Anion Recognition

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A Tridentate Halogen-Bonding Receptor for Tight Binding of Halide Anions[**]

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In memory of Keith Fagnou

The selective recognition of anions by synthetic receptors is a problem that continues to fascinate chemists.[1] Hydrogen bonding has been the most frequently employed noncovalent interaction for the design of such receptors: molecular scaffolds that place H-bond donor groups in geometries suitable for an anion of interest demonstrate remarkable levels of selectivity and affinity.[2] Nonetheless, anion receptors that rely upon other noncovalent forces, including Lewis acid–base[3] and anion–π[4] interactions, have been investigated, with considerable success. Such studies have provided insight into the interactions employed, and have offered new opportunities to achieve selectivity in anion recognition. Here, we describe simple receptors capable of tight binding of halide anions through multidentate halogen bonding interactions (Figure 1). These represent the first systems in which the cooperative action of multiple halogen-bond donors is employed to achieve high-affinity binding in dilute solution. The selectivities of these receptors differ substantially from those of related receptors based on hydrogen bonding.

Although halogen bonds between electron-deficient organohalides and electron donors were observed decades ago, it is only recently that the generality and utility of this noncovalent interaction have gained widespread appreciation.[5] Halogen bonding has now been established as a powerful strategy for self-assembly in condensed phases, and its implications in biological systems are emerging.[6] Anions, particularly halides, participate readily as halogen-bond acceptors in the solid state,[7] including examples of crystalline networks in which a single anion accepts multiple halogen bonds.[8] This last observation suggests that a multidentate halogen-bond donor capable of donating several halogen bonds in a convergent fashion might be capable of anion binding in dilute solution.[9]

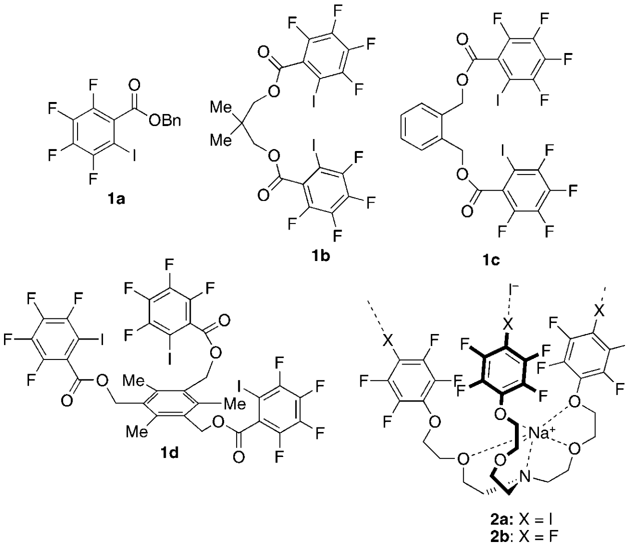

Figure 1. Structures of the multivalent halogen-bond donors **1a**–**1d**, and the ion-pair receptor **2a** of Resnati and co-workers (Ref. [11a]).

Designing such a receptor presented a challenge. Applications of halogen bonding in self-assembly have relied extensively on *para*-substituted iodotetrafluorobenzene derivatives prepared by nucleophilic aromatic substitution (for example, **2a**).[10] This strategy results in *divergent* arrays of halogen-bond donors useful for constructing noncovalent polymers as well as two- and three-dimensional networks. In contrast, it is poorly suited for orienting multiple donors in a *convergent* fashion for binding to a single acceptor as is generally required of a high-affinity host.[1,2] The most successful example of anion binding by a halogen-bond donor achieved to date makes use of ion-pair recognition: receptor **2a** shows a 20-fold higher affinity for sodium iodide than does control receptor **2b**, indicating a modest but measurable increase in affinity resulting from halogen bonding of iodide to the iodoarene groups (Figure 1).[11]

We chose to explore *ortho*-substituted iodoperfluoroarenes as the basis for receptors capable of multidentate halogen bonding. Esters of 2,3,4,5-tetrafluoro-6-iodobenzoic acid (which is easily prepared on multigram scale in one step)[12] emerged as attractive targets (**1a**–**1d**, Figure 1): we anticipated that the electron-withdrawing carboxy group would promote halogen-bond donor ability, while enabling a straightforward receptor synthesis through coupling reactions of readily available diols and triols.[13] Receptors **1b** and **1c** were prepared to test the feasibility of bidentate halogen

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bonding of anions. Based on the well-studied conformational behavior of hexasubstituted benzene derivatives and the application of these species in receptor design,[14] we anticipated that **1d** would act as a preorganized tridentate receptor.[15] Calculations (HF, 6-31 + G*-LANL2DZdp[16]) suggested that multipoint binding of halides by such hosts would be geometrically feasible (Figure 2, left).[17] The calculated gas-phase geometry of the **1d**–Cl^- complex is characterized by I···Cl halogen-bond distances of 3.20 Å and C-I···Cl^- angles of 178°, results that are consistent with data from the crystallographic literature.[18] The computed electrostatic potential surface of **1d** in its chloride-bound conformation (B3LYP/6-31G*-LANLdp: Figure 2, right) illustrates the extended region of partial positive charge created by the three electron-deficient iodo groups. The relationship between such sites of partial positive charge (termed the "σ hole") and the halogen-bond interaction has been elucidated by Politzer and co-workers.[19]

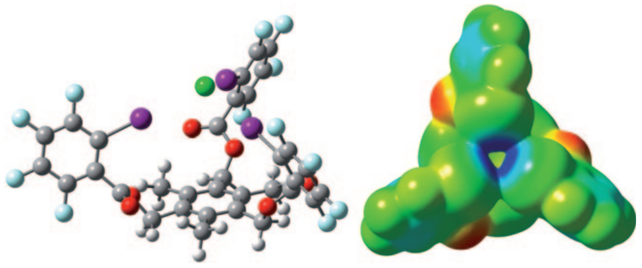

Figure 2. Left: Calculated structure of the **1d**–Cl^- complex (HF/6-31 + G**-LANL2DZdp:[17] H white; C gray; O red; F blue; I purple; Cl green). Right: Electrostatic potential surface of **1d** (chloride-bound conformation, B3LYP/6-31G*-LANL2DZdp: blue indicates sites of partial positive charge and red sites of partial negative charge).

The addition of monovalent anions as their tetrabutylammonium salts to **1a–d** (acetone, 295 K) resulted in downfield shifts of the ^{19}F NMR spectra that are diagnostic of halogen bonding (Figure 3, top).[20,21] Binding constants calculated by curve-fitting 1:1 binding isotherms to these data are assembled in Table 1. The Job plots of the **1c**–Cl^- (see the Supporting Information) and **1d**–Cl^- interactions (Figure 3, bottom) display maxima at a mole fraction χ of 0.5, consistent with a 1:1 binding stoichiometry.[22] Electrospray ionization mass spectrometry (ESI-MS) provided additional support for the formation of a **1d**–Cl^- complex of 1:1 stoichiometry (m/z 1151 amu; see the Supporting Information). Adducts **1d**-Br^- (m/z 1195) and **1d**–I^- (m/z 1243) were also observed by ESI-MS.

The significant effect of "chelate cooperativity"[23] in halogen bonding is evident from the binding data shown in Table 1: the chloride affinities of the bidentate receptors **1b** and **1c** are more than an order of magnitude higher than that of benzyl ester **1a**, which serves as the control experiment in this study. Likewise, the additional halogen-bonding interaction possible in tridentate receptor **1d** results in a further increase in association constant of an order of magnitude in comparison to the bidentate systems ($K_a = 1.9 \times 10^4\,M^{-1}$). To probe the possibility that receptors **1a**–**1d** interact with halides through anion–π interactions rather than halogen bonding, a modified version of receptor **1c** was prepared in which the two iodo groups were replaced by fluorine substituents (see the Supporting Information). This modified receptor showed no detectable affinity for chloride in acetone ($K_a < 10\,M^{-1}$), suggesting that halogen bonding is the dominant contributor to the observed binding.[24] This observation is consistent with previous observations of anion recognition by electron-deficient, uncharged π systems, which have shown that such interactions are generally weaker than those studied here.[25]

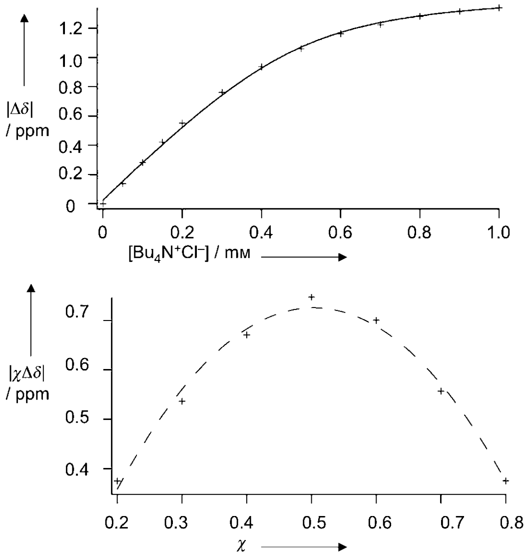

Figure 3. Top: ^{19}F NMR titration of **1d** (acetone, 295 K; change in chemical shift $|\Delta\delta|$ (in ppm) vs [$nBu_4N^+Cl^-$] (in mM)). Curve represents the fit of a 1:1 binding isotherm. Bottom: Job plot ([**1d** + $nBu_4N^+Cl^-$] = 11 mM, $|\chi\Delta\delta|$ vs mole fraction χ).

Table 1: Binding constants of **1a–d** with $nBu_4N^+X^-$ (acetone, 295 K).

Entry	Halogen-bond donor	X^-	K_a [M^{-1}][a]
1	**1a**	Cl^-	70
2	**1b**	Cl^-	1.1×10^3
3	**1c**	Cl^-	1.8×10^3
4	**1d**	Cl^-	1.9×10^4
5	**1d**	Br^-	3.8×10^3
6	**1d**	I^-	7.6×10^2
7	**1d**	TsO^-	10
8	**1d**	HSO_4^-	<10
9	**1d**	NO_3^-	<10

[a] Binding constants K_a were determined by curve-fitting 1:1 binding isotherms to ^{19}F NMR titration data. Each reported binding constant reflects an average of two or three independent determinations, with an estimated error of ±10%. See the Supporting Information.

While the **1d**–Cl^- association constant is modest in comparison to those of the best synthetic chloride receptors,[26,27] it represents, by several orders of magnitude, the highest-affinity receptor developed to date that operates in dilute solution using halogen bonding alone. The affinity of **1c** and **1d** for chloride compare favorably to binding constants of neutral, hydrogen-bond donors that employ two or three contacts to halide anions, respectively.[28]

The anion selectivity displayed by **1d** differs significantly from those of hydrogen-bonding-based receptors: while **1d** interacts with bromide and iodide more weakly than with chloride, it shows negligible affinity for *p*-toluenesulfonate, nitrate, and bisulfate (Table 1).[29] In contrast, hydrogen-bonding receptors with similar geometries show measurable affinity for such oxoanions.[30] We speculate that receptor **1d** is sufficiently flexible to accommodate a variety of guests, and that the differences in **1d**–anion association constants do not result from discrimination based on anion size. Instead, we propose that the selectivity of **1d** reflects the intrinsic preference of the halogen-bonding interaction for this series of anions. Quantitative thermodynamic data for halogen bonding of anions in solution are not available,[31] and even qualitative comparisons are lacking. Crystallographic data and the behavior of receptor **2a** have been used to support the trend in acceptor ability $\mathrm{I^-} > \mathrm{Br^-} > \mathrm{Cl^-}$,[5b,11a] while other data from the solid state suggest the reverse ($\mathrm{Cl^-} > \mathrm{Br^-} > \mathrm{I^-}$).[32] Calculations support the latter proposal.[33]

We measured the binding constants of iodopentafluorobenzene to the anions shown in Table 1 (see the Supporting Information), and found that the affinities decrease in the order $\mathrm{Cl^-} > \mathrm{Br^-} > \mathrm{I^-} \gg \mathrm{TsO^-}$, $\mathrm{NO_3^-}$, $\mathrm{HSO_4^-}$, in accordance with the data of Brammer and co-workers.[32] The preference of the halogen-bond donor for the anion having the highest charge density is consistent with the formulation of halogen bonding as an interaction involving a dominant electrostatic component.[19,34] However, the weak binding to oxoanions known to act as hydrogen-bond acceptors points towards a fundamental difference between halogen bonding and hydrogen bonding. A non-negligible contribution of dispersion and/or charge transfer to the halogen-bond interaction is a plausible explanation. Additional experiments and calculations are underway to clarify this point.

Clearly, improvements are needed if receptors of this type are to be employed in "real-world" applications where high selectivity and the ability to function in competitive media are required. Nonetheless, the ability to develop anion sensors based on a class of interaction that differs from hydrogen bonding in its geometric and energetic features represents an important fundamental step. Our ongoing efforts are aimed at developing halogen-bonding-based receptors with lower conformational mobility and altered anion selectivity, and at exploring the potential for cooperativity or complementarity between halogen- and hydrogen-bonding-based molecular recognition in solution.

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