic upon increasing size of bisammonium ions.

Table 2. The charge transfer (CT, in a.u) between the host and guests obtained from Mullikan charges at M06-2X/cc-pVTZ level on PCM-M06-2X/6-31G(d) structures. The numbers inside the parenthesis are CT for **C4TB-Am*** complexes.

m =	C4TB···Am		C5TB···Am	
	gas	sol	gas	sol
1[a]	0.611	0.534	0.695	0.644
2	0.558 (0.616)	0.489 (0.534)	0.632	0.605
3	0.572 (0.623)	0.503 (0.560)	0.721	0.673
4	0.556 (0.574)	0.489 (0.502)	0.674	0.644
5	0.483 (0.628)	0.428 (0.599)	0.625	0.591
6	0.590 (0.660)	0.535(0.595)	0.649	0.615

[a]The initial folded conformation of **A1** in **C4TB-A1*** complex collapsed to the extended conformation (**C4TB-A1**) upon geometrical optimization.

In a few cases the BEs seem to decrease (Figure 4 & Table S3) as increase in chain length of '**Am**' observed from **A1-A5** (for **C4TB···Am** both gas & solution phases BEs and for **C5TB···Am** gas BEs). The strength of **A6** interaction with **C4TB**/**C5TB** found to increase further as predicted by all methods. However, none of the BE curves in Figure 4 explain the trend of association constant (K_a) as a function of '**Am**'. To understand the contrast between BEs and K_a trends, we have further explored the bisammonium ion in folded conformation ('**Am***', see Figure S1) for binding with **C4TB**.

The minimum energy structure of **C4TB···A1*** complex was not fixed on the potential energy surface (PES), since geometry optimization of **C4TB-A1*** yields **C4TB-A1**, where **A1** exits in its extended form. Other five structures of **C4TB···Am*** (**m = 2-6**) obtained as bisammonium ions with the folded conformations (**Am***). The BE calculations at M06-2X/cc-pVTZ//M06-2X/6-31G* level have also been carried out for **C4TB···Am*** complexes and taken up for the discussion. Interestingly, all **C4TB···Am*** complexes shown higher BEs than the corresponding **C4TB···Am** complexes (the difference is, for **A2*** = 3.01 kcal/mol, **A3*** = 5.79 kcal/mol, **A4*** = 4.06 kcal/mol, **A5*** = 11.68 kcal/mol and **A6*** = 10.51 kcal/mol). These results reveal that the equilibrium between folded and extended conformation is more towards folded conformation owing to the strong affinity of folded bisammonium ions with the host molecule. More number of gauge conformations of bisammonium ion leads to greater affinity with the host molecule (**C4TB**) and thus the difference increases from **A2*** to **A6***.

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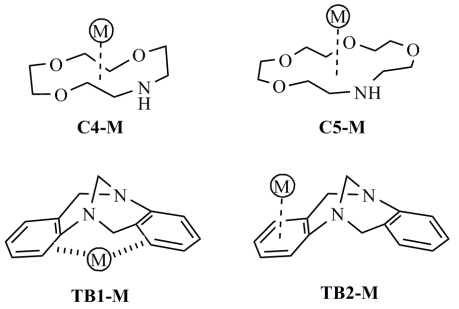

Scheme 3. The model systems considered in the study, M=NH_4^+. Only for C4-M complex, M= NH_4^+, $MeNH_3^+$, $EtNH_3^+$ and *n*Pr–NH_3^+.

Energy decomposition analysis

Energy decomposition analysis (EDA) has become a useful computational tool to decipher the role of various energy components of host-guest interaction. EDA splits the total binding energy into electrostatic (E_{es}), exchange repulsion (E_x), polarization (POL) and charge transfer (CT). The POL and CT terms are further divided into POL_h, POL_g, CT_{h-g} and CT_{g-h}. The EDA calculations on the supramolecular host-guest complexes are computationally cost. Therefore, we have used the more compact truncated model systems for the EDA calculations, as shown in Scheme 3.

The EDA results aid in delineating the role of various components in modulating the binding strength upon increasing alkyl chain length and increasing the crown ether size. It is also important to scrutinize, why cation-π interactions are not preferred in the host-guest complexes since, they are believed to be the strong noncovalent interactions.[16] The EDA results shown in Table 3, illustrate that, as alkyl chain length of ammonium ion increases, the attractive components decrease systematically.

The EDA calculations in Table 3 show that the increasing BE as the crown ether (**C4→C5**) size increases is mainly due to the reduction of repulsive interaction even though it appears to be due to electrostatic component (see Table S6).

Table 3. The energy components of the host-guest model systems considered. The values are reported in kcal/mol

	CAHB				Cation-π		
BE-comp	**C4-NH_4^+**	**C4-Me–NH_4^+**	**C4-Et–NH_4^+**	**C4-*n*–Pr–NH_4^+**	**C5-NH_4^+**	**TB1- NH_4^+**	**TB2- NH_4^+**
E_{es}	63.13	57.30	54.63	52.77	73.08	18.45	12.42
E_x	-40.62	-37.77	-37.01	-37.51	-39.16	-11.76	-7.79
POL_h	14.96	12.42	11.66	10.93	16.31	10.05	7.40
POL_g	2.44	2.62	3.01	2.80	2.09	0.10	0.11
CT_{h-g}	11.18	9.24	8.81	9.04	10.15	6.62	4.50
CT_{g-h}	0.53	0.60	0.55	0.54	0.47	0.16	0.09
E_{tot}	51.61	44.4	41.64	38.58	62.94	23.62	16.73

The 'h' is for crown ether or tröger's base and, 'g' is for the ammonium ion.

This was in line with the earlier report[17] i.e., the increasing BEs of Li^+-pyridine (49 kcal/mol) to Li^+-pyridazine (57 kcal/mol) in π-fashion, is mostly due to the reduction of repulsive component, (E_x) .The EDA results given in Table 3, it is clear that, formation of cation-π interaction is less preferred compared to the CAHB complexes due to the strong electrostatic interactions between host and guest molecules. Although the short range interactions like POL and CT components of BEs are higher in percentage (Table S6) for cation-π complexes larger E_{es} component of **C4-NH_4^+/C5-NH_4^+** is the main factor for such propensity to form CAHB host-guest complexation over cation-π complex formation.

Conclusions

In summary, two flexible ditopic Tröger's base receptors incorporating monoaza crown ethers have been designed and synthesized for bisammonium ions recognition. Receptors bind bisammonium ion of various chain lengths demonstrating that the flexibility of the host molecule. The incorporation of a flexible linker has a special role in selective binding of shorter chain length bisammonium ions by overcoming the rigidity factor. Further in-depth computational studies rationalized the experimental findings. Computational studies reveal that the gauge conformations (folded) of flexible alkyl chain in host-guest complexes lead strong binding with the host molecules and this is due to the higher charge transfer in host-guest interaction. These calculations also explain that the unusual higher binding constant (K_a) of longer chain length bisammonium ions with the host molecule, is due to the conformational folding of bisammonium ions. The observed upfield shift of δ values in case of **$CH_3NH_3^+$** is attributed to the sandwiched type complex.

Experimental Section

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General Methods: All the starting materials were obtained from commercial sources and used without further purification. Organic layers were dried over anhydrous Na_2SO_4. TLC analyses were performed on glass plates coated with silica gel 60 F_{254}. Plates were visualized using UV light (254 nm) and/or iodine. Column chromatography was performed on silica gel (60×120 mesh) on a glass column. Melting points (mp) were determined in capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra (300, 500, 600 and 75 MHz respectively) were recorded using TMS as an internal standard (0 ppm). Mass (ESI) data were recorded on quadruple mass spectrometry. HRMS data were obtained by the ESI ionization sources. IR spectra were recorded on a FTIR spectrometer as KBr pellets or neat.

Synthesis of 10-(2-(4-nitrophenoxy)ethyl)-1,4,7-trioxa-10-azacyclododecane (2)

To a mixture of aza crown ether **C4** (1.0 g, 5.714 mmol) and K_2CO_3 (1.18 g, 8.57 mmol) in 30 mL of dry acetonitrile, 1-(2-bromoethoxy)-4-nitrobenzene **1** (1.41 g, 5.714 mmol) was added. Reaction was refluxed for 7 days, after completion of the reaction (monitored by TLC), solvent was removed under reduced pressure. Water was added (30 mL), reaction mixture was extracted with dichloromethane (3 × 50 mL) and combined organic extracts were washed with water (3 × 20 mL). Solvent was removed under reduced pressure, dried over Na_2SO_4 and purified by column chromatography to afford the product **2** as light brown solid in 68% yield (1.32 g), mp 79-80 ºC. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.18 (d, J = 9.3 Hz, 2H), 6.95 (d, J = 9.3 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 3.66-3.59 (m, 12H), 2.99 (t, J = 6.0 Hz, 2H), 2.81 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.7, 141.3, 125.8, 114.3, 70.9, 70.2, 67.3, 55.6, 55.1; IR (KBr, cm^{-1}) 2929, 1663, 1591, 1337; MS (ESI) *m/z* (%) 341 ([M + H], 100), HRMS (ESI) calcd for $C_{16}H_{25}N_2O_6$ 341.1712, found 341.1725.

Synthesis of 2,8-bis(2-bromoethoxy)-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine (5)

To a mixture of 4-(2-bromoethoxy)aniline **4** (obtained by the $-NO_2$ reduction of **1**) (5 g, 23.1 mmol) in 20 mL ethanol, 50 mL of 37% formaldehyde solution was added followed by 45 mL of concentrated HCl (slow addition) at 0 ºC. After HCl addition, the reaction mixture was stirred at r. t. for 24 h. After completion of the reaction (monitored by TLC), the mixture was concentrated under reduced pressure until one half of the original volume remained and made basic with aq. NH_4OH. The aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 × 100 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure and purified by column chromatography using 30% ethyl acetate in hexane as eluent afforded **5** in 27% yield (2.92 g) as a white solid, mp 105-106 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, J = 8.7 Hz, 2H), 6.75 (dd, J = 2.6, 8.9 Hz, 2H), 6.44 (d, J = 2.5 Hz, 2H), 4.64 (d, J = 16.6 Hz, 2H), 4.28 (s, 2H), 4.18 (t, J = 6.4 Hz, 4H), 4.07 (d, J = 16.8 Hz, 2H), 3.57 (t, J = 6.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.4, 141.5, 128.7, 126.0, 114.6, 112.1, 68.0, 67.1, 58.8, 29.1; IR (neat, cm^{-1}) 2936, 2882, 1486, 1265, 1151, 1034, 750; MS (ESI) *m/z* (%) 469 ([M + H], 100), HRMS (ESI) calcd for $C_{19}H_{21}N_2O_2Br_2$ 466.99643, found 466.99695.

Synthesis of (5S,11S)-2,8-bis(2-(1,4,7-trioxa-10-azacyclododecan-10-yl)ethoxy)-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine (C4TB)

Method A. To a stirred mixture of **3** (obtained by the $-NO_2$ reduction of **2**) (310 mg, 1.0 mmol) and paraformaldehyde (90 mg, 3.0 mmol) TFA (10 mL) was added drop wise at -5 ºC. Stirring was continued at room temperature for 48 h. After completion of the reaction (monitored by TLC), reaction mixture was basified (p^H = 8 to 9) with 25% aq. NH_4OH and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography to afford compound **C4TB** as colourless foam in 12% yield (79 mg).

Method B. Tröger's base **5** (500 mg, 1.07 mmol) was added to the mixture of aza crown ether **C4** (376 mg, 2.15 mmol) and K_2CO_3 (440 mg, 3.22 mmol) in 20 mL of acetonitrile. The reaction mixture was refluxed for 36 h. After completion of the reaction (monitored by TLC) acetonitrile was removed under reduced pressure. Water was added (30 mL), reaction mixture was extracted with dichloromethane (3 × 50 mL) and combined organic extracts were washed with water (3 × 20 mL). Solvent was removed under reduced pressure, dried over Na_2SO_4 and purified by column chromatography using 1:19 of NH_4OH:MeOH to afford the compound **C4TB** light brown foam in 68% yield (479 mg). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.02 (d, J = 8.3 Hz, 2H), 6.72 (dd, J = 2.1, 9.4 Hz, 2H), 6.42 (d, J = 2.1 Hz, 2H), 4.61 (d, J = 17.7 Hz, 2H), 4.26 (s, 2H), 4.04 (d, J = 16.6 Hz, 2H), 3.97 (t, J = 5.2, 6.2 Hz, 4H), 3.68-3.63 (m, 16H), 3.62 (t, J=4.2, 5.2 Hz, 8H), 2.90 (t, J = 5.2, 6.2 Hz, 4H), 2.79 (t, J = 4.2 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.1, 140.9, 128.6, 125.9, 114.4, 111.6, 70.7, 70.1, 69.9, 67.1, 66.3, 58.8, 55.4, 55.3; IR (KBr, cm^{-1}) 2929, 1663, 1591, 1337; MS (ESI) *m/z* (%) 657 ([M + H], 100), HRMS (ESI) calcd for $C_{35}H_{53}N_4O_8$ 657.38579, found 657.38765.

Synthesis of (5S,11S)-2,8-bis(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)ethoxy)-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine (C5TB)

Tröger's base **5** (500 mg, 1.07 mmol) was added to the mixture of aza crown ether **C5** (470 mg, 2.15 mmol) and K_2CO_3 (440 mg, 3.22 mmol) in 20 mL of acetonitrile. The reaction mixture was refluxed for 36 h. Acetonitrile was removed under reduced pressure. Water was added (30 mL), reaction mixture was extracted with dichloromethane (3 × 50 mL) and combined organic extracts were washed with water (3 × 20 mL). Solvent was removed under reduced pressure, dried over Na_2SO_4 and purified by column chromatography using 1:19 of NH_4OH:MeOH to afford the compound **C5TB** as light brown foam in 74% yield (591 mg). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.03 (d, J = 9.0 Hz, 2H), 6.72 (dd, J = 2.6, 9.0 Hz, 2H), 6.41 (d, J = 2.6 Hz, 2H), 4.62 (d, J = 16.6 Hz, 2H), 4.28 (s, 2H), 4.05 (d, J = 16.6 Hz, 2H), 3.94 (t, J = 6.0 Hz, 4H), 3.68-3.58 (m, 32H), 2.92 (t, J = 6.0 Hz, 4H), 2.84 (t, J = 6.0 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.1, 140.9, 128.6, 125.9, 114.4, 111.6, 70.7, 70.1, 69.9, 67.1, 66.3, 58.8, 55.4, 55.3; IR (KBr, cm^{-1}) 2929, 1663, 1591, 1337; MS (ESI) *m/z* (%) 745 ([M + H], 100), HRMS (ESI) calcd for $C_{39}H_{61}N_4O_{10}$ 745.43822, found 745.43909.

Experimental Procedure for NMR titrations

Accurately weigh receptor into a NMR tube and dissolved in 0.6 mL of CD_3OD. Then hosts were titrated by adding each time 1.0 mg of the guest until no chemical shift change was observed for a distinguishable proton. The concentration of substrate in CD_3OD is varied from 0.25 equivalents to 2 equivalents to the concentration of the receptor's solution in CD_3OD. ^1H NMR spectra were recorded after each addition. The solvent signal (CD_3OD, 3.30 ppm) was used as reference peak. The chemical shift of the bindicated proton(s) of hosts was used for calculating binding constants.

Computational details

The initial conformational search of host molecules (**C4TB** and **C5TB**) have been done with discovery studio using Fast conformation module between the energetics of 0.00 - 20.00 kcal/mol.[18] The obtained low

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energy conformers of **C4TB** and **C5TB** were considered for building the model structures of host-guest complexes with set of six bisammonium ions **Am (m = 1-6)** (Figure 2). The complexes **C4TB**$^{\cdots}$**Am (m = 1-6)** and **C5TB**$^{\cdots}$**Am (m = 1-6)** and the simple model structures such as **C4-(NH_4)+, C5-(NH_4)+, TB1-(NH_4)+, TB2-(NH_4)+, C4-(CH_3NH_3)+, C4-($CH_3CH_2NH_3$)+ and C4-($CH_3CH_2CH_2NH_3$)$^+$** in Scheme 3 were optimized at PCM-M06-2X/6-31G(d) level of theory. The absence of imaginary frequencies confirmed that all the structures were minima in the potential energy surface at PCM-M06-2X/6-31G(d) level of theory. The energetics of the dicationic complexes were further fine tuned by improving the quality of the basis set. We used M06-2X[19] method and the correlation consistent basis set with triple zeta quality cc-pVTZ[20] for the binding energy calculations. The reported binding energies (BEs) were calculated by subtracting the total energy of the complex ($E_{complex}$) and the sum of the total energies of the individual fragments (E_{host} and E_{guest}) in their distorted environment. The BEs were calculated in three ways as shown in the equations 2, 3 and 4. Here, E_{guest*} indicates that the energy of the folded conformation bisammonium ion in the host-guest complex.

$$BE^1 = [E_{complex} - (E_{host} + E_{guest})] \quad (2)$$

$$BE^2 = [E_{complex} - (E_{host} + E_{guest*})] \quad (3)$$

$$BE_{avg} = (BE^1+BE^2)/2 \quad (4)$$

All the geometry optimization and the BEs calculations have been done using Gaussian 09 program package.[21] The influence of bulk solvent were included by means of PCM[22] considering methanol as a solvent. The effect of solvation has been looked with various solvent with dielectric constant 80.0 D (water) 47.0 D (DMSO) and 33.6 D (methanol) for the **C4-NH_4^+** system (see Table S5). The BEs of **C4-NH_4^+** in presence of water and in presence of methanol are found to be closer and the difference is lower than 1.00 kcal/mol. Thus we have considered 'Methanol' for finding the solvent effect on supramolecular host-guest binding energy, since the difference between the dielectric constants of 'Methanol' and '*Deuterated*-methanol' (33.7 D) is 0.1 D. Energy decomposition analysis have been carried out using the reduced variational space (RVS) technique implemented in the GAMESS program package[23] at HF/6-31G(d) level of theory. This technique splits the binding energy of a dimer into various components, such as electrostatic (E_{es}), exchange repulsion (E_x), polarization (POL) and, charge transfer (CT) components. The E_{es} component corresponds to the classical electrostatic interaction between the unperturbed charge distributions of the prepared fragments and it is usually attractive. The E_x term is the energetic contribution arising from the repulsion between the occupied molecular orbitals of the two fragments. The POL and CT components are associated with the intramolecular and intermolecular orbital relaxation energies of the two fragments. The POL and CT components can be further divided into two individual components viz., POL_g, POL_h, CT_{g-h} and CT_{h-g}.

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Notes and references

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Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra of all new compounds, optimization structures at DFT level and the cartesian coordinates are provided in the supporting information. See DOI: 10.1039/b000000x/

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