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Lithium cation enhances anion binding in a tripodal phosphine oxide-based ditopic receptor†

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Abstract

A tripodal ditopic receptor presents H-bond donors and a phosphine oxide to potential guests. In the idealized binding conformation, an endohedral P=O functionality provides enhanced halide binding in the presence of lithium with the greatest $\Delta\Delta G^\circ$ observed for bromide, while minimal changes in K_a are observed in the presence of sodium.

Anion binding by synthetic receptors has garnered much attention due to emerging applications in waste remediation and studies aimed at elucidating biological structure and function.¹ Triamines such as 1,3,5-tris(aminomethyl)benzene^{2–4} and tris(2-aminoethyl)-amine (TREN)⁵ have proven to be workhorse scaffolds for tripodal anion receptors. The popularity of these scaffolds arises from the facile, modular synthetic modifications of their primary amino groups into strong hydrogen bond donors like secondary amines,⁶ amides,⁷ ureas,⁸ and thioureas.⁹ Furthermore, their C_{3v} -symmetric geometry allows for incorporation of multiple binding groups, which is very attractive for host–guest chemistry and molecule/ion recognition studies.

Herein we introduce anion recognition to a core scaffold based on the known tris(aminomethyl)phosphine oxide **1b**.¹⁰ This scaffold provides for facile synthetic manipulation, a tripodal geometry, and the incorporation of a Lewis basic phosphine oxide as a possible endohedral¹¹ cation binder or hydrogen bond acceptor. We envisioned that the phosphine oxide moiety could serve as a ligand for small cations such as lithium. Lithium is an attractive target because of its roles in the treatment of manic depressive behaviors,¹² in battery technologies,¹³ and as a surrogate probe for monitoring Na^+ ion channels.¹⁴ We report the preparation of a neutral tripodal ditopic receptor derived from **1b** that surprisingly exhibits increased affinity for halides in the presence of Li^+ , but *not* in the presence of Na^+ .

Receptor **2** was synthesized *via* reaction of Boc-protected glycine with **1b** (obtained from the trihydrobromide salt **1a**) under common peptide coupling conditions in DMF (Scheme 1). The desired product was isolated in 76% yield as a white powder upon precipitation from ethyl acetate. Single crystals of **2** suitable for X-ray diffraction analysis were obtained by slow evaporation of methanol.¹⁵ In the solid state receptor **2** forms an up-down-up conformation and accepts two hydrogen bonds from a bound water molecule (Fig. 1). A

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second water molecule also forms a hydrogen bond to the bound water molecule (hydrogen bond distances and angles are provided in the cif files†).

While single crystals of **2**·Li⁺ halide complexes unfortunately remain elusive, the single crystal X-Ray structure of a related receptor¹⁶ (Fig. S36†) exhibits a “bowl-shaped” cavity which displays an endohedral phosphine oxide stabilized by three DMSO solvates. This all up conformation shows that this receptor class is capable of adopting a conformation that presents an endohedral Lewis basic phosphine oxide to create a ditopic binding pocket capable of binding ion pairs. The possibility of such an endohedral binding geometry is corroborated by a DFT model of **2**·LiBr (Fig. S37†).

Anion binding studies of **2** with various halide salts were performed *via* ¹H NMR spectroscopy titrations in acetonitrile-*d*₃ (MeCN-*d*₃) (Table 1). Association constants were determined by monitoring the downfield shift of the carbamate proton signal and fitting the data to a 1 : 1 binding model¹⁷ using WinEQNMR2.¹⁸ The amide *NH* resonances do not shift downfield appreciably during the titrations with halides, indicating that these protons do not contribute to the affinity of **2** for anions. Association constants of **2** with tetrabutylammonium (TBA) halides gave the expected Hoffmeister trend of Cl[−] > Br[−] > I[−].

The affinity for several halides by **2**·Li⁺ was determined using lithium perchlorate as a lithium source,¹⁹ and yielded noticeable increases in the association constants of all the anions tested. Remarkably, the affinity of **2** for bromide increases one order of magnitude in the presence of Li⁺, even in a polar coordinating solvent such as MeCN. The unusual shift in anion binding trends between **2**·Li⁺ vs. **2** was illuminated upon investigation of the methylene region of the ¹H NMR spectrum (Fig. 2). Addition of a lithium or halide salt induces a downfield shift and divergence of the eclipsed methylene resonances from a broad multiplet to a triplet representing the H_a protons from the scaffold and a doublet representing the H_b protons from the glycine unit. The relative magnitude of the downfield shifts of the methylene resonances are dependent on the identity of the guest.

In the presence of *ca.* 1 equiv. of lithium perchlorate a small but noticeable downfield shift for the triplet (H_a, blue squares) was observed, while the position of the doublet (H_b, green circles) was relatively unchanged. In the presence of *ca.* 10 equiv. of lithium perchlorate further downfield shifting was observed for the triplet. These observations are consistent with the coordination of lithium by the scaffold portion of **2** (Fig. 2a). Significant lithium coordination is further supported by ³¹P NMR which shows a *ca.* 6.6 ppm downfield shift of the phosphorus signal of **2** upon addition of *ca.* 30 fold excess of lithium perchlorate to a solution containing **2** and *ca.* 30 equiv. of TBA perchlorate.²⁰

Conversely, addition of TBA halide to **2** induces significant downfield shifting of H_b (green circles) as result of the anion hydrogen bonding to the nearby carbamate protons, whereas the triplet remained relatively unchanged (Fig. 2b). The shift of this resonance was strongest for chloride followed by bromide and then iodide which trends well with the observed association constants. Titrations of **2** with lithium bromide and lithium iodide also showed increased anion association constants of 200 M^{−1} and 30 M^{−1}, respectively, over the analogous experiments with the halides alone, lending further evidence that Li⁺ is promoting increased halide binding by **2**.

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Titration of **2**·Li⁺ with TBA halides resulted in significant downfield shifting of both methylene resonances. This observation suggests binding by both lithium and halides simultaneously, again consistent with the hypothesis that Li⁺ binding modulates halide binding in this receptor class. The magnitude of the downfield shifts in H_b (green circles) again increases with increasing basicity of guest. The largest binding enhancement is observed for bromide, with a $\Delta\Delta G^\circ$ of $-1.2 \text{ kcal mol}^{-1}$ (Table 1). Interestingly, in the case of chloride the doublet resonance (H_b) shifts further downfield than for iodide or bromide, whereas the triplet methylene resonance (H_a) shows reduced shifting compared to iodide and bromide (Fig. 2c). The diminished downfield shift of H_a in the presence of chloride *and* lithium suggests that lithium is not a good guest in the presence of chloride, and therefore, lithium is not enhancing the binding of chloride as significantly, resulting in only a minor increase in association constant and a $\Delta\Delta G^\circ$ of $-0.15 \text{ kcal mol}^{-1}$ (Table 1).

Lithium ion appears to modulate anion binding exclusively in this receptor: the presence of sodium²¹ had little to no effect on the affinity of the halides toward **2** (Table 1). Although a small downfield shift of *ca.* 3.6 ppm in the ³¹P NMR was observed upon addition of *ca.* 30 equiv. of sodium tetraphenylborate to a solution of **2** and *ca.* 30 equiv. of TBA tetraphenylborate¹⁹ only downfield shifting of the H_b resonance was observed by ¹H NMR (Fig. S34†). The magnitude of these shifts follows the same trend as titrations of the halides and **2** suggesting that sodium is not coordinated to **2** as strongly as lithium. The preferential binding of lithium over sodium and the resulting enhancement of bromide binding is presumably due to a combination of optimum size fit, ion pairing strength, and differences in solvation.

In conclusion, we have presented the use of a tris-(aminomethyl)phosphine oxide as a scaffold for the neutral ditopic tripodal receptor **2**. This unusual receptor shows a greater enhancement in the binding of bromide over chloride and iodide in the presence of *ca.* 1 equiv. of a lithium source, while sodium has little to no effect on anion association. Determination of association constants of lithium and sodium by **2**·X[−] are currently underway as are investigations into possible cooperative effects of other positively charged species on anion binding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. Crystal data for **2**·2(H₂O): C₂₄H₄₉N₆O₁₂P *M_r* = 644.66, 0.18 × 0.05 × 0.02 mm, triclinic, *P*1 (N 2), *a* = 11.1651(19) Å, *b* = 13.264(2) Å, *c* = 13.360(2) Å, α = 93.405(3)°, β = 109.288(3)°, γ = 111.239(3)°, *V* = 1704.3(5) Å³, *Z* = 2, ρ_{calcd} = 1.256 g cm⁻³, μ = 0.144 mm⁻¹, 2θ_{max} = 50.00°, *T* = 173(2)K, 16644 measured reflections, 6003 independent reflections [*R*_{int} = 0.0446], 428 parameters, *R*₁ = 0.0476, *wR*₂ = 0.1097 (with *I* > 2σ(*I*)), *R*₁ = 0.0729, *wR*₂ = 0.1320 (all data), GOF = 1.012, max/min residual electron density +0.226/−0.294 e Å⁻³.
16. Crystal data for **3**·3(DMSO): C₃₀H₃₆N₉O₁₉PS₃, *M_r* = 953.83, 0.80 × 0.02 × 0.01 mm, hexagonal, *R*3̄ (N 146), *a* = *b* = 26.969(4) Å, *c* = 4.7896(9) Å, 90°, 90°, 120°, *V* = 3016.8(8) Å³, *Z* = 3, ρ_{calcd} = 1.575 g cm⁻³, μ = 0.315 mm⁻¹, 2θ_{max} = 50.00°, *T* = 173(2)K, 8003 measured reflections, 2156 independent reflections [*R*_{int} = 0.0874], 191 parameters, *R*₁ = 0.0474, *wR*₂ = 0.0701 (with *I* > 2σ(*I*)), *R*₁ = 0.0686, *wR*₂ = 0.0768 (all data), GOF = 0.838, max/min residual electron density +0.251/−0.226 e Å⁻³.
17. Job's method of continuous variations was used to confirm the 1 : 1 host : guest binding stoichiometry (Fig. S7–S9†).
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19. No observable anion binding was observed with LiClO₄ or TBAClO₄ indicating that the role of perchlorate is strictly as a spectator anion.

20. The presence of excess TBA salt ensures that the observed chemical shift is due to coordination and not changes in the ionic strength of the receptor milieu.
21. NaB(Ph)_4 was used as the source of sodium. ^1H NMR titrations of TBA tetraphenylborate with **2** furnished no measurable binding event meaning the role of the tetraphenylborate anion is innocent.

Fig. 1.
X-Ray crystal structure of **2**. Red = O, orange = P, blue = N, gray = C, and white = H.

Fig. 2.
 ^1H NMR spectra of methylene resonances of (a) receptor **2** with 0, 1 and 10 equiv. of Li^+ ; (b) receptor **2** with excess iodide, bromide and chloride; (c) complex $2\cdot\text{Li}^+$ with excess iodide, bromide and chloride. Filled blue square = H_a and filled green circle = H_b . Empty blue square = cation binding units and empty green circles = anion binding units.

Scheme 1.

Synthesis of ditopic receptor **2** using *O*-(benzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and Hunig's base (DIPEA).

Table 1

Association constants K_a (M^{-1}) of **2**, **2**·Li⁺ and **2**·Na⁺ with TBA⁺ X[−]. Determined by an average of three ¹H NMR titration experiments in MeCN-*d*₃ at 298 K. Data fit to a 1 : 1 binding model. Errors < 10%.

	Cl [−]	Br [−]	I [−]
2	320	50	— ^a
2 ·Li ⁺	410 ^b	400 ^b	60 ^b
2 ·Na ⁺	450 ^c	90 ^c	— ^{a,c}
$\Delta\Delta G^\circ_{Li^+}$ (kcal mol ^{−1}) ^d	−0.15	−1.2	−0.82 ^f
$\Delta\Delta G^\circ_{Na^+}$ (kcal mol ^{−1}) ^e	−0.16	−0.34	—

^a Association constant < 15 M^{−1} and could not be accurately determined.

^b Lithium perchlorate used as lithium source.

^c Sodium tetraphenylborate used as sodium source.

^d $\Delta\Delta G^\circ_{Li^+} = (\Delta G^\circ_{\mathbf{2}\cdot Li^+} - \Delta G^\circ_{\mathbf{2}})$.

^e $\Delta\Delta G^\circ_{Na^+} = (\Delta G^\circ_{\mathbf{2}\cdot Na^+} - \Delta G^\circ_{\mathbf{2}})$.

^f Association constant of 15 M^{−1} was assumed for **2**·I[−].