

Article

Studies of Halogen Bonding Induced by Pentafluorosulfanyl Aryl Iodides: A Potential Group of Halogen Bond Donors in a Rational Drug Design

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Abstract: The activation of halogen bonding by the substitution of the pentafluorosulfanyl (SF₅) group was studied using a series of SF₅-substituted iodobenzenes. The simulated electrostatic potential values of SF₅-substituted iodobenzenes, *ab initio* molecular orbital calculations of intermolecular interactions of SF₅-substituted iodobenzenes with pyridine, and the ¹³C NMR titration experiments of SF₅-substituted iodobenzenes in the presence of pyridine or tetra (*n*-butyl) ammonium chloride (TBAC) indicated the obvious activation of halogen bonding, although this was highly dependent on the position of SF₅-substitution on the benzene ring. 3,5-Bis-SF₅-iodobenzene was the most effective halogen bond donor followed by *o*-SF₅-substituted iodobenzene, while the *m*- and *p*-SF₅ substitutions did not activate the halogen bonding of iodobenzenes. The 2:1 halogen bonding complex of 3,5-bis-SF₅-iodobenzene and 1,4-diazabicyclo[2.2.2]octane (DABCO) was also confirmed. Since SF₅-containing compounds have emerged as promising novel pharmaceutical and agrochemical candidates, the 3,5-bis-SF₅-iodobenzene unit should be an attractive fragment of rational drug design capable of halogen bonding with biomolecules.

Keywords: Halogen bonding; Fluorine; Iodine; Pentafluorosulfanyl; Titration; *Ab initio* calculation; NMR study; Drug design

1. Introduction

Halogen bonding has attracted considerable attention in recent decades, [1–4] in particular, after the pioneering work of halogen bonding in supramolecular chemistry by Resnati, Metrangolo, and co-workers. [5] The application of halogen bonding has expanded to a wide variety of fields including crystal engineering, supramolecular assemblies, liquid crystals, rational drug design, and organic reactions. [1–5] Halogen bonding is a noncovalent attraction between an electron-deficient region of a halogen atom (σ -hole, a halogen bond donor) and an electron-rich center of molecules such as nitrogen, oxygen, and sulfur (Lewis base, a halogen bond acceptor). The strength of the halogen bond increases with an increase of the positive electrostatic potential of the σ -hole, which can be activated by substitution of an electron-withdrawing group in the neighborhood of the halogen atom. Thus, perfluoroalkyl iodides and perfluoroiodobenzenes are well-studied halogen bond donors. In particular, aromatic iodides are of great interest due to the design of halogen bond donors activated by substitution with several electron-withdrawing substituents, [6,7] such as pentafluoroiodobenzene [8,9] and 1-iodo-3,5-dinitrobenzene [10] as representative examples (Figure 1a). Besides, in these planar halogen bond donors, the intermolecular π – π charge-transfer, [11] anion-

π , [12,13] cation- π , [14] and lone pair- π [16–19] interactions are always competition for and/or a combination of halogen bonding in molecular assemblies. These aspects make the design of halogen bond donors more elaborate, especially for application in the rational design of drugs. [20] Statistical analysis of the protein structure database (PDB) showed that a noncovalent interaction between halogenated ligands (halogen-containing drugs, halogen bond donors) and proteins (halogen bond acceptors) frequently contributes to increasing selectivity and binding affinity. [21,22] This survey revealed that a potential rational drug design is possible when the focus is on halogen bonding interactions of halogenated drug candidates and nitrogen, oxygen, sulfur and phosphate groups on biomolecules such as peptides, protein, and DNA. [1, 23]

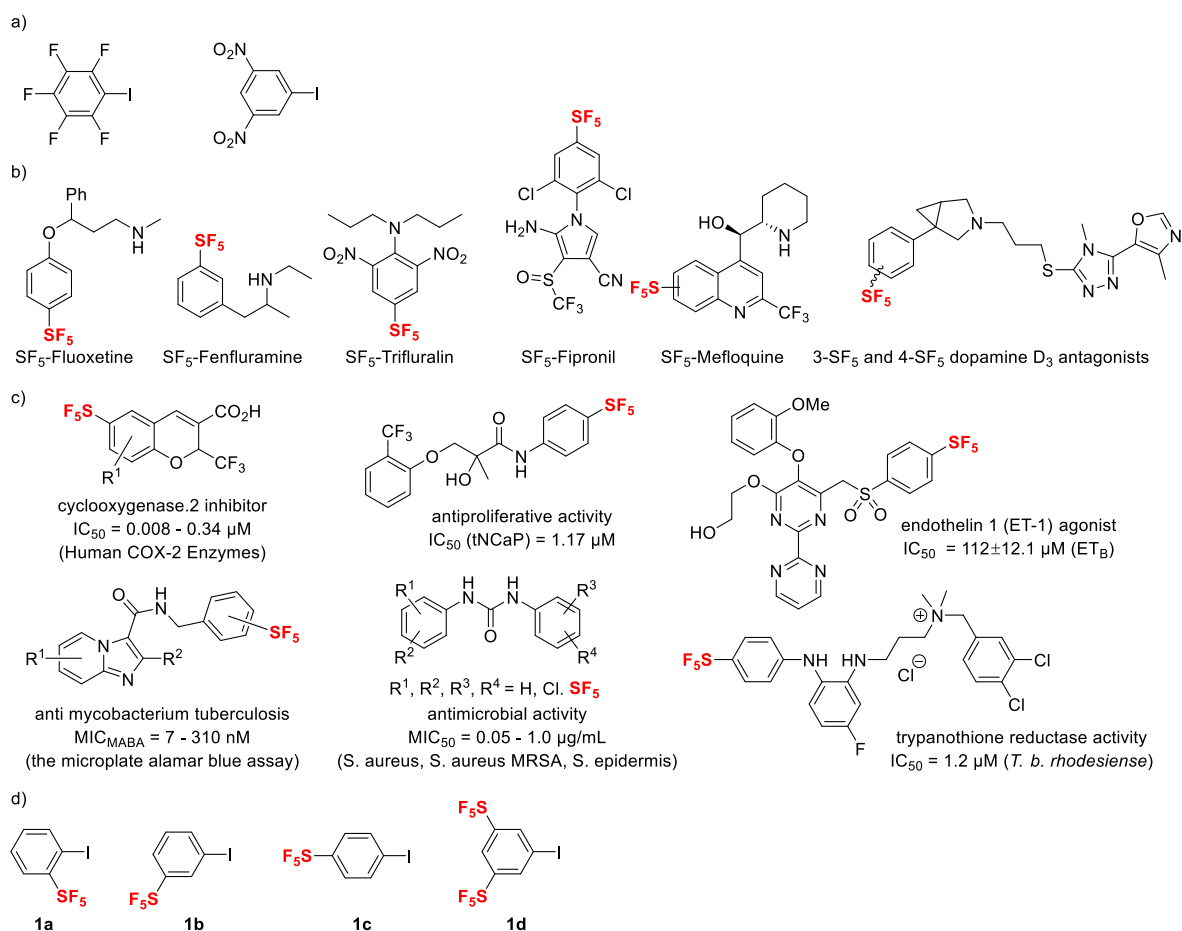


Figure 1. a) Standard halogen bond donors, pentafluoroiodobenzene and 1-iodo-3,5-dinitrobenzene. b) Examples of SF₅-containing analogues of marketed drugs. c) Examples of SF₅-containing biologically active molecules. d) Potential halogen bond donors containing SF₅-group(s) (this work).

In this context, we became interested in the pentafluorosulfanyl (SF₅)-substituted iodobenzenes **1** as a new group of halogen bond donors. The SF₅ group has attracted much attention in the field of pharmaceuticals and agrochemicals. [24–29] Given the impressive physiochemical properties of the SF₅ unit, including its high electronegativity ($\sigma_m = 0.61$, $\sigma_p = 0.68$; nearly equivalent to the nitro (NO₂) group), [30,31] high lipophilicity ($\pi = 1.51$; greater than the CF₃ group) [32,33] and steric hindrance (nearly equivalent to the *tert*-butyl group), [34,35] the SF₅-containing analogues of marketed drugs are attractive candidates in the future drugs market (Figure 1b). [36–41] More and more examples of biologically active SF₅-containing drug candidates have been reported in recent years (Figure 1c). [34,37–41] Extending our research to the design and synthesis of SF₅-containing biologically attractive molecules [42–54] and a halogen bonding research program, [55,56] we are interested in aryl iodides **1a–d** consisting of SF₅-group(s) in the benzene ring as potential drug fragments capable of halogen bonding, in particular, 3,5-bis-pentafluorosulfanyl iodobenzene **1d** (Figure 1d).

2. Results and discussion

The preparation of *o*-, *m*-, *p*-(pentafluoro- λ^6 -sulfanyl)-iodobenzenes (*o*-, *m*-, *p*-SF₅-iodobenzenes, **1a-c**), and 3,5-bis-pentafluorosulfanyl iodobenzene (3,5-bis-SF₅-iodobenzene, **1d**) was achieved by the copper-catalyzed halogen exchange reaction of corresponding aryl-bromides according to our previous report. [45,57] We first simulated the electrostatic potential values for the iodine atoms of the targeted SF₅-iodobenzenes, along with the corresponding values for iodobenzene, pentafluoriodobenzene, and 1-iodo-3,5-dinitrobenzene for comparisons. Molecular electrostatic potential surfaces of iodobenzenes were calculated with density functional B3LYP level of theory with 6-311++G** basis set in a vacuum. [58] The numbers indicate the interaction energy (kJ/mol) between the positive point probe and the surface of the molecule at that particular point. A positive value indicates a positive surface potential. The results disclose that **1d** shows a more positive electrostatic potential value, 20 kJ/mol more than a well-known halogen bond donor, 1-iodo-3,5-dinitrobenzene, [10] while pentafluoriodobenzene had the highest value. It should be noted that *m*- and *p*-substituted SF₅-iodobenzenes (**1b**, **1c**) had negative charges of the iodine atom indicating the poor ability of halogen bonding, while iodobenzene had the most negative value and was thus most de-activated (Figure 2).

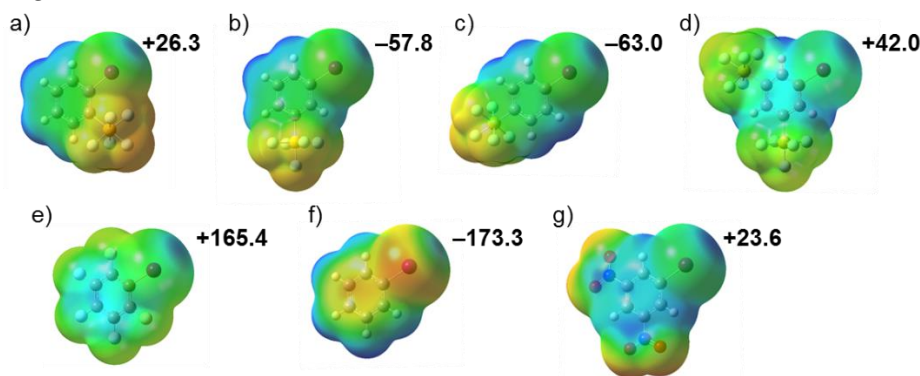


Figure 2. Electrostatic potential maps of molecules with their electrostatic potential values for the iodine atoms of iodobenzenes (in kJ / mol); a) *o*-SF₅-iodobenzene (**1a**), b) *m*-SF₅-iodobenzene (**1b**), c) *p*-SF₅-iodobenzene (**1c**), d) 3,5-bis-SF₅-iodobenzene (**1d**), e) pentafluoriodobenzene, f) iodobenzene, g) 1-iodo-3,5-dinitrobenzene.

Next, the intermolecular interactions of iodobenzenes and pyridine were investigated by *ab initio* molecular orbital calculations. The MP2/cc-pVTZ level intermolecular interaction energies [59] for the *o*-, *m*-, *p*-SF₅-iodobenzene---pyridine (**2a-c**), and 3,5-bis-SF₅-iodobenzene---pyridine complexes (**2d**) were calculated by changing the intermolecular separation. The interaction energy potentials calculated for the complexes were compared with the interaction energy potential calculated for the iodobenzene---pyridine complex (Figure 4). The depths of interaction energy potentials of the SF₅-iodobenzene---pyridine complex (**2a-d**) are deeper than those of the iodobenzene---pyridine complex **3**. We note that the potential for *o*-SF₅-substituted **2a** is much deeper than for *m*-SF₅-**2b** and *p*-SF₅-**2c**, while the potential for 3,5-bis-SF₅-**2d** is deepest. The CCSD(T) level interaction energies at the basis set limit [*E*_{CCSD(T)(limit)}] for the optimized geometries of **2a-d** were calculated. [60] The *E*_{CCSD(T)(limit)} and the contribution of each intermolecular force are summarized in Table 1. The calculations show that the electrostatic (*E*_{es}) and dispersion (*E*_{corr}) interactions are the primary sources of the attraction and the substituent dependence of the electrostatic interactions is mainly responsible for the substituent effects on the magnitude of the attraction of the halogen bonds. These calculated results strongly indicate that substitution of the SF₅ group induces halogen bonding, whose strength depends on the position of the substitution and numbers. As expected, 3,5-bis-SF₅-iodobenzene **1d** is the most efficient template to induce halogen bonding. The 3,5-bis-substitution is also attractive for improved biological activity, as evidenced in medicinal research. [43, 57]

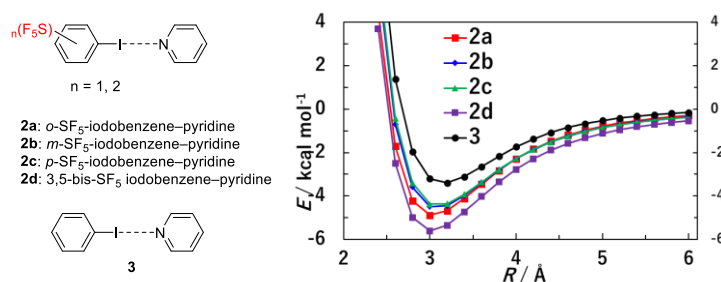


Figure 3. Interaction energy curves (energies versus I...N distance (R)) calculated for the iodobenzenes---pyridine complexes (2a-d, 3).

Table 1. Electrostatic, induction and dispersion energies of halogen-bonded complexes^a

	E [kcal mol ⁻¹]				
	E_{int}^a	E_{es}^b	E_{ind}^c	E_{short}^d	E_{corr}^e
<i>o</i> -SF ₅ -iodobenzene---pyridine 2a	-4.88	-4.48	-1.32	4.43	-3.52
<i>m</i> -SF ₅ -iodobenzene---pyridine 2b	-4.27	-4.20	-1.20	4.40	-3.27
<i>p</i> -SF ₅ -iodobenzene---pyridine 2c	-4.28	-4.02	-1.15	4.02	-3.13
3,5-bis-SF ₅ -iodobenzene---pyridine 2d	-5.21	-5.60	-1.65	5.54	-3.49
iodobenzene---pyridine 3 ^f	-3.27	-2.73	-0.82	3.30	-3.01

^aEstimated CCSD(T) interaction energy at the basis set limit [$E_{\text{CCSD(T)}(\text{limit})}$]. ^bElectrostatic energy. ^cInduction energy.

^dContribution of short-range (orbital-orbital) interactions ($=E_{\text{HF}}-E_{\text{es}}-E_{\text{ind}}$). The HF/aug-cc-pVTZ interaction energy was used as E_{HF} . E_{short} is mainly the contributions of exchange-repulsion interactions. ^eContribution of electron correlation ($=E_{\text{int}}-E_{\text{HF}}$). E_{corr} is mainly dispersion energy. ^fref 58

Encouraged by the results of these calculations, ¹³C NMR titration experiments of SF₅-iodobenzenes in the presence of pyridine or tetra(*n*-butyl)ammonium chloride (TBAC) in CDCl₃ to detect the existence of halogen bonding were carried out with comparisons using pentafluoriodobenzene and iodobenzene. ¹³C NMR is a well-studied technique to probe halogen bonding. [61–64] Namely, the increase of chemical shifts of the carbon atom bonded to iodine in Ar–I indicates stronger halogen bonding, due to lengthening of the carbon–iodine bond by the donation of electrons from the halogen bond acceptor into iodine orbitals. [65,66] Our ¹³C NMR experiments are shown in Figures 4 and 5. First, the chemical shift of the carbon atom bonded to iodine in pentafluoriodobenzene increased with an increase in the addition of pyridine or TBAC. This phenomenon confirms the formation of halogen bonding interaction on the σ -hole of the iodine atom with a Lewis base (nitrogen atom of pyridine, or Cl anion). The observed up-field shift is a consequence of the donation of electron density from the halogen bond acceptor to the iodine group, and the more significant shifts donated by TBAC with respect to pyridine are consistent with the fact that anions function as better electron donors than pyridines, and form a stronger halogen bond than the nitrogen atom which possesses a neutral lone-pair. On the other hand, the addition of pyridine or TBAC to iodobenzene leads to a decrease of the chemical shift of the carbon atom bonded to the iodine atom. This observation could be explained by the competitive interaction of the intermolecular π - π interaction [67] (with pyridine) or the cation- π interaction [68] (with tetra (*n*-butyl) ammonium cation), although this explanation needs further experimental support. Despite this, pentafluoriodobenzene is an activated halogen bond donor but iodobenzene is not.

We next examined the titration experiments of a series of SF₅-substituted iodobenzenes **1a-d**. As mentioned above, the changes in chemical shift of pyridine titration are much smaller than those of TBAC titration, while the occurrence of halogen bonding is fundamentally the same. The chemical shifts of the carbon atom bonded to iodine in *o*-SF₅-iodobenzene **1a** and 3,5-bis-SF₅-iodobenzene **1d** increased after the addition of TBAC, which confirms the occurrence of halogen bonding. On the other hand, opposite phenomena were observed in the case of *m*- and *p*-SF₅-iodobenzene **1b**, **1c** with TBAC, which confirms the absence of halogen bonding. These results of the occurrence/absence of

halogen bonding depend on the position of SF₅-substitution, and are in good agreement with the calculations, as shown in Figure 2.

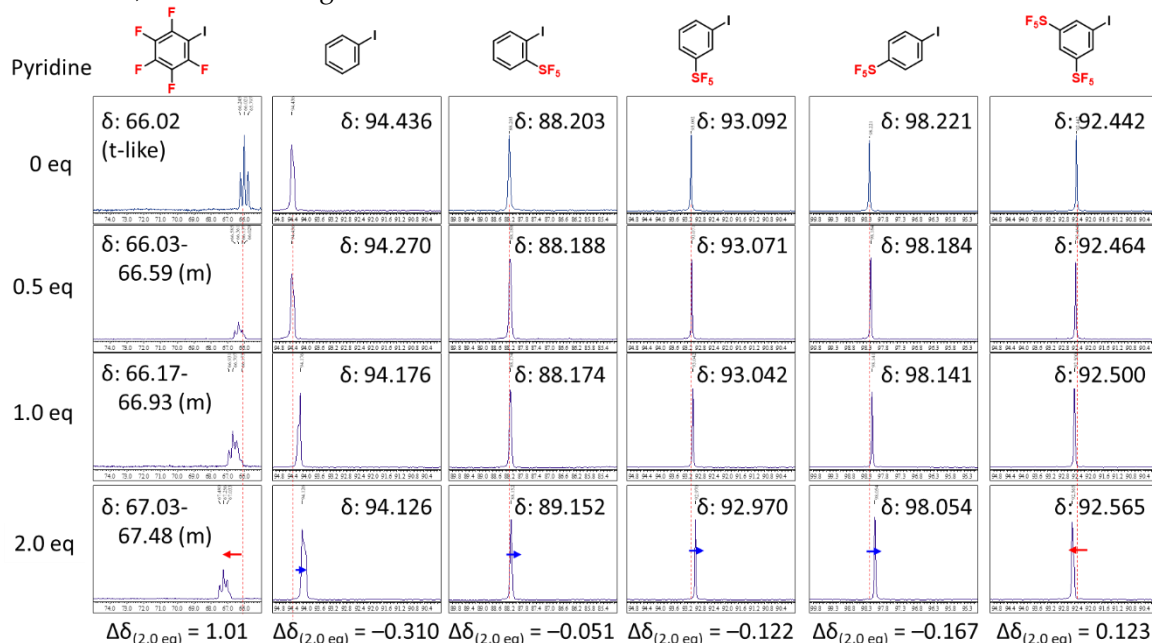


Figure 4. Change in the ¹³C NMR chemical shift of the carbon atom bonded to iodine in Ar-I with equivalents of pyridine in CDCl₃.

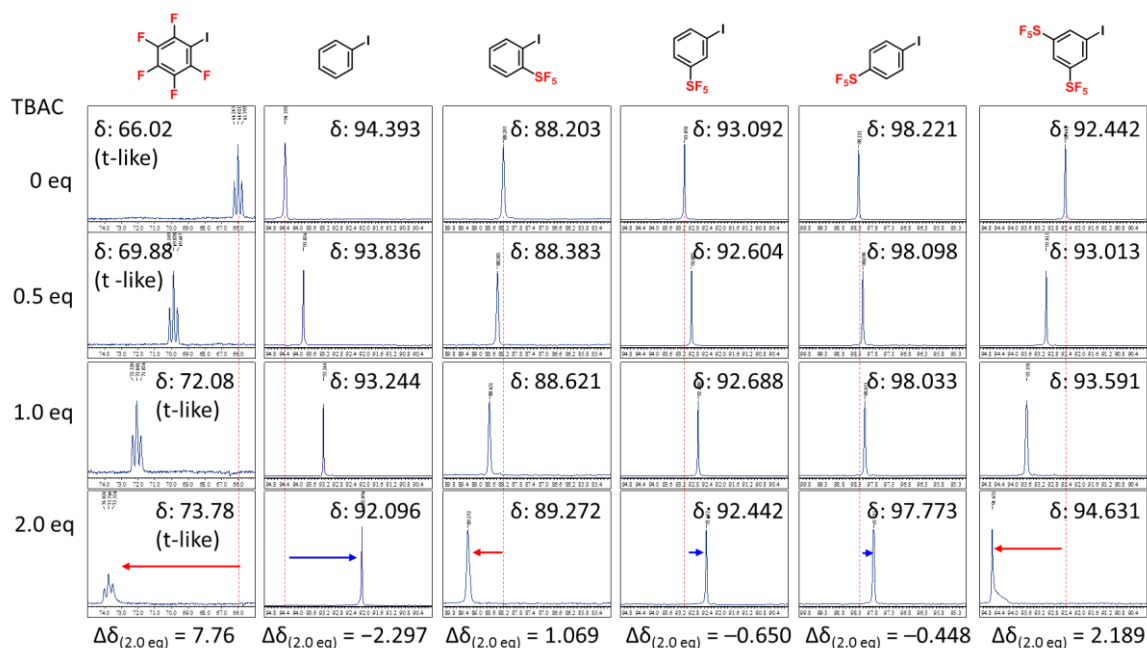


Figure 5. Change in the ¹³C NMR chemical shift of the carbon atom bonded to iodine in Ar-I with equivalents of TBAC in CDCl₃.

Finally, we examined the formation of halogen bonding interaction between 3,5-bis-SF₅-iodobenzene **1d** and 1,4-diazabicyclo[2.2.2]octane (DABCO). Since DABCO is a bisfunctional halogen bond donor, the 2:1 halogen bonding complex of **1d** and DABCO is expected. Indeed, X-ray crystallographic analysis of 1-iodo-3,5-dinitrobenzene with DABCO revealed the formation of a 2:1 halogen bonding complex. [69] We thus examined the titration of **1d** by the addition of DABCO (Figure 6). With an increasing amount of DABCO, the chemical shift of carbon attached to iodine

increased, providing proof of the formation of halogen bonding of I---N. More interestingly, one singlet peak at 92.442 ppm gradually changed to double singlets at 93.454 and 93.352 ppm, which provides evidence of two halogen bonds in the complex from **4** to **5**. This phenomenon suggests that the 2:1-complex **5** is not completely symmetrical, as in the case of 1-iodo-3,5-dinitrobenzene. [69]

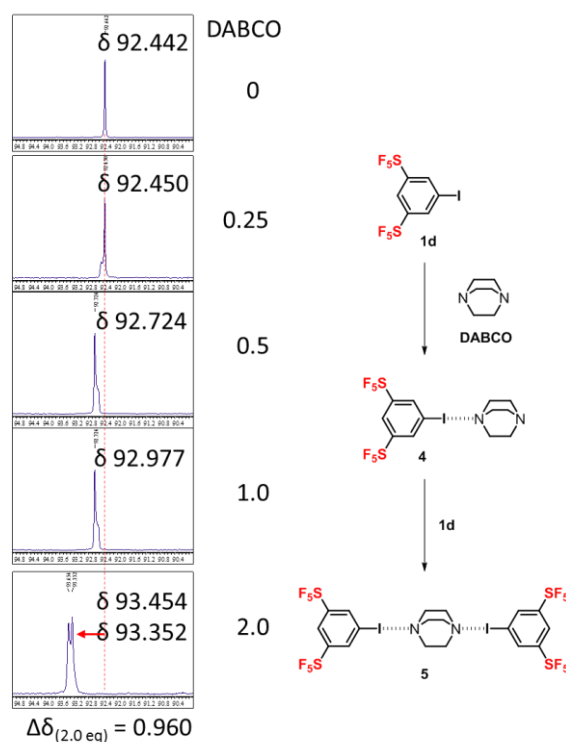
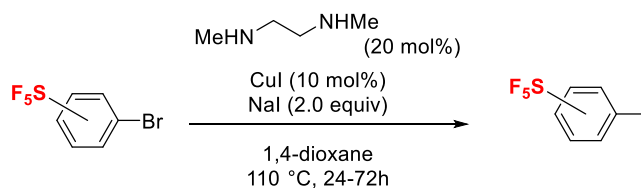


Figure 6. Change in the ^{13}C NMR chemical shift of the carbon atom bonded to iodine in **1d** with equivalents of DABCO in CDCl_3 .

3. Materials and Methods

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred *via* syringe and were introduced into the reaction vessels through a rubber septum. Chemicals were purchased and used without further purification unless otherwise noted. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on a 0.25 mm Merck silica gel (60-F₂₅₄). TLC plates were visualized with UV light and 7% phosphomolybdic acid or KMnO_4 in water/heat. Column chromatography was carried out on a column packed with silica gel (60N spherical neutral size 50–63 μm). The ^1H NMR (300 MHz), ^{19}F NMR (282 MHz) and ^{13}C NMR (126 MHz) spectra for each solution in CDCl_3 were recorded on a Varian Mercury 300 and Bruker Avance 500 NMR spectrometers. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane ($\delta = 0.0$ ppm) for ^1H NMR, C_6F_6 ($\delta = -162.2$ ppm) for ^{19}F NMR, and CDCl_3 ($\delta = 77.00$) for ^{13}C NMR. Mass spectrometries were recorded on a SHIMADZU LCMS-2020 (ESI-MS).

3.1. General procedure of pentafluoro- λ^6 -sulfanyl iodobenzene



o-, *m*-, *p*-SF₅-iodobenzenes (**1a–c**), and 3,5-bis-SF₅-iodobenzene (**1d**) were prepared from corresponding aryl bromides by a copper-catalyzed halogen exchange reaction. [70]. To a flame-dried

Schlenk-tube, CuI (10 mol %), NaI (2.0 equiv) and aryl bromide (1.0 equiv) were added and evacuated and backfilled with argon. 1,4-Dioxane (1.0 mL/mmol for ArBr) and *N,N'*-dimethylethylenediamine (20 mol %) were added, and the mixture was stirred at room temperature for 3 min and at 110 °C for 24–72 h. The resulting suspension was cooled to room temperature and filtered through a pad of SiO₂. The filtrate was diluted in NaHCO₃ aq and extracted with CH₂Cl₂ three times. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane) to give the desired product.

3.1.1. Pentafluoro(2-iodophenyl)-λ⁶-sulfane (**1a**) [57]

92% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.45 (t-like, *J* = 7.5 Hz, 1H), 7.12 (t-like, *J* = 7.4 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ: 83.5 (quintet, *J* = 152.6 Hz, 1F), 63.5 (d, *J* = 151.7 Hz, 4F) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 158.4 (quintet, *J* = 16.3 Hz), 143.9, 132.2, 130.1 (t-like, *J* = 5.4 Hz), 127.9, 88.2 ppm. MS (ESI) *m/z*: 353 [(M+Na)⁺].

3.1.2. Pentafluoro(3-iodophenyl)-λ⁶-sulfane (**1b**) [45,71–73]

91% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.22 (t-like, *J* = 8.4 Hz, 1H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ 82.5 (quintet, *J* = 150.9 Hz, 1F), 62.3 (d, *J* = 151.7 Hz, 4F) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 154.4 (quintet, *J* = 17.7 Hz), 140.6, 134.7 (t-like, *J* = 4.5 Hz), 130.3, 125.2, 93.1 ppm. MS (ESI) *m/z*: 353 [(M+Na)⁺].

3.1.3. Pentafluoro(4-iodophenyl)-λ⁶-sulfane (**1c**) [45,72,73]

91% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ 83.0 (quintet, *J* = 150.0 Hz, 1F), 62.3 (d, *J* = 150.0 Hz, 4F) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 153.5 (quintet, *J* = 18.2 Hz), 137.9, 127.5 (t-like, *J* = 4.5 Hz), 98.2 ppm. MS (ESI) *m/z*: 353 [(M+Na)⁺].

3.1.4. (5-Iodo-1,3-phenylene)bis(pentafluoro-λ⁶-sulfane) (**1d**) [45]

95% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H), 8.12–8.07 (m, 2H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ 80.1 (quintet, *J* = 151.7 Hz, 1F), 62.7 (d, *J* = 151.7 Hz, 4F) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 154.0 (quintet, *J* = 20.0 Hz), 137.8, 123.5 (t, *J* = 4.5 Hz), 92.4 ppm. MS (ESI) *m/z*: 479 [(M+Na)⁺].

3.2. Computational method

3.2.1. Calculations for Electrostatic potential values

The Gaussian 09 program [74] was used for the *ab initio* molecular-orbital calculations. Molecular electrostatic potential surfaces for iodobenzenes were calculated with density functional B3LYP level of theory with 6-311++G** basis set for C, H, S, F, O and DGDZVP basis set for I in vacuum. [58] All molecules were geometry optimized with the maxima and minima in the electrostatic potential surface (0.002 e/au isosurface) determined using a positive point charge in the vacuum as a probe. The numbers in figure 2 indicate the interaction energy (kJ/mol) between the positive point probe and the surface of the molecule at that particular point. A positive value for the interaction energy indicates a positive surface potential.

3.2.2. Calculations for Interaction energies

The Gaussian 09 program [74] was used for the *ab initio* molecular-orbital calculations. The basis sets implemented in the program were used. Electron correlation was accounted for by the second-order Møller–Plesset perturbation (MP2) method [75,76] and by coupled cluster calculations with single and double substitutions with non-iterative triple excitations [CCSD(T)]. [60] The basis-set

superposition error (BSSE) [77] was corrected for all calculations by using the counterpoise method. [78] The geometries of the complexes were optimized at the counterpoise-corrected MP2/6-311G* level. The DGDZVP basis set [79] was used for iodide. The MP2 interaction energies of the complexes at the basis set limit [$E_{\text{MP2}(\text{limit})}$] were estimated by the method of Helgaker et al. [80] from the calculated MP2 interaction energies (E_{MP2}) by using the aug-cc-pVDZ and aug-cc-pVTZ basis sets. The CCSD(T) interaction energies at the basis set limit [$E_{\text{CCSD(T)}(\text{limit})}$] were calculated as the sum of $E_{\text{MP2}(\text{limit})}$ and the estimated CCSD(T) correction term at the basis set limit [$\Delta\text{CCSD(T)}(\text{limit})$], which was estimated from the difference between the interaction energies calculated at the CCSD(T) and MP2 levels [$\Delta\text{CCSD(T)} = E_{\text{CCSD(T)}} - E_{\text{MP2}}$] by using the cc-pVDZ basis set. [81,82] Electrostatic energies were calculated as the interactions between distributed multipoles [83,84] of interacting molecules by using the ORIENT program. [85] Distributed multipoles up to hexadecapole were obtained on all atoms from the MP2/6-311G** level wave functions of isolated molecules by using the GDMA program. [86] Induction energies were calculated as the interactions of polarizable sites with the electric field produced by the distributed multipoles of the monomers. [87] The atomic polarizabilities of carbon ($\alpha=10$ a.u.), nitrogen ($\alpha=8$ a.u.), oxygen ($\alpha=6$ a.u.), fluorine ($\alpha=3$ a.u.), sulfur ($\alpha=20$ a.u.), and iodine ($\alpha=34$ a.u.) were used for the calculations. [88] The distributed multipoles were used only to estimate the electrostatic and induction energies. The MP2/6-311G** level optimized geometries of isolated molecules were used to calculate the intermolecular interaction energy potentials.

4. Conclusion

In conclusion, we have studied the potential of SF₅-substituted iodobenzenes as halogen-bonding donors. The simulated electrostatic potential values of SF₅-substituted iodobenzenes, *ab initio* molecular orbital calculations of intermolecular interactions with pyridine, and the ¹³C NMR titration experiments of SF₅-substituted iodobenzenes in the presence of halogen bonding acceptors were investigated to assess the existence of halogen bonding. It should be noted that halogen bonding of iodobenzenes induced by the SF₅-substituted group is strictly dependent on the position of SF₅-substitution on the benzene ring, and 3,5-bis-SF₅-iodobenzene is the most effective halogen bond donor in the series, and it is even a stronger halogen bond donor than well-known 1-iodo-3,5-dinitrobenzene, as supported by our calculations. Since SF₅-containing compounds are promising drug candidates, the present results should be useful information for the rational design of drugs capable of halogen bonding with biomolecules. The X-ray crystallographic analyses of 3,5-bis-SF₅-iodobenzene with halogen bond acceptors are now being considered.

Supplementary Materials: The following are available online, ¹H, ¹³C and ¹⁹F NMR spectra of compounds.

Author Contributions: N.S. conceived and designed the experiments and directed the project; K.S. and Y.S. performed the experiments and analyzed the data; S.T. performed the *ab initio* calculation; Y.S. and N.S. wrote the paper.

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503 **Sample Availability:** Samples of the compounds **1a-d** are available from the authors.