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Do CH–Anion and Anion–π Interactions Alter the Mechanism of 2:1 Host–Guest Complexation in Arylethynyl Monourea Anion Receptors?

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Abstract

Selective tuning of arylethynyl urea scaffolds for anionic guests requires an understanding of preferred binding motifs of the host–guest interaction. To investigate the binding preference of receptors without a pre-organized binding pocket, two electron-deficient phenylacetylene receptors with a single urea moiety have been prepared and were found to bind halides as 2:1 host–guest complexes that feature key CH–anion or anion–π interactions. These supporting interactions also appear to influence the mechanism of the 2:1 binding event.

Keywords

anions; host–guest systems; hydrogen bonds; supramolecular chemistry

For the past few decades, the field of anion sensing has been dominated by supramolecular receptors.[1] Supramolecular hosts have been shown to bind anionic guests through a variety of host–guest interactions, including anion–π interactions, hydrogen bonds, and weak σ interactions.[1–3] Disregarding the larger molecular structure or type of guest, supramolecular hosts are currently designed to include some degree of preorganization and an attractive binding pocket.[1,2,4] Ideally, such probes can be easily tuned for analyte specificity and optoelectronic responses.[1–5]

Arylethynyl urea scaffolds make up the foundation of the supramolecular anion-sensing scaffolds in our studies. A preorganized binding cavity is formed by a rigid alkyne linkage between arene rings and urea-based hydrogen-bond (HB) donors.[6,7] The easily

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Conflict of interest

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functionalized core and pendant arenes are strategic designs, because they can be modified with electron-donating or electron-withdrawing substituents to modulate the acidity of the HB donors.[7b] Our previously reported arylethynyl bis-urea (e.g., **1**) and tris-urea receptors (**2**) have exhibited a variety of binding motifs for anions.[6–9] The majority of the bipodal hosts bind anions by aryl CH or pyridinium HB donors at the core of the host, with the urea groups forming a U-shaped pocket that dominates the binding event, as shown in Figure 1.[7,8] This binding pattern is altered in trifluorophenyl tripodal receptor **2**, however, in which anion–π interactions influence selectivity in favor of binding nitrate over chloride.[9] Furthermore, the crystal structure of the tris-urea host indicated that only two of the three available urea "arms" were interacting with an anionic guest.[9] This suggested that the number of urea donors may influence anion binding as much as the type of binding motif utilized in the host–guest interaction. Anion–π interactions have been observed in a myriad of receptors, and the ability to tune arenes to increase their selectivity for anion–π binding has been shown in other arene-based hosts.[1,9,10]

To elucidate both the degree of tunability of the anion-binding motifs and the number of arylethynyl urea recognition elements necessary to bind an anion, we designed mono-urea host scaffolds **3** and **4** (Figure 1). The single "arm" permits more aggressive tuning of the arene core than what is synthetically accessible on the bis-arylethynyl scaffold, and the increased rotational freedom around the single ethynyl unit permits the core arene to rotate to facilitate the preferred binding motif (i.e., anion–π, aryl CH H bond, or weak σ interactions). Berryman et al. utilized dinitro-substituted arenes in a tris-arene scaffold to host anions.[11] It was calculated that the 3,5-dinitro groups sterically block the aryl CH, preventing an H-bond interaction between the phenyl core and an anionic guest.[11] With the additional rotational freedom of scaffold **3**, we hypothesized that the 3,5-dinitrobenzene substitution pattern would promote anion–π or weak σ interactions between the host scaffold and an anionic guest. Similarly, the pentafluoroarene scaffold **4** was inspired by the trifluorophenyl tripodal receptor **2**.[9] We hypothesized that the combination of an electron-deficient aromatic ring and the removal of aryl H-bond donors would result in a scaffold that hosts anionic guests exclusively through an anion–π interaction in combination with the urea HB donors.

Monopodal hosts **3** and **4** were synthesized as shown in Scheme 1. Desilylation of known ethynylaniline **5**[8b,f] and subsequent Sonogashira cross-coupling with 1-iodo-3,5-dinitrobenzene or iodopentafluorobenzene gave cores **6** and **7** in 87 and 73 % yield, respectively. Reaction of **6** or **7** with *p*-nitrophenyl isocyanate gave receptors **3** and **4** in 73 and 71 % yield, respectively. The final compounds were fully characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, and 2D $^{1}H/^{13}C$ heteronuclear single quantum coherence (HSQC) NMR spectroscopy was used to assign the aryl and urea proton resonances of **3**.

The anion-binding characteristics of **3** and **4** were investigated with tetrabutylammonium (TBA) halide salts in 10 % DMSO/$CHCl_3$ or the perdeutero equivalent. Titration experiments were performed at 1.0 mM concentration of chosen host (Figure 2).[12] Association constants (K_a) for **3** and **4** with halides Cl^-, Br^-, and I^- were calculated by using non-linear regression, non-cooperative fitting models in MatLab by simultaneously fitting

the downfield shifting of the urea protons (H^b, H^c for **3**; H^a, H^b for **4**).[13] The internal aryl proton (H^a) resonance shifts were also included in the fitting of **3**.

Titrations were initially fit to a 1:1 host–guest model, but residual errors were large, indicating a poor fit. In addition, the serpentine-like shift of urea proton H^c in the titrations of **3** hinted at the possibility of higher-order binding stoichiometry (Figure 2a).[14–16] Job's plot analysis revealed a 2:1 host–guest model might be more appropriate for the binding stoichiometry (see the Supporting Information). Indeed, titrations fit to a 2:1 host–guest model provided minimalized residual errors.[15] The previous arylethynyl urea probes studied by our lab included at least two urea-recognition motifs to host a guest anion, and the fit of the mono-arylethynyl urea probes **3** and **4** to a 2:1 host–guest system further signifies the necessity of including multiple urea recognition motifs in a scaffold's design.

The stepwise K_a1 and K_a2 values for both **3** and **4** with the various halides were determined across three titrations with less than a 15 % error (Table 1). The K_a1 values for **3** are within error of each other, but the K_a2 values increase by an order of magnitude with increasing guest size. The trend could be related to the ability of the recognition scaffolds to donate increasingly linear hydrogen bonds in the assembled binding pocket. Interestingly, there is a clear statistically significant difference in the K_a1 values for **4** with the halides, and the overall trend of association constants appears to be opposite in **4** versus **3**; that is, in **3** there is a slight reverse Hofmeister trend in anion binding of $I^- > Br^- > Cl^-$, and in **4** the opposite is true: $Cl^- > Br^- > I^-$. The change in anion preference could be due to the formation of an anion–π interaction in **4**·X^-, and the smaller anions are capable of a closer interaction with the π systems.[2] The preference for larger halides in **3** could be the result of both aryl CH hydrogen bonds becoming more linear, increasing the strength of the interactions.

The order, in which the anion binds the two hosts, could shed additional light on the nature of the interactions of these hosts with anions. There are two likely mechanisms, in which a 2:1 host–guest complex can form: two hosts associate, then an anion binds in the dimer pocket (Figure 3a), or one host binds the anion, followed by a second host binding the 1:1 complex (Figure 3b).[13,14] If a complex initially dimerizes/aggregates, the K_a1 value would likely be independent of the nature of anion present; this rings true for scaffold **3**. Additionally, these K_a1 values are on the same order of magnitude as the dimerization constant for **3** in the absence of an anion/salt, suggesting that K_a1**3** might resemble a receptor dimerization event.[18] It is also possible the supporting "weak" interaction in **3** (e.g., CH anion from the dinitrophenyl ring) creates a competing trend in anion binding that prefers the softer iodide over chloride/bromide, and thus mechanism (b) is still at play, but this competing selectivity cancels the anion-binding dependence in K_a1.

The 2:1 assembly situation is much more clear for the anion complexes of **4**. Both K_a1 and K_a2 values of **4** change across the anion series, as was predicted by relative anion basicity, supporting the 2:1 complex forming via a step-wise mechanism dominated by traditional hydrogen-bonding interactions with the ureas and possible supporting anion–π interactions with the pendant pentafluorphenyl rings (Figure 3b).

The 2:1 host–guest stoichiometry was further confirmed in the solid-state by X-ray crystallography. Single crystals of **3** grown in the presence of TBA^+Br^- were obtained by slow evaporation from $CHCl_3$/DMSO.[19] Two receptors asymmetrically encapsulate the Br^- atom through a total of six weak hydrogen bond contacts (Figure 4). Each receptor donates two hydrogen bonds through the urea moiety, and another weak CH hydrogen bond through the dinitrophenyl core with distances N^d–Br 3.27(1) Å, N^c–Br 3.63(2) Å, C^b–Br 3.62(2) Å, $N^{d'}$–Br 3.29(2) Å, $N^{c'}$–Br 3.64(2) Å, and $C^{b'}$–Br 3.69(2) Å; and angles N^d-H^d···Br 141.3(4)°, N^c-H^c···Br 146.3(2)°, C^b-H^b···Br 161.8(6)°, $N^{d'}$-$H^{d'}$···Br 172.6(4)°, $N^{c'}$-$H^{c'}$···Br 151.2(9)°, and $C^{b'}$-$H^{b'}$ ···Br 133.3(1)°.

Although previous calculations predicted the aryl CH HBs would be inaccessible due to the steric hindrance of the nitro substituents,[11] the importance of aryl CH HBs is not lost in the crystal structure of scaffold **3**. The ability for two equivalents of **3** to encapsulate an anionic guest by six weak hydrogen bonds also contributes to the large association constants seen in the solution-state studies. Though solid-state data has yet to be obtained, it is reasonable to hypothesize that **4** shows a similar binding interaction as **3**, with the CH HBs replaced by anion–π interactions, because **4** lacks CH HB donors. A color change was not seen upon the addition of anion, indicating that a weak σ interaction/charge-transfer complex is not involved. This lends further credence to our speculation that anion–π is the most probable supporting interaction in the host–guest complex of **4**, whereas CH–anion interactions are present in **3**. An anionic guest can interact with **4** through two anion–π interactions, along with the four urea HB donors.

In summary, the solid-state data in combination with the solution-phase K_a values provided a convincing argument for the necessity of at least two urea recognition motifs in a strong arylethynyl receptor scaffold. The inclusion of a phenyl core with the ability to host an anionic guest by an aryl CH HB or an anion–π interaction also appears to influence the order of the halide binding within the self-assembled binding pocket. Further research on the effect of cooperativity of these monopodal arylethynyl urea scaffolds is currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Host concentration for titrations of 3 with TBA^+Cl^- was held constant at 0.4 mM. All other titrations were performed with host concentration of 1.0 mM.
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16. During the titrations of 3, the saturation point was determined by loss of signals of urea protons H^c and H^b. Further analysis with a 2:1 host–guest system indicates NMR time-scale averaging across two asymmetric probes binding to a single guest. This is consistent with the conformation and stoichiometry found in the crystal structure shown in Figure 4.
17. Value is at the limit of detection provided by ^1H NMR titrations and would be more appropriately determined by UV/Vis spectroscopy.[10,11] The μM concentrations needed to obtain UV/Vis spectroscopy titration data dilute out the expected 2:1 host–guest model, however, leading to titrations only appropriately fit to a 1:1 host–guest model. Association constants determined by these UV/Vis titrations gave a K_a of 32800 M^{-1} (see the Supporting Information).
18. Value of K_{dimer} 3 is 500 M^{-1}. Although the experiments were done in the same solvent system, it is important to note that the dimerization constants were determined in a solution with different ionic strengths compared to the titrations that produced the association constants. Additionally, the concentration at which the titrations were performed is low, leading to approximately 10 % of

"free" (non-anion-bound) dimer formed in solution at any given time. Thermodynamic equilibria could drive more dimer to form to promote the sandwich-like interaction with the anion.

19. CCDC 1507418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

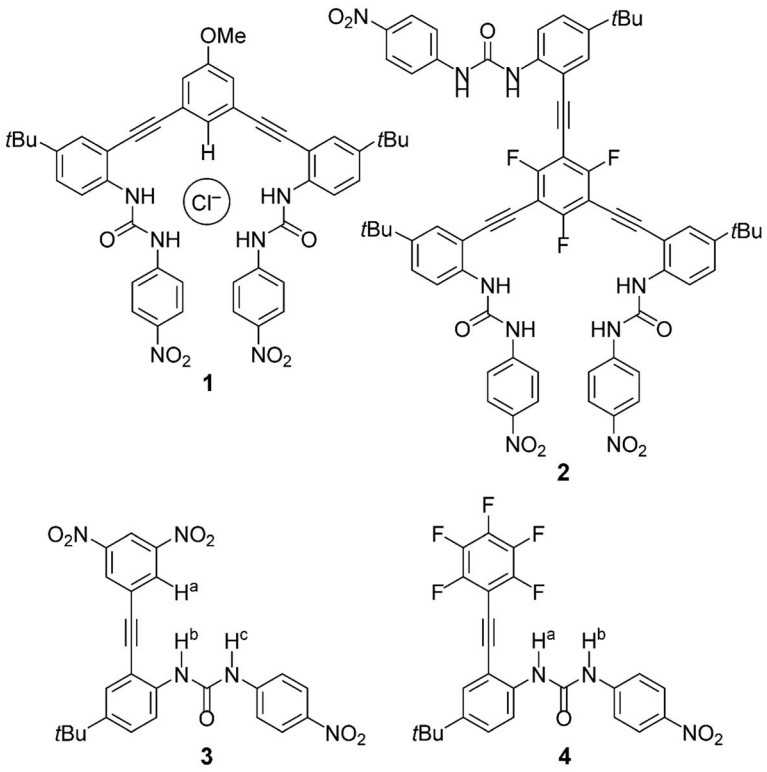


Figure 1.

Previously reported bipodal bis-urea (**1**) and tripodal tris-urea (**2**) receptors along with the new monopodal arylethynyl mono-urea scaffolds (**3**, **4**).

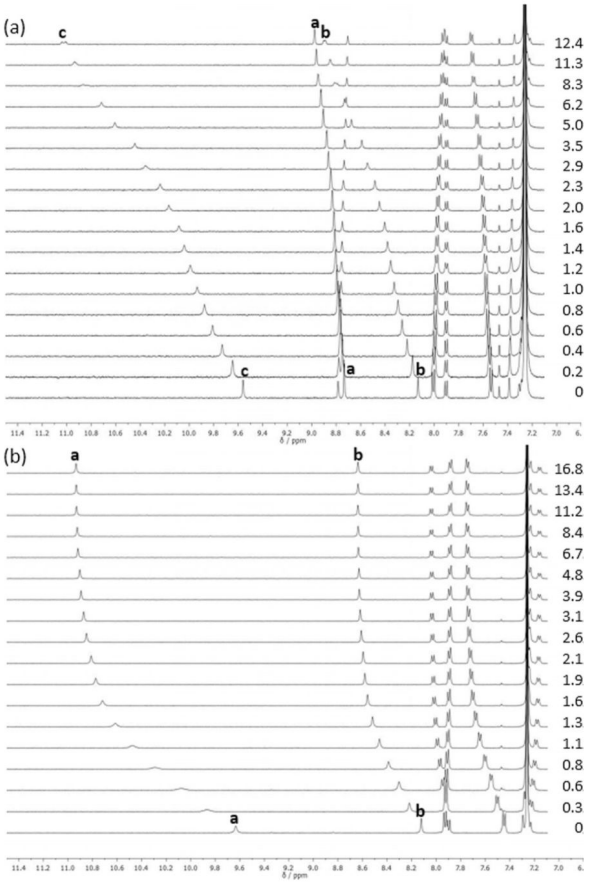


Figure 2.

a) ^{1}H NMR titration of **3** with $TBA^{+}Cl^{-}$ at 298 K; [**3**] =0.4 mM in 10% water-saturated [D_6]DMSO/$CDCl_3$. b) ^{1}H NMR titration of **4** with $TBA^{+}Br^{-}$ at 298 K; [**4**] =1.0 mM in 10 % water-saturated [D_6]DMSO/$CDCl_3$. Peak assignments refer to labelled hydrogen atoms presented in Figure 1.

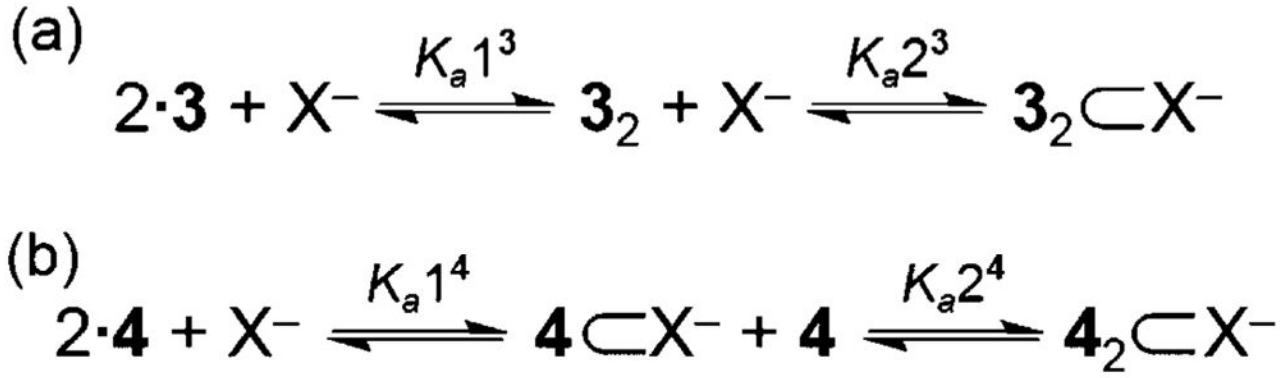


Figure 3.

Simplified equilibrium equations illustrating the two possible modes for formation of a 2:1 host–guest complex: a) initially a dimer forms, followed by the anion addition to form the 2:1 complex, or b) a 1:1 host–guest complex forms, and a second host binds to form a 2:1 complex.

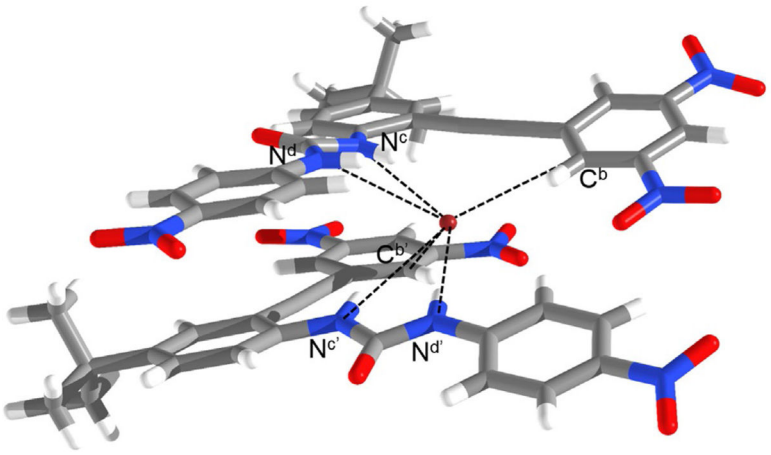
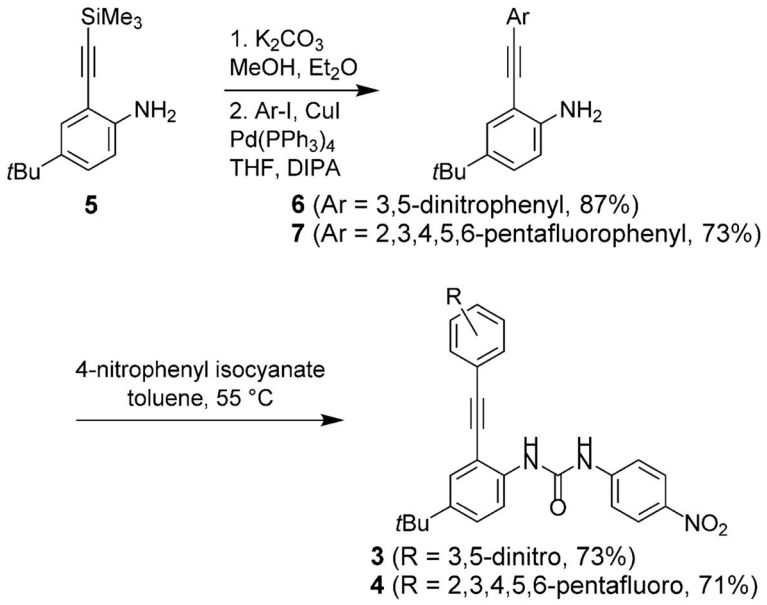


Figure 4.

X-ray crystal structure of $\mathbf{3_2 \cdot Br^-}$. Hydrogen-bond interactions shown as dotted line. TBA^+ countercation and solvent molecules have been omitted for clarity.



Scheme 1.

Synthesis of arylethynyl mono-urea receptors **3** and **4**.

Table 1

Anion-association constants (K_a) for receptors **3** and **4** obtained by fitting titration data to a stepwise 2:1 host–guest model in MatLab.[a]

Host	Cl^-/[M^{-1}][a]		Br^-/[M^{-1}][a]		I^-/[M^{-1}][a]	
	K_a1	K_a2	K_a1	K_a2	K_a1	K_a2
3	300	740	320	1040	360	6570
4	11 8000[b]	10200	930	2500	130	750

[a]Anions were added as tetrabutylammonium salts in 10 % water-saturated [D_6]DMSO/$CDCl_3$. Values represent an average of three ^{1}H NMR titrations. Error is approximately ± 15 %.

[b]See Reference [17].