Measurements of weak halogen bond donor abilities with tridentate anion receptors†

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The chelate effect of a tridentate receptor is exploited to determine halogen bonding association constants that vary by several orders of magnitude, including interactions of weak donors for which thermodynamic data were not previously available. Free energy relationships with computed and experimental properties hold over this wide range of donors. The strengths of iodine- and bromine-based halogen bonds, CH–anion and anion–arene interactions are compared.

Halogen bonding (XB), the class of noncovalent interactions in which covalently bound halogen atoms function as electrophilic species, has attracted widespread recent interest from fundamental and applied perspectives.[1] The majority of applications of XB—including crystal engineering,[2] chemical separations,[3] magnetic and conductive materials,[4] and liquid crystal assembly[5]—have been carried out in condensed phases. While studies of XB in solution are at a less advanced stage, a handful of applications in anion recognition,[6] catalysis,[7] and pseudorotaxane formation[8] suggest that XB will be a valuable addition to the arsenal of noncovalent interactions available for molecular recognition.

A significant challenge to implementation of XB in solution is the paucity of thermodynamic data available in comparison to other noncovalent interactions such as hydrogen bonding,[9] ion-pairing,[10] and interactions of π systems.[11] Data of this type are essential for advancing understanding of the fundamental properties of supramolecular interactions.[12] Studies of the strengths of halogen bonds have been restricted to perfluoroalkyl, perfluoroaryl, or alkynyl iodides, which possess among the highest donor abilities of neutral compounds studied to date.[13] The weak nature of XB interactions involving less electron-deficient halocarbon donors renders determinations of such association constants a challenge. Indirect approaches are promising in this regard, but only two such studies have been published: cleft receptors were employed to estimate the strength of Cl···N and Br···N halogen bonds,[14] and (repulsive) arene–halogen interactions were studied using chemical double-mutant cycles.[15] Quantitative data regarding the donor ability of a wide range of halocarbons are not currently available, and would be of value, particularly from the standpoint of developing a quantitative understanding of the importance of XB in biological and medicinal chemistry. Despite speculation regarding the contribution of XB to the functions of halogen-containing pharmaceuticals and biomolecules,[16] the thermodynamics of the relatively weak halogen bonds proposed to be involved in such systems have not been studied by experiment. Computational studies of XB would also benefit from experimental data for a diversity of interaction strengths.

Here, we employ tridentate anion receptors to determine, in acetone solution with the tetrabutylammonium counterion, XB association constants that vary by almost four orders of magnitude. The chelate cooperativity exhibited by these receptors enables quantitative studies of the XB donor ability of modestly electron-deficient iodoarenes, a class of compounds for which thermodynamic data were not previously available. The data are used to construct relationships of XB strength with computationally and empirically derived quantities. The tridentate receptor scaffold also enables direct comparisons of the strengths of iodine-based halogen bonds with other weak interactions, including a bromine-based halogen bond, CH–anion hydrogen bond, and anion–π interaction.

The starting point for our study was triester **4a**, a halogen-bonding receptor that displays high affinity for anions in organic solution. The **4a**–Cl^- association constant (acetone, 298 K) is 1.9×10^4 M^{-1}, with all four signals in the ^{19}F-NMR spectrum of **4a** displaying characteristic upfield changes in chemical shift upon halogen bond formation. This observation suggested that the synthesis of partially fluorinated derivatives of **4a** would represent a unique opportunity to determine, by ^{19}F-NMR titrations, the strengths of halogen bonds involving electronically diverse donors. Likewise, variation of the donor atom (iodine in **4a**) would enable measurements of association constants involving bromine-based halogen bonding, CH–anion hydrogen bonding, and anion–arene interactions. Mono-, di- and trifluorinated variants (**1–3**), as well as receptors in which the iodine donor atom of **4a** was replaced with a bromine, fluorine, and hydrogen substituent (**4b–d**) were prepared from tri(bromomethyl)mesitylene (Fig. 1; see the ESI†). Methyl esters of the benzoic acids used to construct receptors **1–4** vary markedly in electron density at iodine: representative molecular electrostatic potential surfaces (B3LYP/6-31 + G**-LANL2DZdp)[17] are depicted (Fig. 1). The 'σ-hole' model of XB characterizes the interaction as an electrostatic attraction between a Lewis base and the region of electron deficiency at the halogen atom:[18] accordingly, these compounds should vary appreciably in donor ability. In particular, the mono- and difluorinated iodobenzoates, and the bromine-substituted derivative, are significantly less electron-deficient than the donors employed in previous quantitative studies of XB.[13]

Association constants of **1–4** with tetra-*n*-butylammonium chloride ($Bu_4N^+Cl^-$) were determined by ^{19}F-NMR titrations

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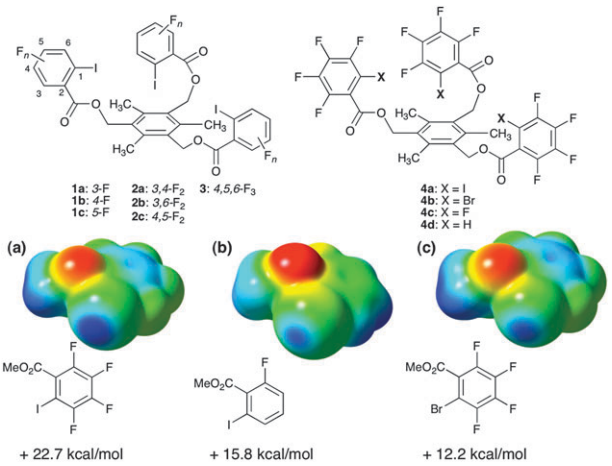

Fig. 1 Structures of tridentate halogen bonding receptors and electrostatic potential surfaces (B3LYP/6-31 + G**-LANL2DZdp) of representative XB donor groups studied here. Blue indicates regions of partial positive charge and red regions of partial negative charge. Maximum values of the electrostatic potential at iodine are indicated below each structure.

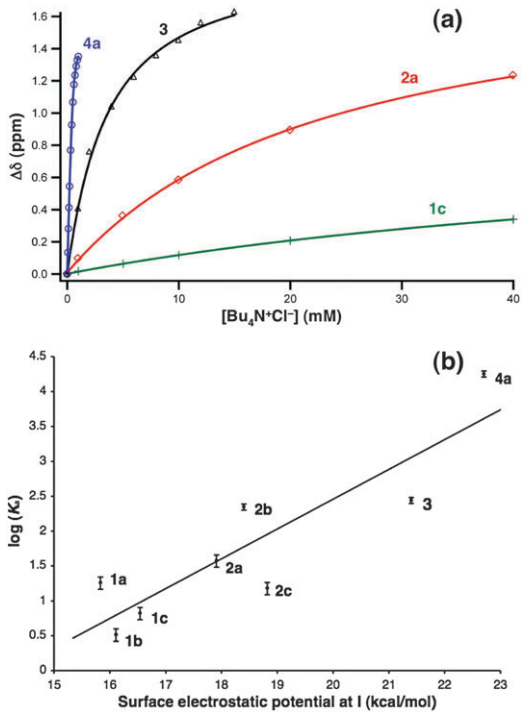

Fig. 2 (a) ^{19}F NMR titration data for the interactions of $Bu_4N^+Cl^-$ with **1c**, **2a**, **3** and **4a** ([receptor] = 0.5–1.0 mM in acetone). Curves of best fit to a 1 : 1 binding model are shown. (b) Correlation between $\log(K_a)$ and calculated electrostatic potential at I for **1a–1c**, **2a–2c**, **3** and **4a**.

(acetone, 298 K) and curve fitting to 1 : 1 binding models (Fig. 2a and Table 1). Analysis by the method of continuous variation (Job plot) was consistent with 1 : 1 stoichiometry for each complex. The effect of the number and position of fluorine substituents on the receptor's affinity for chloride is striking (entries 1–5, 10–12): the **1b**–Cl^- association constant is almost four orders of magnitude lower than that of **4a**–Cl^-.

Table 1 Association constants (K_a) of receptors **1–4** with $Bu_4N^+X^-$

Entry	Receptor	X^-	$K_a{}^a/M^{-1}$	$V_S{}^b{}_{,max}$/kcal mol^{-1}
1	**1a**	Cl^-	18 ± 4	15.8
2	**1b**	Cl^-	3 ± 1	16.1
3	**1c**	Cl^-	7 ± 1	16.5
4	**2a**	Cl^-	38 ± 8	17.9
5	**2b**	Cl^-	(2.2 ± 0.2) × 10^2	18.4
6	**2b**	Br^-	91 ± 18	
7	**2b**	I^-	44 ± 9	
8	**2b**	$PhCO_2^-$	22 ± 4	
9	**2b**	$H_2PO_4^-$	2 ± 0.5[c]	
10	**2c**	Cl^-	15 ± 3	18.8
11	**3**	Cl^-	(2.8 ± 0.3) × 10^2	21.4
12	**4a**	Cl^-	(1.9 ± 0.2) × 10^4 [d]	22.7
13	**4b**	Cl^-	<10 (decomp.)	12.2
14	**4c**	Cl^-	<5	—
15	**4d**	Cl^-	<5	16.7

[a] Association constant (acetone, 298 K) by ^{19}F-NMR titration. [b] Calculated (B3LYP/6-31 + G**-LANL2DZdp) molecular electrostatic potential at the donor atom. [c] In acetonitrile. [d] Data from ref. 6*a*.

This wide range of free energies of interaction represents an opportunity to evaluate relationships between XB thermodynamics and computed quantities. Relationships of this type represent useful tools for probing the mechanisms of binding events and for guiding structural optimization.

Calculated molecular electrostatic potentials are employed extensively in linear free energy relationships involving noncovalent interactions. In a study of *para*-substituted iodoperfluorobenzene derivatives, we observed a relationship between free energies of XB and the maximum electrostatic potential calculated at iodine ($V_{S,max}$).[13] It was unclear whether this relationship would extend to the wide range of XB association constants explored here. Values of $V_{S,max}$ for the methyl ester analogs of **1–4** (B3LYP/6-31 + G**-LANL2DZdp: see above) are assembled in Table 1. A linear relationship between $\log(K_a)$ and $V_{S,max}$ is evident (Fig. 2b);[19] the relationship may be stronger than the correlation coefficient (r^2 = 0.79) might indicate, since receptors not having a 3-fluoro substituent (**1b**, **1c**, **2c**, and **3**) are grouped below the trendline in Fig. 2. Calculations suggest that the 3-fluoro substituent serves to gear the ester group, promoting a conformation that favors tridentate binding. We conclude that relationships between electrostatic potential and XB strength hold for iodoarenes varying significantly in electron density, in agreement with computational predictions.

A plot of $\log(K_a)$ against $\delta^{13}C$, the chemical shift of the carbon atom bound to iodine, also reveals a modest correlation (see the ESI†). The direction of this trend (the strongest XB donors having lowest values of $\delta^{13}C$) is perhaps counter-intuitive;[20] we speculate that increased shielding of the *ipso* carbon arises from polarization of the C–I bond in response to increased substitution of the arene by fluoro substituents.[21] We note that studies of iodoalkynes have revealed unusual substituent effects on $\delta^{13}C$,[13] as well as unexpected, downfield changes in $\delta^{13}C$ upon halogen bonding.[22] The latter have been modeled computationally.

The observation that moderately electron-deficient iodo compounds display measurable anion affinities confers a practical benefit: while highly fluorinated **4a** underwent decomposition in the presence of the basic anions benzoate

and dihydrogenphosphate, clean 1 : 1 binding of these anions by **2b** was observed. The low affinity of **2b** for $PhCO_2^-$ and $H_2PO_4^-$ relative to the halides (entries 5–9) is unusual, as it does not follow the trend of anion hydration enthalpies. The preferential binding of the spherical halides over oxygen-based anions may be a useful feature of XB from the standpoint of receptor design.[6b]

The low anion affinities of receptors **4b–4d**, in which the iodine group involved in the interaction is replaced by other substituents, are revealing (entries 12–15). Decomposition of bromine-based XB donor **4b** was evident at high $Bu_4N^+Cl^-$ concentrations. However, the upper limit of the binding constant is three orders of magnitude lower than the value of K_a for **4a**–Cl^- in acetone. Given that halogen bonds of organobromine donors are proposed to play roles in drug–receptor interactions and biomolecule conformations, it is noteworthy that an attractive Br···Cl^- interaction was not observed in the context of this optimized receptor system. This result suggests that the stabilization gained from close contacts of the lighter halogen atoms may be modest.[23]

Perfluorobenzoic acid-derived receptor **4c** shows no detectable affinity for chloride. This result is consistent with studies of anion–arene interactions involving neutral hosts, which indicate that these are weak in moderately polar organic solvents.[24] Similarly, receptor **4d**, designed to probe the relative magnitudes of CH–anion hydrogen bonding and XB, interacts with Cl^- with an association constant at least one thousand times less than that of **4a**. Competition between hydrogen bonding and XB has been the subject of crystal engineering studies.[25] Our data indicate that direct replacement of a given proton with an iodine substituent increases donor ability significantly, presumably due to the high polarizability of iodine in comparison to hydrogen.

In conclusion, tridentate receptors have proved to be a powerful platform for probing the strengths of halogen bonds involving weak donors. This study demonstrates that species other than the exotic perfluorinated iodo compounds studied previously are capable of attractive halogen bonding interactions with anions in solution. The ability to tune halogen bonds by systematic variation of electronic structure may prove useful in future applications in molecular recognition or medicinal chemistry.

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