they do is in itself an interesting question that can be addressed by qualitative molecular orbital theory[6] and will be the subject of another study. The pattern of topologically determined charge densities in the homoatomic frame allowed us to order the relative stabilities of the heteroatomic isomers. For structures of particularly high symmetry, the charge densities in the homoatomic system were everywhere the same. In these cases we introduced a single heteroatom that sufficiently perturbed the system to allow accurate prediction of the location of the second heteroatom. The results summarized in Table I are in excellent agreement with experiment and with more detailed calculations. We have been able to make more predictions of relative stabilities of carborane positional isomers than can be confirmed with available experimental evidence or with total energies calculated by advanced molecular orbital methods. A remarkable feature of Table III is the lack of any calculations for two or more isomers for $C_2B_6H_8$, $C_2B_7H_9$, or $C_2B_9H_{11}$. We are now completing a series of ab initio SCF-MO calculations at the same level of basis set for the complete series $C_2B_{n-2}H_n$ and including several isomers in each case. The results will be published elsewhere.

The rule of topological charge stabilization is easy to apply. Even such a crude method as the extended Hückel method is apparently adequate to produce the pattern of charge densities from which reliable predictions of structures and relative stabilities can be made. The predictions could be useful as a guide to future synthetic efforts. Topological charge stabilization can serve as a unifying principle for the organization or systemization of chemical information.

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Angular Preferences of Intermolecular Forces around Halogen Centers: Preferred Directions of Approach of Electrophiles and Nucleophiles around the Carbon–Halogen Bond[1a]

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Abstract: During our studies of Se···Se interactions in selenides, it was observed that halogen atoms X of C–X bonds were engaged in both a "head-on" and a "side-on" fashion to Se atoms. To understand such interactions, we have analyzed the crystallographic environment around halogen centers and find that, in general, "electrophiles" tend to approach halogens of C–X (X = Cl, Br, I) at an angle of $\sim$100° and nucleophiles at $\sim$165° and that C—X···X—C type interactions fall into two groups, one forming an "electrophile–nucleophile pairing" interaction and the other forming no such pairing. These interactions are interpreted in terms of HOMO and LUMO frontier orbitals centered on the halogens and the approaching atoms. Such "electrophile–nucleophile pairing" interactions are quite general for several systems like sulfides and selenides and no doubt are important in the interaction of small molecules containing halogens since halogen atoms often are in a situation to make short contact with a variety of other atoms, owing to their exposed positions in many molecules.

Although the potential energy between two atoms that are parts of a molecule must have a complicated and specific dependence on their relative orientations, in most calculations, this orientational dependence of energy contribution is either lost or modified due to the use of spherically symmetric atom–atom potentials. Introduction of an anisotropic potential introduces complexities in modelling atom–atom interactions. Besides, such anisotropic potential parameters are not known and are not readily calculable. Consequently, even at the cost of accuracy, only spherically symmetric potential functions are usually used in calculating potential energy values.[2] To regard the attractive and repulsive terms of the potential function as spherically symmetric ignores the nonsphericity of the electron distribution[3a] and density[3b] and the anisotropic shapes of atoms.[4,5] Earlier studies from our laboratories and elsewhere have shown (from an examination of nonbonded interatomic distances in crystals) that when two chemical groups come within the sum of the van der Waals radii of contacting atoms, certain directional preferences exist depending on the chemical nature and stereochemistry of the contacting atoms and groups.[5-10] Such intermolecular associations have been

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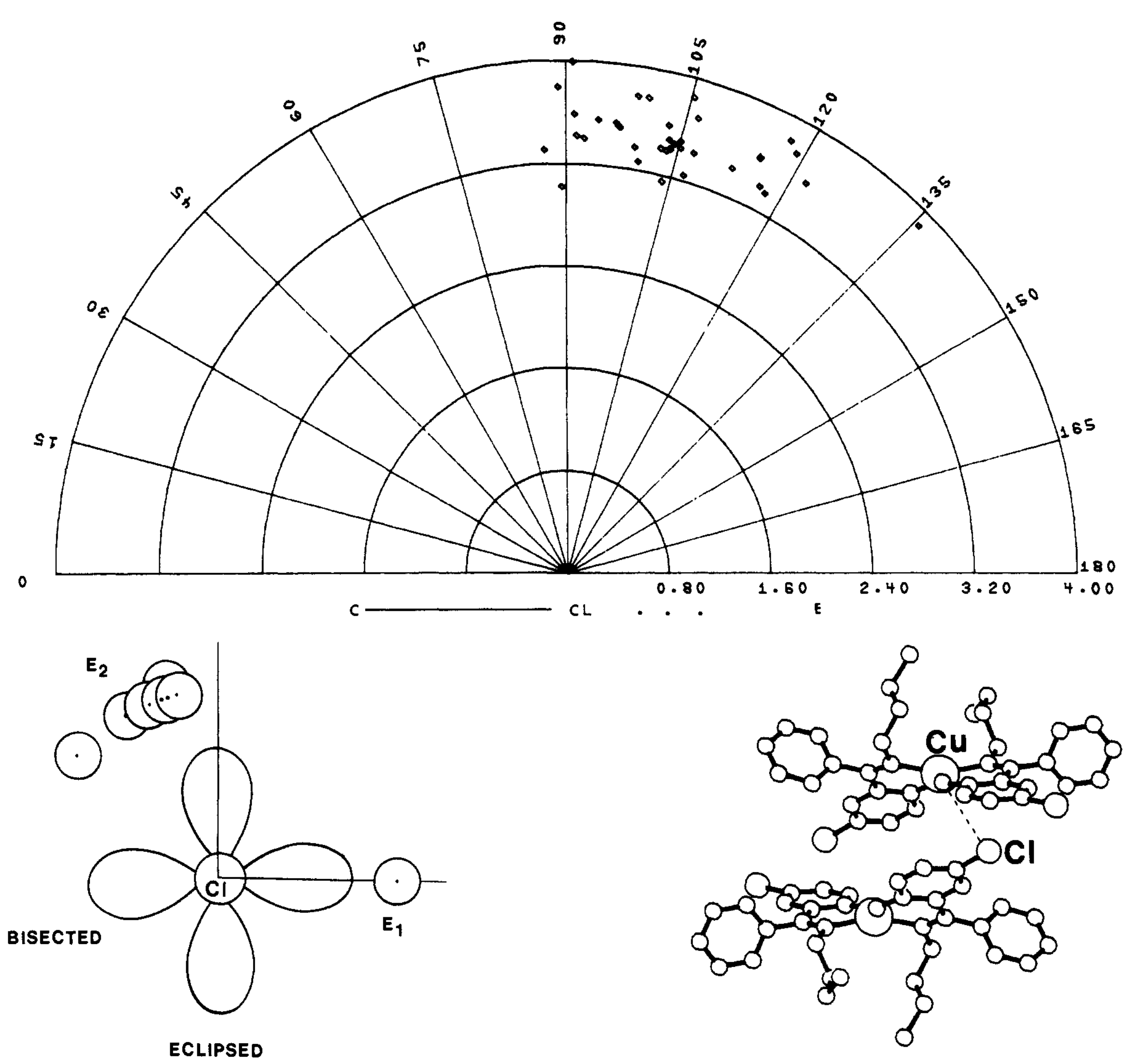

Figure 1. (a) Polar scatter plot of contact distance r vs. polar angle θ; 39 contacts of metal ions with Cl. Note that the approach of metal ions is clustered around 104° (11), (b) the approach of two metal ions projected down the Cl–C bond. The p orbitals of Cl are also drawn to show the relative orientation of E_1 and E_2 with respect to them. (c) A typical example of C–Cl···E contact (refcode NBHBCU) is shown here.

referred to earlier[10] as "donor–acceptor" interactions, "secondary interactions", and "charge transfer" interactions and more recently[6] as interactions of highest occupied molecular orbital with the lowest unoccupied molecular orbitals[11] (HOMO–LUMO) and "incipient electrophilic and nucleophilic attack".[5,6] In all such interactions (e.g., for S, Se, and halogens[5,6,8]) we have noticed that recurring patterns of contacts exist with characteristic stereochemical features appropriate for electrophile–nucleophile pairing, and hence we call these interactions as "electrophile–nucleophile pairing". The angular dependence of intermolecular forces is one of the least understood features of our knowledge of the ways in which atoms act as part of molecules.[10] For understanding better such interactions from a theoretical point of view, it is important to get more data on the stereochemical characteristics of such interactions. For this reason and for others explained below, we have studied the angular preferences of intermolecular forces around halogen centers. During our studies of interaction of selenides and sulfides with electrophiles and nucleophiles,[5,6,8] we encountered many examples of halogens of R–X groups (X = Cl, Br, I) that exhibited directions of approach appropriate for both nucleophilic and electrophilic groups toward sulfides and selenides. This observation prompted us to investigate the crystallographic environment around halogen centers. Earlier, many authors, including Bent,[10] have reported and discussed short intermolecular contacts between halogen atoms.[12,13] Such interactions have been used in designing molecules to exhibit specific types of photochemical reactivities.[13] A feasibility study on the computer retrieval and geometry of C—I···O interactions was carried out earlier.[7] It has also been suggested that C—I···O interactions may be important in the binding of thyroid hormones to their specific binding proteins.[14] The intermolecular interactions of the C–F bond with alkali metals and proton donors have been discussed recently.[15] In a search for antisickling agents,[16] it has been found that compounds that contain dihalogenated aromatic rings with polar side chains have the highest antisickling activity. It was also found that the primary binding forces that govern these small-molecule drug interactions with hemoglobin arise predominantly from weak dipolar van der Waals and hydrophobic forces.

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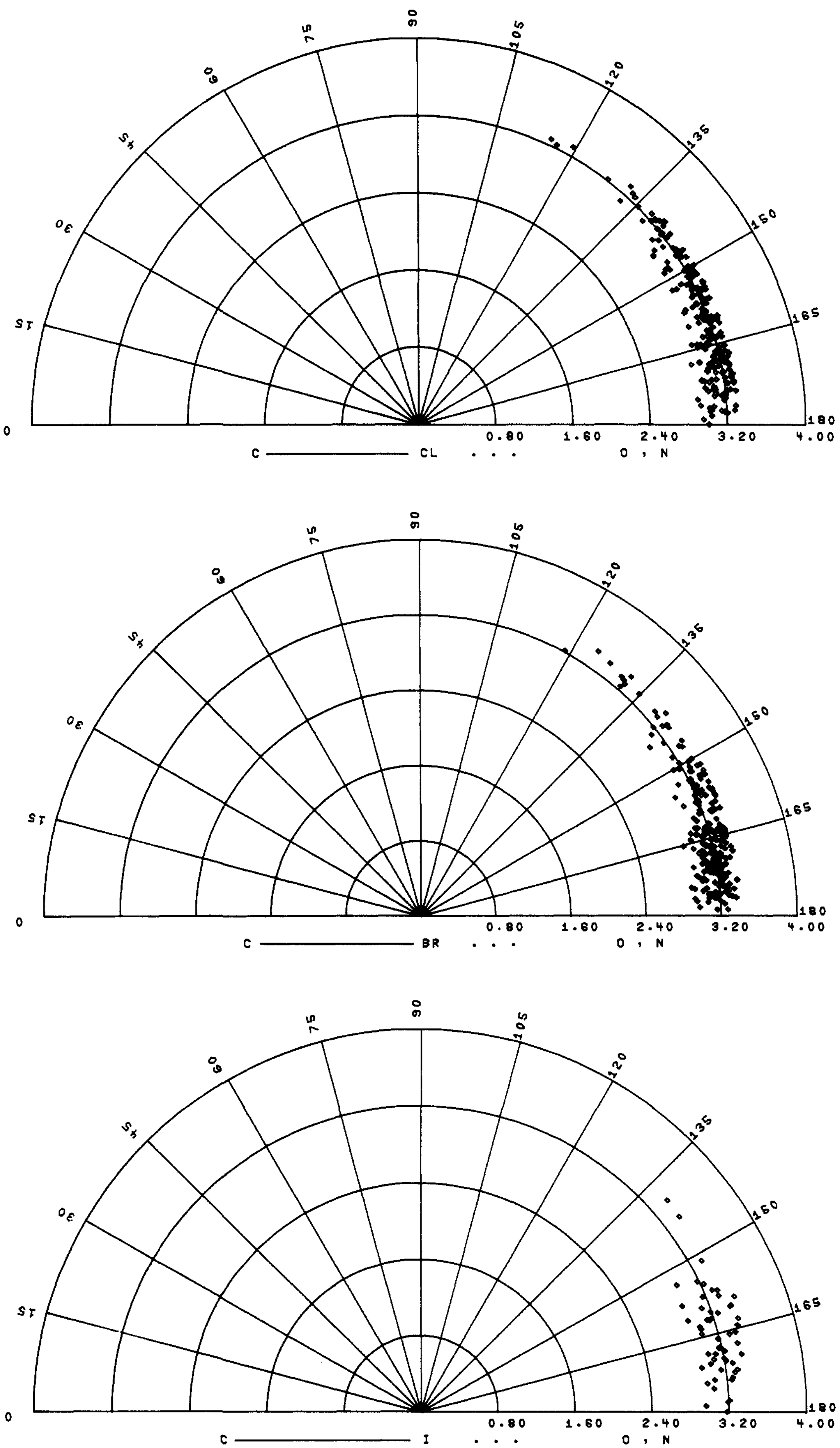

Figure 2. Polar scatter plot (r vs. θ) for nucleophiles O or N around Cl, Br, and I in a, b, and c, respectively. The average values of for these contacts are 158 (13)° (Cl), 162 (12)° (Br), and 165 (8)° (I). Note the crowding around 165° for Br is more pronounced than that for Cl or I.

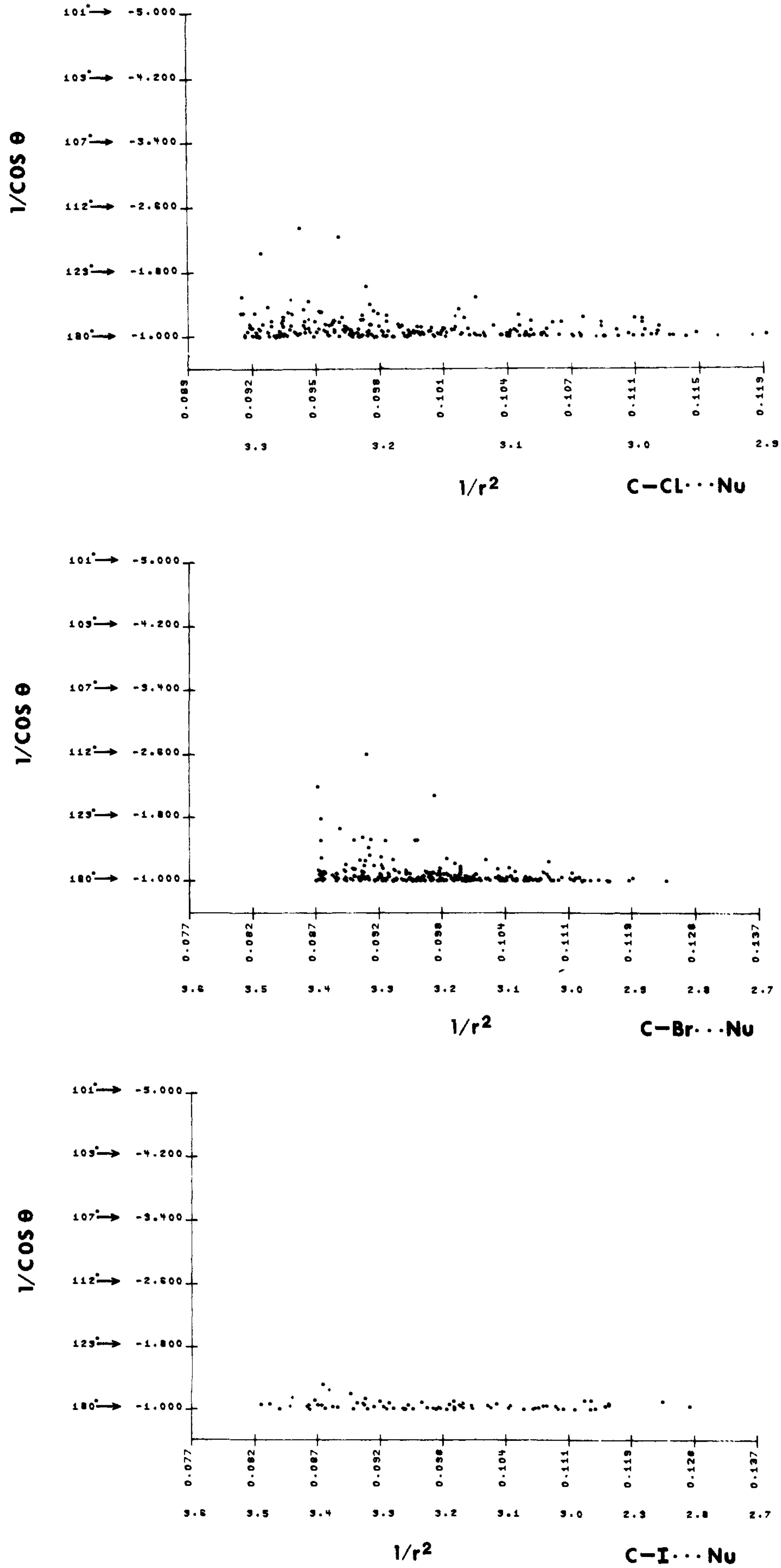

Figure 3. Scattergram depicting the annular distribution of C—X···Nu contacts projected in two dimensions with appropriate geometrical corrections applied to scales of r/θ. A uniform density of points in three-dimensional space around a polar axis transforms to uniform density on two-dimensional scattergram of $1/r^2$ against $1/\cos\theta$. Clearly the annular distribution is not uniform around X (=Cl, Br, I) in a, b, and c, respectively.

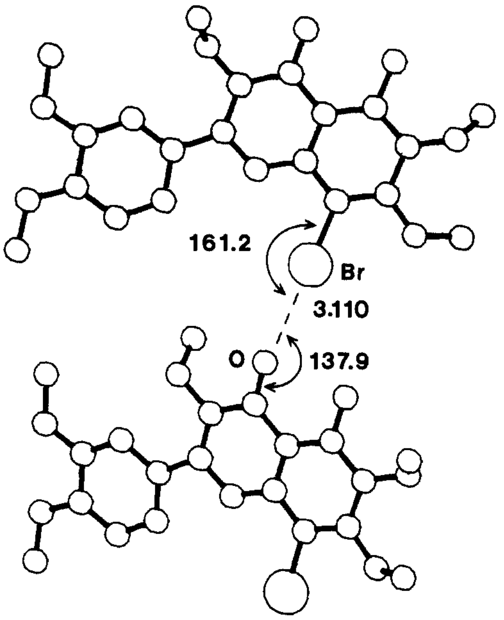

Figure 4. An Illustrative example of a C—Br···O contact (refcode ARTEMT) is shown here.

Here, using a computer we have analyzed the environment around halogen centers in hundreds of crystal structures and find that there are angular preferences of intermolecular forces around halogen centers; nucleophiles approach X of C–X along the back side of the bond whereas electrophiles approach X nearly perpendicular to C–X. We also find that these preferred directions may be understood in terms of HOMO–LUMO interactions. A preliminary report of these results was presented by us recently[8].

Computer Retrieval and Analysis of Structures with C–X Bonds (X = Cl, Br, I)

The crystallographic data used in this analysis were retrieved from the Cambridge Crystallographic Data Base (1984). This data base contains *over 40 000* structures of which 4587 had C–X bonds. The criteria used to select data containing C–X bonds are as follows: (i) each structure contains at least one C–X bond and the coordinates of these atoms have been reported, and (ii) only structures with R values less than 0.12 are included in this analysis. We modified the programs associated with the Cambridge Crystallographic Data Files[17] to search for environment around C–X bonds and to calculate the distance r of X···Z and the angle θ in C—X···Z where Z is an atom contacting X. A contact distance $r_{X\cdots Z}$ between X and Z, if less than the sum of their van der Waals radii (i.e., $r < r_X^W + r_Z^W$), is taken to be a short contact and is stored for further analysis. At this stage, we considered only intermolecular contacts, since short intramolecular contacts may be constrained to be so due to covalent forces. The packing in a molecular crystal is a compromise among many different intermolecular (and intramolecular) forces. We assumed that the stereochemistry of the contacting atoms around X will be decided by the strongest of these forces corresponding to the shortest of these contacts, especially since the halogens of C–X rarely, if at all, take part in hydrogen bonding. Therefore, to a first approximation, when there are more than one short contact, to a given halogen X, we considered only that contact for which Δr is the largest, where $\Delta r = r_X^W + r_Z^W - r_{X\cdots Z}$. We used the atomic radii given by Bondi.[18] For all contacts that survived the closest contact criteria, the parameters $r_{X\cdots Z}$ and θ were calculated and used for further analysis.[19] The data are presented in Figures

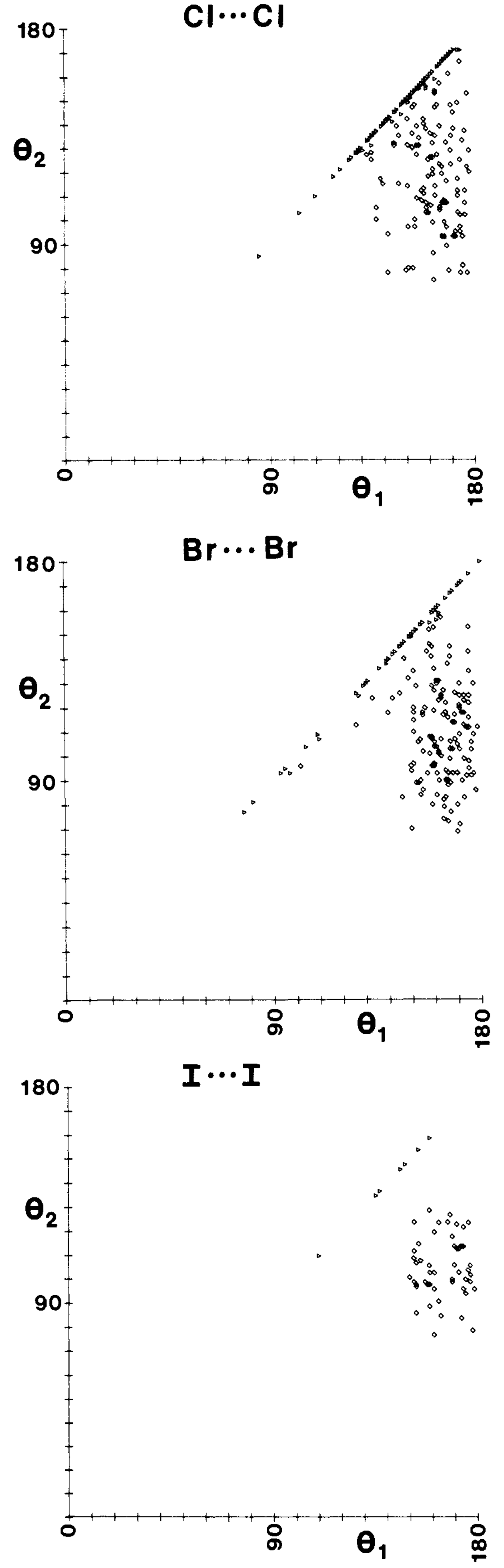

Figure 5. (a–c) The $X_1 \cdots X_2$ interactions in θ_1, θ_2 space and the correlation of θ_1 to θ_2. Note the concentration of points around θ_1 = 180° and θ_2 = 90°, indicating the nucleophilic–electrophilic pairing. The squares represent type I and type II contacts; triangles represent type III contacts. For type III contacts, X_1 and X_2 are related by a crystallographic symmetry.

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1 and 2 as plots of *r* vs. θ. A table containing the contact distances, the angles, the names of compounds where they occur, and the literature references is contained in the supplementary material.

Results

(i) Contacts to Metals (Type I Contacts). Although it is quite common for halide ions to be liganded to metal ions, a covalently bound halogen is normally not a good electron donor. For example, despite the polarity of the C–F bond, it lacks the ability to act as a proton acceptor. We found from our search that X of the C–X group is "liganded" to metal ions. We found 39 entries of C–Cl, 4 for C–Br, 4 for C–I, and 7 for C–F where the halogens make contacts to metal ions. The approach of metal ions around C–X is plotted in Figure 1a, which shows a preference for θ around 100°. When a halogen is liganded to two metal ions ($Z = E_1$ and E_2) simultaneously, it is found from Figure 1b that the angle $E_1 \cdots X \cdots E_2$ ranges from about 110 to 130°. A typical structure containing a $C—X \cdots E_1$ contact is illustrated in Figure 1c.

(ii) Contacts to O,N (Type II Contacts). The contacts to O,N and their distribution around X are summarized in Figure 2. It is quite clear from this set of figures that these contacts of O or N with X are nearly "head on" with O,N approaching X along the backside of C–X.[19,20] In Figure 3, the angular distribution of $C—X \cdots O,N$ contacts are shown after appropriate geometrical corrections for statistical factors (see ref 5 and 7). From these plots, it is seen that (i) O,N approach X in a specific direction with a preference for θ about 165° and (ii) this specificity is essentially the same for all halogens. A typical structure containing one such contact is shown in Figure 4. If the angular distributions of the contacts that are *outside* the van der Waals contact limit are examined,[7] they show essentially uniform distribution in the range of θ from 90 to 160°.

(iii) Halogen–Halogen Interactions in $C—X \cdots X—C$. Because of their exposed positions in many molecules, halogen atoms often are in a situation to make a short contact with a variety of other atoms. Many of these interactions are of the type $C—X \cdots O$,N,(metals), etc. In the absence of a contacting atom like O or N, it is known[13,21] that halogen atoms do participate in halogen–halogen ($X_1 \cdots X_2$) interactions which appear to play a significant role in determining the crystal structure. In many situations, these interactions are in the range of contact distances just above that of the sum of van der Waals radii of contacting halogens, and these interactions are usually atributed to dispersion forces. However, there are many instances in which the $X_1 \cdots X_2$ contacts are shorter than the sum of the van der Waals radii of contacting atoms by ca. 0.5 Å.

Our analysis of these interactions was based on the shortest contact criteria discussed earlier in this paper. The distributions of these contacts are represented in graphs (Figure 5a–c). Almost in all cases, X_1 and X_2 are the same halogens (=X) and are related by a crystallograhic symmetry operation. It is clear from Figure 5 that there are two preferred regions where the points fall in the θ_1–θ_2 space (disregarding momentarily, the subscripts 1 and 2), one corresponding to $\theta \sim 90°$ (type I) and another to $\theta \sim 180°$ (type II). The correlation of θ_1 vs. θ_2 shows that when $\theta_1 \sim 90°$, θ_2 falls near 180° and vice versa. There is clearly a set of points for which this reciprocal relation is not maintained corresponding to $\theta_1 \sim \theta_2$ (type III), and these contacts seem to arise when a particular crystallographic symmetry relates X_1 to X_2. An illustrative example showing the E–Nu reciprocal pairing interaction is shown in Figure 6.

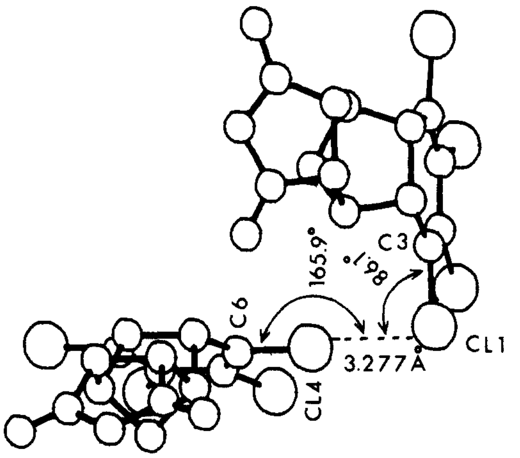

Figure 6. An illustrative example of $C—X \cdots X—C$ contact is shown here (refcode BABXUS).

(iv) HOMO–LUMO Interactions. These interactions of halogens, namely type I with metals (electrophiles), type II with nucleophiles (O, N, etc.), and the reciprocal type I–type II pairing in $X \cdots X$ interactions, all may be understood at first from a heuristic point of view with use of a simple molecular orbital consideration of the interactions of the highest occupied molecular orbital (HOMO) with the lowest unoccupied molecular orbital (LUMO) corresponding to the interacting molecules. For CH_3–F, the three lone pair molecular orbitals divide into two degenerate, purely p-type orbitals and a deeper σ-type orbital.[22] The p-type lone-pair orbitals can occupy any set of mutually orthogonal directions in the plane normal to the C–F axis, but substitution of any of the hydrogens by R reduces the C_{3v} symmetry to C_s and leads to p-type orbitals on F that are "eclipsed" and "bisected", and these orbitals lie at higher energy than the coaxial lone-pair orbital. Further, the substitution allows the eclipsed and coaxial orbit to mix, giving rise to the eclipsed orbital not being strictly perpendicular to the C–F bond though it remains in the R–C–F plane.[22] The approach of electrophiles (type I contacts) nearly normal to the C–X bond is along these eclipsed or bisected orbitals that are the HOMO's. In fact, when two electrophiles simultaneously contact X, they approach nearly normal to each other and nearly normal to the C–X bond. There are seven cases when two electrophiles E_1 and E_2 approach a Cl atom; for these, $E_1 \cdots Cl \cdots E_2$ ranges from 110 to 130° (Figure 1b). It may be noted that the deep lying coaxial σ-type lone-pair orbital has no interaction with electrophiles.

The nucleophiles Nu (type II contacts) approach X nearly "head-on"[23] at $\theta \sim 165°$, along the LUMO for CH_3X and centered at X corresponding to the σ^* antibonding orbital along the back of the C–X bond. We examined the stereochemistry of $C—X \cdots O═C$ interactions from the point of view of the nucleophile oxygen center. Though the HOMO centered on the O atom may be expected, to a first approximation, to be at an angle about 90° with respect to the C—O bond,[22] the angle $C—O \cdots X$ (plotted in Figure 7) is found to have broad distribution around 120°. To understand better these incipient reactions and the observed stereochemistry, one has to use more complicated molecular orbital calculations. Morokuma and his co-workers[24] have carried out detailed molecular orbital studies of electron donor–acceptor complexes of halogens and have also carried out energy and charge decomposition analysis using the LCAO–SCF approximation with the 4-31G basis set. The optimized geometry of $H_3N \cdots F_2$ indicates clearly that the linear arrangement in which one end of F_2 approaches N of NH_3 head-on maintaining the overall C_{3v} symmetry is preferred, and the charge transfer from the highest occuppied

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[19] There are 332 $Cl \cdots (O,N)$ contacts, 397 $Br \cdots (O,N)$, and 60 $I \cdots (O,N)$ contacts in 4587 structural entries containing at least one C–X bond. These were analyzed by using locally modified GEOM78. The scatterplots shown in Figures 1, 2, and 3 were drawn with programs written by one of us (N.R.)

[20] There are four kinds of environments possible for a halogen that is covalently bound to a C in organic compounds. They are (1) halogen attached to 1° C, (2) to 2° C, (3) to 3° C, and (4) to an sp^2 C. We have retrieved separately compounds belonging to each of these kinds and noticed that regardless of the class to which a halogen belongs there is a preponderance of the approach of Nu to be about 165° to C–X bond.

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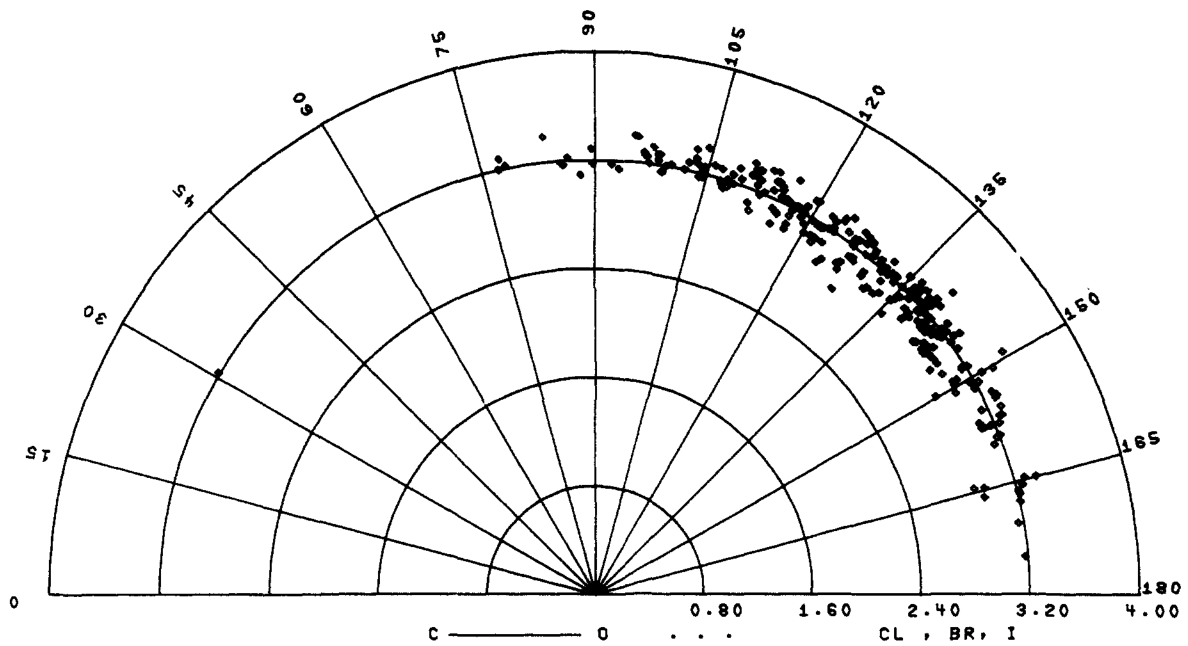

Figure 7. The distribution of halogens around a carbonyl oxygen. Although these approaches range from 75 to 180°, the concentration of points is clustered more around 105–140° and agrees well with an angular distribution representative of the lone pair(s) in a conventional sp^2 orbital drawing.

N lone pair (n) orbital of NH_3 to the lowest vacant σ^* orbital of F_2 is the principal contribution to the charge transfer stabilization. Calculations for the $H_3N\cdots ClF$ complex also yield similar results except that the approach of the Cl end of ClF to N is preferred over the approach of the F end. Optimization of the geometry for $(F_2)_2$ indicates that $(F_2)_2$ has an open "L" structure rather than a "T" with an angle around 120° between the L arms. For the anti-hydrogen bonded FCl···FH complex, the L is more open with an Cl···F—H angle of 141 (15)°. However, gas-phase molecular cluster studies have established[25] that the F—Cl···F—H complex has an L shape with the Cl···F—H angle of 115 (5)° and indicate that $(Cl_2)_2$ which forms a polar complex has an "L" shape.[26] These theoretical considerations and the corresponding electron-density distributions, so far as they can be extended to our halogen complexes, indicate that they are in broad agreement with our experimental results, namely that halogens X (of C–X) accept electrophiles nearly normal to the C–X bond and nucleophiles nearly head-on and behind the C–X bond. The stereochemistry of these interactions as derived from our experiments favor "L"-shaped $(X_2)_2$ clusters in agreement with gas-phase experiments of Klemperer and co-workers.[25,26]

Discussion

Our analysis here shows that the halogen X in a C–X bond is capable of significant interactions with electrophiles, nucleophiles, and other halogens. The electrophiles approach X of the C–X "side-on", nearly normal to C–X, and the nucleophiles nearly "head-on" and behind the C–X bond. However, in X···X interactions, one X acts as an electrophile while the other acts as a nucleophile, forming an electrophile–nucleophile pair as judged by the relative directions of approach. The interactions of X with other atoms are clearly anisotropic, depending on their chemical nature and directions of approach. The presence of such interactions of X even in structures with a number of hydrogen bonds shows that these interactions are significant, if not dominant.[13,21,27] These interactions are quite similar to what we have observed for sulfides[5] and selenides[6] and indicate a general pattern of interactions.

Supplementary Material Available: Table of contacts and REFCODES (34 pages). Ordering information is given on any current masthead page.

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