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Toward Molecular Recognition: Three-Point Halogen Bonding in the Solid State and in Solution

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Supporting Information

ABSTRACT: A well-defined three-point interaction based solely on halogen bonding is presented. X-ray structural analyses of tridentate halogen bond donors (halogen-based Lewis acids) with a carefully chosen triamine illustrate the ideal geometric fit of the Lewis acidic axes of the former with the Lewis basic centers of the latter. Titration experiments reveal that the corresponding binding constant is about 3 orders of magnitude higher than that with a comparable monodentate amine. Other, less perfectly fitting multidentate amines also bind markedly weaker. Multipoint interactions like the one presented herein are the basis of molecular recognition, and we expect this principle to further establish halogen bonding as a reliable tool for solution-phase applications.

Halogen bonding (XB) is the noncovalent interaction between an electrophilic halogen substituent and a Lewis base.[1] Even though its strength can be comparable to hydrogen bonding,[2] this interaction has received little attention[3] until the late 1990s.[4] Applications so far have mainly focused on the solid state and crystal engineering,[5] e.g. toward the development of conductive materials[6] and liquid crystals.[7] Lately, investigations of halogen bonding in solution have also started to appear,[8] concerning mostly fundamental studies,[9] anion receptors,[10] anion transport,[11] and catalysis.[12]

Most reports on halogen bonding so far feature a 1:1 interaction between the halogen bond donor (i.e., the halogen-based Lewis acid) and the Lewis base (Figure 1, left). In some cases, especially for receptors[10] and catalysts,[12] 2:1 or 3:1 interactions are the basis for the desired application (Figure 1, middle). This often involves coordination of spherical Lewis bases such as halides to multidentate XB donors. While these adducts are stronger than monodentate ones and may also feature some selectivity, the molecular recognition of Lewis bases by XB donors could be improved by *multipoint* interactions, i.e. the binding of multiple XB donating sites on one molecule to multiple electron-rich sites on the Lewis base (Figure 1, right). To the best of our knowledge, definite examples for this kind of interaction motif in the form of solid state structures are restricted to very few cases: Ouahab et al. reported two-point S--I interactions for iodinated tetrathiofulvalene derivatives,[13] whereas Stoddart et al. very recently described a two-point halogen bonding interaction involving crossed X--O (X = Cl, Br, I) binding patterns.[14] In addition, Aakeroy et al. reported solid-state studies on the assembly of an XB-based molecular capsule.[15]

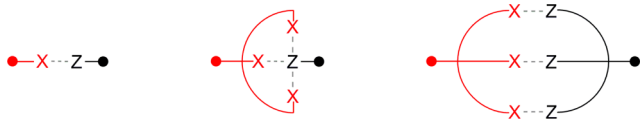

Figure 1. Schematic representation of different halogen bonding motifs: left, 1:1 binding; middle: 3:1 binding; right: 3:3 multipoint binding (X = halogen, Z = Lewis basic atom).

It is likely that multipoint interactions also occur in solution between multidentate XB donors and corresponding Lewis bases.[10b,c,g,i,16] It is difficult, however, to characterize the binding pattern unambiguously in solution, and no cases of solution-phase studies on *multipoint* halogen bonding accompanied by X-ray structural analyses have been published.

Herein we present the first example of a distinct three-point (3:3) interaction based solely on halogen bonding. This binding motif ensures strongly bound and very rigid adducts and thus constitutes a first step toward XB-based molecular recognition.[17]

Recently, we reported organocatalyst **1** (Scheme 1),[12c] in which three XB donating moieties (polyfluoropolyiodoarenes) are orientated perpendicular to the central benzene core, forming a tridentate halogen-based Lewis acidic motif on the two symmetrical sides of the molecule. Reasoning that XB donor **1** might be suitable for the formation of a three-point halogen bond, we focused on the identification of a fitting multidentate Lewis base.

Achieving multipoint interactions is much more challenging for halogen bonding than it is, for instance, for hydrogen bonding, as the former features a much higher directionality (the R-X--LB angle needs to be close to 180° for a reasonably strong interaction to occur; X = halogen, LB = Lewis base).[1] In addition, for a given set of atoms involved in strong halogen bonding, the interacting distances are also relatively predetermined to be around 80−90% of the sum of the van der Waals radii.[1] Thus, the geometric orientation of the Lewis basic centers is quite strictly defined by the structure of the XB donor.

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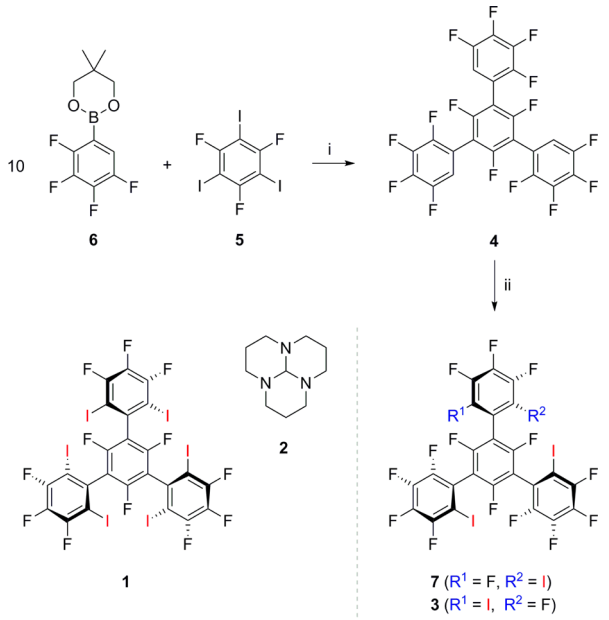
Scheme 1. Two-Sided Tridentate Halogen Bond Donor 1, Triamine 2, and Synthesis of Tridentate Halogen Bond Donor 3[a]



[a](i) $[Pd_2(dba)_3]$ (3 mol %), SPhos (18 mol %), Na_2CO_3, toluene/THF/H_2O, 95 °C, 24 h, yield (relative to **5**): 79%; (ii) *N*-iodosuccinimide (NIS; 20 equiv), HOTf, 0 °C, yields 39% (**7**), 21% (**3**); dba = dibenzylideneacetone, HOTf = trifluoromethanesulfonic acid, SPhos = 2-Dicyclohexylphosphino-2′,6′-dimethoxy-biphenyl.

Extensive computational screening using DFT methods resulted in the identification of orthoamide **2**[18] as an ideal binding partner. Indeed, when XB donor **1** and orthoamide **2** were mixed in solution, single crystals were rapidly formed, and the corresponding X-ray structural analysis confirmed the aspired three-point halogen bond (Figure 2).

Each Lewis acidic side of XB donor **1** is complexed by one molecule of orthoamide **2**, and except for some minor deviations

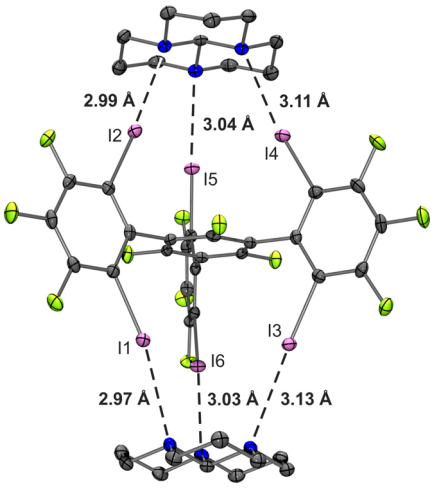


Figure 2. X-ray structural analysis of the complex of halogen bond donor **1** with orthoamide **2** (hydrogen atoms omitted for clarity; ellipsoids at 50% probability).[19] Selected bond distances [Å] and angles [deg]: C–I1 = 2.105, C–I2 = 2.104, C–I3 = 2.103, C–I4 = 2.102, C–I5 = 2.106, C–I1–N = 172, C–I2–N = 171, C–I3–N = 174, C–I4–N = 175, C–I5–N = 171, C–I6–N = 174.

the binding can be described as a symmetrical 3:3 halogen bond. The corresponding N–I distances vary from 2.97 to 3.13 Å (mean value: 3.04 Å) and are thus markedly shorter than the sum of the van der Waals radii of the involved atoms (3.53 Å).[20] In agreement with halogen bonding theory, the C–I–N angles are all close to 180°, ranging from 171° to 175° (mean value: 173°).

In order to analyze the binding situation in solution, we decided to synthesize a topologically simpler analogue of **1**, namely XB donor **3**, which features only one Lewis acidic side per molecule. This eliminates the possibility that two molecules of orthoamide **2** might bind to one XB donor **1** and considerably simplifies the analysis of NMR titration experiments in solution.

Initially, we attempted to prepare noniodinated precursor **4** by the procedure used in the synthesis of **1**,[12c] namely the Suzuki-type cross-coupling of 1,3,5-trifluoro-2,4,6-triiodobenzene (**5**) with the corresponding boronic acid, catalyzed by $[Pd_2(dba)_3]$ and XPhos.[21] No product was obtained, though, indicating the strong influence of one further fluorine substituent on the reactivity of the boronic acid. A broad screening of reaction conditions revealed, however, that the intended cross-coupling can be realized by the reaction of **5** with 10 equiv of neopentyl ester **6** in the presence of a catalyst formed from $[Pd_2(dba)_3]$ and SPhos (Scheme 1).

Compound **4**, which was obtained in 79% yield, showed one set of NMR signals, indicating that rotation around the aryl–aryl bonds is unhindered at rt. Subsequent polyiodination of intermediate **4** was then performed by its treatment with *N*-iodosuccinimide in triflic acid.[22] In contrast to precursor **4**, two isomers were obtained as products in 60% overall yield. Separation by column chromatography with pentane yielded 21% of the all-*syn* isomer **3** and 39% of isomer **7**.

Co-crystallizaton of XB donor **3** with orthoamide **2** resulted in the expected symmetrical multipoint adduct shown in Figure 3.

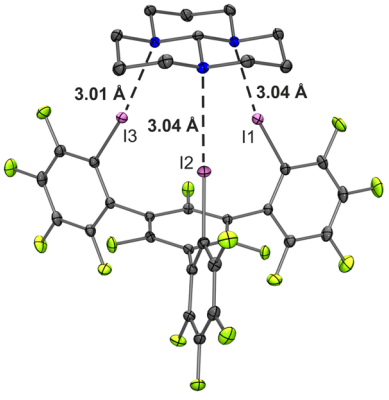


Figure 3. X-ray structural analysis of the complex of halogen bond donor **3** with orthoamide **2** (hydrogen atoms omitted for clarity; ellipsoids at 50% probability).[23] Selected bond distances [Å] and angles [deg]: C–I1 = 2.104, C–I2 = 2.103, C–I3 = 2.102, C–I1–N = 168, C–I2–N = 172, C–I3–N = 172.

Again, the interacting distances are almost identical, with two N–I lengths of 3.04 Å and one of 3.01 Å (mean value: 3.03 Å). The C–I–N angles vary from 168° to 172°, and no clear trend is apparent between minor bond variations and angle variations, further indicating that the observed deviations from ideal symmetry are indeed negligible.

As one of our goals was to determine the effect of the multipoint binding motif on the association strength in solution, we first determined the solvent dependency of the adduct

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formation. To this end, XB donor **3** was titrated with orthoamide **2** in a range of solvents (Table 1). The shift of the ^{19}F NMR signal of the fluorine atoms *ortho* to the iodine substituents was used to follow adduct formation.[24]

Table 1. Binding Constants of XB Donor 3 with Orthoamide 2 in Various Solvents[a]

solvent	CH_2Cl_2	$CHCl_3$	THF	CH_3CN
K [M^{-1}]	30	33	53	73
solvent	acetone	C_6H_6	toluene	cyclohexane
K [M^{-1}]	1.1×10^2	5.6×10^2	6.3×10^2	5.8×10^3

[a]Binding constants were determined by ^{19}F NMR titration in dry deuterated solvents and fitting to a 1:1 stoichiometry. THF = tetrahydrofuran.[25]

In agreement with previous studies,[8,9] nonpolar solvents such as benzene, toluene, and cyclohexane provided the highest binding constants.[26] The association constant in cyclohexane (5.8×10^3 M^{-1}) is 3 orders of magnitude higher than that of the analogous single-point complex of pentafluoroiodobenzene with triethylamine in the same solvent ($K = 1$ M^{-1}).[9c] Tetrahydrofuran, acetonitrile, and acetone as solvents were somewhat less suitable, while the weakest binding was observed in the chlorinated solvents dichloromethane and chloroform (Table 1). No binding constants could be obtained for dimethyl sulfoxide and methanol, as rapid precipitation ensued.

Based on these findings, we finally titrated several other amines with XB donor **3** (Figure 4). Due to the low solubility of some of the amines in cyclohexane, toluene, the second-best solvent, was chosen for these investigations.

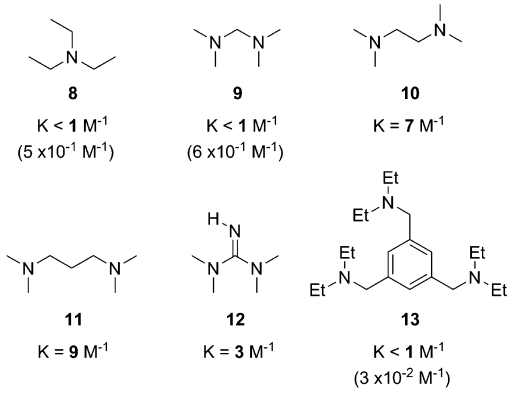

Figure 4. Binding constants for the complex of halogen-bond donor **3** with various amines in toluene as determined by ^{19}F NMR titrations (1:1 complex stoichiometry).

The effect of the three-point binding on the interaction strength was studied by the comparison of **2** with an electronically similar but monodentate analogue, triethylamine (**8**). The association constant of the latter with XB donor **3** in toluene was found to be 3 orders of magnitude lower than that of triamine **2**.

Investigating how other *multidentate* nitrogen-based Lewis bases bind to XB donor **3** allowed the influence of the number of amine centers and of their relative orientation on the binding constants to be judged. Presumably, the ideal fit of triamine **2** for the Lewis acidic axes of XB donor **3** would enhance the corresponding adduct formation compared to that of other, less perfectly fitting (or lesser dentate) amines. In these titrations, bidentate amines **9**, **10**, and **11** yielded binding constants of <1, 7, and 9 M^{-1}. Thus, as expected, the strength of the XB adduct was markedly lower for the bidentate variants.

As representative tridentate nitrogen-based Lewis bases, we chose guanidine **12** and triamine **13**. Guanidine **12** features N−N distances that are very roughly comparable to compound **2**, but its electronic structure is obviously quite different. Accordingly, its binding constant is still about 2 orders of magnitude lower than that of **2**. The amine substituents of triamine **13** are electronically roughly comparable to those of compound **2**, but are too far apart to engage in a three-point interaction with XB donor **3**. The corresponding binding constant seems to be even lower than that of triethylamine **8**, possibly because of steric hindrance by the central benzene core.

In summary, the first example of a well-defined three-point halogen bonding[27] interaction was presented. The solid state structure of the adduct of neutral polyfluorinated XB donor **3** with its Lewis basic counterpart **2** demonstrates the ideal geometric fit of the Lewis acidic axes of **3** with the nitrogen donors of triamine **2**. Titration experiments in solution revealed that the binding of XB donor **3** to **2** features a binding constant that is about 3 orders of magnitude higher than that of a comparable monodentate amine (**8**). Other bi- and tridentate amines also bind comparably weakly, illustrating the importance of the near-perfect receptor/substrate match in the present case.

Multipoint interactions are important for molecular recognition, for the transfer of chirality, and to achieve structural rigidity in materials. Herein, we could show that well-defined multipoint interactions can be achieved solely based on halogen bonding. In the future, we expect that more sophisticated variations of this principle will help to further establish halogen bonding as a reliable tool for solution-phase applications.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization data, and X-ray structural analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) To obtain a rough error estimation, we have performed the titration in cyclohexane several times, yielding association constants of 5.8×10^3, 5.4×10^3, and 6.2×10^3 M^{-1}. Overall we consider only a difference in K values exceeding a factor of 2−3[9g] to be significant (see also ref 26).
(26) The binding of **3** to **2** in cyclohexane was also investigated by isothermal titration calorimetry, yielding $K = 7.5 \times 10^3$ M^{-1}. The overall binding free energy of $\Delta G = -22$ kJ/mol consists of $\Delta H = -55$ kJ/mol and $-T\Delta S = 33$ kJ/mol.
(27) It was not possible to obtain a binding constant of *hydrogen* bond donor **4** with orthoamide **2** in cyclohexane due to the low solubility of **2**, but preliminary data indicate weak binding ($K \ll 10$ M^{-1}). No NMR shifts were observed in similar titration experiments in toluene.