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Anion Receptors Composed of Hydrogen- and Halogen-Bond Donor Groups: Modulating Selectivity With Combinations of Distinct Noncovalent Interactions

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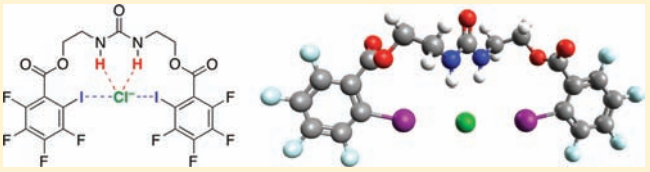
Supporting Information

ABSTRACT: Studies of a series of urea-based anion receptors designed to probe the potential for anion recognition through combinations of hydrogen and halogen bonding are presented. Proton- and fluorine-NMR spectroscopy indicates that the two interactions act in concert to achieve binding of certain anions, a conclusion supported by computational studies. Replacement of the halogen-bond donating iodine substituent by fluorine (which does not participate in halogen bonding) enables estimation of the contribution of this interaction to the free energy of anion binding. Evidence for attractive contacts between anions and electron-deficient arenes arising from the use of perfluoroarene-functionalized ureas as control receptors is also discussed. The magnitude of the free energy contribution of halogen bonding depends both on the geometric features of the group linking the hydrogen- and halogen-bond donor groups and on the identity of the bound anion. The results are interpreted in relation to fundamental features of the halogen-bonding interaction, including its directionality and unusual preference for halides over oxoanions. Cooperation between two distinct noncovalent interactions leads to unusual effects on receptor selectivity, a result of fundamental differences in the interactions of halogen- and hydrogen-bond donor groups with anions.



INTRODUCTION

Halogen bonding (XB) between electron-deficient halogen compounds and Lewis bases is gaining widespread recognition as a useful class of noncovalent interactions.[1] Applications of XB in condensed phases are extensive, including the assembly of functional materials, supramolecular polymers and crystalline assemblies.[2] Proposed roles for XB in medicinal chemistry,[3] as well as in controlling the structure and the function of biomolecules,[4] are also emerging at a rapid pace. Similarities are often invoked between XB and hydrogen bonding (HB):[5] Both are directional interactions for which a dominant electrostatic contribution to the binding enthalpy is generally proposed.[6] While applications of HB in solution phase molecular recognition are abundant, only a handful of instances in which XB has been employed for this purpose have been reported. A growing body of thermodynamic data suggests that certain halogen bonds are sufficiently strong to drive molecular recognition processes in solution,[7] and recently developed anion receptors[8] and interlocked supramolecular architectures[9] demonstrate that this goal is indeed achievable.

Here, we describe the development of receptors capable of anion binding by combinations of XB and HB interactions. We were interested in pursuing this goal for two reasons: First, Ho and co-workers recently pointed out numerous instances in which a basic site (often a carbonyl group in a biomolecule) simultaneously participates in XB and HB in the solid state; they observed that XB and HB donors often adopt orthogonal geometries when interacting with a common guest and carried out calculations suggesting that the two interactions may be energetically independent of each other (that is, that the formation of halogen bonds may not significantly weaken existing hydrogen bonds and vice versa).[4c,10] Small-molecule receptors capable of guest binding using these two interactions in solution might serve as models for such situations and provide information regarding the extent of stabilization possible. Second, research from our laboratories led to the development of the first receptors capable of high-affinity anion recognition by XB alone and revealed unusual differences in the intrinsic selectivities of HB and XB for anionic guests: XB hosts show a preference for halide anions over oxoanions (phosphate, nitrate, sulfate), perhaps due to a greater contribution of charge-transfer or dispersion contributions to XB in comparison to HB.[8c] This latter observation suggested that it might be possible to create receptors in which selectivity arises not from size and shape matching with a particular anionic guest (a well-precedented strategy in anion recognition)[11] but rather from the combined intrinsic anion preferences of two distinct noncovalent interactions. We are aware of only a single example of an anion receptor that employs both XB and HB: Beer and co-workers recently reported the synthesis and the preliminary anion binding properties of an iodotriazolium-derived rotaxane.[9b] The preference of

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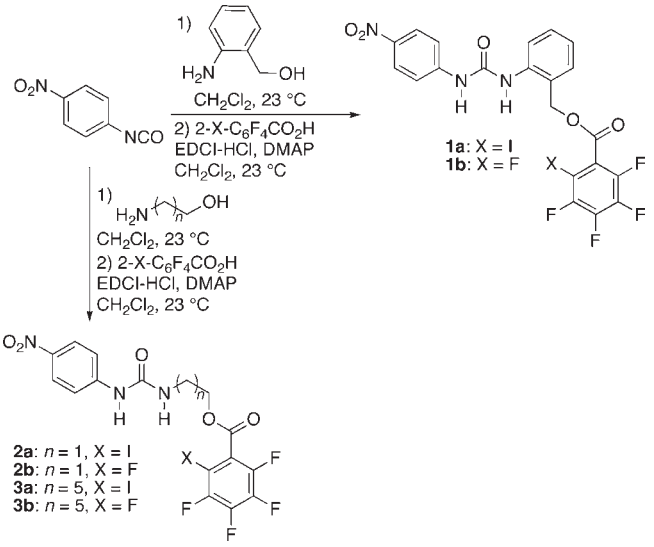
Scheme 1. Synthesis and Structures of Anion Receptors 1a−3b



this system for iodide over the other halide anions was rationalized in terms of size matching of the binding site and solvation effects in protic medium. Here, we present detailed anion binding studies of a series of urea receptors that incorporate either one or two iodoperfluorobenzoate groups as halogen-bond donors and demonstrate that the incorporation of these groups results in a significant alteration of the anion selectivity of the urea functional group. The origin of this effect is the selective stabilization of halides by the XB donor groups, as revealed by evaluation of the free energy contributions of XB to the overall thermodynamics of binding. Experiments probing the directionality of halogen bonds in solution and evidence for attractive anion−arene interactions of oxoanions with perfluoroaryl groups are also described.

UREA-BASED RECEPTORS BEARING A SINGLE HALOGEN-BOND DONOR: EFFECTS OF LINKER STRUCTURE

The urea functional group, well-known for its ability to interact with anions through HB interactions,[12] was chosen as a scaffold for the construction of combined HB/XB receptors. 2-Iodoperfluorobenzoic acid, the XB subunit used in our previous study of multidentate anion receptors, was coupled to amino alcohol-derived ureas to yield receptors **1a**−**3a**, which differ by the nature of the linker that connects the XB donor to the urea moiety (Scheme 1). Perfluorinated receptors **1b**−**3b**, which lack the 2-iodo substituent participating in the proposed halogen bond, were synthesized to provide a measure of the contribution of the XB interaction to the anion affinities of **1a**−**3a**. Strictly speaking, control receptors **1b**−**3b** provide measures of the relative contributions of XB and anion−arene interactions[13] in this system; this point is discussed in greater detail below.

The association constants of receptors **1a**−**3a** and **1b**−**3b** with halide anions (tetrabutylammonium cation, acetonitrile solvent) are assembled in Table 1. Addition of halide anions to each receptor resulted in changes in the ^{1}H-NMR chemical shifts

Table 1. Association Constants (K_a) of Receptors 1a−3a and 1b−3b with Halide Anions and Free Energy Contributions of the XB Interaction ($\Delta\Delta G_{XB}$)

receptor	anion	K_a (M^{-1})	$\Delta\Delta G_{XB}$ (kcal/mol)
1a	Cl^-	$8.5 \times 10^{3\,a}$	-0.2 ± 0.1
1b	Cl^-	$6.5 \times 10^{3\,a}$	
1a	Br^-	$1.7 \times 10^{3\,b}$	-0.1 ± 0.1
1b	Br^-	$1.4 \times 10^{3\,b}$	
1a	I^-	$1.3 \times 10^{2\,b}$	-0.2 ± 0.1
1b	I^-	$1.0 \times 10^{2\,b}$	
2a	Cl^-	$8.0 \times 10^{3\,a}$	-0.9 ± 0.1
2b	Cl^-	$1.7 \times 10^{3\,a}$	
2a	Br^-	$2.4 \times 10^{3\,b}$	-1.1 ± 0.1
2b	Br^-	$3.7 \times 10^{2\,b}$	
2a	I^-	$2.2 \times 10^{2\,b}$	-0.9 ± 0.1
2b	I^-	55^b	
3a	Cl^-	$4.9 \times 10^{3\,a,b}$	-0.3 ± 0.1
3b	Cl^-	$3.1 \times 10^{3\,b}$	
3a	Br^-	$9.4 \times 10^{2\,b}$	-0.4 ± 0.1
3b	Br^-	$5.0 \times 10^{2\,b}$	
3a	I^-	$1.1 \times 10^{2\,b}$	-0.3 ± 0.1
3b	I^-	61^b	

[a] Determined by fitting changes in solution absorbance as a function of anion concentration to a 1:1 binding isotherm (n-Bu_4N^+ cation, acetonitrile solvent, carried out in duplicate: uncertainty in K_a values estimated to be ±20%). [b] Determined by fitting changes in ^{1}H- and ^{19}F-NMR chemical shift as a function of anion concentration to a 1:1 binding isotherm (n-Bu_4N^+ cation, d_3-acetonitrile solvent, carried out in duplicate: uncertainty in K_a values estimated to be ±20%). The reported values are the averages of K_a determinations using changes in chemical shift for one urea N−H signal and one fluoro substituent. See the Supporting Information.

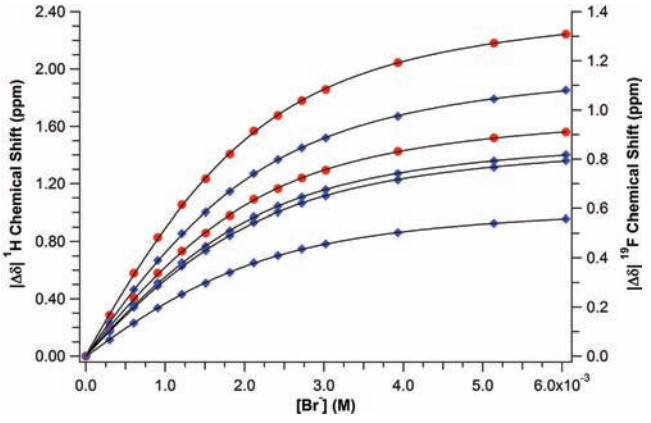


Figure 1. Changes in ^{1}H- (red, ●) and ^{19}F-NMR (blue, ♦) chemical shift ($\Delta\delta$) of receptor **1a** upon addition of n-$Bu_4N^+Br^-$ (d_3-acetonitrile). Curves represent equations of best fit to a 1:1 binding model.

of both N−H resonances as well as the ^{19}F-NMR chemical shifts of all magnetically distinct fluorine substituents. Figure 1 depicts the changes in ^{1}H- and ^{19}F-NMR chemical shift upon addition of n-$Bu_4N^+Br^-$ to **1a**: the significant downfield shift of the urea N−H NMR signal, along with the upfield change in δ^{19}F of the four fluorine substituents, are consistent with anion binding through a combination of XB and HB. The association constants

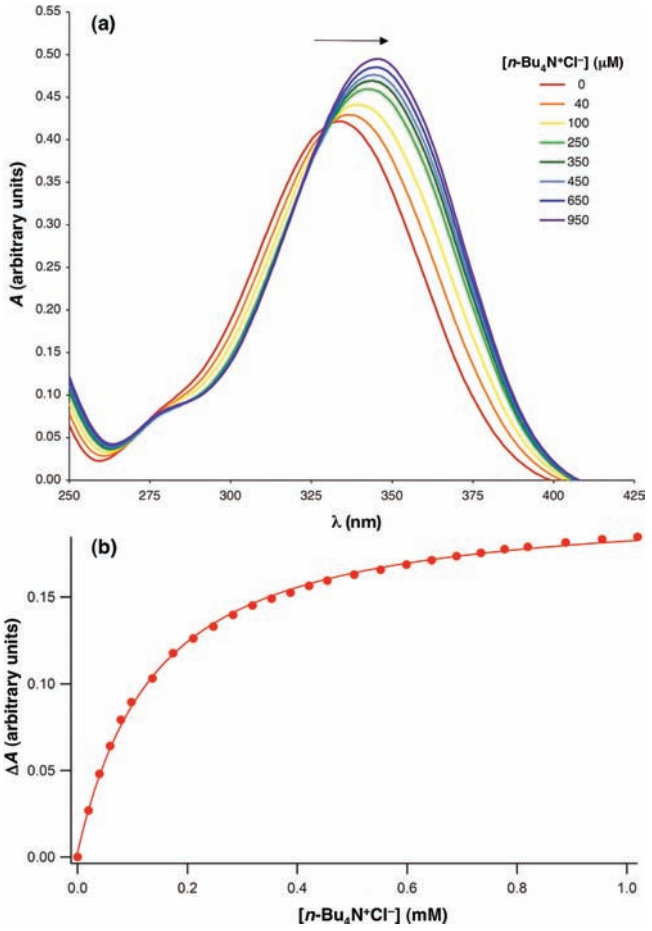


Figure 2. (a) UV−vis absorption spectra of **2a** upon addition of *n*-$Bu_4N^+Cl^-$ (acetonitrile) and (b) absorbance of **2a** (λ = 362 nm) as a function of [*n*-$Bu_4N^+Cl^-$]. Curve represents the equation of best fit to a 1:1 binding model.

of the chloride anion, which exceed those of Br^- and I^-, were determined by UV−vis absorption spectroscopy, taking advantage of the 4-nitroaniline chromophore present in these receptors. The spectroscopic changes accompanying binding of chloride by **2a** are shown in Figure 2a. In each case, analysis by the method of continuous variation (Job plot) was consistent with a 1:1 host:guest binding stoichiometry. Values of K_a were determined by fitting the changes in NMR chemical shift or absorbance as a function of anion concentration to 1:1 binding isotherms by standard methods.[14] When NMR was employed, the average of the values of K_a determined by ^{1}H NMR (the urea N−H signal) and by ^{19}F-NMR (the 3-F signal) is reported. Each determination was carried out in duplicate or triplicate, and an uncertainty of ±20% is estimated for all reported K_a values. In cases where the magnitude of the association constant was appropriate for determination by either method (NMR or UV−vis spectroscopy), data obtained using the two techniques were in good agreement, for example, NMR yielded values of $(10.4 \pm 2.1) \times 10^3$ M^{-1} and $(6.5 \pm 1.3) \times 10^3$ M^{-1}, respectively, for the **1a**−Cl^- and **1b**−Cl^- association constants compared to $(8.5 \pm 1.7) \times 10^3$ M^{-1} and $(6.5 \pm 1.3) \times 10^3$ M^{-1} as determined by UV−vis spectroscopy.

The difference $\Delta\Delta G_{XB}$ between the free energies of interaction of the iodinated and fluorinated receptors with a given anion (for example, for receptors **1a** and **1b** $\Delta\Delta G_{XB} = \Delta G_{binding(1a)} - \Delta G_{binding(1b)}$) provides a rough estimate of the contribution of the XB interaction to the overall thermodynamics of binding.[15] Based on previous observations from our laboratories, we anticipated negative values of $\Delta\Delta G_{XB}$ for the halide anions, which are good acceptors of halogen bonds. The data reveal a significant influence of the structure of the amino alcohol linker group on the strength of the halogen bond formed. Receptor **1a** shows a barely measurable contribution of the XB interaction to anion affinity, while receptor **2a** binds to each of the halide anions with association constants an order of magnitude higher than those of receptor **2b**, corresponding to values of $\Delta\Delta G_{XB}$ of approximately 1 kcal/mol. Receptor **3a**, in which the HB and XB donor groups are linked by a flexible hexamethylene spacer, gave values of $\Delta\Delta G_{XB}$ lower than those of **2a** for each anion.

Presumably, the low value of $\Delta\Delta G_{XB}$ for **3a** in comparison to **2a** reflects the increased entropic cost for chloride binding of the former, due to the flexible linker tethering the urea and iodoperfluorobenzoate groups. Effects of this type are well precedented and underlie the use of rigid, preorganized scaffolds in receptor design. The differences in behavior between receptors **1a** and **2a**, on the other hand, are less clear; computational modeling of their chloride complexes was undertaken to probe this issue. For this purpose, simplified models **1a′**−**3a′** (which lack the 4-nitro substituent) were considered. The gas-phase geometries of the receptor−Cl^- complexes were optimized using density functional theory (DFT), employing the B3LYP functional.[16] The 6-31++G(d,p) basis set was used for C, H, N, O, F, and Cl atoms, and the LANL2DZ effective core potential,[17] augmented with polarization functions of d symmetry and diffuse functions of p symmetry (LANL2DZdp),[18] was employed for iodine. For each receptor, the chloride anion interacts with both hydrogen- and halogen-bond donor groups in the energy-minimized structure (Figure 3). However, a difference in the halogen-bond angles is evident, with the C−I···Cl^- angle in **1a′** (155°) distorted from the preferred 180° geometry by 15° more than that of **2a′** (170°). Receptor **3a′** is predicted to accommodate a near-linear halogen bond (179.6°).

While the differences in XB angle between **1a′**−Cl^- and **2a′**−Cl^- might seem to be modest, data from X-ray crystallography,[1a,19] gas-phase microwave spectroscopy,[20] and computation[21] indicate that halogen bonds show a more stringent preference for linearity than do hydrogen bonds. To probe the potential magnitude of this effect in the current system, we carried out calculations of the gas-phase binding energy of the C_6F_5I−Cl^- halogen-bonded complex as a function of the C−I···Cl^- angle. These calculations were conducted at the MP2 level of theory: The complex geometry was optimized (MP2/aug-cc-pVDZ, with the aug-cc-pVDZ-PP effective core potential for iodine),[22] and the single-point energy calculations (MP2/aug-cc-pVTZ, with the aug-cc-pVTZ-PP effective core potential for iodine) were carried out while incrementally altering the halogen-bond angle. Two limiting cases were investigated: (1) The chloride anion was held in the plane of the perfluoroaryl group (a C−C−I···Cl^- dihedral angle of 180°); and (2) the chloride anion was held in the plane perpendicular to that of the perfluoroaryl group (a C−C−I···Cl^- dihedral angle of 90°), as the C−I···Cl^- angle was varied. The electronic energy of the complex is plotted as a function of halogen-bond angle for each of these two limiting dihedral angles in Figure 4. For comparison, the energy of the pyrrole−Cl^- hydrogen-bonded complex (which has a similar calculated gas-phase energy of interaction

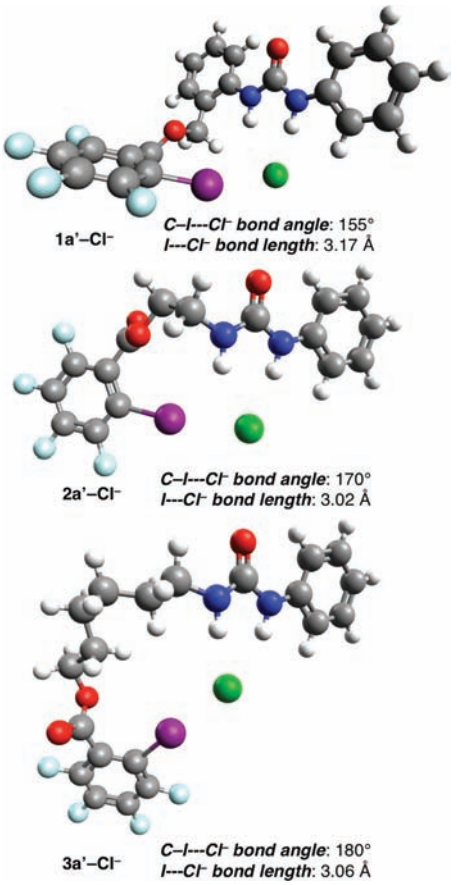


Figure 3. Structures of the **1a**′−Cl^-, **2a**′−Cl^-, and **3a**′−Cl^- complexes calculated by DFT (B3LYP/6-31++G(d,p)-LANL2DZdp, gas-phase: see the text). Values of the I···Cl^- halogen-bond distance and C−I···Cl^- halogen-bond angle are listed beneath each structure.

as the C_6F_5I−Cl^- complex at this level of theory)[23] as a function of N−H···Cl^- angle, for each of these two limiting dihedral angles, is shown on the same graphs.

The data indicate that the halogen-bonded complex incurs a significantly higher energetic penalty than does the hydrogen-bonded complex upon distortion from the ideal linear geometry, for example, a bond angle of 155° destabilizes the halogen-bonded complex by roughly 5 kcal/mol, in comparison to 1 kcal/mol for the hydrogen-bonded complex. (As an aside, the two systems differ in terms of the dihedral angle that incurs the smallest energetic penalty: For the C_6F_5I−Cl^- complex, the 90° dihedral angle (which allows for a potentially attractive anion−arene interaction as the Cl^- is brought closer to the electron-deficient π face of the arene) is preferred over the 180° dihedral (in which the anion approaches the electronegative fluorine substituents). The reverse is predicted for the pyrrole−Cl^- complex: In this case, the contact between the anion and the electron-rich π face of the heterocycle is predicted to be a repulsive interaction, and the calculations indicate that the 180° dihedral (which may benefit from a stabilizing CH···anion hydrogen bond) is preferred. In any case, the magnitude of these differences is relatively minor, and the halogen bond is predicted to be the more directional interaction regardless of the dihedral angle chosen). Electrostatic models of XB interpret its pronounced directionality as arising from the localized nature of the 'σ-hole', the region of partial positive charge at a halogen that

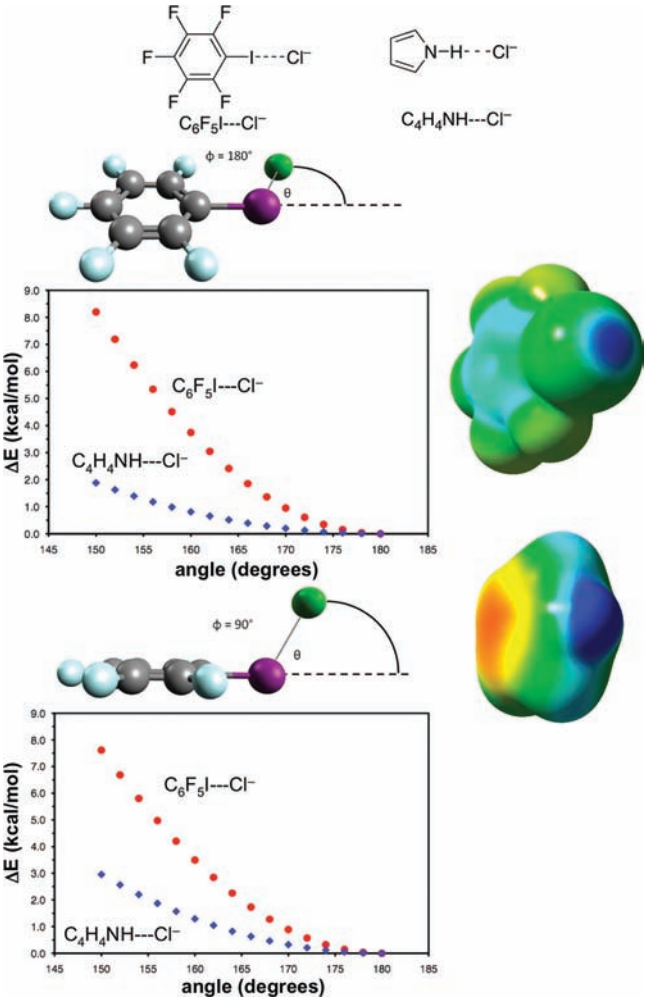


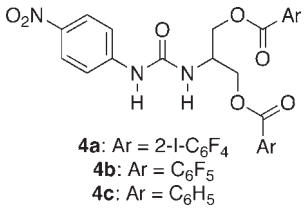
Figure 4. Calculated gas-phase energies of the iodoperfluorobenzene−chloride and pyrrole−chloride complexes (MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ) as a function of C−I···Cl^- and N−H···Cl^- angle, respectively. Graphs for dihedral angles (C−C−I···Cl^- and C−N−H···Cl^-, respectively) φ = 180° (top) and φ = 90° (bottom) are shown. Calculated molecular electrostatic potential energy surfaces of C_6F_5I (top right) and pyrrole (bottom right) (MP2/aug-cc-pVDZ) are shown for comparison: blue indicates regions of partial positive charge.

arises when it is bound to a sufficiently electronegative group;[24] calculated molecular electrostatic potentials (Figure 4) indicate that this region is spatially restricted in C_6F_5I relative to pyrrole. The differences in solution-phase binding data for **1a** and **2a** complement previous gas- and solid-phase studies of the angular preference of XB and suggest that this feature must be considered carefully when designing rigid receptors based on XB.

■ UREA-BASED RECEPTORS INCORPORATING TWO HALOGEN-BOND DONOR GROUPS

We anticipated that the more balanced combination of two HB and two XB donor groups could give rise to significant alterations in receptor selectivity as a result of the increased contribution of the XB interaction to guest binding. Serinol-derived receptor **4a** presents such an ensemble of binding groups, with perfluorinated **4b** serving as a control. The affinities of these receptors for a range of halides and oxoanions, determined by NMR or absorption spectroscopy titrations, are assembled in

Table 2. Association Constants (K_a) of Receptors 4a−4c with Anions and Estimated Free Energy Contributions of the XB ($\Delta\Delta G_{XB}$) and Anion−arene Interactions ($\Delta\Delta G_{AA}$)



4a: Ar = 2-I-C_6F_4
4b: Ar = C_6F_5
4c: Ar = C_6H_5

receptor	anion	K_a (M^{-1})	$\Delta\Delta G_{XB}$ (kcal/mol)	$\Delta\Delta G_{AA}$ (kcal/mol)
4a	BzO^-	$1.9 \times 10^{5\,a}$	-0.2 ± 0.1	
4b	BzO^-	$1.4 \times 10^{5\,a}$		-0.5 ± 0.1
4c	BzO^-	$6.6 \times 10^{4\,a}$		
4a	Cl^-	$2.1 \times 10^{4\,a}$	-1.3 ± 0.1	
4b	Cl^-	$2.5 \times 10^{3\,a}$		-0.1 ± 0.1
4c	Cl^-	$2.3 \times 10^{3\,a}$		
4a	Br^-	$6.5 \times 10^{3\,b}$	-1.5 ± 0.1	
4b	Br^-	$4.9 \times 10^{2\,b}$		-0.1 ± 0.1
4c	Br^-	$4.6 \times 10^{2\,b}$		
4a	TsO^-	$1.1 \times 10^{3\,b}$	-0.1 ± 0.1	
4b	TsO^-	$9.6 \times 10^{2\,b}$		-0.3 ± 0.1
4c	TsO^-	$5.5 \times 10^{2\,b}$		
4a	I^-	$5.6 \times 10^{2\,b}$	-1.4 ± 0.1	
4b	I^-	60^b		0 ± 0.1
4c	I^-	55^b		
4a	HSO_4^-	$4.4 \times 10^{2\,b}$	-0.1 ± 0.1	
4b	HSO_4^-	$3.8 \times 10^{2\,b}$		-0.3 ± 0.1
4c	HSO_4^-	$2.3 \times 10^{2\,b}$		
4a	NO_3^-	$2.9 \times 10^{2\,b}$	-0.1 ± 0.1	
4b	NO_3^-	$2.6 \times 10^{2\,b}$		-0.3 ± 0.1
4c	NO_3^-	$1.6 \times 10^{2\,b}$		

[a] Determined by fitting changes in solution absorbance as a function of anion concentration to a 1:1 binding isotherm (n-Bu_4N^+ cation, acetonitrile solvent, carried out in duplicate: uncertainty in K_a values estimated to be ±20%). [b] Determined by fitting changes in ^{1}H- and, for **4a** and **4b**, ^{19}F-NMR chemical shift as a function of anion concentration to a 1:1 binding isotherm (n-Bu_4N^+ cation, d_3-acetonitrile solvent, carried out in duplicate: uncertainty in K_a values estimated to be ±20%). The reported values are the averages of K_a determinations using changes in chemical shift for one urea N−H proton and one fluoro substituent in **4a** and **4b**. See the Supporting Information.

Table 2, along with the contribution of the halogen bonds to the free energy of binding $\Delta\Delta G_{XB}$ (as defined above).

Comparison of the association constants of **4a** and **4b** for the series of anions reveals the pronounced preference of the halogen-bond donor groups to interact with the halides over oxoanions, an observation consistent with our previous work. The oxygen-based anions tested, which vary widely in Brønsted basicity, do not show a significant stabilizing interaction with the halogen-bond donor groups in **4a**, while the values of $\Delta\Delta G_{XB}$ for the halide anions are each greater than 1 kcal/mol. The magnitudes of the ^{19}F-NMR chemical shift changes of **4a** upon anion binding are considerably higher for the halides Br^- and I^- (the maximum changes in chemical shift $\Delta\delta_{max}$ obtained from curve fitting of the NMR titration data are −1.7 and −1.9 ppm, respectively) than for the oxoanions TsO^-, HSO_4^-, and NO_3^- ($\Delta\delta_{max}$ = −0.32, −0.34, and −0.27, respectively). These data are consistent with the idea that receptor **4a** interacts with halide anions through combinations of HB and XB, while the latter interaction is weak or absent in the case of the oxoanions. A contribution of dispersion or charge transfer to the XB interactions of halides is a possible explanation for this behavior; high-level computational studies suggest that halogen bonds cannot be modeled as purely electrostatic interactions. Figure 5 illustrates the alteration of the anion selectivity of the urea receptor resulting from selective stabilization of the halide anions by the XB donor groups in **4a**.

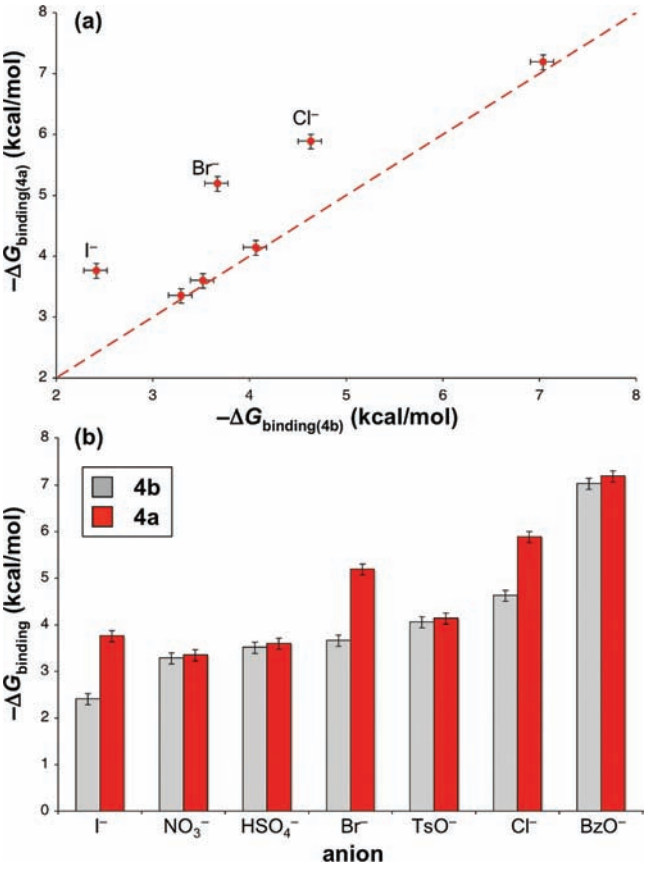


Figure 5. (a) Plot of $-\Delta G_{binding}$ of **4a** against $-\Delta G_{binding}$ of **4b** for the series of anions tested. The dotted line represents $y = x$. (b) Bar graph illustrating the differences in anion selectivity between receptors **4b** and **4a** (gray and red bars, respectively).

Anion−Arene Interactions in Perfluorinated Receptor 4b. As alluded to earlier, the perfluoroaryl moieties present in the "control" receptors **1b**−**4b** are not innocent with respect to noncovalent interactions; these electron-deficient aryl groups are capable of anion−arene interactions.[25] Despite significant interest in the fundamental nature and the potential applications of anion−arene interactions, definitive evidence for attractive contacts of this type in solution is rare.[26] To estimate the magnitude of putative anion−arene interactions in complexes of **4b**, we prepared benzoate ester **4c** and determined the difference in binding energies $\Delta\Delta G_{AA}$ ($\Delta\Delta G_{AA} = \Delta G_{binding(3b)} - \Delta G_{binding(3c)}$).[27]

Estimation of the strength of anion−arene interactions in receptor **4b** by this approach revealed surprising results. Previous publications suggested that interactions between anions and

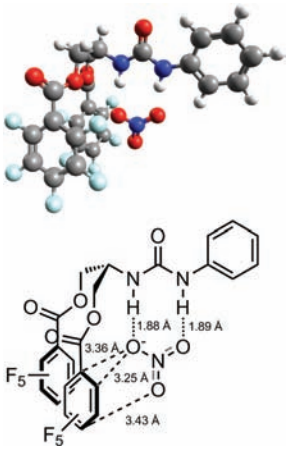


Figure 6. Structure of the **4b′**−NO_3^- complex calculated by DFT (B3LYP/6-31++G(d,p), gas phase). Hydrogen-bond distances and nitrate−perfluoroarene contact distances are indicated.

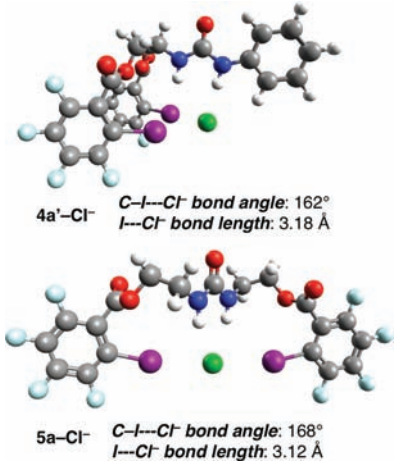
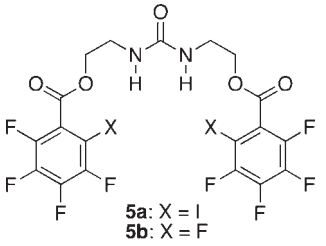


Figure 7. Structure of the **4a′**−Cl^- and **5a**−Cl^- complexes calculated by DFT (gas-phase, B3LYP/6-31++G(d,p)-LANL2DZdp: see text). Values of the I···Cl^- halogen-bond distance and C−I···Cl^- halogen-bond angle are listed beneath each structure.

uncharged, substituted phenyl groups would be weak in a moderately polar solvent, such as acetonitrile,[26c,d] and the binding data for the halides are consistent with this notion ($-\Delta\Delta G_{AA} \leq 0.1$ kcal/mol for Cl^-, Br^-, and I^-). However, appreciable values of $\Delta\Delta G_{AA}$ (−0.3 to −0.5 kcal/mol) were observed for the oxoanions BzO^-, TsO^-, HSO_4^-, and NO_3^-. A significant change in ^{19}F-NMR chemical shift upon oxoanion binding ($\Delta\delta_{max} \sim -0.7$ ppm for the fluoro substituent para to the carboxyl group) and a relatively short nitrate−perfluoroarene contact distance ($d_{O\cdots C}$ = 3.25 Å) in the calculated structure of the **4b′**−NO_3^- complex (Figure 6: **4b′** lacks the nitro substituent present in **4b**) are consistent with the proposed anion−arene interaction. This result represents an addition to the small set of experimental data supporting such interactions in solution and is noteworthy because interactions of oxoanions with arenes are particularly poorly documented in the solution state. It is not clear whether the difference in behavior between the halides and the oxoanions is the result of the geometry of receptor **4b** or a reflection of an intrinsic trend in the strength of

Table 3. Association Constants (K_a) of Receptors 5a and 5b with Halide Anions and Free Energy Contributions of the XB Interaction ($\Delta\Delta G_{XB}$)



receptor	anion	K_a (M^{-1})[a]	$\Delta\Delta G_{XB}$ (kcal/mol)
5a	BzO^-	3.3×10^3	−0.7 ± 0.1
5b	BzO^-	1.0×10^3	
5a	Cl^-	2.4×10^3	−2.0 ± 0.1
5b	Cl^-	86	
5a	$H_2PO_4^-$	8.3×10^2	−0.8 ± 0.1
5b	$H_2PO_4^-$	2.0×10^2	
5a	Br^-	7.0×10^2	−2.0 ± 0.1
5b	Br^-	24	
5a	I^-	1.4×10^2	−1.7 ± 0.1
5b	I^-	8.5	
5a	TsO^-	54[b]	−0.2 ± 0.1
5b	TsO^-	38[b]	
5a	HSO_4^-	30[b]	−0.3 ± 0.1
5b	HSO_4^-	19[b]	
5a	NO_3^-	21	−0.2 ± 0.1
5b	NO_3^-	14	

[a] Determined by fitting changes in ^{1}H NMR and ^{19}F-NMR chemical shift as a function of anion concentration to a 1:1 binding isotherm (n-Bu_4N^+ cation, d_3-acetonitrile solvent, carried out in duplicate: uncertainty in K_a values estimated to be ±20%). The reported values are the averages of K_a determinations using changes in chemical shift for one urea N−H proton and one fluorine substituent. [b] Association constants for TsO^- and HSO_4^- were determined by ^{19}F-NMR because of significant broadening of the signals corresponding to the N−H protons in the ^{1}H NMR spectrum.

interactions of the perfluoroarene group with this series of anions. The former would seem to be more consistent with existing computational data.[28]

Achieving Halide Selectivity in Combined HB/XB Receptors. Continued evaluation of the effects of the geometry and strength of the XB and HB donor groups led us to explore symmetrical, ethanolamine-based receptor **5a**. Computational modeling of **4a′**−Cl^- and **5a**−Cl^- complexes (Figure 7: **4a′** is a simplified model of **4a** lacking the nitro group) suggested that the halogen bonds in the latter are closer to linearity than in the former, and the four donor groups presented by **5a** more efficiently surround the anion than do those of **4a**. In addition, the hydrogen-bond donor ability of dialkylurea **5a** was anticipated to be weaker than that of nitroaniline-based **4a**, offering the possibility that the halogen bonds might contribute in a more balanced way to the observed order of anion affinities. These predictions were borne out by the anion binding data for **5a** and its perfluorinated analog **5b** (Table 3).

Of the receptors studied, **5a** shows the most significant effect of XB on the overall thermodynamics of anion binding. The

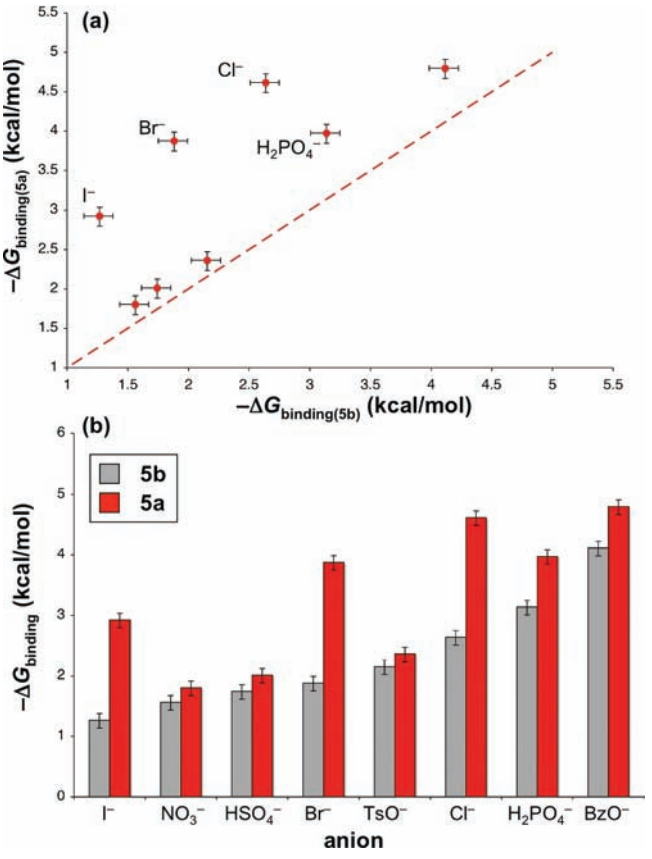


Figure 8. (a) Plot of $-\Delta G_{binding}$ of **5a** against $-\Delta G_{binding}$ of **5b** for the series of anions tested. The dotted line represents $y = x$. (b) Bar graph illustrating the differences in anion selectivity between receptors **5b** and **5a** (gray and red bars, respectivley).

association constants for the halides are nearly 30 times higher for **5a** than for the control receptor **5b**. We also note that the binding data for dihydrogenphosphate ($H_2PO_4^-$) and benzoate indicate that these anions participate in stabilizing XB interactions with the iodoperfluoraryl groups in **5a** and that the magnitude of these effects is higher than those observed for the less basic oxoanions. Halogen bonding involving phosphate oxygens has been proposed to play a role in controlling the secondary structure of modified DNA oligomers,[29] but reliable estimates for the strengths of such interactions have proved to be elusive. The current work indicates that these interactions are indeed attractive in acetonitrile solution, although weak (roughly 0.4 kcal/mol per halogen bond).

The overall effect of incorporating halogen-bond donors to a urea receptor is to confer a significant level of halide selectivity to a class of compounds known to interact tightly with Y-shaped anions (Figure 8). Conventionally, tuning of receptor selectivity has been accomplished by varying the number of donor groups (generally HB donors) and their orientation in space;[30] taking advantage of differences in the intrinsic preferences of two distinct noncovalent interactions to achieve this result represents an unusual approach. As our fundamental understanding of "exotic" noncovalent interactions (that is, those other than HB, such as anion−arene,[13] cation-π,[31] XB and related interactions)[32] continues to improve, new opportunities to exploit this second approach, and to combine it with the first, may emerge.

CONCLUSIONS

Studies of anion receptors equipped with both halogen- and hydrogen-bond donor functional groups demonstrate that it is indeed possible to employ these interactions cooperatively in molecular recognition. Several types of evidence—including the nature of the anion-induced ^{1}H- and ^{19}F-NMR spectroscopic changes, the association constants of control receptors lacking the XB donor functional group, and calculated geometries of receptor−anion complexes—indicate that the two interactions occur simultaneously upon binding of XB acceptor anions, such as halides. Among the key findings to emerge from this study are:

(1) The free energy contribution of the halogen bonds formed is dependent on the identity of the spacer group linking the HB and XB donor groups. Calculations suggest that this dependence is a manifestation of the strong preference of halogen bonds to adopt a linear EWG−X···B geometry, a property inferred from solid-state and gas-phase studies but not previously explored in solution. The stringent directionality of XB will likely be an important feature to consider when developing applications of the interaction in solution-phase molecular recognition.

(2) An anion participating in two HB interactions with a urea functional group is able to engage in attractive halogen bonds with iodoperfluoroaryl groups. Control experiments provide a rough estimate of the contribution of the XB interactions to the overall thermodynamics of binding in acetonitrile solvent. The estimated incremental free energy per halogen bond is negligible for most oxoanions (< 0.2 kcal/mol for NO_3^-, HSO_4^- and TsO^-), is small for BzO^- and $H_2PO_4^-$ (0.3 and 0.4 kcal/mol, respectively), and approaches 1 kcal/mol for the halide anions. These results are consistent with conclusions regarding the intrinsic anion selectivity of the XB interaction reached through studies of XB receptors in moderately polar organic solvent and highlight the significant distinctions between the XB and HB interactions that have emerged from several studies by our research group.

(3) Comparisons of the anion affinities of urea receptors bearing pendant perfluorobenzoate functional groups with those bearing unsubstituted benzoate groups provide evidence for attractive anion−arene interactions with perfluoroaryl groups in acetonitrile solution. The observation of weakly attractive contacts with oxoanions ($-\Delta\Delta G_{AA}$ roughly 0.3−0.5 kcal/mol for NO_3^-, HSO_4^-, TsO^- and BzO^-), but not with halide anions, was unexpected and represents one of only a handful of studies enabling a quantitative estimate of the magnitude of such interactions in solution.

(4) Receptors composed of both halogen- and hydrogen-bond donor groups display anion selectivities that represent a "compromise" between the distinct preferences of the two interactions. Incorporating iodoperfluoroaryl groups into a urea receptor selectively boosts its affinity for halide anions, while having a minor to negligible effect on its interactions with oxoanions. This represents an unconventional approach to modulating receptor selectivity, and one that may become more prevalent as new information regarding poorly understood noncovalent interactions emerges.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures, representative binding curves and Job plots, methods of data analysis, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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