Anion Binding

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Selective Nitrate Binding in Competitive Hydrogen Bonding Solvents: Do Anion–π Interactions Facilitate Nitrate Selectivity?**

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Anions are increasingly recognized as problematic environmental contaminants. For example, excess nitrate in soil from over-fertilization has led to contamination in water sources worldwide. Nitrate run-off into water sources causes algal blooms, a process known as eutrophication, which ultimately deprives water of oxygen and leads to dead zones in the world's lakes and oceans. Given the negative impact nitrate has on water sources, there has been considerable interest in the design and synthesis of receptors capable of sensing the molecule in solution. A number of studies have reported synthetic neutral receptors capable of binding nitrate in solution; however, most exhibit low affinity.[1] Some reports have shown enhanced nitrate binding in polar solvents, such as $CHCl_3$,[2] and even a few demonstrate high nitrate binding in more competitive solvents;[3,4] however selectivity for nitrate remains rare.[1a,c,g,4] We report new tripodal receptor **1** that exhibits strong binding of nitrate in polar, competitive solvents and shows modest selectivity for nitrate over common interferents, such as chloride. Control receptor **2**, lacking an electron-deficient aromatic ring, exhibits no such selectivity for nitrate. A close contact between nitrate and an alkyne within the receptor suggests an anion–π-type interaction may enhance nitrate binding.

Recently, examples indicating the presence of anion–π interactions in solution have emerged, often accompanied by complementary solid-state evidence. A functionalized naphthalenediimide chain has shown a high selectivity for transporting nitrate over acetate in vesicles.[5] Similarly, a perfluorobenzene calixarene-based ditopic receptor showed chloride ion transport across a lipid membrane, despite a lack of detectable chloride binding from ^{19}F NMR spectroscopy.[6] Attempts to quantify non-charge-transfer anion–π interactions have proved difficult because of their innate weakness; however, an "enforced proximity" approach has been used to quantify a small but favorable anion–π interaction in a nitro-substituted octamethyl calix[4]pyrrole.[7] Most recently, nitrate–π interactions have been further quantified for a series of disubstituted calix[4]pyrroles in which nitrate is likely sandwiched between two electron-deficient aryl substituents.[8] Two such receptors showed selectivity for the transport of nitrate over chloride across lipid membranes.[8] The work presented herein suggests an influence of anion–π-type interactions in the observed nitrate selectivity.[9]

We have previously modified a bis(arylethynyl)pyridine scaffold to make a collection of receptors studied for their anion-binding capabilities.[10] Binding of these systems has been characterized through an electronic response by fluorescence. In the work presented herein, we sought to design and synthesize a three-fold symmetric receptor (**1**) for binding nitrate. Molecular models suggested the tripodal structure and urea functionalities are likely to bind trigonal planar anions. Nitrate should be able to accommodate six hydrogen bond donors, which is more easily accomplished with diprotic donors, such as ureas.[11] Furthermore, the electron-deficient central arene of **1** would enhance the chances of a three-fold symmetric binding motif. For comparison, an unsubstituted, more electron-rich version (**2**) was synthesized. The 1,3,5-trifluorobenzene core (**3**) was obtained in 93% yield through a Sonogashira cross-coupling at 70 °C between 1,3,5-trifluoro-2,4,6-triiodobenzene[12] and 4-*tert*-butyl-2-ethynylaniline (Scheme 1).[10d,13] Similarly, the unsubstituted core (**4**) was synthesized in 60% yield from triiodobenzene.[14] Subsequent reaction of **3** and **4** with *p*-nitrophenylisocyanate in toluene provided receptor **1** in 67% yield and **2** in 57% yield, respectively.

Single crystals of **1** were obtained by vapor diffusion of pentane into acetone. The solid state structure shows a tight dimer held together by an intricate network of hydrogen bonds (Figure 1). Two monomers stack on top of each other through slip-stacked π–π interactions of the central benzene. Two urea arms on one host molecule bind two urea arms on the second host with one as the donor, the other as the acceptor. The urea protons not involved in interactions of self-association bind acetone molecules. The third arm of each monomer sticks out of the plane defined by the core and the other two arms. The dimer is capped on each side by a total of eight acetone molecules. Each dimer interacts with another through π-stacking of the third protruding arm.

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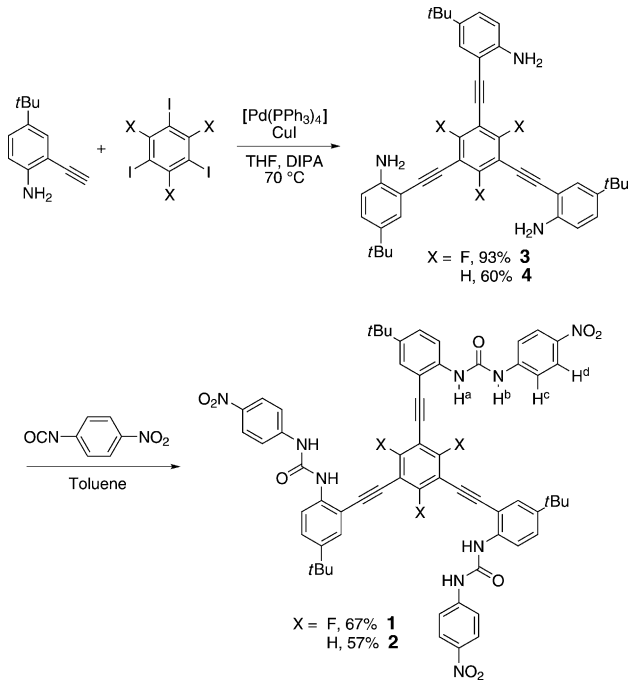

Scheme 1. Synthesis of tripodal receptors **1** and **2**.

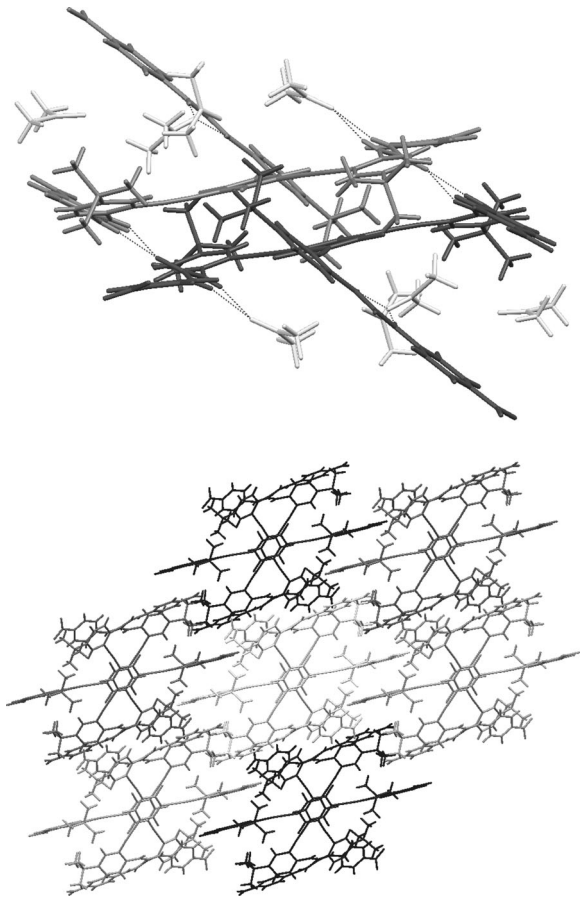

Figure 1. Crystal packing of **1** (top) showing a dimer capped by a total of eight acetone molecules and (bottom) showing these dimers are mostly discrete, interacting with each other through only π-stacking (solvent omitted for clarity).

Interaction of **1** with anions in solution was investigated by ^{1}H NMR spectroscopy. Initial titration experiments were performed at 0.5 mM of **1** in [D_6]acetone owing to its limited solubility in other solvents, despite the potential solvent competition as a hydrogen bond acceptor. Addition of tetrabutylammonium (TBA) salts of chloride, bromide, and nitrate resulted in a downfield shift of both urea protons H^a and H^b (labels refer to assignments shown in Scheme 1). Changes in chemical shifts of H^c and H^d were also observed, but to a lesser extent, with H^d moving upfield (see the Supporting Information). Large downfield shifts of the urea protons indicate hydrogen bonds of the ureas to the anion as the main mode of binding. Change in chemical shift corresponding to the addition of NO_3^- or Br^- begins to maximize at approximately 0.5 equiv of guest, indicating a possible 2:1 binding model in acetone. Non-linear regression analysis[15] of these data failed to provide reproducible binding constants with 1:1 or 2:1 models for NO_3^- or Br^-. The sharp transition seen in the binding curves often indicates strong binding with $K_a > 10^4\,L\,mol^{-1}$, which is typically too large to be accurately determined by NMR spectroscopy.[16] Titrations with Cl^- showed the $\Delta\delta$ maximizing closer to 1 equiv of guest. Non-linear regression analysis[15] of these data provided a 1:1 binding constant for Cl^- of $8620 \pm 1170\,L\,mol^{-1}$. This evidence alone is not enough to demonstrate the proposed stronger binding of NO_3^- than Cl^- for **1**; however, it does indicate a strong binding of NO_3^- in acetone and suggests a lower limit for the NO_3^- association constant.[17] For comparison, to the best of our knowledge, the largest association constants previously reported in the literature for nitrate binding of neutral receptors in acetone are $3470\,L\,mol^{-1}$ for a *p*-ureapyridine-based receptor[3d] and $910\,L\,mol^{-1}$ for a 1,4-diaryl triazole oligomer.[3c]

Preferential binding of chloride and nitrate to **1** over the competitive solvent acetone was also demonstrated in the solid state (Figure 2). Single crystals of **1** binding TBACl and $TBANO_3$ were grown through vapor diffusion of pentane into acetone. Comparison of the solid state structures shows the packing of **1** with NO_3^- (Figure 2c,g) and with Cl^- (Figure 2d,h) to be remarkably similar. A single host molecule binds two anions through hydrogen bonds to the ureas of two arms (Figure 2a,b). The hydrogen bonds between **1** and NO_3^- are shorter than those of **1** and Cl^-, with $N_{urea}\cdots O_{nitrate}$ distances of 2.874(6) and 3.089(6) Å for one urea and 3.008(5) and 2.887(5) Å for the other, compared to $N_{urea}\cdots Cl^-$ distances of 3.324(3) and 3.244(3) Å for one urea and 3.175(3) and 3.314(3) Å for the other. Each anion is located over the alkyne of a single monomer. Once again, NO_3^- is held closer to the monomer than Cl^-, as seen in Figure 2e,f. The closest interaction of Cl^- to the monomer is to one alkyne carbon with a distance of 3.796 Å. However, for nitrate the anionic π-system appears to align with the π-system of the receptor, supporting some intermolecular distances less than 3.7 Å (Figure 2f). Crystal packing shows an overall 1:1 binding where the host and anion are arranged in an infinite chain of host–guest–host–guest, and so on (Figure 2c). As mentioned, the anion is bound to the host through hydrogen bonds to both urea hydrogens on a single arm of the structure. The urea carbonyl of the same arm is hydrogen bonded to an arm on

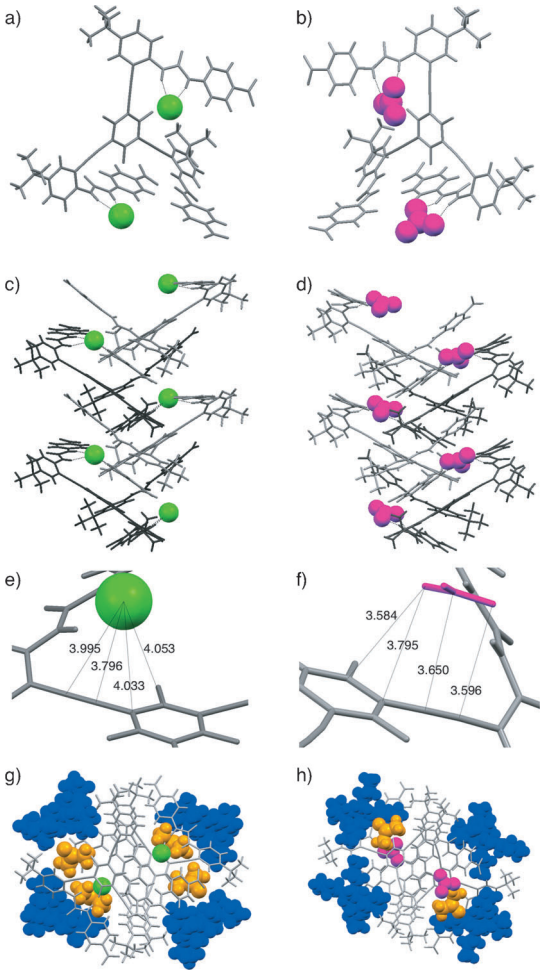

Figure 2. Crystal packing of **1** with (a,c,e,g) TBACl and (b,d,f,h) $TBANO_3$, highlighting the overall 1:1 interactions between host and anionic guest in the (a,b) monomer, (c,d) stacked column, and with the conjugated π-system (e,f). Cation (blue) and solvent (orange) interactions are shown in g and h.

the receptor, which shares binding to the anion. TBA countercations form solvent-separated ion pairs with both NO_3^- (Figure 2 g) and Cl^- (Figure 2 h) and are in approximately the same location in each crystal structure.

To simplify the mode of binding in these receptors, as well as to lower the association constant of nitrate and bromide to a measurable amount, other solvent systems were investigated. Low solubility of the tripodal receptors limited the solvent possibilities. We also aimed to maintain competition between binding of the anion and solvent molecules to provide further evidence for the strong binding of nitrate in competitive solvents, a critical feature for applications in environmental monitoring. Increasing concentrations of DMSO in chloroform have been shown to simplify binding models by breaking up self-association and, as a result, higher order binding.[3b,4,18] Furthermore, DMSO is a strong hydrogen-bond acceptor, and thus a lower association constant would be expected.[19] Initial upfield shifts, followed by downfield shifts of the urea protons, were observed upon the addition of $TBANO_3$ 1 mM solutions of **1** in 2% $[D_6]$DMSO/$CDCl_3$ and 5% $[D_6]$DMSO/$CDCl_3$. The titration curves indicate a more complicated system than a 1:1 model (see the Supporting Information); however, the data still could not be fit to a standard model.[20] Raising the DMSO concentration to 10% $[D_6]$DMSO/$CDCl_3$ decreased the overall change in chemical shift of the urea protons (Figure 3), but a smooth binding curve is observed, indicating self-aggregation (and likely ion-pairing) is no longer occurring. As suspected, titrations of TBA salts of nitrate, bromide, chloride, and iodide fit to a 1:1 model when performed in 10% $[D_6]$DMSO/$CDCl_3$ (Table 1).

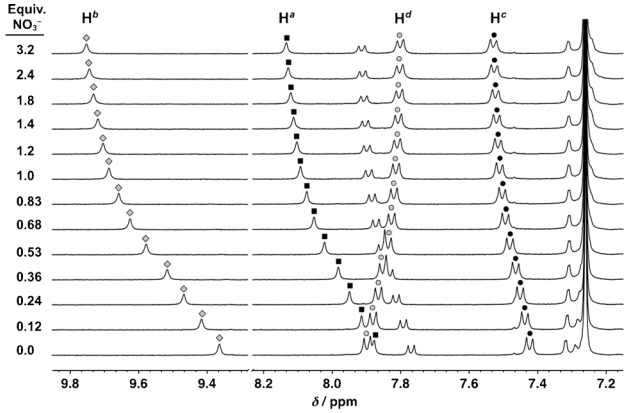

Figure 3. Example of a stacked ^{1}H NMR spectra for the titration of nitrate into a 1 mM solution of receptor **1** in 10% $[D_6]$DMSO/$CDCl_3$.

Titrations in 10% $[D_6]$DMSO/$CDCl_3$ were performed at a constant 1 mM concentration of **1**. The change in chemical shift was monitored throughout the titration and fit to a 1:1 model using non-linear regression analysis.[15] Titrations of NO_3^-, Cl^-, and Br^- performed with **1** showed $\Delta\delta$ level off at approximately 1 equiv of guest, while I^- began to maximize closer to 3 equiv (see Supporting Information). The binding constants of each anion investigated and the calculated total $\Delta\delta$ values based on the determined constant are presented in Table 1. The largest changes in chemical shift for each anion are observed in the urea protons of **1**, namely H^a and H^b. H^b moves farthest downfield, demonstrating a stronger hydrogen bond between the anion and this proton. Chloride has the largest shift in H^b but its measured K_a of 12200 $L\,mol^{-1}$ was not the highest observed association with **1**.

The largest association constant of 24100 $L\,mol^{-1}$ was obtained with NO_3^-, which also had the largest observed shift in H^a, $\delta = 0.26$ ppm versus $\delta = 0.21$, 0.16, and 0.12 ppm for Cl^-, Br^-, and I^-, respectively. Comparing the other values of H^a with the binding constants, a trend is observed; the larger shift in H^a, the higher the measured 1:1 association constant. Not only is **1** capable of binding anions out of competitive media, the binding of nitrate is significantly higher than chloride.[21] The only comparison in 10% $[D_6]$DMSO/$CDCl_3$ these authors are aware of is a neutral tripodal cyclic peptide with a 1:1 NO_3^- binding constant of 126 $L\,mol^{-1}$ and no selectivity for NO_3^- is observed.[3b] Selectivity for NO_3^- over Cl^- and I^- has been demonstrated in 100% $[D_6]$DMSO for a NHBoc-substituted macrocyclic triamide with a NO_3^-

Table 1: Association constants K_a of **1** and **2** determined by monitoring urea protons H^a and H^b and *p*-$NO_2C_6H_4$ protons H^c and H^d during ^1H NMR titrations.[a]

Anion[b]	**1**					**2**					
	$\Delta\delta(H^a)$[c] [ppm]	$\Delta\delta(H^b)$[c] [ppm]	$\Delta\delta(H^c)$[c] [ppm]	$\Delta\delta(H^d)$[c] [ppm]	K_a[d] [L mol^{-1}]	$\Delta\delta(H^a)$[c] [ppm]	$\Delta\delta(H^b)$[c] [ppm]	$\Delta\delta(H^c)$[c] [ppm]	$\Delta\delta(H^d)$[c] [ppm]	$\Delta\delta(H^{core})$[e] [ppm]	K_a[d] [L mol^{-1}]
NO_3^-	0.26	0.39	0.10	−0.10	24100 (1050)	0.19	0.27	0.12	−0.06	< 0.01	11800 (1570)
Cl^-	0.21	0.99	0.17	−0.15	12200 (934)	0.12	0.97	0.21	−0.07	0.31	63700 (814)
Br^-	0.16	0.62	0.17	−0.11	8320 (876)						–[g]
I^-[f]	0.12	0.29	0.16	−0.07	755 (85)						–[g]

[a] In 10% $[D_6]$DMSO/$CDCl_3$; determined at 25 °C. [b] Anions added as tetrabutylammonium salts. [c] Averaged calculated values are based on the determined binding constants. [d] Values are an average of three titrations. Standard deviation is given in parenthesis. All errors are less than 15%. [e] Averaged values from the observed changes in chemical shift. [f] $\Delta\delta$(H) values are over a larger equivalency range for iodide than nitrate, chloride, or bromide. [g] Not determined.

association constant of 20 L mol^{-1}.[4] To the best of our knowledge, tripodal host **1** exhibits the strongest nitrate binding for a neutral receptor in competitive solvents, and an anion–π interaction appears to facilitate, if not enhance, this binding.

More detailed analysis of the binding modes of anions with **1** and the selectivity of NO_3^- in this system will be investigated in the near future; however, some observations are worth noting. The trend in binding constants corresponds to the observed $\Delta\delta$ values of H^a. A larger value of $\Delta\delta$ would typically indicate a stronger and shorter hydrogen bond of the urea proton to the anion, which would correspond to the anion being in closer proximity to the aryl core. This presents an argument for the presence of an anion–π interaction. The crystal structure of the nitrate-bound host supports this hypothesis, and reveals a clear interaction between the nitrate anion and the π-system of the aryl core and the alkyne (for example, see Figure 2 f showing $N/O_{nitrate}\cdots C_{alkynyl}$ contacts distances of 3.596 and 3.650 Å). As previously discussed, the distances of NO_3^- to the aryl core and alkyne are significantly shorter than those of Cl^-. An electrostatic potential map of **1** indicates a lack of electron density in the arene as well as the conjugated alkynes (see the Supporting Information). The question arises as to why nitrate would have a stronger interaction with the π-system than chloride. Nitrate itself possesses a conjugated π-system, so this could be suggestive of a favorable π–π type interaction; nevertheless, one of the partners in this interaction is anionic making this a clear example of an anion–π interaction of some type or a "π–π-assisted anion–π" interaction.[22]

To further investigate this claim, unsubstituted and more electron-rich receptor **2** was synthesized for comparison to electron-deficient **1**. Along with the change in the electronics providing weakened anion–π interactions, the extra proton in **2**, H^{core}, could provide further insight into the binding mode.

Similar to **1**, host–guest complexes of **2** were investigated through ^1H NMR spectroscopy titrations in 10% $[D_6]$DMSO/$CDCl_3$. Titrations were performed at approximately 1 mM **2** with TBA salts of Cl^- and NO_3^-. The urea protons (H^a and H^b), nitrophenyl protons (H^c and H^d), and core proton (H^{core}) were monitored throughout the titrations. For consistency, only H^a, H^b, H^c, and H^d were used to fit the data to a 1:1 model, as was done with **1**. All changes in chemical shift began to level off near 1 equiv of anion and are presented in Table 1 with the association constants corresponding to NO_3^- and Cl^-. The values reported for H^a, H^b, H^c, and H^d are averages derived from the individual association constants of each titration, while the values for H^{core} are averaged from the observed changes during the titration.

Replacing the fluorine atoms with hydrogens changes not only the electronics, but also the number of hydrogen bond donors. This combination leads to a loss in selectivity for NO_3^- over Cl^-. Chloride binding is now enhanced, with an association constant for **2** of 63700 L mol^{-1}, whereas nitrate binding is weakened to 11800 L mol^{-1}. Any anion–π interactions would be weakened or now repulsive owing to the change in electronics within the central ring, so weakening of the binding would be expected, as seen with NO_3^-. The large increase in K_a for Cl^- can be attributed to the addition of a hydrogen bond with H^{core},[23] assigned from the titration of **2** (Figure 4 a). This hydrogen bond is observably stronger ($\Delta\delta =$ 0.31 ppm versus $\delta = 0.12$ ppm) than that of H^a, which correlated to K_a for **1**. The association constant for NO_3^- with **2** trends with the noted correlation and indicates **2** may bind NO_3^- by a similar mode as **1**, but binds Cl^- through a different mode. More importantly, no significant shift of H^{core} occurs upon the addition of nitrate to **2** (Figure 4 b), thus there is no hydrogen bonding of the anion to H^{core}, indicating an anion–π interaction may still be the preferred mode of

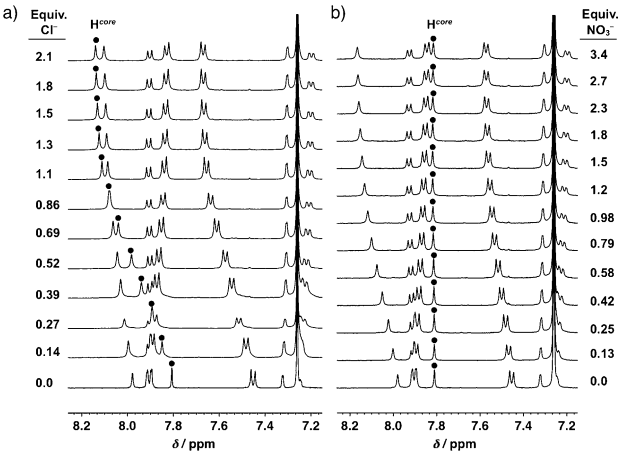

Figure 4. Stacked ^1H NMR spectra for the titration of (a) Cl^- and (b) NO_3^- into a 1 mM solution of receptor **2** in 10% $[D_6]$DMSO/$CDCl_3$.

binding, despite the more electron-rich arene. Three important results stem from the investigation of **2**: nitrate selectivity is lost, the association constant of nitrate is diminished, and nitrate binds via a different mode than chloride. These data support a model in which nitrate binds to the receptor through an anion–π-type interaction regardless of the electronics, while chloride prefers to bind through a hydrogen bond to the core of **2** rather than to the π-system, effectively raising the association constant.

The tripodal receptors presented herein demonstrate preferential binding of anions over competitive hydrogen bonding solvents, namely [D_6]acetone and 10% [D_6]DMSO/$CDCl_3$. The binding of nitrate and bromide to **1** in [D_6]acetone could not be accurately determined. The association of chloride to **1** is actually higher in the 10% [D_6]DMSO/$CDCl_3$ solution than in [D_6]acetone, whereas the association of both bromide and nitrate are lower. Receptors **1** and **2** bind anions out of 10% [D_6]DMSO/$CDCl_3$ in a 1:1 stoichiometry. A strong affinity for the anions is observed even in the presence of [D_6]DMSO and the binding of **1** trends: $NO_3^- > Cl^- > Br^- > I^-$, with a moderate selectivity for nitrate possibly resulting from an anion–π interaction. Binding studies of **2** support the existence of a favorable anion–π interaction by demonstrating a loss in nitrate selectivity and indicating an anion–π-type interaction still is the preferred mode of binding for nitrate. We intend to expand the investigation of **1** and **2** to other anionic substrates as well as further probing the influence of an anion–π interaction.

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[9] We recognize the observed interaction between nitrate and the π-system may simply be π-stacking between nitrate and an arylalkyne; however, such an interaction might still be broadly described as "anion–π", as one partner in the association is anionic.

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[16] Values obtained using the 1:1 Thordarson fitting program consistantly gave association constants on the order of $10^4\,L\,mol^{-1}$ for bromide and $10^5\,L\,mol^{-1}$ for nitrate, albeit with high errors and poor overall fit.

[17] Given the possibility of 2:1 binding modes for NO_3^- or Br^- in [D_6]acetone, and evidence of solid-state dimerization, self-association of **1** in acetone was investigated. The data obtained could not be fit to a self-association/dimerization model (even when dimerization was assumed). While this evidence provides little assistance in fitting NO_3^- or Br^- titration data, it shows the receptor aggregates in acetone. This, coupled to the potential for association constants larger than $10^4\,L\,mol^{-1}$, led us to investigate the binding in other solvents.

[18] W.-J. Chu, Y. Yang, C.-F. Chen, *Org. Lett.* **2010**, *12*, 3156 – 3159.

[19] No changes in chemical shift were observed upon titration of nitrate into **1** in neat [D_6]DMSO.

[20] Results indicate a 2:1 binding model breaking up to 1:1 upon the further addition of anion. The 2:1 model likely results from self-aggregation of the receptor in these polar solvent mixtures.

[21] Statistical significance determined by a t-test comparing the values obtained for nitrate binding versus those of chloride

binding. The difference between the two was found to be significant with 99.9% certainty.
[22] The authors would like to thank an anonymous reviewer for describing this interaction as a "π–π-assisted anion–π" interaction, which we think aptly describes such an attraction.
[23] a) B. W. Tresca, L. N. Zakharov, C. N. Carroll, D. W. Johnson, M. M. Haley, *Chem. Commun.* **2013**, *49*, 7240 – 7242; b) J. V. Gavette, N. S. Mills, L. N. Zakharov, C. A. Johnson II, D. W. Johnson, M. M. Haley, *Angew. Chem.* **2013**, *125*, 10460 – 10464; *Angew. Chem. Int. Ed.* **2013**, *52*, 10270 – 10274.

