A synthetic receptor for hydrogen-bonding to fluorines of trifluoroborates†

Per Restorp, Orion B. Berryman, Aaron C. Sather, Dariush Ajami and Julius Rebek, Jr.*

Received (in Austin, TX, USA) 15th July 2009, Accepted 19th August 2009
First published as an Advance Article on the web 4th September 2009
DOI: 10.1039/b914171e

A tripodal receptor featuring three inwardly-directed hydrogen-bond donors binds covalently bound fluorine atoms of trifluoroborates through hydrogen-bonding.

The introduction of a fluorine atom in an organic molecule can dramatically change its reactivity and properties.[1] In medicinal chemistry the incorporation of fluorine in drug lead compounds is especially popular since the organofluorine can affect nearly all relevant molecular properties for the drug discovery process including adsorption, distribution, metabolic stability and sometimes even the binding affinity for its target.[2] As a consequence, understanding the nature and strength of the non-covalent interactions of covalently bound fluorine atoms is desirable for drug development.[3]

The fluorine atom is the most electronegative element and roughly isosteric to oxygen,[4] and this raises the question whether covalent fluorine atoms can mimic the hydrogen-bonding acceptor ability of oxygen.[5] While inorganic fluorides are notoriously powerful proton-acceptors,[6] a survey of the Cambridge Structural Database (CSD) as well as the Protein Data Bank (PDB) by Dunitz and Taylor revealed very few examples of short-range contacts between covalently bound fluorines and typical proton donors.[5a] To examine whether or not such fluorines can act as hydrogen-bond acceptors in solution we took a supramolecular approach[7] using the synthetic receptor molecule **1** (Scheme 1) and here we report its binding to covalently bound trifluoroborates.

The 1,3,5-trisubstituted 2,4,6-triethylbenzene scaffold **2** is an appealing building block for supramolecular systems.[8] To avoid unfavorable steric clashes alternating substituents are oriented on one face of the phenyl ring and different functional groups can be incorporated that complement the surface and geometry of the targeted molecule. Receptor **1** can readily adopt a conformation where the three acylhydrazide NH's are projected into the cavity above the plane of the phenyl ring and poised to hydrogen-bond to a guest. The spatial orientation of the NH's in **1** presents hydrogen-bonding interactions to acceptors of appropriate size and C_{3V} symmetry. The electron-rich pyrroles on the rim of **1** provide the possibility for additional stabilizing interactions with the bound guest, *e.g.*, through CH–π or π–π interactions as well as shielding the guest from approaching solvent molecules.

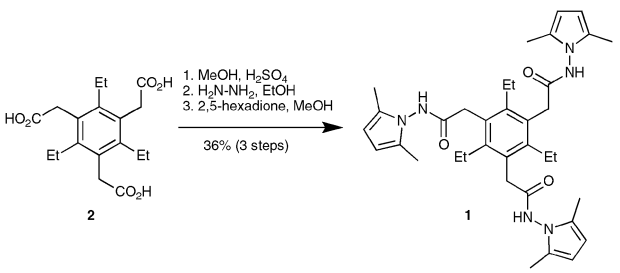
The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Rd, La Jolla, CA 92037, USA. E-mail: jrebek@scripps.edu

† Electronic supplementary information (ESI) available: Synthesis of **1**, spectral data characterizations, details of computational studies and NMR titration data for the binding constant determinations. See DOI: 10.1039/b914171e

NMR-titration experiments[9] of **1** with trifluorotoluene (**3**) in $CDCl_3$: CD_3CN (97 : 3) showed no downfield shift of the NH signals (Table 1, entry 1); the covalently bound fluorines in $PhCF_3$ (**3**) do not hydrogen-bond to **1** under these conditions. This result provides additional support for the observation that covalently bound organic fluorines rarely engage in hydrogen-bonding.[5] Fluorines covalently bound to boron should be stronger acceptors than those involving C–F bonds.[5c] However, a survey of the literature showed few examples of short-range contacts between B–F fluorines and typical proton donors.[10]

The tetrafluoroborate anion is a commonly used weakly coordinating counterion and hydrogen-bonding interactions between such fluorines and proton donors in the solid state[11] and by the fastest of IR methods in aqueous media[12] have been reported. To determine whether our synthetic receptor **1** can bind fluoroborates through hydrogen-bonding we performed NMR-titration experiments of **1** with tetra-*n*-butylammonium tetrafluoroborate (**4**). However, these experiments show no detectable binding of the tetrafluoroborate anion with **1** (entry 2). In contrast, titration experiments with the tetra-*n*-butylammonium phenylfluoroborate (**5**) resulted in a downfield shift of the NH signals in **1** of about 0.5 ppm (Fig. 1).[13] The association constant for **5** was determined to be 75 M^{-1} by taking the average value of three NMR titration experiments (entry 3).[9]

It should be noted that the association constant between **1** and fluoroborate **5** is measured in competition with the electrostatic interactions of the ion-pair of **5** in solution and the binding event involves breaking of this ion-pair. We suggest that the enhanced binding affinity of phenylfluoroborate **5** over tetrafluoroborate **4** is, in part, due to the dipole moment of **5** not present in the symmetrically substituted **4** and results in stronger hydrogen-bonding interactions with **1**. To probe the steric and electron effects of binding with receptor **1** we investigated a series of fluoroborates. The similar binding constants of phenylfluoroborate **5** and methylfluoroborate **6** suggest that secondary stabilizing interactions



Scheme 1 Synthesis of **1**.

Table 1 Average K_a (M^{-1}) for receptor **1** with guests **3–6**[ab]

Entry	Guest	K_a/M^{-1}
1	$PhCF_3$ (**3**)	—
2	$NBu_4^+BF_4^-$ (**4**)	—
3	$NBu_4^+PhBF_3^-$(**5**)	75
4	$NBu_4^+MeBF_3^-$ (**6**)	70
5	NBu_4^+4-NO_2-$PhBF_3^-$ (**7**)	25
6	NBu_4^+4-Me-$PhBF_3^-$ (**8**)	80

[a] Average K_a reported for 2–3 titration experiments. [b] All titrations were performed in $CDCl_3$: CD_3CN (97 : 3) with receptor concentrations of ~0.5 mM; experimental errors are estimated at ±10%.

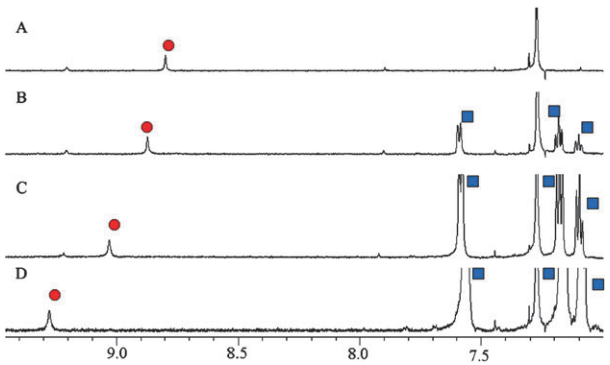


Fig. 1 ^1H NMR spectra from titrations of receptor **1** (0.45 mM) with $NBu_4^+PhBF_3^-$ (**5**) highlighting the NH proton chemical shift changes in receptor **1** (red circle) in the presence of 0 (A), 4 (B), 15 (C), 56 (D) equiv. of **5**, respectively. The aromatic signals from fluoroborate **5** are marked with blue squares.

between the electron-rich pyrroles in the rim of **1** (CH–π or π–π interactions) and the bound guest have negligible impact on the binding constant (compare entry 3 and 4). The electronic effects of the binding to **1** were examined with arylfluoroborates **7** and **8** (entries 5 and 6). The *p*-nitrophenylfluoroborate (**7**) showed significantly weaker binding to **1** (entry 5) whereas *p*-methyl-phenylfluoroborate (**8**) exhibited stronger binding (entry 6). This observation supports the notion that electron-poor arylfluoroborates drain the fluoroborate fluorines of electron-density making them less potent hydrogen-bond acceptors whereas the opposite holds true for electron-rich arylfluoroborates. Additional support of the binding mode for these fluoroborates to receptor **1** was provided by DFT calculations.[14] The 1 : 1 complex between fluoroborate **5** and receptor **1** obtained in this way is shown in Fig. 2.

The minimized representation shows that **1** adopts an averaged C_{3V} symmetry (C_3 symmetry shown in Fig. 2) and binds to **5** through three bifurcated hydrogen-bonds between the fluorines and the acylhydrazide NH's in **1** (N···F = 2.8 Å). Additionally, the distances between the CH's of the phenyl ring in **5** and the electron-rich pyrrole subunits in **1** are approximately 3.2 Å, which suggests that some CH–π interactions are involved in the binding.

In conclusion, we have fashioned a neutral receptor molecule based on the 1,3,5-trisubstituted 2,4,6-triethylbenzene scaffold that offers three convergent NH's. These acyl hydrazides feature perpendicular arrangement between the amide and pyrrole planes that can interact with a bound guest

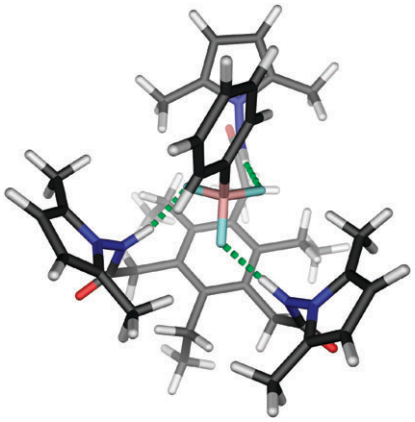


Fig. 2 Minimized representation (B3LYP/6-311 + G(2d,p)//B3LYP/6-31G(d)) of fluoroborate **5** bound in receptor **1**. Carbon colored gray, nitrogen blue, oxygen red, fluorine light blue, boron pink and hydrogen white.

through convergent[15] hydrogen-bond donors in a shallow cavitand.[16] This study confirms that organofluorines and tetrafluoroborates rarely engage in hydrogen-bonding.[5] Organic trifluoroborates showed binding to the receptor. To the best of our knowledge, this represents the first example of a supramolecular receptor for trifluoroborates and illustrates that covalenty bound fluorines can function as hydrogen-bond acceptors.

We are grateful to the Skaggs Institute and the National Institute of Health (GM 50174) for support, and we thank Prof. G. Molander for samples of trifluoroborates. P. R. is a Swedish Knut and Alice Wallenberg Post-doctoral Fellow. O.B.B and A.C.S are Skaggs Post-doctoral and Skaggs Pre-doctoral Fellows, respectively. We are indebted to Dr Laura Pasternak for invaluable NMR support. The reviewers are thanked for insightful comments.

Notes and references

1 (*a*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*b*) J. C. Biffinger, H. W. Kim and S. G. DiMagno, *ChemBioChem*, 2004, **5**, 622.
2 (*a*) K. Mueller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) H. C. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Mueller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637; (*c*) B.-S. Park, W. Widgerb and H. Kohn, *Bioorg. Med. Chem.*, 2006, **13**, 1; (*d*) J. A. Olsen, D. W. Banner, D. W. Seiler, U. Obst-Sander, A. D'Arcy, M. Stihle, K. Mueller and K. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 2507.
3 (*a*) F. Hof, D. M. Scofield, W. B. Schweizer and F. Diederich, *Angew. Chem., Int. Ed.*, 2004, **43**, 5056; (*b*) F. R. Fischer, W. B. Schweizer and F. Diederich, *Angew. Chem., Int. Ed.*, 2007, **46**, 8270.
4 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
5 (*a*) J. D. Dunitz and R. Taylor, *Chem.–Eur. J.*, 1997, **3**, 89; (*b*) J. A. K. Howard, V. J. Hoy, D. O'Hagan and G. T. Smith, *Tetrahedron*, 1996, **52**, 12613; (*c*) J. D. Dunitz, *ChemBioChem*, 2004, **5**, 614.
6 The hydrogen-bonding energy of the bifluoride anion $[HF_2]^-$ is approximately 37 kcal mol^{-1}. S. A. Harrell and D. H. McDaniel, *J. Am. Chem. Soc.*, 1964, **86**, 4497.
7 For extensive reviews on anion binding in synthetic receptors, see: (*a*) V. Amendola, D. Esteban-Gomez, L. Fabbrizzi and M. Licchelli, *Acc. Chem. Res.*, 2006, **39**, 343; (*b*) K. Bowman-James, *Acc. Chem. Res.*, 2005, **38**, 671; (*c*) F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr, *Angew. Chem., Int. Ed.*, 2002, **41**, 1488; (*d*) K. S. Jeong, A. V. Muehldorf and J. Rebek, Jr, Molecular Recognition. Asymmetric Complexation of Diketopiperazines, *J. Am. Chem. Soc.*, 1990, **112**, 6144–6145; (*e*) J. L. Sessler,

P. A. Gale and W.-S. Cho, *Anion Coordination Chemistry*, Royal Society of Chemistry, Cambridge, 2006; (*f*) J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17.
8 (*a*) E. V. Anslyn and G. Hennrich, *Chem.–Eur. J.*, 2002, **8**, 2219; (*b*) A. H. McKie, S. Friedland and F. Hof, *Org. Lett.*, 2008, **10**, 4653; (*c*) O. B. Berryman, A. C. Sather, B. P. Hay, J. S. Meisner and D. W. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 10895.
9 K. Hirose, *J. Inclusion Phenom. Macrocycl. Chem.*, 2001, **39**, 193.
10 For an example of intermolecular hydrogen-bonding involving B–F···H–C bonds in the solid state, see: C. M. Clarke, M. K. Das, E. Henecker, J. F. Mariategui, K. Niedenzu, P. M. Niedenzu, H. Noth and K. R. Warner, *Inorg. Chem.*, 1987, **26**, 2310.
11 (*a*) W. L. Driessen, R. A. G. De Graaf and W. G. R. Wiesmeijer, *Acta Crystallogr.,Sect. C*, 1987, **43**, 2319; (*b*) T. W. Hudnall, J. F. Bondi and F. P. Gabbai, *Main Group Chem.*, 2006, **5**, 319.
12 D. E. Moilanen, D. Wong, D. E. Rosenfeld, E. E. Fenn and M. D. Fayer, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**(2), 375.
13 Receptor **1** had low solubility in $CDCl_3$. When receptor **1** was titrated with **5** in $CDCl_3$ a lower concentration of guest was required to reach saturation conditions, suggesting a larger K_a in this solvent. However, the low solubility and complex speciation present in $CDCl_3$ prohibited accurate K_a determination. We also performed titration experiments on the ^{19}F resonance of **5**. The ^{19}F signal shifts slightly upon addition of receptor **1** but the broad character of this peak due to coupling of ^{19}F to ^{10}B and ^{11}B prevented accurate analysis.
14 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin and J. C. Burant, *et al.*, *Gaussian 03*, Gaussian, Inc., Pittsburgh, PA, 2003, for complete list of authors see ESI†.
15 B. Verdejo, G. Gil-Ramrez and P. Ballester, *J. Am. Chem. Soc.*, 2009, **131**, 3178.
16 F. C. Tucci, D. M. Rudkevich and J. Rebek Jr., *J. Org. Chem.*, 1999, **64**, 4555.

