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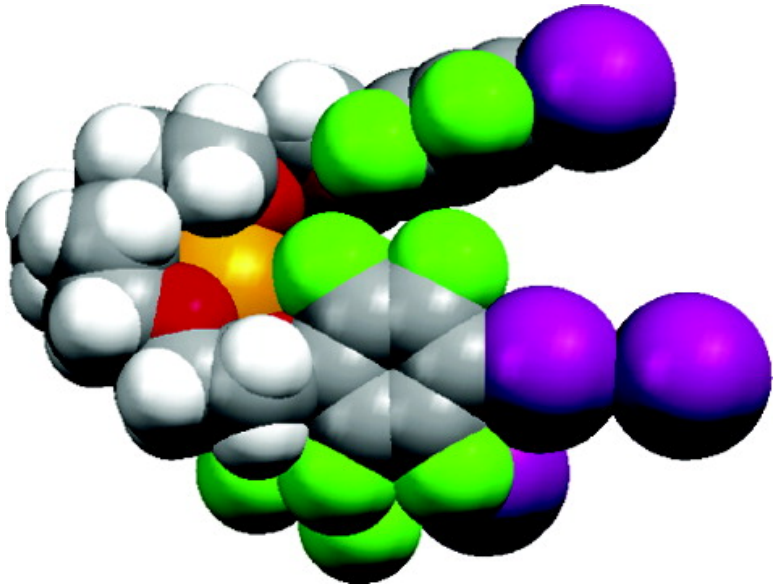

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A Halogen-Bonding-Based Heteroditopic Receptor for Alkali Metal Halides

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The design and synthesis of neutral ditopic receptors capable of simultaneous binding of both the counterions in a target salt is a subject of great current interest.[1] Most of the efforts on the design of suitable anion-binding sites focused on the use of electrostatic interactions,[2] hydrophobicity,[3] Lewis acidic centers and metals,[4] and more recently anion−π bonding.[5] Nevertheless, hydrogen bonding is, by far, the noncovalent interaction most frequently used for directing anion binding.[6]

Halogen bonding (XB) is the noncovalent interaction between halogen atoms, which work as electron density acceptors (XB donors) and neutral or anionic electron density donors (XB acceptors).[7] As the profile of this interaction strictly parallels that of hydrogen bonding, we reasoned that XB was nicely tailored for the specific binding of anions within heteroditopic receptors. We thus designed, synthesized, and studied a heteroditopic receptor comprised of a well-established motif for cation binding and a motif for XB-based anion recognition. Thanks to the electron-withdrawing ability of fluorine atoms, iodo-perfluoroaromatics are very effective XB donors. Tris(4-iodotetrafluorophenyl) derivative **1a** was thus identified as a particularly promising candidate (Figure 1, left). Strength and selectivity toward alkali metal halides' coordination by the tripodal receptor **1a** was studied in the solid, liquid, and gas phases. The single-crystal X-ray structure of the [NaI(**1a**)] complex **2** proved the ability of **1a** to dissociate the ion pair through simultaneous binding of I^- and Na^+ by two different recognition arrays of atoms. Solution NMR experiments on **1a** and **1b** clearly evidenced the boosting effect of XB-mediated anion binding on the cation complexation. Finally, the selectivity for different halides in solution has been established by competitive tandem ESI-MS/MS experiments, revealing a higher affinity of **1a** for I^- over Br^- and Cl^-anions.

Following a modular construction principle, **1a** was derived from tris[2-(2-hydroxyethoxy)ethyl]amine **3** and iodopentafluorobenzene under basic conditions (Cs_2CO_3, 56% yield; for details see Supporting Information). The S_NAr of the alcoholate is highly regioselective on the para fluorine atom, which is substituted preferentially.[8] Similarly, **1b** was obtained from **3** and hexafluorobenzene (60% yield).

Naked anions are particularly effective XB acceptors,[9] and in solution the tendency to form strong interactions is $I^- > Br^- > Cl^- > F^-$, consistent with charge-transfer contributions to XB.[10] We thus challenged **1a** with NaI (2-fold excess, $CHCl_3$, heating). On filtering of the excess salt, a pale yellow solution was obtained which, on cooling, afforded the complex **2** as a crystalline solid (mp 177−178 °C). Solutions of **1a** with KI also gave crystalline complexes,[11] but up to now we failed with anions other than I^-, as when **1a** was reacted with NaBr and NaCl, liquid residues were obtained. These differences among the three sodium halides are consistent with the relative effectiveness of different halide anions to form strong XBs with iodo-perfluorocarbons. Several examples are reported wherein iodide anions are more effective than bromide and chloride anions in forming high-melting-point adducts through XB-driven self-assembly with iodocarbons.[9]

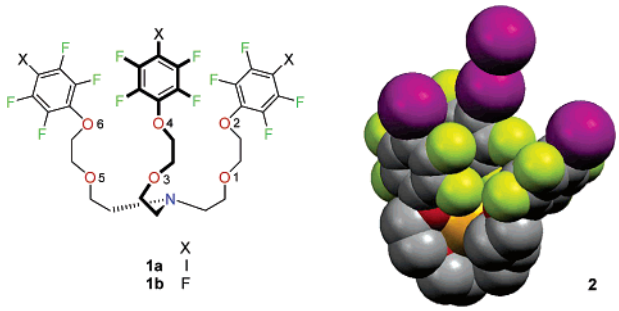

Figure 1. Tripodal receptor **1a** (left). Single-crystal X-ray structure of the asymmetric unit cell of **2** (right); H atoms are omitted for clarity. Color code: gray = C, red = O, green = F, blue = N, violet = I, orange = Na.

The single-crystal X-ray analysis of **2** gave details about its supramolecular organization. Na^+ is completely surrounded by the three arms of the receptor (Figure 1, right) and separated by 5.585 Å from the I^-. Na^+ is a small cation and accepts only six ligands, namely N, O1, O2, O3, O4, and O5. The polyhedron formed by these atoms is much distorted, with Na−Het (Het = N, O) distances varying in the range of 2.322−2.661 Å and Het−Na−Het angles in the range of 65.56−136.76° (in a regular octahedron they are 90 and 180°). The limited space around the cation does not allow the coordination of O6, so the relative receptor arm is much more elongated out of the Na^+ coordination sphere than the other two arms.

Strong $I^-\cdots I$ XBs drive the anion exo-binding. I^- anions bridge two iodotetrafluorophenyls of two different podand molecules, and rolled-up infinite chains are formed wherein the $I1\cdots I4^-\cdots I3^i$ distances [$i = 1 - x, 1/2 + y, 3/2 - z$] are 3.448(1) and 3.531(1) Å. These distances correspond to a 17% and 14% shortening of the sum of their van der Waals radii (4.14 Å). The $I1\cdots I4^-\cdots I2^i$ and $I1\cdots I4^-\cdots I3^i$ angles are 151.51 and 138.14°, respectively. A third weaker XB involves the third iodotetrafluorophenyl residue of the podand [$I4^-\cdots I2^{ii}$, $ii = 1 - x, -1/2 + y, 3/2 - z$; 3.908(1) Å, 6% shortening of van der Waals radii] and folds up the infinite chain formed by the noncovalent interactions ($I2\cdots I4^-\cdots I3^i$ angle is 65.30°). Both the podand **1a** and the iodide anion thus work as tridentate modules.

The driving force for the self-assembly of complex **2** is provided by a cooperativity of exo and endo recognition processes. Exo recognition operates by the acidic aromatic iodines forming XBs with I^-, and endo recognition occurs thanks to the lone pairs of the polyoxyethylene-amine moiety binding Na^+.

Although **2** is comprised of intrinsically achiral components, it crystallized in the chiral space group $P2_12_12_1$. The chiral and enantiopure arrangement of the modules in the crystal packing becomes quite apparent when looking at the homochiral helixes, which develop thanks to the noncovalent connectivity of the strong $I^-\cdots I$ XBs (Figure 2). This is the second case reported so far of spontaneous resolution occurring under XB control.[12]

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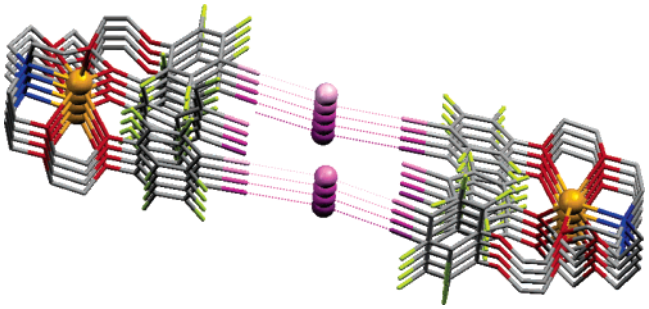

Figure 2. Crystal packing (Mercury 1.3.1. view) of the [NaI(**1a**)] complex **2** showing the homochiral helix formed by the rolled-up infinite chain where iodide anions and podate modules alternate. XBs are dashed lines. Color code as in Figure 1; the violet of iodine atoms and I···I$^-$ interactions becomes darker approaching the bottom of the perspective view.

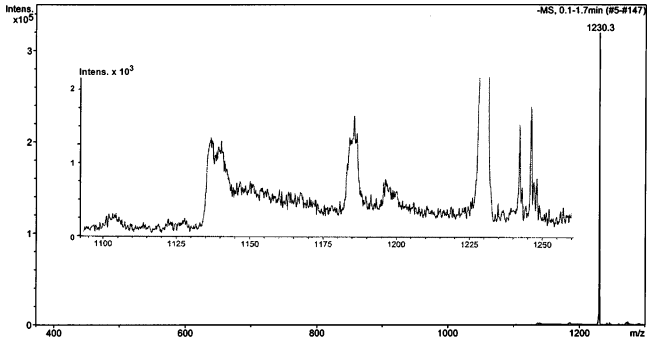

Figure 3. ESI-MS spectrum of a competitive binding experiment wherein **1a** was dissolved in a solution containing equimolar amounts of I$^-$, Br$^-$, and Cl$^-$.

Additional (qualitative) evidence for the heteroditopic binding was gained by using ESI-MS. When **1a** was treated with alkali metal chlorides in a 1:1:1:1 ratio (**1a**:Na^+:K^+:Cs^+), the peaks corresponding to [**1a** + H]$^+$, [**1a** + Na]$^+$, [**1a** + K]$^+$, and [**1** + Cs]$^+$ were observed in the positive ion polarity mode, and that corresponding to [**1a** + Cl]$^-$ was observed in the negative ion polarity mode. Solutions of **1a** containing either I$^-$, Br$^-$, or Cl$^-$ were analyzed in the negative ion polarity ESI-MS mode. The corresponding spectra showed as the only signals the peaks at *m*/*z* 1230, 1182−1184, and 1138−1140, respectively, in turn assigned to [**1a** + I]$^-$, [**1a** + Br]$^-$, and [**1a** + Cl]$^-$. Isotopic cluster were resolved in all cases. Interestingly, the ESI-MS spectrum of a mixture containing **1a** and equimolar amounts of I$^-$, Br$^-$, and Cl$^-$ (competitive experiment) afforded a strong signal at *m*/*z* 1230, consistent with [**1a** + I]$^-$, with broad peaks of relative abundance <1% centered at *m*/*z* 1182−1184 (consistent with [**1a** + Br]$^-$ with nonresolved isotopic cluster), and *m*/*z* 1138 (consistent with [**1a** + Cl]$^-$ with nonresolved isotopic cluster) (Figure 3). These findings show the preferential binding of **1a** to iodide anion and are consistent with the scale of XBs established in solution, where the strength of different XBs was decreasing in the order I$^-$ > Br$^-$ > Cl$^-$ > F$^-$.[10] This trend is opposite to that shown by most anion receptors that function through hydrogen bonding.[6] Further evidence of stronger binding of **1a** with I$^-$ came from MS/MS experiments. Isolation and collision-induced decomposition (CID) of [**1a** + Cl]$^-$ and [**1a** + Br]$^-$ adducts gave *m*/*z* 291 as the only fragmentation product, consistent with the decomposition of the podand and the formation of the iodotetrafluorophenolate moiety. Conversely, CID of the parent ion [**1a** + I]$^-$ at *m*/*z* 1230 gave I$^-$ at *m*/*z* 127 as the only fragment.

The complexation ability of **1a** in solution was finally studied by NMR (Supporting Information). In all the NMR experiments, a single signal was observed corresponding to the average of the complexed and free receptors. Clearly, the binding process is fast on the NMR time scale. The binding constants of **1a** (K_{1a}) and **1b** (K_{1b}) with NaI were determined by calibrated competitive ^{1}H NMR studies in $CDCl_3$.[13] As "calibrant" we chose the well-characterized complex between Na^+ and [18]crown-6 (log K = 6.11).[14] K_{1a} is approximately 20 times larger than K_{1b} (2.6×10^5 and 1.3×10^4 mol^{-1}, respectively), thus proving the boosting effect of I···I$^-$ XB on the Na^+ complexation ability of **1a**.

In summary, the new heteroditopic ligand **1a** has been demonstrated to simultaneously bind both the counterions of alkali metal halides thanks to the presence of both anion and cation binding sites. **1a** binds NaI more efficiently than the monotopic ligand **1b**, and it also effectively discriminates different halides in XB-driven exo recognition processes wherein I$^-$ is coordinated preferentially over Br$^-$ and Cl$^-$. XB has already widely proven its strength and directionality but, to the best of our knowledge, no precedents have been reported prior to now where it was exploited as a specific interaction for selective anion recognition processes within heteroditopic receptors. The described protocol might be a new design principle for anion-sensing receptors. Considering the easy introduction of the iodotetrafluorophenyl residue on any scaffold, and the effectiveness of this moiety as anion recognition site, the design principle described here may produce even more powerful heteroditopic receptors, provided size- and shape-optimized frameworks are chosen.

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Supporting Information Available: Synthetic procedures, spectroscopic and X-ray structural data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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