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Janus-Like Squaramide-Based Hosts: Dual Mode of Binding and Conformational Transitions Driven by Ion-Pair Recognition

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Abstract: New tripodal squaramide-based hosts have been synthesised and structurally characterised by spectroscopic methods. In 2.5% (v/v) [D_6]DMSO in $CDCl_3$, compound **4** formed dimeric assemblies [$\log K_{dim} = 3.68(8)$] as demonstrated by ^{1}H NMR spectroscopy and UV dilution experiments. AFM and SEM analyses revealed the formation of a network of bundled fibres, which indicates a preferential mechanism for aggregation. These C_3-symmetric tripodal hosts exhibited two different and mutually exclusive modes of binding, each one easily accessible by simultaneous reorientation of the squaramide groups. In the first, a convergent disposition of the NH squaramide protons allowed the formation of an array of N–H···X$^-$ hydrogen bonds with anions. In the second mode, reorientation of carbonyl squaramide groups allowed multiple C=O···H interactions with ammonium cations. The titration of **4** with different tetraalkylammonium iodides persistently showed the formation of 1:1 complexes, as well as 1:2 and 1:3 complexes. The corresponding stoichiometries and binding affinities of the complexes were evaluated by multi-regression analysis. The formation of high-order complexes, supported by ROESY, NOESY and mass spectrometry experiments, has been attributed to the insertion of NR_4I ion pairs between the carbonyl and NH protons of the squaramide groups located in adjacent arms of **4**. The observed effects reflect the induction of significant conformational changes in the hosts, mainly in relation to the relative orientation of the squaramide groups adapting their geometries to incoming ion-pair complementary substrates. The results presented herein identify and fully describe two different modes of ion-pair recognition aimed at directing conformational transitions in the host, therefore establishing a base for controlling more elaborate movements of molecular devices through ion-pair recognition.

Keywords: conformation analysis · host–guest systems · ion pairs · molecular recognition · supramolecular chemistry

Introduction

The development of effective receptor systems for ion pairs is an on-going challenge in supramolecular chemistry.[1] This is not as a result of a natural evolution from cation- and anion-alone host–guest chemistry, but according to the evidence, from both ionic components of an ion pair being involved in host–guest recognition events.[2] In particular, the design of ion-pair receptors that induce changes in response to discriminative stimulus is very engaging. Such systems are interesting not only as switches,[3] but also in drug delivery[4] and molecular sensing[5] or as templates for inducing the formation of complex supramolecular structures.[6]

To gain insight into the possibilities of chemically regulated conformational transitions in artificial systems, we have designed new neutral hosts aimed at alternatively recognising both the cationic or anionic portions of ion-pair substrates within a reversible binding pocket. This paper describes the synthesis of a series of tripodal hosts based on the use of bis-secondary squaramides as binding units and the characterisation of the different conformational transitions that take place upon recognition of selected tetraalkylammonium compounds.

Previous studies have shown that neutral bis-disecondary squaramides are difunctional binding units. First, they are effective hydrogen-bond donors for complexing anions.[7] This effect is a result of the simultaneous participation of two polarised NH bonds in a favourable disposition similar to that in urea and other amide-type compounds but featuring enhanced charge transfer from the anion guest to the electron-deficient squaramide ring in the anion–squaramide complex.[8] In a second role, squaramides are rare examples of neutral groups capable of binding tetraalkylammonium cations without using the most conventional means (i.e., electrostatic or cation–π interactions).[9,10] The two adjacent carbonyl groups of the squaramide are well suited to binding tetraalkylammonium groups through CH···O hydrogen bonding with the diffuse positive charge located on the methyl or methylenic protons closest to the quaternary nitrogen atom.[10a,11] Remarkably, theoretical calculations also

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predict a positive cooperative effect when the same squaramide unit binds simultaneously to anion and cation guests through its NH and C=O groups. In this case, the calculations predict a net gain in energy in the cation–squaramide–anion system due to the enhanced aromatic character of the squaramide ring in the ternary complex.[12]

Like a molecular Janus,[13] these two-faced squaramides are unique among related amide-type binding units. In this work, taking advantage of this feature, we synthesised and studied a host capable of changing its hydrogen-bonding pattern from an all-donor to an all-acceptor. In our design, three bis-disecondary squaramide units were covalently attached to a tris-aminopropargylbenzene spacer. The resulting hosts have a semi-rigid framework to avoid intramolecular collapse due to intramolecular hydrogen bonding of the squaramide units. However, they are flexible enough to allow unrestricted rotation of the squaramide units due to the presence of a methylenic bridge in each arm. A preliminary structure optimisation of a basic host complexed to a tetramethylammonium cation or a trimesoate anion by DFT calculations at the B3LYP/6-31G* level of theory supported the design.[14] The resulting structures showed that the C_3-symmetric host can simultaneously interact through the hydrogen bonding of six squaramide carbonyls with at least nine protons of the tetramethylammonium cation. After reorientation, the same host can interact simultaneously with three carboxylate groups of a trimesoate anion (Figure 1). In both cases, the calculated parameters are well within the limits of typical CH···O[15] and NH···O[16] hydrogen bonds.

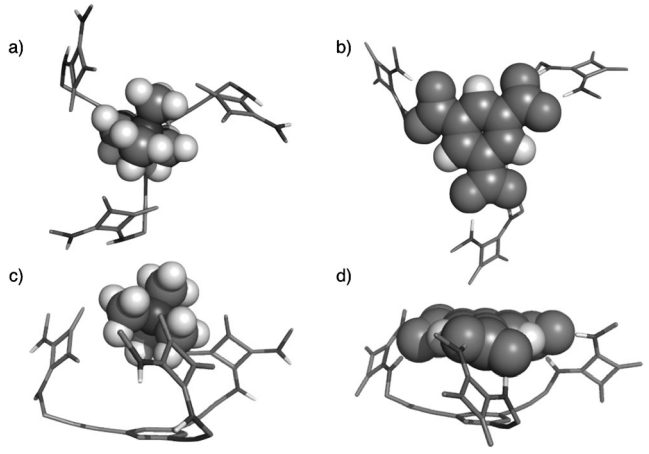
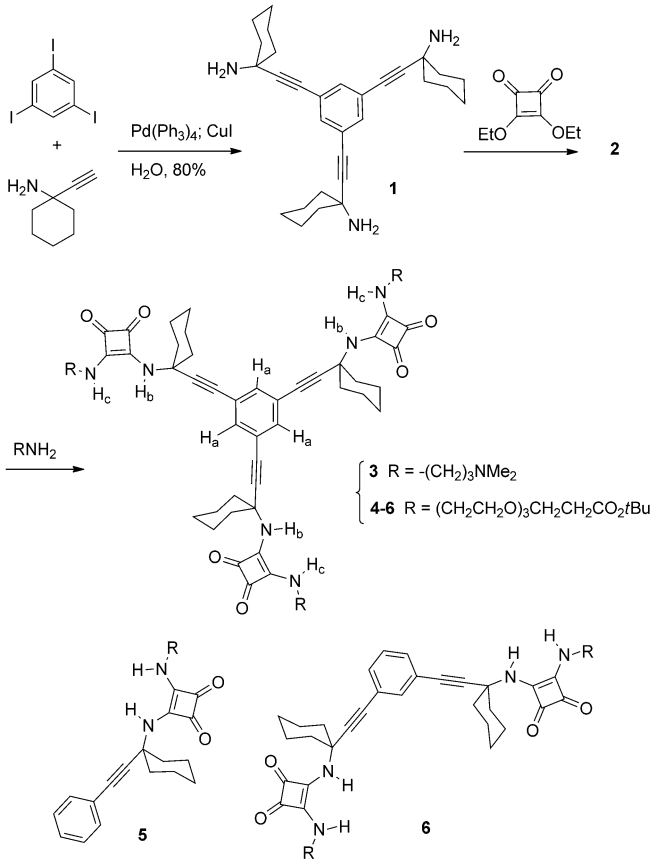


Figure 1. Representative axial and side views (B3LYP/6-31G*) of C_3 complexes of a squaramide-based tripodal receptor with $^{+}NMe_4$ (a,c) and a trimesoate anion (b,d), respectively. Non-acidic hydrogen atoms have been omitted for clarity.

Results and Discussion

Synthesis: A convenient tripodal spacer was prepared by triple Sonogashira cross-coupling of 1,3,5-triiodobenzene with commercially available 1-ethynylcyclohexylamine according to a previously reported "on water" procedure to give tris(aminoalkynyl)benzene derivative **1** in a yield of 80% (Scheme 1).[17] Condensation of **1** with a slight excess of diethyl squarate in EtOH gave the mixed squaramide



Scheme 1. Synthesis of tripodal squaramides. The labelling of key hydrogen atoms (H_a, H_b and H_c) indicated in the scheme is used throughout the text.

ester **2** in a yield of 50% without having to use high-dilution conditions. Subsequent condensation with *N*,*N*-dimethylpropane-1,3-diamine or *tert*-butyl 3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoate gave tripodal squaramides **3** and **4** in yields of 82 and 54%, respectively. Mono- and bis-aminopropargyl squaramides **5** and **6**, analogues of **4** with only one and two arms, respectively, were also prepared for comparison purposes and to provide information on aggregation.

Studies of aggregation: Model compounds **5** and **6** are soluble in neat $CDCl_3$, however, tripodal host **4**, which also contains poly-oxyethylene chains, was only slowly solubilised up to 1×10^{-3} M, giving a gel-like viscous solution. In this solvent, tripodal squaramide host **3** is totally insoluble. The ^{1}H NMR spectra of **5** and **6** show two exchangeable NH-(H_b,H_c) signals at around 6.4–6.5 ppm in $CDCl_3$ and CD_2Cl_2. These values, typical of non-hydrogen-bonded secondary squaramides, were taken as references and, at the same

time, showed the absence of significant intramolecular hydrogen bonding in model compound **6**, which has two potentially interacting squaramide rings. By analogy, we also inferred that intramolecular hydrogen bonding could be neglected in tripodal receptor **4**. Although in neat $CDCl_3$ the NH protons of **4** were undetectable, the propensity of **4** to aggregate was readily deduced from the broad signals in the rest of the spectrum, even at dilute concentration (5×10^{-4} M). All these compounds are soluble in dimethyl sulfoxide. The ^{1}H NMR spectra of compounds **3**–**6** in neat [D_6]DMSO at 298 K exhibit only sharp resonances. The two distinct NH-(H_b,H_c) squaramide resonances appear shifted around 1.2–1.4 ppm downfield in [D_6]DMSO compared with in apolar solvents due to hydrogen bonding between the NH groups and the solvent dimethyl sulfoxide. In addition, the ^{1}H NMR spectra of **3** and **4** in [D_6]DMSO are independent of concentration, thereby indicating their monomeric nature. Accordingly, the chemical shifts of the squaramide NH moieties are temperature-dependent within the range 295–343 K. Upon heating, the two NH groups experience upfield shifts of −0.2 and −0.3 ppm, respectively, due to partial breakage of the hydrogen bonds between polar dimethyl sulfoxide molecules and the squaramide NH groups.[18]

The macroscopic gel-like morphology of **4** in $CDCl_3$ was also supported by atomic force microscopy (AFM) and scanning electron microscopy (SEM; Figure 2). Analysis of the AFM images obtained from a solution of **4** in chloroform after evaporation on a mica surface showed the formation of non-radial fibrous networks (Figure 2a). In addition, a SEM image of a dried gel-like material obtained by drop-casting **4** into chloroform on carbon-coated grids revealed an entangled network of cylindrical fibres. The widths of thinner distinguishable fibre bundles were 20–22 nm, whereas the thicker fibres consisted of bundles of thinner fibres, which split or fused to create a more or less regular network. Although the mechanism of formation is uncertain,[19] molecular modelling (MMFF) suggests the formation of cylindrical elemental fibres (4–5 nm diameter) of **4** packed through a combination of multiple hydrogen-bonding and π-stacking interactions. These results are relevant to this study as they highlight the hydrogen-bonding donor–acceptor duality of squaramides. The addition of a small percentage of [D_6]DMSO to a solution of **4** in $CDCl_3$ transforms the initial gel-like solution into a clear mobile solution. Therefore, to minimise the self-aggregation of hosts and guests and to enhance the solubility of **4**, all subsequent experiments were carried out in $CDCl_3$ incorporating 2.5% (v/v) [D_6]DMSO. However, dilution experiments performed in this solvent mixture revealed that some degree of aggregation still remained. Upon dilution, the two protons of **4** experienced considerable downfield shifts (Figure 3). In comparison, parallel dilution experiments performed on model compounds **5** and **6** revealed only very minor changes in the chemical shifts in the same concentration range. These observations reflect a distinctive behaviour of **4** in comparison with **5** and **6**. The enhanced aggregation of tripodal compound **4** can be accounted for by the simultaneous participation of the three arms of the tripodal host in an *n*-mer of **4** obtained by the displacement of solvating dimethyl sulfoxide molecules to give oligomeric head-to-tail aggregated structures (Figure 2c,d); this is likely to occur in a low polarity solvent as the concentration of **4** increases. The observed shifts were successfully fitted to a simple monomer/dimer model by using the HypNMR[20] program to obtain a dimerisation constant [$K_{dim}=4770\,M^{-1}$, $\log K_{dim}=3.68(8)$]. The distribution diagram shows that up to 50% of the dimer is present at a concentration of around 5×10^{-4} M (Figure 3, inset). This dimerisation constant was incorporated into all subsequent calculations involving ^{1}H NMR titrations of the tripodal host **4**.

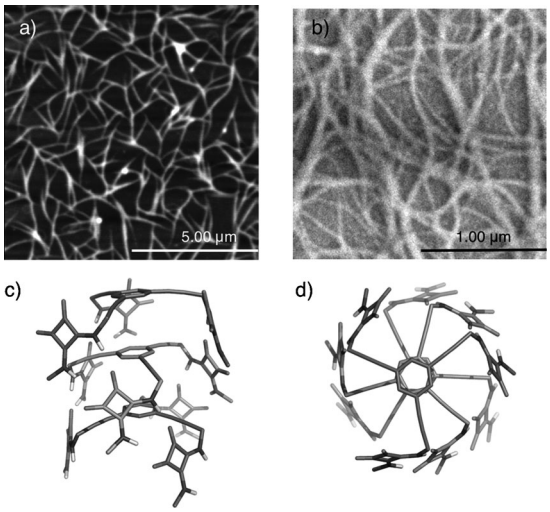


Figure 2. a,b) AFM and SEM images of aggregate structures of **4** obtained by the evaporation of **4** (5.0×10^{-4} M) in chloroform. c,d) Perspective and top partial views of an energy-minimised (MMFF) head-to-tail trimer of **4**. The average distance between two consecutive aryl ring centroids is 4.5 Å. The calculated O···N hydrogen-bond distances are within the range 2.4–3.3 Å and the NHO angles are in the range 161–165°. In these views, all non-participating substituents as well as non-acidic hydrogen atoms have been omitted for clarity.

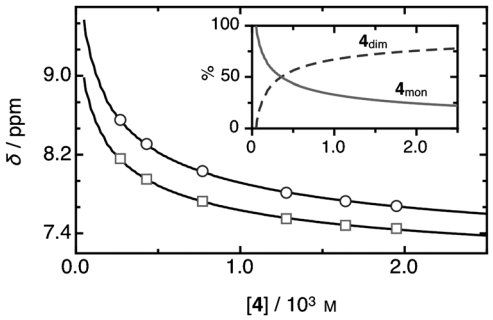


Figure 3. Concentration dependence of the ^{1}H NMR chemical shifts of **4** in 2.5% [D_6]DMSO/$CDCl_3$ (v/v) at ambient temperature (298 K) for a range of concentrations from 1.0×10^{-4} to 2.0×10^{-3} M. The symbols are experimental data points. The curves were calculated by simultaneous non-linear regression of experimental data assuming a monomer/dimer model. The inset shows the distribution of monomer and dimer species.

Additional evidence for dimerisation was obtained by UV/Vis spectroscopy (see the Supporting Information). The UV/Vis absorption spectra of the mono-, bis- and tris-squaramide compounds **4**–**6** display a band with a maximum at 293 nm, which indicates the presence of a common chromophore assigned to the squaramide group.[21] Although compounds **5** and **6**, which feature one and two squaramides arms, respectively, gave a linear response, the intensity of the absorption observed with **4** clearly deviated from linearity. In addition, **4** also shows a characteristic concentration-dependent shoulder at around 316 nm, compatible with π-stacking interactions of the aromatic chromophores.[22] A dimer of **4** was also detected by mass spectrometry: a weak peak with $m/z = 3036.325$ Da corresponding to $[\mathbf{4}_2+\mathrm{Na}]^+$ was observed by positive MALDI-TOF mass spectrometry.

At this point, the structure of the dimer remains uncertain. In particular, we considered the formation of capsular dimeric assemblies as described for related amide-type and urea compounds.[23] Unfortunately, so far we have been unable to find any evidence supporting the formation of dimeric capsules of **4**. Thus, without neglecting other possibilities, we turned our attention to variants that involve the preferential head-to-tail dimerisation of tripodal receptor **4** by the simultaneous NH···O=C hydrogen bonding of three pairs of NH and carbonyl groups of the squaramides.[24]

Binding studies with tetraalkylammonium tricarboxylate salts: Neutral and charged squaramide-derived hosts are known to form complexes with a variety of monoanions, for example, F^-, Cl^-, Br^-, NO_3^-, SO_4^{2-}, HPO_4^{2-} and AcO^-,[7c,d,e,18,25] and also with di- and tricarboxylate anions, such as oxalate, citrate, glutarate[7a,f] and trimesoate anions.[7b] Based on this experience, we expected that tripodal squaramide receptors **3** and **4** would also form host–guest complexes with anions (Figure 1).

To gain information about this mode of binding, the complexation-induced shifts (CIS) of tripodal hosts **3** and **4** were examined by ^{1}H NMR spectroscopy on complexation with the tetraalkylammonium salts of tricarboxylic acids in 2.5% (v/v) $[D_6]$DMSO/$CDCl_3$. In this rather apolar medium, the carboxylate salts are found as associated ion pairs capable of interacting with neutral hydrogen-bond donors.[26] Initial experiments with the tetrabutylammonium (TBA) salts of tricarboxylic acids, such as nitrilotriacetic, *cis*-1,3,5-cyclohexanetricarboxylic, and Kemp's triacid, resulted in the formation of host–guest complexes by interaction between the carboxylate groups of the guests and both NH groups on the squaramide moieties. Unfortunately, with these guests, the experimental data could only be partially characterised by manual fitting using the downfield shifts of both NH resonances of the squaramides. In all these cases, the data available suggested the formation of 1:1 and 2:1 host–guest complexes. Further work was carried out with the TBA salts of the trimesoate anion (TBAT) because this salt offers a well-separated aromatic hydrogen useful as a ^{1}H NMR probe. Upon titration of **4** with TBAT, the NH protons shifted around −1 ppm upfield to reach an inflexion point, beyond which the observed shifts were shifted downfield by around 2 ppm (Figure 4). These apparently contradictory CIS changes clearly indicate the existence of at least two different host–guest equilibria. Here, the overall movement of both NH groups is accounted for by the strong hydrogen-bonding interactions N–H···O^- formed with the carboxylate groups of the trimesoate replacing the solvating dimethyl sulfoxide molecules and disturbing the monomer/dimer equilibrium of **4**. In addition, the aromatic signals ArH_a on the receptor and ArH_T on the substrate guest shifted upfield, which suggests their close proximity within the limits of mutual diamagnetic shielding by aromatic stacking.

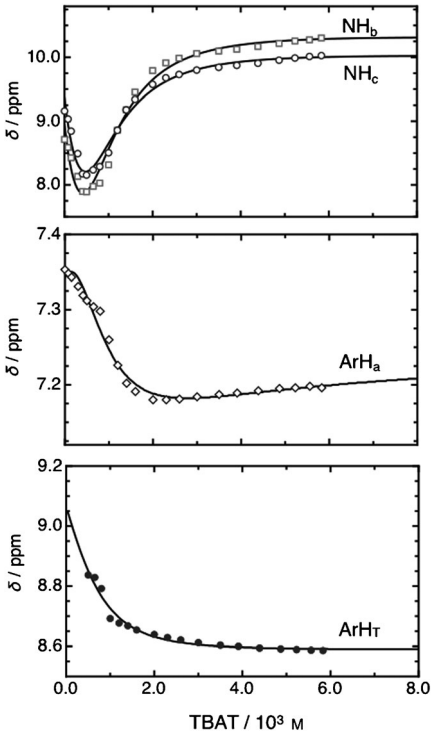


Figure 4. Plots of simultaneous changes in the chemical shifts of significant ^{1}H NMR (300 MHz) signals of **4** (5.9×10^{-4} M) with increasing amounts of TBAT in titration experiments performed in 2.5% $[D_6]$DMSO/$CDCl_3$ (v/v) at 298 K. The symbols are experimental data points. The solid lines are best fit curves obtained by simultaneous non-linear regression of the shifting resonances of NH_b, NH_c and ArH_a in the receptor and ArH_T in the substrate.

After investigating several plausible models, all available shift changes were simultaneously fitted by taking into account the formation of 1:1 as well as 2:1 host–guest complexes and by including the dimerisation constant of **4** already calculated [Equations (1)–(3)]. This model is based on the assumption that TBAT is present as associated ion pairs,[27] therefore $[L]\approx[TBAT]$. Several attempts to include the ion-pair dissociation equilibrium of TBAT and the complexation of the individual ions did not produce any improvement in fitting.[28] The calculated values for the stepwise association constants have the same order of magnitude for both the 1:1 and the 2:1 host–guest complexes TBAT⊂**4** [$K_{11}=1.59\times10^4$ M^{-1}, $\log K_{11}=4.20(9)$] and TBAT⊂$\mathbf{4}_2$ [$K_{21}=$

$1.12\times10^4\,\text{M}^{-1}$, $\log K_{21}=4.05(9)$]. Remarkably, the fitting of data failed completely when the dimerisation constant of **4** was removed from the overall equilibria. In this regard, it is worth mentioning the work by Roelens et al. on the participation of dimers of a related tripodal ureido host in the binding of tetraalkylammonium compounds in a three-reagent model.[28]

$$R + L \rightleftharpoons RL K_{11} = \frac{[RL]}{[R][L]} \quad (1)$$

$$R_2 + L \rightleftharpoons R_2L K_{21} = \frac{[R_2L]}{[RL][L]} \quad (2)$$

$$2R \rightleftharpoons R_2 K_{dim} = \frac{[R_2]}{[R]^2} \quad (3)$$

To avoid interference due to aggregation phenomena, the binding of the trimesoate anion was also investigated by using tetramethylammonium trimesoate (TMAT) in neat [D_6]DMSO. In contrast to the previous titrations, in this media the two non-equivalent squaramide NH protons experienced large downfield shifts (Figure 5). In turn, the aromatic hydrogen atoms of the host (H_a) and guest (H_T) experienced moderate upfield shifts, whereas the rest of the spectra remained essentially unchanged. Qualitatively, these observations indicate that the two squaramide NH groups are involved in strong hydrogen bonding with the carboxylate groups of the trimesoate even in the presence of a strong competing agent such as dimethyl sulfoxide. Moreover, the upfield shifts of the aromatic hydrogen atoms are consistent with the mutual shielding effect of the aromatic stack formed upon binding. In this regard, the moderate magnitude can be explained on the basis of the calculated average distance of 4.0–4.2 Å between the two aromatic rings in the complex formed between a tripodal squaramidic host and the trimesoate anion, which is larger than the typical aryl–aryl stacking distance of 3.6–3.7 Å observed in crystal structures.[29]

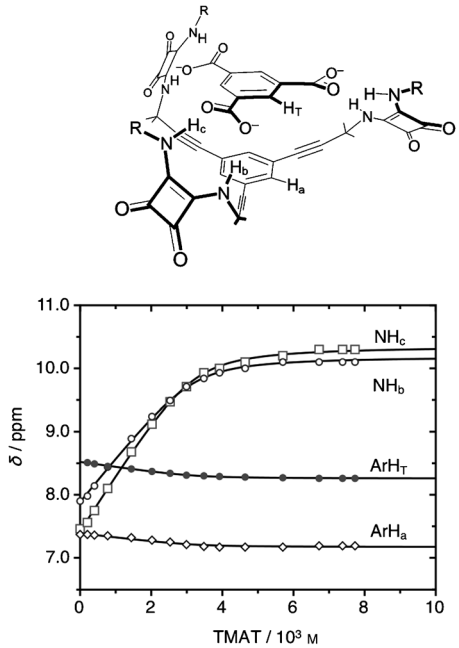


Figure 5. Representative plots of the changes in the chemical shifts of significant 1H NMR (300 MHz) signals of **3** (3.2×10^{-3} M) with increasing amounts of TMAT in titration experiments performed in [D_6]DMSO at 298 K. The symbols are experimental data points. The lines are best fit curves obtained by simultaneous non-linear regression of the four shifting resonances of NH_b, NH_c, ArH_a and ArH_T to a 1:1 model of complexation.

The binding affinities in these systems were calculated from the corresponding ^{1}H NMR titration data by simultaneously fitting the changes in the chemical shifts of the H_a–H_c protons of receptors **3** and **4** and H_T of the trimesoate anion to a 1:1 two-reagent model. As expected, in [D_6]DMSO, both tripodal receptors afforded only 1:1 complexes, giving TMAT⊂**3** [$K_1=7440\,\text{M}^{-1}$, $\log K_1=3.87(3)$] and TMAT⊂**4** [$K_1=4600\,\text{M}^{-1}$, $\log K_{as}=3.66(3)$], respectively. Spectral examination greatly contributed to the elucidation of the precise structures of the complexes. The structures of **3** and **4** complexed with the trimesoate anion were determined by ROESY and NOESY experiments. In particular, the ROESY spectrum of a 1:1 mixture of **3** and TMAT in [D_6]DMSO shows key intermolecular cross-peaks between the two aromatic protons H_a and H_T and between H_T and the two squaramide NH_b and NH_c hydrogen atoms, thus confirming that the trimesoate anion is located in a cavity created by the tripodal receptor in a C_3-symmetric conformation. Moreover, the TMA cations must remain in close proximity to the complex, probably as solvent-separated ion pairs, because they show intermolecular contacts with the aromatic protons of both the trimesoate (H_T) and **3** (H_a). Plausible structures of these complexes, which account for all the observed NOE effects, are proposed in Figure 6a.

Binding studies with tetraalkylammonium iodides: A distinctive feature of squaramides compared with urea or other amide-type groups is the hydrogen-bond accepting abilities of the two adjacent carbonyl oxygen atoms of squaramides. We previously demonstrated the potential of the binding of the carbonyl groups of squaramides through the design of

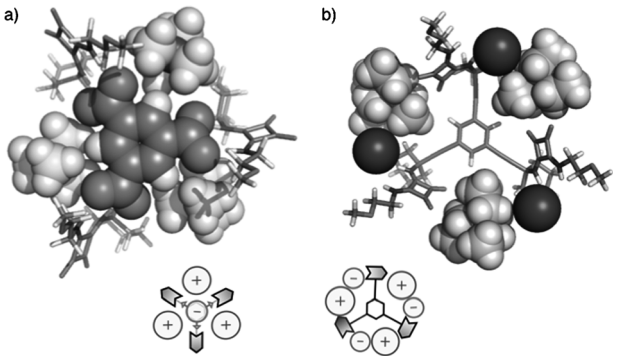


Figure 6. MMFF optimised structures and schematic representations proposed for the complexes a) TMAT⊂**4** and b) TEAI⊂**4**.

a fluorescent molecular sensor based on this exclusive ability in choline-containing phospholipids.[9c] In addition, the interaction energy between a single plain squaramide and a TMA cation (-22.00 kcal mol^{-1}) is clearly favourable compared with that of urea with TMA (-16.53 kcal mol^{-1}).[11] In this regard, host **4** was initially expected to provide optimal size and shape complementarity to tetraalkylammonium cations through multiple NCH···O=C hydrogen bonding (Figure 2a,c) without too much competition from the weakly basic iodide counterions.

Complexation-induced changes in the chemical shifts ($\Delta\delta$) of both the host and guest were examined by ^{1}H NMR spectroscopy for the complexation of **4** with selected tetraalkylammonium iodides. Thus, upon addition of a 24-fold molar excess of tetraethylammonium iodide (TEAI), the squaramide NH protons underwent parallel limiting upfield shifts of -1.04 and -0.87 ppm for NH_c and NH_b, respectively (Figure 7), which indicates a similar participation in hydrogen bonding. Remarkably, the observed shift changes contrast the usual observations of downfield shifts for protons involved in hydrogen bonding. Here, the observed upfield shifts of the NHs are due to the displacement of the dimer/monomer equilibrium of **4** and subsequent hydrogen bonding of the NH groups to iodide anions. In turn, the NCH_α protons of TEAI are shifted downfield by $+0.05$ ppm, which suggests a deshielding effect is operating in the complex.[30] This is in contrast to the absence of any significant shifts of the alkylammonium protons of TBA and TMA observed with the trimesoate salts. A downfield shift is what one might expect of a proton involved in hydrogen bonding with the squaramide carbonyl. In addition, the downfield shift of the NCH_α protons suggests that TEA cations are outside of the cavity away from the diamagnetic influence of the aromatic ring of **4**.[9a,10c] In all the cases studied, only one set of signals was observed, which indicates a fast-exchange regime at room temperature on the NMR timescale.

Qualitatively, the CIS changes observed for TEAI are similar to those of several of the tetraalkylammoniums already tested. Quantitative evaluation of the binding affinities of **4** towards TEAI, benzyltrimethylammonium iodide (BTAI) and tetrabutylammonium iodide (TBAI) was carried out by titration of **4** with increasing amounts of the NR_4I. In all cases, the protons available for fitting were the two exchangeable squaramide NHs and ArH_a of **4** and NCH_α of the ammonium compound. Upon titration, both NH protons shifted upfield due to their sensitive response to changes in the media. Other CH protons, although less affected by external factors, were also important for improving the goodness of fit.[31] After several attempts using different equilibrium models of increasing complexity, we realised that the distances between the carbonyl groups of one squaramide unit and the NHs of the adjacent squaramide in **4** were suitable for accommodating up to three NR_4X ion-pair guests between two consecutive arms. This fact was incorporated into a model of multiple equilibria that included the formation of 1:1 to 1:3 host–guest complexes. These equilibria were characterised by three microscopic association constants, K_1, K_2 and K_3, as well as the dimerisation constant of the host K_{dim}. Analysis of the titration data with this model gave a consistent fit, as shown in Figure 7 for TEAI. Table 1 summarises the association constants calculated for the binding of the tripodal receptor **4** to several NR_4I compounds. Overall, these data reveal that receptor **4** not only binds to NR_4I compounds to give complexes with 1:1 stoi-

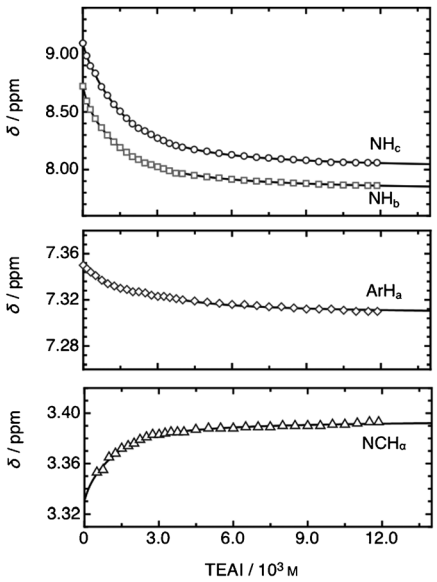


Figure 7. Representative plots of changes in the chemical shifts of significant ^{1}H NMR (300 MHz) signals of **4** (5.2×10^{-4} M) with increasing amounts of TEAI in titration experiments performed in 2.5% [D_6]DMSO/$CDCl_3$ (v/v) at 298 K. The symbols are experimental data points. The solid lines are best fit curves obtained by simultaneous non-linear regression of the four shifting resonances of NH_b, NH_c, ArH_a and NCH_α to a model of multiple complexation that includes the dimerisation of the receptor (see Table 1).

Table 1. Macroscopic ($\log K_i'$) and microscopic binding constants ($\log K_i$) for the 1:1, 2:1 and 3:1 complexes formed between **4** and tetraalkylammonium iodide compounds.[a,b]

	R+L⇄RL				RL+L⇄RL$_2$				RL$_2$+L⇄RL$_3$		
NR_4I	$\log K_1'$	$\log K_1$[c]	K_1	α_1[d]	$\log K_2'$	$\log K_2$[c]	K_2	α_2	$\log K_3'$	$\log K_3$[c]	K_3
TEAI	3.30(5)	2.82	660	4.16	3.44(1)	3.44	2750	1.78	3.22(1)	3.70	5000
TBAI	4.39(9)	3.91	8200	1.65	4.13(18)	4.13	13500	0.18	2.90(15)	3.38	2400
BTAI	3.72(4)	3.24	1740	3.16	3.74(4)	3.74	5500	0.19	2.53(2)	3.01	1020

[a] Measured for 0.5×10^{-3} M of **4** in 2.5% [D_6]DMSO/$CDCl_3$ (v/v) at 298 K. The dimerisation constant for **4** was fixed at $\log K_{dim}=3.68(8)$. [b] Standard deviations are given in parentheses. [c] Statistical corrections applied: $K_1=K_1'/3$, $K_2=K_2'$ and $K_3=3K_3'$. [d] Molecular interaction parameters: $\alpha_1=K_2/K_1$ and $\alpha_2=K_3/K_2$.

chiometry, but it provides three non-independent binding sites capable of accommodating up to three NR_4I ion pairs. At the molecular level, the cooperativity of the systems is described by the corresponding interaction parameters α_1 and α_2.[32] In the three cases studied so far, the system exhibited an initial positive cooperativity, $\alpha_1 = K_2/K_1 > 1$, which favours a second complexation of the NR_4I pair. However, complexation of a third ion pair of TBAI and BTAI showed negative cooperativity, $\alpha_2 = K_3/K_2 < 1$, probably due to steric crowding arising from the relatively large volume of these cations hindering the formation of higher-order complexes.

Although the origin of the observed cooperativity is uncertain, it can be presumed that large entropic effects arising from the solvation effects of the host and guests could be neglected in the apolar solvent mixture used in this work.[33] In our case, the observation of the initial positive cooperativity can be explained on the basis of the existence of three identical, non-independent binding sites in **4**. In such systems, the first complexation restricts the conformational motion of two arms of the host, thus increasing its pre-organisation and facilitating a second complexation event. In this scenario, given the tripodal structure of **4**, the binding of a third guest molecule would be disfavoured unless the ion pair exactly matched the optimal distances of binding, a condition that apparently is only satisfied by TEAI ($\alpha_1,\alpha_2 > 1$).

The interplay between TEA cations and host **4** was determined by NOESY and ROESY experiments (see the Supporting Information). The ROESY spectra revealed strong intramolecular contacts between NH_b and at least two different hydrogen atoms on the cyclohexylidene ring, which indicates the close spatial proximity of the squaramide NH_b and the cyclohexylidene substituent. Remarkably, any comparable cross-peak between NH_b and the cyclohexylidene protons in the TBAT⊂**4** and TMAT⊂**4** complexes already described was lacking. Furthermore, ROESY experiments revealed strong intermolecular contacts between the aromatic proton of **4** (ArH_a) and the ethyl chains of TEA. As these contacts are dependent on distance, this strongly suggests a close spatial proximity between NH_b, ArH_a and the cyclohexylidene ring of the host **4** on the one hand, and between these protons and TEA on the other. Figure 6b shows an energy-minimised molecular structure that encompasses all the NOE effects observed. In these complexes the angle between the alkynyl and the squaramide moieties is 55–60°, as defined in Figure 8B.

Additional evidence for the existence of NR_4I⊂**4** complexes was obtained by MALDI-TOF mass spectrometry (see the Supporting Information). The mass spectra of solutions of host **4** containing TEAI or the better BTAI exhibit peaks corresponding to the loss of one or other component of the ion pair. These results support the remarkable affinity

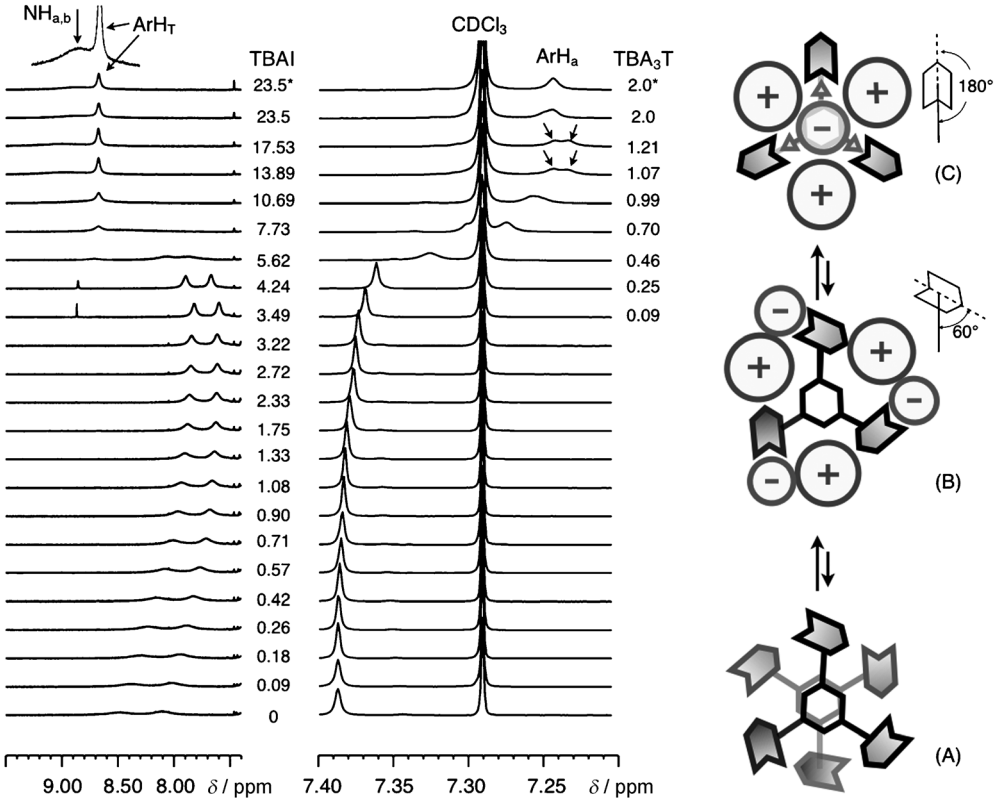


Figure 8. Left: Partial stacked ^1H NMR (300 MHz) spectra of **4** (5.0×10^{-4} M) with increasing amounts of first TBAI and then TBAT at the concentrations (mM) indicated, recorded in 2.5% $[D_6]$DMSO/$CDCl_3$ (v/v) at 298 K. *The last spectrum in this series reflects the equilibrium after 24 h. The inset between 8.3 and 9.3 ppm, shows the shift and shape of the $NH_{a,b}$ protons at the equilibrium. Right: Schematic representation of the conformational transition of **4** driven by the binding of TBAT.

of **4** for both the anionic and cationic components of the NR_4I ion pairs.

Conformational transitions driven by the ion pair: The different behaviour of the tripodal squaramide host **4** in the presence of the tetraalkylammonium iodide or trimesoate compounds prompted us to use two ammonium compounds to drive the precise conformational transitions in **4**. Thus, in a preliminary experiment, we initially added increasing amounts of TBAI to induce a transition from the dimer/monomer **4** to a TBAI⊂**4** complex and then added TBAT to induce a second conformational transition. Note that TBA was used as the cation in each ion pair to avoid interference. Therefore the observed shift changes had to be attributed mainly to the effect of the counterions, namely iodide and trimesoate (Figure 8).

Initially, upon addition of increasing amounts of TBAI to **4** (0.5×10^{-3} M), the resonances of the NHs became sharper and their shifts moved upfield, as described above, as the complex represented in Figure 8B was formed. Subsequent addition of TBAT caused a significant reorientation of the system, as evidenced by pronounced effects on several key resonances. Among them, the signal of the aromatic proton of **4** (H_a) broadened and moved upfield due to the influence of the shielding of the phenyl ring of the trimesoate. Before completion, some splitting of this signal was observed, evidencing the existence of several species in a relatively slow exchange regime. The aromatic proton of trimesoate (H_T), initially a sharp singlet at 8.80 ppm, evolved to a broad signal upfield at 8.60 ppm, also due to the influence of shielding of the tris-alkynylbenzene portion of **4**. Furthermore, the signal of the two NH protons broadened and shifted to around 9.0 ppm due to strong hydrogen bonding with the trimesoate anion. Comparative NOESY and ROESY experiments (see the Supporting Information) revealed intramolecular contacts between NH_b and three different protons of the cyclohexylidene ring, which indicates the spatial proximity of NH_b to the cyclohexylidene residue of **4**. Moreover, the ROESY spectrum reveals intermolecular contacts between the butyl residues of TBAI and H_a due to the spatial proximity between the aromatic portion of **4** and the TBA cations typical of associated ion pairs.[26e] In contrast, the ROESY spectrum of a solution containing **4** and TBAT shows intermolecular contacts not only between the butyl chains of TBA and H_a but also with H_T and, significantly, between the two aromatic protons ArH_a and ArH_T. All together, these observations are accommodated by assuming an initial transition of **4** from the initial monomer/dimer state to a complexed state dictated by intramolecular head-to-tail binding of TBAI. The addition of TBAT triggered a drastic conformational transition by rotation of the squaramide units. The resulting outward movement of the squaramides created an array of three pairs of NH hydrogen-bond donors that converged on the trimesoate anion guest located in the centre of the tripodal cavity created by **4** (Figure 8C). This conformational transition supposes a competitive displacement of iodide anions by trimesoate due to the high basicity of trimesoate anions compared with iodide and the optimal C_3-symmetric pre-organisation of the host.

Conclusion

We have shown that effective ion-pair recognition can be obtained with squaramides. The squaramide-based tripodal hosts described herein exhibit dual behaviour as cascade-type ligands in the presence of alkylammonium trimesoate salts. This host–guest relationship is driven by the high basicity of the carboxylate groups of the trimesoate anion ideally disposed for hydrogen-bond formation. In sharp contrast, these tripodal hosts are tris-heteroditopic ligands able to form 1:3 complexes with NR_4I ion pairs. These host–guest interactions, which are based on hydrogen bonding, overcome the observed tendency for the tripodal squaramides to dimerise. Note, the formation of well-defined complexes with trimesoate and other tricarboxylate anions triggered a drastic reorientation response of the host. Given its modular structure and neutral character, this approach should be well suited to ion sensing and the development of movable molecular devices.

Experimental Section

General: All temperatures quoted are uncorrected. Tetraalkylammonium iodides were purchased from Aldrich and stored under vacuum over P_2O_5 for several days prior to use. The tris-tetrabutylammonium salts of the tricarboxylic acids were prepared according to the literature.[34] NMR spectra were recorded with Bruker Avance 300 and Avance III 600 MHz spectrometers equipped with a cryoprobe (2D-NOESY and ROESY). Chemical shifts are given in parts per million referenced to the residual peak of $CDCl_3$ or [D_6]DMSO. In the NMR titrations, typically, solutions of **4** (ca. 0.5 mM) were prepared in $CDCl_3$ containing 2.5% (v/v) of [D_6]DMSO. The tetraalkylammonium compound (ca. 1–2 mM) was dissolved in the above solvent just prior to use. Titrations were carried out by adding small volumes of the solution of the tetraalkylammonium compound to the solution of the host (0.5 mL) in a NMR tube. After each addition the solution was shaken well and left to stand for 4 min before recording the spectra. The chemical shifts of all the NH and CH protons that undergo changes upon titration were taken into consideration in the fitting. Stability constants were calculated by non-linear least-square regression with HypNMR2008.[20] Mass spectra were recorded with Micromass Autospec 3000 (HRMS-ESI) and Bruker Autoflex (MALDI-TOF) spectrometers with *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix.

Synthesis of squaramide ester 2: A solution of **1**[17] (0.33 g, 0.76 mmol) in diethyl ether (15 mL) was added dropwise to a solution of diethyl squarate (0.7 g, 5.4 mmol) in ethanol (10 mL) and the resulting solution was stirred at 35 °C for 3 d. After removal of the solvents by rotary evaporation, the residue was purified by silica gel column chromatography with ethyl acetate/dichloromethane (30:70, v/v) as eluent ($R_f=0.27$) to afford **3** in 48% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.25$ (m, 3H), 1.41 (t, $J=7.2$ Hz, 9H), 1.64–1.82 (m, 21H), 2.23 (m, 6H), 4.79 (q, $J=7.2$ Hz, 6H), 6.55 (br s, 3H), 7.37 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta=$ 184.3, 177.0, 134.1, 123.9, 91.5, 83.6, 69.6, 55.0, 38.1, 24.6, 23.2, 16.1 ppm; HMRS (ESI): *m/z*: calcd for $C_{48}H_{51}N_3NaO_9$: 836.3523 $[M+Na]^+$; found: 836.3349.

Synthesis of host 3: A solution of 3-dimethylamino-1-propylamine (100 mg, 98 mmol) in ethanol (10 mL) was added dropwise to a solution of **2** (200 mg, 0.24 mmol) in ethanol (20 mL) under stirring. Then the

temperature of the reaction mixture was warmed to 30 °C and maintained at that temperature for 4 d. The resulting precipitate was collected by centrifugation and purified by digesting twice with chloroform (10 mL). The insoluble material was dried in vacuo to afford **3** as an amorphous white solid in 82% yield. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.20 (m, 6H), 1.63 (m, 12H), 1.87 (t, J = 9.3 Hz, 6H), 2.08 (s, 18H), 2.20 (m, 12H), 3.50 (m, 6H), 7.37 (s, 3H), 7.45 (brs, 3H), 7.88 ppm (brs, 3H); ^{13}C NMR (75.4 MHz, [D$_6$]DMSO): δ = 183.9, 181.0, 169.2, 167.7, 134.2, 123.7, 93.9, 82.5, 79.6, 56.5, 54.0, 45.5, 42.2, 38.4, 29.1, 24.7, 23.0 ppm; HMRS (ESI): m/z: calcd for $C_{57}H_{75}N_9NaO_6$: 1004.5738 $[M+Na]^+$; found: 1004.5757.

Synthesis of host 4: Compound **4** was produced by following the above procedure, starting from **2** (100 mg, 0.12 mmol) and *tert*-butyl 12-amino-4,7,10-trioxadodecanoate (200 mg, 0.72 mmol). The initial precipitate was crystallised in chloroform/ethanol 8:2 v/v to afford **4** as a waxy off-white solid in 54% yield. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 1.30 (m, 3H), 1.38 (s, 27H), 1.55–1.71 (m, 15H), 1.89 (t, J = 10.0 Hz, 6H), 2.19 (d, J = 10.0 Hz, 6H), 2.40 (t, J = 6.0 Hz, 6H), 3.45–3.71 (m, 42H), 7.37 (s, 3H), 7.59 (brs, 3H), 7.98 ppm (brs, 3H); ^{13}C NMR (75.4 MHz, [D$_6$]DMSO): δ = 183.9, 181.0, 170.8, 169.1, 167.7, 134.2, 123.7, 93.9, 82.5, 80.1, 75.0, 70.2, 70.1, 66.7, 65.4, 54.0, 43.8, 38.4, 36.3, 28.2, 24.7, 23.0, 15.6 ppm; HMRS (ESI): m/z: calcd for $C_{81}H_{114}N_6NaO_{21}$: 1529.7935 $[M+Na]^+$; found: 1529.7954; elemental analysis calcd (%) for $C_{81}H_{114}N_6O_{21}$: C 64.52, H 7.62, N 5.57; found: C 64.01, H 7.37, N 5.70.

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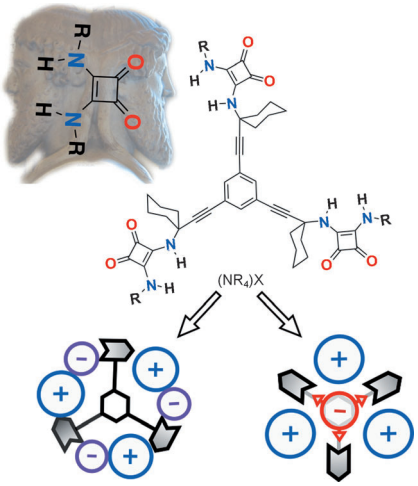
Two-faced hosts! Tripodal squaramide-based hosts form host–guest complexes with NR_4I compounds with stoichiometries of 1:1 to 1:3 (see scheme). However, in the presence of ammonium trimesoate compounds, the same host drastically changes its conformation to form a distinct 1:1 complex with the trimesoate anion. This property has been used to drive a controlled conformational transition of the host.



Molecular Janus Host

*B. Soberats, L. Martínez, E. Sanna, A. Sampedro, C. Rotger, A. Costa** ..... ▮▮▮▮–▮▮▮▮

Janus-Like Squaramide-Based Hosts: Dual Mode of Binding and Conformational Transitions Driven by Ion-Pair Recognition