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Expanding reversible chalcogenide binding: supramolecular receptors for the hydroselenide ( $\text{HSe}^-$ ) anion

Despite its critical roles in biological systems, the highly-reactive hydroselenide anion ( $\text{HSe}^-$ ) has not previously been targeted in synthetic supramolecular receptor studies. We report the first example of reversible  $\text{HSe}^-$  binding using two distinct synthetic supramolecular receptors, graphically represented by an homage to a classic comic book cover. The binding properties of  $\text{HSe}^-$  were compared to those of the related anions  $\text{HS}^-$ ,  $\text{Cl}^-$ , and  $\text{Br}^-$ , providing a basis for understanding how to better bind hydrochalcogenide anions. Artwork by co-author Dr. Nathanael Lau.

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## Expanding reversible chalcogenide binding: supramolecular receptors for the hydroselenide (HSe<sup>-</sup>) anion†

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Synthetic supramolecular receptors have been widely used to study reversible solution binding of anions; however, few systems target highly-reactive species. In particular, the hydrochalcogenide anions hydrosulfide (HS<sup>-</sup>) and hydroselenide (HSe<sup>-</sup>) have been largely overlooked despite their critical roles in biological systems. Herein we present the first example of reversible HSe<sup>-</sup> binding in two distinct synthetic supramolecular receptors, using hydrogen bonds from N–H and aromatic C–H moieties. The arylethynyl bisurea scaffold **1**<sup>TBU</sup> achieved a binding affinity of  $460 \pm 50 \text{ M}^{-1}$  for HSe<sup>-</sup> in 10% DMSO-*d*<sub>6</sub>/CD<sub>3</sub>CN, whereas the tripodal-based receptor **2**<sup>CF<sub>3</sub></sup> achieved a binding affinity of  $290 \pm 50 \text{ M}^{-1}$  in CD<sub>3</sub>CN. Association constants were also measured for HS<sup>-</sup>, Cl<sup>-</sup>, and Br<sup>-</sup>, and both receptors favored binding of smaller, more basic anions. These studies contribute to a better understanding of chalcogenide hydrogen bonding and provide insights into further development of probes for the reversible binding, and potential quantification, of HSe<sup>-</sup> and HS<sup>-</sup>.

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## Introduction

Synthetic supramolecular receptors have been used with great success for investigating the solution binding of biologically- and environmentally-relevant anions.<sup>1–5</sup> By using reversible, mostly non-covalent interactions such as hydrogen bonding, electrostatic interactions, and anion- $\pi$  interactions, a diverse palette of anions can be bound ranging from relatively inert anions such as halides and oxoanions<sup>6–10</sup> to highly reactive anions.<sup>11–16</sup> Although targeting the latter poses many challenges, reversible binding in supramolecular hosts can be used to stabilize high-energy anions through non-covalent interactions in a manner reminiscent of certain active sites in proteins.<sup>17</sup> Despite this potential, examples of receptors targeting highly-reactive anions remain rare.<sup>11–16</sup> In particular, the hydrochalcogenide anions hydroselenide (HSe<sup>-</sup>) and hydrosulfide (HS<sup>-</sup>) have been largely overlooked despite their considerable environmental and biological significance. These anions are weak bases that exist in equilibrium with their gaseous conjugate acids, hydrogen selenide (H<sub>2</sub>Se,  $pK_a = 3.74$ )

and hydrogen sulfide (H<sub>2</sub>S,  $pK_a = 7.00$ ).<sup>18</sup> The anionic species dominate at physiological pH, as H<sub>2</sub>Se exists almost entirely as HSe<sup>-</sup> and HS<sup>-</sup> is favored over H<sub>2</sub>S by a 3 : 1 ratio.<sup>19–21</sup>

Although HSe<sup>-</sup> and HS<sup>-</sup>/H<sub>2</sub>S are highly toxic at elevated levels,<sup>19,22,23</sup> both are essential to life at low concentrations and are produced endogenously.<sup>18–20</sup> For example, H<sub>2</sub>S has been classified as the third gasotransmitter alongside carbon monoxide (CO) and nitric oxide (NO) and plays regulatory roles in the cardiovascular, immune, and gastrointestinal systems, among others.<sup>19,24–27</sup> Similarly, HSe<sup>-</sup> is the common but highly-reactive intermediate generated in the metabolism of dietary selenium (Fig. 1),<sup>18,20</sup> and it is required for the synthesis of the essential 21<sup>st</sup> amino acid selenocysteine (Se-Cys).<sup>28,29</sup> Se-Cys is then incorporated into selenoproteins, such as thioredoxin reductases and glutathione peroxidases<sup>18,20</sup> that play important roles in redox biochemistry.<sup>30,31</sup> However, the high reactivity of HSe<sup>-</sup> toward both electrophiles and oxygen makes it difficult to observe directly in biological systems or to target through the design of selective synthetic receptors.<sup>20,32</sup>

Understanding the reversible binding requirements for hydrochalcogenides could provide valuable insights into possible receptor motifs in biological environments. However, we are not aware of any reports showing HSe<sup>-</sup> as a viable target for molecular recognition by anion receptors. Similarly, few examples of reversible HS<sup>-</sup> binding exist,<sup>12–14</sup> the first of which were reported by our groups using two distinct families of modular receptor scaffolds (Fig. 2). The initial report was based on a rigid arylethynyl bisurea receptor (**1**<sup>H</sup>)<sup>12</sup> and the second on a flexible tripodal arylamide unit (**2**<sup>H</sup>),<sup>13</sup> both of which bound

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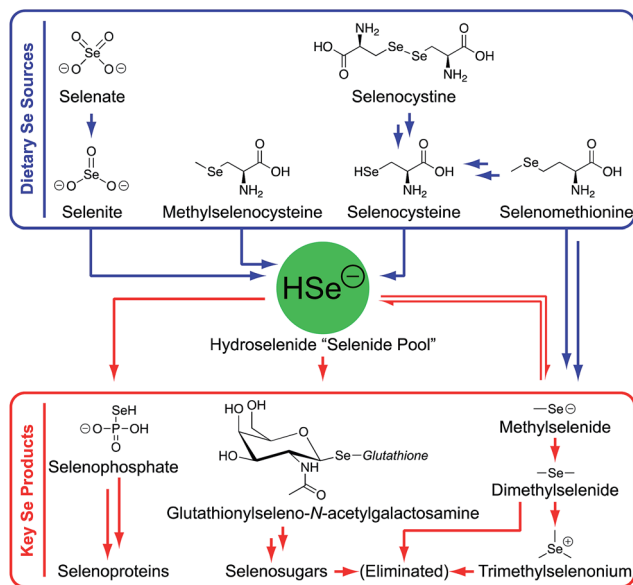


Fig. 1 Summary of selenium metabolism in the human body.<sup>20</sup>

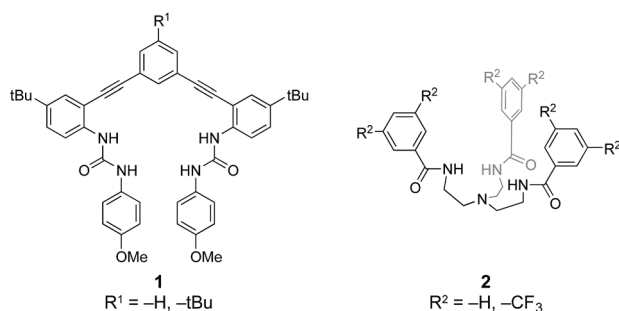


Fig. 2 The two families of receptors used for binding  $\text{HS}^-$  and  $\text{HSe}^-$ .<sup>12,13,34</sup>

$\text{HS}^-$  through  $\text{N-H}\cdots\text{S}$  and aryl  $\text{C-H}\cdots\text{S}$  hydrogen bonds. Building from these early insights into  $\text{HS}^-$  binding, we investigated whether these receptors could also bind and stabilize the substantially more reactive  $\text{HSe}^-$  anion. This was not a trivial descent down the periodic table; although sulfur and selenium share similar chemical and physical properties,  $\text{HSe}^-$  is over three orders of magnitude more acidic and both a more potent nucleophile and reducing agent than  $\text{HS}^-$ .<sup>18</sup> In addition, selenium is larger and more diffuse than sulfur ( $\text{Se}^{2-}$ : 1.84 Å;  $\text{S}^{2-}$ : 1.70 Å),<sup>33</sup> making non-covalent and reversible binding more difficult.<sup>34,35</sup>

Herein we report the first examples of using supramolecular receptors to reversibly bind the  $\text{HSe}^-$  anion, as clearly demonstrated by  $^1\text{H}$  nuclear magnetic resonance (NMR) titration studies and X-ray crystallography. The binding affinities of the receptors with other related anions ( $\text{HS}^-$ ,  $\text{Cl}^-$ , and  $\text{Br}^-$ ) were also measured to determine the importance of factors such as anion size and basicity in binding. Our analysis revealed that our receptors favor smaller and more basic anions; thus, the greatest affinities observed were for  $\text{HS}^-$ . Ultimately, these studies provide a starting point for designing receptors capable

of selective binding to  $\text{HSe}^-$ , which may provide future insights into the role of hydrochalcogenide anions in biology.

## Results and discussion

### Synthesis of tetrabutylammonium hydroselenide ( $\text{NBu}_4\text{SeH}$ )

To investigate  $\text{HSe}^-$  binding to  $1^{\text{tBu}}$  and  $2^{\text{CF}_3}$ , which are both insoluble in water, we prepared  $\text{NBu}_4\text{SeH}$  by reducing elemental Se with  $\text{NBu}_4\text{BH}_4$  in anhydrous  $\text{CH}_3\text{CN}$  (Fig. 3a).<sup>36</sup> The crude  $\text{NBu}_4\text{SeH}$  oil was repeatedly washed with tetrahydrofuran (THF) to precipitate pure  $\text{NBu}_4\text{SeH}$  as a white powder. Single crystals of  $\text{NBu}_4\text{SeH}$  suitable for X-ray diffraction were obtained by layering a  $\text{CH}_3\text{CN}$  solution of  $\text{NBu}_4\text{SeH}$  with diethyl ether ( $\text{Et}_2\text{O}$ ) (Fig. 3b).

Much like the related structure of  $\text{NBu}_4\text{SH}$ ,<sup>37</sup> short contacts (3.954–4.248 Å) between the Se atom and C1, C3, and C6 of the  $\text{NBu}_4^+$  counterion are indicative of weak hydrogen bonding between the aliphatic C–H bonds of the counterion to the chalcogenide. The  $\text{HSe}^-$  proton was located in the solid-state structure and found to be pointed away from the  $\text{NBu}_4^+$  counterion. In addition, the  $^1\text{H}$  NMR spectrum of  $\text{NBu}_4\text{SeH}$  showed the  $\text{HSe}^-$  resonance at  $-6.61$  ppm in  $\text{CD}_3\text{CN}$ . The greater upfield shift of  $\text{HSe}^-$  compared to that of  $\text{HS}^-$  ( $-3.85$  ppm)<sup>37</sup> is consistent with the greater electron density around  $\text{Se}^{2-}$  relative to  $\text{S}^{2-}$ . We note that the salt is extremely sensitive to  $\text{O}_2$ , and colorless solutions of  $\text{NBu}_4\text{SeH}$  turn dark green upon exposure to the atmosphere.

### Binding experiments of $1^{\text{tBu}}$ and $2^{\text{CF}_3}$ with $\text{HSe}^-$

Equipped with an organic soluble source of  $\text{HSe}^-$ , we next used  $^1\text{H}$  NMR spectroscopy to investigate whether  $1^{\text{tBu}}$  and  $2^{\text{CF}_3}$  could bind  $\text{HSe}^-$  (Fig. 4). Solutions of each host (1.0–2.0 mM) were titrated with  $\text{NBu}_4\text{SeH}$  in either anhydrous 10%  $\text{DMSO}-d_6/\text{CD}_3\text{CN}$  (for  $1^{\text{tBu}}$ ) or anhydrous  $\text{CD}_3\text{CN}$  (for  $2^{\text{CF}_3}$ ), due to solubility differences between the hosts. We observed a significant downfield shift in the urea  $\text{N-H}_{\text{b/c}}$  and aromatic  $\text{C-H}_{\text{a}}$  proton resonances in  $1^{\text{tBu}}$  and in the amide  $\text{N-H}_{\text{a}}$  and aromatic  $\text{C-H}_{\text{b}}$  proton resonances in  $2^{\text{CF}_3}$ . Both of these results indicated that these protons are involved in binding  $\text{HSe}^-$ , and matched the recognition units that were previously observed to be involved in the binding of  $\text{HS}^-$  with  $1^{\text{H}}$  and  $2^{\text{H}}$ .<sup>12,13</sup> Association constants ( $K_{\text{a}}$ ) were determined by fitting the changes in the chemical shifts of these hydrogen bond donating moieties to a 1 : 1 host : guest model using Thordarson's method (Table 1, *vide infra*).<sup>38,39</sup>

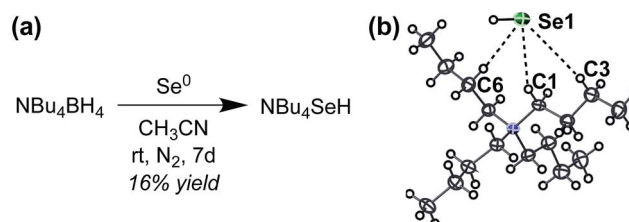


Fig. 3 (a) Preparation of  $\text{NBu}_4\text{SeH}$ . (b) Thermal ellipsoid diagram (at 50% probability) depicting the molecular structure of  $\text{NBu}_4\text{SeH}$ .



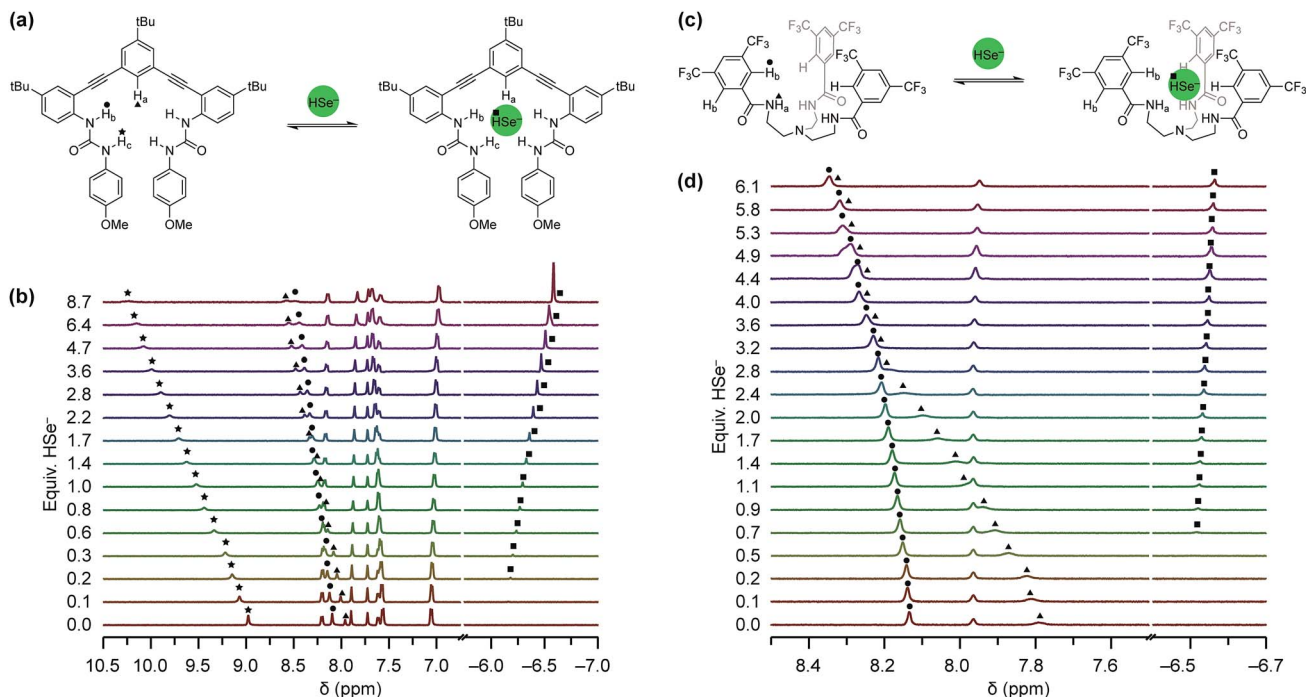


Fig. 4 (a) Representation of the host-guest equilibrium between  $1^{tBu}$  and  $HSe^-$ . (b)  $^1H$  NMR titration of 1.6 mM  $1^{tBu}$  with  $NBu_4SeH$  in 10%  $DMSO-d_6$  in  $CD_3CN$ . (c) Representation of the host-guest equilibrium between  $2^{CF_3}$  and  $HSe^-$ . (d)  $^1H$  NMR titration of 2.0 mM  $2^{CF_3}$  with  $NBu_4SeH$  in  $CD_3CN$ .

To ensure that the observed binding was reversible and not due to reaction with  $HSe^-$  as a nucleophile, we next looked for evidence of covalent modification of our receptors. In particular,  $1^{tBu}$  has several electrophilic sites, such as the urea carbonyl and alkyne moieties, that could potentially undergo nucleophilic attack by  $HSe^-$ . Although no evidence of receptor modification was observed in titrations of  $1^H$  with  $HS^-$ ,<sup>12</sup> treatment of  $1^{tBu}$  with 20 equiv.  $HSe^-$  resulted in the appearance of new aromatic signals after approximately 30 min (ESI, Fig. S3†).

To determine whether  $1^{tBu}$  was covalently modified by  $HSe^-$  over the course of the titration, 6 equiv.  $HSe^-$  were added to a 2 mM solution of  $1^{tBu}$  in 10%  $DMSO-d_6/CD_3CN$  (ESI, Fig. S5†). After 1 h there was little evidence of new aromatic signals; however, after 3 h new peaks appeared in the spectra. Addition of 20 equiv. of zinc acetate ( $Zn(OAc)_2$ ) to the mixture removed  $HSe^-$  as  $ZnSe$ . The resulting  $^1H$  NMR spectrum showed that the receptor signals return to the same shifts as unmodified  $1^{tBu}$  along with the presence of smaller decomposition signals, demonstrating that the binding process of  $HSe^-$  is reversible within 1 h and over the timescale of the titration experiment.

To further investigate the minor decomposition products of  $1^{tBu}$  with  $HSe^-$ , we used negative mode mass spectrometry (MS) to look for Se-containing species. We observed peaks consistent with fragments containing a molecule of  $HSe^-$  added across one alkyne bond (ESI, Fig. S4†), which corroborates the observed desymmetrization of the aromatic peaks in the decomposition products in the  $^1H$  NMR spectrum of  $1^{tBu}$ . Furthermore, the isotope patterns and mass accuracy of these peaks unambiguously show that these species incorporate  $HSe^-$ . These results underscore the challenges in binding such a highly reactive species and confirm that careful receptor choice and design (e.g., bulky *t*-Bu group to protect  $1^{tBu}$  from nucleophilic aromatic substitution) is needed to accomplish this task.

The simpler tripodal receptor proved to be more resistant to attack by  $HSe^-$ , since we have not observed any evidence of modification of  $2^{CF_3}$  by  $HSe^-$ , even though the electrophilicity of the amide carbonyl moieties should be enhanced due to the presence of the *meta*  $CF_3$  groups. Coupled with the resistance of  $1^{tBu}$  to  $HSe^-$ , this result demonstrates how the presence of relatively weak, non-covalent interactions can stabilize

Table 1 Binding parameters for hosts  $1^{tBu}$  and  $2^{CF_3}$  with the anions used in this study<sup>a</sup>

Host	Solvent	$HSe^-$		$Br^-$		$HS^-$		$Cl^-$	
		$K_a$ ( $M^{-1}$ )	$\Delta G$ (kcal mol <sup>-1</sup> )	$K_a$ ( $M^{-1}$ )	$\Delta G$ (kcal mol <sup>-1</sup> )	$K_a$ ( $M^{-1}$ )	$\Delta G$ (kcal mol <sup>-1</sup> )	$K_a$ ( $M^{-1}$ )	$\Delta G$ (kcal mol <sup>-1</sup> )
$1^{tBu}$	10% $DMSO-d_6/CD_3CN$	460 ± 50	-3.63 ± 0.06	110 ± 20	-2.79 ± 0.09	3600 ± 500	-4.85 ± 0.09	1700 ± 200	-4.41 ± 0.06
$2^{CF_3}$	$CD_3CN$	290 ± 50	-3.35 ± 0.10	67 ± 7	-2.49 ± 0.06	840 ± 80	-3.93 ± 0.06	430 ± 50	-3.59 ± 0.07

<sup>a</sup> The minimum error is assumed to be 10% in cases where the standard deviation is less than 10%.



a normally reactive species. As with  $1^{tBu}$ ,  $HSe^-$  binding was also shown to be reversible by conducting a similar  $Zn(OAc)_2$  extrusion experiment (ESI, Fig. S5†). After 2 equiv.  $HSe^-$  were added to  $2^{CF_3}$ , the addition of 12 equiv. of  $Zn(OAc)_2$  returned a  $^1H$  NMR spectrum identical to that of pure  $2^{CF_3}$ . The ability of these two distinct receptor classes to reversibly bind  $HSe^-$  demonstrates the generality of binding of this previously uninvestigated anion, despite the highly reactive and reducing nature of  $HSe^-$ .

### Binding experiments of $1^{tBu}$ and $2^{CF_3}$ with other anions

To better understand the factors influencing  $HSe^-$  binding, we also measured the binding affinities of  $1^{tBu}$  and  $2^{CF_3}$  towards the related anions  $HS^-$ ,  $Cl^-$ , and  $Br^-$  (Table 1). Several notable trends emerged from these studies. For example,  $1^{tBu}$  maintains a higher binding affinity for  $HSe^-$  than  $2^{CF_3}$ , even in a more competitive solvent system (10% DMSO- $d_6$  in  $CD_3CN$  vs. neat  $CD_3CN$ ). This difference in binding affinity between the two receptors holds true for all of the other anions investigated and is consistent with our previous studies,<sup>12,13</sup> and may reflect the increased number of N–H H-bond donors in  $1^{tBu}$  compared to  $2^{CF_3}$ . Furthermore, this result underscores the importance of preorganization and directionality in hydrogen bonding in supramolecular systems, as the rigid ethynyl backbone of  $1^{tBu}$  offers more directed hydrogen bonds than the more flexible aliphatic backbone of  $2^{CF_3}$ . Supporting this hypothesis, previous work on  $1^{tBu}$  and derivatives have shown that the central aromatic C–H hydrogen bond is unusually strong, contributing more than 1 kcal mol<sup>-1</sup> in anion binding energy.<sup>34</sup> In contrast, although receptor  $2^{CF_3}$  should donate three hydrogen bonds between three *ortho* aromatic C–H hydrogen atoms to a guest molecule,  $^1H$  NMR spectroscopy suggest that these interactions are relatively weak, as they are not strong enough to prevent free rotation of the aromatic rings since the *ortho* protons are not resolved.

Interestingly, both receptors demonstrated a clear preference for binding the hydrochalcogenide anions over the halide anions in the same row. By binding affinities,  $1^{tBu}$  showed a two-fold preference for  $HS^-$  over  $Cl^-$  and a four-fold preference for  $HSe^-$  over  $Br^-$ , despite the nearly identical ionic radii of anions within the same periodic row (Table 1). The protonation state of each anion is unlikely to explain the preferential binding towards hydrochalcogenide anions in  $1^{tBu}$  because this receptor contains no hydrogen bond accepting motifs in the binding pocket. The distinguishing factor may instead be basicity, as the chalcogenides are far better bases than the halides (Table 2) and should thus form stronger hydrogen bonds with the receptors. In contrast, the ionic size of the different anions appears to be

a dominant factor in determining binding affinity in  $1^{tBu}$  and  $2^{CF_3}$ . In both cases, the smaller row 3 anions ( $HS^-$  and  $Cl^-$ ) exhibit an order of magnitude stronger binding than those of the larger row 4 anions ( $HSe^-$  and  $Br^-$ ), despite the higher basicity of  $HSe^-$  over  $Cl^-$ . Alternatively, because all the anions have the same charge, the row 3 anions have a higher surface charge density, which may result in greater electrostatic interactions between the anion and receptor, thus contributing to the stronger binding.

We further investigated the impact of anion size on receptor geometry in the solid-state. Single crystals of  $[NBu_4][1^{tBu}(SeH)]^-$  suitable for X-ray diffraction were obtained by layering an equimolar THF mixture of  $1^{tBu}$  and  $NBu_4SeH$  under  $Et_2O$  in a glovebox (Fig. 5). We compared the metrical parameters of  $[1^{tBu}(SeH)]^-$  to those of the previously reported  $[1^H(SH)]^-$  (ref. 12) and  $[1^H(Cl)]^-$  (ref. 41) to determine the effect of guest size on  $1^R$  receptors. The  $HSe^-$  guest is bound by  $1^{tBu}$  in the pocket created by one aromatic proton and four urea protons. The C...Se and N...Se distances suggest that the strongest hydrogen bonds are formed by the distal urea protons (N2 and N4,  $(N...Se)_{ave} = 3.385 \text{ \AA}$ ), followed by the central aryl proton ( $C1...Se = 3.769 \text{ \AA}$ ) then the proximal urea protons (N1 and N3,  $(N...Se)_{ave} = 3.892 \text{ \AA}$ ). These results suggested that the Se atom did not fit well inside the binding pocket of  $1^{tBu}$ , since the more constrained proximal urea protons had weaker interactions to the anion than the more flexible distal urea protons. Additionally, none of the C...H...Se or N...H...Se angles formed were in the preferred linear geometry (Table 3). Although similar behavior was observed for  $[1^H(SH)]^-$  (ref. 12) and  $[1^H(Cl)]^-$ ,<sup>41</sup> the larger  $HSe^-$  guest distorted the binding pocket more than the smaller  $HS^-$  or  $Cl^-$  guests. When distances between the distal urea nitrogen atoms to the plane formed by the central aryl ring were investigated,  $[1^{tBu}(SeH)]^-$  (2.273  $\text{\AA}$ ) exhibited much longer average distance than  $[1^H(SH)]^-$  (2.109  $\text{\AA}$ ) or  $[1^H(Cl)]^-$  (2.029  $\text{\AA}$ ). In tandem, these results suggest that the larger  $HSe^-$  guest distorts the binding cavity more than related row 3 anions, perhaps explaining the poorer binding affinity for  $HSe^-$  in these systems.<sup>42,43</sup>

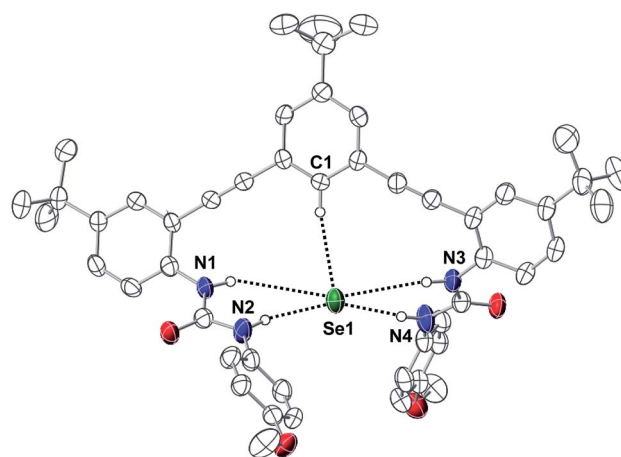


Fig. 5 Thermal ellipsoid diagram (at 50% probability) depicting the molecular structure of  $[1^{tBu}(SeH)]^-$ . Hydrogen atoms not interacting with the bound  $HSe^-$  are omitted for clarity.

Table 2 Physical properties of the anions used in this study

	$HS^-$	$HSe^-$	$Cl^-$	$Br^-$
Ionic radius ( $\text{\AA}$ ) <sup>33</sup>	1.70 <sup>a</sup>	1.84 <sup>b</sup>	1.67	1.82
pK <sub>a</sub> (conj. Acid, H <sub>2</sub> O) <sup>18,40</sup>	7.0	3.7	−8.0	−9.0

<sup>a</sup> Ionic radius of  $S^{2-}$ . <sup>b</sup> Ionic radius of  $Se^{2-}$ .



Table 3 Bond lengths and angles in  $[1^{tBu}(SeH)]^-$ 

	Atomic distance (Å)	Bond angle (°)
C1(H)⋯Se1	3.769	168.4
N1(H)⋯Se1	4.073	144.2
N2(H)⋯Se1	3.373	173.2
N3(H)⋯Se1	3.710	
N4(H)⋯Se1	3.397	172.7

## Conclusions

In this study we have presented the first example of reversible  $HSe^-$  binding with two separate supramolecular receptors. Both receptors interact with  $HSe^-$  through N–H and aryl C–H hydrogen bonds and the ability of two structurally distinct receptors to bind  $HSe^-$  demonstrates the generality of this type of reversible supramolecular interaction. Additional studies with the related anions  $HS^-$ ,  $Cl^-$ , and  $Br^-$  suggested basicity and anion size impact the binding affinities of the receptors in polar, aprotic organic solvents. Both receptors show the greatest binding affinity for the smallest and most basic anion,  $HS^-$ . The dramatic decrease in binding affinity for larger anions suggests that smaller anions fit better in these systems, giving our receptors a preference for  $HS^-$  over  $HSe^-$ . The size of the anion appears to impact binding more significantly than basicity, as the binding affinity of the relatively basic anion  $HSe^-$  is surprisingly almost four times less than that of the substantially less basic but smaller anion  $Cl^-$ . The predictability of these trends suggests clear enthalpic driving forces behind binding preference, but the role of entropy cannot be discounted. The analysis of entropy *versus* enthalpy in our hosts will be followed up in a future report.

These results, coupled with the development of the first synthesis for  $NBu_4SeH$ , provide a solid platform for development of future supramolecular  $HSe^-$  receptors. Reversible receptors for  $HSe^-$  certainly require scaffolds resistant to nucleophilic attack and should be able to bind selenium through suitable hydrogen bond donors such as urea N–H, amide N–H, or aromatic C–H groups, likely among many others. Furthermore, receptors more selective for  $HSe^-$  may require binding cavities larger than either  $1^{tBu}$  or  $2^{CF_3}$  possess. Such developments will ultimately provide better tools toward understanding the supramolecular chemistry of the biologically- and environmentally-relevant hydrochalcogenide anions.

## Conflicts of interest

There are no conflicts to declare.

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