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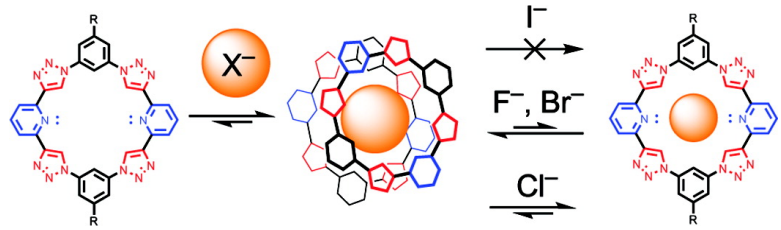

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Dipole-Promoted and Size-Dependent Cooperativity between Pyridyl-Containing Triazolophanes and Halides Leads to Persistent Sandwich Complexes with Iodide

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Encapsulation of a guest by the cooperative dimerization of a host to form "sandwich" complexes is an effective means to increase dimensionality[1] for optimizing complex stability. Lessons provided by crown ether binding with alkali metals[2] indicate the importance of a size difference between an ion and the cavity of the receptor for forming sandwiches. This mismatch provides a means to decrease the stability of the 1:1 complex (K_1) relative to the 2:1 (K_2). The relative magnitudes of K_1 and K_2 thereby provide insights into cooperative effects.[3] Only a few 2:1 sandwich complexes are known for anionic guests. Here, the 1:1 and 2:1 complexes are observed either depending upon the stoichiometry in solution[4] or solely as 2:1 complexes in the solid state.[5] Only an "anti-crown" mercuracarborand[6] shows only 2:1 sandwiches in solution with halides; however, the binding constants were not characterized. Cooperativity has been quantified[4] in two instances to result from interactions between receptors. Here we present findings on a new class of triazolophane[7] incorporating pyridyl ring systems (Figure 1) that forms strong and persistent 2:1 complexes with the large I^- ion in solution. Quantitative binding studies with F^-, Cl^-, and Br^- show both 2:1 and 1:1 complexes implicating the importance of the electronic character of the cavity in modulating cooperativity.

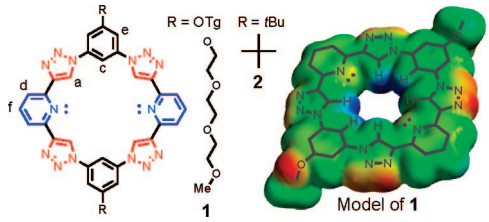

Figure 1. Representations of pyridyl-containing triazolophanes **1** and **2**, and the electrostatic potential surface of a model of **1** (blue sections represent regions of positive electrostatic character).

Prior studies on tetraphenylene-based triazolophanes[7,8] show size-dependent 1:1 binding with halides ($Cl^- > Br^- > F^- \gg I^-$), using only $CH\cdots X^-$ hydrogen bonding,[9] and a propensity for self-association. Molecular modeling indicated the I^- ion was not fully encapsulated. This tendency could lead[2] to dimerization-induced binding of iodide ions, yet the 2:1 complexes were not observed. To elaborate on this idea, pyridyl ring systems were considered as a replacement for the phenylenes. Pyridines have been used previously[8b,10] to alter the electronic character and size of binding sites. Consequently, compounds **1** and **2** were designed with pyridyl rings replacing the C-linked phenylenes in the west and east directions. Modeling (HF/3-21G) confirms the predictions: Pyridyls generate negative electrostatic potentials inside the cavity (Figure 1) and the cavity becomes oval (the vertical axis gets smaller by ~0.3 Å and the horizontal axis increases by >0.2 Å). We hypothesize that the cumulative effect of these features will destabilize the 1:1 complex in favor of the 2:1 sandwich.

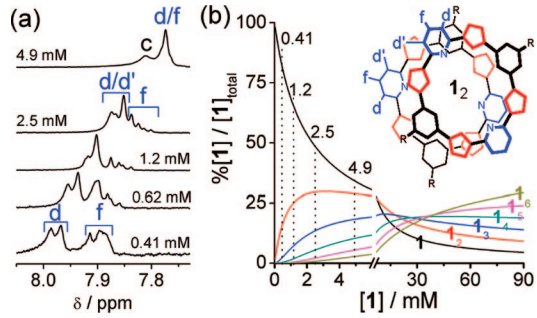

Figure 2. (a) ^{1}H NMR spectra of **1** (pyridyl region) as a function of concentration (CD_2Cl_2, 298 K, 400 MHz) and (b) calculated speciation curves for self-association up to the hexamer $\mathbf{1}_6$ with $K_E = 255\ M^{-1}$

The triazolophanes were prepared following prior methods[7] of symmetric chain extension followed by macrocyclization under conditions of high dilution and Cu(I) catalysis. The electrospray ionization mass spectrometry (ESI-MS) and ^{1}H NMR spectra confirm[11] the identity of the triazolophane.

Triazolophane **2** was only soluble as the tetrabutylammonium (TBA) salt: [$\mathbf{2}_2$•I]TBA. Crystals grown for X-ray analysis diffract weakly. A partial solution[11] shows (a) formation of the 2:1 sandwich with the I^- ion located between both triazolophanes, (b) the triazolophanes within π stacking distance (3.4 Å), and (c) that the angle of rotation (θ) between the two triazolophanes is ~56°.

The triazolophane **1** was examined in dichloromethane for its propensity to self-associate using both ^{1}H NMR (Figure 2) and UV studies.[11] The aromatic protons shift upfield with concentration (0.4−90 mM) indicating π-stacking and leading to the self-association constant,[11] $K_E = 255 \pm 70\ M^{-1}$. Consistently,[7b] continual changes in the diffusion coefficient[11] are observed from 2 to 100 mM. Modeling[12] of the equilibria shows that with increasing concentration (Figure 2b), the amount of monomer decreases and the dimer shows a maximum in its population at ~3 mM, thereafter, both species are replaced by higher order species. The splitting pattern in the pyridyl region of the ^{1}H NMR spectra (Figure 2a) agrees with this picture. At 0.41 mM, the pyridyl H^d and H^f protons are observed to form an A_2X spin system corresponding to the monomer **1**. This pattern transforms into an ABC spin system at 2.5 mM, which can arise when the two H^d protons are no longer equivalent as expected (inset, Figure 2b) from a rotated ($0° < \theta < 90°$), π-stacked pair of triazolophanes, $\mathbf{1}_2$. A doublet of doublets (H^f) sits upfield from the partially overlapping doublets of the inequivalent H^d and $H^{d'}$ protons. At 4.9 mM, a broad singlet replaces the ABC pattern indicating a shift to rapidly equilibrating higher-order aggregates. The UV spectra of **1** (2 μM−1 mM) show a decrease in the normalized intensities consistent with self-association.[7b] We attribute the rotated configuration in $\mathbf{1}_2$ to

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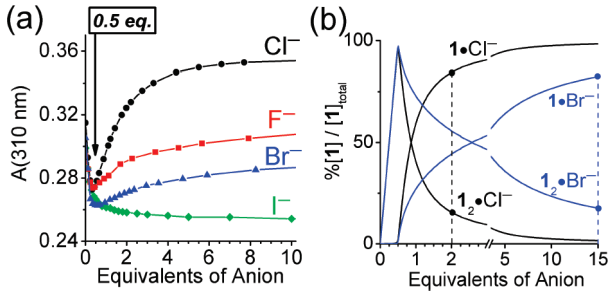


Figure 3. (a) UV binding curves for **1** (20 μM) with halides (CH_2Cl_2, 298 K) and (b) the speciation curves calculated[12] from K_1 and K_2 (Table 1) for Cl^- and Br^- at 5 mM.

electrostatic complementarity between the opposite dipoles on the pyridines (−2.4 D) and the triazoles (+5.0 D) of the triazolophane dimer pair.

Halide binding was investigated using UV titration (Figure 3a). Upon addition of F^-, Cl^-, and Br^- to **1** (20 μM) the absorbance decreases to a minimum at 0.5 equiv as a consequence of the π-stacked structure in the 2:1 complex. The absorbance then increases with the addition of more halide leading to the 1:1 complex. For I^-, the peak intensity decreases continuously during the titration. When repeated at 1 μM,[11] addition of F^-, Cl^-, and Br^- appears to proceed directly to the 1:1 complex while only I^- forms the 2:1 sandwich.

Table 1. Binding Energies (kcal mol^{-1}, ±10%) between **1** (20 μM) and the TBA Halides in CH_2Cl_2 Determined by Equilibrium-Restricted Factor Analysis of UV Titration Data

	ΔG_1 (K_1/M^{-1})	ΔG_2 (K_2/M^{-1})	ΔG (β_2/M^{-2})
F^-	−7.4 (275 000)	−7.6(380 000)	
Cl^-	−8.5(1 600 000)	−7.2(190 000)	
Br^-	−7.5 (315 000)	−7.9(580 000)	
I^-			$-14.9(8.6\times10^{10})$

Quantitative analysis of the UV titration data was conducted using an equilibrium-restricted factor analysis[13] of the entire wavelength range[11] to characterize the binding constants (Table 1). The models used the stepwise formation equilibria

$$\mathbf{1} + X^- = \mathbf{1}\cdot X^- \qquad K_1$$
$$\mathbf{1}\cdot X^- + \mathbf{1} = \mathbf{1}_2\cdot X^- \qquad K_2$$

or the direct formation of the sandwich complex

$$2\mathbf{1} + X^- = \mathbf{1}_2\cdot X^- \qquad \beta_2 = K_1 \times K_2$$

For the I^- ion, the best fit was obtained from the direct formation of the 2:1 dimer (β_2) at both concentrations. At the higher concentration, the titration data for F^-, Cl^-, and Br^- are best fit with the stepwise equilibria (K_1 and K_2): The data obtained from the 20 μM titration contains reasonable proportions of all three absorbers, **1**, $\mathbf{1}_2\cdot X^-$ and $\mathbf{1}\cdot X^-$, and is under moderate binding conditions,[14] therefore, it is more accurate than fitting the data at either lower (1 μM) or higher (5 mM, NMR) concentrations. The accuracy of these models was confirmed by inspecting the speciation curves calculated[11] from the K_1, K_2, and β_2 values. At 1 μM, these curves confirm that the 2:1 complex is present at <10%, consistent with its apparent absence in the fitting.

The relative values of K_1 and K_2, as well as the behavior of I^-, indicate[3] that positive cooperativity follows the order $I^- \ll Br^- < F^-$ whereas Cl^- displays negative cooperativity. The halides were defined as having two identical binding sites and the triazolophane with one binding site. Statistical binding would occur if $K_2 = K_1/4$ and deviations higher or lower signify positive and negative cooperativity, as observed. These cooperative effects were verified graphically utilizing linear Scatchard plots.[11,15]

The 2:1 complex $\mathbf{1}_2\cdot I^-$ is persistent in solution. To estimate the stepwise binding constants, speciation curves[11] were generated[12] for K_1 values while keeping β_2 constant. The NMR concentration of 2 mM was used to provide the greatest opportunity of observing the 1:1 complex. This approach generates upper and lower limits: K_1 < 3200 and K_2 > 32 000 000 M^{-1}. The former concurs with the K_1 value (5000 M^{-1}) for the related tetraphenylene triazolophane.[7b]

Solution structures of **1** with halides were characterized (Figure 4) by ^1H NMR spectroscopy (CD_2Cl_2, 400 MHz). While different chemical shift behaviors are observed for the various halides, each follows the calculated[11] speciation curves ([**1**] = 5 mM). Upfield and downfield shifts are attributed to the relative importance of π-stacking and halide binding, respectively. In the simplest case, titration of **1** with TBAI (Figure 4a) displays shifts in all positions up to the addition of 0.5 equiv consistent with 2:1 stiochiometry, $\mathbf{1}_2\cdot I^-$, as confirmed by a Job's Plot.[11] The stability of the sandwich complex is maintained in the presence of 150 equiv of I^-. The inner triazole (H^a) and phenylene (H^c) CH protons both shift downfield by ~0.2 ppm indicating the dominance of I^- binding on their positions.[7b] The outer protons on the pyridyl rings (H^d and H^f) shift modestly downfield while the phenylene H^e moves slightly upfield, showing the importance of π-stacking. Diffusion NMR is consistent with sandwich formation. Addition of 0.5 equiv of I^- steps the diffusion coefficient from 3.5 to 3.4 × 10^{-10} m^2 cm^{-1} where it stays up to 3 equiv.

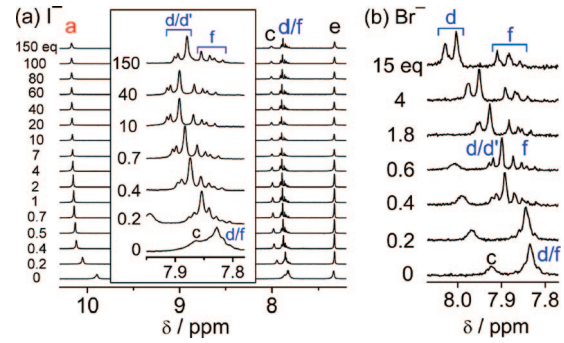


Figure 4. ^1H NMR spectra showing the titration of **1** (5 mM, CD_2Cl_2, 400 MHz, 298 K) with (a) I^- (inset, pyridyl region) and (b) Br^- (pyridyl region).

The solution structure of $\mathbf{1}_2\cdot I^-$ is consistent with dimer $\mathbf{1}_2$ and the preliminary crystal structure of [$\mathbf{2}_2\cdot$I]TBA. An ABC spin system for the pyridyl protons (inset, Figure 4a) indicates two rotated face-to-face triazolophanes. In support of this geometry, a $^1H-^1H$ ROSEY experiment shows through-space cross peaks from (a) the phenylene H^e and (b) both the α- and β-methylene protons on the OTg substituent to the pyridyl H^d and $H^{d'}$ protons. In the parent triazolophane, the distances are too large (>6.4 Å) to support an NOE. These observations indicate an average solution structure with a centrally located halide.

The TBACl and TBABr salts behave the same as TBAI up to ~0.5 equiv (e.g., Br^-, Figure 4b). Further additions indicate the shift from 2:1 to 1:1 complexes with the ABC spin system becoming replaced by the A_2X system. The relative intensities of these two spin patterns signify the population ratio between the 2:1 and 1:1 species. The point where the A_2X system dominates occurs at 2.0 equiv for the Cl^-,[11] whereas for the Br^- it is as late as 15 equiv, perfectly consistent with the differences in the speciation curves (Figure 3b, dashed lines) between these two halides.

In the case of TBAF, the titration behavior shows[11] a cross over to the A_2X system beyond 22 equiv. The *shifts* in the proton signals, however, are more complicated than in the Cl^- and Br^- cases. Beyond 0.5 equiv all the proton signals except H^e shift steadily upfield. The upfield shifts normally indicate increasing self-association. Molecular modeling (HF/3-21G)[11] indicates that in the 1:1 complex $\mathbf{1}\cdot F^-$, all six CH H-bond donors bind symmetrically with the F^- ion. Consequently, the proton shifts that occur upon transformation into the 1:1 complex are attributed to the conformational changes of **1** in addition to the effects of halide binding and dedimerization.

Complex formation was confirmed by ESI-MS. The ESI-MS is often taken to reflect the solution species present in solution.[4] The analysis[11] of solutions ([**1**] = 50 μM, CH_2Cl_2) with 2 equiv of Cl^- showed the peak for the 1:1 complex stronger than the 2:1. For the Br^-, the two peaks were equal. Under these conditions, the I^- sample retained the dominance of its 2:1 dimer peak. These observations agree with the calculated speciation curves[11] and the change from negative (Cl^-) to positive cooperativity (Br^-, I^-). A competition experiment for halide binding with **1** was conducted, in which a solution containing all four halides at 0.125 equiv was analyzed. The peak intensities indicate the relative stabilities of the sandwiches: $I^- \gg Br^- > Cl^-$. The F^- complexes were not observed. In the same spectrum, the 1:1 peaks followed $Cl^- > Br^- \approx I^-$. These observations again concur with the speciation curves.

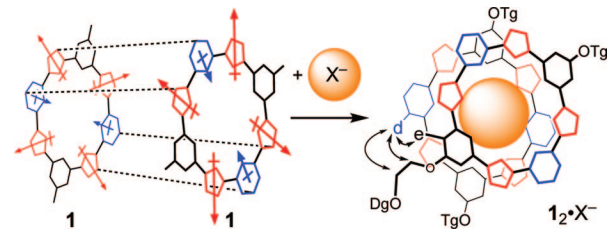
All of the titration data validate the accuracy of the K_1, K_2, and β_2 values and the presence of cooperativity. The propensity for 2:1 halide binding by the pyridyl triazolophanes can be best explained by comparison to the tetraphenylene ones.[7b] For the Cl^- and Br^- ions, the ΔG_1 values for **1** are 0.5 and 0.9 kcal mol^{-1} *lower*, respectively, than for the tetraphenylenes.[7b] Modeling (HF/3-21G)[11] shows both 1:1 complexes are planar with the halides fitting snugly inside the cavity. These observations confirm our hypothesis that the lone pairs of electrons on the nitrogens are acting in a destabilizing way. The fact that the 1:1 Br^- complex is more greatly affected is consistent with its larger size and therefore closer proximity to the nitrogen lone pairs.

In the case of F^-, the 1:1 complex is more stable by 0.3 kcal mol^{-1}, which is consistent with the centrally located F^- ion in **1**: Being able to engage with six CH H-bond donors rather than three, as is the case for tetraphenylenes,[7b] more than overcomes the repulsions from the pyridyl nitrogens. The K_2 value has been measured[13b] for a related tetraphenylene-triazolophane at -6 kcal mol^{-1}, which indicates that the 2:1 sandwich dimer has in fact gained in strength by $\sim$1.5 kcal mol^{-1} for **1**.

Lastly, I^- binding shows highly positive cooperativity. In contrast to the smaller halides, modeling (HF/3-21G) of the 1:1 complex shows[11] the iodide ion to be less encapsulated in $\mathbf{1}\cdot I^-$, relative to the tetraphenylene. This structural feature is a hallmark[2] for favoring sandwich complexes. A calculation on the 1:1 complex shows that the negative electrostatic potentials on the pyridyls are retained in the presence of the I^- ion. The increase in K_2, therefore, must stem from the novel configuration of the π-stacked and rotated pair of triazolophanes: Registration between opposite dipoles (pyridine and triazole), which guides the angle of rotation between dimers, also aids in partially extinguishing (Scheme 1) the pyridyl-based repulsions in the 2:1 sandwiches.

The smaller halides fit snugly inside the cavity and they all have similar 2:1 binding strengths (Table 1). Consequently, the dipole-stabilized dimers must be primarily responsible for their sandwich formation. Positive cooperativity is seen (F^-, Br^-) when the 1:1 binding strength is not significant enough to overcome the dimer's affinity. The F^- is too small and the Br^- too large for favorable 1:1 complexes. The Cl^- has large 1:1 binding strength to offset the dimer leading to slight negative cooperativity.

Scheme 1. Representations of the Opposite Dipoles Participating in the Formation of $\mathbf{1}_2\cdot X^-$[a]



[a] NOE cross peaks are labeled in $\mathbf{1}_2\cdot X^-$.

In conclusion, pyridyl units destabilize the 1:1 triazolophane complexes on account of the N:···:X^- electron pair repulsions. In the 2:1 sandwich complexes, the repulsions become reduced by partial cancelation of opposite dipoles. This phenomenon can only occur in the π-stacked dimers. These elements lower K_1 and increase K_2 turning on cooperativity. The size matching between F^-, Cl^-, and Br^- and the central cavity leads to modest cooperative effects. However, when these factors are coupled to a large size mismatch, highly positive cooperativity leads to the enhanced stability and persistent nature of the I^- sandwich complex.

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Supporting Information Available: Synthesis, characterization, titration, modeling, ESI-MS, and X-ray analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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