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Conformationally flexible hosts with relatively small binding pockets are seldom shown to bind oxoanions preferentially over other guests. Herein, we disclose the binding of diprotic, monoprotic, and aprotic tetrahedral oxoanions with three different pyridylethynyl bis-urea scaffolds. In less polar solvent, the trend in association constants appears to be heavily influenced by solvation and entropic effects. However, in a more polar solvent, the trend in association constants matches that of the pK_a of the conjugate acid of the anionic guest, as expected for H-bond donating hosts.

Nitrogen and phosphorous species from agricultural run-off, particularly nitrate (NO_3^-) and phosphates (e.g., HPO_4^{2-}), are attributed to the hypoxic zone that appears in the Gulf of Mexico and other bodies of water each spring.[1,2] Sulfate (SO_4^{2-}) and perchlorate (ClO_4^-) are also problematic environmental pollutants originating from sources such as nuclear waste and jet fuels, respectively.[3,4] Recognition and dynamic monitoring of these weakly basic and charge-diffuse anions relies heavily on supramolecular receptors.[5]

Binding sensitivity toward protic and aprotic oxoanions in supramolecular host-guest systems, however, poses challenges. Many studies have reported designer supramolecular receptors for the purpose of binding these diffuse anionic systems by utilizing cages, flexible alkyl linkages, and charged binding units.[6-8] Additional fundamental understanding of the factors influencing the binding of these anions will help advance receptor design for specific anions utilizing neutral, conformationally flexible receptors.

Generally, larger, pre-organized binding pockets enhance the ability of a synthetic receptor to bind oxoanions.[5,6,8] For instance, tetracarboxamide-based macrocycles and shape-persistent cyanostar macrocycles have been shown to bind oxoanions via higher-order binding stoichiometries.[8] Herein, we investigate a class of receptors featuring conformational flexibility that apparently allows guests of varying sizes to be accommodated in what we previously considered as relatively small binding pockets. Additionally, we explore the impact of supporting attractive interactions (e.g., aryl C–H hydrogen bond donors and pyridine lone pair hydrogen bond acceptors) on the binding affinities of protic and aprotic oxoanions.

While we have reported a number of examples of recognition of spherical anions by pyridyl bis-urea receptors,[9] only a few of these receptors have shown affinities for oxoanions.[9e,10,11] One reason for this is the apparent size of the binding pocket: at first glance it does not intuitively appear large enough to bind oxoanions. However, an extended bipyridyl bis-urea host in this receptor class showed binding selectivity to dihydrogen phosphate ($H_2PO_4^-$) by rotating along the bipyridyl and/or alkynyl bonds, suggesting other binding pockets might be accessible through conformational changes within this receptor class (Fig. 1).[10,12]

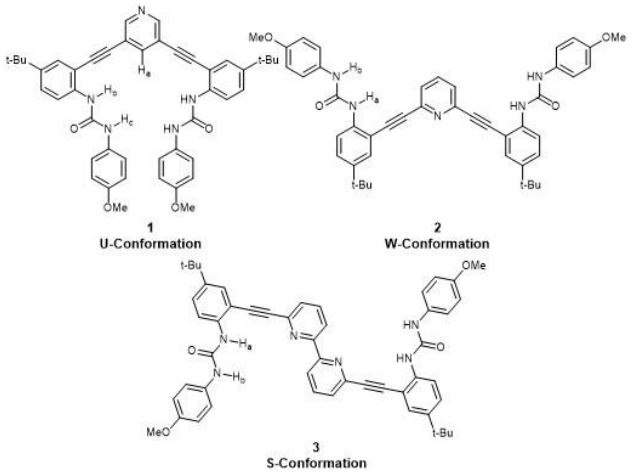

Figure 1 Pyridine core bis-urea receptors utilized in this study. New receptor with 3,5-pyridine core (**1**) shown in the "U"-conformation, along with the previously reported Chemdraw representation of 2,6-pyridine receptor (**2**) in the "W"-conformation and the modified bipyridine receptor (**3**) shown in the "S"-conformation.[9a,10]

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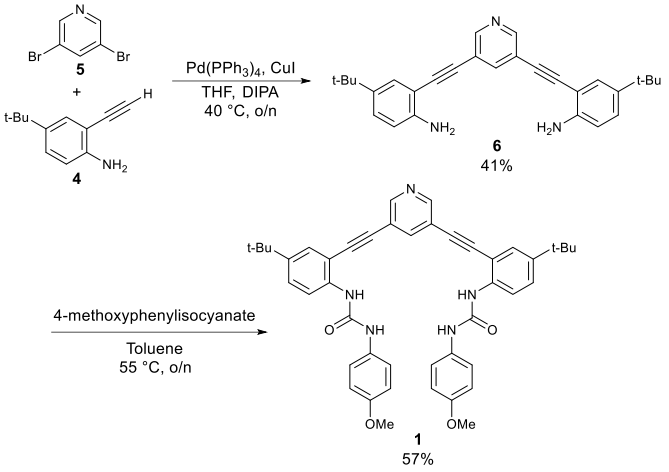
An extension of these studies revealed that a pyridine-based mono-urea receptor served as a model for the "W" conformation and bound oxoanions at a similar magnitude as a bipyridyl bis-urea, supporting the potential affinity of this alternate binding pocket to oxoanions.[11] Subsequent studies of aryl mono-urea receptors indicated two urea binding units were preferred when binding anions (to the extent that even 2:1 host:guest complexes were favourable in this mono-urea host), indicating the next logical step was to investigate the affinity of pyridyl bis-urea receptors toward oxoanions.[12] Herein we report the solution-state association constants and computed binding geometries of three pyridine-based bis-urea receptors (Fig. 1) in the presence of three disparate tetrahedral oxoanions and find that they are all excellent hosts for these anions.

To investigate the differences in oxoanion affinity between different binding interactions, we compared two similar pyridine-based receptors (3,5- and 2,6-bis(2-anilinoethynyl)pyridine bis(4-methoxyphenyl)urea; Fig. 1, **1** and **2**, respectively) as well as a bipyridyl-based bis-urea (Fig. 1, **3**). In all interactions between hosts **1**, **2**, and **3** and the respective oxoanions, there are three major factors at play: the H-bond accepting or donating ability of the aromatic core of the receptor, the inherent properties of the anion (i.e., number of protons, pK_a of corresponding acid, and ionic radii), and the size/shape of the binding pocket within each receptor.

These pyridine receptors directly probe the preference of aryl H-bond acceptors or donors in protic and aprotic oxoanions. All receptors have the ability to bind anions in several conformations, including the U, W, and S conformation (Fig. 1, **1**, **2**, and **3**, respectively).[9b] Newly designed host **1** allows for a weak aryl C–H hydrogen bond to anions; the presence of five hydrogen bond donors (one C–H and four N–H bonds) in the W-shaped pocket suggested **1** should preferentially bind more basic and/or aprotic oxoanions and halides.[9]

We compared this to known host **2**, which features our traditional 2,6-pyridyl core. We hypothesized **2** would prefer monoprotic oxoanions, as the nitrogen lone pair in the pocket acts as an H-bond acceptor. When investigating the 1-to-1 host-guest interaction, the homologous bipyridine receptor **3** was expected to have the greatest binding preference toward oxoanions, particularly diprotic oxoanions, due to the large binding pocket and its ability to accept multiple



Scheme 1 Synthesis of 3,5-pyridine bis-urea receptor **1**.

H-bonds from the (di)protic oxoanions in the bipyridyl core.[11]

The syntheses of **1** and modified host **3** are based on previously reported strategies for related aryl acetylene bis-urea systems (Scheme 1, see SI for detailed procedures).[9a,10] The anion-binding characteristics of **1**-**3** were probed by spectroscopic titrations in 10% DMSO/90% water-saturated $CHCl_3$ solutions, the perdeutero equivalent, or acetonitrile, with anions introduced as tetrabutylammonium (TBA) salts. ^{1}H NMR titrations were performed at 1.0 mM concentration of host, while UV-Vis titrations were performed at a host concentration of 25 μM. Association constants (K_a) for **1**-**3** with dihydrogen phosphate ($H_2PO_4^-$), hydrogen sulfate (HSO_4^-), and perchlorate (ClO_4^-) were obtained using non-linear regression fitting models in Bindfit by simultaneously fitting the change in absorbance for each host–guest complex at the attributed λ_{max} (Fig. 2).[13,14] K_a's for receptors **1**-**3** with bromide (Br^-) were either previously reported or obtained using non-linear regression fitting models in MatLab by simultaneously fitting the downfield shifting of the urea protons (H_b, H_c for **1**; H_a, H_b for **2** and **3**).[13] The shifts of the internal aromatic proton (H_a) were also used in the fitting of **1**.

Initial ^{1}H NMR titration experiments were performed on **1** with bromide, a spherical anion with relatively well-characterized binding behavior.[9] Consistent with other aryl CH hydrogen bonding phenylacetylene bis-urea receptors, the

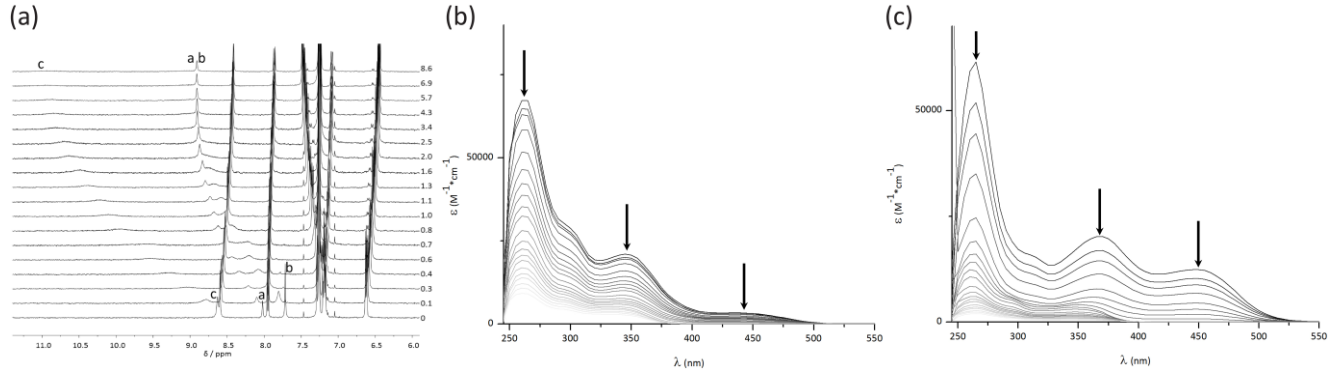


Figure 2 (a) ^{1}H NMR titration of **1** with $TBA^+H_2PO_4^-$ at 298K; [**1**] = 1.0 mM in 10% d_6-DMSO / 90% H_2O-saturated $CDCl_3$. Equivalents of guest labelled at the right of spectra. Peak assignments refer to labelled hydrogens in Fig. 1. (b) UV-Vis titration of **2** with up to 36.7 equiv. of $TBA^+H_2PO_4^-$ at 298K; [**2**] = 25 μM in 10% DMSO / 90% H_2O-saturated $CHCl_3$. Arrows represent the change in ε at the wavelengths of HG as guest is added. (c) UV-Vis titration of **3** with up to 7.4 equiv. of $TBA^+H_2PO_4^-$ at 298K; [**3**] = 25 μM in in 10% DMSO / 90% H_2O-saturated $CHCl_3$. Arrows represent the change in ε at the wavelengths of HG as guest is added.

Table 1 Association constants (K_a) and free energies of binding (ΔG, kcal mol^{-1}) reported for receptors **1**-**3**. Observed free energies obtained by fitting titration data to a step-wise 1:1 host-guest model in Bindfit.[a,13,14] Quantum mechanical free energies computed at PBE/6-31G(d) in PCM(DMSO).[17]

			1				**2**			**3**		
Anion	pK_a[15]	logK_a	ΔG_{obs}	ΔG_{QM}	logK_a[b]	ΔG_{obs}[b]	logK_a	ΔG_{obs}	ΔG_{QM}	logK_a	ΔG_{obs}	ΔG_{QM}
Br$^-$	–9.0	2.07[c]	–2.80[c]	–	–	–	2.00[d]	–2.72[d]	–	1.78	–2.42	–
$H_2PO_4^-$	2.1	4.74	–6.44	–4.6	5.02	–6.83	4.77	–6.48	–9.7	4.83	–6.56	–12.8
HSO_4^-	–3.0	4.68	–6.37	1.3	3.21	–4.36	4.78	–6.49	–3.5	4.76	–6.47	–4.8
ClO_4^-	–10.0	4.66	–6.33	6.2	*N.D.*[e]	~0[e]	4.65	–6.32	7.3	4.71	–6.39	2.4

[a]Anions added as TBA$^+$ salts in 10% DMSO/90% water-saturated $CHCl_3$ or the perdeutero equivalent (unless noted). Values represent an average of three UV-Vis titrations at 25 μM host concentration. Error is *ca.* ±15%. [b]Measured in acetonitrile. [c]Value obtained using ^{1}H NMR titrations at 1 mM host concentration. [d]Value previously reported.[9] [e]Value not detectible.

association constant for **1** with Br$^-$ was relatively low (Table 1). Nonetheless, ^{1}H NMR titrations were used in an attempt to characterize the affinity of **1** with dihydrogen phosphate (Fig. 2a). Fitting the downfield shifts of the selected protons resulted in a K_a value nearing the detection limits of ^{1}H NMR spectroscopy. Furthermore, the serpentine-like shifts of multiple aromatic resonances and the appearance of peak-splitting, particularly in the presence of excess guest, indicated higher-order binding stoichiometries were likely occurring.[8,12,13] To support this conclusion, fitting the titration data to a 2:1 host–guest binding model resulted in better fitting (as indicated by the shape of the residual asymptotic errors) than the 1:1 host–guest binding model (see ESI for detailed titration data).[13]

UV-Vis titration experiments were implemented to further investigate the surprising interaction strength between receptors **1**-**3** and the selected series of oxoanions. At the more dilute 25 μM host concentration (dissolved in 10% DMSO/90% H_2O-saturated $CHCl_3$), a 1-to-1 host–guest interaction dominates the binding and 1:1 fitting models proved a better fit than higher binding stoichiometry models (i.e., 2:1 or 1:2 host:guest).[12,13] Job's method of continuous variation further confirms this 1:1 binding stoichiometry (Figs. S33-S36).

To our surprise, all three receptors exhibited similar affinities toward all three oxoanions, with observed free-energies of binding (ΔG) ranging from –6.56 to –6.32 kcal mol^{-1}. In an attempt to understand the lack of trends in binding between the receptors with different supporting binding interactions and the disparate anions, we turned to quantum mechanical (QM) computations. Interestingly, the trend in computed free energies of binding (ΔG_{QM}) closely follows the trend in aqueous conjugate acid pK_a (2, –3, and –10 for H_3PO_4, H_2SO_4, and $HClO_4$, respectively; Table 1).[15]

The conformational freedom within these receptors appears to allow for the formation of binding pockets of appropriate size to host these oxoanions. In fact, DFT structures reveal all three receptors prefer the U-shaped binding conformation, with each binding pocket spanning roughly 5.9 Å between the proximal urea hydrogens (H_b for **1** and H_a for **2** and **3**, see ESI). The ionic radii of each oxoanion is also similar (~2.4 Å),[16] and space-filling models show that $H_2PO_4^-$ is able to fit neatly into each of the receptors in their lowest-energy U-conformations (Fig. 3). Curiously, however, the secondary interactions with the varying pyridyl cores (CH donor versus pyridyl/bipyridyl H-bond acceptors) appear significant in the computed structures but did not contribute to dramatic changes in observed binding energies in the low-polarity mixed solvent system studied (10% DMSO/90% H_2O-saturated $CHCl_3$). Considering the accuracies of the experimental measurements and the wide range of computational methods tested,[17] it appears that the discrepancies between the experimental and computational values are not simply in error. In the absence of other effects, we hypothesized that entropic and/or solvation effects in this solvent mixture contribute to these differences.

To further investigate the presence of solvation effects, titrations were performed in neat acetonitrile, a more competitive, polar solvent (ε = 36.6 for CH_3CN versus effective ε ~8.1–8.5 for 10% DMSO/90% water-saturated $CHCl_3$ mixture).[18] Due to solubility restrictions with **2** and **3** in pure CH_3CN, titrations were only performed with receptor **1** and the array of oxoanions. In this more polar solvent, the observed binding energies follow the expected basicity trend, with **1** showing no detectible affinity toward the least basic ClO_4^- anion. Additionally, the higher K_a value of **1** with $H_2PO_4^-$ in acetonitrile versus that determined in the less polar, mixed solvent system indicates that this receptor has a particularly high selectivity toward this relatively large anion, even in competitive solvents. The stark contrasts between the binding energies in the less polar solvent mixture and more polar solvent lends to the hypothesis that entropy/solvation plays a significant role in the binding events at play between these receptors and the tetrahedral oxoanions. To further understand the influence of

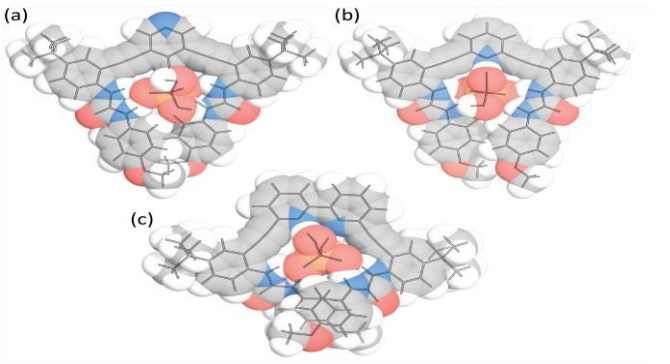


Figure 3. Space-filling models of receptors (a) **1**, (b) **2**, and (c) **3** binding $H_2PO_4^-$. Complexes computed at PBE/6-31G(d) in PCM(DMSO).

the solvent and entropic effects on binding energies within this class of arylethynyl bis-urea receptors, we are currently

pursuing the synthesis of receptors soluble in solvents with a range of polarities (i.e., soluble in solvents ranging from neat $CHCl_3$ through DMSO).

In conclusion, while the flexibility around the alkyl linkages in this class of receptors leads to a sizable binding pocket perfectly suited for tetrahedral oxoanions, we suspect that entropy and dynamic solvation effects are major contributors to the free energies of binding in these systems. Thus, we are currently pursuing studies to tease-out the enthalpic and entropic contributions involved in these host-guest systems. While intuitively one might first look to pK_b / conjugate acid pK_a trends in predicting affinity of protic and aprotic oxoanions toward hydrogen bonding hosts, these studies serve as a reminder that—especially in conformationally flexible hosts—this might not always be the dominant factor influencing the binding of oxoanions.

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Conflicts of interest

There are no conflicts to declare.

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Despite competing trends and computational predictions to the contrary, three bis-urea receptors bind disparate oxoanions (ClO_4^-, HSO_4^-, $H_2PO_4^-$) with equal affinities in a non-polar solvent; in a more polar solvent the trend in association constants for one receptor matches that of the pK_b of the guest, as expected for H-bond donating hosts.