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σ-hole bonding: molecules containing group VI atoms

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Abstract It has been observed both experimentally and computationally that some divalently-bonded Group VI atoms interact in a noncovalent but highly directional manner with nucleophiles. We show that this can readily be explained in terms of regions of positive electrostatic potential on the outer surfaces of such atoms, these regions being located along the extensions of their existing covalent bonds. These positive regions can interact attractively with the lone pairs of nucleophiles. The existence of such a positive region is attributed to the presence of a "σ-hole." This term designates the electron-deficient outer lobe of a half-filled p bonding orbital on the Group VI atom. The positive regions become stronger as the electronegativity of the atom decreases and its polarizability increases, and as the groups to which it is covalently bonded become more electron-withdrawing. We demonstrate computationally that the σ-hole concept and the outer regions of positive electrostatic potential account for the existence, directionalities and strengths of the observed noncovalent interactions.

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Introduction

Extensive analyses of the crystal structures of compounds containing divalent sulfur, R_1R_2S, have revealed that close contacts occurring between sulfurs and nucleophilic atoms (e.g., nitrogens and oxygens) on neighboring molecules have a marked directionality, being approximately along the extensions of the R_1-S or R_2-S bonds (usually within 20° of them) [1–3]. A "close" contact is one in which the internuclear distance is less than the sum of the atoms' van der Waals radii, and implies a noncovalent interaction.

This observation brings to mind the analogous finding for crystalline halides RX, where X=Cl, Br or I, that close intermolecular contacts with nucleophiles tend to be along the extensions of the R-X bonds [4–6]. This highly directional interaction is now termed "halogen bonding," and is of considerable importance in crystal engineering and drug design [7–10]. Halogen bonding typically involves X and a Lewis base; it increases in likelihood and in strength in going from X=Cl to X=Br to X=I. (There is now computational evidence that it can sometimes also take place when X=F, although rarely [10].) Halogen bonding has been shown experimentally to be competitive with hydrogen bonding [11–13].

Halogen bonding and the σ-hole

It was pointed out some time ago [14, 15] and again more recently [7], that halogen bonding can readily be explained in terms of the electrostatic potential on the surface of X.

(For this purpose, a molecular surface is defined as an outer contour of the electronic density, most often $\rho(\mathbf{r})=0.001$ electrons/bohr^3 [16]). While covalently-bonded halogen atoms are usually overall negative, some chlorines and even more bromines and iodines have the rather surprising feature of a region of positive electrostatic potential on the outermost portion of their surface, centered around the extension of the R-X bond. (The remainder of the halogen surface is generally negative.) The positive region becomes stronger as R becomes more electron-withdrawing relative to X and as the latter becomes more polarizable. (Halogen polarizability increases in the order F < Cl < Br < I [17]). Thus it is not observed for alkyl chlorides, but is present, for instance, in chloroacetylene and trifluoromethyl chloride; however it does appear in methyl bromide [9, 10].

The electrostatic interaction between the positive region on the halogen and a lone pair of a Lewis base, e.g., an NH$_2$ group, provides a straightforward interpretation of halogen bonding [7, 14, 15]. It is consistent with computed interaction energies [9, 10, 18, 19] and experimental observations [7, 8, 20]. What determines whether the halogen X in a halide RX has a positive outer region, and how strong it is? Two factors, as has already been noted, are the electron-withdrawing power of R relative to X and the polarizability of X. However these do not explain the directional feature, i.e., why the positive potential is centered about the extension of the R-X bond. To address this point, Clark et al. carried out a natural bond orbital (NBO) [21] analysis of the four trifluoromethyl halides F$_3$C-X, X=F, Cl, Br, and I [22]. In this series, when X=F, it does not have a positive outer region; when X=Cl, Br and I, it does, the strength increasing in that order.

The NBO study showed that when X=Cl, Br or I, the R-X bond along, say, the z-axis involves essentially just the half-filled p_z orbital of X. The contribution of the s is only 12%, 9% and 9%, respectively. Since the lone p_z electron is interacting with R, there is a deficiency of electronic charge in the outer lobe of the p_z orbital. This creates what was termed a "σ-hole" along the extension of the R-X bond, resulting in a positive electrostatic potential [22]. The σ-hole is most pronounced for Br and I, which have the purest p_z orbitals. It is enhanced by electron-withdrawal on the part of R, which increases as the halogen becomes less electronegative and more polarizable (from Cl to Br to I). Meanwhile the four p_x and p_y electrons produce a negative belt around the central portion of X.

In F$_3$C-F, on the other hand, each fluorine has significant sp hybridization, its s orbital contributing 25% to its R-F bond. Thus the σ-hole (which is the electron-deficient outer lobe of a half-filled p bonding orbital) is to some extent filled by s electronic charge. This counters the formation of a region of positive potential, unless R is extremely

electron-withdrawing relative to fluorine. (We also determined the relative levels of sp hybridization for F and Cl in H$_3$C-X and NC-X, X=F, Cl, and found them to be similar to those in F$_3$C-X [10]). For a given R, therefore, halogen hybridization, electronegativity and polarizability all indicate that the likelihood and magnitude of a positive outer region - and therefore the strength of halogen bonding - increase in the order F < Cl < Br < I. This is exactly what is observed both experimentally and computationally [7–10, 18–20].

Electrostatic potentials of R$_1$R$_2$Z molecules, Z=O, S, Se

It is natural to speculate that the directional close contacts with nucleophiles that have been found for divalent sulfur in molecular crystals [1–3], discussed earlier, also reflect the presence of positive σ-holes. The valence configuration of a free sulfur atom is $3s^2 3p_x^2 3p_y^1 3p_z^1$. If the sulfur contributes to the R$_1$-S and R$_2$-S bonds involve nearly pure half-filled $3p_y$ and $3p_z$ orbitals, then there should be electron deficiencies in their outer lobes and therefore, for sufficiently electron-withdrawing R$_1$ and/or R$_2$, σ-holes and regions of positive electrostatic potential along the extensions of the R$_1$-S and/or R$_2$-S bonds.

To test this possibility, we computed the electrostatic potential V(**r**) at the density functional B3PW91/6-31G** level on the 0.001 electrons/bohr^3 surfaces of several divalent sulfur molecules. V(**r**) is given rigorously by

$$V(\boldsymbol{r}) = \sum_A \frac{Z_A}{|\boldsymbol{R}_A - \boldsymbol{r}|} - \int \frac{\rho(\boldsymbol{r}')d\boldsymbol{r}'}{|\boldsymbol{r}' - \boldsymbol{r}|} \tag{1}$$

in which Z_A is the charge on nucleus A, located at **R**$_A$, and $\rho(\mathbf{r})$ is the electronic density. V(**r**) is a physical observable, which can be obtained experimentally, by diffraction methods [23, 24], as well as computationally. When V(**r**) is calculated on a molecular surface, we designate it $V_S(\mathbf{r})$.

In H$_2$S, the sulfur surface is completely negative. When bonded to the electronegative fluorine atom in F$_2$S, however, the sulfur does have a positive outer region, with two local maxima $V_{S,max}$ of 34.4 kcal mol^{-1} (see Fig. 1). The rest of the sulfur surface is negative. The two $V_{S,max}$ are located within 7° of the extensions of the F-S bonds, as predicted by the σ-hole concept. With the more strongly electron-withdrawing cyano group, in (NC)$_2$S, the sulfur $V_{S,max}$ increase to 42.7 kcal mol^{-1}. We verified that these positive potentials can be attributed to σ-holes by means of NBO analyses, which showed that the contributions of the sulfur to the S-F and S-CN bonds involve largely its 3p orbitals (see below). These results help to explain the close contacts, and their directionality, observed for sulfur in molecular crystals [1–3], as involving electrostatic attrac-
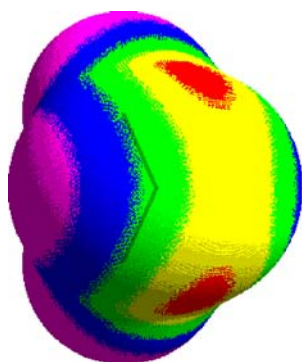
Fig. 1 Calculated B3PW91/6-31G** electrostatic potential of F_2S, computed on the 0.001 electrons/bohr^3 contour of the electronic density. Color ranges, in kcal mol^{-1}, are: red, greater than 30; yellow, between 20 and 30; green, between 10 and 20; blue, between 0 and 10; purple, less than 0. The sulfur atom is toward the reader; the red areas indicate the most positive potentials, reaching +34.4 kcal mol^{-1}, along the extensions of the F-S bonds. The purple region (negative) on the left and the one (not totally visible) on the right side of the sulfur are due to its nonbonded s and p electrons. The fluorines (top left and bottom left) also have negative regions of potential (purple areas)
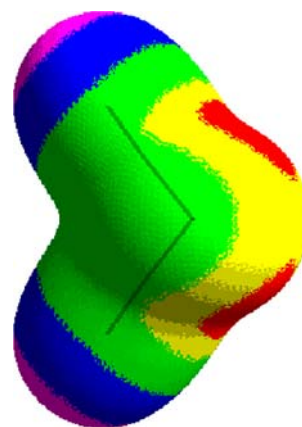

Fig. 2 Calculated B3PW91/6-31G** electrostatic potential of $(NC)_2Se$, computed on the 0.001 electrons/bohr^3 contour of the electronic density. Color ranges, in kcal mol^{-1}, are: red, greater than 35; yellow, between 20 and 30; green, between 0 and 20; blue, between −15 and 0; purple, more negative than −15. The selenium is at the right; the red areas indicate the most positive potentials, reaching 46.9 kcal mol^{-1}, along the extensions of the NC-Se bonds. The entire selenium surface is positive, due to the strong electron-withdrawing power of CN groups

tions between positive outer regions on the sulfurs and neighboring nucleophiles.

Can σ-holes also be exhibited by the other atoms in Group VI? We have computed $V_S(\mathbf{r})$ for a series of R_1R_2Z molecules, where Z=O, S and Se. Nearly all of them do show positive local maxima, $V_{S,max}$, on the surfaces of the atoms Z (Table 1). Consistent with the σ-hole concept, these $V_{S,max}$ are all located approximately on the extensions

Table 1 Computed (B3PW91/6-31G**) electrostatic potentials, kcal mol^{-1}

Molecule	Maximum positive potential, $V_{S,max}$, on surface of Group VI atom[a]
$(H_3C)_2O$	none
$(H_3C)FO$	11.9[b]
F_2O	13.8, 13.8
$(NC)_2O$	31.0, 31.0
$(H_3C)_2S$	3.6, 3.6
$(H_3C)FS$	28.8,[c] 4.9[d]
F_2S	34.4, 34.4
$(NC)_2S$	42.7, 42.7
$(H_3C)_2Se$	6.4, 6.4
$(H_3C)FSe$	34.8,[e] 9.6[f]
F_2Se	41.8, 41.8
$(NC)_2Se$	46.9, 46.9

[a] Surface defined by 0.001 electrons/bohr^3 contour of electronic density.
[b] On extension of F-O bond.
[c] On extension of F-S bond.
[d] On extension of C-S bond.
[e] On extension of F-Se bond.
[f] On extension of C-Se bond.

of the R_1-Z and R_2-Z bonds; the average deviation is 11° (see Figs. 1 and 2).

Table 1 shows that when R_1 or R_2 is CH_3, it does not produce a positive region on oxygen; note the cases of $(H_3C)_2O$ and $(H_3C)FO$. However when CH_3 is bonded to the more polarizable S or Se, then weak positive potentials do appear on these atoms. When R_1 or R_2 is the electronegative fluorine, then all three Group VI atoms have positive $V_{S,max}$, and these increase further for the even more electron-withdrawing CN. (In Fig. 2, the entire Se surface is positive, reflecting the strong effects of the CN groups.) For a given R_1 or R_2, $V_{S,max}$ becomes more positive in going from O to S to Se (see Table 1). These trends parallel those found for the halogens in the halides RX [9, 10]. We anticipate, therefore, that they will extend to tellurium, which should have the most positive $V_{S,max}$ values for Group VI (as does iodine for the halogens).

In order to more fully characterize these molecules, an NBO analysis (B3PW91/6-31G**) was carried out for those in Table 1 having $R_1=R_2$. In Table 2 are listed the percents of the electrons in each R_1-Z and R_2-Z bond that are associated with Z, as well as its s and p contributions to the bonds and to the nonbonding orbitals of Z. Also included in the table are the optimized R_1-Z-R_2 angles.

First it should be noted that one of the nonbonding orbitals of Z in each molecule is a pure p, with no s contribution. Thus the maximum hybridization that might be anticipated is sp^2. Second, the R_1-Z and R_2-Z bonds of the sulfur and selenium atoms involve largely their half-filled p orbitals; the % s (always less for Se) ranges from 6%–16%. This is true as well for the oxygen in F_2O.

Table 2 Natural bond orbital analysis, B3PW91/6-31G**, of valence electron distributions of atoms Z in molecules R_1R_2Z, Z = O, S, Se

Molecule, R_1R_2Z	Angle,[a] R_1-Z-R_2	R_1-Z, R_2-Z bonds[b]			Z nonbonding orbitals[b]	
		% Z	% s	% p	% s	% p
$(H_3C)_2O$	112	67	28	72	44	55
					0	100
$(H_3C)_2S$	101	46	15	84	69	31
					0	100
$(H_3C)_2Se$	99	44	12	87	76	24
					0	100
F_2O	104	43	8	92	86	14
					0	100
F_2S	100	24	7	91	87	13
					0	100
F_2Se	98	22	6	94	91	9
					0	100
$(NC)_2O$	118	68	30	70	40	60
					0	100
$(NC)_2S$	100	45	16	83	68	32
					0	100
$(NC)_2Se$	97	41	13	87	75	25
					0	100

[a] Optimized at the B3PW91/6-31G** level.
[b] In those instances in which % s + % p ? 100, it is due to small d contributions.

Finally, for a given R_1 and R_2, the percent of the bonding electrons associated with Z decreases in the order O >> S > Se, as expected from their electronegativities and polarizabilities.

All of this is consistent with the σ-hole concept as an interpretation of the observed trends with regard to positive outer regions on the atoms Z (Table 1). The oxygens in $(H_3C)_2O$ and $(NC)_2O$ differ from the others in that they approach sp^2 character; this can be seen in their high % s in the R_1-O and R_2-O bonds, and in the large R_1-O-R_2 angles. This, together with the high electronegativity and low polarizability of oxygen, precludes its having positive $V_{S,max}$ in $(H_3C)_2O$. The very strong electron-withdrawing power of the CN group is evidently able to overcome these factors, as evidenced by the two oxygen $V_{S,max}$ in $(NC)_2O$ (Table 1). The increasingly p natures of the S and Se contributions to the R_1-Z and R_2-Z bonds, plus their progressively lower electronegativities and greater polarizabilities, explain the correspondingly stronger positive potentials. Tellurium presumably continues this trend.

Noncovalent interactions

In addition to the analyses of sulfur-containing molecular crystals [1–3], already mentioned, there have been a number of other studies, both experimental and computational, of noncovalent interactions between divalently-bonded Group VI atoms and nucleophiles. Many of these, summarized by Iwaoka et al. [25] have involved selenium. Complexes of nitrogen bases with divalent S, Se, and Te have been reported by Cozzolino et al. [26]. There have also been found, for a given Group VI atom Z, interactions of the type R_1R_2Z----ZR_3R_4 [2, 3, 27]. In the latter, the relative orientations of the two molecules are such that the positive outer region on one Z is approaching a negative region on a lateral side of the other Z (see Fig. 1).

As part of the present investigation, we have looked at the interactions of the F_2Z and $(NC)_2Z$ molecules in Tables 1 and 2 with the nitrogens of NH_3 and HCN. The density functional B3PW91/6-311G(3df,2p) procedure was used for geometry optimizations, with minima being verified by the absence of imaginary vibration frequencies. Interaction energies ΔE were obtained by means of Eq. (2),
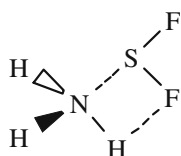
$$\Delta E = E_{complex} - \sum E_{reactants} \quad (2)$$

in which the E correspond to the energy minima at 0 K. ΔE was computed at both the B3PW91/6-311G(3df,2p) and the MP2/6-311++G(3df,2p) levels, using the B3PW91 geometries. Basis set superposition error (BSSE) was not explicitly taken into account, since it should be minimal with these large basis sets.

The calculated interaction energies are in Table 3, as are the optimized N-Z-R_1 angles. The latter are all between 166° and 180°, indicating that the interactions are essentially along the extensions of the R_1-Z bonds, as would be predicted from the positions of the $V_{S,max}$ on the surfaces of the atoms Z. The MP2 ΔE are generally somewhat more negative than the corresponding B3PW91, particularly for the HCN complexes; the largest difference is 2.4 kcal mol^{-1}. This may be due to the larger MP2 basis set and/or the MP2 being better able to take account of dispersion effects.

The interactions with NH_3 are stronger than those with HCN, because of the nitrogen of the former having a more negative electrostatic potential; it reaches −46.3 kcal mol^{-1} in NH_3 vs. −32.9 kcal mol^{-1} in HCN (B3PW91/6-31G**). For a given R_1, R_2 pair (F, F or CN, CN) and nucleophile (NH_3 or HCN), the magnitude of ΔE increases from Z=O to Z=S to Z=Se, as the $V_{S,max}$ on the atom Z become more positive (Table 1). Thus the interactions become progressively stronger in going from the lightest to the heaviest Group VI atom, the same trend found by Cozzolino et al. in a survey of intermolecular distances in the crystal structures of Group VI diazoles,[26] and by Bleiholder et al. for their $(H_3C)_2Z$----ZCH_3R complexes.[27]

It is important to recognize that the ΔE in Table 3 reflect not only the interactions with NH_3 or HCN along the extensions of the R_1-Z bonds, but also any that may be occurring between R_2 and the NH_3 or HCN. A notable example is hydrogen bonding in the H_3N----SF_2 and H_3N----SeF_2 complexes, as depicted in **1** for the former:

The relevant H----F separations in H_3N----SF_2 and H_3N----SeF_2 are 2.58 and 2.47 A, both less than the sum of the H and F van der Waals radii, 2.67 A [28]. Hydrogen bonding is not a factor in H_3N----OF_2, in which the N----O interaction is much weaker due to the low $V_{S,max}$ of the oxygen, and the N----O distance consequently considerably greater (by about 0.5 A) than the N----S in H_3N----SF_2 and the N----Se in H_3N----SeF_2. The shortest H----F separation in H_3N----OF_2 is accordingly 3.39 A. The hydrogen bonding in H_3N----SF_2 and H_3N----SeF_2 can explain why their interaction energies are more negative relative to those of H_3N----$S(CN)_2$ and H_3N----$Se(CN)_2$ than would be expected from the $V_{S,max}$ in Table 1.
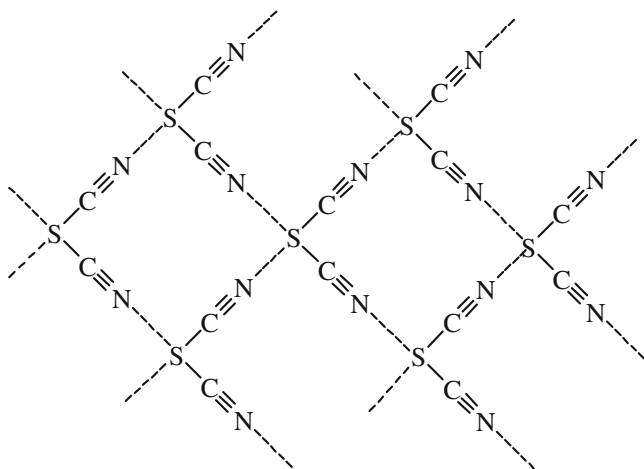
Summary

We have demonstrated that the σ-hole concept and the regions of positive potential on the outer surfaces of some divalently-bonded Group VI atoms provide a ready explanation of their highly-directional noncovalent interactions with nucleophiles: the electrostatic attraction between a positive $V_{S,max}$ of the Group VI atom and the negative potential of a lone pair of the nucleophile. This accounts for the known trend in the strengths of these interactions: O < S < Se < Te [26, 27]. Unlike some other interpretations, which involve an unoccupied antibonding orbital of R_1R_2Z, [2, 3, 25–27] our focus is upon the electron-deficient outer lobe of a p bonding orbital of Z.

As has been pointed out [26, 27], these interactions offer interesting possibilities for crystal engineering, just as does halogen bonding [8–10]. For example, one can imagine a two-dimensional network such as **2**. The feasibility of such structures remains to be investigated.

Table 3 Computed interaction energies (kcal mol^{-1}) and angles (degrees)[a]

Complex, H_3N, HCN----ZR_1R_2	Angle, N-Z-R_1	ΔE, B3PW91/6-311G(3df,2p)	ΔE, MP2/6-311++G(3df,2p)
H_3N----OF_2	170	−1.3	−1.9
H_3N----SF_2	175	−8.4	−7.7
H_3N----SeF_2	169	−13.2	−12.2
H_3N----$O(CN)_2$	166	−3.8	−4.5
H_3N----$S(CN)_2$	174	−7.7	−8.0
H_3N----$Se(CN)_2$	170	−9.5	−9.7
HCN----SF_2	180	−2.4	−4.4
HCN----SeF_2	176	−4.7	−6.4
HCN----$S(CN)_2$	177	−3.5	−5.9
HCN----$Se(CN)_2$	173	−4.4	−6.8

[a] Geometries were optimized at the B3PW91/6-311G(3df,2p) level.

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