Anion–π interaction augments halide binding in solution†

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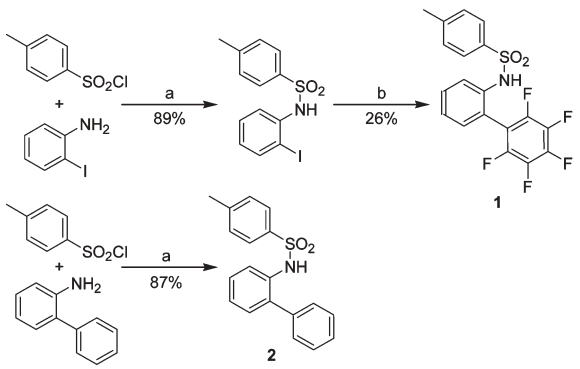
^{1}H NMR spectroscopic data and complementary theoretical predictions suggest that a designed receptor exhibits the anion–π interaction in solution.

Molecular receptors designed to target anions utilize a variety of interactions to accomplish their goal. Some of the more common reversible bonds employed include hydrogen bonding, electrostatic interactions, hydrophobic effects, and coordination to a metal ion.[1–4] A promising binding strategy to target anions that has recently garnered much attention in the literature is the anion–π interaction. Currently, numerous computational studies[5–9] and single crystal X-ray structures[6,10–14] support the viability of using this noncovalent interaction as a design strategy to target anions. Several of these reports compare the anion–π interaction to the familiar cation–π interaction[5,15] where a positively charged ion attractively interacts with an electron-rich aromatic ring.[16] The anion–π interaction is similarly proposed to arise from a *negatively charged* species having a coulombic attraction to an area of low electron density in an *electron-deficient* aromatic ring. Despite the numerous solid state examples and theoretical treatments, surprisingly few solution phase examples recognize the anion–π interaction.[13]



Scheme 1 *Reagents and conditions*: (a) dry pyridine, rt, 4 h; (b) C_6BrF_5, dry DMSO, $Pd(PPh_3)_4$, Cu^0, 105 °C, 5.5 h.

In an attempt to probe the efficacy of the anion–π interaction to bind anions in solution, two receptor molecules were prepared (**1** and **2**, Scheme 1). Design of receptor **1** focused on a two point recognition motif utilizing both a hydrogen bond and an electron-deficient aromatic ring.[17] In contrast to **1**, control receptor **2** lacked the electron-deficient aromatic substituent required for the anion–π interaction. Any enhanced association for anions that receptor **1** exhibits over receptor **2** should be a result of the favorable anion–π interaction present in the **1**·anion complex. To the best of our knowledge, a neutral receptor molecule *designed* to incorporate the anion–π interaction to bind anions in solution is unknown. Herein we report solution data illustrating the enhanced association for anions that designed receptor **1** shows over control receptor **2**. Receptor **1** was synthesized by converting *o*-iodoaniline to the corresponding *p*-toluenesulfonamide[18] followed by a palladium-mediated Ullmann coupling (Scheme 1).[19,20] ^{1}H NMR spectroscopy and single crystal X-ray diffraction confirmed the structure of receptor **1** (see ESI). A similar procedure provides **2** in 87% yield starting from 2-aminobiphenyl.

Single crystals of **1** suitable for X-ray diffraction were grown by diffusing pentane into a chloroform solution of the receptor.‡ Receptor **1** crystallizes as a hydrogen bonded dimer in spacegroup *P*-1 with two molecules of **1** per unit cell. It is interesting to note that one sulfonamide oxygen from each receptor molecule is located 3.1 Å from the electron-deficient aromatic ring of an adjacent molecule.[21,22] In the crystalline state **1** is preorganized in the optimal conformation to interact with an anion through *both* a hydrogen bond *and* an anion–π interaction.

Electrostatic potential surfaces (EPS) of molecules have been used to illustrate areas of low electron density that can interact with electron-rich anions.[7,15] To highlight both the pre-organization of receptor **1** for binding anions and the predictive power that electrostatic potential surfaces have for the anion–π interaction, the

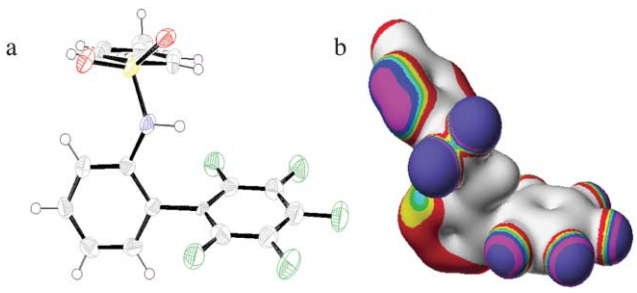


Fig. 1 (a) ORTEP representation of the single crystal X-ray structure of **1**. Ellipsoids are at the 50% probability level with sulfur yellow, oxygen red, carbon gray, nitrogen blue, fluorine green and hydrogen light gray. (b) Calculated EPS plot of receptor **1**, scaling areas of highest electron density (blue) to lowest (white).

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crystal structure of **1** is shown alongside a minimized (CAChe 5.0, EHT) electrostatic potential surface plot of receptor **1** in the optimal conformation for complexing an anion (Fig. 1).[23] The center of the electron-deficient aromatic ring of receptor **1** (Fig. 1) exhibits a surface of low electron density (white) that is optimal for interacting with an anion.

Following the synthesis of receptors **1** and **2**, ^{1}H NMR spectroscopic titration experiments were performed for each receptor with the tetra-*n*-butylammonium salts of chloride, bromide and iodide. The downfield shifts of the N–H resonances of **1** and **2** were monitored as aliquots from a stock solution of the corresponding salt in $CDCl_3$ were added to the receptors in $CDCl_3$. WinEQNMR[24] was used to fit the raw data to a 1 : 1 association model (see ESI). Iterative calculations using WinEQNMR yielded the stability constants of the receptors with each anion[25] (Table 1); each reported K_a for **1** represents the average of three titrations.

The titration experiments depict a stark contrast between the association constants of receptors **1** and **2** with a given halide. Receptor **1** binds all the halides screened (iodide, bromide and chloride) with a measurable, albeit modest association constant. However, in the case of receptor **2**—where an electron-deficient aromatic ring is not present—there is no measurable association with any of the halides tested. Comparison of the association constants for the nearly isosteric receptors **1** and **2** allows for an initial assessment of the anion–π interaction in solution. The association constants measured for receptor **1** and the series of halides iodide, bromide and chloride fall in the range of 20–34 M^{-1}. The measured association constants are similar in magnitude with reported anion–π binding constants.[13] Receptor **2** on the other hand shows a significantly weaker binding to the same halides. The change in chemical shift from the titration experiments was so small for receptor **2** that no association constant could be determined. The association constants for receptors **1** and **2** provide strong support demonstrating the anion–π interaction in solution, highlighting the possibility of utilizing the anion–π interaction to bind anions by design.

The trend in association constant strength for receptor **1** and the halides chloride, bromide and iodide cannot solely be explained by the strength of the hydrogen bond with each anion. In a similar system containing only a sulfonamide substituent (but no adjacent aromatic ring), it was observed that chloride forms the strongest association by an order of magnitude whereas bromide and iodide are significantly weaker and equal to each other.[26] However, receptor **1**, which contains an electron-deficient aromatic ring designed to interact with anions, shows a deviation from this trend with the most polarizable anion (iodide) exhibiting a comparable association to that of the more basic chloride ion. One plausible explanation for this enhanced binding observed with iodide could be that the more polarizable iodide anion provides a stronger interaction with the electron-deficient aromatic ring, which supplements the weaker hydrogen bond.[16,27]

Table 1 K_a (M^{-1}) for receptors **1** and **2** with selected halides[a]

	Receptor **1**[b]	Receptor **2**[b]
Cl^-	30 ± 3	< 1[c]
Br^-	20 ± 2	< 1[c]
I^-	34 ± 6	< 1[c]

[a] The NEt_4^+ salts of each halide were used. [b] Initial receptor concentrations fall in the range of 9–25 mM; full details of the titration experiments are contained in the ESI. [c] Association constants for receptor **2** were too small to be determined by ^{1}H NMR titration experiments.

An alternative explanation for the differences in measured K_a values between receptors **1** and **2** could be their variation in sulfonamide N–H acidities. It is apparent that the electronic differences between receptors **1** and **2** result in sulfonamide N–H protons with different pK_a values. Abraham *et al.*[28] have shown by comparing a family of receptors, the change in association constant based on hydrogen bonding acidity is only a fraction of the pK_a difference between the H-bond donors.[29] Receptors **1** and **2** exhibit at least a two order of magnitude difference in anion binding affinity, while the pK_a values are only 2.5 log units different (see ESI). Therefore, the pK_a of the sulfonamide N–H cannot alone explain the difference in association constants for anions. The difference in pK_a values is an issue with any receptor that utilizes both a hydrogen bond and an anion–π interaction, therefore new receptors are being synthesized without this feature to investigate the anion–π interaction further.

While a crystal structure of a **1**·anion complex in the proper orientation remains elusive—presumably a result of the low association constant of **1** with anions—Fig. 2 illustrates the only solid state structure of receptor **1** and an anion observed to date.‡ In this structure the sulfonamide N–H is drastically rotated out of conjugation with the adjacent phenyl ring in order to form a very weak hydrogen bond with a bromide ion (avg. Br–H–N angle = 129.7°). This conformation precludes formation of an anion–π interaction and is adopted to allow for a polymeric ion pair between tetra-*n*-butylammonium counterions and the bromide anion to form in the crystal state (Fig. 2, inset). This solid state structure likely does not represent the solution structure of **1** when bound to an anion: first, Hartree–Fock (6-31+G*) geometry optimizations for the complex of each receptor **1** and **2** with chloride showed two different energy minima for both receptors. Receptor **1** exhibited one minimum with the chloride over the face of the electron-deficient aromatic ring (Fig. 3a) and one minimum with the chloride positioned to the side of the electron-deficient aromatic ring. Receptor **2** on the other hand showed no reasonable structure positioning the halide over the face of the aromatic ring (Fig. 3b). These calculations suggest that the chloride anion is

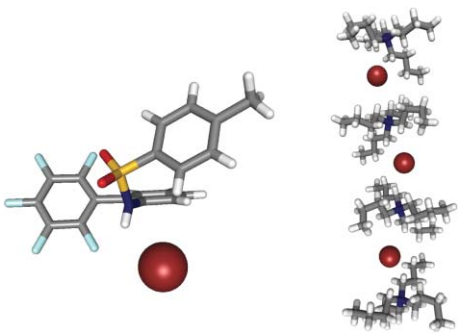

Fig. 2 Stick representation of the X-ray crystal structure of receptor **1** and tetra-*n*-butylammonium bromide where the ion pairing in the solid state is forcing the sulfonamide N–H away from the preferred conformation. The inset shows the polymeric ion pair formed in the solid state.

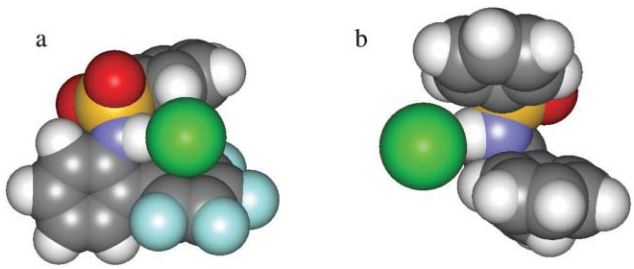

Fig. 3 HF geometry minimizations of receptors **1** and **2** with chloride using a 6-31+G* basis set. (a) Energy minimization of receptor **1** with chloride (green) showing the halide over the face of the electron-deficient aromatic ring. (b) One of the representative minimizations of receptor **2** with chloride (green) not positioned over the face of the aromatic ring.

repulsed by the aromatic ring in receptor **2** while being less repulsed by the electron-deficient aromatic ring of receptor **1**.

Secondly, the polymeric ion pair observed in the crystalline state is clearly not maintained in $CDCl_3$ solutions. Furthermore, this ion pair forming in solution would not explain the ^{1}H NMR chemical shift dependence of the N–H resonance of **1** on anion concentration (Table 1). Additionally, since receptors **1** and **2** are nearly isosteric, **2** could equally-well adopt this twisted conformation to bind anions in solution. If this were the case, **1** and **2** would have very similar binding constants for anions, which they do not. Despite this perplexing structure, the solution data are best corroborated by invoking an attractive anion–π interaction when **1** binds anions.

The solution data presented herein underscore the hypothesis that electron-deficient aromatics can be used as a component of a design strategy to target anions in solution. A pair of receptors that differ only by the substituents on their aromatic rings were designed and synthesized. Analysis of the association constants of each receptor with an array of halides has demonstrated the enhanced affinity for anions that receptor **1** shows in solution over a control receptor lacking an electron-deficient aromatic ring. The enhanced binding that receptor **1** displays results from an attractive anion–π interaction. These experiments support the use of the anion–π interaction as an emerging noncovalent interaction for the selective targeting of anions in solution.

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Notes and references

‡ *Crystal data* **1**: $C_{19}H_{12}F_5NO_2S$, M = 413.36, triclinic, P-1, a = 9.0547(11), b = 10.2933(12), c = 10.4106(13) Å, α = 97.125(2)°, β = 112.783(2)°, γ = 101.424(2)°, V = 854.95(18) Å^3, Z = 2, μ(Mo-Kα) = 0.257 mm^{-1}. Final residuals (242 parameters) $R1$ = 0.0818 for 3444 reflections with $I > 2\sigma(I)$, and $R1$ = 0.1570, $wR2$ = 0.2413, GooF = 1.030 for all 6901 data. CCDC 261862. **1**·(n-Bu_4N·Cl): $C_{35}H_{47}BrF_5N_2O_{2.5}S$, M = 742.72, triclinic, P-1, a = 10.863(4), b = 16.807(6), c = 21.000(7) Å, α = 74.118(6)°, β = 83.011(6)°, γ = 89.974(6)°, V = 3658(2) Å^3, Z = 4, μ(Mo-Kα) = 1.240 mm^{-1}. Final residuals (498 parameters) $R1$ = 0.0916 for 4148 reflections with $I > 2\sigma(I)$, and $R1$ = 0.1400, $wR2$ = 0.2477, GooF = 1.013 for all 6598 data. CCDC 286064. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511570a

1 P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486.
2 A. P. Bisson, V. M. Lynch, M.-K. C. Monahan and E. V. Anslyn, *Angew. Chem., Int. Ed.*, 1997, **36**, 2340.
3 J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17.
4 A. Bianchi, K. Bowman-James and E. Garcia-Espana, Editors, *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, 1997.
5 D. Quinonero, C. Garau, C. Rotger, A. Frontera, P. Ballester, A. Costa and P. M. Deya, *Angew. Chem., Int. Ed.*, 2002, **41**, 3389.
6 A. Frontera, F. Saczewski, M. Gdaniec, E. Dziemidowicz-Borys, A. Kurland, P. M. Deya, D. Quinonero and C. Garau, *Chem. Eur. J.*, 2005, **11**, 6560.
7 M. Mascal, A. Armstrong and M. D. Bartberger, *J. Am. Chem. Soc.*, 2002, **124**, 6274.
8 D. Kim, P. Tarakeshwar and K. S. Kim, *J. Phys. Chem. A*, 2004, **108**, 1250.
9 C. Garau, A. Frontera, D. Quinonero, P. Ballester, A. Costa and P. M. Deya, *J. Phys. Chem. A*, 2004, **108**, 9423.
10 P. de Hoog, P. Gamez, W. L. Driessen and J. Reedijk, *Tetrahedron Lett.*, 2002, **43**, 6783.
11 P. de Hoog, P. Gamez, I. Mutikainen, U. Turpeinen and J. Reedijk, *Angew. Chem., Int. Ed.*, 2004, **43**, 5815.
12 S. Demeshko, S. Dechert and F. Meyer, *J. Am. Chem. Soc.*, 2004, **126**, 4508.
13 Y. S. Rosokha, S. V. Lindeman, S. V. Rosokha and J. K. Kochi, *Angew. Chem., Int. Ed.*, 2004, **43**, 4650.
14 J. Pang, Y. Tao, S. Freiberg, X.-P. Yang, M. D'Iorio and S. Wang, *J. Mater. Chem.*, 2002, **12**, 206.
15 C. Garau, A. Frontera, D. Quinonero, P. Ballester, A. Costa and P. M. Deya, *Chem. Phys. Chem.*, 2003, **4**, 1344.
16 J. C. Ma and D. A. Dougherty, *Chem. Rev.*, 1997, **97**, 1303.
17 A hydrogen bonding interaction is included in our first receptor design to enhance the association of the receptor for anions. ^{1}H NMR and UV-Vis spectroscopic studies of simple electron deficient aromatics such as hexafluorobenzene, 1,3,5-trifluorobenzene, 1,3,5-tribromobenzene and 1,3,5-trichlorobenzene showed no measurable binding with the halides. This suggested that a single anion–π interaction using a halogenated aromatic would not be strong enough to drive binding in solution.
18 T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano and H. Yamanaka, *Chem. Pharm. Bull.*, 1988, **36**, 1305.
19 N. Shimizu, T. Kitamura, K. Watanabe, T. Yamaguchi, H. Shigyo and T. Ohta, *Tetrahedron Lett.*, 1993, **34**, 3421.
20 M. G. Banwell, B. D. Kelly, O. J. Kokas and D. W. Lupton, *Org. Lett.*, 2003, **5**, 2497.
21 The X-ray crystal structure of **1** is in agreement with recent theoretical studies regarding the attractive interaction between the lone pair of a heteroatom and an electron-deficient aromatic ring.
22 I. Alkorta, I. Rozas and J. Elguero, *J. Org. Chem.*, 1997, **62**, 4687.
23 CAChe, version 5.0, Fujitsu America, Beaverton, USA, 2002.
24 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.
25 The dimerization constants for receptors **1** and **2** were measured by ^{1}H NMR titrations (see method described in: A. P. Bisson, C. A. Hunter, J. C. Morales and K. Young, *Chem. Eur. J.*, 1998, **4**, 845). Receptor **1** exhibits weak dimerization ($K_a \sim 2$ M^{-1}) in $CDCl_3$, whereas receptor **2** shows no measurable dimerization. Attempts to correct anion binding constants for the dimerization of receptor **1** using either WinEQNMR or the method reported by Hunter *et al.* failed to produce acceptable fits to the data with reasonable precision. Presumably, the weak dimerization in receptor **1** plays a negligible role in the binding of anions (see ESI).
26 O. B. Berryman and D. W. Johnson, *unpublished results*, 2005.
27 D. Quinonero, C. Garau, A. Frontera, P. Ballester, A. Costa and P. M. Deya, *Chem. Phys. Lett.*, 2002, **359**, 486.
28 M. H. Abraham, P. L. Grellier, D. V. Prior, P. P. Duce, J. J. Morris and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1989, 699.
29 Reference 28 presents a scale of hydrogen bond acidities based on log K values. While the sulfonamide functionality is not specifically addressed, data for other acidic functionalities are presented with the equation log $K = L_b\, pK_a + D_b$ relating pK_a and hydrogen bonding K_a, where L_b and D_b are constants specific for a given family of molecules. Estimates using the upper limit of these constants result in predicted K_a values for receptor **2** sufficient to be detected by ^{1}H NMR spectroscopy.

