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Electroactive Anion Receptor with High Affinity for Arsenate
Samuel I. Etkind, Douglas A. Vander Griend, and Timothy M. Swager*

ABSTRACT: Herein, we present the synthesis and characterization of a macrocyclic polyamide cage that incorporates redox-active 1,4-dithiin units. UV/vis titration experiments with eight anions in acetonitrile revealed high affinity for \( \text{H}_2\text{AsO}_4^- \) (log \( \beta_2 = 10.4^{+0.4}_{-0.4} \)) and \( \text{HCO}_3^- \) (log \( \beta_2 = 8.3^{+0.4}_{-0.4} \)) over other common anionic guests, such as \( \text{Cl}^- \) (log \( K_1:1 = 3.20^{+0.02}_{-0.02} \)), \( \text{HSO}_4^- \) (log \( K_1:1 = 3.57^{+0.02}_{-0.02} \)), and \( \text{H}_2\text{PO}_4^- \) (log \( K_1:1 = 4.24^{+0.04}_{-0.04} \)), by the selective formation of HG complexes. The recognition of arsenate over phosphate is rare among both proteins and synthetic receptors, and though the origin of selectivity is not known, exploiting the difference in the binding stoichiometry represents an underexplored avenue toward developing receptors that can differentiate between the two anions. Additional analysis by \( ^1\text{H} \) NMR in 1:3 CD\(_2\)Cl\(_2/\)MeCN-\( d_3 \) found a strong dependence of anion binding stoichiometry with the solvent employed. Finally, titration experiments with cyclic voltammetry provided varying and complex responses for each anion tested, though reaction between the anion and receptors was observed in most cases. These results implicate 1,4-dithiins as interesting recognition moieties in the construction of supramolecular receptors.

INTRODUCTION
Simple anions can often act as potent environmental pollutants. For example, nitrate and phosphate leached from fertilizers can lead to algal blooms, depriving aquatic ecosystems of oxygen needed to sustain animal life.\(^1\) The increasing levels of atmospheric CO\(_2\) is coupled with an increase in oceanic bicarbonate concentration and therefore ocean acidity, resulting in the degradation of CaCO\(_3\), a protective layer for many organisms.\(^2\) Millions in Bangladesh are at risk of arsenic poisoning, which could be mitigated by the environmental monitoring of arsenate levels.\(^3\) Typically, the accurate quantification and detection of anions at environmentally relevant concentrations require the use of costly analytical methods, such as high-performance liquid chromatography (HPLC) and inductively coupled plasma mass spectrometry (ICP-MS).\(^4-7\) These methods, however, could be potentially supplanted by cost-effective techniques that use supramolecular receptors to aid in the detection of anionic species.

To apply anion receptors to the detection of anions in complex mixtures, researchers utilize a variety of methods, such as changes in fluorescence,\(^8-11\) absorbance (i.e., colorimetric sensors),\(^12-14\) or NMR resonance,\(^15-19\) in the presence of guests. More recently, there have been efforts by a number of groups to employ electrochemical methodology toward the detection of anions via chemiresistive,\(^20\) potentiometric,\(^21,22\) capacitive,\(^23\) or redox-based sensing,\(^24\) due to their potential application in the development of cost-effective devices. We were particularly drawn to the development of redox-active receptors, as the effect of transiently creating cationic species has the potential to effectively bind anions in competitive media, such as water.\(^25\)

Electroactive anion receptors have been well described.\(^25\) Most designs involve appending a redox transducer, most commonly ferrocene,\(^26-28\) to a known anion receptor; however, other strategies have been employed, such as the use of electroactive ureas\(^29\) and mixed-valence systems.\(^30\) The change in reduction potential upon introduction of an anionic guest is proposed to proceed via a variety of mechanisms, including through-space interactions between the redox-active moiety and anion, as well as conformational changes of the redox transducer upon anion complexation, which result in the guest binding to the oxidized host with a greater affinity than...
to the nonoxidized host.31 The reduction potential of the host−guest complexes may differ depending on the included guest. Additionally, the observation of "two-wave" behavior, in which the host and guest are in slow equilibria, could potentially be useful in differentiating between multiple anionic species.25 We hypothesized that the modification of an existing anion receptor with a carefully chosen redox transducer that is in close proximity to the binding site could give large shifts in the reduction potential of the host−guest complex upon oxidation.

The modification of known supramolecular receptor scaffolds, such as in the introduction of halogen bonding,32,33 altering distal functionalities to bias host−guest34 or host−guest35 or systematically altering the size and electronic biases of the binding site,36−41 has been demonstrated to be an effective approach toward designing receptors with high affinity toward various anions, in addition to giving novel insights in structure−property relationships. Additionally, we recognized 1,4-dithiin, a sulfur-rich heterocycle that exhibits a well-behaved single-electron oxidation that is coupled with a geometric change from bent to planar, as largely overlooked in supramolecular scaffolds.32 Herein, we present our work on the incorporation of 1,4-dithiin moieties into Receptor 1 to form Receptor 3, which was previously reported as a nitrate-selective receptor by Anslyn and co-workers (Figure 1).43 Notably, Kim, Sessler, and co-workers have demonstrated the effectiveness of systematic alterations to Anslyn’s Receptor 1 in the development of pyrrole- and imine-containing Receptor 2, which shows a stronger preference for tetrahedral anions via the incorporation of hydrogen-bond-accepting moieties.44 Placement of the 1,4-dithiin units adjacent to the binding site could give large electrochemical responses via both through-space interactions between the anionic guest and redox transducer and the conformational change of the redox-active moiety upon oxidation. We also postulated that the formation of a tricationic cavity upon oxidation may form sufficiently strong interactions with anions to overcome their large solvation energy in highly polar media.

- RESULTS AND DISCUSSION

Synthesis. The preparation of Receptor 3 was carried out according to Scheme 1 (see Section S1.1 (Supporting Information) for preparation of starting materials). The treatment of ethyl acetoacetate (4) with disulfur dichloride in hexanes, 35 °C, 1 h, 40%; (i) NaH, tetrahydrofuran (THF), 0 °C to room temperature (rt), 4 h; (ii) KOH, EtOH, 50 °C, 2 h, 60%; (v) (COCl)2, cat. dimethylformamide (DMF), CH2Cl2, 2 h, quant.; (vi) NaH, tetrahydrofuran (THF), 0 °C to rt, 16 h, 80%; (vii) HCl, dioxane, 1 h, 98%; and (ix) 9 (slow addition), CH2Cl2, 0 °C, 80%, and (x) 9 (slow addition), various conditions, <5%.

Figure 1. Previously reported polyamide cages 1 and 2 and new cage 3.

Scheme 1. Preparation of Receptor 3a

| Step | Reagents and conditions |
|------|------------------------|
| (i)  | S2Cl2, hexanes, 35 °C, 1 h, 40% |
| (ii) | NaH, tetrahydrofuran (THF), 0 °C to room temperature (rt), 4 h |
| (iii) | Na2S·9H2O, EtOH, 1.5 h, 64% (two steps) |
| (iv) | KOH, EtOH, 50 °C, 2 h, 60% |
| (v)  | (COCl)2, cat. dimethylformamide (DMF), CH2Cl2, 2 h, quant. |
| (vi) | NaH, tetrahydrofuran (THF), 0 °C to rt, 16 h, 80% |
| (vii) | HCl, dioxane, 1 h, 98% |
| (viii) | 9 (slow addition), CH2Cl2, 0 °C, 80%, and 9 (slow addition), various conditions, <5% |

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scope. In addition, gram-scale synthesis of diacid 8 was enabled via this synthetic route. Conversion to diacyl chloride 9 can be accomplished by oxalyl chloride under standard conditions.

We initially attempted the direct cyclization of acyl chloride 9 with triamine 10 to form Receptor 3; however, this resulted primarily in the formation of oligomeric species. A more robust approach involves molecule 13, which can be synthesized starting with the preparation of protected amine 11, followed by coupling with acyl chloride 9 to form 12 and deprotection under acidic conditions. Use of HCl in dioxane as a deprotecting agent was crucial as the use of trifluoroacetic acid resulted in the formation of unidentified side products. Slow addition of acyl chloride 9 to a dilute solution of 13 in chloroform with gentle heating provided Receptor 3 in a 20% yield (Section S4, Supporting Information). The structure was confirmed by NMR, high-resolution mass spectrometry (HRMS), and X-ray crystallography (Section S6, Supporting Information). Notably, the X-ray structure shows all amide N–H bonds oriented toward the cavity of the receptor, potentially reorganizing the scaffold toward interacting with anions (Figure 2).

**Binding Characterization.** Association constants of Receptor 3 in acetonitrile with various tetrabutylammonium or tetraethylammonium salts were determined via UV/vis titrations, using SIVVU for data analysis (Table 1 and Section S2, Supporting Information). We chose a list of environmentally and biologically relevant monoanionic guests to probe the binding behavior of Receptor 3. Asymmetric errors on the binding constant terms were calculated by bootstrapping each data set column-wise 1000 times. The errors of at least three separate titrations were then combined according to model 2 of Barlow’s paper and were reported as 95% confidence intervals. The absorbance of all species, including the host, guest, and complexes thereof, was refined as part of our data analysis. As a result of the low concentration used for titration experiments (<35 μM) and the polar solvent employed, ion-pairing interactions were ignored. Binding stoichiometries were assessed by applying various binding models in the formation of HG and HG2 species to each experiment and selecting the binding stoichiometry that gave the lowest error, as is currently considered best practices. Additionally, when measuring the stability constants of Receptor 3 with HCO3−, binding isotherms were produced that could not be accurately fit to a 1:1 binding model, and with H2AsO4−, the application of a 1:1 binding model provided fits that were associated with higher error than our other anion binding experiments. Instead, it was found that the binding of H2AsO4− and HCO3− could be more accurately fit with a 1:2 host/guest binding mode in accordance with the following equations

\[ H + G \rightleftharpoons HG \quad K_{1,1} \]
\[ HG + G \rightleftharpoons HG_2 \quad K_{1,2} \]
\[ H + 2G \rightleftharpoons HG_2 \quad \beta \]

From the \( K_{1,1} \) and \( K_{1,2} \) values, the binding cooperativity can be assessed by calculation of the interactivity parameter \( \alpha \) (Table 1). Interestingly, while HCO3− demonstrates negative

![Figure 2](https://dx.doi.org/10.1021/jacs.jc01236)

**Table 1. Stability Constants of 3 with Various Anions**

| anion        | \( \log K_{1,1} \) | \( \log K_{1,2} \) | \( \log K_d \) | \( \Delta G_{K_{1,1}} \) | \( \Delta G_{K_{1,2}} \) | \( \Delta G_{K_0} \) | \( \alpha \) |
|--------------|--------------------|--------------------|----------------|--------------------------|--------------------------|--------------------------|---------|
| H2AsO4−     | 5.0±0.05           | 5.4±0.03           | 10.4±0.04      | −27±1                    | −29±1                    | −57±1                    | 9       |
| HCO3−        | 4.76±0.03          | 3.53±0.09          | 8.3±0.04       | −26.1±0.7                | −19.4±1.1                | −45±2                    | 0.25    |
| OAc−         | 5.22±0.10          | −d                 | −d             | −28.7±0.5                | −d                        | −d                        | −d      |
| H3PO4−       | 4.24±0.05          | −d                 | −d             | −23.3±0.3                | −d                        | −d                        | −d      |
| CN−          | 3.69±0.05          | −d                 | −d             | −20.3±0.2                | −d                        | −d                        | −d      |
| HSO4−        | 3.57±0.05          | −d                 | −d             | −19.6±0.2                | −d                        | −d                        | −d      |
| NO3−         | 3.47±0.05          | −d                 | −d             | −19.1±0.2                | −d                        | −d                        | −d      |
| Cl−          | 3.20±0.05          | −d                 | −d             | −17.6±0.1                | −d                        | −d                        | −d      |

*Titrations were performed at 20 °C in MeCN using the tetrabutylammonium salt of each anion. UV/vis data fitting was performed using SIVVU. Errors are given from at least three experiments with asymmetric errors at 95% confidence intervals. Interaction parameter, defined as \( \alpha = \frac{4K_{1,1}}{K_{1,1}} \). Tetraethylammonium bicarbonate was employed. Not applicable.*
cooperativity ($\alpha = 0.25$), $\text{H}_2\text{AsO}_4^-$ demonstrates positive cooperativity ($\alpha = 9$), indicating that the binding of one anionic species makes the binding of the second more favorable. Such binding stoichiometry may be indicative of the formation of anti-electrostatic hydrogen bonds; however, we have been able to obtain neither solution- nor solid-state evidence for the exact binding mode of these two anions.

We were especially surprised to discover that the 1:2 binding behavior in the case of $\text{H}_2\text{AsO}_4^-$ does not hold for $\text{H}_2\text{PO}_4^-$, given their similar sizes and properties. We closely scrutinized this behavior by subjecting several arsenate and phosphate titrations to both 1:1 and 1:2 binding models to assess the best fit. The absorbance and accompanying fits from 1:1 and 1:2 binding models at 292 nm are shown in Figure 3. We found analysis of the residuals to be particularly useful in the determination of the binding stoichiometry, and such analysis has been demonstrated to be significantly more informative and robust than Job’s plot analysis. As shown in Figure 3a,b, the application of a 1:1 binding model for $\text{H}_2\text{AsO}_4^-$ results in residuals that trace a sinusoidal curve, which has been demonstrated to be indicative of an additional binding event. Additionally, a global fit of this experiment results in extinction coefficients for the HG complex of 0 at certain wavelengths, a nonrealistic value, and large absorbance of the guest, an artifact not observed in the absence of the host (Figure S81). Removing guest absorbance from the binding model does not improve the resulting fit. Application of a 1:2 binding model, instead, provides significantly reduced residuals and realistic extinction coefficients for all species involved (H, G, HG, and HG₂) (Figure S83). Application of the same process to titration experiments with $\text{H}_2\text{PO}_4^-$ provides similar residuals for both the 1:1 and 1:2 binding models, which is indicative that a 1:2 binding model is not necessary to account for the change in absorbance (Figure 3c,d). Thus, evidence from UV/vis titration experiments indicates that phosphate and arsenate undergo different binding events with Receptor 3 in acetonitrile (see Section S2 (Supporting Information) for global fits of all titrations and three-dimensional (3D) plots of residuals). Indeed, strong selectivity between arsenate and phosphate is rare in both proteins and synthetic receptors, and only a few reports are present in the literature.

We sought to further probe the difference in binding behavior between $\text{H}_2\text{AsO}_4^-$ and $\text{H}_2\text{PO}_4^-$ by electrospray ionization mass spectrometry (ESI-MS) studies in acetonitrile. Although ESI-MS studies are, by themselves, insufficient in determining the stoichiometry of a host–guest interaction, results of such experiments can serve as supporting evidence for the observed binding stoichiometry from solution-phase experiments. While experiments with $\text{H}_2\text{PO}_4$ only revealed evidence of a 1:1 complex (Section S3.2, Supporting Information), similar experiments with $\text{H}_2\text{AsO}_4$ revealed a mass corresponding to $[\text{M} + \text{NBu}_4 + \text{H}_2\text{As}_2\text{O}_7]^{-}$, which could provide additional evidence of the formation of a 1:2 complex (Section S3.1 and Figure 4). The preparative formation of pyroarsenate salts requires temperatures in an excess of 150 °C, typically for several hours, and they degrade rapidly in the presence of water. Given that the ESI source was held at 100 °C, it could be possible that the guest induces dehydration of $\text{H}_2\text{AsO}_4^-$ at elevated temperatures or in the gas phase, due either to hydrogen bonding or by simply holding two guest molecules in close proximity to one another. The formation of pyroarsenate induced by Receptor 3 in solution, however, could potentially explain the difference in binding energies between $\text{H}_2\text{PO}_4^-$ and $\text{H}_2\text{AsO}_4^-$, as computational studies indicate that the formation of pyroarsenate is ∼20 kJ/mol less unfavorable than the formation of pyrophosphate. Solution-phase evidence to confirm or refute pyroarsenate formation, however, is currently elusive, and we are actively investigating the possibility of this phenomenon.

We also endeavored to further probe the binding interactions with all anions by $^1\text{H}$ NMR titration, as observation of similar binding interactions at different concentrations can serve as further evidence for assigned binding behavior (Section S5, Supporting Information). As a result of aggregation and solubility issues observed in pure MeCN–d$_3$ at concentrations greater than 0.25 mM, a mixed-solvent system, 25% CD$_3$Cl in MeCN–d$_3$, was employed.

A representative titration experiment with $\text{HCO}_3^-$ is shown in Figure 5. In all cases, the resonances corresponding to the amide protons shift downfield with increasing equivalents of

Figure 3. Comparison of 1:1 and 1:2 fits of Receptor 3 at (a) 28.7 µM after the addition of 5.08 equiv of $\text{TBAH}_2\text{AsO}_4$ with (b) the resulting residuals from the application of 1:1 and 1:2 binding models and (c) 30.0 µM after the addition of 15.5 equiv of $\text{TBAH}_2\text{PO}_4$ with (d) the resulting residuals from the application of 1:1 and 1:2 binding models. Absorbance data from 275 to 500 nm were used to determine the association constant and absorbance of all species in solution. Full binding models for these experiments are available in the Supporting Information in Figures S81–S84 and S65–S68 for $\text{TBAH}_2\text{AsO}_4$ and $\text{TBAH}_2\text{PO}_4$, respectively.
anion, which is indicative of hydrogen-bonding interactions. Interestingly, titration with TBAH₂AsO₄ resulted in exceptionally broad receptor peaks, which may be a result of the inclusion of quadrupolar nuclei (Figure S110). This may implicate Receptor 3 as a probe for the presence of arsenate by ¹H NMR. Due to the decreased solvent polarity, similar, but slightly higher, association constants were obtained for HSO₄⁻ (Figure S112) and NO₃⁻ (Figure S113). For experiments with HCO₃⁻, different values were obtained for $K_{1:1}$ and $K_{1:2}$ than from UV/vis titration experiments, but data analysis indicated the same binding stoichiometry and similar value for $\beta_2$.

In the case of Cl⁻, a small $K_{1:2}$ is observed (log $K_{1:2} \sim 1.0$) that may arise due to ion-pairing equilibria from both the higher concentration and less polar solvent system employed (Figure S114). ¹H NMR titrations with OAc⁻ provided a lower association constant, but such activity is unsurprising given that OAc⁻ has a $K_{1:1}$ beyond the detection limit for ¹H NMR experiments (Figure S108).³⁵ For H₂PO₄⁻, ¹H NMR titration revealed a $K_{1:1}$ that is greater than that measured in our UV/vis titration experiments (log $K_{1:1} \sim 4.6$), as well as a relatively small $K_{1:2}$ (log $K_{1:2} \sim 3.4$, log $\beta_2 \sim 8.1$) (Figure S109). As evidenced by our experiments with arsenate and bicarbonate, the size of the binding site does not preclude the inclusion of two anionic species, and it may be that the slightly less polar solvent system induces further burying of the hydrophilic surface area of H₂PO₄⁻, forming higher-order complexes. Additionally, switching of the binding stoichiometry is not uncommon upon changing the solvent polarity.⁶⁴,⁶⁸,⁶⁹ Finally, ¹H NMR titrations with CN⁻ were inconsistent with our UV/vis experiments, but we also observed a change in solution color (colorless to orange), which may indicate some reaction of cyanide with the receptor, complicating the binding model (Figure S111). Such behavior was not observed at lower concentrations in the case of the UV/vis experiment. See Section S5.1 (Supporting Information) for further discussion on the ¹H NMR experiments.

The overall affinities of Receptor 3 with the anions surveyed are surprisingly high. Although Receptor 1 demonstrates relatively high affinity for NO₃⁻ and OAc⁻ (log $K_{1:1} \sim 2.5$ and 2.9 in 25% CD₂Cl₂ in MeCN-$d_3$), the overall anion affinity is significantly decreased compared to that of Receptor 3.⁴³ We speculate that this may be due to repulsive interactions between the pyridine nitrogen and anionic guest. The sulfur atom, on the other hand, is bent out of the plane of the amide hydrogens, preventing such repulsive interactions, as observed from the crystal structure and density functional theory (DFT)-calculated geometry (Figures 2 and S169). Additionally, modeling of Receptor 3 with either one or two molecules of H₂AsO₄⁻ or H₂As₂O₇²⁻ indicated the formation of C–H hydrogen-bonding interactions with the methyl groups on the 1,4-dithiin rings, which may enhance interactions with guests (Figures S170–S172, Section S11, Supporting Information). This increase in affinity is advantageous in that it could help to overcome the large solvation energy of anions, allowing binding in more polar solvents.

It is important to note, however, that Receptor 1 was not subjected to titration experiments with H₂AsO₄⁻, and its binding selectivity for H₂PO₄⁻ over H₂AsO₄⁻ is unknown. Most receptors that have been found to complex phosphate, in fact, have not been tested with arsenate. Due to the environmental and biological relevance of arsenate, we believe that this anion should become a more standard guest in the

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Figure 4. ESI-MS of Receptor 3 (95 μM) in the presence of 2 equiv of TBAH₂AsO₄ in MeCN. The attached table shows the observed masses and their assigned adducts.

| adduct                          | m/z (Calc.) | m/z (Obs.) |
|---------------------------------|-------------|------------|
| [M-H]⁻                          | 1085.3295   | 1085.3326  |
| [M+H₂AsO₄]⁻                     | 1227.2543   | 1227.2572  |
| [M+NBu⁺+H₂AsO₄]⁻                | 1592.4454   | 1592.4459  |

Figure 5. (a) ¹H NMR titration of Receptor 3 (1.02 mM) with TEAHCO₃ in 25% CDCl₃ in MeCN-$d_3$ (the arrow indicates the resonance associated with the amide proton), (b) assignment of protons in Receptor 3, and (c) derived changes in the chemical shift for nonamide hydrogens.
characterization of supramolecular receptors to help establish trends in arsenate−phosphate discrimination.

**Electrochemical Characterization.** 1,4-Dithiins, similar to thianthrenes, are known to undergo a reversible, single-electron oxidation under anhydrous conditions.42 As a result of the proximity of the redox-active moiety to the binding site, as well as the planarization of 1,4-dithiin moieties upon single-electron oxidation, we hypothesized that the inclusion of different anions could give rise to different electrochemical responses, such as varying cathodic perturbations in the observed $E_{1/2}$.31 In a solution of 0.1 M TBAPF$_6$ in MeCN, the macrocycle undergoes a single quasi-reversible oxidation event (Figures 6a and S124). Although Receptor 3 has limited solubility in pure acetonitrile, the addition of TBAPF$_6$ allows for effective dissolution. In comparison with model compound SS, both are oxidized at similar potentials (3, $E_{1/2} = 0.65$ V vs Fc/Fc$^+$, SS, $E_{1/2} = 0.71$ V vs Fc/Fc$^+$; Figure S125), but the oxidation of Receptor 3 is kinetically slower, as indicated by the larger shift in peak potential with the scan rate. To determine the electron-transfer number for the oxidation of Receptor 3, we performed chronoamperometry and cyclic voltammetry with a microelectrode. Analysis of the data as established by Amatore and co-workers indicated that the oxidation event involved a degenerate or near-degenerate transfer of three electrons (Section S7.2, Supporting Information).70 Formation of a tricationic complex would foster stronger interactions with guests via electrostatic interactions.
attraction, further enhancing the affinity of the oxidized complex with each anion.

Next, the electrochemical behavior of Receptor 3 in the presence of various anions was surveyed (Figure 6b–h). Due to the relatively low oxidation potential of chloride ($E^{1/2} = 0.52$ V vs Fe/C/Pc'; Figure S132), it was excluded from this study. Receptor 3 exhibits complex oxidation behavior for each anionic guest, which we believe results from unique binding behavior of the oxidized receptor, changes in the $E^{1/2}$ and electron-transfer kinetics upon complexation, and subsequent reaction of the anion with Receptor 3 upon oxidation. Upon addition of NO$_3^-$, the oxidation wave shifts to less positive potentials and becomes chemically irreversible (Figure 6h). This can be rationalized by the oxidation of the tri-radical cation by nitrate, a known behavior in thianthrene radical cations.\(^7\) The addition of H$_2$PO$_4^-$, H$_3$AsO$_4^-$, HCO$_3^-$, CN$^-$, and OAc$^-$ gave irreversible redox couples as well, but analysis of subsequent scans demonstrated varying degrees of precipitation on the electrode surface (Figure 6b–f and Section S7.4). In the case of H$_3$PO$_4^-$ (Figure S135), HCO$_3^-$ (Figure S145), and CN$^-$ (Figure S139), the acquisition of subsequent scans by cyclic voltammetry resulted in little signal, indicating the formation of an insulating film on the electrode surface. Subsequent scans, however, in the case of NO$_3^-$ (Figure S141), H$_3$AsO$_4^-$ (Figure S137), and OAc$^-$ (Figure S143) gave similar voltammograms but with lower current, indicating that the fidelity of the electrode surface is maintained, but that Receptor 3 proximate to the electrode surface was consumed due to an irreversible chemical reaction with the anionic guest. Finally, while HSO$_4^-$ exhibited a moderate association constant with the neutral receptor as determined by UV/vis titrations, we found that the addition of bisulfate caused dramatic changes in the shape of both the oxidation and reduction waves while maintaining chemical reversibility (Figures 6g and S133). Interestingly, in the case of NO$_3^-$, “two-wave” behavior is observed (Figure 6h). Such behavior is indicative of slow-exchange interactions and is potentially useful in the differentiation of anions in a similar fashion that has been described for slow host–guest exchange in NMR studies.\(^17\) In other cases, such as H$_3$AsO$_4^-$, H$_2$PO$_4^-$, OAc$^-$, HCO$_3^-$, and CN$^-$, as many as three distinct oxidation waves can be observed after the addition of various equivalents of the anion (Figure 6b–f). Due to the irreversible nature of these redox couples, exact analysis of the oxidation event is difficult, and we abandoned further electrochemical experiments due to the high reactivity of Receptor 3 in its oxidized form. Additionally, more complex mechanisms, such as the loss of degeneracy in the oxidation of Receptor 3 or the formation of additional electroactive materials, may be at play, further complicating the response.

The results of the electrochemical anion titrations are summarized in Table 2. Although the magnitude of the change in peak potential is similar to the more common strategy of appending receptors with well-known redox transducers, such as ferrocene, changes in the peak shape and degree of chemical reversibility vary widely based on the identity of the anionic guest. In our case, we also believe that the conformational activity of the electroactive moiety may participate in enhancing the response toward anions. Geometry of the triply oxidized host, as generated from DFT calculations, indicates that the planarization of the 1,4-dithio moiety generates a cationic binding site of unique size as compared to the neutral receptor, which may aid in enhancing the change in association constant with the oxidized receptor (Figure S173, Section S11, Supporting Information). Interestingly, we found that Receptor 3 exhibits a moderate association constant to the supporting electrolyte, TBAPF$_6$ ($\log K_{ass} \sim 3.7$; Figures S130 and S131, Section S7.3, Supporting Information). In spite of this, the addition of other anionic guests, even those with comparable $K_{ass}$ gave altered voltammograms. This may indicate that binding occurs almost solely with the oxidized host under the conditions for electrochemical measurements. Finally, we found that after the addition of 5 equiv of TBAHSO$_4$ with a shift in $E^{1/2}$ of 126 mV and a three-electron process, a binding enhancement factor (BEF) of 2.5 $\times$ 10$^6$ could be estimated.\(^31\) Moreover, larger perturbations in the peak potential of oxidation were observed with other anions, but the lack of return waves precluded estimation of the BEFs. Although the use of 1,4-dithiins as redox transducers may be too sensitive for practical applications in the presence of nucleophilic species, the incorporation of multiple redox-active moieties adjacent to the binding site could give molecules with sufficiently high ion affinities when oxidized to effectively bind to anions in polar media.

| Anion$^a$ | $\Delta E_{as}$ (mV)$^b$ |
|-----------|----------------------|
| H$_3$AsO$_4^-$ | -334$^c$ |
| HCO$_3^-$ | -235 |
| OAc$^-$ | -105 |
| H$_2$PO$_4^-$ | -480 |
| CN$^-$ | -142 |
| HSO$_4^-$ | -118 |
| NO$_3^-$ | -102 |
| Cl$^-$ | N/D$^d$ |

$^a$Tetraethylammonium salts were employed. $^b$Change in the peak potential of the oxidation event upon the addition of 5 equiv of anion. $^c$Two oxidation events are observed. The more cathodic peak is reported here. $^d$Tetraethylammonium bicarbonate was employed. $^e$Not determined.

**CONCLUSIONS**

In conclusion, we have synthesized and characterized an anion receptor with novel 1,4-dithio moieties. The receptor shows high selectivity and affinity toward HCO$_3^-$ and H$_3$AsO$_4^-$, which were observed to bind in a 1:2 host/guest binding mode. Additionally, H$_3$AsO$_4^-$ was found to undergo different binding behavior with Receptor 3 than H$_2$PO$_4^-$, an uncommon characteristic given the two anions’ similar size and properties. The origin of arsenate–phosphate discrimination, however, is currently unknown. Further analysis by cyclic voltammetry revealed unique responses upon the addition of anionic guests, but due to the high reactivity of Receptor 3 when oxidized, deconvolution of the response proved difficult in many cases. Due to the interest in the detection and binding of arsenate and the lack of effective strategies toward selective complexation, we hope this report will encourage other researchers to include this anion in their studies to help establish trends in arsenate–phosphate discrimination. Future experiments in our laboratory will involve the further synthesis and characterization of anion receptors with potential application in the monitoring of environmentally relevant anion contaminants.
**EXPERIMENTAL SECTION**

**General Experimental Considerations.** All reagents were purchased from commercial sources and used without further purification unless otherwise specified. Tetrabutylammonium dihydrogen arsenate was prepared according to a literature procedure. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH2Cl2) were purified using an Inert solvent purification system by passage through two alumina columns and were stored in a Schlenk flask over 4 Å molecular sieves under an argon atmosphere. Tetrabutylammonium hexafluorophosphate for electrochemical analysis was recrystallized from EtOH three times and dried in a vacuum oven at 60 °C. All chemical manipulations were performed under an argon atmosphere in flame-dried glassware unless otherwise specified. The reported reaction temperatures refer to the temperature of external water or oil baths.

Chromatographic purifications were performed with a Biotage Isolera using Biotage SNAP Ultra columns with the specified solvent gradient. Typically, columns were performed with 1 column volume of the initial solvent gradient, followed by a linear gradient over 10 column volumes to the final solvent composition, followed by an additional 2 column volumes at the final solvent composition. NMR spectra were recorded on either a 400 MHz Bruker Avance-III HD Nanobay spectrometer, 500 MHz Bruker Avance Neo spectrometer, or 600 MHz Bruker Avance Neo spectrometer. Chemical shifts δ are reported in parts per million (ppm) downfield from tetramethylsilane by referencing to residual solvent signals (CDCl3; δ 1H 7.26 ppm, δ 13C 77.16 ppm; dimethyl sulfoxide (DMSO)-d6; δ 1H 2.500 ppm, δ 13C 39.52 ppm; CD3CN: δ 1H 1.94, δ 13C 118.26). Coupled constants J are listed in hertz (Hz) with multiplicities s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a JEOL Accu-TOF system equipped with either a direct analysis in real time (DART) (DART-MS) or ESI (ESI-MS) source or an Agilent 6450 quadrupole time-of-flight (TOF) equipped with an AJS-ESI (Q-TOF-ESI-MS) source.

**Titration Experiments.** All UV/vis titrations were carried out on an Agilent Cary-4000 UV/vis spectrometer, recording from 300 to 200 nm at intervals of 0.5 nm. Tetrabutylammonium salts were stored in a vacuum desiccator prior to titration. UV/vis titrations were carried out in HPLC-grade MeCN in 1 cm cuvettes at the specified host concentration. Host concentration was determined using the Beer’s law absorbance of Receptor 3 at 292 nm, which is linearly correlated with concentration (Figures S3, S4). Anionic guests were dissolved in a solution of the host to keep the host concentration constant over the course of the experiment. Guests were added using 10 or 50 μL syringes (Hamilton), followed by manual agitation for 5–10 s. Association constants were then determined using SIVVVU with absorbance data from 275 to 500 nm. 1H NMR titrations were performed in 25% CD2Cl2 in CD3CN. Anionic guests were dissolved in a solution of the host to keep the host concentration constant over the course of the titration. Solutions of the anion were added in 5 or 25 μL aliquots using either 10 or 50 μL syringes (Hamilton) followed by manual agitation for 10–15 s followed by immediate measurement by 1H NMR at the specified field. In all cases, the spectra were referenced to residual CDCl3 (δ 7.26 ppm).

**Electrochemical Experiments.** Electrochemical experiments were performed in a nitrogen-filled glovebox (O2 < 20 ppm, H2O < 2 ppm) with a BioLogic SP-150 potentiostat. Platinum working electrodes (2 mm or 10 μm diameter) were polished using first suspensions of 1.0 μm, then 0.3 μm, then 0.05 μm alumina in water on a polishing pad followed by sonication in methanol to remove excess alumina and then chemical polishing by cycling the electrode in 1 M H2SO4 over the potential window of water until the resulting traces overlapped. The electrode was then rinsed with methanol and blown-dry with nitrogen before being transferred into the glovebox. A platinum wire was used as the counter electrode. A silver pseudoreference electrode was used, and all measurements were referenced to Fc/Fc’.

All titration experiments were performed at 1.0 mM of the active material in MeCN, with 0.1 M TBAPF6 as a supporting electrolyte. In the case that the oxidation was chemically irreversible, which is the case with all anions except for TBAHSO4, the first scan is reported. In the case of TBAHSO4, the third scan is reported, which is similar to the first two scans.

**ESI-MS Experiments.** Electrospray ionization (ESI) binding experiments were carried out on a JEOL Accu-TOF equipped with an ESI source. All ions were observed in negative mode, with the orifice and desolvating chambers held at 100 °C. The samples were run via direct infusion at the specified concentration at a rate of 1.0 mL/h using a syringe pump. All experiments were run, holding the host concentration at approximately 100 μM in acetonitrile.

**Computational Studies.** Theoretical calculations were carried out with the Spartan18 (1.4.4, Wave function Inc., Irvine CA) software packages on a computer operating with Windows 10 OS. Geometry optimizations were performed with density functional theory (DFT) calculations using the B3LYP functional with the 6-31G** basis set in the gas phase. Frequency calculations were performed to confirm that the structures were at a local energy minimum. Outputs were visualized with CYLview. 

**Synthetic Procedures.** Diethyl 2,2’-Thiobis(3-oxobutanoate) (5). Caution: This reaction produces stoichiometric amounts of HCl gas and must be performed in a fume hood or similarly well-ventilated area. The title compound was prepared according to a modified literature procedure. To a round-bottom flask open to the atmosphere, ethyl acetocetate (4) (10.0 mL, 78.5 mmol, 1.0 equiv) and hexanes (16 mL) were added. The mixture was then heated to 40 °C, upon which the solution became homogeneous. Disulfur dichloride (3.14 mL, 39.2 mmol, 0.5 equiv) was then added in one portion. After 1–2 min, the solution developed a yellow color and began to bubble vigorously. After the bubbling had subsided, the solution was allowed to react for a further 30 min, over which a solid precipitated. The reaction was then cooled in an ice bath, and the white solid was collected by vacuum filtration, washed first with hexanes and then water, and subsequently dried under vacuum at 50 °C to remove residual water. The solid was purified by recrystallization in acetone (25 mL) to give the target compound as colorless needles (4.59 g, 15.8 mmol, 40%). 1H NMR (500 MHz, CDCl3) δ 13.40 (s, 2H), 4.23 (q, J = 7.1 Hz, 4H), 2.42 (s, 6H), 1.30 (t, J = 7.1 Hz, 6H). 13C (1H) NMR (126 MHz, CDCl3) δ 181.4, 172.9, 95.1, 61.4, 21.1, 14.3. HRMS (ESI-MS) m/z: [M + H]+ calc for C12H19O6S+ 291.0897; found 291.0900.

Diethyl 3,5-Dimethyl-1,4-dithiine-2,6-dicarboxylate (7). THF (50 mL) was added to a round-bottom flask containing sodium hydride (3.31 g, 60% dispersion in mineral oil, 82.8 mmol, 3.0 equiv). The mixture was cooled to 0 °C, and compound 5 (8.0 g, 27.6 mmol, 1.0 equiv) was added as a solution in THF (125 mL) via cannula transfer over approximately 10 min, resulting in the evolution of H2 gas. After completion of the addition, the mixture was allowed to stir for a further 30 min at 0 °C, after which tosyl anhydride (19.8 g, 60.7 mmol, 2.2 equiv) was added as a solution in THF (150 mL) via cannula transfer over approximately 10 min, during which the reaction mixture became viscous. The reaction was then allowed to warm to room temperature. After conversion was complete, as judged by TLC (approximately 3 h), the reaction was quenched slowly with the addition of water (20 mL) and then 4 M HCl (20 mL). The reaction was concentrated under reduced pressure to a total volume of about 100 mL. The resulting mixture was then extracted with diethyl ether (3 × 100 mL), and then the organic layers were combined, washed with saturated NaHCO3 (100 mL) and brine (100 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure to give approximately 15 g of a red oil containing compound 6 as a mixture of isomers. The mixture was used without purification in the next step. The red oil was dissolved in EtOH (125 mL), and sodium sulfide nonhydrate (4.96 g, 20.7 mmol, 0.75 equiv) was added in one portion, resulting in the appearance of an orange solution and the precipitation of a solid. After 1.5 h, CH3Cl (125 mL) was added to further precipitate additional salts, and the mixture was filtered through a bed of celite, and the volatiles were removed under reduced pressure. The dark oil was then purified by flash chromatography (1 → 15% EtOAc in hexanes) to give the title compound as an orange oil.
that solidifies upon storage at 2–5 °C (5.08 g, 17.6 mmol, 64%). 1 H NMR (400 MHz, CDCl3) ω 4.25 (q, J = 7.1 Hz, 4H), 2.41 (s, 6H), 1.32 (t, J = 7.2 Hz, 6H). 13C{1H} NMR (101 MHz, CDCl3) ω 162.9, 149.6, 122.3, 61.9, 22.7, 14.3. HRMS (DART-MS) m/z: [M + H]+ calcd for C11H18O5S2: 289.0563; found 289.0558.

3.5-Dimethyl-1,4-dithiane-2,6-dicarboxylic Acid (8). Potassium hydroxide (58.55 g, 100 mmol) was added, and the vessel was subsequently evacuated and resealed with hydrogen five times. The reaction was purged with hydrogen several times until conversion was complete as observed by 1 H NMR (typically 3 days). After the reaction was complete, the reaction mixture was filtered through a pad of celite. The filtrate was then concentrated under reduced pressure, giving the title compound as a pink solid (10.5 g, 42.1 mmol, >95%). 1 H and 13C NMR spectra were consistent with those reported in the literature. 46 1 H NMR (500 MHz, CDCl3) ω 3.87 (s, 6H), 2.82 (q, J = 7.5 Hz, 6H), 1.37 (2, J = 7.5 Hz, 9H). 13C{1H} NMR (126 MHz, CDCl3) ω 140.5, 137.6, 39.8, 22.7, 16.9.

Di-tert-butyl (5-([(Benzyloxy)carbonyl]amino)methyl)-2,4,6-triethyl-1,3-phenylene(bis[methylene])dicarbamate (54). The title compound was prepared according to a modified literature procedure. 46 Compound 10 (4.00 g, 16.0 mmol, 1.0 equiv) and sodium hydroxide (960 mg, 24.0 mmol, 1.5 equiv) were added to a round-bottom flask and dissolved in dioxane (80 mL) and water (50 mL), and the solution was cooled to 0 °C. Benzylchloroforomate (3.87 mL, 27.2 mmol, 1.7 equiv) and di-tert-butyl dicarbonate (11.0 g, 50.5 mmol, 3.15 equiv) were dissolved in a minimal amount of dioxane to give a total volume of 20 mL and added over 4 h via a syringe pump. After the addition was complete, the reaction was allowed to come to room temperature and stirred for further 2 h. The dioxane was then removed under reduced pressure, and the resulting aqueous layer was extracted with CH3Cl (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), filtered, and concentrated under reduced pressure to give an orange solid. For all transformations, the conversion of diazo to acyl chloride was assumed to be quantitative. Diacetyl chloride 9 was prepared from diaacetyl 8 directly when needed. 1 H NMR (500 MHz, CDCl3) δ 2.46 (s, 6H). 13C{1H} NMR (126 MHz, CDCl3) δ 163.0, 156.9, 125.3, 23.3.

1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene (S2). The title compound was prepared in accordance with a literature procedure. 43, 45 1,3,5-Trithiabenzene (S1) (100.0 mL, 53.1 mmol, 1.00 equiv) and paraformaldehyde (16.8 g, 560 mmol, 10 equiv) were dissolved in a solution of 30% HBr in HOAc (100 mL). Zinc bromide (19.8 g, 87.8 mmol, 1.65 equiv) was added, and the reaction was then brought to 90 °C and stirred overnight. The mixture was cooled to room temperature, and the solid was collected by vacuum filtration and washed with water to give the title compound as an off-white powder (21.1 g, 47.8%, 90%). 1 H and 13C NMR spectra were consistent with those reported in the literature. 43, 45 1 H NMR (500 MHz, CDCl3) δ 4.58 (s, 6H), 2.95 (q, J = 7.6 Hz, 6H), 1.34 (t, J = 7.6 Hz, 9H). 13C{1H} NMR (126 MHz, CDCl3) δ 145.2, 132.8, 28.7, 22.9, 15.5.

1,3,5-Tris(azidomethyl)-2,4,6-triethylbenzene (S3). Caution: Azeides are potentially explosive. While we never experienced any explosions with the title compound, appropriate hazards should be observed when preparing and working with it. The title compound was prepared according to a modified literature procedure. 44 Compound S2 (2.27 g, 3.89 mmol, 1.0 equiv) in MeOH (40 mL). The reaction vessel was then evacuated and refliled with hydrogen five times. A solution of compound S4 (2.27 g, 3.89 mmol, 1.0 equiv) in MeOH (40 mL) was added, and the vessel was then evacuated and refliled with hydrogen five times. The reaction was repeatedly purged with hydrogen until conversion was complete, as observed by 1 H NMR (around 2.5 h). After the reaction was complete, the reaction was filtered through a pad of celite. The filtrate was then concentrated under reduced pressure, giving the title compound as a white solid (1.75 g, 3.89 mmol, quant.). 1 H and 13C NMR spectra were consistent with those reported in the literature. 44 1 H NMR (500 MHz, DMSO-d6) δ 6.61 (t, J = 4.8 Hz, 2H), 4.17 (d, J = 4.8 Hz, 2H), 3.70 (s, 2H), 2.71 (q, J = 7.5 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 1.38 (s, 18H), 1.10 (t, J = 7.5 Hz, 6H), 1.06 (t, J = 7.3 Hz, 3H). 13C{1H} NMR (126 MHz, DMSO-d6) δ 155.8, 155.2, 143.0, 142.7, 137.2, 132.3, 131.80, 128.3, 127.7, 127.6, 77.7, 65.3, 38.7, 38.1, 28.3, 22.5, 22.4, 16.2, 16.1. Di-tetr-butyl-(5-(Aminomethyl)-2,4,6-triethyl-1,3-phenylene)bis-(methylene) Dicarbamate (11). The title compound was prepared according to a modified literature procedure. 44 A round-bottom flask was charged with 5% palladium on carbon (172 mg) and MeOH (40 mL). The reaction vessel was then evacuated and refliled with hydrogen five times. A solution of compound S4 (2.27 g, 3.89 mmol, 1.0 equiv) in MeOH (40 mL) was added, and the vessel was then evacuated and refliled with hydrogen five times. The reaction was repeatedly purged with hydrogen until conversion was complete, as observed by 1 H NMR (around 2.5 h). After the reaction was complete, the reaction was filtered through a pad of celite. The filtrate was then concentrated under reduced pressure, giving the title compound as a white solid (1.75 g, 3.89 mmol, quant.). 1 H and 13C NMR spectra were consistent with those reported in the literature. 44 1 H NMR (500 MHz, DMSO-d6) δ 6.61 (t, J = 4.8 Hz, 2H), 4.17 (d, J = 4.8 Hz, 2H), 3.70 (s, 2H), 2.71 (q, J = 7.5 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 1.38 (s, 18H), 1.10 (t, J = 7.5 Hz, 6H), 1.06 (t, J = 7.3 Hz, 3H). 13C{1H} NMR (126 MHz, DMSO-d6) δ 155.2, 141.9, 141.8, 136.9, 132.0, 77.6, 38.2, 28.3, 22.4, 22.1, 16.5, 16.3. Tetra-tet-butyl (((((3,5-Dimethyl-1,4-dithiine-2,6-dicarbonyl)bis((azanediyl))bis(methylene))bis(2,4,6-triethylbenzene-5,1-diyl))tetraakis(methylene))tetracarbamate (12). A round-bottom flask containing compound 11 (1.75 g, 3.89 mmol, 2.1 equiv) and triethylamine (0.65 mL, 4.6 mmol, 2.5 equiv) in CH3Cl (10 mL) was cooled to 0 °C. In a separate flask, diacetyl chloride 9 that was freshly prepared from diacetyl 8 (430 mg, 1.85 mmol, 1.0 equiv) was dissolved in CH3Cl (10 mL) and added dropwise to the solution of compound 11. After the addition was complete, the reaction was allowed to come to room temperature and was stirred overnight. The solution was then poured into 1 M HCl (40 mL), and the layers were separated. The aqueous layer was further extracted with CH3Cl (2 × 40 mL) and the organic layers were combined, washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to give an orange residue, which was purified by flash chromatography (0 → 3% MeOH in CH3Cl) to give the title compound as an orange solid.
(1.62 g, 1.48 mmol, 80%). 1H NMR (500 MHz, MeCN-d3) δ 6.62 (t, J = 4.8 Hz, 2H), 5.18 (s, 4H), 4.43 (d, J = 4.8 Hz, 4H), 4.29 (d, J = 5.0 Hz, 8H), 2.74 (q, J = 7.5 Hz, 4H), 2.69 (q, J = 7.5 Hz, 8H), 2.26 (s, 6H), 1.41 (s, 36H), 1.15 (t, J = 7.4 Hz, 6H), 1.10 (t, J = 7.4 Hz, 12H). 13C{1H} NMR (126 MHz, MeCN-d3) δ 164.0, 156.5, 144.8, 144.5, 133.7, 132.3, 125.1, 79.4, 39.4, 39.0, 28.6, 23.6, 21.9, 16.6. HRMS (Q-TOF-ESI-MS) m/z: [M + H]+ calc for C23H47N2O2S2 = 411.3011; found 411.3014.

N²,N°-Bis(3,5-bis(aminomethyl)-2,4,6-triethylbenzyl)-3,5-dimethyl-1,4-dithiane-2,6-dicarboxamide (13). A round-bottom flask, compound 13 (400 mg, 0.476 mmol, 1.0 equiv) was dissolved in CHCl3 (300 mL) and CH2Cl2 to give the title compound as a solvate. To remove the residual solvent, the compound was sonicated in PhMe, then 0% MeOH in hexanes) to give the title compound as a solvate. To remove the residual solvent, the solution was concentrated under reduced pressure to give an orange solid. The residue was purified by flash chromatography (15 → 25% acetone in PhMe, then 0 → 100% EtOAc in hexanes) to give the title compound as a solvate. To remove the residual solvent, the compound was sonicated in PhMe (5 mL), and the PhMe was removed under reduced pressure. This procedure was repeated five times to give the title compound as a pale yellow solid (104 mg, 0.0956 mmol, 20%). 1H NMR (600 MHz, DMSO-d6) δ 6.80 (s, 12H), 8.30 (t, J = 4.9 Hz, 2H), 4.39 (d, J = 4.5 Hz, 4H), 4.03 (s, 8H), 2.78 (q, J = 6.9 Hz, 12H), 2.14 (s, 6H), 1.11 (t, J = 7.3 Hz, 18H). 13C{1H} NMR (151 MHz, DMSO-d6) δ 163.3, 145.3, 144.4, 139.3, 132.3, 128.8, 125.0, 36.0, 23.2, 22.8, 21.6, 15.9, 15.9. HRMS (Q-TOF-ESI-MS) m/z: [M + H]+ calc for C58H91N6O10S2 = 1085.3342; found 1085.3342.

Receptor 3. In a 1 L round-bottom flask, compound 13 (400 mg, 0.476 mmol, 1.0 equiv) was dissolved in CHCl3 (300 mL) and triethylamine (0.67 mL, 4.8 mmol, 10 equiv), and the mixture was stirred for a further 20 h and was then allowed to cool to room temperature. The volume of the reaction was reduced to approximately 50 mL under reduced pressure, and the solution was washed with 1 M HCl (50 mL). The aqueous layer was then extracted with CHCl3 (2 × 50 mL), and the organic layers were combined and washed with 10% NaOH (100 mL), dried over Na2SO4, and concentrated under reduced pressure to give an orange precipitate. The reaction was allowed to stir for 2 h, after which isopropanol was added to dissolve all materials, and the volatiles were removed under reduced pressure, giving the title compound as a light orange powder (1.18 g, 1.40 mmol, 98%). 1H NMR (600 MHz, DMSO-d6) δ 8.40 (s, 12H), 8.30 (t, J = 4.9 Hz, 2H), 4.39 (d, J = 4.5 Hz, 4H), 4.03 (s, 8H), 2.78 (q, J = 6.9 Hz, 12H), 2.14 (s, 6H), 1.11 (t, J = 7.3 Hz, 18H). 13C{1H} NMR (151 MHz, DMSO-d6) δ 163.3, 145.3, 144.4, 139.3, 132.3, 128.8, 125.0, 36.0, 23.2, 22.8, 21.6, 15.9, 15.9. HRMS (Q-TOF-ESI-MS) m/z: [M + H]+ calc for C54H65N6O6S6 = 1005.9095; found 1005.9095.

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Notes
The authors declare no competing financial interest.

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REFERENCES
(1) Fried, S.; Mackie, B.; Nothwehr, E. Nitrate and Phosphate Levels Positively Affect the Growth of Algae Species Found in Penny Pond. *Tillers* 2003, 4, 21–24.
(2) Doney, S. C.; Fabry, V. J.; Feely, R. A.; Kleypas, J. A. Ocean Acidification: The Other CO2 Problem. *Annu. Rev. Mar. Sci.* 2009, 1, 169–192.
(3) Smith, A. H.; Lingas, E. O.; Rahman, M. Contamination of Drinking Water by Arsenic in Bangladesh: A Public Health Emergency. *Bull. W. H. O.* 2000, 78, 1093–1103.
(4) Narukawa, T.; Inagaki, K.; Kuroiwa, T.; Chiba, K. The Extraction and Speciation of Arsenic in Rice Flour by HPLC-ICP-MS. *Talanta* 2008, 77, 427–432.
(5) Day, J. A.; Montes-Bayón, M.; Vonderheide, A. P.; Caruso, J. A. A Study of Method Robustness for Arsenic Speciation in Drinking Water Samples by Anion Exchange HPLC-ICP-MS. *Annu. Rev. Mar. Sci.* 2002, 373, 664–668.
(6) Sadiq Khan, S.; Riaz, M. Determination of UV Active Inorganic Anions in Potable and High Salinity Water by Pair Reversed Phase Liquid Chromatography. *Talanta* 2014, 110, 209–213.
(7) Alahi, M. E. E.; Mukhopadhyay, S. C. Detection Methods of Nitrate in Water: A Review. *Sens. Actuators, A* 2018, 280, 210–221.
Multiple Amines by 19F NMR. Angew. Chem., Int. Ed. Separation. Adv. Funct. Mater. Anions. J. Am. Chem. Soc. Binding Strength, and Structure. Org. B.; Gale, P. A. Fluorescent Carbazolylurea Anion Receptors. The Journal of Organic Chemistry pubs.acs.org/joc Sensors for Chiral Carboxylate Anions. Org. Lett. Appended Aryl Triazole for Electrochemical Recognition of Triazolophanes: A New Class of Halide-Selective Lonophores for Synthesis and Applications in Colorimetric Anion Sensing. Chem. Commun. Halogen-Bonding Foldamer Molecular Film for Selective Reagentless Chloride and Sulfate Anions. J. Am. Chem. Soc. Chloride Transport by Single Molecules in Large Unilamellar Vesicles. J. Am. Chem. Soc. Sensors for Chiral Carboxylate Anions. J. Am. Chem. Soc. −1366. 4476. 7162. 75 73. 6637 7 4389. 7 1783. 11321. 4389. 11771. 4596. 10060 103 8777. 21 1986−Amino- und Hydroxy-Carbonylverbindungen mit -Amino- und Hydroxy-Carbonylverbindungen mit −140-140−140 Helix- and Lone-Pair-π Interactions in Host-Guest Chemistry. Eur. J. Org. Chem. 2014, 135, 11314−11321. 5317−5323. 5317−5323. 5317−5323. Water.

(30) Zubi, A.; Wragg, A.; Turega, S.; Adams, H.; Costa, P. J.; Félix, V.; Thomas, J. A. Modulating the Electron-Transfer Properties of a Mixed-Valence System through Host-Guest Chemistry. Chem. Sci. 2015, 6, 1334−1340. (31) Beer, P. D.; Gale, P. A.; Chen, G. Z. Mechanisms of Electrochemical Recognition of Cations, Anions and Neutral Guest Species by Redox-Active Receptor Molecules. Coord. Chem. Rev. 1999, 185−186, 3−36. (32) Robinson, S. W.; Mustoe, C. L.; White, N. G.; Brown, A.; Thompson, A. L.; Kennepolh, P.; Beer, P. D. Evidence for Halogen Bond Covalency in Acyclic and Interlocked Halogen-Bonding Receptor Anion Recognition. J. Am. Chem. Soc. 2015, 137, 499−507. (33) Mullaney, B. R.; Partridge, B. E.; Beer, P. D. A Halogen-Bonding Bis-Triazolium Rotaxane for Halide-Selective Anion Recognition. Chem. − Eur. J. 2015, 21, 1660−1665. (34) Sheetz, E. G.; Qiao, B.; Pink, M.; Flood, A. H. Programmed Negative Allostery with Guest-Selected Rotamers Control Anion-Anion Complexes of Stackable Macrocycles. J. Am. Chem. Soc. 2018, 140, 7773−7777. (35) Destecroix, H.; Renney, C. M.; Mooibroek, T. J.; Carter, T. S.; Stewart, P. F. N.; Crump, M. P.; Davis, A. P. Affinity Enhancement by Dopamine Side Chains in Synthetic Carbohydrate Receptors. Angew. Chem., Int. Ed. 2015, 54, 2057−2061. (36) Valkenier, H.; Judd, L. W.; Li, H.; Hussain, S.; Sheppard, D. N.; Davis, A. P. Reorganized Bi-Trioureas as Powerful Anion Carriers: Chloride Transport by Single Molecules in Large Unilamellar Vesicles. J. Am. Chem. Soc. 2014, 136, 12507−12512. (37) McNally, B. A.; Koulou, A. V.; Lambert, T. N.; Smith, B. D.; Joos, J.-B.; Sisson, A. L.; Clare, J. P.; Sgarlata, V.; Judd, L. W.; Magro, G.; Davis, A. P. Structure-Activity Relationships in Cholapod Anion Carriers: Enhanced Transmembrane Chloride Transport through Substituent Tuning. Chem. − Eur. J. 2008, 14, 9599−9606. (38) Edwards, S. J.; Valkenier, H.; Busschaert, N.; Gale, P. A.; Davis, A. P. High-Affinity Anion Binding by Steroidal Squaramide Receptors. Angew. Chem., Int. Ed. 2015, 54, 4592−4596. (39) Leung, A. N.; Degenhardt, D. A.; Bühmann, P. Effect of Spacer Geometry on Oxoanion Binding by Bis- and Tetrakis-Triourea Hosts. Tetrahedron 2008, 64, 2530−2536. (40) Wang, M.-X.; Yang, H.-B. A General and High Yielding Fragment Coupling Synthesis of Heteroatom-Bridged Calixarenes and the Unprecedented Examples of Calixarene Cavity Fine-Tuned by Bridging Heteroatoms. J. Am. Chem. Soc. 2004, 126, 15412−15422. (41) Wang, D.-X.; Zheng, Q.-Y.; Wang, Q.-Q.; Wang, M.-X. Halide Recognition by Tetraoxacalix[2]Arene[2]Triazine Receptors: Concurrent Noncovalent Halide-π and Lone-Pair-π Interactions in Host-Halide-Water Ternary Complexes. Angew. Chem., Int. Ed. 2008, 47, 7485−7488. (42) Kobayashi, K.; Gajurel, C. L. The Chemistry of 1,4-Dithiins. Sulfur Rep. 1986, 7, 123−148. (43) Bisson, A. P.; Lynch, V. M.; Monahan, M.-K. C.; Anslyn, E. V. Recognition of Anions through NH-π Hydrogen Bonds in a Bicyclic Cyclophane—Selectivity for Nitrate. Angew. Chem., Int. Ed. 1997, 36, 2340−2342. (44) Oh, J. H.; Kim, J. H.; Kim, D. S.; Han, H. J.; Lynch, V. M.; Sessler, J. L.; Kim, S. K. Synthesis and Anion Recognition Features of a Molecular Cage Containing Both Hydrogen Bond Donors and Acceptors. Org. Lett. 2019, 21, 4336−4339. (45) Gompper, R.; Euchner, H.; Kast, H. Umsetzungen −140-140−140 Helix- and Lone-Pair-π Interactions in Host-Halide-Water Ternary Complexes. Angew. Chem., Int. Ed. 2008, 47, 7485−7488. (46) Merschky, M.; Schmuck, C. Synthesis and Kinetic Studies of a Low-Molecular Weight Organocatalyst for Phosphate Hydrolysis in Water. Org. Biomol. Chem. 2009, 7, 4895−4903. (47) SIVVU. https://sivvu.org (accessed May 1, 2020). (48) Vander Giend, D. A.; Bediako, D. K.; DeVries, M. J.; Dejong, N. A.; Heeringa, L. P. Detailed Spectroscopic, Thermodynamic, and Kinetic Characterization of Nickel(II) Complexes with 2,2′-
Bipyridine and 1,10-Phenanthroline Attained via Equilibrium-Restricted Factor Analysis. *Inorg. Chem. 2008, 47, 656–662.*

(49) Kazmierczak, N.; Chew, J. A.; Vander Griend, D. A. Bootstrap Methods for Estimating the Uncertainty of Binding Constants in the Hard-Modeling of Spectrophotometric Titration Data. *J. Intell. Lab. Syst.*, submitted for publication, 2020.

(50) Barlow, R. Asymmetric Errors, In *PHYSTAT2003;* Lyons, L.; Mount, R.; Reitmeyer, R., Eds.; SLAC National Accelerator Laboratory: Menlo Park, CA, Sept 8–11, 2003; pp 250–255.

(51) Parks, F. C.; Liu, Y.; Debnath, S.; Stutsman, S. R.; Raghavachari, K.; Flood, A. H. Allosteric Control of Photofoldamers Switching. *J. Am. Chem. Soc.* 2011, 133, 1746–1756.

(52) Hibbert, D. B.; Thordarson, P. The Death of the Job Plot, Transparency, Open Science and Online Tools, Uncertainty Estimation Methods and Other Developments in Supramolecular Chemistry Data Analysis. *Chem. Commun.* 2016, 52, 12792–12805.

(53) Thordarson, P. Determining Association Constants from Titration Experiments in Supramolecular Chemistry. *Chem. Soc. Rev.* 2011, 40, 1305–1323.

(54) White, N. G. Antielectrostatically Hydrogen Bonded Anion Dimers: Counter-Intuitive, Common and Consistent. *CrystEngComm 2019, 21, 4855–4858.*

(55) Weinhold, F.; Klein, R. A. Anti-Electrostatic Hydrogen Bonds. *Angew. Chem., Int. Ed. 2014, 53, 11214–11217.*

(56) Fatila, E. M.; Twum, E. B.; Sengupta, A.; Pink, M.; Karty, J. A.; Raghavachari, K.; Flood, A. H. Anions Stabilize Each Other inside Macrocyclic Hosts. *Angew. Chem., Int. Ed. 2016, 55, 14057–14062.*

(57) Zhao, W.; Qiao, B.; Chen, C.-H.; Flood, A. H. High-Fidelity Multistate Switching with Anion–Anion and Acid–Anion Dimers of Organophosphates in Cyanostar Complexes. *Angew. Chem., Int. Ed.* 2017, 56, 13083–13087.

(58) He, Q.; Tu, P.; Sessler, J. L. Supramolecular Chemistry of Anionic Dimers, Trimers, Tetramers, and Clusters. *Chem 2018, 4, 46–93.*

(59) Tawfik, D. S.; Viola, R. E. Arsenate Replacing Phosphate: Alternative Life Chemistries and Ion Promiscuity. *Biochemistry 2011, 50, 1128–1134.*

(60) Ulatowski, F.; Dabrowsa, K.; Balakier, T.; Jurczak, J. Recognizing the Limited Applicability of Job Plots in Studying Host-Guest Interactions in Supramolecular Chemistry. *J. Org. Chem. 2016, 81, 1746–1756.*

(61) Edgal, R. K.; Raber, G.; Bond, A. D.; Hussain, M.; Espino, M. P. B.; Francesconi, K. A.; McKenney, C. J. Selective Recognition and Binding of Arsenate over Phosphate. *Dalton Trans. 2009, 9718–9721.*

(62) Elias, M.; Wellner, A.; Goldin-Azulay, K.; Chabriere, E.; Vorholt, J. A.; Erb, T. J.; Tawfik, D. S. The Molecular Basis of Phosphate Discrimination in Arsenate-Rich Environments. *Nature 2012, 491, 134–137.*

(63) Dutta, R.; Bose, P.; Ghosh, P. Arsenate Recognition in Aqueous Media by a Simple Tripodal Urea. *Dalton Trans. 2013, 42, 11371–11374.*

(64) Fatila, E. M.; Pink, M.; Twum, E. B.; Karty, J. A.; Flood, A. H. Phosphate-Phosphate Oligomerization Drives Higher Order Co-Assemblies with Stacks of Cyanostar Macrocycles. *Chem. Sci. 2018, 9, 2863–2872.*

(65) Kempen, E. C.; Brodbelt, J. S. A Method for the Determination of Binding Constants by Electrospray Ionization Mass Spectrometry. *Anal. Chem. 2000, 72, 5411–5416.*

(66) Richmond, T. G.; Johnson, J. R.; Edwards, J. O.; Rieger, P. H. Kinetics of Pyroarsenate Hydrolysis in Aqueous Solution. *Aust. J. Chem. 1977, 30, 1187–1194.*

(67) Park, J. W.; Rhee, Y. M.; Kim, M. S. S. Can Adenosine Triarsenate Role as an Energy Carrier? Bull. Korean Chem. Soc. 2013, 34, 361–362.

(68) Liu, Y.; Sengupta, A.; Raghavachari, K.; Flood, A. H. Anion Binding in Solution: Beyond the Electrostatic Regime. *Chem 2017, 3, 411–427.*

(69) Dobscha, J. R.; Debnath, S.; Fatila, E. M.; Pink, M.; Raghavachari, K.; Flood, A. H. Host–Host Interactions Control Self-Assembly and Switching of Triple and Double Decker Stacks of Tricarbazole Macrocycles Co-Assembled with Anti-Electrostatic Bisulfate Dimers. *Chem. – Eur. J. 2018, 24, 9841–9852.*

(70) Amatore, C.; Azzabi, M.; Calas, P.; Jutand, A.; Lefrou, C.; Rollin, Y. Absolute Determination of Electron Consumption in Transient or Steady State Electrochemical Techniques. *J. Electroanal. Chem. Interfacial Electrocho. 1990, 288, 45–63.*

(71) Shine, H. J.; Silber, J. J.; Bussey, R. J.; Okuyama, T. Ion Radicals. XXV. The Reactions of Thi anthrene and Phenothiazine Perchlorates with Nitrite Ion, Pyridine, and Other Nucleophiles. *J. Org. Chem. 1972, 37, 2691–2697.*

(72) Legault, C. Y. *Cylview*, 1.0b; Université de Sherbrooke, 2009. [http://www.Cylview.Org](http://www.Cylview.Org).

(73) Sather, A. C.; Berryman, O. B.; Rebek, J. Selective Recognition and Extraction of the Uranyl Ion. *J. Am. Chem. Soc. 2010, 132, 13572–13574.*

(74) Latour, A.; Lorca, R.; Zamora, F.; Somorza, Á. Enhanced Fluorescence of Silver Nanoclusters Stabilized with Branched Oligonucleotides. *Chem. Commun. 2013, 49, 4950–4952.*

(75) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. Preparation of 1,3,5-Tris(Aminomethyl)-2,4,6-Triethylbenzene from Two Versatile 1,3,5-Tri(Halosubstituted) 2,4,6-Triethylbenzene Derivatives. *Synthesis 2005, 2005, 2080–2083.*