Anion Recognition

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A Bidentate Halogen-Bonding Bromoimidazoliophane Receptor for Bromide Ion Recognition in Aqueous Media**

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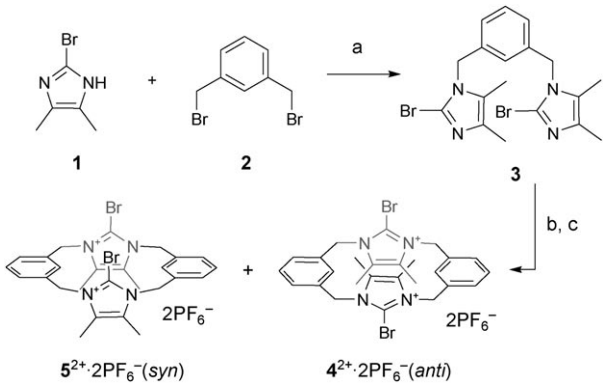
The term halogen bonding is used in analogy with well-known hydrogen bonding and is the noncovalent bonding interaction between halogen atoms that function as electrophilic centers (Lewis acids) and neutral or anionic Lewis bases.[1] The origin of the attraction is attributed to a positive region on the halogen atom that corresponds to the electronically depleted outer lobe of the R–X σ bond. The resulting positive electrostatic potential lies on the surface of the halogen atom, located at the terminus of the R–X axis (σ hole), while a band of negative charge remains around the equator of the halogen atom. The intermolecular force known as halogen bonding arises from the interaction of the positively charged σ hole with electron-donating species, thus resulting in a strongly linear geometry that maximizes the interface of opposite charges.[2] To date, almost all the investigations into halogen bonding have been conducted in the solid state, where the noncovalent interaction has been imaginatively exploited in the crystal engineering[3] of magnetic, conducting, and liquid-crystalline materials.[4] In contrast, halogen bonding in the solution phase is still in its infancy and only a few studies in solution have been reported recently,[5] which is surprising given its potentially powerful analogy to ubiquitous hydrogen bonding.[6]

The development of abiotic receptors for anions has received considerable attention in recent years,[7] stimulated by the important roles of these ions in a range of chemical, biological,[8] medical,[9] and environmental processes.[10] Complementary electrostatic, hydrogen-bonding, Lewis acid–base,[11] and more recently, anion–π interactions[12] have all been exploited in the construction of a wide variety of highly efficient complexing reagents for anions. By virtue of a positive charge and relatively acidic C–H groups, the imidazolium motif in particular has proven to be a potent anion-recognizing site to be incorporated into molecular receptor framework design.[13] Inspired by the polyimidazolium receptor systems reported to date[14] and with the aim of contributing to the meagre quantitative data reported on halogen bonding receptor–anion association in solution, we describe herein the synthesis of a novel bidentate halogen-bonding bromoimidazoliophane receptor which, by cooperative action of two preorganized halogen-bonding bromine donor atoms, is capable of selectively binding bromide ions strongly in competitive aqueous solvent media. Importantly, by comparison the protic imidazoliophane receptor analogue is a nonselective weak binder of halide ions.

2-Bromo-4,5-dimethyl-1*H*-imidazole (**1**) was synthesized in a stepwise procedure from 4-methyl-5-imidazolemethanol hydrochloride.[15] Alkylation of bromoimidazole **1** with *meta*-xylyl dibromide **2** in the presence of NaOH provided the bisimidazole compound **3**. The coupling of **3** with dibromide **2** afforded two imidazoliophane conformers *anti* $\mathbf{4}^{2+}\cdot 2\,Br^-$ and *syn* $\mathbf{5}^{2+}\cdot 2\,Br^-$ in good yield (82%), which were separated by repeated recrystallization in methanol. Presumably the steric demands of the bromine atom imidazolium substituents inhibit intramolecular ring rotation, which results in the isolation of the two conformers; the ratio between the *anti* and the *syn* isomer was 68:32 respectively. The bromide salts readily underwent anion exchange to the corresponding hexafluorophosphate salts on addition of aqueous NH_4PF_6 (Scheme 1).

The corresponding protic imidazoliophane receptor $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ (Scheme 2) was synthesized by following an analogous procedure using 4,5-dimethyl-1*H*-imidazole as the starting material. In contrast to the bromoimidazoliophanes, as expected[14] only one conformer species was detected and isolated.

Single crystals suitable for X-ray diffraction structural analysis were obtained for the *anti* isomer $\mathbf{4}^{2+}$, and the



Scheme 1. Synthesis of the receptors $\mathbf{4}^{2+}\cdot 2\,PF_6^-$ and $\mathbf{5}^{2+}\cdot 2\,PF_6^-$. Reagents and conditions: a) NaOH (1 M in water), acetonitrile, reflux, yield: 80%; b) 1,3-bis(bromomethyl)benzene, acetonitrile, 82 °C, yield: 82%; c) wash with saturated NH_4PF_6 (aq).

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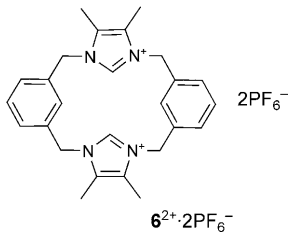

Scheme 2. Structure of the imidazoliophane $\mathbf{6}^{2+}\cdot 2\,PF_6^-$.

syn isomer $\mathbf{5}^{2+}$ as both the bromide and hexafluorophosphate salts. As expected, halogen-bonding interactions in the hexafluorophosphate salts are negligible—with no halogen bonding (defined as a Br···X distance less than the sum of Br + X van der Waals (vdW) radii) observed in the structure of the *anti* isomer and a very weak halogen-bonding interaction observed in the *syn* isomer (93 % of sum of vdW radii, Table 1).

Table 1: Details of halogen bonding in the solid state.

Compound	C–Br [Å]	Br···X [Å]	Br···X vdW Radii [%]	C-Br···X Angle [°]
$\mathbf{4}^{2+}\cdot 2\,PF_6^-$ (*anti*)	1.842(4)	–	–	–
$\mathbf{5}^{2+}\cdot 2\,PF_6^-$ (*syn*)	1.845(3)	3.078(2)	93	160.56(12)
$\mathbf{4}^{2+}\cdot 2\,Br^-$ (*anti*)	1.861(4)	3.191(1)	86	174.16(14)
$\mathbf{5}^{2+}\cdot 2\,Br^-$ (*syn*)	1.878(4)	3.217(1)	87	166.81(12)

Conversely, both the *anti* and *syn* bromide structures show significant halogen bonding (Table 1). In the case of the *anti* structure, each bromoimidazolium group interacts with one bromide ion (Figure 1), while in the case of the *syn* isomer, bidentate halogen bonding between two bromoimidazolium groups and one bromide ion is observed, with the second bromide ion involved only in hydrogen bonding to methanol solvent molecules (Figure 2).

The halogen bonding in the *syn* structure is less linear than may be expected (166.81(12)°) compared to the angle of 174° in the *anti* isomer and the mean angle of 174° for previously reported bromoimidazolium bromide halogen bonds.[6c] This finding is presumably due to steric demands on the bromoimidazolium rings that prevent them rotating fully inwards and also due to repulsion between the two electropositive bromine atoms of the bromoimidazolium groups.

The strength of the halogen bonds can be inferred from the increase in the imidazolium C–Br distance from 1.842(4) Å in the *anti* hexafluorophosphate salt (with no halogen bonding), to 1.845(3) Å in the *syn* hexafluorophosphate salt (with extremely weak halogen bonding) to 1.861(4) Å in the monodentate *anti* bromide salt to 1.878(4) Å in the *syn* halogen bond. The observed trend is consistent with weakening of the C–Br bond by electron donation from the bromide ion into the C–Br σ* orbital,[16] despite the fact that the *syn* halogen bond is less linear.

The *syn* structure has a calixlike shape, because the bromoimidazolium rings point towards a bromide ion, thus leading to an open cleft on the other side of the macrocycle (bromoimidazolium–bromoimidazolium mean plane angle =

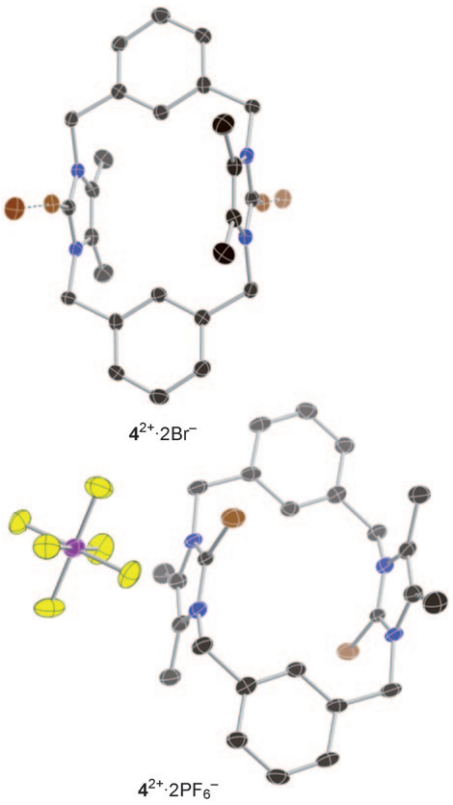

Figure 1. Views of the *anti* isomers of macrocycle **4** as the bromide (left) and hexafluorophospate (right) salts. Hydrogen atoms and solvent molecules are omitted for clarity; thermal ellipsoids are shown at 50% probability. Only one of the two symmetry-equivalent hexafluorophosphate ions is shown. Gray = carbon, blue = nitrogen, brown = bromine, purple = phosphorus, yellow = fluorine

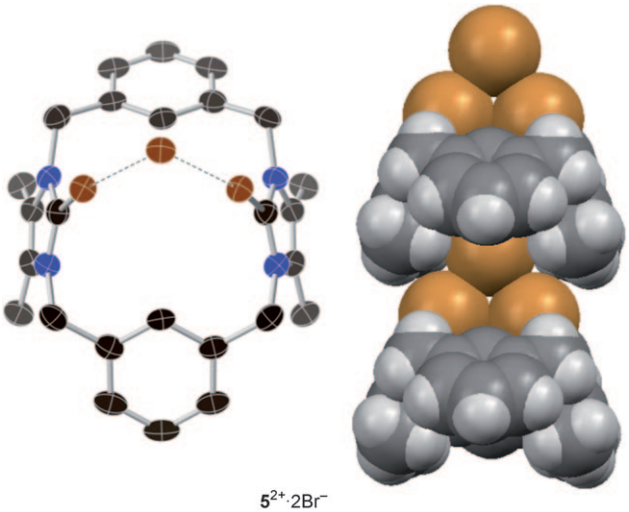

Figure 2. Perspective (left) and space-filling packing (right) views of the *syn* isomer of the bromide macrocycle. Hydrogen atoms, methanol solvates, and the noncoordinated bromide ion are omitted for clarity. Thermal ellipsoids are shown at 50% probability. Gray = carbon, blue = nitrogen, brown = bromine

40°). This space is occupied by a halogen-bonded bromide ion of an adjacent molecule, such that the calixes stack into one another (see Figure 2 right and the Supporting Information). The two *anti* structures do not have this arrangement, as the bromoimidazolium rings are parallel to one another. A similar calixlike structure is observed for the hexafluorophosphate salt of $\mathbf{5}^{2+}$ but with a far smaller angle between the bromoimidazolium mean planes (23°), presumably because the hexafluorophosphate salt does not contain a bidentate halogen-bonding interaction to "pull" the two bromoimidazolium rings towards one another. This stacking arrangement is not observed in the hexafluorophosphate structure.

The ^{1}H NMR spectra of the receptors $\mathbf{4}^{2+}\cdot 2\,PF_6^-$ and $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ are very similar although slight differences in some chemical shifts are present. Receptors $\mathbf{4}^{2+}\cdot 2\,PF_6^-$ (*anti*) and $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ (*syn*) show four sets of signals, the first of which at $\delta = 2.21$ ppm (*anti*) and $\delta = 2.18$ ppm (*syn*) attributed to a methyl group. The two methylene protons have different environments and appear as two doublets around $\delta =$ 5.54 ppm and 5.65 ppm. The greatest difference in the ^{1}H NMR spectra between the two isomers corresponds to the internal phenyl proton (H_a) $\delta = 6.02$ ppm (*anti*) and $\delta =$ 5.87 ppm (*syn*). The rest of the aromatic protons appear at the same chemical shift in the two isomers (multiplet at $\delta =$ 7.65 ppm). Unlike the bromoimidazoliophanes $\mathbf{4}^{2+}\cdot 2\,PF_6^-$ and $\mathbf{5}^{2+}\cdot 2\,PF_6^-$, the macrocycle $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ shows a sharp singlet for the methylene protons at $\delta = 5.49$ ppm, a single signal for the methyl group ($\delta = 2.05$ ppm) and the H2 of the imidazolium ring ($\delta = 9.06$ ppm), thus indicating the rapid interconversion of the different possible conformations on the NMR timescale.

The anion-binding properties of the receptors $\mathbf{4}^{2+}\cdot 2\,PF_6^-$, $\mathbf{5}^{2+}\cdot 2\,PF_6^-$, and $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ with fluoride, chloride, bromide, and iodide ions from their tetrabutylammonium salts were investigated by ^{1}H NMR titration experiments by the addition of aliquots of the different anions to solutions of the receptors in CD_3OD/D_2O 9:1.

Addition of even a large excess of halide ions to a solution of the *anti* bromoimidazoliophane $\mathbf{4}^{2+}\cdot 2\,PF_6^-$ caused no changes in the ^{1}H NMR spectrum of the receptor. In contrast significant perturbations in the ^{1}H NMR spectrum of the *syn* isomer $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ were observed upon the addition of chloride, bromide, and iodide ions. On closer inspection, the ^{1}H NMR titration data revealed a moderate downfield shift for the signals associated with the internal aromatic proton (H_a), which ranges from $\Delta\delta = 0.12$ ppm for iodide to $\Delta\delta =$ 0.02 ppm for chloride ions. A slight downfield shift was observed only in one methylene proton resonance (Figure 3). With the macrocycle $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ the addition of chloride, bromide, and iodide ions caused significant downfield shifts of the C–*H* proton of the imidazolium ring ($\delta = 0.13$ ppm) and the internal aromatic proton (H_a, $\delta = 0.11$ ppm). Interestingly, the addition of equimolar and excess amounts of fluoride ions to a solution of the *syn* $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ and $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ receptors caused no significant changes.

The chemical shift of proton H_a was monitored during anion addition to $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ (*syn*) and $\mathbf{6}^{2+}\cdot 2\,PF_6^-$. Job plot analysis of the titration data revealed a 1:1 receptor to anion binding stoichiometry for chloride, bromide, and iodide ions

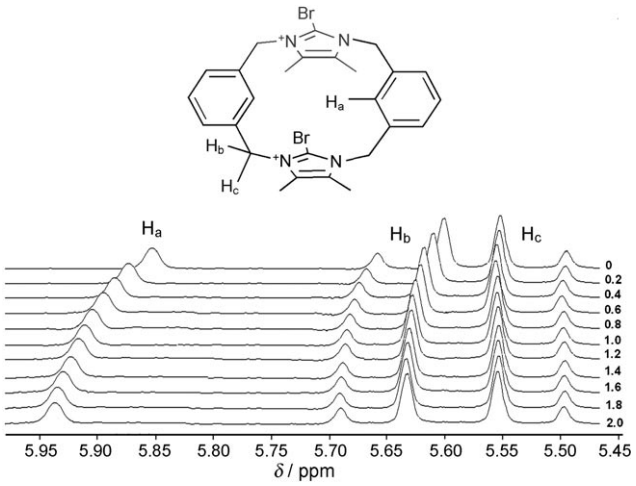

Figure 3. ^{1}H NMR spectral changes observed in $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ *syn* in CD_3OD/D_2O 9:1 during the addition of up to 2 equivalents of iodide ions.

(see the Supporting Information). The association constants were obtained by fitting the respective titration data (Figure 4) to a 1:1 host–guest binding model using the WinEQNMR program[17] (Table 2). The *syn* bromoimidazoliophane $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ exhibits an impressively high binding affinity for bromide ions ($K_a = 889\,M^{-1}$) relative to the rest of the halide ions, the trend of halide-binding strength being bromide > iodide ≫ chloride > fluoride ions. In stark contrast the association constant values determined for the hydrogen-bonding receptor $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ are all significantly smaller in magnitude when compared to the strength of the bromide-binding affinity exhibited by halogen-bonding macrocycle $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ (*syn*).

It is noteworthy that the hydrogen-bonding receptor $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ shows little discrimination between chloride, bromide, and iodide ions. Thus the incorporation of bromine atoms into the bis(imidazolium) macrocyclic receptor frame-

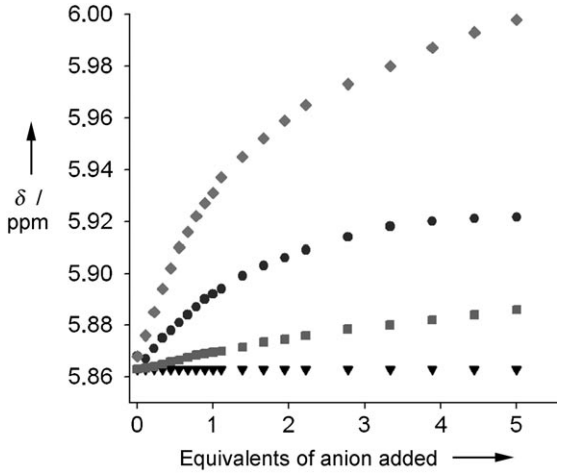

Figure 4. ^{1}H NMR titration curves for *syn* $\mathbf{5}^{2+}\cdot PF_6^-$ with tetrabutylammonium fluoride (▼), chloride (■), bromide (●), and iodide (◆) in CD_3OD/D_2O 9:1 at 295 K.

Table 2: Association constants K_a for $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ (*syn*) and $\mathbf{6}^{2+}\cdot 2\,PF_6^-$ with different halide ions.[a]

Receptor	Anion[b]	K_a [M^{-1}][c]
$\mathbf{5}^{2+}\cdot PF_6^-$	F^-	–[c]
	Cl^-	<10
	Br^-	889 (37)
	I^-	184 (15)
$\mathbf{6}^{2+}\cdot PF_6^-$	F^-	–[c]
	Cl^-	133 (12)
	Br^-	130 (10)
	I^-	102 (7)

[a] In 9:1 CD_3OD/D_2O at 295 K. [b] Anions have been used as a tetrabutylammonium salt. [c] Obtained from monitoring the internal phenyl proton. [c] No detectable evidence of binding observed; error in parentheses.

work dramatically influences the anion-recognition capabilities of the cyclic host, hence enabling pure halogen bonding–bromide ion recognition to take place in aqueous media.

In conclusion we have demonstrated that a bidentate bromoimidazoliophane receptor is capable of selectively binding bromide ions in competitive aqueous media by cooperative convergent interactions between the bromine atoms on the receptor and the bromide ion. Importantly the bromine atom substituents present in the macrocyclic *syn* isomer $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ not only serve as halogen-bond donors but also sterically create a preorganized host system. Hence, as clearly demonstrated with respective halogen- and hydrogen-bonding imidazolium receptors $\mathbf{5}^{2+}\cdot 2\,PF_6^-$ and $\mathbf{6}^{2+}\cdot 2\,PF_6^-$, the integration of halogen atoms into anion-receptor frameworks at the expense of hydrogen bonding greatly influences the anion-recognition behavior of the receptor from both electronic and geometric considerations.

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