

Article

σ -Hole Interactions: Perspectives and Misconceptions

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Abstract: After a brief discussion of the σ -hole concept and the significance of molecular electrostatic potentials in noncovalent interactions, we draw attention to some common misconceptions that are encountered in that context: (1) Since the electrostatic potential reflects the contributions of both the nuclei and the electrons, it cannot be assumed that negative potentials correspond to “electron-rich” regions and positive potentials to “electron-poor” ones; (2) The electrostatic potential in a given region is determined not only by the electrons and nuclei in that region, but also by those in other portions of the molecule, especially neighboring ones; (3) A σ -hole is a region of lower electronic density on the extension of a covalent bond, not an electrostatic potential; (4) Noncovalent interactions are between positive and negative regions, which are not necessarily associated with specific atoms, so that “close contacts” between atoms do not always indicate the actual interactions.

Keywords: σ -holes; noncovalent interactions; electrostatic potential; close contacts

1. A Brief History of the σ -Hole

The σ -hole concept was introduced by Clark in the context of halogen bonding, at a conference in 2005 [1], although it did not appear in the chemical literature until 2007 [2]. Halogen bonding involves a favorable noncovalent interaction between a covalently-bonded halogen and a negative site, such as a lone pair. Such interactions were already known to experimentalists in the 19th century [3,4], and were studied extensively in the 20th [5–10], with crystallography playing a major role [10–13]. Nevertheless the basis for halogen bonding was not really understood. It was frequently rationalized as “charge transfer” from an electron “donor” (e.g., the lone pair) to an “acceptor” (the halogen), invoking the valence bond formalism of Mulliken [14] (which was later put in molecular orbital terms by Flurry [15,16]).

However, the halogen is the most electronegative atom in each row of the periodic table, and a singly-bonded halogen atom is generally viewed as being negative in character. So why should it interact attractively with a donor of electronic charge? It was in fact pointed out long ago [7,17] that Mulliken’s charge-transfer formalism was not intended to be an elucidation of the bonding in a ground-state noncovalent complex; it was purely a mathematical modeling of the transition of the ground-state complex to a low-lying excited state. The existence of halogen bonding was thus viewed by many as an enigma.

The key to resolving the enigma was the molecular electrostatic potential. This is the potential $V(\mathbf{r})$ that is created at any point \mathbf{r} in the space of a molecule by its nuclei and electrons, given rigorously by Equation (1):

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

Z_A is the charge on nucleus A, located at \mathbf{R}_A , and $\rho(\mathbf{r})$ is the molecule’s electronic density. Regions in which $V(\mathbf{r})$ is positive, indicating the dominance of the nuclear contribution, are attractive to

negative sites; regions of negative $V(\mathbf{r})$ reflect a dominant electronic contribution and are attractive to positive sites.

The electrostatic potential, as given by Equation (1), is a real physical property, and observable. It can be determined experimentally by diffraction techniques [18–20] as well as computationally. It is accordingly a physically meaningful representation of the electrostatic effects of the charge distribution in a molecule, unlike calculated atomic charges, which have often been used for the same purpose. These have no physical basis [21–24]; they are arbitrarily defined by any one of numerous proposed methods and can vary greatly depending upon which method is used. For instance, seven different schemes for assigning atomic charges produced values for the carbon in nitromethane that ranged from -0.478 to $+0.564$ [23].

What could have been a first step in resolving the enigma of halogen bonding was a study in 1977 by Kollman, who calculated the electrostatic potentials at selected single points around several diatomic molecules [25]. For both F_2 and Cl_2 , he found points with positive potentials to the outsides of the nuclei, on the extensions of the bonds, and points with negative potentials directly above the nuclei, perpendicular to the bonds. He used this observation to explain the fact that the Cl_2 dimer does not have the expected T-shaped structure but rather is L-shaped, the positive end of one Cl_2 molecule interacting with the negative potential above a nucleus of the other. This is also the orientation of the molecules in the lattice structure of crystalline Cl_2 [26,27].

These Cl_2-Cl_2 interactions are examples of halogen bonding, and Kollman's points with positive and negative potentials could have been an early clue to its nature. If Mulliken had known about the positive potentials on the outer sides of the halogen atoms, he might not have predicted (incorrectly) that the complex formed between the iodine molecule and benzene has the I_2 parallel to the benzene ring [14].

The full explanation of halogen bonding came later, through much more extensive studies by Brinck et al. in which $V(\mathbf{r})$ was computed on the entire molecular surfaces of several molecules containing univalent halogen atoms [28,29], e.g., CH_3Br and CCl_4 . The surfaces were taken to be the 0.001 au contours of the molecular electronic densities, as suggested by Bader et al. [30]; the potential computed on such a surface is labeled $V_S(\mathbf{r})$.

It was found that the halogen atoms in these molecules have regions of positive electrostatic potential on their outer sides, on the extensions of their bonds, while their lateral sides are negative. Brinck et al. recognized that these positive regions can interact attractively with negative sites, and thus explain halogen bonding [28,29]. The simultaneous presence of both positive and negative regions also accounts for the observation, in a survey of halide crystal structures [13], that the halogen atoms can interact attractively with negative sites (nucleophiles) along the extensions of their bonds and with positive sites (electrophiles) in lateral directions. In fact it is possible to have a favorable interaction between a positive region on a halogen atom in one molecule and a negative region on the same halogen atom in another, identical molecule [31].

As an example of the positive and negative regions on a univalent halogen atom, Figure 1 shows the electrostatic potential on the 0.001 au surface of the molecule H_2PBr , **1**. (All calculations to be reported are at the density functional M06-2X/6-31G* level, using the Gaussian 09 [32] and WFA-SAS [33] codes. The 6-31G* basis set has been demonstrated to give reliable electrostatic potentials [34].) In Figure 1a, note the positive potential on the outside of the bromine, along the extension of the P–Br bond; its most positive value (the local $V_{S,max}$) is 5 kcal/mol. The lateral sides of the bromine are negative.

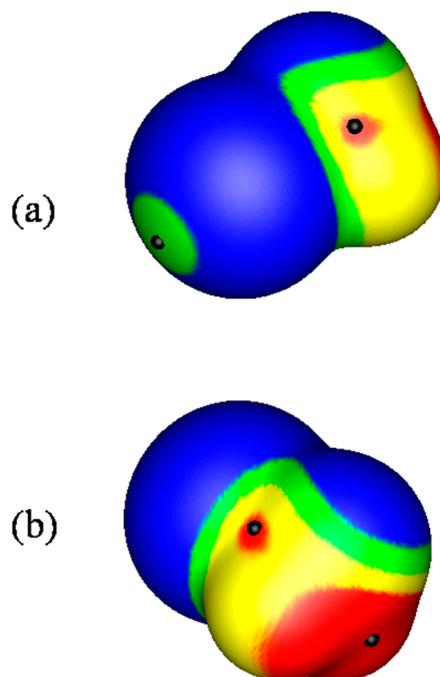
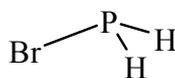


Figure 1. Computed electrostatic potential on the 0.001 au molecular surface of H_2PBr , **1**. In (a), the bromine is in the foreground, to the left. In (b), it is in the rear, to the left. Color ranges, in kcal/mol: red, greater than 16; yellow, between 16 and 8; green, between 8 and 0; blue, less than 0 (negative). The black hemispheres show the locations of the most positive potentials, the $V_{S,\text{max}}$. In (a) is shown the $V_{S,\text{max}}$ on the bromine and one of the three on the phosphorus; In (b) are shown the other two $V_{S,\text{max}}$ on the phosphorus. The hydrogens do not have separate $V_{S,\text{max}}$ in this molecule.



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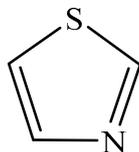
What is the origin of such positive potentials on electronegative atoms? It has been known for quite some time that atoms involved in covalent single (and sometimes double) bonds have lesser electronic densities (and shorter radii) on the extensions of the bonds than on their lateral sides [12,26,27,35–40]. This has sometimes been called “polar flattening”. For the bromine in Figure 1, the distance from its nucleus to the 0.001 au surface along the extension of the P–Br bond is 2.10 Å, compared to 2.25 Å from the nucleus to a lateral side.

The region of lower electronic density on the extension of a bond is what Clark labeled the σ -hole [2]. Very often there is a positive electrostatic potential associated with it that can interact favorably with a negative site. This is the basis for halogen bonding, as was pointed out by Brinck et al. [28,29].

It is not only covalently-bonded halogens that have lower electronic densities (σ -holes) on the extensions of their bonds; this is true as well of covalently-bonded atoms in other Groups of the periodic table [12,35–38,40]. In the years 2007–2009, positive σ -hole potentials were found for atoms in Groups VI [41], V [42], and IV [43]. For instance, the phosphorus atom in H_2PBr , **1**, has three positive σ -hole potentials; the strongest is on the extension of the Br–P bond, Figure 1b, with a maximum value ($V_{S,\text{max}}$) of 33 kcal/mol. Two weaker phosphorus $V_{S,\text{max}}$ of 17 kcal/mol are due to the H–P bonds (see Figure 1a,b). The phosphorus also has a negative potential associated with its lone pair.

Just as for the halogens, these positive regions can interact attractively with negative sites, and thus account for noncovalent interactions involving Groups IV–VI that have been known experimentally (and later computationally) for many years [35,37,44–49]. However, they were not recognized as σ -hole

interactions until 2007–2009 [41–43]. Particularly notable was the work of Burling and Goldstein [45], who computed the electrostatic potential in the molecular plane of 1,3-thiazole, **2**, and found positive regions on the sulfur that would now be described as positive σ -hole potentials. This explained an intramolecular S—O close contact that stabilizes a biologically active 1,3-thiazole conformation in a nucleoside drug.

**2**

To understand Group IV–VII noncovalent interactions, it is essential to recognize that the electrostatic potentials on the surfaces of covalently-bonded atoms can and frequently do have both positive and negative regions. (Some exceptions that have only positive potentials include atoms linked to very electron-attracting residues and tetravalent Group IV atoms, which have all of their valence electrons in σ bonds.) Atomic charges, whereby each atom is assigned a single positive or negative charge, cannot account for the possibility of simultaneous positive and negative regions.

The interactions that have been discussed are all examples of σ -hole bonding. In recent years, there has developed the unfortunate tendency to label them according to the group: Group IV, tetrel bonding; Group V, pnictogen bonding; Group VI, chalcogen bonding; Group VII, halogen bonding. This obscures the essential point that these are all essentially the same type of interaction.

2. Characteristics of σ -Holes: Some Common Misconceptions

2.1. Locations and Strengths of Positive Potentials

In interpreting molecular electrostatic potentials, it is often assumed that they track the electronic density, i.e., that “electron-rich” regions will have negative potentials and “electron-poor” ones will have positive potentials. While this may sometimes appear to be the case, it cannot, in general, be correct: As Equation (1) shows, and as has been stressed earlier [50–54], the electrostatic potential $V(\mathbf{r})$ at any point \mathbf{r} does not reflect only the electronic density at \mathbf{r} ; $V(\mathbf{r})$ is the resultant of contributions from all of the electrons and all of the nuclei in the molecule. The effect of the nuclei can be very significant. For example, the electrostatic potential of a neutral ground-state atom is positive everywhere despite the electronic charge being exactly equal to the nuclear charge [55]; the effect of the latter dominates over that of the dispersed electrons. It is well established both crystallographically and computationally that the internuclear regions of covalent bonds generally feature buildups of electronic density [20,56,57], yet the electrostatic potentials in bond regions are usually positive [18,50,58]. The contributions of the nuclei prevail. It cannot be assumed that high (low) electronic densities correspond to negative (positive) electrostatic potentials. The potential in a given region is the net result of negative contributions from the electrons and positive ones from the nuclei of the entire molecule, their effects of course being greater as they are closer to the region in question.

A key point in the context of σ -hole interactions is that the term σ -hole refers to a region of lower electronic density along the extension of a covalent bond, not to an electrostatic potential (as is often implied). The lower electronic density (the σ -hole) is usually (not always) reflected in a region of positive potential, but this is subject to influences from other portions of the molecule that frequently affect its magnitude and location [53,54,59].

The situation is most straightforward for halogens. A singly-bonded halogen atom, having only one close neighbor, tends to somewhat protrude from the molecule; note the bromines in H_2PBr , **1** (Figure 1) and in 4-bromo-1,2-diazole, **3** (Figure 2). This means that its electrostatic potential is less

subject to influences from neighboring atoms, so that the more positive (or less negative) potential due to the σ -hole is typically rather focused along the extension of the bond. In H_2PBr , **1**, the $V_{S,\text{max}}$ of the bromine σ -hole deviates by only 5° from the extension of the P–Br bond; in the diazole **3**, the deviation from the extension of the C–Br bond is only 1° . As a result, in a R–X–B complex, where X is a halogen atom and B is the negative site, the angle R–X–B tends to be nearly linear [47,60]; for instance in the complex $\text{H}_2\text{PBr–NCH}$, **4**, which has a calculated interaction energy of -2 kcal/mol, the P–Br–N angle is 174° . (In **4**, the phosphorus is yellow, the bromine is red, and the nitrogen is blue.)

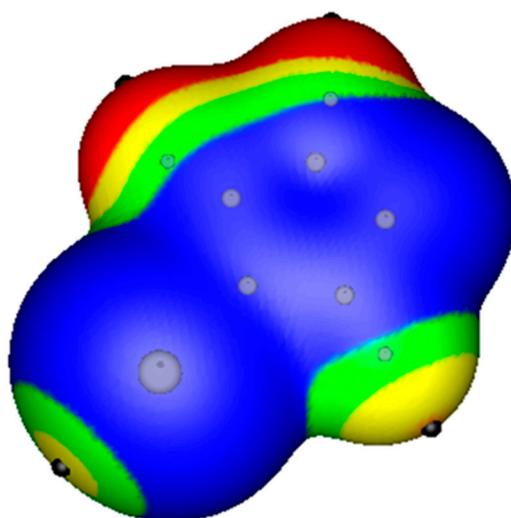
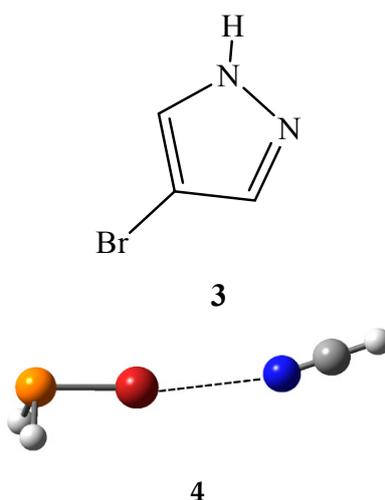


Figure 2. Computed electrostatic potential on the 0.001 au molecular surface of 4-bromo-1,2-diazole, **3**. The atom positions are as in structure **3**, the bromine being at the lower left. Color ranges, in kcal/mol: red, greater than 16; yellow, between 16 and 8; green, between 8 and 0; blue, less than 0 (negative). The black hemispheres show the locations of the most positive potentials, the $V_{S,\text{max}}$, one on the bromine, and one on each hydrogen.



For singly-bonded halogens, the magnitudes of the potentials related to their σ -holes tend qualitatively to become more positive as the remainder of the molecule is more electron-attracting. Thus they depend upon the relative electronegativities and polarizabilities of the halogen and the molecular residue [47,60,61]. This is why crystal engineering through halogen bonding has so frequently involved iodides [62,63]; iodine is the least electronegative and most polarizable halogen, and thus its σ -hole potentials are usually more positive than those of the other halogens. It also explains why fluorine, with its high electronegativity and low polarizability, often has negative potentials

associated with its σ -holes, although they are less negative than their surroundings. For example, the fluorines in hexafluorothiacyclobutane, **5** (Figure 3), clearly have σ -holes; the distances to the 0.001 au contour along the bond extensions are 1.55 Å vs. 1.59 Å to their lateral sides. However, the electrostatic potentials on the bond extensions are negative, although less so than on the lateral sides of the fluorines. On the other hand, sulfur does have a positive σ -hole potential when the remainder of the molecule is very strongly electron-attracting [64–66], e.g., in FCN.

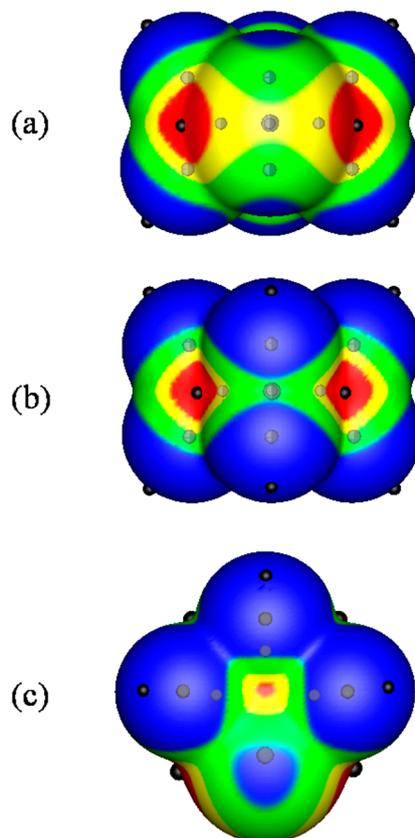
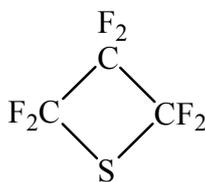


Figure 3. Computed electrostatic potential on the 0.001 au molecular surface of hexafluorothiacyclobutane, **5**. In (a), the sulfur is in the foreground, with CF₂ groups behind it on both sides. In (b), a CF₂ group is in the foreground, the other two being behind it on both sides; the sulfur is in the rear, not visible. In (c), the view is from above the four-membered ring.



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For atoms of Groups IV–VI, rationalizing the locations and strengths of electrostatic potentials linked to σ -holes is likely to be more difficult than for the halogens. These atoms can be involved in two or more covalent bonds and the potentials on their surfaces are accordingly more subject to influences from neighbors. Consider the molecule AsFBr(CN), **6** (Figure 4). As would be expected, the arsenic has positive potential regions that can be attributed to σ -holes, with a local $V_{S,max}$ corresponding to each of its three bonds. However, the locations of the $V_{S,max}$ deviate by 19°, 16° and 21° from the extensions of

the Br–As, F–As, and NC–As bonds, respectively [54]. In contrast, the $V_{S,max}$ on the bromine deviates by only 4° from the extension of the As–Br bond.

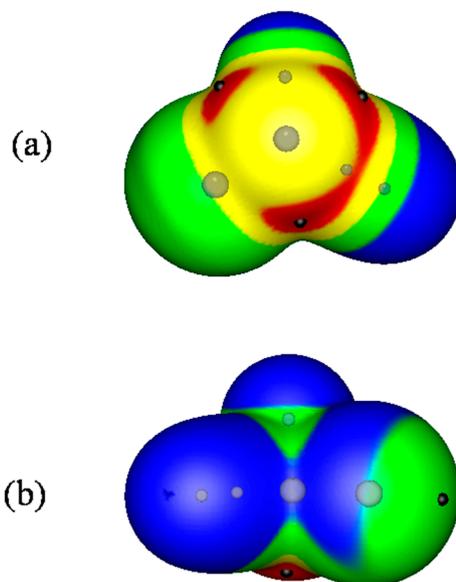
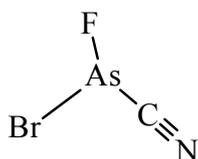
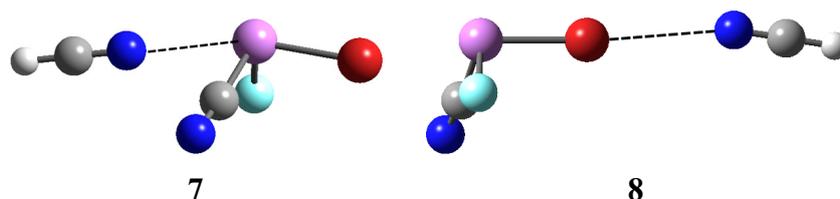


Figure 4. Computed electrostatic potential on the 0.001 au molecular surface of AsFBr(CN), **6**. In (a), the arsenic is in the foreground, the bromine is to the lower left and the CN is to the lower right. In (b), the fluorine is in the foreground to the left, the bromine is in the foreground to the right and the CN is at the top. Color ranges, in kcal/mol: red, greater than 30; yellow, between 30 and 15; green, between 15 and 0; blue, less than 0 (negative). The black hemispheres show the locations of the locally most positive potentials, the $V_{S,max}$. In (a) can be seen the three $V_{S,max}$ on the arsenic, and in (b) the one on the bromine.



6

The interactions of **6** with a negative site roughly follow the locations of these $V_{S,max}$. In complex **7**, which involves a positive region on the extension of the Br–As bond, the angle Br–As–N is 166° . However, in **8**, the interaction with the bromine positive region is nearly linear; the angle As–Br–N is 176° . (In **7** and **8**, the bromine is red, the arsenic is violet, and the nitrogen is blue.)



Furthermore, the $V_{S,max}$ on the arsenic are not in accordance with the relative electron-attracting powers of its bond partners. The CN group is much more electron-attracting than either fluorine or bromine [67], yet the arsenic $V_{S,max}$ due to the NC–As bond is the least positive, 37 kcal/mol. Fluorine is more electron-attracting than bromine, but the $V_{S,max}$ due to the F–As and Br–As bonds are the

same, 42 kcal/mol. Thus, while there has been some success in relating relative $V_{S,max}$ values to electronegativities and polarizabilities [61,68], we nevertheless echo our earlier statement [61]: "... in the final analysis the safest approach is to simply compute them."

On a more positive note, interaction energies do approximately follow the interacting positive and negative potentials, becoming more negative as these potentials are larger in magnitude [47], for Groups IV–VI as well as the halogens. Thus the interaction energies in **7** and **8** are -9 and -3 kcal/mol, respectively, consistent with the $V_{S,max}$ of the positive potentials on the arsenic and the bromine being 42 and 15 kcal/mol.

2.2. Van der Waals Radii and Close Contacts

A widely used criterion for the existence of a noncovalent bond is that the distance between the interacting atoms should be less than or approximately equal to the sum of their van der Waals radii. When this is observed in a crystal lattice for a given pair of atoms, it is called a "close contact" and is taken to indicate an attractive noncovalent interaction.

As has been pointed out, however, there are some problems with this [69–71]. One is that van der Waals radii are typically based upon the assumption that the atoms, despite being covalently bonded, are spherical. It is well known that this is not true [12,35–40]; σ -holes are in fact a manifestation of the asymmetry of covalently-bonded atoms, which can be quite substantial. From analyses of crystal data, Nyburg and Faerman estimated the radii of chlorines bonded to carbons to be, on the average, 0.2 Å shorter along the extensions of the bonds than perpendicular to them [36]; for sulfurs doubly-bonded to carbons, they found a difference of 0.4 Å. Eramian et al. predict somewhat smaller but still significant asymmetries [40]. How meaningful, then, is it to assign a single radius to the atom?

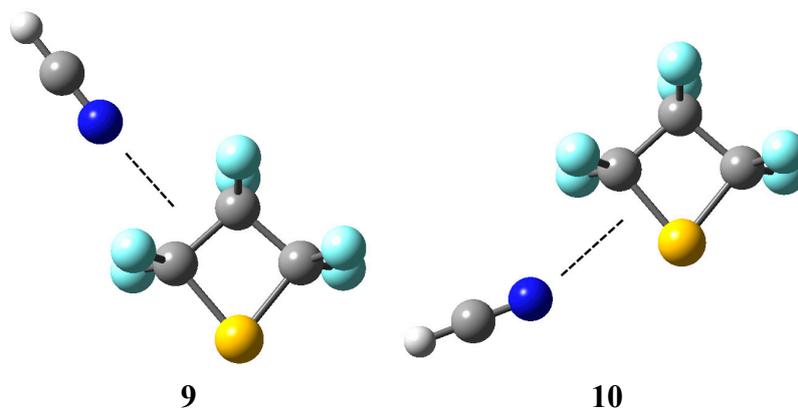
Another problem is that noncovalent interactions between a given pair of atoms in crystal lattices cover a range of separations; an intermediate one is used in assigning van der Waals radii [69,70,72]. It was pointed out by Dance [69] and by Alvarez [70] that using the sum of van der Waals radii as a criterion is accordingly likely to miss many noncovalent bonds, which can be several tenths of an Angstrom greater than that sum.

This suggests that an internuclear separation less than the sum of the van der Waals radii of the respective atoms should be viewed as a sufficient but not necessary condition for an attractive noncovalent interaction. However, this assumes that the interaction can be attributed to those specific atoms. This is indeed very often the case; crystallography shows numerous examples of close contacts that do indicate noncovalent interactions [12,73]. Similarly, in the complexes **4**, **7** and **8** the interactions are specifically between the positive σ -hole potentials of the bromine or arsenic and the negative lone pair of the nitrogen, and their separations (3.22 Å in **4**, 2.82 Å in **7** and 3.19 Å in **8**) are well below the sums of the respective van der Waals radii (3.52 Å for Br–N and 3.54 Å for As–N [70]).

On the other hand, it is not unusual to find that the most positive (or most negative) potential in a molecular region cannot be associated with a particular atom [53,54,59,73–75]. A good example of this is hexafluorothiacyclobutane **5**. Given the abundance of highly electronegative fluorines, it is reasonable to expect positive σ -hole potentials on the carbons as well as the sulfur, on the extensions of the bonds to these atoms. Instead, what is found are four positive regions in the plane of the ring (Figure 3), each with a $V_{S,max}$ that is in an intermediate position between the extensions of parallel C–C and C–S bonds. The two $V_{S,max}$ that are between carbons deviate by 19° and 21°, respectively, from the extensions of these bonds, the two that are between a carbon and the sulfur deviate by 22° and 40°. These positive regions cannot be linked to any specific atoms, nor can the resulting interactions with negative sites, as shall be seen.

Two complexes formed between **5** and HCN are shown as structures **9** and **10**. In each of these, the lone nitrogen pair is clearly interacting with the strong positive potential that is intermediate between adjacent carbons or a carbon and the sulfur; it is not interacting with any atom individually. The calculated interaction energies are very similar, both about -5 kcal/mol, which is not surprising since the four $V_{S,max}$ range only from 30 to 32 kcal/mol. (In **9** and **10**, the sulfurs are yellow, the fluorines

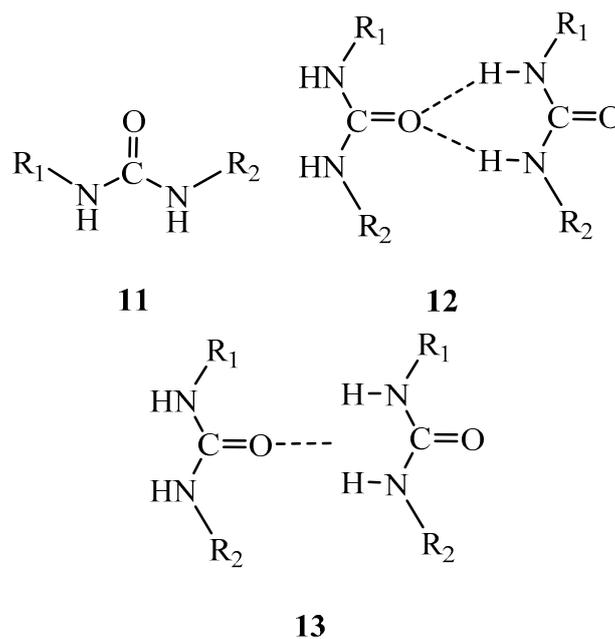
are light blue, and the nitrogens are blue. The HCN is slightly tilted in **10**, probably due to an attractive interaction between its hydrogen and the nearby fluorines).



The C—N distances in **9** and the S—N and C—N distances in **10** are all between 2.99 Å and 3.03 Å, so they are considerably less than the sums of the van der Waals radii, 3.43 Å for C—N and 3.55 Å for S—N [70]. Accordingly, these all fit the definition of close contacts; however, they do not correspond to the actual interactions, which are with the intermediate positive potentials.

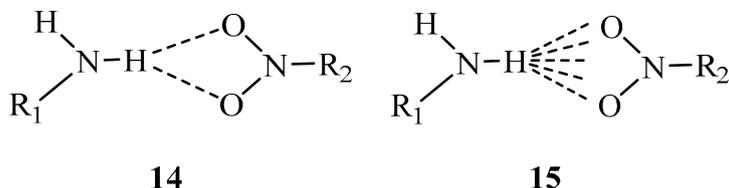
Analogous situations have been found, both computationally and crystallographically, for a number of other four- and five-membered heterocyclic rings [53,54,59,73]. In each case, the negative site is in close contacts with two neighboring atoms of the ring but the interaction is in reality with the strong positive potential located between the extensions of the bonds to these atoms.

When two atoms with positive σ -hole potentials are in close proximity in a molecule, their positive regions may overlap and result in just a single strong $V_{S,max}$ at some intermediate point rather than two separate ones. The ureas, **11**, are a good example of this. Instead of each N—H hydrogen having a σ -hole $V_{S,max}$, as would be expected, there is just a single one approximately midway between them [73,74]. Thus intermolecular interactions, e.g., in their crystal lattices, that have customarily been described as bifurcated hydrogen bonds, **12** [76,77], are more realistically viewed as in **13**. The N—H—O close contacts do not actually correspond to the dominant interactions.



Overlapping of potentials can also produce another interesting effect, shown for instance by the oxygens in many nitro (NO₂) groups. While each oxygen potential does have a minimum

(most negative) value at a certain point, these two points are quite close to each other and they are separated by a ridge of essentially the same potentials as the minima (within 1 kcal/mol) [74]. Accordingly the interaction with a positive site, e.g., an amine hydrogen, which is usually described by **14**, should actually be regarded as involving this whole ridge of essentially uniform negative potential, as in **15**.



3. Discussion and Summary

Noncovalent interactions are Coulombic in nature. This follows rigorously from the Hellmann–Feynman theorem, in the formulation given by Feynman [78], and it can be seen as well from the fact that the potential energy terms in the Hamiltonian for a noncovalent complex are all Coulombic. The molecular electrostatic potential is accordingly an effective means of analyzing such interactions. However, it is very important to note that the term Coulombic includes the effects of polarization. Some interactions that appear inexplicable in terms of the electrostatic potentials of the ground-state unperturbed molecules become understandable when the polarization is taken into account, i.e., the effect of each molecule's electric field upon the charge distribution of the other. This has been discussed in detail on a number of occasions [53,54,79–81].

In this paper, we have tried to clarify four misconceptions that are often associated with the interpretation of molecular electrostatic potentials:

- a. It cannot be assumed that, in general, regions of higher electronic density will have negative electrostatic potentials and that regions of lower electronic density will have positive ones. The electrostatic potential reflects the effects of the nuclei as well as the electrons.
- b. A corollary to this is that the electrostatic potential in a given region is not determined only by the electrons and nuclei in that region but also by those in the remainder of the molecule, particularly those in neighboring portions.
- c. A σ -hole is a region of lower electronic density on the extension of a covalent bond, not a region of electrostatic potential.
- d. Noncovalent interactions are between positive and negative regions, and these may not be associated with specific atoms. Accordingly, close contacts between atoms are not always a reliable indicator of the actual interactions.

These points should be kept in mind in using molecular electrostatic potentials to analyze noncovalent interactions.

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Conflicts of Interest: The authors declare no conflict of interest.

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