ChemComm

COMMUNICATION

View Article Online
View Journal

Superior perrhenate anion recognition in water by a halogen bonding acyclic receptor†

Jason Y. C. Lim and Paul D. Beer*

Cite this: DOI: 10.1039/c4cc10130h

Received 18th December 2014,
Accepted 26th January 2015

DOI: 10.1039/c4cc10130h

www.rsc.org/chemcomm

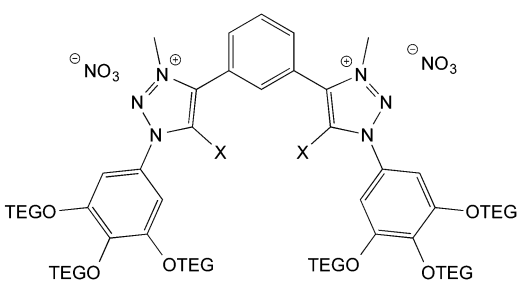
A halogen bonding bis-iodotriazolium water-soluble acyclic receptor exhibits enhanced perrhenate anion recognition in water compared to the hydrogen bonding analogue, and is shown to be capable of sensing the oxoanion *via* a fluorescence response.

As a result of anthropogenic activities, oxoanions of many d-block metals have increasingly found their way into the environment.[1] Among which, radioactive pertechnetate ($^{99}TcO_4^-$), a by-product of the nuclear industry, is an especially hazardous environmental pollutant due to its long half-life and stability,[2] physiological toxicity,[3] and high mobility through the biosphere.[4] However, direct studies on $^{99}TcO_4^-$ have been thwarted by its radioactive nature, and hence, the perrhenate anion (ReO_4^-) has been commonly used as a model for studying pertechnetate binding in solution due to their comparable physical properties such as hydration energies and size.[5–7] Nevertheless, perrhenate detection in aqueous media is also of scientific interest due to the oxoanion being a precursor to medical beta-emitting radioimmunotherapeutic agents arising from the radioisotopes ^{186}Re and ^{188}Re,[8,9] and as a convenient starting material for rhenium-based industrial catalysts.[10] In spite of this, there are very few synthetic receptors capable of recognising perrhenate in water, with the majority operating in organic solvents utilising convergent hydrogen bonding interactions[5–7] and metal-coordination.[11]

In recent years, halogen bonding (XB) has emerged as a powerful complement to hydrogen bonding (HB) for anion recognition in solution,[12–16] exhibiting the highly-directional intermolecular XB interaction between a Lewis-acidic halogen atom on the host receptor and the Lewis-basic guest anion.[17–19] However, its exploitation in aqueous-phase anion recognition remains in its infancy.[20–24] Recently, we reported a water-soluble XB rotaxane, which displayed a remarkable enhancement in iodide binding in pure water compared to HB rotaxane analogues.[25] Herein, we report the superior perrhenate anion binding properties of a XB bis-iodotriazolium acyclic receptor over a HB analogue in pure water and demonstrate its capability to detect the oxoanion *via* a fluorescence response.

Inspired by the plethora of water-soluble hydrophilic systems used in drug delivery,[26,27] we employed a tris-tetra(ethylene glycol) (TEG)-based unit to confer water solubility onto the lipophilic HB (**1a**) and XB (**1b**) host systems (Fig. 1). The rigid phenyl spacer unit between the triazolium motifs preorganises the binding site for convergent XB and HB interactions with a potential anion guest, while the dicationic nature of the hosts serves to electrostatically enhance the binding strength in water. In addition, the conjugated nature of the host molecules facilitates the opportunity of anion sensing by optical spectroscopic techniques.

The water-soluble terminal units were synthesised by copper(I)-mediated Ullmann amination of the TEG-functionalised aryl bromide to form the aniline intermediate, followed by Sandmeyer-type substitution to afford the aryl-azide **2** in excellent overall yield (Scheme 1). Copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) of two equivalents of **2** with 1,3-diethynylbenzene produced the bis-prototriazole compound **3a** (Scheme 2). Surprisingly, one-pot protocols[28,29] to synthesise the corresponding bis-iodotriazole **3b** from **2** and the bis-alkyne gave no product. Hence, **3b** was prepared utilising a two-pot methodology[30] by first synthesising 1,3-bis-(iodoethynyl)benzene, followed by CuAAC with two equivalents of

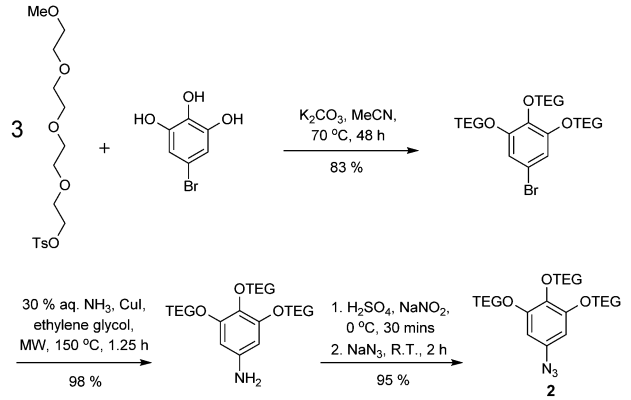


1a X = H
1b X = I

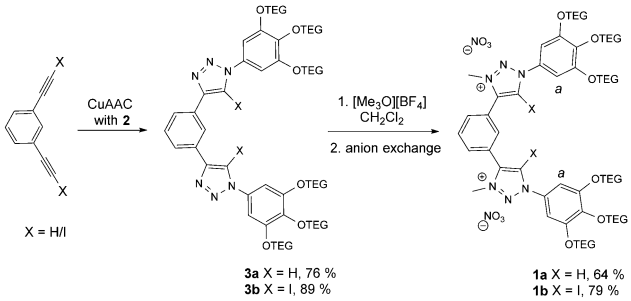
Fig. 1 Structures of the target dicationic water-soluble acyclic HB and XB host molecules. OTEG = $(OCH_2CH_2)_4OMe$.

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: paul.beer@chem.ox.ac.uk

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc10130h



Scheme 1 Synthesis of aryl azide **2**. OTEG = $(OCH_2CH_2)_4OMe$.



Scheme 2 Synthesis of the nitrate salts of water-soluble receptors **1a** and **1b**. OTEG = $(OCH_2CH_2)_4OMe$.

2 in 89% yield. The triazole moieties of **3a** and **3b** were then methylated using trimethyloxonium tetrafluoroborate followed by anion exchange to the weakly coordinating nitrate anion‡ using an Amberlite® column, to produce the water soluble host systems, **1a** and **1b** (Scheme 2).

The anion recognition properties of receptors **1a** and **1b** were investigated using ^{1}H NMR titration experiments in D_2O at 298 K, by adding increasing quantities of the sodium salts of Cl^-, Br^-, I^-, SO_4^{2-}, ClO_4^- and ReO_4^- to the respective host solution. The addition of anions caused downfield perturbations§ of the signal arising from the *ortho*-aromatic protons (H_a in Scheme 2) of the tris-TEG units, as well as from the phenyl spacer proton in between the triazolium units. This indicated that anion binding was taking place within the acyclic receptors' cleft flanked by the triazolium units. WinEQNMR2[31] analysis of the titration data determined 1 : 1 stoichiometric association constants shown in Table 1.¶

Both receptors **1a** and **1b** showed Hofmeister bias for halide binding in water, with iodide being bound the strongest. The XB receptor **1b** was found to bind bromide and iodide more strongly than the HB receptor **1a** which is consistent with previous observations.[25]

Most importantly, the XB receptor **1b** was found to bind perrhenate almost as strongly as iodide. In stark contrast, the analogous HB receptor **1a**, although capable of binding iodide, did not show any clear evidence of perrhenate binding in water. This observation clearly demonstrates the superiority of XB over HB bonding for perrhenate recognition in water. Furthermore, in spite of perchlorate's lower and chloride's similar hydration

Table 1 Anion association constants (K_a/M^{-1}) in water[a]

	1a	**1b**	ΔG_{hyd}/kJ mol^{-1}
Cl^-	11	10	−340[32]
ClO_4^-	14	12	−205[32]
Br^-	14	22	−315[32]
ReO_4^-	—[b]	44	−330[5]
I^-	29	51	−275[32]
SO_4^{2-}	—[b]	—[b]	−1295[32]

[a] 1 : 1 stoichiometric association constants were calculated from ^{1}H NMR titrations in D_2O at 298 K using the WinEQNMR2 software[31] by monitoring H_a (see Scheme 2 for assignment); anions were added as their sodium salts (see ESI for further details). Errors were found to be less than 15%. [b] No binding observed.

energies to perrhenate, the association constant for perrhenate binding with XB receptor **1b** is approximately four times larger in magnitude. Interestingly, despite being dianionic, sulfate did not show any evidence of binding to either receptor, presumably due to its very high hydration energy.

In order to determine the thermodynamic driving force for perrhenate binding in water by the XB receptor **1b**, van't Hoff analysis was undertaken *via* variable-temperature (VT) ^{1}H NMR titration experiments (Fig. 2). It is noteworthy that perrhenate binding is driven by a favourable enthalpic contribution (ΔH = −12 ± 1 kJ mol^{-1}) and is disfavoured entropically (ΔS = −9 ± 3 J K^{-1} mol^{-1}). This is a clear indication that the classical hydrophobic effect, well-known to be driven largely by an entropic increase arising from desolvation,[33] may not be the dominant factor accounting for binding in this case. The enthalpic gain may arise from the iodotriazolium moieties of **1b** forming strong XB interactions with the perrhenate anion. Indeed, iodide binding by a XB rotaxane host system in water was also shown to be enthalpically favoured and opposed by entropy.[25]

The conjugated nature of receptors **1a** and **1b** also enabled perrhenate binding to be investigated by preliminary fluorescence spectroscopic titration experiments in an aqueous solution (10 mM HEPES, pH 7.4).‖ Upon titration of sodium perrhenate with receptor **1a**, no significant spectral changes were observed (Fig. 3A), which is consistent with the results obtained from ^{1}H NMR titrations

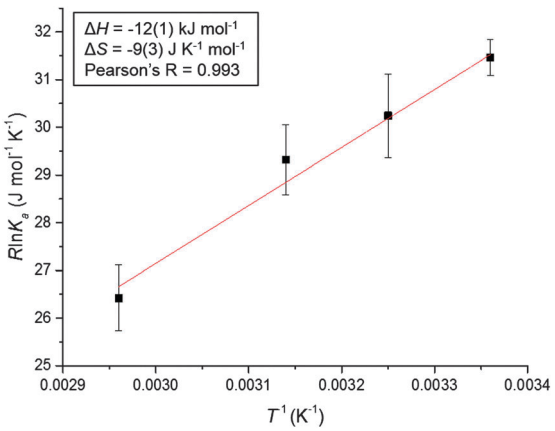


Fig. 2 Van't Hoff plot showing the variations of association constants (K_a) with temperature (T), determined from VT NMR titrations (500 MHz, D_2O, T = 298 K, 308 K, 318 K, 338 K). Errors in parentheses.

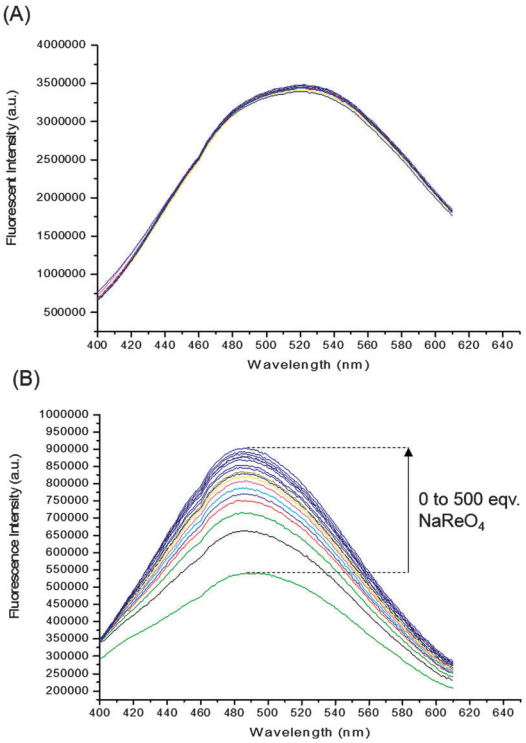


Fig. 3 Luminescence spectra of (A) HB receptor **1a** and (B) XB receptor **1b** upon titration of increasing quantities of ReO_4^- up to 500 equivalents ([host] = 10 μM in 10 mM aqueous HEPES buffer, pH = 7.4, λ_{ex} = 320 nm, T = 293 K).

indicating that no binding occurred with the HB receptor. In contrast, the analogous titration of perrhenate with XB receptor **1b** resulted in a significant increase in fluorescence intensity (Fig. 3B) without any detectable change in sample emission wavelength (λ_{em} = 485 nm). This may be attributed to the increased rigidification of the host that results from XB recognition of perrhenate, which disfavours non-radiative decay pathways.

In summary, a water-soluble XB bis-iodotriazolium acyclic receptor has been shown to exhibit superior perrhenate anion recognition behaviour in water compared to the hydrogen bonding analogue. Thermodynamic analysis has revealed that the halogen bond-driven perrhenate binding is favoured enthalpically and disfavoured entropically. Furthermore, the XB receptor is capable of sensing perrhenate in water *via* a fluorescent response. To the best of our knowledge, this is the first example of fluorescent perrhenate sensing utilising halogen bonding interactions. The design and construction of XB receptors for anion recognition and sensing applications in water is continuing in our laboratories.

J.Y.C.L acknowledges the Agency for Science, Technology and Research (A*STAR), Singapore, for a postgraduate scholarship.

Notes and references

‡ A control ^{1}H NMR titration experiment was performed using **1a.2PF$_6$** with sodium nitrate in water (see ESI†), which showed no evidence of nitrate binding even at a nitrate: **1a.2PF$_6$** mole ratio of 120 : 1.
§ All anions gave downfield perturbations of the tris-TEG aromatic *ortho*-proton signal for receptor **1a** except ClO_4^-, which showed an *upfield* shift (see ESI†). All anions gave downfield perturbations of this signal for receptor **1b**, including ClO_4^-.
¶ The ^{1}H NMR signal arising from proton of the phenyl spacer in between the triazoliums was not used to probe anion binding as coalescence of the signal was observed with those arising from the other phenyl protons during the titration experiments. Instead, the *ortho*-aromatic tris-TEG proton signals for **1a** and **1b** were monitored for consistency.
‖ A ^{1}H NMR titration was also performed on **1b** using 10 mM HEPES solution in D_2O (pD = 7.4) with perrhenate at 298 K. The association constant obtained (K_a = 45 ± 4 M^{-1}) was consistent with those obtained from the titrations carried out in pure D_2O (see ESI†).

1 L. Keith and W. Telliard, *Environ. Sci. Technol.*, 1979, **13**, 416–423.
2 B. Wakoff and K. L. Nagy, *Environ. Sci. Technol.*, 2004, **38**, 1765–1771.
3 R. Amano, A. Ando, T. Hiraki, H. Mori, H. Matsuda and K. Hisasa, *Radioisotopes*, 1990, **39**, 583–586.
4 B. M. Rambo and J. L. Sessler, *Chem. – Eur. J.*, 2011, **17**, 4946–4959.
5 E. A. Katayev, G. V. Kolesnikov and J. L. Sessler, *Chem. Soc. Rev.*, 2009, **38**, 1572–1586.
6 R. Alberto, G. Bergamaschi, H. Braband, T. Fox and V. Amendola, *Angew. Chem., Int. Ed.*, 2012, **51**, 9772–9776.
7 V. Amendola, G. Bergamaschi, M. Boiocchi, R. Alberto and H. Braband, *Chem. Sci.*, 2014, **5**, 1820–1826.
8 L. S. Zuckier, O. Dohan, Y. Li, C. J. Chang, N. Carrasco and E. Dadachova, *J. Nucl. Med.*, 2004, **45**, 500–507.
9 F. Jaubert, *Appl. Radiat. Isot.*, 2008, **66**, 960–964.
10 W. A. Herrmann, A. M. J. Rost, J. K. M. Mitterpleininger, N. Szesni, S. Sturm, R. W. Fischer and F. E. Kühn, *Angew. Chem., Int. Ed.*, 2007, **46**, 7301–7303.
11 R. Cao, B. D. McCarthy and S. J. Lippard, *Inorg. Chem.*, 2011, **50**, 9499–9507.
12 L. C. Gilday, N. G. White and P. D. Beer, *Dalton Trans.*, 2013, **42**, 15766–15773.
13 N. L. Kilah, M. D. Wise, C. J. Serpell, A. L. Thompson, N. G. White, K. E. Christensen and P. D. Beer, *J. Am. Chem. Soc.*, 2010, **132**, 11893–11895.
14 B. R. Mullaney, A. L. Thompson and P. D. Beer, *Angew. Chem., Int. Ed.*, 2014, **53**, 11458–11462.
15 G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, M. Sansotera and G. Terraneo, *Chem. Soc. Rev.*, 2010, **39**, 3772–3783.
16 P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *Acc. Chem. Res.*, 2005, **38**, 386–395.
17 T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667–1680.
18 M. G. Sarwar, B. Dragisić, E. Dimitrijević and M. S. Taylor, *Chem. – Eur. J.*, 2013, **19**, 2050–2058.
19 E. A. L. Gillis, M. Demireva, M. G. Sarwar, M. G. Chudzinski, M. S. Taylor, E. R. Williams and T. D. Fridgen, *Phys. Chem. Chem. Phys.*, 2013, **15**, 7638–7647.
20 A. Caballero, S. Bennett, C. J. Serpell and P. D. Beer, *CrystEngComm*, 2013, **15**, 3076–3081.
21 L. C. Gilday, T. Lang, A. Caballero, P. J. Costa, V. Félix and P. D. Beer, *Angew. Chem., Int. Ed.*, 2013, **52**, 4356–4360.
22 A. Caballero, F. Zapata, N. G. White, P. J. Costa, V. Félix and P. D. Beer, *Angew. Chem., Int. Ed.*, 2012, **51**, 1876–1880.
23 N. L. Kilah, M. D. Wise and P. D. Beer, *Cryst. Growth Des.*, 2011, **11**, 4565–4571.
24 A. Caballero, N. G. White and P. D. Beer, *Angew. Chem., Int. Ed.*, 2011, **50**, 1845–1848.
25 M. J. Langton, S. W. Robinson, I. Marques, V. Félix and P. D. Beer, *Nat. Chem.*, 2014, **6**, 1039–1043.
26 R. S. Dhanikula, A. Argaw, J.-F. Bouchard and P. Hildgen, *Mol. Pharmaceutics*, 2008, **5**, 105–116.
27 M. Liu, K. Kono and J. M. J. Fréchet, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 3492–3503.
28 W. S. Brotherton, R. J. Clark and L. Zhu, *J. Org. Chem.*, 2012, **77**, 6443–6455.
29 Y.-M. Wu, J. Deng, Y. Li and Q.-Y. Chen, *Synthesis*, 2005, 1314–1318.
30 J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2009, **48**, 8018–8021.
31 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311–312.
32 B. A. Moyer and P. V. Bonnesen, in *Supramolecular Chemistry of Anions*, ed. A. Bianchi, K. Bowman-James and E. Garcia-Espana, Wiley-VCH, Inc., New York, 1979, pp. 1–44.
33 S. Kubik, *Chem. Soc. Rev.*, 2010, **39**, 3648–3663.