Chapter 10
A Unified View of Halogen Bonding, Hydrogen Bonding and Other σ-Hole Interactions

Peter Politzer and Jane S. Murray

Abstract The term "σ-hole" refers to a region of diminished electronic density along the extension of a covalent single bond to a hydrogen or an atom of Groups IV—VII. This region often has a positive electrostatic potential through which the atom can interact attractively with a negative site (such as a lone pair of a Lewis base, π electrons or an anion) to form a noncovalent complex. Hydrogen bonding and halogen bonding are the most prominent examples of such σ-hole interactions, although they have long been known experimentally for Groups IV—VI as well (but without the σ-hole label). σ-Holes result from the anisotropic charge distributions of covalently-bonded atoms. It follows from the Hellmann-Feynman theorem that σ-hole interactions can be understood and described as Coulombic, which includes polarization and dispersion. In the context of noncovalent interactions, charge transfer is simply a mathematical formulation of polarization.

10.1 Noncovalent Interactions: The Chemistry of the Twenty-First Century

Recent years have seen a remarkable surge of research activity in the area of noncovalent interactions. One indication of this is the number of review and perspective papers that have appeared just since the year 2000; some of them (certainly not all) are cited here [1–17]. Indeed, an observation made by Schneider appears thus far to be borne out: ". . . one might assert that the chemistry of the last century was largely the chemistry of covalent bonding, whereas that of the present century is more likely to be the chemistry of noncovalent binding." [18].

Much of this recent interest has focused upon what is known as "halogen bonding," a highly-directional attractive interaction that is found to occur between many covalently-bonded halogen atoms and negative sites (lone pairs of Lewis bases, π electrons, anions, etc.). The interest is due in part to the applications of halogen bonding, existing and potential, in fields such as crystal engineering, molecular biology and pharmacology [5, 8, 10, 15], but it also reflects the intriguing fact that an

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P. Politzer (✉) · J. S. Murray
Department of Chemistry, University of New Orleans, 70148 New Orleans, LA, USA
e-mail: ppolitze@uno.edu

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electronegative halogen is attracted to a negative site. This was sometimes described as an enigma!

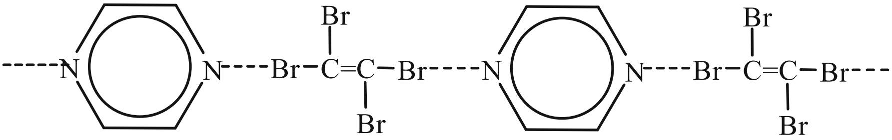
Our primary focus in this chapter will be upon halogen bonding. We emphasize, however, that this is simply a subset of a much larger category of noncovalent interactions, "σ-hole bonding," that can involve covalently-bonded atoms of Groups IV—VI as well as Group VII (the halogens) and also includes hydrogen bonding. The nature of the interaction is essentially the same in all of these cases, as shall be discussed. The formation of noncovalent complexes between Group IV—VII atoms and negative sites has been known to experimentalists for decades, although the unifying σ-hole interpretation is of more recent origin.

10.2 Some Historical Background

A very early example of what we now call halogen bonding was the report, in 1814, of an interaction between iodine and ammonia [19]. The product was later purified by Guthrie [20] and formulated as $I_2 \cdot NH_3$. Additional complexes of Cl_2, Br_2 and I_2 with amines were subsequently observed [21, 22], as well as an adduct between iodoform and quinoline [23].

The twentieth century saw many more R-X—B systems being identified, where RX is a halide molecule and B is a Lewis base; a number of these studies are cited by Blackstock et al [24]. Of particular note was the spectral characterization of complexes of molecular iodine with benzene and other aromatic hydrocarbons by Benesi and Hildebrand [25, 26]. Their observations were a factor in Mulliken's development of his "charge-transfer" formalism [27], which is frequently invoked as a mathematical (but not physical) description of noncovalent bonding. However Mulliken incorrectly suggested that in the I_2—C_6H_6 complex, the I_2 axis is parallel to the benzene plane.

Important advances in elucidating the structure of halogen bonding have come through crystallography. In the 1960's, Hassel and his colleagues determined the crystal structures of a number of complexes between organic halides and oxygen/nitrogen Lewis bases; this work contributed to his receiving the Nobel Prize in 1969. These studies showed the crystals to be composed of chain-like structures *held together by weak X–B bonds*, e.g. **1** [28]. For a review, see Bent [29]. At about the same time, attractive Br—O intermolecular interactions were found in solid $POBr_3$ [30] and Cl—O in solid $POCl_3$ [31].



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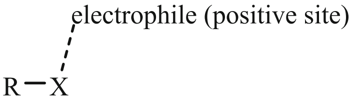
A few years later, Murray-Rust et al conducted extensive surveys of halide (RX; X = Cl, Br, I) crystal structures, using the Cambridge Structural Database [32–34]. Their objective was to identify close contacts between halogen atoms and atoms of neighboring molecules. Close contact was defined as being less than the sum of the respective van der Waals radii, and was taken to reflect an attractive interaction. A very significant pattern was revealed: Close contacts of halogen atoms with electrophilic sites, such as metal ions, were primarily at angles of 90–120° relative to the R–X bond (**2**); close contacts with nucleophilic sites, e.g. nitrogens and oxygens, tended to be nearly linear, the angles being 160–180° (**3**).



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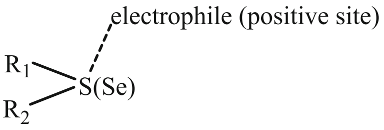
Thus a given halogen atom can interact favorably, but in different directions, with both positive and negative sites.

The near-linear interactions of covalently-bonded halogens with nucleophiles, as in **3**, are what we call halogen bonding, R-X—B. To our knowledge, this term was first used in 1976 [35, 36]. In the past, halogen bonding was sometimes viewed as very puzzling, since univalent halogens are generally regarded as being negative in character; how then can they be attracted to negative sites? This question was answered in 1992, as shall be discussed in Sect. 10.3.2.

During the last two decades, the practical significance and potential applications of halogen bonding have increasingly been recognized. Imakubo et al prepared semiconducting crystals and a superconductor by linking iodine-containing organic sulfides via negative ions (acting as the bases) [37, 38]. An important development was the realization that the role of halogen bonding in formulating new materials is enhanced if the halogen-containing molecule also contains strongly electron-attracting groups, e.g. perfluorination [39]. This helped to stimulate a great deal of activity in the area of crystal engineering, with applications in electronics, nonlinear optical activity, magnetic materials, liquid crystals, etc. [5, 8, 10, 40–42]. Catalysis through halogen bonding is also being explored [43, 44].

In chemical biology as well, there is a growing awareness of the importance of halogen bonding. A milestone was the survey of the Protein Data Bank by Auffinger et al [45], revealing C-X—O close contacts (X = Cl, Br, I); it was subsequently expanded by Lu et al to C-X—Y (X = Cl, Br, I; Y = O, N, S) [46]. Such interactions are now known to affect protein-ligand binding, recognition and assembly processes, docking, conformational stability, protein folding, etc. [5, 15, 41, 47], and are being exploited in drug design.

During roughly the same years as the surveys of halide crystal structures by Murray-Rust et al [32–34], discussed above, analogous studies of close contacts in organic sulfides and selenides were being carried out [48–50]. Very similar results were obtained. Electrophilic sites interacted with the lateral sides of the sulfur or selenium (**4**), while interactions with nucleophiles were close to linear, along the extensions of the R_1–S(Se) and/or R_2–S(Se) bonds (**5**). Some of the close contacts were between a sulfur in one molecule and the same sulfur in another identical molecule [49], i.e. "like attracting like" (**6**); the interactions were linear for one of the sulfurs and lateral for the other.



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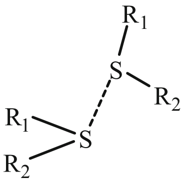

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10.3 The Electrostatic Potential and the σ-Hole

All of these observations were explained and the "enigma" of halogen bonding was resolved in 1992—through the analysis of molecular electrostatic potentials. We will accordingly give some brief background concerning this property.

10.3.1 The Electrostatic Potential

The nuclei and electrons of a molecule (or other system) create an electrostatic potential $V(\mathbf{r})$ at each point $\mathbf{r}$ in the surrounding space:

$$V(\mathbf{r}) = \sum_{A} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (10.1)$$

In Eq. (10.1), which is simply one form of Coulomb's Law, Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the molecule's electronic density distribution. $V(\mathbf{r})$ is positive or negative in any given region depending upon whether the effects of the positive nuclei or the negative electrons are dominant there.

If a point charge Q is placed at $\mathbf{r}$, then its interaction energy ΔE with the molecule's nuclei and electrons is,

$$\Delta E = QV(\mathbf{r}) \qquad (10.2)$$

If Q and V($\mathbf{r}$) have the same sign (positive or negative), then $\Delta E > 0$ and the interaction is repulsive; if they have opposite signs, then $\Delta E < 0$ and the interaction is attractive.

The electrostatic potential is accordingly an effective means of predicting close contacts and noncovalent interactions [51–53]. In general, regions of positive V($\mathbf{r}$) tend to interact favorably (at least initially) with negative sites and negative V($\mathbf{r}$) with positive sites. (A more detailed analysis needs to take polarization into account, as shall be discussed.)

We want to emphasize that the electrostatic potential is a real property of a system, a physical observable. It can be determined experimentally by diffraction methods [54–56], as well as computationally.

When V($\mathbf{r}$) is used for interpreting and predicting noncovalent interactions, it is typically computed on the molecular "surface" defined by the 0.001 au (electrons/bohr^3) contour of the molecule's electronic density $\rho(\mathbf{r})$. This was suggested by Bader et al [57] as a reasonable representation of a molecular surface; it encompasses roughly 97 % of the electronic charge and reflects specific features such as lone pairs, π electrons and atomic anisotropies. V($\mathbf{r}$) on the 0.001 au surface is labeled $V_S(\mathbf{r})$, and its locally most positive and most negative values (of which there may be several) are designated by $V_{S,max}$ and $V_{S,min}$, respectively.

10.3.2 The σ-Hole

In 1992, Brinck et al reported something quite unexpected [58]: covalently-bonded halogens with regions of positive electrostatic potential on their outer sides, on the extensions of the covalent bonds. The lateral sides of the halogens were negative, as anticipated. Additional studies in the next two years produced similar results [59, 60]. See, for instance, Fig. 10.1; the outer sides of the bromines, on the extensions of the C–Br bonds, have positive $V_S(\mathbf{r})$ while the lateral sides of the bromines are negative (although less so after perfluorination).

Such positive outer regions appear to contradict the common view that univalent halogens are negative in character. However, as Brinck et al pointed out [58, 59], these findings do provide an immediate explanation of halogen bonding and of the patterns of crystallographic close contacts observed by Murray-Rust et al [32–34], i.e. structures **2** and **3**. Halogen bonding is the attractive interaction between the positive outer portion of the halogen and a negative site. Since the positive region on the halogen surface is on the extension of the covalent bond to the halogen, the same will be true of the interaction with the negative site; it will be near-linear, as shown in **3**. The halogen can also interact favorably with positive sites through its negative lateral sides, as in **2** (except for occasional instances in which the halogen's entire surface is positive). Some years later, Auffinger et al [45] and Awwadi et al [61] presented analogous intepretations of halogen bonding.

In 2007, the term "σ-hole" was introduced to denote the outer regions of positive potential on univalent halogens [62, 63]. The name reflects their being along the

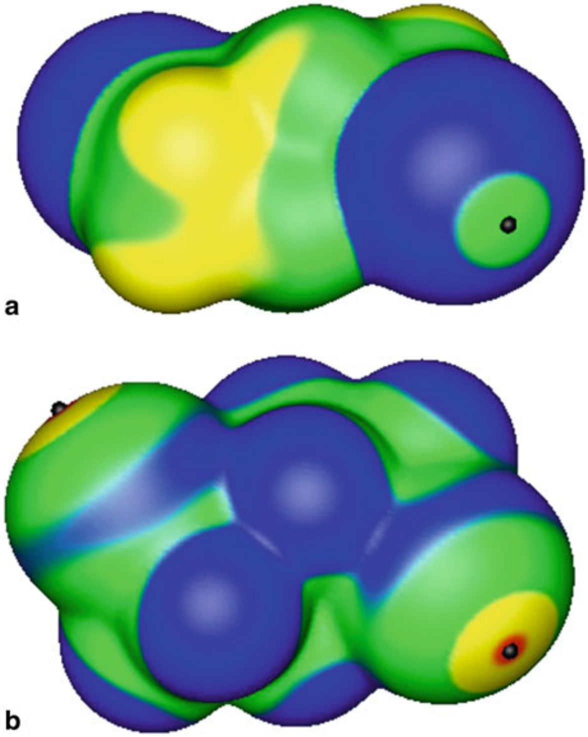


Fig. 10.1 Computed electrostatic potentials on 0.001 au molecular surfaces of **a** 1,4-dibromo-*n*-butane and **b** 1,4-dibromoperfluoro-*n*-butane. Bromines are at far *left* and far *right*. Black hemispheres indicate positive potential maxima on bromines, on extensions of C–Br bonds. Color ranges, in kcal/mol: *red*, greater than 25; *yellow*, between 25 and 15; *green*, between 15 and 0; *blue*, less than 0 (negative). Note that bromines become more positive after perfluorination. Computational level: M06-2X/6-311G(d, p)

extensions of σ bonds. As will be pointed out, however, σ-holes can sometimes also have negative potentials.

At about the same time that regions of positive potential were found on the extensions of covalent bonds to halogens [58–60], an analogous discovery was made for divalent sulfur. In a computational analysis of the heterocycle **7** [64], Burling and Goldstein showed that the sulfur has positive potentials on the extensions of the C–S bonds, with negative ones on its lateral sides. It was noted that this is consistent with the crystallographically-revealed patterns of close contacts in divalent sulfides and selenides [48–50], structures **4–6**; it also explains intramolecular S—O and Se—O close contacts that stabilize certain biologically-active thiazole and selenazole conformations [64]. (See also a later computational study involving other substituted sulfur—and selenium-containing heterocycles [65].) The basis for “like attracting like,” **6**, now becomes apparent—for halides as well as for sulfides and selenides: The positive outer region on one of these atoms interacts favorably with a negative side of the same atom in another, identical molecule, as in **6**.

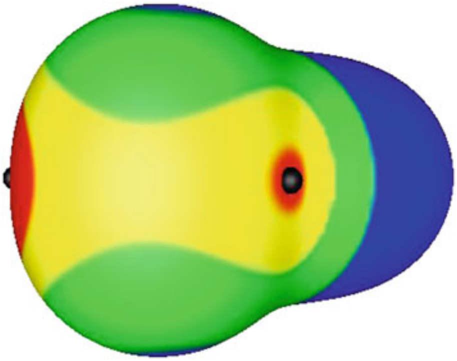
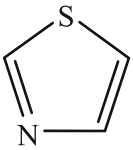


Fig. 10.2 Computed electrostatic potential on 0.001 au molecular surface of HSeCN. The selenium is in the foreground, cyano group at the *right*. *Black* hemispheres indicate selenium positive σ-holes on extensions of C–Se and H–Se bonds, the former being more positive. Color ranges, in kcal/mol: *red*, greater than 25; *yellow*, between 25 and 15; *green*, between 15 and 0; *blue*, less than 0 (negative). Computational level: M06-2X/6-311G(d, p)



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What Burling and Goldstein described are simply more examples of what are now called positive σ-holes: Regions of positive electrostatic potential on the outsides of singly-bonded atoms, along the extensions of the covalent bonds. Between 2007 and 2009, numerous positive σ-holes were found computationally on atoms of Groups IV—VI as well as Group VII (the halogens); this work in summarized in several reviews [11, 15, 16]. Through these regions, the atoms can interact favorably with negative sites (lone pairs of Lewis bases, π electrons, anions, etc.), forming noncovalent complexes. This is σ-hole bonding, of which halogen bonds are a subset. The interactions are highly directional, close to linear, along the extensions of the covalent single bonds to the atoms (see **3** and **5**).

Since Group IV—VI atoms can form four, three and two single bonds (or more if hypervalent [66, 67]), they can have the same numbers of σ-holes on the extensions of these bonds. This can be seen in Figs. 10.2, 10.3 and 10.4, which show that the σ-holes on a given atom can have different potentials, depending upon the partners in the bonds that gave rise to the σ-holes.

Some reports in the recent literature describe noncovalent interactions between Group IV—VI atoms and negative sites as new discoveries. This is incorrect (an error of which we have also been guilty [68]). Experimentalists have been familiar with

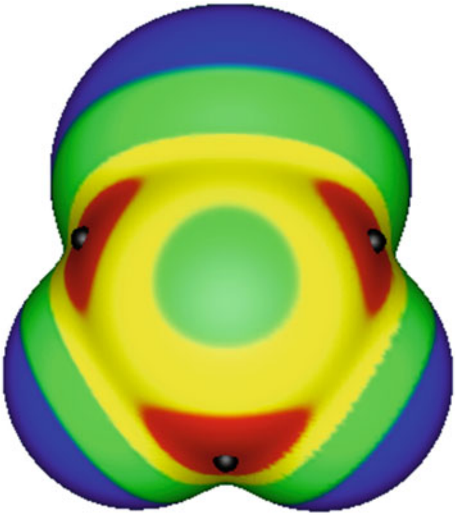


Fig. 10.3 Computed electrostatic potential on 0.001 au molecular surface of PF_2Br. The phosphorus is in the foreground, bromine at top. *Black* hemispheres indicate phosphorus positive σ-holes on extensions of Br–P and F–P bonds, the former being more positive. Color ranges, in kcal/mol: *red*, greater than 25; *yellow*, between 25 and 15; *green*, between 15 and 0; *blue*, less than 0 (negative). Computational level: M06-2X/6-311G(d, p)

them for decades, as is well documented in two reviews [16, 69]. What is new is the unifying σ-hole interpretation of a great many of these interactions [11,14–17].

10.4 Origins of σ-Holes

10.4.1 Anisotropies of Covalently-Bonded Atoms

The electronic density of a free neutral atom is, on the average, spherically-symmetrical [70]. The electrostatic potential $V(\mathbf{r})$ due to its nucleus and electrons is positive for all $r < \infty$ [71], the effect of the nucleus dominating over that of the dispersed electrons. When two atoms begin to interact, at large separations, the electronic density of each of them becomes somewhat polarized toward the other [72], in response to the electric field of the latter. This results in the electronic density being less on the outer side of each atom (along the internuclear axis) than on its lateral sides. These diminished outer electron densities are incipient σ-holes!

As the atoms continue to approach and to interact in forming a covalent single bond, there is further redistribution of electronic densities, depending upon the atoms' relative polarizabilities and electronegativities. However the σ-holes continue to have lesser electronic densities than the surrounding portions of the atoms. It is indeed well established that covalently-bonded atoms have anisotropic charge distributions [14, 17, 49, 50, 61, 73–79]; their "radii" are less along the extensions of single bonds than perpendicular to them. For example, in the bromines in Fig. 10.1a, the distances to the 0.001 au surface are 2.06 Å along the extensions of the C–Br bonds and 2.28 Å in the perpendicular directions. In Fig. 10.1b, the same distances are 2.02 Å and

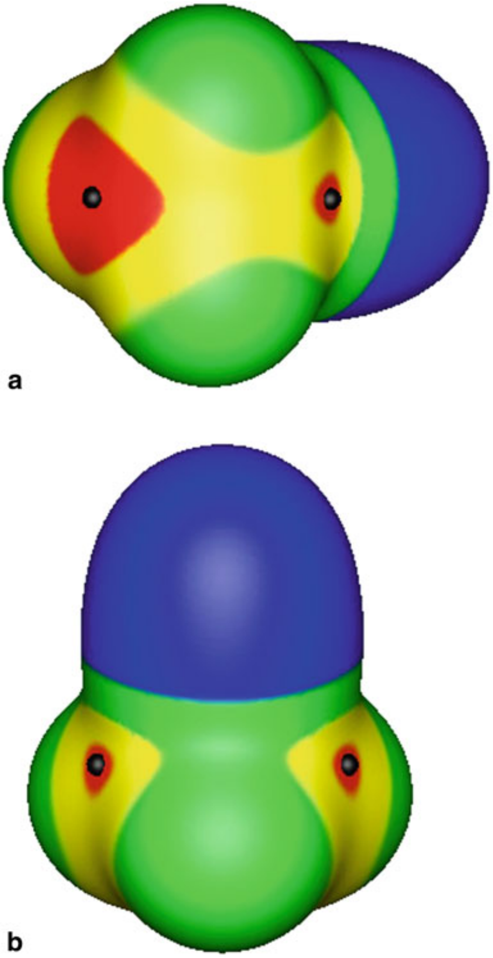


Fig. 10.4 Two views of the computed electrostatic potential on the 0.001 au molecular surface of SiH_3CN. In **a** the silicon is in the foreground, cyano group at *right*. In **b** a hydrogen is in the foreground, cyano group at *top*. *Black* hemispheres indicate silicon positive σ-holes on extensions of C–Si and H–Si bonds, the former being more positive. Color ranges, in kcal/mol: *red*, greater than 25; *yellow*, between 25 and 15; *green*, between 15 and 0; *blue*, less than 0 (negative). Computational level: M06-2X/6-311G(d, p)

2.24 Å. These values show the effect of the fluorines in attracting electronic density from the bromines.

The electronic density in a σ-hole is often sufficiently low that a positive electrostatic potential $V_S(\mathbf{r})$ results (Figs. 10.1, 10.2, 10.3 and 10.4). This is then a positive σ-hole, and favorable interactions with negative sites can be anticipated. In some instances, on the other hand, the electronic density in the σ-hole is high enough that its $V_S(\mathbf{r})$ is negative, i.e. a negative σ-hole, although less negative than its surroundings; see Fig. 10.5a. Examples of the $V_{S,max}$ of both positive and negative σ-holes are in Table 10.1 for the halogens [80, 81] and in Table 10.2 for Group IV—VI atoms [81]. The tables also give the most negative potentials ($V_{S,min}$) on these atoms.

It is very important to keep in mind, however, that the $V_S(\mathbf{r})$ computed for a free molecule in its unperturbed ground state, e.g. Figs. 10.1, 10.2, 10.3, 10.4 and 10.5, does not reflect the polarization induced by the electric field of another molecule

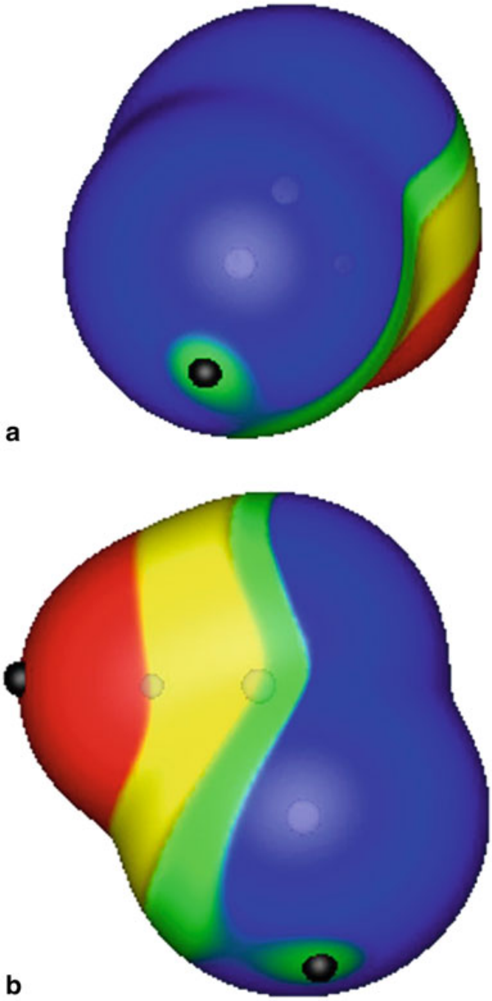


Fig. 10.5 Two views of the computed electrostatic potential on the 0.001 au molecular surface of FOH. In **a** the fluorine is in the foreground; the *black* hemisphere indicates its σ-hole, which is negative, on the extension of the O–F bond. In **b** the hydrogen is to the *left;* the *black* hemisphere on the hydrogen indicates the positive σ-hole on the extension of the O–H bond. Color ranges, in kcal/mol: *red*, greater than 30; *yellow*, between 30 and 0; *green*, between 0 and—8; *blue*, more negative than—8. Computational level: M06-2X/6-311G(d, p)

when they begin to interact. It has been demonstrated [82, 83] that polarization due to an external field can strengthen or weaken a σ-hole, and can sometimes convert it from negative (positive) to positive (negative). Thus one can occasionally find that a σ-hole complex forms even though the σ-hole may have been negative or near-neutral prior to the interaction; the negative site *induced* the positive σ-hole [84]. Some examples are $H_3C\text{-}Cl$—$O=CH_2$ [85] and H_3P—NSH [86], in which positive σ-holes were induced on the chlorine of H_3C–Cl and the phosphorus of H_3P.

Table 10.1 Most positive σ-hole potentials ($V_{S,max}$) and most negative potentials ($V_{S,min}$) on 0.001 au surfaces of the halogens shown in bold type, in kcal/mol. Computational method:M06–2X/6-311G(d, p)

Molecule	Bond producing σ-hole	$V_{S,max}$ (σ-hole)	$V_{S,min}$	Reference
HO–**F**	O–**F**	– 6.9	– 19.7	Present work
F–**F**	**F**–**F**	11.2	– 2.6	17
F–**Cl**	F–**Cl**	45.1	+ 0.3	80
F–**Br**	F–**Br**	53.2	– 0.1	80
Cl–**Cl**	**Cl**–**Cl**	25.4	– 2.7	80
Br–**Br**	**Br**–**Br**	29.0	– 4.1	80
H_3C–**F**	C–**F**	– 24.6	– 25.3	Present work
H_3C–**Cl**	C–**Cl**	– 0.9	– 15.6	Present work
H_3C–**Br**	C–**Br**	5.6	– 14.8	Present work
Br–$(CH_2)_4$–**Br**	C–**Br**	5.8	– 13.5	Present work
F_3C–**F**	C–**F**	– 1.3	– 2.8	81
F_3C–**Cl**	C–**Cl**	19.9	– 0.8	81
F_3C–**Br**	C–**Br**	25.3	– 2.0	81
Br–$(CF_2)_4$–**Br**	C–**Br**	26.3	– 1.7	Present work
F_3C–**I**	C–**I**	31.9	– 1.9	81
NC–**F**	C–**F**	12.8	10.9	17
NC–**Cl**	C–**Cl**	36.0	10.3	17
NC–**Br**	C–**Br**	42.7	8.6	17
NC–**I**	C–**I**	48.7	7.1	17
H_3Si–**Br**	Si–**Br**	0.2	– 11.9	Present work
H_3Ge–**Br**	Ge–**Br**	– 2.1	– 13.7	Present work
H_2P–**Br**	P–**Br**	3.5	– 14.3	Present work
F_2P–**Br**	P–**Br**	9.6	– 7.6	80
Cl–C≡C–**Cl**	C–**Cl**	23.7	– 0.6	Present work
Br–C≡C–**Br**	C–**Br**	30.1	– 2.1	17
C_6H_5–**Cl**	C–**Cl**	4.5	– 13.7	Present work
C_6H_5–**Br**	C–**Br**	10.2	– 13.7	Present work

10.4.2 Trends in σ-Hole Potentials

Since σ-holes are created by the shifting of electronic charge away from the outer portion of a singly-bonded atom, it is reasonable that the σ-hole electrostatic potential should become more positive as the atom is more polarizable and as it is less electronegative relative to the remainder of the molecule (particularly its bonding

Table 10.2 Most positive σ-hole potentials ($V_{S,max}$) and most negative potentials ($V_{S,min}$) on 0.001 au surfaces of the Group IV—VI atoms shown in bold type, in kcal/mol. Computational method: M06-2X/6-311G(d, p). The data are from the present work except as otherwise indicated

Molecule	Bond producing σ-hole	$V_{S,max}$ (σ-hole)	$V_{S,min}$
F**O**Br	F–**O**	10.5	– 11.7
	Br–**O**	−3.4	– 11.7
F**S**Br	F–**S**	35.9	– 4.0
	Br–**S**	27.2	– 4.0
F**Se**Br	F–**Se**	43.5	– 4.9
	Br–**Se**	35.2	– 4.9
H**Se**CN	H–**Se**	26.4	– 2.3
	C–**Se**	43.5	– 2.3
F_2**N**Br	F–**N**	13.2	– 9.4
	Br–**N**	11.8	– 9.4
H_2**P**Br	H–**P**	18.6	– 9.3
	Br–**P**	35.0	– 9.3
F_2**P**Br	F–**P**	32.3	11.4
	Br–**P**	35.1	11.4
F_2**As**Br	F–**As**	39.7	20.9
	Br–**As**	38.6	20.9
F_3**C**Br	F–**C**	16.0[a]	none[a]
	Br–**C**	21.6[a]	none[a]
F_3**Si**Br	F–**Si**	39.0[a]	none[a]
	Br–**Si**	45.0[a]	none[a]
F_3**Ge**Br	F–**Ge**	45.3[a]	none[a]
	Br–**Ge**	44.5[a]	none[a]
H_3**Si**CN	H–**Si**	26.8	none
	C–**Si**	37.7	none

[a] Reference 81

partner). Two common generalizations are [11,15–17]: (1) Within a given Group and for a particular molecular framework, the σ-hole potential ($V_{S,max}$) tends to become more positive in going from the lighter to the heavier (more polarizable and less electronegative) atoms, and (2) for a given atom, $V_{S,max}$ increases as the remainder of the molecule becomes more electron-attracting. These are useful empirical generalizations; supporting evidence can be seen in Tables 10.1 and 10.2. They explain, for example, why much of the early crystal engineering involving halogen bonding focused upon iodine, but in perfluorinated molecules [5, 8, 39]. Figure 10.1 and Table 10.1 show that perfluorination of the carbon chain of 1,4-dibromo-*n*-butane increases the bromine $V_{S,max}$ from 5.8 to 26.3 kcal/mol. The empirical generalizations also account for the fact that changing the bonding partner of bromine from the more electronegative carbon to silicon and germanium (in H_3C–Br, H_3Si–Br and H_3Ge–Br) causes the bromine σ-hole $V_{S,max}$ to become less positive and even negative (Table 10.1).

The first-row atoms N, O and F, being least polarizable and most electronegative, often have negative σ-holes (Fig. 10.5). It was indeed believed at one time that fluorine does not halogen bond. However it is well established since 2007 that fluorine *can* have a positive σ-hole and *can* participate in halogen bonding when it is in a sufficiently electron-attracting molecular environment [87–89]. In FCN, in fact, the portion of the molecular surface that is associated with the fluorine is entirely positive [87]; this is true as well of the other halocyanides (Table 10.1), demonstrating that positive σ-holes are not always surrounded by negative regions but sometimes simply by less positive ones. It has also been known since 2007–2009 that carbon [67], nitrogen [68] and oxygen [90] can also have positive σ-holes in appropriate molecular environments, and participate in σ-hole interactions. In the case of tetravalent Group IV atoms (which have no lone pairs), we have customarily found their entire exposed surfaces to be positive [67, 81].

It must be acknowledged that the generalizations concerning trends in σ-hole potentials, mentioned above, are somewhat oversimplified (although frequently valid). Consider, for instance, the molecule F_2PBr in Table 10.2 and Fig. 10.3. The phosphorus σ-hole produced by the bond to the bromine is more positive than that due to the bond to the fluorine, despite the fluorine's greater electronegativity. A detailed analysis [80] has shown that it is not only the polarizability and relative electronegativity of the σ-hole atom that are involved, but also the polarizability and electron-attracting power of the remainder of the molecule, plus factors such as overlapping with the electrostatic potentials of other parts of the molecule.

10.4.3 Covalently-Bonded Hydrogen

σ-Holes are not necessarily limited to singly-bonded atoms of Groups IV—VII. In particular, we must consider covalently-bonded hydrogen. Its electronic charge distribution, which involves just a single electron, is certainly anisotropic; it is centered in the internuclear region. This is why standard crystallographic techniques underestimate the lengths of covalent bonds to hydrogens [91, 92]. Accordingly, there is generally a positive σ-hole on the outer side of a hydrogen. This was in fact observed for the hydroxyl hydrogen in ethanol already in 1991 [93], although it was not labeled a σ-hole. Figure 10.5b clearly shows the hydrogen σ-hole in FOH. In some instances, as in Fig. 10.4b, a $V_{S,max}$ is not found on a hydrogen surface because the hydrogen's positive potential is overlapped by that of a larger neighboring atom. In Fig. 10.1a, the hydrogens do have $V_{S,max}$ but they are not shown explicitly. The interactions of such positive regions with negative sites readily explains hydrogen bonding as a σ-hole interaction [14, 15, 94, 95]; indeed, electrostatic interpretations of hydrogen bonding long preceded the discovery of σ-holes [55,93,96–100].

Since hydrogen has only the one valence electron, its lateral sides have relatively low electronic densities and the positive σ-hole usually covers a larger area than is typical of the Group V—VII atoms. Thus hydrogen σ-holes are less focused, as can be seen in Fig. 10.5b and in earlier reports [11, 15, 17, 94, 101]. It is accordingly not surprising that hydrogen bonds are overall less directional than are other σ-hole bonds [94, 102, 103].

10.5 σ-Hole Interactions

10.5.1 Interaction Energies

Attractive interactions between positive σ-holes and negative sites can give rise to numerous noncovalent complexes. Some examples are presented in Table 10.3 for the complexes R-X—B, R-Y—B and R-H—B, where X is a halogen, Y is a Group IV—VI atom and B represents the negative sites; in Table 10.3, these are the lone pairs of NH_3, HCN, $(H_3C)_2O$ and H_2S, the π electrons of C_6H_6, and the Br^- ion. The table includes the $V_{S,max}$ of the σ-holes, the $V_{S,min}$ of the negative sites, the interaction energies ΔE, the angles R-X—B, R-Y—B and R-H—B and the separations X—B, Y—B and H—B. The interaction energies were obtained with Eq. (10.3),

$$\Delta E = E(\text{complex}) - \sum_{i=1}^{2} E(\text{component } i) \tag{10.3}$$

Table 10.3 confirms that the X—B, Y—B and H—B distances are less than or similar to the sums of the respective van der Waals radii [104, 105]. The interactions are approximately linear, i.e. along the extensions of the R–X, R–Y and R–H bonds. Deviations from linearity generally reflect secondary interactions involving neighboring atoms; this is illustrated in Figs. 10.6 and 10.7.

In view of the structural similarity between halogen and hydrogen bonds (both are due to positive σ-holes on univalent atoms), it is natural to compare them. For a given R and B, the R-H—B interaction is generally stronger than the R-X—B (ΔE more negative) when X = F or Cl, but they become competitive when X = Br or I, with halogen bonding sometimes being stronger [106–108]. Compare, for instance, the ΔE values for $F_3C\text{-}H—NH_3$ (−4.2 kcal/mol), $F_3C\text{-}Cl—NH_3$ (−2.5 kcal/mol) and $F_3C\text{-}Br—NH_3$ (−3.7 kcal/mol) in Table 10.3. Instances of halogen bonding dominating over hydrogen bonding have long been observed experimentally [109, 110].

Table 10.3 Computed data for various types of σ-hole complexes. Interaction energies ΔE and geometries were obtained by optimizations with the M06-2X/aug-cc-pVTZ procedure. σ-Hole $V_{S,max}$ and negative site $V_{S,min}$, *prior* to interaction, were calculated at the M06-2X/6-311G(d) level

Complex	ΔE	σ-Hole $V_{S,max}$	Negative site $V_{S,min}$	Separation^a (Å)	Angle (degrees)
	(kcal/mol)				
Halogen-bonded:					
F-**F**—NH$_3$	– 1.5	11.2	– 46.7	**F**—N: 2.60 (3.05)	F-**F**—N: 177
F$_3$C-**Cl**—NCH	– 1.6	19.9	– 33.5	**Cl**—N: 3.13 (3.35)	C-**Cl**—N: 179
F-**F**—O(CH$_3$)$_2$	– 1.8	11.2	– 34.8	**F**—O: 2.48 (3.00)	F-**F**—O: 169
Br$_2$C = CBr(**Br**)—NCH	– 2.1	24.1	– 33.5	**Br**—N: 3.09 (3.46)	C-**Br**—N: 178
F$_3$C-**Cl**—NH$_3$	– 2.5	19.9	– 46.7	**Cl**—N: 3.03 (3.35)	C-**Cl**—N: 180
Br-C≡C-**Br**—NCH	– 2.7	30.1	– 33.5	**Br**—N: 3.05 (3.46)	C-**Br**—N: 180
Cl-**Cl**—SH$_2$	– 2.9	25.4	– 20.2	**Cl**—S: 3.13 (3.53)	Cl-**Cl**—S: 178
F$_3$C-**Br**—NH$_3$	– 3.7	25.3	– 46.7	**Br**—N: 3.07 (3.46)	C-**Br**—N: 180
N≡C-**Cl**—O(CH$_3$)$_2$	– 4.0	36.0	– 34.8	**Cl**—O: 2.77 (3.30)	C-**Cl**—O: 169
Br-C≡C-**Br**—O(CH$_3$)$_2$	– 4.1	30.1	– 34.8	**Br**—O: 2.86 (3.41)	C-**Br**—O: 172
Br-C≡C-**Br**—NH$_3$	– 4.2	30.1	– 46.7	**Br**—N: 2.99 (3.46)	C-**Br**—O: 180
F-**Br**—NCH	– 7.1	53.2	– 33.5	**Br**—N: 2.60 (3.46)	F-**Br**—N: 180
F$_3$C-**Cl**—Br$^-$	– 8.8	19.9	– 136.4	**Cl**—Br: 3.19 (3.59)	C-**Cl**—Br: 179
F$_3$C-**Br**—Br$^-$	– 12.9	25.3	– 136.4	**Br**—Br: 3.09 (3.70)	C-**Br**—Br: 180
Group IV-VI σ-hole-bonded:					
Cl$_2$**Se**—NCH	– 4.0	36.1	– 33.5	**Se**—N: 2.92 (3.51)	Cl-**Se**—N: 179
H$_2$F**P**—SH$_2$	– 4.1	38.8	– 20.2	**P**—S: 3.25 (3.59)	F-**P**—N: 166
H$_3$F**Si**—NCH	– 4.2	34.7	– 33.5	**F**—Si: 2.89 (3.54)	F-**Si**—N: 180
F$_2$**S**—NCH	– 4.5	40.2	– 33.5	**S**—N: 2.79 (3.40)	F-**S**—N: 174
H$_2$F**P**—NCH	– 4.7	38.8	– 33.5	**P**—N: 2.81 (3.41)	F-**P**—N: 164
H$_3$F**Ge**—NCH	– 4.9	43.0	– 33.5	**Ge**—N: 2.89 (–)	F-**Ge**—N: 180
HF**S**—SH$_2$	– 5.0	45.9	– 20.2	**S**—S: 3.08 (3.58)	F-**S**—S: 170
H$_2$F**As**—NCH	– 5.7	44.5	– 33.5	**As**—N: 2.82 (3.46)	F-**As**—N: 163
H$_2$F**P**—NH$_3$	– 7.2	38.8	– 46.7	**P**—N: 2.71 (3.41)	F-**P**—N: 167
HF**S**—NH$_3$	– 8.4	45.9	– 46.7	**S**—N: 2.48 (3.40)	F-**S**—N: 170
H$_2$F**As**—NH$_3$	– 8.7	44.5	– 46.7	**As**—N: 2.73 (3.46)	F-**As**—N: 165
ClF$_3$**Si**—NH$_3$	– 10.5	47.6	– 46.7	**Si**—N: 2.07 (3.71)	Cl-**Si**—N: 180
HF**Se**—NH$_3$	– 11.3	50.9	– 46.7	**Se**—N: 2.51 (3.51)	F-**Se**—N: 170

Table 10.3 Continued

Complex	ΔE	σ-Hole	Negative site	Separation[a] (Å)	Angle (degrees)
		$V_{S,max}$	$V_{S,min}$		
	(kcal/mol)				
Hydrogen-bonded:					
NC–**H**—SH_2	– 2.6	51.3	– 20.2	**H**—S: 2.71 (2.88)	C-**H**—S: 178
F_3C-**H**—NCH	– 3.0	34.8	– 33.5	**H**—N: 2.39 (2.70)	C-**H**—N: 178
H_3CO-**H**—SH_2	– 3.1	44.4	– 20.2	**H**—S: 2.53 (2.88)	O-**H**—S: 168
H_3CO-**H**—NCH	– 4.1	44.4	– 33.5	**H**—N: 2.13 (2.70)	O-**H**—N: 160
F_3C-**H**—NH_3	– 4.2	34.8	– 46.7	**H**—N: 2.31 (2.70)	C-**H**—N: 178
NC-**H**—NCH	– 4.7	51.3	– 33.5	**H**—N: 2.21 (2.70)	C-**H**—N: 180
H_3CO-**H**—C_6H_6	– 4.8	44.4	– 19.4	b	b
NC-**H**—NH_3	– 6.6	51.3	– 46.7	**H**—N: 2.11 (2.70)	C-**H**—N: 180
H_3CO-**H**—NH_3	– 6.7	44.4	– 46.7	**H**—N: 1.96 (2.70)	O-**H**—N: 176
F_3C-**H**—Br^-	– 14.0	34.8	– 136.4	**H**—Br: 2.45 (2.94)	C-**H**—Br: 180
H_3CO-**H**—Br^-	– 14.5	44.4	– 136.4	**H**—Br: 2.34 (2.94)	O-**H**—Br: 160
NC-**H**—Br^-	– 19.5	51.3	– 136.4	**H**—Br: 2.29 (2.94)	C-**H**—Br: 180

[a] Values in parentheses are the sums of the van der Waals radii of the interacting atoms, references 104 and 105. No van der Waals radius was found for germanium

[b] The hydroxyl hydrogen is above the center of the benzene ring, and thus is not directly in line with any particular atom

10.5.2 Interaction Energy Relationships

Since we consider σ-hole interactions to be electrostatic, does it follow that the ΔE values should correlate directly with the magnitudes of the $V_{S,max}$ and $V_{S,min}$? Not necessarily, for several reasons. First, the attractive interactions are not simply between a single point on the σ-hole (the $V_{S,max}$) and a single point on the negative site (the $V_{S,min}$); the whole σ-hole and negative regions can participate, as was shown by Shields et al [94]. Furthermore, interactions involving the remaining portions of the molecules may be significant (Figs. 10.6 and 10.7) [65, 81, 111]. Second, as pointed out in Sect. 4.1, the $V_{S,max}$ and $V_{S,min}$ are for the unperturbed molecules, prior to interaction, and do not reflect their mutual polarizing effects; these can be quite important, as shall be seen.

Despite these potential complications, which can be real, ΔE has been related—perhaps surprisingly well—to $V_{S,max}$ and to combinations of $V_{S,max}$ and $V_{S,min}$. When the negative site is kept the same, good correlations have been obtained between ΔE and the $V_{S,max}$ of the σ-holes [15, 16, 83, 111, 112]; as $V_{S,max}$ is more positive, ΔE tends to become more negative (stronger interaction). For instance, plots of ΔE *vs.* $V_{S,max}$ for two series of Group IV—VII complexes with NH_3 and with HCN had R^2 of

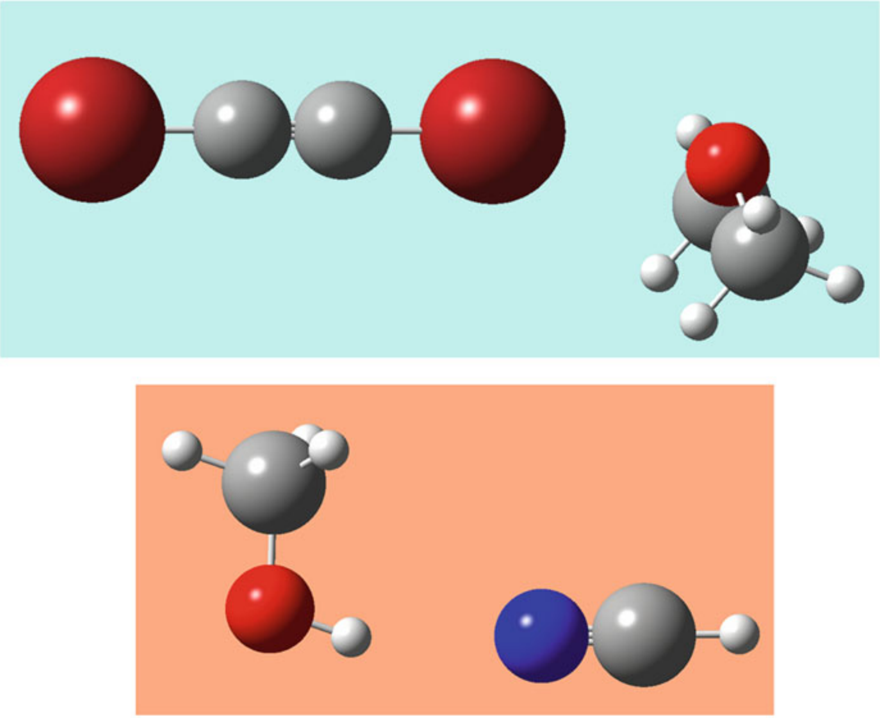


Fig. 10.6 Optimized geometries of Br-C≡C-Br—$O(CH_3)_2$ (*top*) and H_3CO-H—NCH (*bottom*). Carbons are *gray*, nitrogen *blue*, oxygens *red*, bromines *burgundy* and hydrogens *white*. The C-Br—O and O-H—N angles are 172.4 and 160.4°, respectively. Possible reasons for the deviations of these angles from 180° are the secondary interactions of methyl hydrogens with the negative sides of the bromine in the *top* structure and with the nitrogen lone pair in the *bottom* structure. Computational level: M06-2X/aug-cc-pVTZ

0.95 and 0.98, respectively [16]. When different negative sites are involved, then both the $V_{S,max}$ and the $V_{S,min}$ must be taken into account. Thus when the aforementioned complexes with NH_3 and HCN were taken together and ΔE was plotted against the product of the σ-hole $V_{S,max}$ and the negative site $V_{S,min}$, an R^2 of 0.96 was obtained.

We have now carried out a double regression analysis encompassing all 39 complexes in Table 10.3, thereby including σ-hole interactions of hydrogens, halogens and Groups IV—VI with six different negative sites. ΔE was expressed as,

$$\Delta E = c_1 V_{S,max} + c_2 V_{S,min} + c_3 \tag{10.4}$$

The relationship between the predicted and the computed ΔE is presented in Fig. 10.8; the R^2 is 0.91, which is noteworthy considering the varied nature of the database. (When the ΔE in Table 10.3 are correlated with the product of $V_{S,max}$ and $V_{S,min}$, R^2 is 0.88. While using the product may appear to be more consistent with Coulomb's Law, this is actually not the case, since $V_{S,max}$ and $V_{S,min}$ are potentials, not charges.)

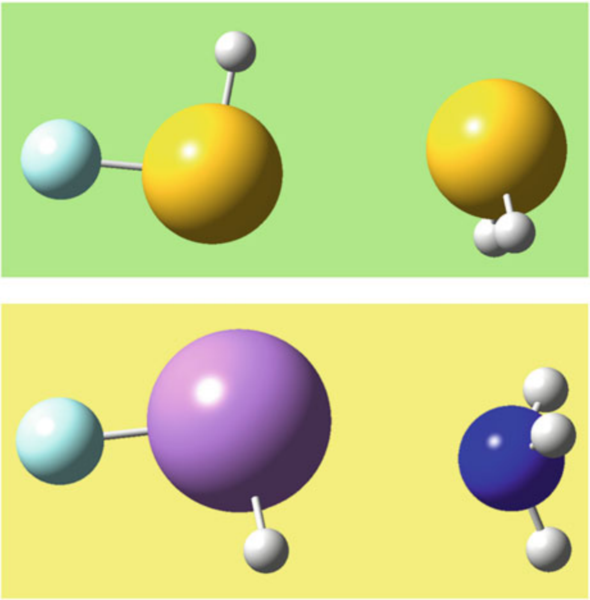


Fig. 10.7 Optimized geometries of HFS—SH_2 (*top*) and H_2FAs—NH_3 (*bottom*). Fluorines are light *blue*, nitrogen royal *blue*, sulfurs *yellow*, arsenic *lavender* and hydrogens *white*. The F-S—S and F-As—N angles are 169.5 and 165.0°, respectively. Possible reasons for the deviations of these angles from 180° are the secondary interactions of the HFS hydrogen with a negative side of the sulfur in the *top* structure and the hydrogens of H_2FAs with the nitrogen lone pair in the *bottom* structure. Computational level: M06-2X/aug-cc-pVTZ

In a variation of these studies, Shields et al looked at ΔE as a function of the positive potentials that would be created by the isolated R–H and R–Br molecules at the positions of the nitrogens in two series of complexes: (a) R-H—NCH and R-Br—NCH, and (b) R-H—NH_3 and R-Br—NH_3 [94]. This was done for R-H—N and R-Br—N angles ranging from 100 to 180°. For each series, ΔE correlated linearly and extremely well with the positive potentials at the nitrogen positions at the different angles; R^2 was 0.986 for the NH_3 complexes and 0.990 for the HCN. All of the interactions had negative ΔE, confirming that the entire σ-hole region can participate.

10.5.3 Thermodynamic Stability

We have discussed the energetics of σ-hole complex formation in terms of the interaction energies ΔE, as is customary. From a thermodynamic standpoint, however, stability is governed by the free energy change ΔG; at a given absolute temperature T,

$$\Delta G = \Delta H - T\Delta S \tag{10.5}$$

where ΔH and ΔS are the changes in enthalpy and entropy that accompany the formation of the complex. For thermodynamic stability, ΔG must be negative.

For a noncovalent interaction $A + B \rightarrow A—B$ in the gas phase at $T = 298$ K, ΔH is normally within 1 kcal/mol of ΔE [16, 113], and if the interaction is attractive, as in Table 10.3, then $\Delta E < 0$ and $\Delta H < 0$. ΔS is also typically negative, because

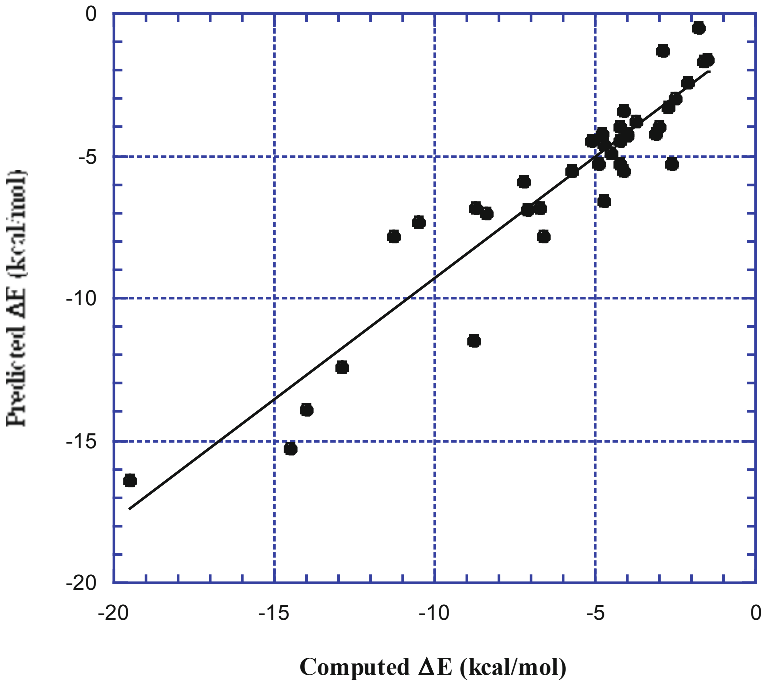


Fig. 10.8 Plot of ΔE predicted by double regression analysis, Eq. (10.4), *vs.* ΔE computed with Eq. (10.3) for the σ-hole complexes in Table 10.3. $R^2 = 0.91$

forming the complex diminishes the degrees of freedom of A and B. This can result in $|T\Delta S| > |\Delta H|$, so that $\Delta G > 0$ and the complex is thermodynamically unstable despite the interaction being attractive and having $\Delta E < 0$ and $\Delta H < 0$.

It has been found that $\Delta G > 0$ for many σ-hole complexes in the gas phase at 298 K [16, 113, 114]; it is only the relatively strong interactions that have $|\Delta H| > |T\Delta S|$ and therefore $\Delta G < 0$. It should be kept in mind, however, that $\Delta G > 0$ does not completely preclude an interaction; it simply means that the equilibrium constant is less than one.

When the interaction takes place in solution or in the solid state, additional factors are involved that may lead to $\Delta G < 0$ even when $\Delta G > 0$ for the gas phase complex. For example, the halogen-bonded solid —Cl-C(O)-C(O)-Cl—1,4-dioxane— was characterized crystallographically already in 1965 [115], although its gas phase ΔG(298 K) has been computed to be + 6.0 kcal/mol [16]. For further discussion of thermodynamic stability in relation to σ-hole interactions, see Politzer et al [16, 113].

10.6 The Nature of σ-Hole Interactions

10.6.1 The Hellmann-Feynman Theorem

We have presented a physical interpretation of σ-hole interactions, which include hydrogen bonding, in terms of electrostatics/polarization (the two are inextricably linked, unless only point charges are involved). This interpretation, which many theoreticians find unacceptably straightforward, has rigorous support: The potential energy terms in the Hamiltonian operator are Coulombic. This leads, via the rigorous Hellmann-Feynman theorem [116–119], to the conclusion that the forces acting upon the nuclei in a molecule or complex can be determined purely classically as Coulombic interactions with the electrons and with the other nuclei. (As an interesting aside, note that the Hellmann-Feynman theorem was originally derived neither by Hellmann nor by Feynman.)

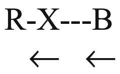
As Levine put it, "... there are no 'mysterious quantum-mechanical forces' acting in molecules." [120] A knowledge of the electronic density distribution, the nuclear positions and Coulomb's Law suffices to determine the forces within the system—in fact the electronic density also locates the positions of the nuclei, and indeed all of the system's properties, according to the Hohenberg-Kohn theorem [121].

Notwithstanding all of the above, theoreticians have happily argued for years about the relative roles of covalency and electrostatics in hydrogen bonding [96, 122, 123]. The argument is unimpeded by the fact that covalent bonds are themselves Coulombic (Hellmann-Feynman theorem) nor by the absence of any rigorous definition of covalency. The latter point is indeed very advantageous: since covalency cannot be measured, no one can be proved wrong and the argument can (and doubtless will) continue indefinitely. To make matters even better, new victims have appeared—halogen bonding and other σ-hole interactions—and can be subjected to the same intense scrutiny!

How can the distressingly simple Coulombic explanation of noncovalent bonding (i.e. electrostatics/polarization) be reconciled with the formidable array of complexities that are typically invoked? These generally consist of some subset of electrostatics, exchange, Pauli repulsion, polarization (or induction), charge transfer (or donor-acceptor interaction), dispersion, orbital overlap, etc. (Different researchers emphasize different subsets.)

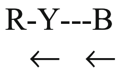
We will begin by separating exchange and Pauli repulsion from the others. They refer to mathematical requirements that must be satisfied by the wave function. Electrons are indistinguishable, which is handled by introducing exchange, and the wave function must be antisymmetric, which results in the Pauli exclusion principle (Pauli "repulsion"). These are mathematical effects [120, 124, 125], not physical forces. In the same context, orbitals are a valuable means of expressing wave functions but they have no physical existence [126]—nor does, therefore, orbital overlap.

Next, it should be recognized that analyses of noncovalent bonding commonly use the term "electrostatics" in a restricted and misleading manner, as referring to the Coulombic interaction between the *unperturbed* molecules *prior* to forming the complex. This is physically unrealistic [84]; it ignores the polarization of each molecule's electronic density distribution by the electric field of the other. This is shown schematically for the σ-hole complexes R-X—B, R-Y—B and R-H—B in **8–10** (X = halogen, Y = Group IV—VI atom). Such polarization is an intrinsic part of the Coulombic interaction [14–16, 85, 86, 95].



$\underset{\leftarrow\ \ \leftarrow}{\text{R-X---B}}$

8



$\underset{\leftarrow\ \ \leftarrow}{\text{R-Y---B}}$

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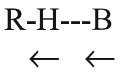


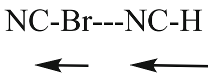
$\underset{\leftarrow\ \ \leftarrow}{\text{R-H---B}}$

10

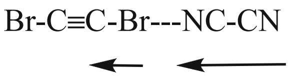
The error incurred in treating the electrostatic interaction as involving only the unperturbed isolated molecules and ignoring their mutual polarization is graphically illustrated by computing the difference between the electron density of the complex and the sum of the electronic densities of the isolated molecules placed at the same separation as in the complex. Such density difference plots for σ-hole complexes show exactly the features depicted in **8–10** [14, 85, 127, 128]: The electric field of the σ-hole polarizes the electronic charge of B toward the σ-hole, while the electric field of the negative site on B polarizes the electronic charge near the σ-hole away from B.

Another demonstration of the importance of polarization was provided by Hennemann et al [82]. They showed computationally that the electric field of a point charge Q placed at a distance of 1.90 Å from one of the hydrogens of a water molecule, Q—H-OH, caused the σ-hole potential of that hydrogen to vary linearly as a function of the charge on Q. In the absence of the point charge, the hydrogen's $V_{S,max}$ was 57 kcal/mol. As Q was made increasingly negative, it repelled electronic charge from the hydrogen σ-hole and made it more positive; thus for $Q = -0.4$ au, the σ-hole $V_{S,max}$ was 75 kcal/mol. As Q was made increasingly positive, on the other hand, it attracted electronic charge to the hydrogen σ-hole and made it less positive; for $Q = 0.4$ au, $V_{S,max} = 38$ kcal/mol. This shows how polarization can affect the electronic density distribution of a molecule, and in particular, that it can strengthen, weaken or even induce a positive σ-hole. It explains why the complexes H_3C-Cl—$O=CH_2$ [85] and H_3P—NSH [86] were found to form despite the chlorine and the phosphorus σ-holes in H_3C–Cl and H_3P being near-neutral or negative; positive σ-holes were induced by the electric fields of $O=CH_2$ and NSH (Sect. 4.1).

The polarization depicted in **8–10** and clearly evident in density difference plots [14, 83, 127, 128] readily explains why the formation of an initial σ-hole bond may promote a second one ("cooperativity") or might inhibit it [11, 15, 79, 89, 129]. Thus, it can be anticipated that **11** will have an enhanced likelihood for further interactions through both the terminal nitrogen and the terminal hydrogen. In **12**, on the other hand, the terminal atoms should be less prone to forming additional σ-hole bonds.


$\mathrm{NC{-}Br{-}{-}{-}NC{-}H}$

11


$\mathrm{Br{-}C{\equiv}C{-}Br{-}{-}{-}NC{-}CN}$

12

It was shown in Sect. 5.2 that the interaction energies of σ-hole complexes correlate quite well with the σ-hole $V_{S,max}$ and the negative site $V_{S,min}$, even though these are computed for the isolated molecules prior to interaction and therefore do not reflect their mutual polarization. An example of such a correlation is Fig. 10.8, which is based upon Table 10.3. Some σ-hole complexes, however, have been found to have unusually negative ΔE and short separations [130, 131], indicating atypically strong interactions. This simply means that polarization, particularly of the negative site, is very significant, and the polarizabilities of the σ-hole and especially of the negative site must be taken explicitly into account along with their $V_{S,max}$ and $V_{S,min}$. When this is done, via regression analyses, good correlations between predicted and computed ΔE are again obtained. For more extensive discussions of this, see Politzer et al [16, 17, 131].

Proceeding to dispersion, this is a very useful concept in interpreting noncovalent interactions since it can always be invoked when all else fails. The relative roles of dispersion and electrostatics are a favorite subject for debate, even though the Hellmann-Feynman theorem tells us that dispersion is part of the Coulombic interaction.

Dispersion is commonly linked to electronic correlation [101, 132, 133]. This refers to the instantaneous correlated movements of electrons as they respond to their mutual electrostatic repulsions. The usual view is that these movements create temporary dipoles, and it is the attraction between these dipoles that accounts for the stabilizing effect of dispersion.

Another view, widely overlooked, was proposed by Feynman [72]. He argued that the attraction is between the nuclei of each molecule and its own electronic charge, which has shifted to some extent into the intermolecular region. A study by Hirschfelder and Eliason [134] and a proof by Hunt [135] supported Feynman.

Whichever explanation one prefers, dipole-dipole or nuclear-electronic attractions, the point is that both are Coulombic. Thus dispersion is fully encompassed by the Hellmann-Feynman theorem.

10.6.2 Charge Transfer or Polarization?

Charge transfer from an “electron donor” to an “electron acceptor” has been widely invoked as an important factor in hydrogen and halogen bonding, and in σ-hole interactions in general. Some small fraction of an electron is supposedly transferred from the negative site B (the donor) into an antibonding orbital of the molecule R–X, R–Y or R–H that has the σ-hole (the acceptor). This weakens the R–X, R–Y or R–H bond and accounts for its stretching frequency often (but not always) being lower in the complex than in the isolated molecule (a red shift).

While this scenario can sometimes be effective as a purely mathematical model, it should not be confused with physical reality. Electrons are indivisible; a small portion of one cannot be plucked away. Orbitals—bonding, antibonding or otherwise—do not really exist [126], however useful and convenient the concept may be. It is increasingly being recognized [136–140] that charge transfer theory is a mathematical attempt to represent a physical process, which is the mutual polarization of the interacting molecules, the so-called "donor" and "acceptor." Thus it is redundant to cite both charge transfer and polarization as separate factors in noncovalent interactions [83, 84].

Hermansson [141] and Qian and Krimm [142] have derived formalisms that explain and predict both the red and the blue shifts in R–X, R–Y and R–H stretching frequencies in terms of just the electric field of B and the permanent and induced dipole moments of the R–X, R–Y and R–H molecules. These procedures have been extensively applied to σ-hole interactions [143, 144].

A simple demonstration of how polarization can produce either a red or a blue shift was provided by Hennemann et al [84]. They put a point charge Q near the hydroxyl hydrogen of methanol, Q—H-O-CH_3, and computed the O–H stretching frequency as a function of the charge on Q. Starting with $Q = 0$, as Q was made increasingly negative, the O–H frequency steadily decreased; when Q was made increasingly positive, the frequency increased until $Q = 0.3$ and then began to decrease. Thus both red and blue shifts could be produced by varying the charge and hence the electric field of Q, thereby polarizing the methanol molecule. The lower O–H frequencies cannot be due to the transfer of electronic charge into an antibonding orbital of the methanol because Q has no electronic charge to transfer. Both the red shifts and the blue shifts are purely polarization effects.

The mathematical rather than physical nature of the charge transfer concept is illustrated by an example due to Stone and Misquitta [145]. The usual quantum chemical description of a noncovalent complex, for example R-Y—B, is in terms of basis orbitals on both R–Y and B. However it could also be done quite satisfactorily using orbitals on only R–Y or only B, if enough of them were used. The polarization shown in **9** would be adequately described, by the computed electronic density distribution of the complex. However the charge transfer from an orbital of B into an orbital of R–Y would necessarily be zero, since either B or R–Y has no orbitals. The physical reality is maintained (by the electronic density distribution, which is an observable), but the mathematical model (charge transfer) fails.

To summarize, "charge transfer" in noncovalent interactions is, physically, polarization and polarization is Coulombic. The Hellmann-Feynman theorem lives on!

10.7 The Fallacy and Inadequacy of Atomic Charges

The preceding discussion is clearly linked to the question: Is it meaningful to assign quantitatively a charge to an atom in a molecule? In the laboratory, experience indicates the usefulness of viewing some atoms as having positive or negative characters relative to others. It is tempting to try to quantify this (a temptation to which one of the current authors yielded in his misspent youth [146]). However the concept of an atom in a molecule, while very useful in practice, does not have a rigorous basis—and therefore neither does giving it a numerical charge [53]. Since there is no correct way to do this, everyone is free to invent his/her own scheme, and many have done so. By 1994, more than 30 different procedures for assigning atomic charges had been proposed [147]. They sometimes produce remarkably varied results; for instance, Wiberg and Rablen cited calculated charges for the carbon in $H_3C–NO_2$ that ranged from—0.478 to + 0.564 [148].

Furthermore, attributing a single positive or negative charge to an atom in a molecule ignores the well-known anisotropies of its charge distribution and its electrostatic potential (Sect. 4.1). Price has referred to this rather bluntly as “a travesty of bonding theory” [149]. As was discussed in earlier sections, it is these anisotropies that account for the observed abilities of many covalently-bonded atoms to interact favorably with both positive and negative sites and for the phenomenon of “like attracting like.” Calculated atomic charges cannot explain such behavior [45, 84, 150].

Auffinger et al [45] pointed out that since many force fields used in molecular mechanics and molecular dynamics do use atomic charges, they may miss some noncovalent interactions; an example was presented by Dobeš et al [151]. Accordingly several research groups have sought to develop more realistic force fields [152–155].

10.8 Concluding Comments

The avalanche of studies that has descended upon the area of noncovalent interactions in recent years has subjected them to minute dissection and extensive compartmentalization. For instance, the literature now mentions at least a dozen types of hydrogen bonding!

Our emphasis, however, has been upon the unifying principle that a great many noncovalent interactions—involving atoms of Groups IV—VII as well as hydrogen—fit under the umbrella of σ-hole bonding (illustrated on the front cover of Physical Chemistry Chemical Physics, volume 15, issue 27, 2013): A region of positive electrostatic potential, on the extension of a single covalent bond to the atom, interacts attractively with a negative site. Closely related to this is so-called “π-hole” bonding, in which the positive potential is perpendicular to an atom or region in a planar portion of a molecular framework. This is examined in detail elsewhere [16, 156, 157].

We have also invoked the rigorous Hellmann-Feynman theorem (which seems to often be overlooked) to point out that these noncovalent interactions can be fully understood and described as being Coulombic, which includes polarization and dispersion. If this seems simplistic to some, we argue that it is because of a tendency to confuse mathematical modeling with physical reality. The latter can be annoyingly straightforward. Newton said that, "Nature is pleased with simplicity" [158]. Einstein seemed to agree: "Nature is the realization of the simplest conceivable mathematical ideas" [158].

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