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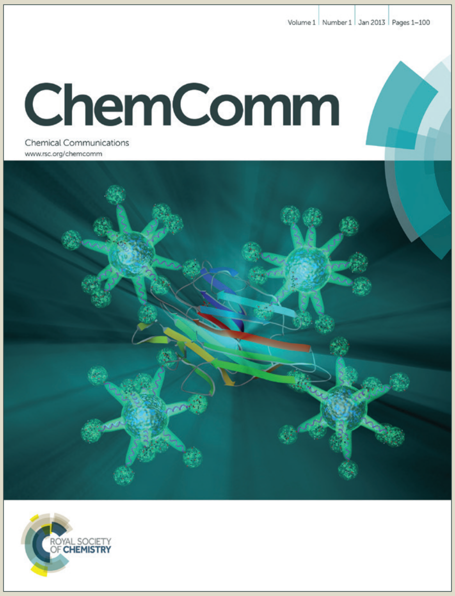

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Solution and Solid-Phase Halogen and C–H Hydrogen Bonding to Perrhenate

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Casey J. Massena,‡[a] Asia Marie S. Riel,‡[a] George F. Neuhaus,[a] Daniel A. Decato,[a] and Orion B. Berryman*[a]

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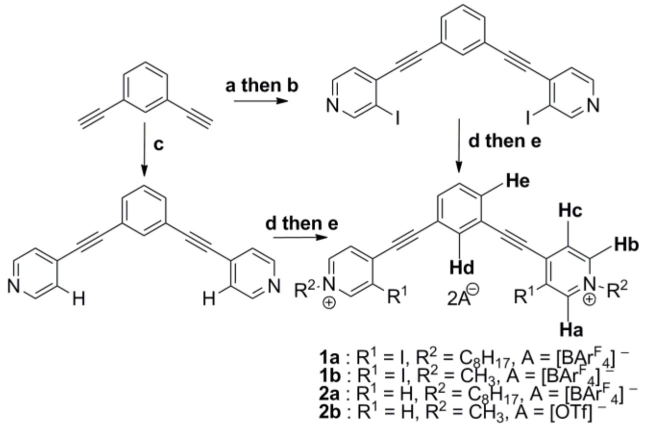
^{1}H NMR spectroscopic and X-ray crystallographic investigations of a 1,3-bis(4-ethynyl-3-iodopyridinium)benzene scaffold with perrhenate reveal strong halogen bonding in solution, and bidentate association in the solid state. A nearly isostructural host molecule demonstrates significant C–H hydrogen bonding to perrhenate in the same phases.

With similar structural and electronic characteristics,[1] perrhenate (ReO_4^-) is a tractable surrogate[2] for the medically ubiquitous and environmentally pernicious[3] oxoanion, pertechnetate (TcO_4^-).[4] The metastable form of technetium[5] and its long half-life[6] decay product ^{99}Tc are standards for radiolabeling[7] and *in situ* radiotherapy. Considering the high mobility of $^{99}TcO_4^-$, its stability,[8] and increasing production,[9] the need for synthetic receptors to function as strong and selective chelating agents, liquid-liquid extractants,[2] and ion-exchange stationary phases[10] is pressing.

ReO_4^- and TcO_4^- are challenging targets due to their low hydration energies and diffuse charge densities.[11] To combat these difficulties, a number of hydrogen bonding (HB) scaffolds and hosts have been developed.[1, 11-12] Elegant HB examples include aza-cryptands with pH-tunable cavities,[12a-c] and charge neutral pyrrole-based macrocycles.[12d-e] In contrast, bidentate halogen bonding (XB) and unconventional C–H[13] HB receptors for ReO_4^- or TcO_4^- have not been reported. XB[14] in particular offers an exciting competitive[15]/cooperative[16] alternative with the benefit of soft-soft HSAB complementarity.[17] *Herein, we report the first two receptors that exhibit strong XB and C–H HB with* ReO_4^- *in solution, and the first bidentate and tridentate structures of each in the solid state.*

We have developed two bidentate receptor molecules based on a diethynyl benzene core (**1** and **2**, Scheme 1). **1** is designed to direct two XB donors towards one anionic guest in a planar conjugated conformation.[19] Molecule **2**—which lacks XB donors—was prepared to quantify C–H HB to ReO_4^-, and serve as a comparison. Both receptor scaffolds were synthesized by Sonogashira[20] cross-coupling of 1,3-diethynyl benzene with either 3-bromo-4-iodopyridine or 4-bromopyridine hydrochloride. The XB donor iodines of **1** were installed by lithium halogen exchange followed by quenching with I_2. Alkylation of the pyridines with octyl triflate activated the XB and HB donors of **1** and **2**, respectively, and enhanced solubility in organic solvents. To minimize competitive intramolecular interactions, triflate counteranions were exchanged by metathesis for non-coordinating $[BAr^F{}_4]^-$ anions.[21] Methyl derivatives **1b** and **2b** were synthesized in a similar manner for X-ray diffraction studies.



Scheme 1. a) 3-Bromo-4-iodopyridine, CuI, $Pd(PPh_3)_2Cl_2$, DMF, DIPEA, rt, 24 h, 88%; b) *n*-BuLi, THF, -78°C, I_2, 24 h, 41%; c) prepared according to literature procedure,[18] 22% d) octyl triflate or methyl triflate, DCM, rt, 24 h, 98%; e) vapor diffusion of ether into DCM solution of TBA^+Cl^-, 55-75%; $Na^+[BAr^F{}_4]^-$, DCM, rt, 30 min, 59-75%.

The crystal structure of **1b**$^{2+}$•2ReO$_4^-$ represents the first bidentate XB[22] to ReO$_4^-$ in the solid state. Yellow single crystals of **1b**$^{2+}$•2ReO$_4^-$ suitable for X-ray diffraction were grown by diffusing DCM into a DMF/MeOH solution of receptor **1b** and tetra-*n*-butylammonium perrhenate (TBA$^+$ReO$_4^-$).[23] **1b**$^{2+}$•2ReO$_4^-$ crystallized in space group P2$_1$/c, forming bidentate XB to separate oxygens of a ReO$_4^-$ anion (Figure 1, top). The C–I···O$^-$ distances 2.97 and 3.06 Å correspond to R_{IO} values of 0.84 and 0.86,[24] and corroborate strong XB interactions. To accommodate the size of ReO$_4^-$, both pyridinium rings rotate 11° from coplanarity. As a result, the observed C–I···O$^-$ bond angles of 175 and 168° also confirm strong XB interactions. Examination of the crystal packing reveals C–H HB and electrostatic contacts between ReO$_4^-$ and five additional molecules of **1b** (see ESI). The second ReO$_4^-$ participates in seven C–H HB interactions, and two weak σ contacts with electron-deficient pyridinium rings.[25] A head-to-tail π-stacking dimer (3.4 Å) is also observed.[26] This arrangement produces columns of **1b** with each ReO$_4^-$ on alternating sides of the receptor.

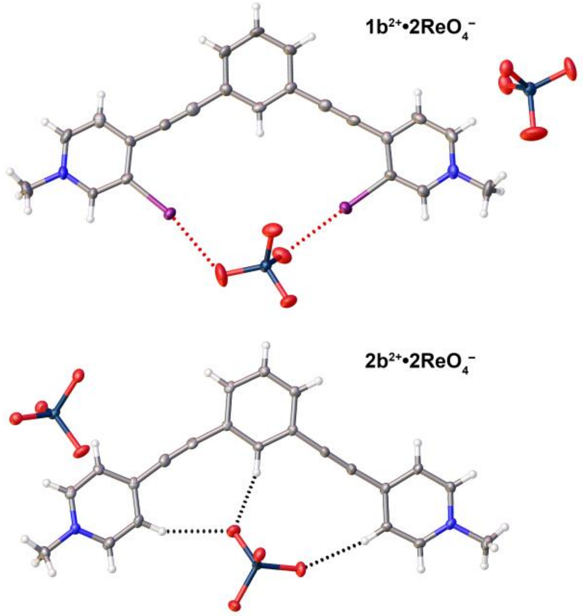


Figure 1. X-ray crystal structures of **1b**$^{2+}$•2ReO$_4^-$ (top) highlighting bidentate XB to ReO$_4^-$ in the solid state (red). Crystal structure of **2b**$^{2+}$•2ReO$_4^-$ (bottom) illustrating tridentate C–H HB to ReO$_4^-$ (black).

In contrast, the crystal structure of **2b**$^{2+}$•2ReO$_4^-$ illustrates unique C–H HB to ReO$_4^-$. Colorless single crystals of **2b**$^{2+}$•2ReO$_4^-$ were obtained by diffusing ether into a MeOH solution of receptor **2b** and TBA$^+$ReO$_4^-$.[27] **2b**$^{2+}$•2ReO$_4^-$ crystallized in space group P2$_1$/n. Notably, tridentate C–H HB to ReO$_4^-$ is formed using two Hc hydrogens and Hd (Figure 1, bottom), with C–H···O$^-$ distances of 2.64, 2.71 and 2.31 Å. In addition, four intermolecular C–H[28] and two weak σ[29] contacts with ReO$_4^-$ are present. The second ReO$_4^-$ is involved in nine C–H HB and two weak σ interactions. To enable tridentate binding to ReO$_4^-$, both pyridinium rings adjust 9° from coplanarity, and one ethynyl spacer deviates 8° from linearity. An off-centered head-to-tail π-stacking dimer (3.1 Å) is also noted (see ESI).[26] Together, the crystal structures of **1b**$^{2+}$•2ReO$_4^-$ and **2b**$^{2+}$•2ReO$_4^-$ illustrate the importance of bidentate/tridentate XB and HB coordination to ReO$_4^-$ in the solid state.

^{1}H NMR spectroscopic titrations involving **1a** and **2a** were conducted to probe their corresponding XB and C–H HB capabilities in solution. Both **1a**, **2a** and TBA$^+$ReO$_4^-$ were independently soluble in CDCl$_3$; however, precipitation of host-guest complexes necessitated a CDCl$_3$/(CD$_3$)$_2$CO (3:2 v/v) mixed solvent. Titrating TBA$^+$ReO$_4^-$ produced noteworthy shifts for the pyridinium (Ha, Hb, and Hc) and phenyl (Hd) hydrogens for both **1a** and **2a** (Figure 2).[30]

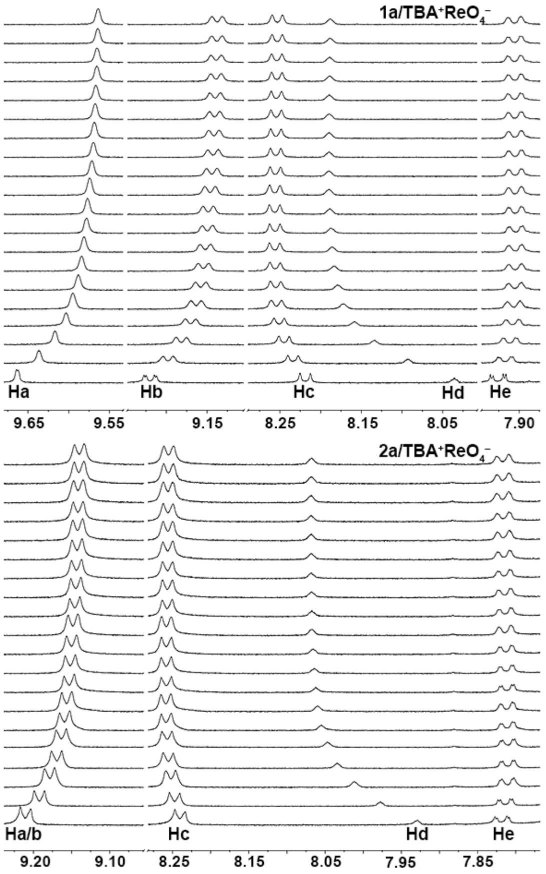


Figure 2. Partial ^{1}H NMR spectra of **1a** (top, 0–4.78 equiv) and **2a** (bottom, 0–4.62 equiv) upon titrating TBA$^+$ReO$_4^-$ (equivalents from bottom to top).

The significant upfield shifting of Ha and Hb (Δδ = -0.099 and -0.082 ppm, respectively) on **1a** is indicative of strong XB in solution.[31] The dominant XB conformation as suggested by the crystal structure of **1b**$^{2+}$•2ReO$_4^-$ is distinctly bidentate (Figure 1, top). Further evidence of XB in solution can be seen in the downfield ^{13}C NMR shifting of **1a**'s C–X carbons (Δδ = 0.150 ppm) upon titrating ReO$_4^-$ (see ESI). Additionally, facile rotation of alkynyl-aromatic C–C bonds enables a second XB mode. Constructive bidentate XB-HB involving a single halogen and Hc/Hd is consistent with the downfield shifting of these hydrogens (Δδ = 0.038 and 0.154 ppm).[32] Taken together, the greater upfield (Ha and Hb) and greater downfield (Hc and Hd) shifting of **1a** is explained by strong bidentate XB in solution as well as XB-HB synergy.

For **2a**, C–H HB and electrostatic contacts are the prevailing interactions in solution. Specifically, a tridentate binding site involving two Hc hydrogens and Hd proves the most active as evidenced by the crystal structure of $\mathbf{2b}^{2+}\bullet 2ReO_4^-$ and the downfield progression of these hydrogens ($\Delta\delta$ = 0.019 and 0.139 ppm, respectively). Upfield shifting of **2a**'s Ha/b ($\Delta\delta$ = -0.071 ppm) is indicative of anion-HB augmentation of ring electron density.[33]

HypNMR 2008[34] was used to fit changes in shift to a stepwise association model:

$$\mathrm{H + G \rightleftharpoons HG,\ K_1 = \frac{[HG]}{[H][G]}} \qquad (1)$$

$$\mathrm{HG + G \rightleftharpoons HG_2,\ K_2 = \frac{[HG_2]}{[HG][G]}} \qquad (2)$$

Iterative and simultaneous refinement of multiple isotherms provided stability constants (K_a) for both **1a** and **2a** with ReO_4^-.[35] For receptor **1a**, the K_1 of 8990 M^{-1} represents the first quantification of XB to ReO_4^- in solution, highlighting XB's effectiveness at targeting this challenging oxoanion.[36] Alternatively, **2a** exhibits C–H HB and electrostatic interactions with ReO_4^-, which result in a K_1 of 7390 M^{-1}. Both **1a** and **2a** display modest K_2 values of 172 and 145 M^{-1}, respectively, that likely result from a combination of weak mono- and bidentate HB, and weak σ bonding.

The earliest quantification of XB and C–H HB to ReO_4^- in solution, and their corresponding bidentate/tridentate complexation in the solid state have been reported. The enhanced association of **1a** to ReO_4^- when compared directly to a nearly isostructural and potent C–H HB molecule validates XB's place alongside HB in an ongoing effort to design rational and selective receptors for $ReO_4^-$and TcO_4^-. Future work with **1a** and **2a** will include liquid-liquid extraction of ReO_4^- from aqueous phase, and exploration of XB and C–H HB with other anionic guests.

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Notes and references

[a] Department of Chemistry, University of Montana, 32 Campus Dr., Missoula, MT 59812.

‡ These authors contributed to this work equally.

† Electronic supplementary information (ESI) available: synthesis and characterization of all novel compounds, ^{1}H NMR titration methods and data, and X-ray crystallographic data and crystal packing.

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