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# Aromatic and Aliphatic CH Hydrogen Bonds Fight for Chloride while Competing Alongside Ion Pairing within Triazolophanes

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**Abstract:** Triazolophanes are used as the venue to compete an aliphatic propylene CH hydrogen-bond donor against an aromatic phenylene one. Longer aliphatic C–H···$Cl^-$ hydrogen bonds were calculated from the location of the chloride within the propylene-based triazolophane. The gas-phase energetics of chloride binding ($\Delta G_{bind}$, $\Delta H_{bind}$, $\Delta S_{bind}$) and the configurational entropy ($\Delta S_{config}$) were computed by taking all low-energy conformations into account. Comparison between the phenylene- and propylene-based triazolophanes shows the computed gas-phase free energy of binding decreased from $\Delta G_{bind} = -194$ to $-182\ kJ\,mol^{-1}$, respectively, with a modest enthalpy–entropy compensation. These differences were investigated experimentally. An $^1H$ NMR spectroscopy study on the structure of the propylene triazolophane's 1:1 chloride complex is consistent with a weaker propylene CH hydrogen bond. To quantify the affinity differences between the two triazolophanes in dichloromethane, it was critical to obtain an accurate binding model. Four equilibria were identified. In addition to 1:1 complexation and 2:1 sandwich formation, ion pairing of the tetrabutylammonium chloride salt ($TBA^+ \cdot Cl^-$) and cation pairing of $TBA^+$ with the 1:1 triazolophane–chloride complex were observed and quantified. Each complex was independently verified by ESI-MS or diffusion NMR spectroscopy. With ion pairing deconvoluted from the chloride–receptor binding, equilibrium constants were determined by using $^1H$ NMR (500 μM) and UV/Vis (50 μM) spectroscopy titrations. The stabilities of the 1:1 complexes for the phenylene and propylene triazolophanes did not differ within experimental error, $\Delta G = (-38 \pm 2)$ and $(-39 \pm 1)\ kJ\,mol^{-1}$, respectively, as verified by an NMR spectroscopy competition experiment. Thus, the aliphatic CH donor only revealed its weaker character when competing with aromatic CH donors within the propylene-based triazolophane.

**Keywords:** anions · macrocycles · molecular modeling · receptors · supramolecular chemistry

## Introduction

Designing receptors that bind ions[1,2] is the cornerstone of supramolecular chemistry. While the field grew up around cations, the recognition of anions carries these early lessons forward.[3] Motivations for these investigations include sensing[4] in biological milieu and the extraction[5] of environmentally deleterious anions. These applications have a long history and they remain active endeavors. The designs begin by employing principles of host–guest chemistry[6] to enhance stabilizing forces (e.g., enthalpic gains of a hydrogen bond) and to moderate any destabilizing factors (e.g., competitive binding from countercations). The present work is designed to test the recent prediction by Hay and Pedzisa that aliphatic CH hydrogen-bond donors[7] form weaker hydrogen bonds than aromatic ones[8–16] by using triazolophane-based anion receptors[8] as the venue in which to host two types of competitions. The first contest involved identifying whether the chloride prefers to sit closer to the aromatic CH donor than to the aliphatic one. The second focused on comparing the chloride binding constants between triazolophanes that differ only in the replacement of a phenylene CH for a propylene one. To get an accurate evaluation of the affinities, it was determined that ion pairing[17] has to be deconvoluted from the receptor's actual anion binding affinity. To the best of our knowledge, this is the first time that such ion-pairing effects have been quantified in the supramolecular chemistry of anions. While the data favor

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the prediction by Hay and Pedzisa, the fight for chloride by the two triazolophanes is not without debate.

Triazolophanes **1**[8a] and **2** (Scheme 1) were designed to compare a phenylene hydrogen bond (CH···$Cl^-$) with a methylene-based ($-CH_2-$) one. Propylene substitution in **2** maintains the 24-membered macrocycle and the similarly sized cavity present in **1**. The rigidity, and therefore the conformational degrees of freedom, of **1** are expected to be similar in **2**. Gas-phase calculations on the binding of chloride to ethane,[7] benzene,[11] and triazolophane **1**[18] suggest that the $Cl^-$ binding energy with **2** will decrease by about 4% after propylene substitution.[19] These calculations also indicate that one linear C–H···$Cl^-$ hydrogen bond will form (rather than bifurcation) such that triazolophanes **1** and **2** will both display eight near-linear C–H···$Cl^-$ hydrogen bonds. These ideas suggest two hypotheses: I) Within triazolophane **2**, the phenylene C–H opposite the propylene will have a greater attraction for the chloride than the propylene's $-CH_2-$ group. II) In a competition between the two triazolophanes, compound **1** will have a stronger affinity for chloride than **2**. Computational studies on the gas-phase structures, the computed thermochemistry of binding ($\Delta G_{bind}$, $\Delta H_{bind}$, $\Delta S_{bind}$), including a correction for configurational entropy ($\Delta S_{config}$),[20] and experimental signal shifts in the $^1$H NMR spectra of **2**·$Cl^-$ were used to validate both of these hypotheses: Phenylene CH···$Cl^-$ hydrogen bonds are stronger than propylene within **2** and **1**·$Cl^-$ is more stable than **2**·$Cl^-$.

To experimentally distinguish a small change in receptor–chloride affinity, the existing methods of analysis needed to be improved as a means to obtain accurate binding constants. To this end, it was critical to gain a true representation of all of the binding equilibria occurring in solution, which are shown herein to be characterized by Equations (1)–(4), in which **M** = **1** or **2**.

$$\mathbf{M} + Cl^- = \mathbf{M}\cdot Cl^- \quad \text{1 : 1 complex} \quad (1)$$

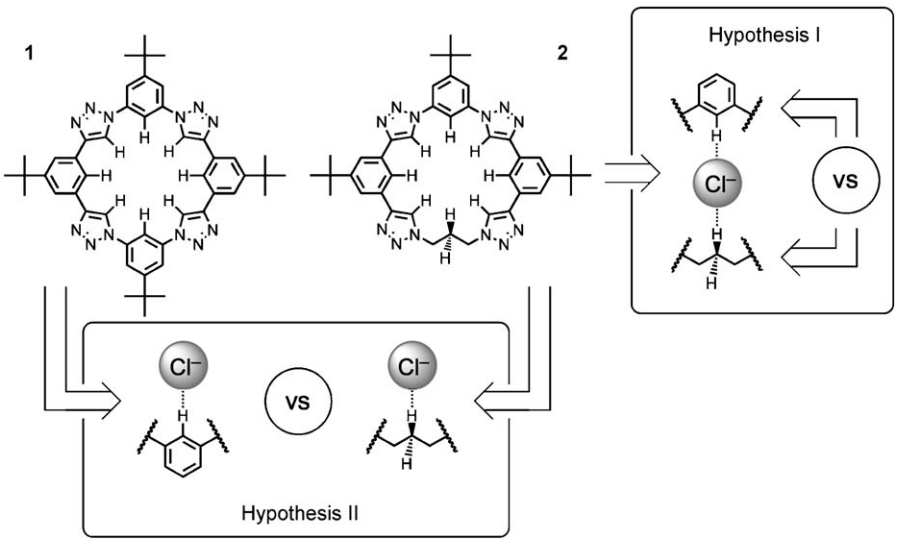
$$\mathbf{M}\cdot Cl^- + \mathbf{M} = \mathbf{M}_2\cdot Cl^- \quad \text{2 : 1 sandwich} \quad (2)$$

$$TBA^+ + Cl^- = TBA^+\cdot Cl^- \quad \text{salt ion pairing} \quad (3)$$

$$\mathbf{M}\cdot Cl^- + TBA^+ = \mathbf{M}\cdot Cl^-\cdot TBA^+ \quad \text{complex ion pairing} \quad (4)$$

Previously, we have shown that 2:1 sandwiches[8c] [Eq. (2)] need to be accounted for in addition to 1:1 complexes [Eq. (1)]. Furthermore, the model needs to include ion pairing[21] [Eq. (3)] in which the chloride resides more with its tetrabutylammonium ($TBA^+$) countercation than the receptor. The Fuoss law[21] tells us that the larger chloride–triazolophane complex, **M**·$Cl^-$, can also pair with the $TBA^+$ cation [Eq. (4)]. Quantitative analyses of ion pairing enjoyed a lot of attention in the binding of alkali metals by crown ethers with the aid of the colored picrate counteranion.[22] In anion–receptor chemistry, however, only qualitative treatments of ion pairing have prevailed.[17,23] While these approaches have yielded insights into ion pairs,[24] anion transport,[25] ion-pair receptors,[26] and opportunities for template-directed syntheses,[27] the effect of the countercation on anion recognition has never been quantified.

The ion-pairing problem, so well laid out by Roelens et al.,[28] is the absence of an accepted and general way to handle multiple equilibria at the same time, such as complexation [Eqs. (1) and (2)] and ion pairing [Eqs. (3) and (4)]. Pioneering work by the group of Roelens on tripodal ureidic receptors focused on the fitting of NMR spectroscopy titration data (chemical shifts versus equivalents of guest) using the software HypNMR.[29] The key challenge is to verify the existence of each solution species in an independent measurement. Otherwise, there is a risk of adding equilibria that may improve the fitted outcome, but are not actually occurring in solution. We follow this approach by using ESI-MS[30] to identify the anionic products **1**·$Cl^-$, $\mathbf{1}_2$·$Cl^-$, **2**·$Cl^-$, and $\mathbf{2}_2$·$Cl^-$. Diffusion NMR spectroscopy is a powerful technique to identify ion pairs,[31] and we use it here in a titration to verify the neutral species, **2**·$Cl^-$·$TBA^+$. Ultimately, this expanded model allowed us to obtain accurate affinities for the 1:1 binding of triazolophanes **1** and **2** with chloride by fitting the UV (50 μM) and NMR (500 μM)[29] spectroscopy titration data. Surprisingly, the binding free energies are the same to within experimental error, that is, we are unable to ascertain the winner. In an attempt to reconcile this outcome, the




Scheme 1. Phenylene (**1**) and propylene (**2**) triazolophanes and hypotheses I and II.

two receptors were placed in direct competition for chloride by means of an NMR spectroscopy titration: This time a draw was observed. Thus, quantitative confirmation of hypothesis II was not attainable even with the use of a high-fidelity model that improves greatly the accuracy (if not the level of uncertainty) of the binding constants obtained from titration analyses. Taken together, these studies support the proposition that propylene CH donors are weaker than phenylene ones based on hypothesis I.

## Results and Discussion

**Synthesis**: The propylene triazolophane **2** was synthesized (Scheme 2) through a combination of cross-coupling reactions[32] and $Cu^{I}$-catalyzed 1,3-dipolar cycloadditions (click chemistry)[33] from 1-*tert*-butyl-3,5-diiodobenzene (**3**). An excess (>6 equiv) of the diacetylene **5**, prepared via protected intermediate **4**, was allowed to react with diazide **6** to favor the formation of the 5/8 oligomer **7**. Subsequent macrocyclization with diazide **8** under high dilution conditions resulted in triazolophane **2** with a yield of 54%.

**Optimized gas-phase structures from DFT**: Computational studies on the triazolophanes and their 1:1 complexes in the gas phase corroborate the prior theoretical work by Hay and Pedzisa that aliphatic CH donors are weaker than aromatic ones.[7] The geometries of the low-energy conformations (Figure 1) of **1** and **2** and their complexes **1**·$Cl^-$ and **2**·$Cl^-$ were fully optimized at the B3LYP/6-31+G(d,p) level of theory. For triazolophane **2** (Figure 1a), there are four low-energy conformations within 9 kJ mol$^{-1}$ of the lowest-energy conformation. Upon formation of **2**·$Cl^-$, these conformations reorder such that the $C_s$-symmetric conformation, with its near-linear C–H···$Cl^-$ hydrogen bond (176°), becomes the most favored. Triazolophane **1** has a similar distribution of conformations (Figure 1b), within a smaller range, 3 kJ mol$^{-1}$, but upon formation of the complex **1**·$Cl^-$ they collapse down to a single $D_{2h}$-symmetric conformation. To account for these thermally accessible conformations, the enthalpy and entropy can be calculated from a Boltzmann weighted average of all of the low-energy conformers using Equation (5), in which $E = H$ or $S$, and $f$ denotes the weighted mole fraction of each conformer.

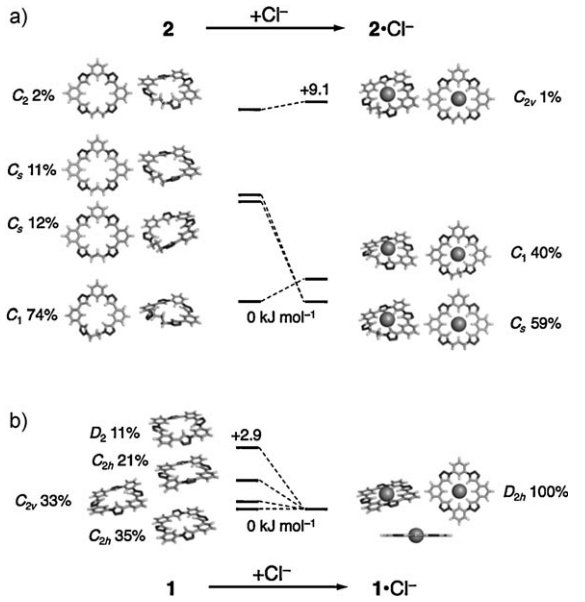
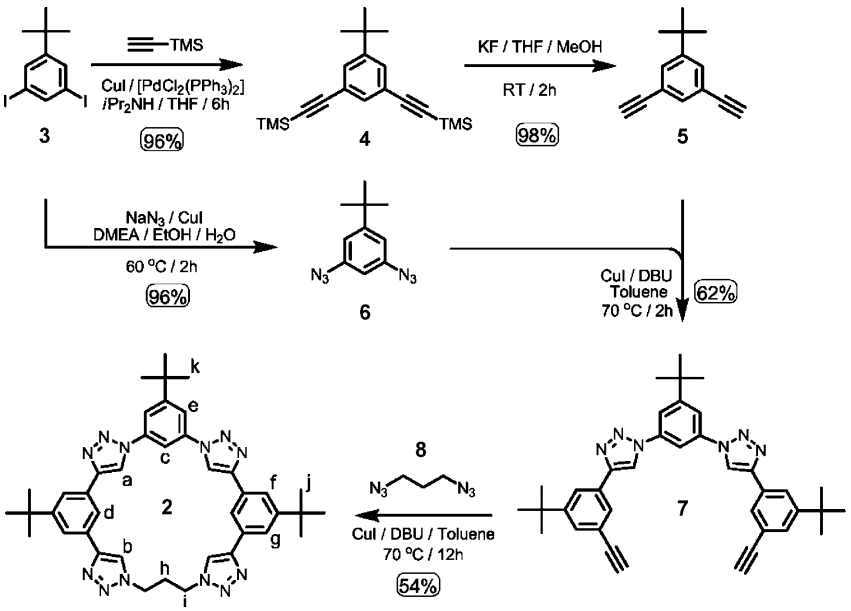



Figure 1. Optimized geometries (B3LYP/6-31+G(d,p)) and relative energies for the low-energy conformations of the triazolophanes a) **1** and b) **2** and their chloride complexes (symmetries and Boltzmann weight percents are annotated).

$$E = \sum_{i=1}^{n} (f_i E_i) \qquad (5)$$

The average structure of **2**·$Cl^-$ is dominated by the $C_s$ (59%) and $C_1$ (40%) conformations. The average geometry of **2**·$Cl^-$ shows the chloride is shifted away from the center and that the strongest interactions are again through the triazole, where the C–H···Cl bonds in one half of the macrocycle (2.62 Å) are slightly shorter on average than the two in the other half (2.69 Å). In the $C_s$ conformation, the aliphatic CH shows a contact distance with $Cl^-$ (3.02 Å), which




Scheme 2. Synthesis of propylene triazolophane **2**. TMS = trimethylsilyl, DMEA = *N*,*N*′-dimethylethylenediamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

is slightly longer than to the phenylene opposite (2.96 Å). For the $C_1$ conformation the propylene is barely involved in hydrogen bonding to the $Cl^-$ ion with both contacts longer than 3.4 Å. Regarding the entire structure, the presence of the chloride leads to a slight decrease in the puckering of each of the conformations of **2**·$Cl^-$ to maximize the strength of the C–H···Cl hydrogen bonds. However, significant residual puckering of the macrocycle remains. Overall, these observations support the argument that within **2**, the phenylene C–H is a stronger donor than the propylene C–H, which either forms longer hydrogen bonds ($C_s$) or almost none at all ($C_1$).

**Computational thermochemistry and enthalpy–entropy compensation**: Thermochemical calculations (B3LYP/6-31+G-(d,p)) for 1:1 complexation were performed to evaluate if stronger binding (enthalpy) exists with **1**·$Cl^-$ and to identify any entropy compensation[34] in the more flexible receptor (**2**). The presence of low-energy conformations predicates the use of weighted averages [Eq. (5)]. The enthalpy ($\Delta H_{bind}$) and entropy ($\Delta S_{bind}$) of binding are therefore defined as the change in the weighted average energy. For $\Delta S_{bind}$, these include changes to translations, rotations, and vibrations. The configurational entropy,[20] $\Delta S_{config}$, arising from any changes in the number of conformations was calculated by using Equation (6).

$$S = -R\sum_{i=1}^{n}(f_i \ln f_i) \qquad (6)$$

In the gas phase, chloride binding is enthalpy driven (Table 1) with the aliphatic substitution leading to a smaller value by about 6%, as expected.[19] Both triazolophanes receive entropy penalties, with the more rigid triazolophane **1** paying a slightly larger penalty, $(-T\Delta S_{bind}-T\Delta S_{config})=+36\ kJ\,mol^{-1}$, than propylene triazolophane **2**, $(-T\Delta S_{bind}-T\Delta S_{config})=+34.8\ kJ\,mol^{-1}$. This enthalpy–entropy compensation,[34] while consistent with expectations, is only modest. This observation is consistent with the high degree of rigid preorganization in these two classes of triazolophanes. The translational entropy is by far the largest entropy factor and is equivalent, as expected, for **1** and **2**. While the change in vibrational entropy favors chloride binding, it primarily corresponds to translational degrees of freedom being converted into vibrations. The configurational entropy was negligible for the propylene triazolophane **2** in which the conformational space before and after binding is largely unchanged (Figure 1a). With triazolophane **1**, an entropy cost of $+0.8\ kcal\,mol^{-1}$ results from the freezing-out of four conformations for the empty receptor into one in the complex **1**·$Cl^-$ (Figure 1b). Overall, the conformation-weighted gas-phase affinities ($\Delta G_{bind}$) are consistent with triazolophane **2** having weaker $Cl^-$ binding than **1**. Thus, the structural and thermochemical data are both consistent with hypotheses I and II.

Table 1. Calculated chloride binding energies [$kJ\,mol^{-1}$] for **1** and **2** in the gas phase (298 K).

| | $\Delta E$[a] | $\Delta H_{bind}$ | $-T\Delta S_{bind}$[b] | $=(-T\Delta S_{trans}$ | $-T\Delta S_{rot}$ | $-T\Delta S_{vib})$ | $-T\Delta S_{config}$ | $\Delta G_{bind}$[c] |
|---|---|---|---|---|---|---|---|---|
| **1** | −229 | −230 | 32 | 45.6 | 1.7 | −15 | 3.3 | −194 |
| **2** | −215 | −216 | 34 | 45.6 | −0.08 | −11 | 0.2 | −182 |

[a] $\Delta E$ at B3LYP/6-31++G(3d,2p) level of theory and all others at B3LYP/6-31+G(d,p). [b] $\Delta S_{bind}=\Delta S_{trans}+\Delta S_{rot}+\Delta S_{vib}$. [c] $\Delta G_{bind}=\Delta H_{bind}-T\Delta S_{bind}-T\Delta S_{configure}$

**Solution-phase characterization of the complexes with 2 by using $^1$H NMR spectroscopy**: The structures of triazolophane **2** and its $Cl^-$ complexes were characterized in $CD_2Cl_2$, utilizing $^1$H NMR spectroscopy to experimentally evaluate hypothesis I. With different donor arrangements in the molecule, two sets of triazole resonances, $H^a$ and $H^b$, were observed in the $^1$H NMR spectrum of **2** (Figure 2).

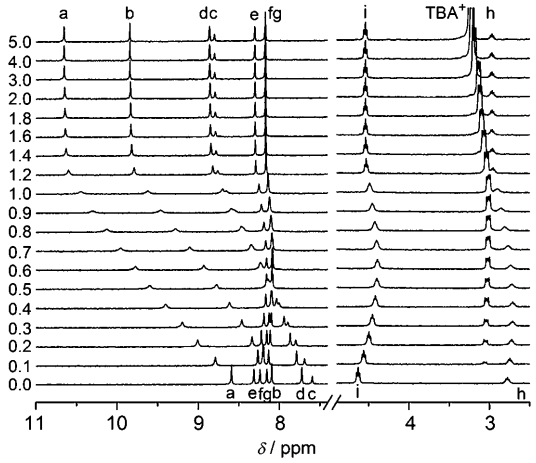



Figure 2. Partial $^1$H NMR spectra of triazolophane **2** (500 μM, $CD_2Cl_2$, 298 K) recorded upon titration with the TBA$^+$·$Cl^-$ (0–5 equiv).

Upon addition of TBA$^+$·$Cl^-$, these triazole signals, together with the interior phenylene C–H signals, $H^c$ (see Scheme 2 for proton labeling) and $H^d$, migrated steadily downfield until 1.2 equivalents of TBA$^+$·$Cl^-$ were added, which was consistent with the ultimate formation of a 1:1 complex [Eq. (1)]. All of the other triazolophane protons stopped moving at the same point in the titration, however, they showed one additional signal movement: Both propylene protons ($H^h$, $H^i$) and all the outer aromatic protons ($H^e$, $H^f$, $H^g$) displayed an upfield-then-downfield migration pattern with an inflection point at about 0.5 equivalents. This behavior corresponds to the formation of the sandwich complex **2**$_2$·$Cl^-$ [Eq. (2)]. The upfield shift arises from a greater sensitivity to the shielding that occurs from ring currents of the neighboring π-stacked triazolophane.[8c]

The weaker hydrogen bond with the aliphatic C–H donors in triazolophane **2** can be inferred by comparing the relative NMR signal migrations.[8b] The interior propylene

C–H$^h$ signal moved downfield from about $\delta = 2.8$ to ~3.0 ppm for 0 and 1.2 equivalents, respectively, consistent with hydrogen bonding. The presence of a single H$^h$ signal is attributed, with the aid of the computations (Figure 1a), to an averaged signal position arising from rapidly equilibrating low-energy conformations. These conformations show both hydrogen-bonded C–H and non-hydrogen-bonded C–H protons. Taking this average effect into account,[35] the signal migration of the inward facing propylene protons is still estimated[35] to be smaller than that observed for the phenylene C–H protons of **2** (H$^c$: $\Delta\delta = 1.2$ ppm, H$^d$: $\Delta\delta =$ 1.1 ppm) and those in compound **1** ($\Delta\delta = 0.9$ ppm).[8a,36] Thus, the propylene's protons are believed to have less contact with the Cl$^-$ ion than the phenylene CH. This finding and the fact that the triazole protons H$^a$ ($\Delta\delta = 2.1$ ppm) displayed a greater shift than those of H$^b$ ($\Delta\delta = 1.8$ ppm) indicate that Cl$^-$ is bound more tightly in one half of the molecule compared with the other.[36] Collectively, these NMR spectroscopy observations and the average calculated gas-phase structures support hypothesis I.

**Ion pairing and the solution-phase binding model**: To quantify the effect of the weaker propylene CH donor on the Cl$^-$ binding strengths of triazolophanes as a means to confirm or refute hypothesis II, it is imperative to use a model that accurately reflects reality. Thus, the next sections outline experiments that are used to identify and confirm the correct binding model. Herein, we started by employing the approach reported by Roelens et al.[28] to analyze the NMR spectra for some insights into additional equilibria. At first glance, a simple 1:1 and 2:1 binding model [Eqs. (1) and (2)] might appear to be consistent with all of the shifts in the triazolophane's protons (Figure 2). However, a second and even a third look reveals details that are a direct result of ion pairing involving the TBA$^+$ countercation. For instance, the α proton of the TBA$^+$ cation barely moves (Figure 3a) during addition of the first 1.2 equivalents ($\delta \approx 3.05$ ppm) and its position is strikingly similar to the free TBA$^+$ ($\delta =$ $(2.95 \pm 0.05)$ ppm).[37] On the basis of the known ion-pair association constant for TBA$^+$·Cl$^-$ in dichloromethane, 72 000 M$^{-1}$ ($\Delta G = -28$ kJ mol$^{-1}$, 298 K),[38] this observation indicates that chloride is bound more tightly by **2** than by the TBA$^+$ cation. Ion pairing between TBA$^+$ and Cl$^-$ [Eq. (3)], which only occurs after the receptor is saturated with Cl$^-$, is subsequently observed in the downfield movement of the α-TBA$^+$ signal towards the chemical shift position of TBA$^+$·Cl$^-$ ($\delta = (3.32 \pm 0.02)$ ppm, see the Supporting Information). Consequently, ion pairing of the salt [Eq. (3)] has to be included in the binding model.

A third look (Figure 3) at the TBA$^+$ signal indicates formation of the ion-pair complex **2**·Cl$^-$·TBA$^+$ [Eq. (4)]. During the addition of the first equivalent of TBA$^+$·Cl$^-$, the TBA$^+$ signal does not actually remain motionless, but migrates slowly upfield from $\delta = 3.06$ to 3.01 ppm towards a position beyond both the free TBA$^+$ and the ion-paired TBA$^+$·Cl$^-$ species. The upfield shift is consistent with partial shielding of the α-TBA$^+$ protons by the π ring currents of **2**·Cl$^-$ in an assumed facial approach to form **2**·Cl$^-$·TBA$^+$. Such shielding was also seen when the TBA$^+$ cation forms an ion pair with the aromatic-based anion tetraphenylborate ($\delta = (2.65 \pm 0.05)$ ppm, see the Supporting Information).[39] The stability of the contact ion pair **2**·Cl$^-$·TBA$^+$ is expected from Fuoss' law[21] to be smaller than TBA$^+$·Cl$^-$ on account of the larger size of the **2**·Cl$^-$ anion. By the same logic, the sandwich complex **2**$_2$·Cl$^-$ is also expected to ion pair with TBA$^+$, albeit with an even lower binding strength. No evidence for such a species was obtained at the concentrations examined herein. Consequently, three species involving TBA$^+$ will contribute to the average chemical shift positions observed throughout the entire titration (0–5 equiv).

Ultimately, a series of four equilibria [Eqs. (1)–(4)] with a total of seven possible solution-phase species are present at different stages throughout the entire titration (Figure 4). To the best of our knowledge, such a fine-grained picture that incorporates ion pairing has not previously been described in the study of anion recognition. Of the seven species, compound **2** and TBA$^+$·Cl$^-$ are added into solution, and both TBA$^+$ and Cl$^-$ ions are known from Equation (3) to be present in solution. Therefore, and in an extension to the work by Roelens et al.,[28] we present independent evidence of the charged complexes **2**·Cl$^-$ and **2**$_2$·Cl$^-$, and of the neutral **2**·Cl$^-$·TBA$^+$ ion-pair complex. After this expanded model is corroborated, only then can it be used with confidence to analyze the titration data as a means to accurately compare the chloride affinities of **1** and **2**.

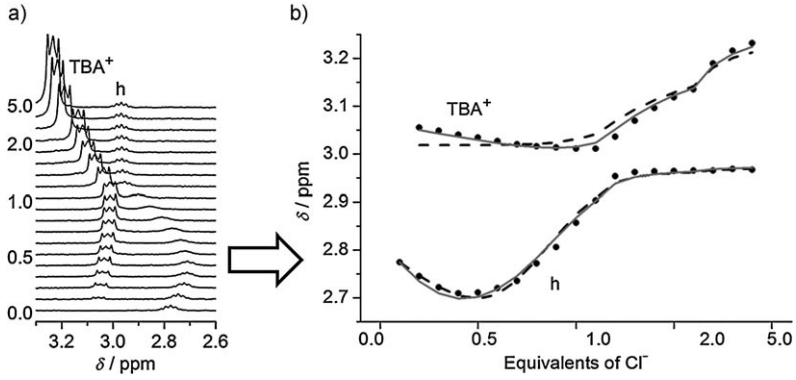



Figure 3. a) Partial $^1$H NMR spectra showing the signal movement of α-methylene protons of the TBA$^+$ cation and the H$^h$ propylene protons of **2** during titration with TBA$^+$·Cl$^-$. b) Signal positions (dots) for H$^h$ and H(α-TBA$^+$) and global fitting using the partial binding model [Eqs. (1)–(3), dashed black line] or the complete binding model [Eqs. (1)–(4), solid line]. Global fit includes the triazole (H$^a$, H$^b$), phenylene (H$^e$), propylene (H$^i$, H$^h$), and the TBA$^+$ protons.

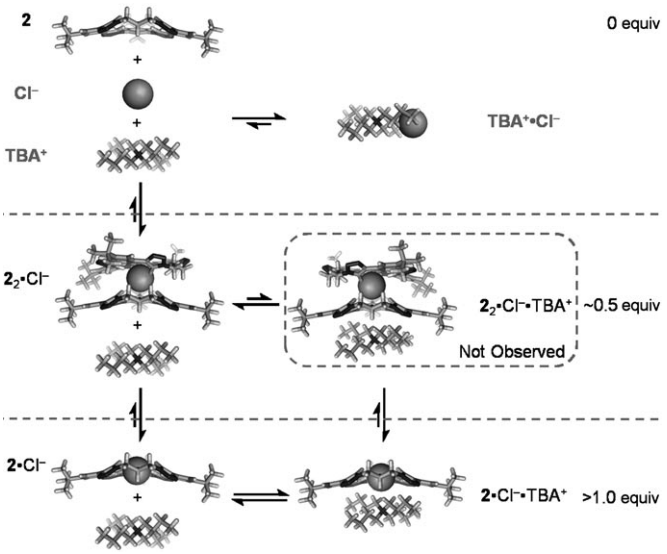



Figure 4. Representation of the solution-phase equilibria involved in triazolophane–chloride binding in dichloromethane. Conformations are not optimized.

**ESI-MS of charged species**: The negatively charged 1:1 and 2:1 complexes for triazolophane **2** were confirmed by ESI-MS analysis of a solution of $TBA^+ \cdot Cl^-$ (0.5 equiv) in dichloromethane at 25 μM (Figure 5). The solution-phase equilibria involving triazolophane **1** are expected to be similar to **2**[40] and the ESI-MS analysis shows the same 1:1 and 2:1 anionic species are present.

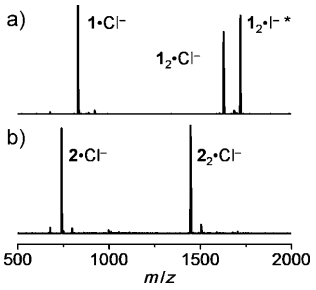



Figure 5. ESI-MS of solutions ($CH_2Cl_2$) with a) triazolophane **1** (25 μM) + $TBA^+ \cdot Cl^-$ (12.5 μM) and b) triazolophane **2** (25 μM) + $TBA^+ \cdot Cl^-$ (12.5 μM). *Impurity peak from ESI-MS.[41]

**Diffusion NMR spectroscopy evidence for the contact ion-pair complex**: Diffusion NMR spectroscopy titrations unambiguously verified the presence of the neutral ion-pair complex $\mathbf{2} \cdot Cl^- \cdot TBA^+$. By considering the inverse relationship [Eq. (7)][31a] between the average self-diffusion coefficients ($D$) and the hydrodynamic radii ($r_H$) of each species present at different stages in the titration (Figure 4), it is possible to distinguish the formation of the large supramolecular complex, $\mathbf{2} \cdot Cl^- \cdot TBA^+$, from the constituent smaller species, $TBA^+$ and **2**.

$$D = (kT)/(6\pi\eta r_H) \quad (7)$$

were $\eta$ is the viscosity. The diffusion coefficients of the individual constituent species were determined (see the Supporting Information) to facilitate the analysis of the average self-diffusion coefficients observed during the titration.

The diffusion coefficients ($\times 10^{-10}\ m^2 s^{-1}$, Table 2) observed from the $TBA^+$ protons follow the expected trends for the four equilibria [Eqs. (1)–(4) and Figure 4] and convincingly reflect the formation of $\mathbf{2} \cdot Cl^- \cdot TBA^+$.[42] On account of its smaller size and its involvement in only three species, the average diffusion coefficient of $TBA^+$ is more sensitive than those from the protons on **2**. The speciation curves calculated by using the binding constants (see Table 2 and Figure 6a) reflect this simplicity. Starting at $D = 10.6$ for $TBA^+ \cdot Cl^-$, the average self-diffusion coefficient of $TBA^+$ reaches its smallest value (9.0) at 1.0 equivalent where the fraction of $\mathbf{2} \cdot Cl^- \cdot TBA^+$ is at its maximum (Figure 6a) with respect to all other $TBA^+$-based species. Up to and beyond this point, the average self-diffusion coefficient of $TBA^+$ is

Table 2. Observed diffusion coefficients ($\pm 0.1 \times 10^{-10}\ m^2 s^{-1}$) generated from control and titration NMR spectroscopy experiments.

| | Triazolophane **2**[a] | $TBA^+$[b] |
|---|---|---|
| $TBA^+ \cdot Cl^-$ | | 10.6 |
| $TBA^+$ | | 10.6 |
| **2**[c] | 6.9 | |
| **2** + 0.5 equiv $TBA^+ \cdot Cl^-$[d] | 6.2 | 9.9 |
| **2** + 1.0 equiv $TBA^+ \cdot Cl^-$[d] | 6.2 | 9.0 |

[a] Average of $H^f$, $H^g$, and $H^i$ signals. [b] Average of α-$CH_2$ and terminal $CH_3$ signals. [c] [**2**] = 0.5 mM. [d] [**2**] = 1 mM.

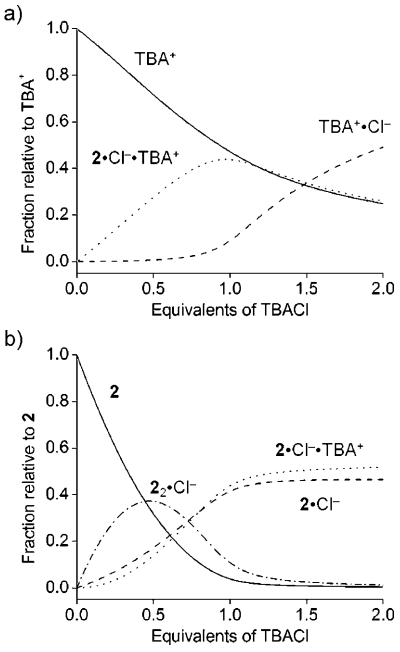



Figure 6. Simulated speciation curves using HySS ([**2**] = 1 mM) with respect to a) $TBA^+$ and b) triazolophane **2** using equilibrium constants obtained from NMR spectroscopic data fitting.

larger because the percentage of the smaller species $TBA^+$ or $TBA^+ \cdot Cl^-$ is greater than $\mathbf{2} \cdot Cl^- \cdot TBA^+$. The average self-diffusion coefficients for **2**, while less straightforward to analyze (see the Supporting Information), also follow the calculated speciation curves (Figure 6b).

**Binding constant determination from NMR spectroscopy and UV titrations**: With all of the solution species unambiguously verified, the equilibrium constants (Table 3) of the four equilibria for both triazolophanes **1** and **2** were quantified by utilizing equilibrium-restricted factor analyses. Global fitting of the NMR spectroscopy titration with triazolophane **2** using HypNMR[29] was based on the chemical shifts of the triazole protons ($H^a$, $H^b$), the outer proton on phenylene ($H^e$), the two propylene protons ($H^h$ and $H^i$), and the α-$CH_2$ protons of $TBA^+$. The literature value of the $TBA^+ \cdot Cl^-$ ion-pair association constant[38] was used as a fixed value in the fitting. The agreement between the measured and modeled chemical shift positions obtained from the fitting improved with the addition of each equilibrium into the model (see the Supporting Information). For example, the aforementioned upfield-then-downfield movements in the α-$TBA^+$ proton were only reproduced (Figure 3b) upon addition of the equilibrium for the $\mathbf{2} \cdot Cl^- \cdot TBA^+$ ion-pair complex [Eq. (4)]. As a means to corroborate the equilibrium constants generated for **2** from the HypNMR analysis, a UV titration was conducted at a lower concentration (50 μM, $CH_2Cl_2$). The UV titration data (275–340 nm) of both triazolophanes **1** and **2**[43] were then fitted according to the same set of four equilibria by using the software Sivvu.[8d,44] The equilibrium constants generated from both NMR spectroscopy (500 μM) and UV (50 μM) titrations for triazolophane **2** agree with each other to within experimental error (Table 3). The fact that reproducible values were obtained from different titrations conducted at different concentrations and with different techniques attests to the accuracy of the model Equations (1)–(4).

Table 3. Free energies [kJ mol$^{-1}$] and equilibrium constants [M$^{-1}$] for triazolophanes **1** and **2** in dichloromethane generated from data fitting.

| | $\Delta G(\mathbf{1})$[a] (UV) | $\Delta G(\mathbf{2})$[a] (UV) | $\Delta G(\mathbf{2})$[b] (NMR) |
|---|---|---|---|
| Eq. (1) | $-38 \pm 2$ | $-39 \pm 1$ | $-38 \pm 1$ |
| | $4.7 \pm 2.1 \times 10^6$ | $5.6 \pm 1.9 \times 10^6$ | $4.0 \pm 0.8 \times 10^6$ |
| Eq. (2) | $-32 \pm 2$ | $-22 \pm 3$ | $-21 \pm 1$ |
| | $4.9 \pm 2.7 \times 10^5$ | $7.2 \pm 5.0 \times 10^3$ | $4.0 \pm 0.8 \times 10^3$ |
| Eq. (3) | $-28 \pm 3$[c] | $-28 \pm 3$[c] | $-28 \pm 3$[c] |
| | $7.2 \pm 5.0 \times 10^4$ | $7.2 \pm 5.0 \times 10^4$ | $7.2 \pm 5.0 \times 10^4$ |
| Eq. (4) | $-22 \pm 2$ | $-23 \pm 3$ | $-19 \pm 1$ |
| | $7.2 \pm 3.2 \times 10^3$ | $1.4 \pm 0.8 \times 10^4$ | $2.5 \pm 0.5 \times 10^3$ |

[a] UV titration data, 50 μM. [b] NMR spectroscopy titration data, 500 μM. [c] Fixed at $-28$ kJ mol$^{-1}$.[38]

The NMR spectroscopy titration data for **1** (Figure 7) was unsuitable for fitting on account of signal broadening. However, the binding constants obtained from fitting the UV titration data on triazolophane **1** helped to interpret, for the first time, some of the features in the NMR spectroscopy titration (Figure 7a).[8a] All of the triazole and phenylene signals sharpened and stopped shifting upon the addition of four equivalents of $TBA^+ \cdot Cl^-$. By contrast, triazolophane **2** (0.5 mM), which has a similarly strong 1:1 $Cl^-$ affinity, stopped changing at 1.2 equivalents of $TBA^+ \cdot Cl^-$. These observations are consistent with the greater propensity of triazolophane **1** to form 2:1 sandwich complexes, as observed in the speciation curves (Figure 7b). Therefore, complex $\mathbf{1}_2 \cdot Cl^-$ persisted beyond two equivalents, whereas nearly all of the $\mathbf{2}_2 \cdot Cl^-$ sandwich was driven to its 1:1 complex $\mathbf{2} \cdot Cl^-$ with only a small excess of $TBA^+ \cdot Cl^-$ (Figure 6a).

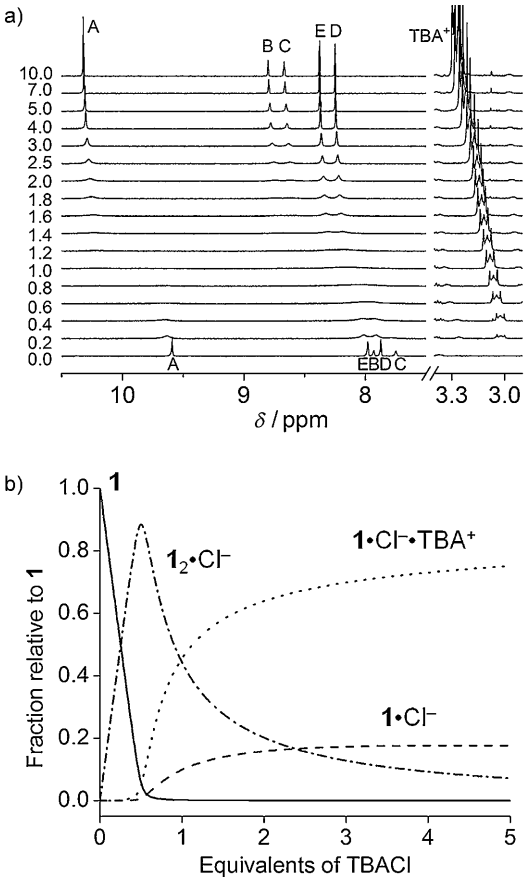



Figure 7. a) Partial $^1$H NMR spectroscopy titration data of triazolophane **1** (2 mM, $CD_2Cl_2$) with $TBA^+ \cdot Cl^-$, as published in reference [8a]. b) Simulated speciation curve at the corresponding NMR spectroscopy titration concentration with equilibrium constants obtained from UV data fitting ([**1**] = 2 mM).

The 2:1 sandwich complex with **1** displayed a much higher stability than **2** ($-32$ vs. $-22$ kJ mol$^{-1}$). Both triazolophanes display negative cooperativity. Presumably, the greater planarity of the complexes with **1** retains more effective π stacking to facilitate formation of sandwiches.[8c]

The stability of the ion-pair complexes ($\mathbf{M} \cdot Cl^- \cdot TBA^+$, $K \approx 10000$ M$^{-1}$) for both triazolophanes are lower than the parent $TBA^+ \cdot Cl^-$ ion pair. This observation is fully consistent with the expectations from Fuoss' law[21] on account of the significant size difference between the $Cl^-$ anion and the anionic $\mathbf{M} \cdot Cl^-$ complexes. Speciation curves were calculated for some typical concentrations used in NMR and UV/Vis

spectroscopy titrations (see the Supporting Information) to identify when each species becomes an important component of the solution. For both **1** and **2**, the ion-pair complexes, **M**·$Cl^-$·$TBA^+$ [Eq. (4), $K \approx 10000\,M^{-1}$], are negligible at 10 μM, but become increasingly significant at the typical concentrations used for UV (50 μM) and NMR (>500 μM) spectroscopy titrations. From these speciation curves, we infer that the concentration used for quantifying multiple equilibria is just as important as the right technique[45] to guarantee that a reasonable amount of the constituent species can contribute to the titration data being analyzed. As noted by others,[17] higher dielectric solvents can be selected to minimize ion pairing and simplify the solution-phase equilibria, but this assumption itself has to be independently verified.

**Chloride binding in 1 and 2 and hypotheses I and II**: Looking first at the 1:1 complexes, replacing the phenylene in **1** with a propylene CH donor in **2** was found, within experimental error, to have no effect on the receptor's affinity for chloride. To corroborate this unexpected finding, an NMR spectroscopy competition experiment was conducted (see the Supporting Information). The protons from **1** and **2** were observed to start and stop moving at the same stage during the titration consistent with the similar binding affinities.

Consistent with hypothesis I, the calculated structure (Figure 1) of **2**·$Cl^-$ indicates that the propylene CH forms a longer, and therefore, weaker hydrogen bond with $Cl^-$ than the phenylene one.[18] The computed gas-phase thermochemistry (Table 1) is consistent with hypothesis II, such that **2** forms a less stable 1:1 complex with chloride than **1**. All of the relative signal shifts in the NMR spectra of **1** and **2** support hypothesis I. However, the use of an accurate and self-consistent binding model [Eqs. (1)–(4)] to quantify the 1:1 binding affinity showed that this weaker hydrogen bond did not lead to a demonstrable change in the free energy of binding, that is, evaluation of hypothesis II could not be precisely determined. The competition NMR spectroscopy experiment provided the same result: no difference. An alternative interpretation is that the stability of the complexes **1**·$Cl^-$ and **2**·$Cl^-$ are actually the same. To support this position, solvation would have to have a more influential role on the entropy–enthalpy compensation than was established in the gas-phase calculations. Ultimately, the sum of all the observations concurs with Hay's prediction that the propylene CH is a weaker donor than the phenylene.

## Conclusion

In a series of competition experiments, aromatic phenylene donors were shown to be stronger than aliphatic propylene C–H groups. Gas-phase calculations and $^1H$ NMR spectroscopy on the triazolophane–chloride complexes were consistent with this conclusion. The generation of a self-consistent model of all the binding equilibria occurring in solution was determined for the first time to quantify the stabilities of the chloride–triazolophane complexes. The model equilibria included the frequently overlooked contribution of ion-pair formation between the 1:1 complex and the countercation as well as ion-pair competition. The precision of the resulting association constants was larger than that required to distinguish between the hydrogen-bond strengths revealed in the structural analyses (calculations and NMR spectra). The greater accuracy provided by such models will be critical for quantitatively examining the design of new receptors.

## Experimental Section

Details of the general methods; syntheses; and compound characterization, computations, titration and data fittings; and simulated speciation curves can be found in the Supporting Information.

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[36] The magnitude of complexation-induced signal migrations ($\Delta\delta$/ppm) for both triazole protons and internal phenylene protons qualitatively correlate to the calculated average H···Cl$^-$ distances ($d$/Å). Order of contact distance: $H^a < H^b < H^c < H^d < H^h$; order of signal migration: $H^a > H^b > H^c > H^d > H^h$. However, it is worthwhile to point out that the magnitude of signal migrations might not be solely dependent on the contact distance.
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[41] An additional signal for triazolophane **1** was observed corresponding to the iodide sandwich **1**$_2$·I$^-$, but not with triazolophane **2** under the same conditions. The iodide sandwich was believed to result from scavenging in the ESI-MS experiment, as seen previously. A competition experiment using ESI-MS (see the Supporting Information), in which 25 μM of **1** and **2** are analyzed in the presence of

  

$TBA^+ \cdot Cl^-$, showed the $\mathbf{1}_2 \cdot I^-$ complex but not $\mathbf{2}_2 \cdot I^-$. Formation of iodide sandwich with triazolophanes has been seen before, see reference [8c].

[42] Evidence for $\mathbf{2}_2 \cdot Cl^- \cdot TBA^+$ from diffusion NMR spectroscopy is weak. On the basis of Fuoss' law,[21] the ion pairing is expected to be too weak in a titration experiment at 1 mM. When titration experiments are conducted at even lower concentrations, the population of $\mathbf{2}_2 \cdot Cl^- \cdot TBA^+$ will be smaller still. Therefore, the quantitative NMR (500 μM) and UV (50 μM) spectroscopy titrations have been modeled with the four primary equilibria [Eq. (1)–(4)]. Consistently, global fitting of the NMR spectroscopy data (see the Supporting Information) shows that addition of the fifth equilibrium for the formation of $\mathbf{2}_2 \cdot Cl^- \cdot TBA^+$ had no effect on the outcome of the fitting.

[43] The NMR spectroscopy titration data for triazolophane **1** (Figure 7a)[8a] was not applicable for HypNMR fitting on account of significant signal broadening.

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