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COMMUNICATION

Halogen bonding two-point recognition with terphenyl derivatives

J. Stoesser,[a] G. Rojas,[b] D. Bulfield,[a] P. I. Hidalgo,[b] J. Pasán,[c] C. Ruiz-Pérez,[c] C. A. Jiménez,*[b] and S. M. Huber*[a]

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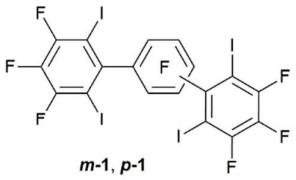
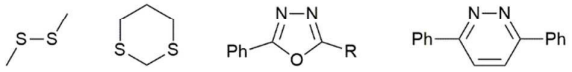
Two-point recognition involving neutral terphenyl-based halogen bond donors (halogen-based Lewis acids) was investigated. Oxadiazole and pyridazole derivatives were identified by DFT as suitable binding partners, even though gas-phase binding was weak. X-ray studies provided convincing evidence of two-point binding in the solid state, while solution data hinted at weak assocation.

In the last two decades or so, halogen bonding has evolved from somewhat of a niche curiosity to a well-established supramolecular tool, especially in crystal engineering. In analogy to hydrogen bonding, the term describes the interaction between an electrophilic halogen substituent (typically bromo or iodo) and a Lewis base.[1] Various applications of halogen bonding in the solid state have been reported,[2] and a high level of sophistication has been reached by now. However, the overwhelming majority of these adducts are based on single-point interactions, i.e. the attraction between one electrophilic halogen site with one Lewis basic site of another molecule. There are also multiple studies on the use of multidentate halogen bond donors, as in anion binding[3] or organocatalysis.[4] Still, in almost all cases[5] the corresponding Lewis base features only one binding site. The most prominent example for the latter are complexes involving halides.[1a, 3c, 6] Thus, overall, there are still only few examples of halogen-bonding-based multipoint interactions, even though they provide stronger and more ordered binding and constitute a prerequisite for recognition.

Two alternative approaches may be identified to realize multipoint halogen bonding, the first being the dimer formation of molecules featuring complementary binding sites. Examples of this strategy include a report by Stoddard et al. on molecules featuring a maleimide as well as a halogen functionality,[7] a study by Bowling et al. on a mixed polyfluoroiodoarene/pyridine system and a paper by Takeda on compounds with carbonyl and bromine groups.[8] In addition, several studies were published by the Philp group on systems involving iodotriazole halogen bonding units and pyridine,[9] phenolate[10] as well as phosphine oxide[11] halogen bond acceptors. An alternative approach is to use an array of halogen bonding moieties on one molecule and an array of Lewis basic sites on a second one.[12] Prominent examples of this are investigations on halogen-bonding-based noncovalent capsules by Aakeroy[13] and Diederich.[14] Several studies on polymers featuring multiple halogen bonding interactions were also published by Taylor et al.[15]



m-1, *p*-1



2 **3** **4a** (R=Ph) **4b** (R=Tol) **5**

Figure 1: *Halogen bonding terphenyl derivatives **m-1** and **p-1** as well as potential Lewis basic counterparts **2** to **5**.*

In 2014, our group introduced a three-point halogen bonding complex between a polyfluorinated and -iodinated quaterphenyl and a carefully chosen orthoamide counterpart featuring a binding strength in cyclohexane of about 5 kcal/mol.[16] Previously, this tridentate halogen bond donor had been used in organocatalysis[17] along with two related terphenyl derivatives. The obvious question was thus whether these two bidentate halogen bond donors ***m*-1** and ***p*-1** (Figure 1) could also form two-point halogen bonding complexes.

[a] *Department of Chemistry and Biochemistry, Ruhr-Universität Bochum, Universitätsstraße 150, 44801 Bochum, Germany. E-mail: stefan.m.huber@rub.de.*
[b] *Department of Organic Chemistry, Faculty of Chemical Sciences, Universidad de Concepción, Concepción, 4070371. Chile. Email: cjimenez@udec.cl*
[c] *Laborarotorio de Rayos X y Materiales Moleculares, Depto. de Física, Facultad de Ciencias, Universidad de La Laguna, Avda. Astrofísico Francisco Sánchez, 38200, La Laguna, Spain.*

Electronic Supplementary Information (ESI) available: experimental details and characterization data, titration data, X-ray structural analyses, details of computations. See DOI: 10.1039/x0xx00000x

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Herein, we present computational, crystallographic, and solution-phase titration data on this issue.

In comparison to hydrogen bonding, the location of the Lewis basic centers is much more predetermined by the halogen bond donor: next to a typical interaction distance of approximately 85-90% of the sum of the van-der-Waals radii, the interaction is also highly linear.[1] Thus, a careful selection of suitable counterparts to halogen bond donors ***m*-1** and ***p*-1** was necessary. To this end, our focus was on molecules featuring either two Lewis basic sulphur or two nitrogen centers in close proximity. Orientating calculations had identified disulphide **2**, thioacetal **3**, oxadiazole **4a** and pyridazine **5** as promising candidates and so their complexes with ***m*-1** and ***p*-1** were investigated by DFT calculations (M06-2X[18]-D3[19] TZVPP[20]) in more detail.

In all cases, minima featuring two-point halogen bonding motifs were obtained. The geometric parameters for the S-based compounds show relatively high linearity for the disulphide complexes (C-I···S = 169-178°; for further details on all computations see the ESI), whereas notable deviations indicating strain were found for the thioacetal complexes (C-I···S = 154-162°). The I-S interaction distances range from 3.31 to 3.47 Å, corresponding to about 90% of the sum of the van-der-Waals radii[21] and indicating relatively weak binding. In line with this, a rough estimate of the gas-phase binding energies provides endergonic Gibbs free energies ranging from 2.4 to 4.2 kcal/mol (enthalpies of binding are favourable by 7-11 kcal/mol for all complexes reported herein). So overall, relatively weak binding is found for the sulphur-based substrates.

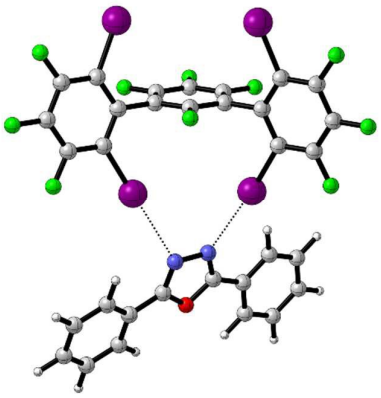

***Figure 2:** Complex between **m-1** and oxadiazole **4a** as obtained by DFT calculations (M06-2X-D3 TZVPP). Halogen bonding distances and angles: I-N = 3.03 and 3.06 Å, C-I···N = 175 and 178°. Graphic generated with CYLview.[22]*

The geometric parameters for the N-based substrates indicate high linearity in all cases (C-I···N = 172-178°), with a slightly more linear arrangement for the oxadiazole complexes. The interaction distances are 3.03-3.08 Å for the latter ones, corresponding to 85% of the sum of the van-der-Waals radii and thus relatively strong binding. In the pyridazole adducts, one shorter halogen bond (C-I···N = 3.04-3.08 A) and one longer one (C-I···N = 3.19-3.24 A) is found. So, while one interaction is as strong as in the oxadiazole complexes, the second one is noticeably weaker (> 90% of sum of van-der-Waals radii).

The thermodynamic estimates confirm a stronger binding for the N-based substrates compared to the S-based ones: except for the complex between ***p*-1** and **4a** (ΔG = 3.7 kcal/mol), all other adducts show Gibbs free energies of binding close to 0 kcal/mol. The strongest interaction is found between ***m*-1** and **4a** with -0.2 kcal/mol. Hence, even though the geometric parameters indicated a weaker binding of pyridazole **5** compared to oxadiazole **4a**, this is not unequivocally confirmed by the binding energies.

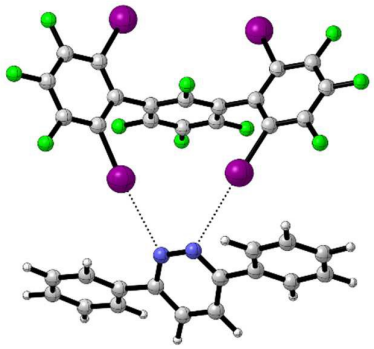

***Figure 3:** Complex between **m-1** and pyridazole **5** as obtained by DFT calculations (M06-2X-D3 TZVPP). Halogen bonding distances and angles: I-N = 3.04 and 3.19 Å, C-I···N = 175 and 172°. Graphic generated with CYLview.[22]*

Overall, the calculations clearly demonstrate a stronger overall binding by the N-based substrates compared to disulphide and thioacetal, so the latter were omitted for the further studies. Since the oxadiazole complexes show two equally strong halogen bonds whereas one interaction is apparently weaker in the pyridazole ones, the former seems to be the better fitting substrate for both ***m*-1** and ***p*-1**. Although the differences in binding energy are small, it also seems that ***m*-1** is binding stronger to both heterocyclic Lewis bases.

With gas-phase binding being comparably weak, we next turned our attention towards solid-state investigations, as these should provide the best option to characterize such adducts. Oxadiazole **4a** was cocrystallized with halogen bond donor ***m*-1**. The compound obtained corresponds to a complex ***m*-1/4a** which crystallizes in the P-1 space group. This adduct showed a 1:1 stoichiometry, but with two crystallographically independent dimers in the asymmetric unit, i.e. *Z'* = 2 (Figure

Table 1. Geometric parameters of the halogen bonds in the complexes ***m*-1/4a** and ***m*-1/4b**.

Complex	X···D	d(N···I)/Å	CIN/°	INC_{ipso}/°[b]
***m*-1/4a**	I1 ··· N1	3.146(5)	175.0(2)	166.9(3)
	I3 ··· N2	2.991(5)	172.5(2)	140.7(2)
	I5 ··· N3	3.143(4)	173.3(1)	168.2(2)
	I7 ··· N4	3.020(5)	178.4(2)	170.0(2)
***m*-1/4b**	I6 ··· N1[a]	3.113(7)	173.8(2)	145.9(3)
	I7 ··· N2[a]	3.050(5)	170.5(2)	167.8(2)

[a] Symmetry code: -x+1, -y+1,-z+1. [b] For oxadiazole rings, C_{ipso} was substituted by the mid-point between C-O bonds.[23]

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S2 in the ESI). The common feature of the dimers is two-point halogen bonding, with a mean donor-acceptor (I···N) separation of 3.075(5) Å (Table 1).

This value illustrates that, in all cases, the halogen-bond distances observed are 10% shorter than the sum of the van-der-Waals radii[21] and are thus in full concordance with the theoretical data. In addition, all C-I···N angles are close to linearity (≥ 170°, Table 1) and so all parameters are in line with halogen bonding theory.[1]

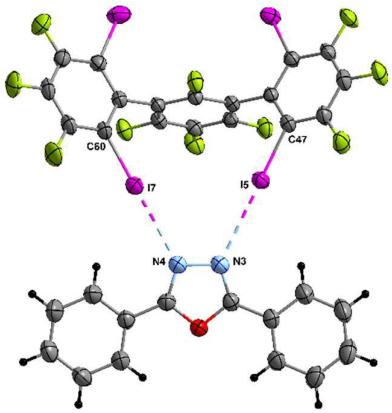

Figure 4: *View of one of the two crystallographically independent two-point halogen bonding dimers in the* ***m-1/4a*** *complex (atoms involved in noncovalent interactions have been numbered).*

The two crystallographically independent ***m-1/4a*** adducts exhibit some structural differences: For the first dimer (Figure S3, see ESI), only one INC_{ipso} angle is approximately linear, with a value slightly above 160º (see Table 1), whereas the second INC_{ipso} angle shows a lower value (140.7(2)º). These differences originate from the relative disposition of **4a** with respect to **m-1** in the two adducts. Both **4a** and **m-1** have little flexibility, with the former being planar and the latter being constrained to have the lateral rings tilted with respect to the central one by ca. 85º (similar to the previously reported values for adducts with **m-1**).[24] While in the second dimer, the C–I bonds lie in the oxadiazole plane (angle between plane and C–I bonds being 0.4 and 3.7º); in the first dimer these values are quite out of plane (6.7 and 43.4º). This is likely due to the packing of these adducts. Firstly, we can observe that the two **m-1** molecules are engaged in an 'embrace' similar to the one observed in tetraphenylphosphonium cations.[25] These pairs of **m-1** molecules form a corrugated layer within the crystallographic *ab* plane (Figure S4). The oxadiazole molecules occupy the interlayer space being stacked along the *b* axis (see Figure S5).

Structural modifications were then made in the oxadiazole moiety, incorporating an electron-withdrawing and an electron-donating group. Nitro and methyl substituents were introduced in one of the side phenyl groups, and it was analyzed how these would affect the formation of two-point halogen bonding (similar to an earlier study with monodentate halogen bond donors).[26] All our efforts to obtain single cocrystals with 2-(4-nitrophenyl)-5-phenyl-1,3,5-oxadiazole were unsuccessful, but the toluyl derivative **4b** allowed to obtain a complex, ***m-1/4b***, which crystallized in the P-1 space group with a 2:1 stochiometry (Figure S6).

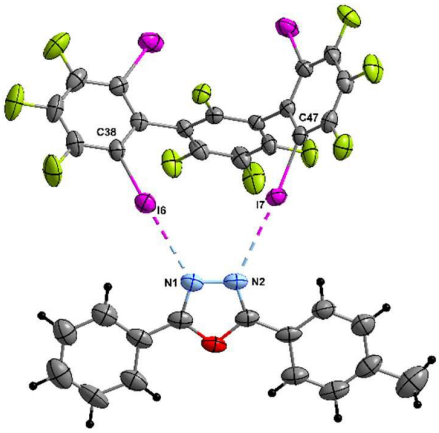

Figure 5: *View of the two-point halogen bonding dimer in complex* ***m-1/4b*** *(atoms involved in noncovalent interactions have been numbered).*

The oxadiazole is connected to one of the ***m*-1** molecules through two-point halogen bonding (Figure 5). The structural parameters of the XB are similar to those of the first dimer in ***m-1/4a***. Remarkably, the two **m-1** molecules of the asymmetric unit in **m-1/4b** are embraced as in the previous compound. The ***m*-1** molecules thus form a layer within the *ab* plane, whereas the oxadiazole molecules occupy the interlayer space.

Even though it is certainly necessary to acquire more experimental data, the toluyl derivative seems to indicate that one substitution on the para-position of the phenyl ring does not have an important influence on the halogen bonding interaction.

As the occurrence of two-point halogen bonding was now also experimentally clearly proven in the solid state, we finally investigated these binding motifs in solution. The tetraiodinated halogen bond donors ***m*-1** and ***p*-1** might seem like the obvious choice for these studies, but they in fact unnecessarily complicate the data analyses since both 1:1 and 2:1 binding is possible with Lewis bases. Hence, following our earlier strategy with the quaterphenyl adduct,[16] we decided to simplify the halogen bond donors by removing the iodine substituents on one of the two sides. DFT calculations on these "one-sided" diiodinated variants (***m*-7** and ***p*-7**, Scheme 1) resulted in nearly identical complexes with the Lewis bases of Figure 1 (see ESI).

The syntheses proceeded according to the previously established protocol[16] by Suzuki-type cross-coupling[26] of *m*- or *p*-tetrafluorodiiodobenzene with (2,3,4,5-tetrafluorophenyl)boronic acid (Scheme 1). The conditions and reagents were based on our earlier procedures but had to be optimized for the current target molecules. Iodination intermediates ***m*-6** and ***p*-6** yielded the desired diiodinated compounds ***m*-7** and ***p*-7** as a mixture of the *syn*- and *anti*-atropisomers, which could be separated by chromatography.

With the *syn*-isomers of ***m*-7** and ***p*-7** in hand, we intended to obtain binding constants to oxadiazole **4a** and pyridazin **5** (as

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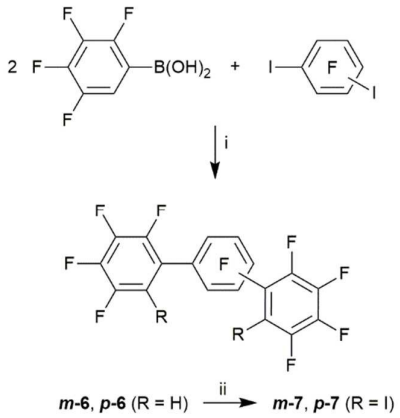
well as pyridine as reference) in solution by ^{19}F-NMR titration experiments. Toluene as solvent represented the best compromise between a non-competing environment and sufficient solubility of all species.



*Scheme 1: Synthesis of one-sided analogues **m-7** and **p-7**; i) Pd_2dba_3 (5 mol%), S-Phos (30 mol%), Boronic ester (6.6 eq), 1,3-diiodotetrafluorobenzene (1 eq), K_2CO_3 (2 eq); ii) HOTf (200 eq), N-iodosuccinimide (4 eq).*

Titration of *syn-**m**-**7*** or *syn-**p**-**7*** with **4a** in this solvent resulted in binding constants of K = 2 M^{-1} and K = 1 M^{-1}, respectively. This rather weak coordination is in line with the DFT computations mentioned above. Various attempts to obtain binding data with **5** failed due to precipitation of the Lewis base or very weak binding. The binding constants of *syn-**m**-**7*** and *syn-**p**-**7*** with pyridine as single-point binding reference compound were only marginally lower (K = 0.9 M^{-1} and 0.8 M^{-1}), which casts severe doubt on whether the oxadiazole is actually bound in a two-point fashion in solution.

Conclusions

This study investigated the use of neutral, terphenyl-based halogen bond donors in two-point recognition. Potential twofold Lewis basic substrates were screened via DFT calculations, and oxadiazole as well as pyridazole core motifs were identified as suitable binding partners, even though gas-phase binding energies indicated weak coordination. Crystallographic studies provided clear evidence of two-point halogen bonding in the solid state between halogen bond donor ***m*-1** and an oxadiazole derivative. Titration experiments in solution, however, indicated that the binding is likely too weak to be exploited in solution-phase applications.

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Conflicts of interest

There are no conflicts to declare.

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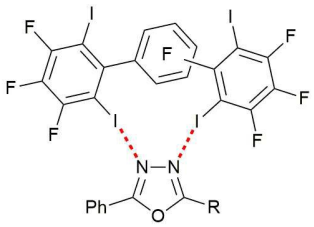

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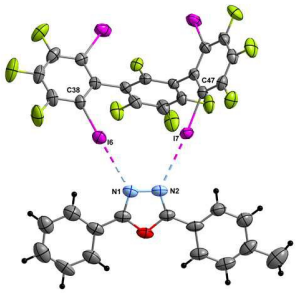

Neutral terphenyl-based halogen bond donors form two-point halogen bonding motifs with oxadiazoles in the solid state.