The Nature and Geometry of Intermolecular Interactions between Halogens and Oxygen or Nitrogen

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Abstract: The nature of intermolecular interactions between carbon-bonded halogens (C−X, X = F, Cl, Br, or I) and electronegative atoms (El = N, O and S) has been analysed, focusing on the role of specific attractive forces and the anisotropic repulsive wall around halogen atoms. Searches of the Cambridge Structural Database show that electronegative atoms in various hybridization states clearly prefer to form contacts to Cl, Br, and I (but not F) in the direction of the extended C−X bond axis, at interatomic distances less than the sum of the van der Waals radii. *Ab initio* intermolecular perturbation theory calculations show that the attractive nature of the X···El interaction is mainly due to electrostatic effects, but polarization, charge-transfer, and dispersion contributions all play an important role. The magnitude of the interaction for the chloro-cyanoacetylene dimer is about 10 kJ/mol, demonstrating the potential importance of these kinds of nonbonded interactions. The directionality of the interaction is explained by the anisotropic electron distribution around the halogen atom, causing a decreased repulsive wall and increased electrostatic attraction for electronegative atoms in the observed preferred position. In contrast, carbon-bonded hydrogens show no directionality in their contacts to the halogen atoms, because the angular dependence of the electrostatic energy is reversed and acts to counter rather then to reinforce the effect of the anisotropic repulsive wall.

Introduction

Knowledge of weak intermolecular interactions is necessary to enable the design and manipulation of molecular systems that depend on noncovalent binding. The importance of this knowledge can be shown by many examples in the fields of rational drug design,[1] crystal engineering,[2] supramolecular chemistry,[3] and physical organic chemistry.[4] This study focuses on intermolecular interactions between carbon-bound halogen atoms (X) and electronegative atoms (El), notably oxygen and nitrogen. Both experimental evidence from crystal structures and quantum mechanical calculations are used.

Databases of crystal structures contain a wealth of information about nonbonded interactions between atoms or functional groups. The Cambridge Structural Database (CSD)[5] currently contains the 3D coordinates of more than 120 000 organic and metalloorganic crystal structures, making it very suitable for investigating preferences for intermolecular contacts of a wide range of chemical entities in many different molecular environments. Previous studies based on the CSD have already demonstrated the existence of short X···El interactions. These appear to have a strong directional preference, the El atom tending to occur along the extension of the C−X axis.[6,7] The contacts occur for X = Cl, Br, I but not for X = F. The

directionality has been explained qualitatively in terms of charge-transfer between the highest occupied molecular orbital (HOMO) of the electronegative atom and the lowest unoccupied molecular orbital (LUMO) of the halogen.[7] This interpretation was largely based on molecular orbital studies of the dimer $H_3N···F_2$, actually an inappropriate model system as short F···El contacts do not appear to occur at all.

Short Cl···N contacts have been found in azaaromatic chloride compounds. Using the model system formimine···formimidoyl chloride, *ab initio* calculations at the 6-31+G* basis set level pointed to an attractive Cl···N interaction, resulting in an energy gain of 5.1 kJ/mol (uncorrected for basis set superposition error) for the dimer in comparison with the separated monomers.[8]

It is usually assumed that abnormally short nonbonded contacts are attractive. In the case of X···El contacts, the above-mentioned *ab initio* results offer some support for this assumption. However, an interesting alternative is raised by a recent study of Cl···Cl nonbonded interactions.[9] In this and previous papers,[10] it was shown that covalently bonded halogen atoms do not occupy spherical volumes in space but are ellipsoidal, due to an anisotropic distribution of electron density around the halogen nucleus. As a consequence, the effective atomic radius of X along the extended C−X bond axis is smaller than the radius perpendicular to this axis (so-called "polar flattening"). It was then demonstrated that the occurrence of short Cl···Cl contacts (of which many are known) is a consequence of the close-packing of these anisotropic atoms and not an indication of a specific attractive force between the chlorines. By extrapolation, this suggests the intriguing possibility that a

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similar explanation might also apply to short contacts between halogen atoms and oxygen or nitrogen atoms. However, the point is controversial: there is still disagreement about the existence and importance of polar flattening,[9,11,12] and its relevance in short X···El interactions has not been thoroughly analysed. We have therefore undertaken such an analysis.

This paper describes an extensive database search of all of the crystal structures in the CSD[5] for short intermolecular distances between halogen atoms (F, Cl, Br, and I) and electronegative atoms (N, O, and S) in their various hybridization states. Since the database information provides accurate data concerning geometrical preferences but gives only qualitative indications of the relative strengths of interactions, the database studies were augmented by theoretical calculations. In particular, the *ab initio* intermolecular perturbation theory (IMPT) method[13] has been applied, since it provides the different constituent interaction energies. This is necessary to afford an understanding of the nature of the X···El interaction and the role of polar flattening therein.

Methods

Experimental Geometries of Nonbonded Systems from Crystal Structures. Crystallographic data were obtained from the Cambridge Structural Database (CSD,[5] version 5.08, October 1994, containing 114 000 crystal structures having atomic coordinates available), using the graphics QUEST 3D software for spatial searches of nonbonded geometries and VISTA for graphical presentation of the data. Searches and additional calculations were carried out on a local SUN SparcStation5. Searches were performed for intermolecular contacts between terminal halogen atoms, covalently bonded to carbon (C−X, X = F, Cl, Br, or I), and electronegative (El = O, N, or S) or hydrogen atoms. It was required that the O, N, and S atoms were covalently bonded to carbon or nitrogen and the H atoms to carbon. In order to enable the production of normalized scatterplots (see below), all contacts were stored up to distances of $2^{1/3} = 1.26$ times the sum of the appropriate van der Waals radii (r_F 1.47 Å; r_{Cl} 1.75 Å; r_{Br} 1.85 Å; r_I 1.98 Å; r_N 1.55 Å; r_O 1.52 Å; r_S 1.80 Å,[14] and for hydrogen r_H 1.09 Å[15]). Both atoms in a contact were required to have a formal charge of zero. C−H bond lengths were normalized to 1.083 Å.

Searches were restricted to better quality CSD entries by use of the secondary search criteria: (a) crystallographic $R \leq 0.10$, (b) error-free coordinates, according to the criteria used in the CSD system, (c) no crystallographic disorder, and (d) no polymeric structures. Both organic and metalloorganic compounds were included.

Distances between the halogen and electronegative atoms (d) as a function of the C−X···El angles (α) give a picture of the distribution of electronegative contacts around a particular halogen atom, as shown in Figure 1. In order to be able to compare the different C−X···El systems, the distances d were normalized according to the sum of the van der Waals radii:

$$R = \frac{d}{r_X + r_{El}} \tag{1}$$

Furthermore, a change of variables $x = R^3$ and $y = 1 - \cos(\theta)$, where $\theta = 180 - \alpha$, was used to obtain better insight

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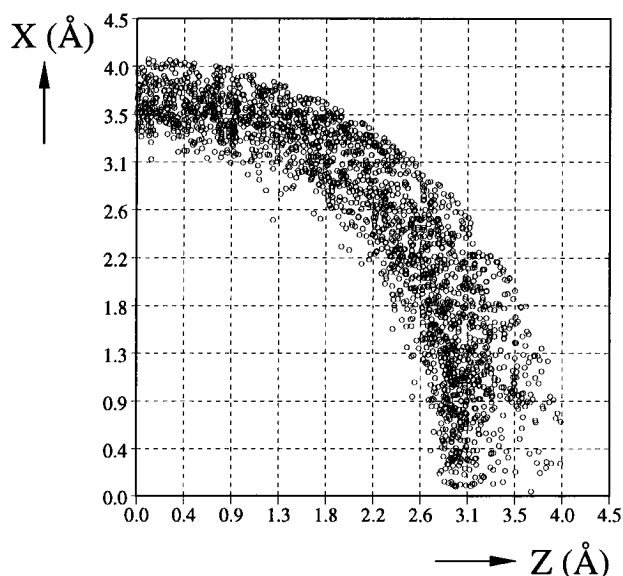(15) Taylor, R.; Rowland, R. S. *J. Phys. Chem.*, in press.

Figure 1. Distribution of oxygen atoms in sp² hybridization states around carbon bonded chlorine atoms found in the crystal structures in the CSD. Each circle represents one unique contact of an oxygen atom to the chlorine atom, placed at the origin.
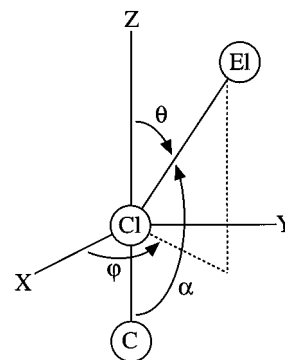

Figure 2. Definition of angles for C−X···El contacts.

into the spatial distribution of short contacts (Figures 2 and 3). The rationale for this transformation is as follows. In spherical polar coordinates (R, θ, φ) the volume element is $R^2 \sin(\theta)\, dR\, d\theta\, d\varphi$. An element of area $dR\, d\theta$ in a plot of R against θ therefore corresponds to a volume in space (integrating over φ) of $2\pi R^2 \sin(\theta)\, dR\, d\theta$. By using instead the variables $x = R^3$, $y = 1 - \cos(\theta)$, we obtain $dx\, dy = 3R^2\, dR \sin(\theta)\, d\theta \propto 2\pi R^2 \sin(\theta)\, dR\, d\theta$, so that equal areas in the x,y plot correspond to equal volumes in space. Consequently, a uniform distribution of the data points in three-dimensional space transforms into a uniform distribution of these data points in the two-dimensional scattergram. Equivalent uniform distributions are not obtained by plotting $1/\cos(\alpha)$ against $1/d^2$, as argued by other authors.[7] Rather, this latter plot represents a kind of reciprocal distribution of data points on three-dimensional surfaces.

Theoretical Values for Energies of Nonbonded Systems. Intermolecular perturbation theory (IMPT) calculations were used to analyze X···El interactions. The method of Hayes and Stone[13] was applied, using the CADPAC software package version 4.2.[16] All IMPT calculations were carried out on a Silicon Graphics Indigo workstation, using 6-31G basis sets taken from the standard CADPAC library. After geometry optimization of the monomers, dimers were constructed with various orientations of the electronegative atom relative to the

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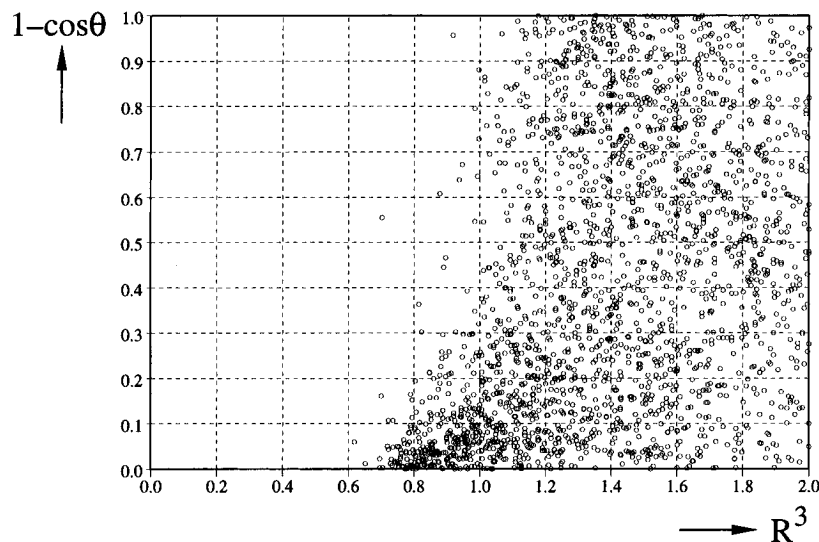
Figure 3. Statistically corrected distribution of oxygen atoms in sp^2 hybridization states around carbon bonded chlorine atoms found in the crystal structures in the CSD. The same data points as in Figure 1 have been plotted. For $R^3 > 1.0$ there is no van der Waals contact, and in that area the data points are roughly evenly distributed. Oxygen atoms which penetrate into chlorine atoms, $R^3 < 1.0$, have a preferred position in the head-on direction of the C−Cl bond $(1 - \cos(\theta) = 0.0)$.

halogen atom. In all cases the intermolecular distances between other atoms were kept as long as possible, thus avoiding van der Waals contacts.

The IMPT calculations result in a number of separate energy terms giving a total interaction energy. At first order, the electrostatic energy (E_{es}) term describes the classical Coulombic interaction of charge distributions between the molecules. This can be an attractive or a repulsive interaction. The exchange-repulsion (E_{er}) term is the sum of an attractive exchange of electrons of parallel spin and a repulsive part, which prevents electrons with parallel spin from occupying the same region in space (the Pauli exclusion principle). The first order energy term E_{er} is always positive (repulsive) for SCF dimers and increases exponentially when the wave functions penetrate. The resulting repulsive wall defines the shape that an atom occupies in space and will be ellipsoidal if the polar flattening phenomenon occurs.

At second order the IMPT gives the polarization or induction (E_{pol}) and the charge-transfer (E_{ct}) energy terms. The polarization of molecule A is described by an intramolecular change of its wave functions, whereas the charge-transfer is due to an actual transfer of electron density from molecule B to A, thus changing the wave functions within A as well. Both second order terms describe distortions of the charge distribution within molecule A and vice versa, which occur only because they are energetically favorable. Using the CADPAC software, the calculation of these terms is free of basis set superposition error (BSSE), but the division between these energy terms is not completely basis set independent.[17] Finally, the dispersion energy (E_{disp}) term is also given by the second order IMPT.

Results and Discussion

General Geometrical Properties. The CSD was searched for all unique, short intermolecular contacts between the halogen atoms F, Cl, Br, and I, and the electronegative atoms O (sp^2 and sp^3 hybridization states), N (sp^1, sp^2, sp^3 (pyramidal) hybridization states as well as planar nitrogen), and S (no distinctions). Figures 1 and 3, for C−Cl···O(sp^2), are typical of the general result found for the C−X···El systems, except when X is fluorine. The scattergram in Figure 1 represents a hemisphere around the nucleus of the chlorine atom at the

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terminal side of the covalent C−Cl bond, up to a maximum Cl···O distance of $d = 4.12$ Å. At distances greater than the sum of van der Waals radii ($d > 3.27$ Å), Figure 3 shows that the data points are roughly evenly distributed, demonstrating an approximately random distribution in space outside the chlorine atom. The "void" around $d = 3.6$ Å and $\alpha = 180°$ in Figure 1, used by other authors in their arguments,[6] is therefore explained on purely statistical grounds.

The cluster of contacts around $R^3 = 0.90$ and $1 - \cos(\theta) = 0$ ($d = 3.1$ Å, $\alpha = 180°$) shows two general phenomena of X···El interactions. Firstly, the very short contacts, representing interpenetration of the van der Waals spheres of the involved chlorine and oxygen atoms, tend to be highly directional, occurring only in the "head-on" direction of the C−Cl bond. Secondly, the higher density of data points in this region, in comparison with the densities at longer interatomic distances, suggests a preference for the oxygen atom to be located in that particular part of space. As this is a general observation for all the C−X···El systems investigated, except for X = F, it appears that there is an attractive force between the heavier halogens and electronegative atoms.

Results for Specific Halogen···Electronegative Atom Systems in the CSD. Although the distribution in Figure 3 is typical of most C−X···El interactions, there are differences between the various systems. Therefore, the tendency of electronegative atoms to penetrate into the head-on region of carbon bonded halogen atoms has been quantified by defining a percentage ratio $f_{DP} = 100 N_{DP}/N$, where N_{DP} is the number of highly directional penetrating contacts and N is the total number of data points found within the forward hemisphere.

A data point is counted in N_{DP} if $R < 1.0$ and $1 - \cos(\theta) < 0.1$ ($0° < \theta < 26°$). The total count N includes all points with $0° < \theta < 90°$ and $R < (2^{1/3}r_X + r_{El})$. The ratios f_{DP} are listed in Table 1.

A high f_{DP} ratio points to a strong preference for head-on penetration. If there is no penetration at all, then the f_{DP} ratio would be zero. If the data points were uniformly distributed in the entire space around the halogen nucleus down to $R = 0$, the ratio would be 5%. As it is physically impossible to have extremely short contacts with $R \ll 1$, this figure is evidently an upper limit for a distribution that is uniform over the angular variables. Therefore, an f_{DP} ratio larger than 5% reliably

Table 1. Ratios f_{DP}[a] (as Percentage) for Directional Penetrations of Electronegative Atoms into the van der Waals Volumes of Halogen Atoms[b]

type of nucleophilic atom	F	Cl	Br	I
all O[c]	2.8	12.3	20.6	35.6
	(2717)	(3774)	(1397)	(281)
all N[c]	1.8	6.9	18.1	28.8
	(621)	(1149)	(431)	(52)
all S[c]	2.5	4.7	12.3	*36.2*
	(318)	(571)	(122)	(47)
O(sp^2)	3.9	18.9	27.1	45.0
	(436)	(1410)	(691)	(120)
O(sp^3)	1.6	10.5	19.4	*0.0*
	(127)	(285)	(124)	(11)
N(sp^1)	2.4	21.6	46.8	*54.5*
	(83)	(116)	(77)	(11)
N(sp^2)	2.1	11.7	24.6	*44.4*
	(95)	(266)	(114)	(9)
N(sp^3; pyramidal)	*0.0*	9.8	*37.5*	*100*
	(47)	(41)	(16)	(4)
N (planar)	2.3	1.4	2.0	*0.0*
	(217)	(503)	(153)	(13)

[a] See text. [b] Values between brackets designate the total number of data points, *N*. If *N* < 50, then the corresponding ratio is given in *italics*. [c] Based on the later version 5.09 of the CSD.

indicates that the observed cluster of highly directional, penetrating contacts has a higher-than-random density. Table 1 shows that the f_{DP} ratio can go up to 40−50%, meaning that up to half the data points are concentrated in less than 5% of the space considered.

In all cases with a reasonably large number of data points ($\geq$50 observations in total), the f_{DP} ratio, and therefore the frequency of directional penetration, increases from Cl to Br to I. In this order, the relative degree of penetration clearly becomes deeper and the preferred direction moves closer to the head-on direction, as shown, for example, in the C−Br O(sp^2) scattergram of Figure 4. There is no evidence of a preferred, directional interaction for any of the F···El systems. In this respect, fluorine is completely different from the other halogens. (However, it is known from observations of gas phase molecular clusters that fluorine may form directional, attractive nonbonded interactions with atoms other than oxygen and nitrogen. For example, in the complex F−Cl···F−H,[18] it has been determined that an anti-hydrogen bonded Cl···F contact exists, having a linear F−Cl···F angle (α = 175°) and a bent Cl···F−H angle (α = 115°)).

The f_{DP} ratios for the various electronegative atoms always show the strongest preference for oxygen atoms, followed by nitrogen atoms, with the weakest preference for sulfur. Furthermore, for both nitrogen and oxygen it is found that the f_{DP} ratios decrease when going to higher hybridization states (from sp^1 to sp^2 to sp^3). Only for planar nitrogen is there no directional preference at all (Figure 5).

The Nature of the Halogen···Electronegative Atom Interaction. On the basis of the experimental data presented, it is likely that electrostatic effects are important in X···El interactions, since the order in which the interactions become stronger (S < N < O) corresponds to the increasing electronegativities of the atoms. Further, the decreasing f_{DP} ratios in higher hybridization states (from sp^1 to sp^2 to sp^3) point again to an electrostatic effect, because the sp^1 and sp^2 hybridized El atoms can attract electrons by resonance. However, steric effects might also be significant: in higher hybridization states,

the local environment of the electronegative atoms generally becomes more crowded, which makes the halogen atom less accessible at shorter distances.

Planar nitrogen, which lacks a lone pair, does not have any tendency to form short contacts to halogen atoms (Figure 5). At first sight, this might be ascribed to steric phenomena, since planar nitrogens are less accessible than, for example, pyramidal nitrogens. However, *if* they were to form short contacts to halogens, the least hindered geometry would be in the head-on direction of the C−X bond, rather than in perpendicular directions. In fact, Figure 5 shows that the data points are evenly distributed around the sum of the van der Waals radii, suggesting that steric effects are not predominant. Thus, it seems that the lack of an available lone pair may be the reason why planar nitrogens do not form short contacts to halogens. In that case, the explanation of X···El interactions might be found in HOMO (of El)−LUMO (of X) overlap,[7] and the charge transfer energy contribution should be one of the key features of these interactions.

The possible involvement of lone pairs was further investigated in a manner analogous to previous analyses of the geometry of hydrogen bonds.[19,20] In these studies, statistically corrected φ (the projection of the X···O=C angle in the lone pair plane) and θ (the angle with the normal of the lone pair plane) were analyzed (Figure 6). It was found from the CSD that amine hydrogens have a geometrical preference to approach the C=O oxygen in the conventionally viewed lone pair direction (φ = 120°, θ = 90°[19]). However, in the present work we find a very slight preference only for this direction in X···El interactions (Figure 7).

Amongst the different halogens, the tendency to form short X···El interactions (I > Br > Cl [>F]) parallels the order of their polarizabilities. This suggests that polarization and/or charge-transfer energies related to the halogen atom play a significant role in the interaction.

All of the explanations considered so far tacitly assume that the short, directional X···El contacts are attractive in nature. Another possibility, suggested by the work on Cl···Cl interactions,[9] is that the short, linear C−X···El contacts are merely a consequence of the close packing of anisotropic (i.e. "polar flattened") X atoms. This would be a fundamentally different explanation, as it would not require the assumption that the interactions are intrinsically attractive. In order to investigate the possible involvement of "polar flattening" of the halogen atoms, we determined the spatial distribution of carbon-bound hydrogens, (C−H) around halogens. It was found that contacts to hydrogens are roughly evenly distributed around the target X atom (Figure 8 for the C−Cl···H−C system). There is a slightly increased density outside the van der Waals contact area, near $R^3 \sim 1.2$ (Cl···H distance $\sim$ 3.21 Å), but no directional preference is observed, here or anywhere else on the plot. This observation suggests that polar flattening is, at most, only a partial explanation of the short X···El contacts, i.e., that these contacts result, at least in part, from specific attractive forces. The IMPT analysis described below will throw further light on this matter and it will be shown that polar flattening does occur but that for linear C−X···H geometries it is countered by a repulsive electrostatic interaction between C−X and H−C.

Effect of C−X···El Interactions on Crystal Packing. On the basis of our statistical analysis of crystal structure data, it appears that an attractive force can exist between the halogen atoms Cl, Br, and I and electronegative O and N atoms. The

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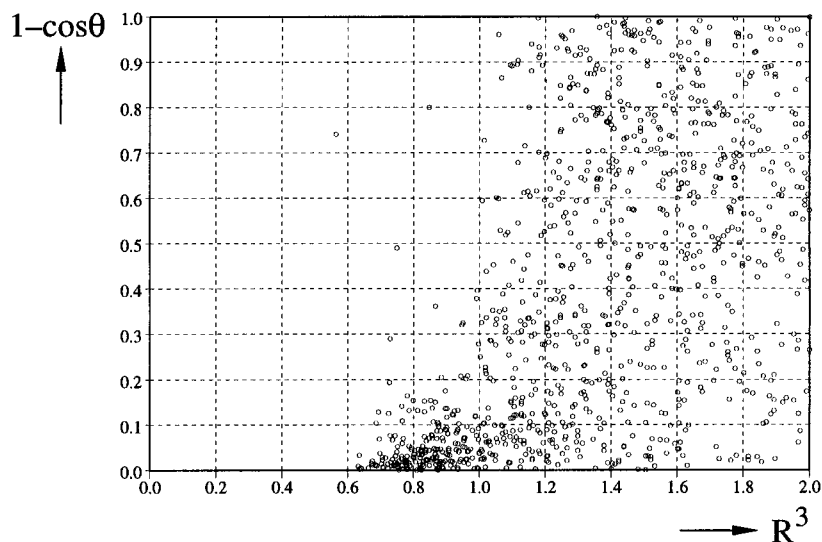(20) Legon, A. C.; Millen, D. J. *Faraday Discuss. Chem. Soc.* **1982**, *73*, 71−87, 127−128.

Figure 4. Statistically corrected distribution of oxygen atoms in sp² hybridization states around carbon bonded bromine atoms found in the crystal structures in the CSD.
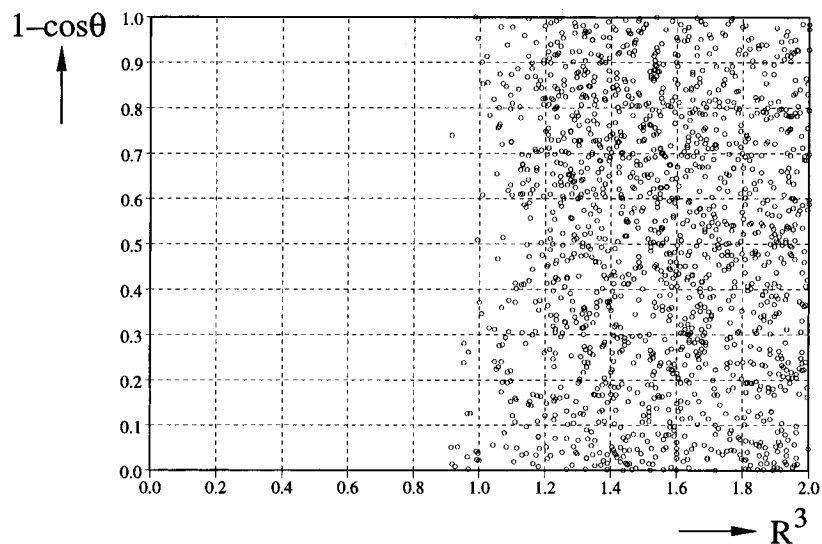

Figure 5. Statistically corrected distribution of planar nitrogen atoms around carbon bonded chlorine, bromine, and iodine atoms found in the crystal structures in the CSD. Penetration of nitrogen into halogen atoms hardly occurs.
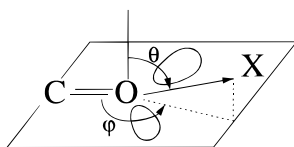

Figure 6. Definitions of angles with respect to the lone pairs of an oxygen atom in its sp²-hybridization state. Halogen atom X is in the conventionally viewed lone pair direction if $\varphi = 120°$ and $\theta = 90°$.

structures of 2,5-disubstituted-1,4-benzoquinones, taken from the CSD, nicely illustrate the existence and importance of the interaction (Table 2, Figure 9a–c). In the 2,5-dichloro-1,4-benzoquinone (**1**) crystal structure,[21] all chlorine and oxygen atoms are involved in 1:1 contacts, with a "normalized" interatomic distance of $R = 0.95$. Similarly, in 2,5-dibromo-1,4-benzoquinone (**2**),[22] all bromine atoms form 1:1 contacts with oxygen atoms ($R = 0.94$). Thus, despite the much larger volume taken up by the bromine atoms, the crystal packing is still isostructural with the dichloro analogue, and the X···El interaction is shown to be an essential driving force in the

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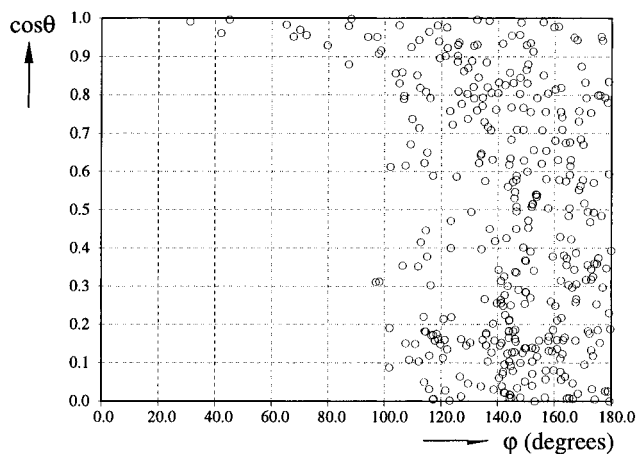

Figure 7. Statistically corrected distribution of chlorine atoms around oxygen atoms in sp² hybridization states found in the crystal structures in the CSD. Only a slight preference for chlorine atoms in the lone pair plane can be observed.

formation of the extended crystal structure. This is confirmed by the structure of 2,5-dimethyl-1,4-benzoquinone (**3**).[23] Although the volume of methyl groups is comparable to that of
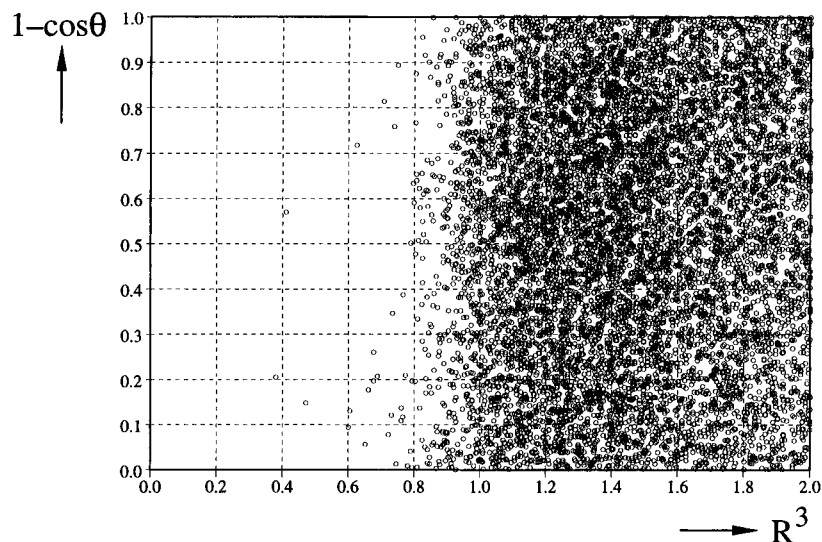
Figure 8. Statistically corrected distribution of carbon bonded hydrogen atoms around carbon bonded chlorine atoms found in the crystal structures in the CSD. There is no preferential approach direction for hydrogen atoms toward chlorine atoms.

Table 2. Geometric Parameters of 2,5-Dihalo-1,4-Benzoquinone, Halo-cyanoacetylene, and 3-Chloro-1,2,4-triazole Crystal Structures in the Cambridge Structural Database (CSD)

CSD-refcode	compd	$X \cdots El$ distance $(Å)^a$	$C-X \cdots El$ angle (deg)	ref
BZQDCL10	2,5-dichloro-1,4-benzoquinone	3.101 (0.95)	164.7	21
DBRBZQ10	2,5-dibromo-1,4-benzoquinone	3.161 (0.94)	163.2	22
DMEBQU01	2,5-dimethyl-1,4-benzoquinone			23
CCACEN	chloro-cyanoacetylene	2.984 (0.90)	178.3	24
BCACEN	bromo-cyanoacetylene	2.978 (0.88)	177.2	24
ICACEN	iodo-cyanoacetylene	2.932 (0.83)	177.3	25
CLTRZL	3-chloro-1,2,4-triazole	3.177 (0.96)	170.0	26

^{a} Relative distance R between brackets: $R = d/(r_X + r_{El})$, see eq 1.

chlorine atoms, **3** has a completely different crystal packing from **1** and **2**. In **3** $C_{3,6}-H \cdots O$ hydrogen bonds ($d_{H \cdots O} = 2.48$ Å) play the predominant role,[27] which strongly suggests that the halogen$\cdots$oxygen interactions in **1** and **2** are at least as attractive as the $C-H \cdots O$ hydrogen bond in **3**, and probably more so.

Another interesting example from the CSD is provided by the halo-cyanoacetylene compounds[24,25] of Table 2. These linear molecules approach each other in a mutually linear head-to-tail arrangement ($\alpha \sim 180$), and penetration of up to 17% of the sum of the van der Waals radii is observed. The penetration is relatively deeper in the case of the heavier halogen atoms, as already observed in the complete CSD analysis. There are no obvious packing phenomena which might force the nitrogen atoms into close proximity to the halogen atoms. Therefore, an overall attractive interaction between the molecules is most probably responsible for the observed contact distances.

IMPT calculations: Chloromethane$\cdots$Formaldehyde Model System. The smallest model system which might reasonably represent the intermolecular $X \cdots El$ interaction is the chloromethane$\cdots$formaldehyde dimer. Approach of the formaldehyde oxygen to the chlorine was defined by the internuclear $Cl \cdots O$ distance (d) and the angle $C-Cl \cdots O$ (α, or its complement $\theta = 180° - \alpha$, see Figure 2). The $C=O \cdots Cl$ axis was kept linear, thus placing the chlorine atom between the oxygen lone pairs. An overview of the interactions for various orientations of oxygen towards chlorine in this model system is given in Figure 10a,b.

The first plot (Figure 10a) shows the distance dependency at a fixed $C-Cl \cdots O$ angle, viz., in the head-on direction of the $C-Cl$ bond ($\theta = 0°$). The approach of oxygen toward chlorine in this direction does not show an overall attractive interaction. The electrostatic interaction E_{es} is largely repulsive, and, after adding the exchange-repulsion term E_{er}, it is clear that the first order terms dominate the total interaction energy of the system. Perpendicular to the $C-Cl$ axis ($\theta = 90°$, not shown), the situation is even more repulsive.

The next plot (Figure 10b) shows the angular dependency at a fixed distance, just shorter than the sum of the van der Waals radii ($R = 0.90$). The electrostatic and exchange-repulsion energy terms are both repulsive, hardly compensated by the weakly attractive second order energy terms. These secondary terms are undoubtedly underestimated in the small basis set, but better calculation is unlikely to change the general conclusions. The exchange-repulsion is clearly anisotropic, being much more repulsive perpendicular to the $C-Cl$ axis than in the head-on direction. This points to polar flattening of the chlorine atom, an effect that will be discussed in greater detail below. At larger distance ($R = 1.10$, not shown), the exchange-repulsion almost vanishes for all θ angles, but the repulsive electrostatic term remains, leading to no attractive interaction at all.

IMPT Calculations: Chloro-Cyanoacetylene Dimer. It is clear that the simple model system considered above does not explain the observations made from the experimental data. Therefore, the CSD was searched for reasonably small molecules which show the typical $X \cdots El$ interaction and are suitable for IMPT calculations. Chloro-cyanoacetylene (Table 2) was chosen. The IMPT calculations on chloro-cyanoacetylene are summarized in Figures 11a–c, which show the distance and

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2,5-dichloro-1,4-benzoquinone

2,5-dibromo-1,4-benzoquinone
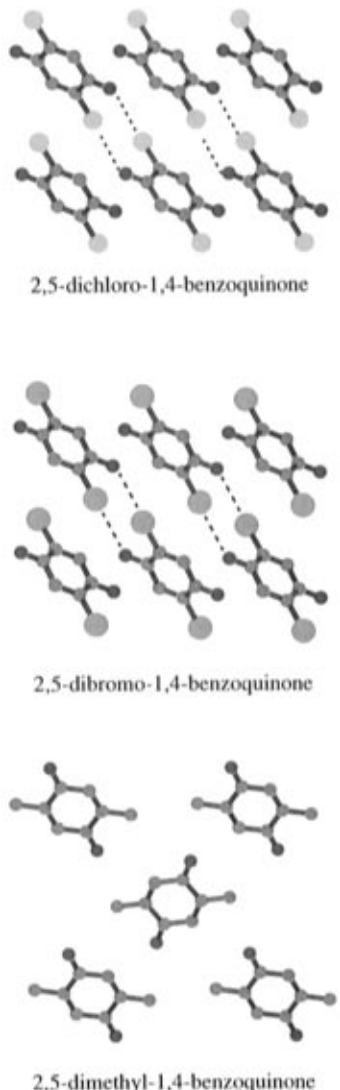

2,5-dimethyl-1,4-benzoquinone

Figure 9. Packing of 2,5-disubstituted-1,4-benzoquinones in crystal structures. Hydrogens have not been plotted. The dotted lines show the contacts of oxygen and halogen atoms: (a) 2,5-dichloro-1,4-benzoquinone, (b) 2,5-dibromo-1,4-benzoquinone, and (c) 2,5-dimethyl-1,4-benzoquinone.

angular dependencies for this system. Considering the head-on direction of interaction (Figure 11a), it is immediately clear that at longer distances the attractive electrostatic energy dominates. This is no surprise, because in the isolated molecule the nitrogen atom has a residual (Mulliken) charge of -0.16e, whereas the chlorine atom has a charge of $+0.51$e, leading to a head-to-tail attraction. When only the first order energy terms are taken into account, the total energy has a minimum close to the sum of the van der Waals radii ($R = 1.0$), the repulsive wall being strong enough to prevent significant intermolecular penetration, i.e., the Coulombic attraction alone is not strong enough to explain the short contact distance observed in the CSD. On including the dispersion, charge-transfer and polarization energies, however, shorter distances become energetically favorable and a minimum appears around $R = 0.90$ ($d = 2.94$ Å). In the direction perpendicular to the C–Cl bond the electrostatic attraction has decreased, and the exchange-repulsion has increased, causing a favorable interaction only at distances outside the van der Waals radii (Figure 11b).

It is interesting to observe that the polarization (E_{pol}) and charge-transfer (E_{ct}) terms make only small contributions to the total attractive intermolecular energy. At $R = 0.90$ and $\theta = 0°$, the energy gain due to the nonbonded polarization, E_{pol}, of
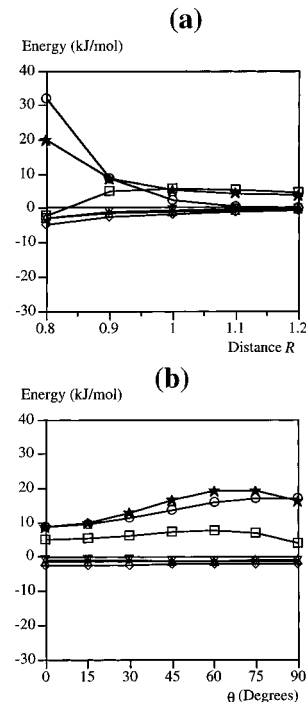

Figure 10. IMPT energies of interaction of chlorine and oxygen atoms in the chloromethane···formaldehyde model system. Calculations have been carried out using the 6-31G basis set. The various symbols designate the following: (○) Exchange repulsion (er), (□) Electrostatic interaction (es), (△) Charge-transfer (ct), (▽) Polarization (pol), (◇) Dispersion (disp), (★) total energy (es + er + ct + pol + disp), and (●) total of first order energies (es + er). (a) Approach of oxygen in the head-on direction, $\theta = 0°$ and (b) angular dependence of penetrated oxygen at fixed distance to the chlorine nucleus, $R = 0.9$.

the molecule with the interacting chlorine is about -1.1 kJ/mol, whereas E_{pol} for the molecule with the interacting cyano group is only -0.3 kJ/mol. The possibility of an underestimation of E_{pol} was investigated by an additional calculation using the better 6-31G* basis set. This resulted in a total polarization energy of -1.6 kJ/mol, i.e., only slightly more attractive. The observed trend in the CSD towards stronger X···El interactions as X becomes more polarizable is therefore likely to be an intramolecular effect; the more polarizable halogens tend to have greater residual positive charges when in electron-withdrawing intramolecular environments, and this leads to a stronger electrostatic attraction to electronegative atoms in nearby molecules.

The charge-transfer E_{ct} is also small. At $R = 0.90$ and $\theta = 0°$, E_{ct} is similar from the chlorine side of the molecule to the nitrogen side and vice versa (-0.6 kJ/mol and -0.8 kJ/mol, respectively). These effects are not very sensitive to the basis set when the effects of BSSE are excluded.[17] It can be concluded that HOMO–LUMO interactions do not play an important role.

The angular dependence of the interaction energy terms in the chloro-cyanoacetylene dimer is shown in Figure 11c for $R = 0.90$. Again, the exchange-repulsion is clearly anisotropic, allowing closer approach of the chlorine and nitrogen atoms in the head-on direction (smaller θ angles). The electrostatic attraction is stronger in the head-on direction, but the second order polarization, charge transfer, and dispersion terms show minimal dependence on the angle of approach.

IMPT Calculations: Chloro-Cyanoacetylene···Chloromethane System. As an attractive interaction was found for the chloro-cyanoacetylene dimer but not for the chloromethane···formaldehyde system, the question remained as to whether the
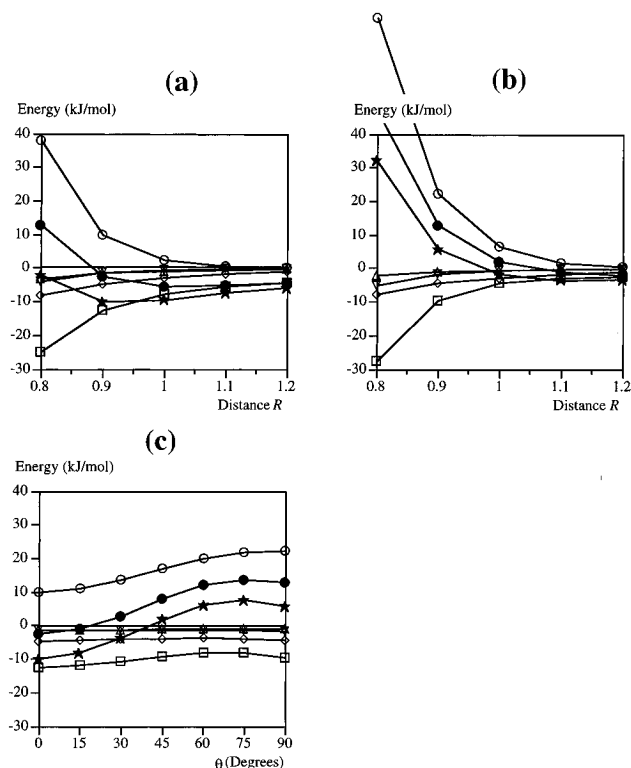
(a)

(b)

(c)

Figure 11. IMPT energies of interaction of chlorine and nitrogen atoms in the chloro-cyanoacetylene dimer system. The same symbols as in Figures 10a,b have been used: (a) approach of oxygen in the head-on direction, $\theta = 0°$, (b) approach of oxygen perpendicular to the C−Cl axis, $\theta = 90°$, and (c) angular dependence of penetrated oxygen at fixed distance to the chlorine nucleus, $R = 0.9$.

difference was due to the change in the El atom or the change in the chemical environment of the chlorine atom. Therefore, IMPT calculations were also carried out for the chloro-cyanoacetylene molecule interacting with chloromethane at its cyano side and, alternatively, interacting with formaldehyde at its chlorine side (discussed later). The chloro-cyanoacetylene···chloromethane system resulted in a very similar picture to the chloromethane···formaldehyde dimer: no overall attractive interaction in any orientation and similar contributions from the various energy terms. We conclude that the molecular environment of the chlorine atom is of crucial importance. For example, the chloromethane chlorine is negatively charged, whereas in the chloro-cyanoacetylene compound the strongly electron-withdrawing triple bonds cause the chlorine atom to be positively charged. However, as has been shown, the Coulombic attraction between chlorine and nitrogen alone is not enough to explain the very short intermolecular distances.

IMPT Calculations: Formaldehyde···Chloro-Cyanoacetylene System. The effect of changing the electronegative atom was investigated with the formaldehyde···chloro-cyanoacetylene system. This system showed the same phenomena as were found in the chloro-cyanoacetylene dimer: a strongly attractive electrostatic interaction, together with small but significant second order energy terms, stabilize close O···Cl approach, but only in the head-on direction of the C−Cl bond. This confirms that the difference between the chloro-cyanoacetylene dimer (attractive interaction) and the chloromethane···formaldehyde system (repulsive interaction) is due to the change in the nature of the chlorine atoms, not to the difference in the electronegative atoms.

The possibility of weak lone-pair directionality, as suggested by the CSD analysis, was also studied with this system. Calculations were performed on various geometries, keeping
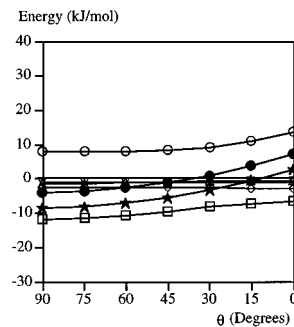

Figure 12. Angular dependence of IMPT energies of chlorine at fixed distance to oxygen nucleus, $R = 0.9$. The orientation of the chlorine atom is at fixed $\varphi = 120°$, whereas θ has been varied from 0° (in the lone pair direction) to 90° (perpendicular to the lone pair plane).

the C−Cl···O angle linear and the Cl···O distance fixed ($R = 0.9$, i.e., Cl and O atoms interpenetrating), but altering the position of the chlorine atom with respect to one of the oxygen lone pairs of the formaldehyde carbonyl group. Specifically, the chlorine atom was fixed at a $\varphi = 120°$, but the out-of-plane angle θ was varied from 90° to 0° (Figure 6). The exchange-repulsion around the oxygen atom remains fairly constant from $\theta = 90°$ to $\theta = 45°$ but increases considerably perpendicular to the C=O bond ($\theta = 0°$, Figure 12). This latter effect is probably due to occupied molecular orbitals of the chlorine atom interfering with those of the C=O double bond, giving an increased repulsive orbital overlap on top of the C=O axis. The attractive electrostatic term slowly decreases from the in-plane towards the perpendicular position. Because the small second order energy terms are almost angle independent, the electrostatic term now primarily determines the form of the total energy as a function of θ. As a result, the total energy well is rather flat, especially in the region $\theta = 90°$ to $\theta = 60°$. This correlates with the weak lone pair directionality observed from the CSD, since a concentration of data points from $\theta = 90°$ to $\theta = 60°$ (cos(θ) from 0.0 to 0.5, $\varphi = 120°$) can be seen in the scattergram of Figure 7.

IMPT Calculations: Chloro-Cyanoacetylene···Methane System. The results given so far show that the polar-flattening hypothesis certainly explains much of the observed directionality of X···El contacts. The generally negatively charged El atom experiences a stronger repulsion when it approaches a halogen atom perpendicular to the C−X axis. It also experiences more electronic charge in that direction, leading to a less favorable electrostatic energy. In the head-on direction, the anisotropy of the repulsive wall and the greater electrostatic attraction combine to allow El to approach X more closely, though the second order terms are required to explain actual interpenetration of van der Waals volumes.

More IMPT calculations were performed to explain the curious experimental observation that, whereas X···El contacts are anisotropic (e.g., Figure 3), X···H contacts are not (e.g., Figure 8). Using chloro-cyanoacetylene···methane system as a model, the angular dependency of the IMPT energies at a fixed Cl···H distance ($R = 0.9$, i.e., H and Cl interpenetrating) were calculated. The results are shown in Figure 13. The exchange-repulsion is still anisotropic, being less repulsive in the head-on direction of the C−Cl bond. However, the angular dependency of the electrostatic interaction has been reversed in comparison with that of an interacting electronegative atom. The approach of the C−H hydrogen atom toward the chlorine atom is now, in terms of the electrostatic energy, less favorable in the head-on direction than it is perpendicular to the C−Cl axis. In other words, the electrostatic attraction between the hydrogen and the chlorine atoms has become stronger in the

direction perpendicular to the C−Cl axis than it is in the head-on direction. The curvature of the exchange-repulsion term is largely compensated by this electrostatic term, resulting in a fairly "flat" angular dependency of the total energy of interaction. This reversed angular dependency of the electrostatic interaction does not depend on the chlorine environment, as very similar results were obtained from IMPT calculations on the chloromethane···methane system (not shown). If this can be generalized for all organic-halogen compounds, then the spherical and equifrequent distribution of hydrogens around halogen atoms in the CSD should indeed be expected, despite the anisotropic distribution of charge-density around the halogen nuclei.

IMPT Calculations: 3-Chloro-1,2,4-triazole. While the IMPT calculations on chloro-cyanoacetylene show that X···El interactions can be very attractive, we were interested to see whether similarly attractive X···El interactions could be expected in molecular moieties more likely to be incorporated in a drug molecule. A suitable example for study was the 3-chloro-1,2,4-triazole dimer[26] (Table 2), since heterocycles frequently occur in medicinally important molecules. The crystal structure of this compound shows a slight penetration of the chlorine atom into a nitrogen atom. The IMPT results for this dimer were similar to those for chloro-cyanoacetylene, but the attractive energy is less (4.4 kJ/mol in a minimum energy orientation at $R = 0.98$, $\theta = 0°$). However, this energy value is still large enough to be worth taking into account, e.g., when designing a putative enzyme inhibitor, especially when it is borne in mind that the corresponding figure for the bromo analogue will surely be larger. We conclude that the exploitation of X···El interactions may be a valuable means of gaining binding energy when designing protein ligands.

Conclusions

The present results concerning intermolecular contacts between halogen (Cl, Br, and I) atoms and electronegative (O and N) atoms demonstrate that a highly directional, attractive interaction can exist, which may lead to interpenetrating van der Waals volumes. The degree of penetration and the directionality of mutual approach can be explained on the basis of *ab initio* IMPT calculations. The *attractive nature* of the interaction is mainly due to electrostatic effects, but polarization, charge-transfer, and dispersion contributions all play an important role in causing interpenetration of van der Waals volumes.

The *directionality* of halogen···oxygen and halogen···nitrogen contacts is primarily the result of the anisotropic distribution of electron density around the halogen nucleus. This causes a strong angular dependence of the first order IMPT energy terms. Both the exchange-repulsion and electrostatic energies lead to a preferred orientation in the head-on direction of the C−X
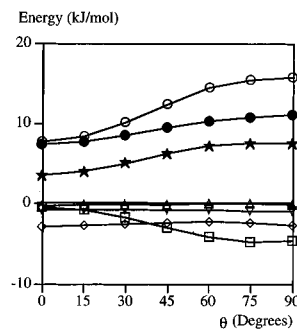
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Figure 13. Angular dependence of IMPT energies of penetrated hydrogen at fixed distance to the chlorine nucleus, $R = 0.9$, for the chloro-cyanoacetylene···methane system.

bond. However, in the case of halogen···hydrogen interactions, the exchange repulsion and electrostatic terms act in opposite directions, resulting in no overall directional preference.

If the carbon-bound halogen atom is in a sufficiently electron-withdrawing environment, then a strong attractive overall interaction will exist. In the case of the chloro-cyanoacetylene dimer the maximum energy gain is about 10 kJ/mol, which is about half the magnitude of an average hydrogen bond. The resulting force is strong enough to influence and drive crystal packing. It explains the structure of the 2,5-dihalo-1,4-benzoquinone type of compounds as well as those of the halo-cyanoacetylene compounds. This attractive force may also have important implications in protein-ligand interactions.

Our analysis demonstrates that information concerning non-bonded interactions obtained from a crystal structure database should be interpreted carefully. This has been shown for polar flattening of halogen atoms, the existence of which was unclear, but which is shown by the IMPT calculations to have an essential role in determining the directionality of X···El interactions. On the other hand, the information obtained from *ab initio* calculations of model systems should also be handled very carefully, certainly if one would like to extrapolate or generalise the resulting data. However, the *combined* approach of crystal structure database analyses and *ab initio* calculations has proven to be extremely powerful in investigating weak nonbonded interactions. The results obtained for the X···El type of interactions, or in general for nonbonded interactions, are of great importance for the synthesis of functional supermolecules, for crystal engineers, and molecular designers. Development of novel compounds and materials strongly depends on the ready availability of this kind of knowledge.