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Lithium-selective phosphine oxide-based ditopic receptors show enhanced halide binding upon alkali metal ion coordination†

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Abstract

Previous work on a ditopic receptor based on a tripodal phosphine oxide core demonstrated preferential enhancement of bromide binding over chloride or iodide in the presence of lithium cation. Current studies on an elongated receptor provide evidence that preferential bromide binding enhancement in the presence of lithium cation is common to this receptor class in general, and that lengthening of the receptor results in an overall increase in halide association. Furthermore, the extended receptor shows a strong preference for Li^+ binding in solution.

Introduction

Ongoing recent research in supramolecular chemistry has focused on the synthesis and investigation of ditopic receptors.^{1–14} This can be attributed to the increases in selectivity and binding strength observed when ion-pairs are cooperatively targeted over a single ion.^{15–17} These receptors have been applied in a number of areas of research such as membrane transport, extraction, salt solubilization and sensing applications.^{18–20}

Given the interest in the coordination chemistry of the Li^+ cation in the synthetic, medicinal chemistry and imaging communities, lithium salts have emerged as desirable targets for molecular recognition.^{21–27} This is largely motivated by the roles these salts play in battery technology²⁸ and biological processes.^{29,30} Lithium is often an elusive guest for selective recognition particularly in polar hydrophilic solvents due in part to the large hydration energy of the lithium cation compared to other alkali metal cations.³¹

Neutral phosphine oxide-based ditopic receptor **1** (Fig. 1) provides enhanced anion binding in the presence of lithium over sodium and the degree of enhancement is greatest for bromide.³² To better understand this phenomenon, the new elongated receptor **2** (Fig. 1) was prepared in an effort to further elucidate the binding trends witnessed for **1**. We were also interested in what effect larger and more charge diffuse cationic guests, like potassium, would have on halide binding for this receptor class.

Jointly presented with a more thorough analysis of our previous studies, we report binding analyses of Cl^- , Br^- and I^- with receptor **2** in the presence and absence of the alkali metals Li^+ , Na^+ and K^+ . Additional halide binding studies were conducted on receptor **1** in the presence of K^+ . The outcomes of these studies show that preferential binding of lithium and

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the selective enhancement of bromide in the presence of this cation are trends inherent to this class of receptor, and that the enhancement of halide binding is all but lost in the presence of potassium. These studies also show that the lengthened receptor possesses an overall larger affinity for halides compared to **1** in both metal-free and metal-containing systems. A consequence of the expanded receptor was a more resolved ^1H NMR spectrum allowing determination of association constants for Li^+ and Na^+ as well as a more critical examination of the complementary ion binding capacity of these tripodal phosphine oxide-based receptors.

Results and discussion

Synthesis

Encouraged by the ion-pair binding properties of our previously synthesized receptor **1**,³² we designed the related receptor **2**, starting from *t*-Boc-protected γ -aminobutyric acid following a literature procedure using di(*tert*-butyl) dicarbonate.³³ The resultant amine-protected amino acid was then combined with tris(aminomethyl)-phosphine oxide (produced *in situ* from the trishydrobromide salt) in a 3-fold HBTU-assisted amide coupling reaction in DMF. The desired product **2** was isolated in 84% yield as a white powder upon repeated precipitation from ethyl acetate. Full experimental details are supplied in the ESI.

^1H NMR binding studies

Negatively charged guests induced the most significant downfield shift δ of the farthest downfield amide *NH* resonances when added to solutions of either receptor (H_b , H_b' in Fig. 2). Only minor downfield shifting was observed for the minimally hydrogen bond donating carbamate *NH* resonances in all cases (Fig 2). The preference of anions for amide *NH* association over the carbamate *NH* was also observed computationally (Fig. S50). The carbamates were initially envisioned to be the major hydrogen bond donors toward anions.³⁴ Although we no longer believe this is the case, they may participate in stabilizing complexes by other means. Elongated receptor **2** experienced minor, but noticeable shifting of the methylene region during ^1H NMR titrations involving cationic guests. These titrations revealed cation-dependent shifting of the triplet observed at 3.60–3.75 ppm, representing the methylene residing between the $\text{P}=\text{O}$ and amide functional groups (H_a , Fig. 2, right). Other ^1H NMR resonances were relatively unaffected by the presence of cationic stimuli. Cation-dependent methylene shifting was observed for **1** as well, but overlapping resonances prevented quantitative comparisons of alkali metal affinity (Fig. 2, left). The site-specific response to cations and anions heralds the heteroditopic nature of this receptor class.

Shown in Table 1 is the result of multiple ^1H NMR spectroscopic titrations that further assessed the ability of receptors **1** and **2** to coordinate ions. Anion binding studies of receptor **2** were performed in $\text{MeCN}-d_3$ and the downfield shift of the more anion sensitive amide *NH* resonance was followed upon addition of Cl^- , Br^- and I^- as tetrabutylammonium (TBA) salts in the absence and presence of ~ 1 equiv. of either Li^+ , Na^+ or K^+ . Cation binding studies of **2** were performed by monitoring the downfield movement of H_a upon addition of Li^+ or Na^+ . Anion binding studies of receptor **1**, in addition to those previously reported, were performed with the listed halides in the presence of ~ 1 equiv. of potassium. In all cases lithium perchlorate was used as the lithium source and tetraphenylborate was used as the counter anion for sodium and potassium salts.³⁵ All binding data were fit to a 1:1 model and association constants were determined using WinEQNMR2.³⁶ Association constants of previously reported receptor **1** are included for reference (Table 1).³²

Multiple titrations of **2** with the halides demonstrated that the strongest association occurs with chloride (580 M^{-1}) followed by bromide (100 M^{-1}), and the association with iodide

was too small to be accurately determined, trending expectedly with the Hofmeister series.³⁷ Titrations of **2**·Li⁺ with the halides followed the same trend compared to the metal-free system, but gave 3- and 12-fold increases in association constants for chloride and bromide, respectively. The enhanced affinity afforded by the presence of Li⁺ allowed for accurate determination of the association constant of iodide (90 M⁻¹). The **2**·Na⁺ complex trended similarly with the **2**·Li⁺ complex, but halide affinities increased only 1.7- and 2.6-fold over the free receptor. Despite the modest binding increase provided by Na⁺, an association constant for iodide (30 M⁻¹) could be measured. Titrations of **1** and **2** with halides in the presence of ~1 equiv. of K⁺ gave nearly identical association constants to those observed for each receptor in the absence of metal ions. The enhancement in halide binding demonstrates the ability of alkali metals to cooperatively affect halide binding, particularly in the case of Li⁺ complexes.

Increased resolution of the ¹H NMR spectra during titrations of **2** over those performed on **1** made it possible to probe the affinity of **2** toward LiClO₄ and NaBPh₄. Data were fit to a 1:1 binding model.³⁸ Surprisingly, **2** displayed association constants of 8610 and 230 M⁻¹ toward lithium and sodium respectively, and no binding was observed for KBPh₄. The significant preference for lithium over sodium is unexpected due to the anticipated competitive solvation in wet solvents based on the relative ΔG^o_{hydration} for lithium (−475 kJ mol⁻¹) and sodium (−365 kJ mol⁻¹).³¹ Slight downfield shifting of the water peak is observed during titrations of **2** with LiClO₄, suggesting that Li⁺ may be bound in its hydrated form. Alternatively, the preference for Li⁺ could be the result of complementary donors of **2** satisfying the preferred coordination number of four for this small cation, whereas accommodating the greater coordination number of the larger Na⁺ cation is less favourable (Fig. 3).^{39,40} An approximate 3 ppm downfield shift of the ³¹P resonance of **2** was observed upon addition of excess LiClO₄ in MeCN-*d*₃ indicating the participation of the P=O group in coordinating Li⁺. Control titrations of trioctylphosphine oxide (TOPO) with LiClO₄ yielded an association constant (*K*_a = 3780 M⁻¹) that is less than half of that observed for the titration of **2** with LiClO₄.⁴¹ This demonstrates that the P=O group in **2** is only partially responsible for cation recognition. Unfortunately, the marginal solubility of the hosts precluded meaningful ¹³C NMR investigations of carbonyl participation in cation coordination. These results confirm the preference for Li⁺ binding that was predicted from the greatly enhanced anion binding observed in the presence of Li⁺, but also highlight that the nature of this preference is unclear. While a model trialkyl phosphine oxide exhibits strong Li⁺ coordination, it is still not as strong as the receptors reported herein, suggesting that the carbonyls at least participate in the interaction.

Limited anion-induced downfield shifting is observed for the proton alpha to the amide group (H_c) in receptor **2**, while the other methylene resonances (H_e and H_d) are relatively unaffected by the addition of cationic or anionic guests during titrations. Additionally, only minimal downfield movement of the carbamate proton resonance (H_f) is observed (Fig. 2, right). This analysis of the ¹H NMR spectroscopic titration data provides solution phase structural information about the cationic and anionic binding sites of these receptors: only protons H_a and H_b are influenced substantially by the cationic and anionic guests, respectively, implying that the ionic guests are associating primarily with the core of this receptor. Ionic stimuli affected receptor **1** similarly, suggesting that the core of this class of receptor wields the brunt of the coordinating prowess, but the receptor extremities cannot be considered completely innocent.

Judicious analysis of the binding data for both receptors revealed that elongated receptor **2** produced a nearly 2–4 fold increase in binding in all cases compared to condensed receptor **1**. Contrary to the observed increased binding by **2**, receptor **1** possesses a slightly more downfield shifted amide proton (~7.50 ppm) in the unbound state compared to **2** (~7.20

ppm), which may suggest increased acidity. The increased binding constants of **2** indicate that functional groups extending from the core may be more involved in binding of ionic species than implied by the subtle NMR shifts revealed by solution studies. Calculated structures suggest **2** promotes more intramolecular hydrogen bonding relative to **1** (Fig. 3, Fig S50) which may allow preorganization and/or stabilization of host and host-guest complexes. It is also conceivable that the greater separation between the binding sites of the receptor and the terminal *t*-butyl groups allows for greater flexibility in achieving a more stabilized host-guest complex. These results demonstrate the significant effects on binding that are possible from relatively minor structural alterations of the receptor.

An enhancement in binding strength is observed for all of the halides by receptor **2** in the presence of ~1 equiv. of Li^+ . The most significant increases were seen with bromide, unexpectedly. This becomes more evident upon observation of the difference in the change in Gibbs free energies ($\Delta\Delta G^\circ$) between **2** and **2**· Li^+ complexes (Table 1). The **2**· Li^+/Br^- complex is favoured over the **2**· Br^- complex by $-1.5 \text{ kcal mol}^{-1}$, whereas the **2**· Li^+/Cl^- and **2**· Li^+/I^- complexes are only favoured over the **2**· Cl^- and **2**· I^- by -0.66 and $-1.1 \text{ kcal mol}^{-1}$ respectively. A similar stability trend is observed for **2**· Na^+ complexes with the halides, but to a lesser degree than for the lithium complexes. The selective lithium-dependent enhancement in binding for bromide was also observed in the previously reported system and therefore seems to be a general effect for these phosphine oxide-based receptors. The changes in anion association for **1** and **2** upon K^+ coordination are not statistically significant confirming the lack of coordination of K^+ by these receptors.

Notably, upon titration of **2**· Li^+ with halides, the methylene (H_a) and amide (H_b) resonances shift in concert. As the halides alone have no effect on the H_a resonance (Fig. 2, right), the shifting must be a result of halide induced perturbation of Li^+ coordination, which demonstrates the complementary nature of the interaction of the anion and cation with the receptor. In titrations with Cl^- the amide resonance (H_b) moved consistently downfield while, curiously, the methylene resonance alpha to the phosphine oxide shifts slightly downfield up to ~1.5 equiv. of Cl^- then begins to shift upfield throughout the remainder of the titration (Fig. 4a,d). The serpentine movement of the methylene resonance is indicative of the lithium cation being evacuated from its binding site within the **2**· Li^+ complex beyond ~1.5 equiv. of Cl^- . The apparent decomplexation of lithium can be readily explained by ion pairing of Li^+ and Cl^- outside of the receptor which has an ion pair association constant (K_{LiCl}) $\approx 2900 \text{ M}^{-1}$ in MeCN,⁴³ and would be expected to provide a competitive association pathway versus the association with **2**. The competitive ion pairing also explains the diminished enhancement of chloride binding in the presence of lithium, although other contributing equilibria cannot be completely ruled out. Similar downfield then upfield shifting of the methylene resonance alpha to the P=O group was observed in titrations of **1**· Li^+ with Cl^- , but overlapping methylene peaks prevented detailed ^1H NMR investigation (Fig. S46). It is assumed that ion pairing of Li^+ and Cl^- is responsible for the relatively diminished chloride binding for this system as well.

Ion pairing appears to be negligible in the binding of **2**· Li^+ with Br^- and I^- . Titrations of **2**· Li^+ with Br^- and I^- showed steady downfield shifting of the H_a resonance (Fig. 4b–d), suggesting limited influence of competitive ion pairing in these systems as the ion pair association constants in MeCN are only $K_{\text{LiBr}} \approx 190 \text{ M}^{-1}$ and $K_{\text{LiI}} \approx 7 \text{ M}^{-1}$.⁴³ Analysis of the H_a methylene region in titrations of **2**· Na^+ gave slightly different shifting trends as observed with the lithium complexes. The titration of **2**· Na^+ with Cl^- did not induce any noticeable changes in the H_a methylene resonance (Fig. 5a,d), revealing the lack of affinity of **2** toward sodium in the presence of chloride. Not until titrations were performed with Br^- did there appear any evidence for improved sodium coordination to **2** (Fig 5b). The anion-dependent shifting of the alkali metal-sensitive resonance for bromide and iodide could be

fit to an apparent binding curve providing an association constant (K_{app}), serving as a metric to compare the relative cooperative effects of anion binding on metal coordination (Table 2). In titrations of **2**·Li⁺ with bromide the apparent increase in association for Li⁺ was 2100 M⁻¹, and the affinity for lithium drops to 140 M⁻¹ when the system becomes saturated with iodide. Titrations of **2**·Na⁺ produced a similar trend, but these values were an order of magnitude lower. Overall, bromide provides for the greatest increases in metal binding affinity, and this is most significant for lithium, reiterating the cooperative binding of lithium and bromide found in this system.

Conclusion

Coordination of alkali metal cations enhances the halide binding in a class of tripodal phosphine oxide-based receptors. Receptors **1** and **2** demonstrate alkali metal cation binding selectivity in the trend Li⁺ > Na⁺ > K⁺. The binding of these cations appears to have a cooperative effect in enhancement of halide binding in general, with the amount of enhancement greatly depending on the metal used where M = Li⁺ > Na⁺ > K⁺. Though significant anion binding enhancement was observed for all anions in the presence of Li⁺ and Na⁺, the greatest enhancement was observed for bromide binding over chloride (presumably due to less competition from ion-pairing for Br⁻ than Cl⁻). The coordination of pre-bound Li⁺ and Na⁺ to **2** was also shown to be positively affected by Br⁻ and I⁻, reiterating the ditopic nature of this receptor. Solution phase studies indicate that the tris-(aminomethyl)phosphine oxide based core common in both **1** and **2** is responsible for the bulk of the ion coordination. However, low level calculations suggest that the functional groups protruding farther from the receptor core in **2** allow them to be more intimately involved in binding, as evidenced by the significant increases in all observed binding for **2** over **1**. The more stable host:guest complexes in **2** might also be due to its increased conformational freedom.

These studies demonstrate that tripodal phosphine oxide-based receptors represent an effective option for the challenging task of lithium ion coordination, or more specifically lithium salt binding (e.g., LiBr). The ability to easily tune this receptor class, coupled with the unusual ditopic coordination of the Li⁺/Br⁻ ion pair yields a system that might warrant consideration for applications where detection of ion pairs is desired. Phosphine oxide-based receptors might prove especially attractive for applications where Li⁺ containing species need to be targeted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Structures of phosphine oxide-based receptors.

Fig. 2. Partial ^1H NMR spectra of (left) **1** and (right) **2** showing selective shifting of amide or methylene resonances in the presence of either excess alkali metal or excess halide. ($\square$) = H_b , ($\circ$) = H_d , (Δ) = H_a , ($\blacksquare$) = H_b , ($\bullet$) = H_f , ($\blacktriangle$) = H_a

Fig. 3. Calculated structures at semi-empirical PM6 level of theory⁴² of (a) **2**, (b) **2**·Li⁺, (c) **2**·Na⁺ and (d) **2**·LiBr. Hydrogens bonded to carbon were removed for clarity. Grey = C, white = H, red = O, blue = N, orange = P, light purple = Li⁺, dark purple = Na⁺ and burgundy = Br⁻. Hydrogen bonds and metal coordination shown as dashed lines.

Fig. 4. Partial ^1H NMR spectra of $2\cdot\text{Li}^+$ showing shifting of the H_a resonance in response to increasing guest concentration (bottom to top) during titrations with (a) tetrabutylammonium chloride, (b) tetrabutylammonium bromide and (c) tetrabutylammonium iodide and (d) a plot of $\Delta\delta(\text{H}_a)$ of $2\cdot\text{Li}$ versus ratio of host saturation by halide salts.

Fig. 5.

Partial ^1H NMR spectra of $2\cdot\text{Na}^+$ showing shifting of the H_a resonance in response to increasing guest concentration (bottom to top) during titrations with (a) tetrabutylammonium chloride, (b) tetrabutylammonium bromide and (c) tetrabutylammonium iodide and (d) a plot of $\Delta\delta(\text{H}_a)$ of $2\cdot\text{Na}$ versus ratio of host saturation by halide salts.

Table 1

Association constants, K_a (M^{-1}), of **1** and **2** with Cl^- , Br^- and I^- (added as the tetrabutylammonium salts) in the absence and presence of ~ 1 equiv. of Li^+ (added as the perchlorate salt), Na^+ or K^+ (added as the tetraphenylborate salts) and **2** with $LiClO_4$ and $NaBPh_4$ in $MeCN-d_3$ at 298 K. All association constants are an average of at least three titrations fit to a 1:1 model using WinEQNMR2, and associated errors are $< 15\%$ unless otherwise noted. na = not applicable.

	Cl^-	Br^-	I^-		Cl^-	Br^-	I^-	Li^+	Na^+	K^+
1	320^a	50^a	— ^{a,c}	2	580	100	— ^c	8610^e	230	— ^c
1 · Li^+	410^a	400^a	60^a	2 · Li^+	1770	1190	100	na	na	na
1 · Na^+	450^a	90^a	— ^{a,c}	2 · Na^+	990	270	30	na	na	na
1 · K^+	300	60	— ^c	2 · K^+	780	110	— ^c	na	na	na
$\Delta\Delta G^\circ_{Li^+}$ (kcal mol ⁻¹) ^b	-0.15^a	-1.2^a	-0.82^a	$\Delta\Delta G^\circ_{Li^+}$ (kcal mol ⁻¹) ^b	-0.66	-1.5	-1.1^b	na	na	na
$\Delta\Delta G^\circ_{Na^+}$ (kcal mol ⁻¹) ^b	-0.16^a	-0.34^a	— ^a	$\Delta\Delta G^\circ_{Na^+}$ (kcal mol ⁻¹) ^b	-0.31	-0.57	-0.33^b	na	na	na
$\Delta\Delta G^\circ_{K^+}$ (kcal mol ⁻¹) ^b	$+0.03$	-0.10	—	$\Delta\Delta G^\circ_{K^+}$ (kcal mol ⁻¹) ^b	-0.17	-0.05	—	na	na	na

^aValues were previously reported.³²

^b $\Delta\Delta G^\circ_{metal} = (\Delta G^\circ_{receptor-metal-halide complex}) - (\Delta G^\circ_{receptor-halide complex})$.

^c $K_a < 15 M^{-1}$ and could not be accurately determined.

^dCalculated assuming $\Delta G^\circ_{receptor \cdot iodide complex} = 15 M^{-1}$.

^eTitrations had errors of 17%.

Table 2

Apparent association constants, K_{app} (M^{-1}), of alkali metals during titrations of $2\cdot\text{M}^+$ complexes with halides in MeCN-d_3 at 298K. All errors are < 15% unless otherwise noted.

$2\cdot\text{M}^+$ Complex/ Halide titrated	<u>Metal (M^+)</u>	
	Li+	Na+
$2\cdot\text{M}^+/\text{Br}^-$	2100 ^{a,b}	340 ^a
$2\cdot\text{M}^+/\text{I}^-$	140 ^{a,b}	30 ^a

^aValues represent an average of the three sets of titration data used for determination of anionic association constants in Table 1 and fit using the methylene resonance alpha to the P=O.

^bErrors of associated titrations are > 15%.