ACCOUNTS of chemical research

Article

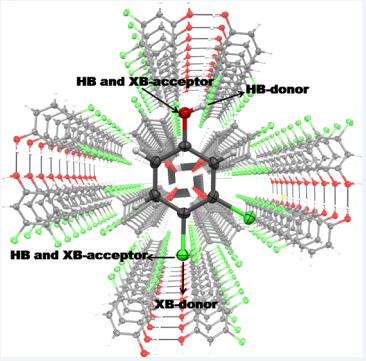
pubs.acs.org/accounts

Halogen Bonds in Crystal Engineering: Like Hydrogen Bonds yet Different

Arijit Mukherjee, Srinu Tothadi, and Gautam R. Desiraju*

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

CONSPECTUS: The halogen bond is an attractive interaction in which an electrophilic halogen atom approaches a negatively polarized species. Short halogen atom contacts in crystals have been known for around 50 years. Such contacts are found in two varieties: type I, which is symmetrical, and type II, which is bent. Both are influenced by geometric and chemical considerations. Our research group has been using halogen atom interactions as design elements in crystal engineering, for nearly 30 years. These interactions include halogen···halogen interactions (X···X) and halogen···heteroatom interactions (X···B). Many X···X and almost all X···B contacts can be classified as halogen bonds.



In this Account, we illustrate examples of crystal engineering where one can build up from previous knowledge with a focus that is provided by the modern definition of the halogen bond. We also comment on the similarities and differences between halogen bonds and hydrogen bonds. These interactions are similar because the protagonist atoms—halogen and hydrogen—are both electrophilic in nature. The interactions are distinctive because the size of a halogen atom is of consequence when compared with the atomic sizes of, for example, C, N, and O, unlike that of a hydrogen atom.

Conclusions may be drawn pertaining to the nature of X···X interactions from the Cambridge Structural Database (CSD). There is a clear geometric and chemical distinction between type I and type II, with only type II being halogen bonds. Cl/Br isostructurality is explained based on a geometric model. In parallel, experimental studies on 3,4-dichlorophenol and its congeners shed light on the nature of halogen···halogen interactions and reveal the chemical difference between Cl and Br. Variable temperature studies also show differences between type I and type II contacts.

In terms of crystal design, halogen bonds offer a unique opportunity in the strength, atom size and interaction gradation; this may be used in the design of ternary cocrystals. Structural modularity in which an entire crystal structure is defined as a combination of modules is rationalized on the basis of the intermediate strength of a halogen bond. The specific directionality of the halogen bond makes it a good tool to achieve orthogonality in molecular crystals. Mechanical properties can be tuned systematically by varying these orthogonally oriented halogen···halogen interactions. In a further development, halogen bonds are shown to play a systematic role in organization of LSAMs (long range synthon aufbau module), which are bigger structural units containing multiple synthons. With a formal definition in place, this may be the right time to look at differences between halogen bonds and hydrogen bonds and exploit them in more subtle ways in crystal engineering.

INTRODUCTION

A halogen bond, R−X···Y−Z, occurs when there is evidence of a net attractive interaction between an electrophilic region on a halogen atom X belonging to a molecule or a molecular fragment R−X (where R can be another atom, including X, or a group of atoms) and a nucleophilic region of a molecule, or molecular fragment, Y−Z.[1] This recent IUPAC definition of the halogen bond is strongly influenced by a recent (re)definition of the hydrogen bond[2] and emphasizes that a halogen atom makes an electrostatic contact when its polar region (region most distant from the atom to which halogen is covalently bonded; see Figure 5a), which is electropositive, approaches a negatively charged species. Only electrophilic halogen makes a halogen bond. This first formal definition of a halogen bond benefits from the wisdom of hindsight, acquired with hydrogen bonds, and is very general. It probably will not need significant modification for some time.

The anomalous layered crystal structures of solid Cl_2, Br_2, and I_2 contrast with the close-packed structures of diatomics like N_2 and H_2 and derive from halogen-atom anisotropy noted since early times.[3] Sakurai, Sundaralingam, and Jeffrey observed that X···X contacts are found in two geometric varieties.[4] These varieties were designated subsequently as a symmetrical type I contact and a bent type II contact (Figure 1) by Desiraju and Parthasarathy.[5] This designation of X···X contacts as type I and type II is used still.[6]

That halogen atoms make polarization mediated contacts was shown clearly by Bent,[7] Hassel,[8] and Kochi.[9] Schmidt invoked halogen atom contacts implicitly in his early studies of crystal engineering and proposed the 4 Å chloro rule, which states that polychlorinated aromatics adopt crystal structures with this short axis.[10] These results were extended and summarized in an Account by Sarma and Desiraju in 1986.[11] Thomas and Desiraju showed that of the six dichlorophenols, only three (the 2,3, 2,4, and 3,4 isomers) obey the 4 Å rule, but these are the

Received: April 18, 2014
Published: May 29, 2014

   dx.doi.org/10.1021/ar5001555 | Acc. Chem. Res. 2014, 47, 2514−2524

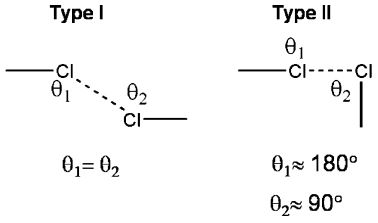


Figure 1. Type I and type II Cl···Cl contacts.

three that crystallize with higher symmetries, violating Kitaigorodskii's[12] close-packing dictum. The three other isomers (2,5, 3,5, and 2,6) do exactly the opposite. They do not have 4 Å axes, but they take low symmetry space groups. So, either Schmidt or Kitaigorodskii is correct, but not both, in any particular instance. This means that violations of the close-packing principle can be rationalized on the basis of effects of specific groups and directional interactions, more specifically Cl···Cl interactions.[13,14] It is in this context of anisotropy that halogen atoms came to be used in crystal engineering, and this is why they resemble hydrogen bonds. They can be used to both design new structures and tailor properties.

Our research group has been engaged for nearly 30 years, since the writing of the 1986 Account, in using halogen···halogen (X···X) and halogen···heteroatom (X···B) interactions as design elements in crystal engineering. Hassel, Kochi, and others recognized such contacts in crystal structures. We took the next step in the early 1990s to deliberately use these interactions in logic driven retrosynthetic approaches to crystal structure targets (Figure 2). Typical examples include the design of the 1:1 cocrystal of urotropin (HMTA) and CBr_4 based on 2:1 $CHBr_3$—urotropin,[15] and the extension CN···Cl and CN···Br based linear chains in 4-chlorobenzonitrile and 4-bromobenzonitrile into molecular tapes using the same interaction twice over (Figure 3).[16] In that they are moderately strong and fairly directional, halogen atom contacts occupy a middle ground between strong and weak hydrogen bonds.

The distribution of C≡N···Cl and C≡N···Br contacts, retrieved in 1989 from the Cambridge Structural Database (CSD) by Desiraju and Harlow, is instructive (Figure 4). The longer contacts represent normal van der Waals (vdW) separations while the shorter ones are the result of polarization from electrophilic halogen. The histograms show that the demarcation in contacts for CN···Br is greater compared with CN···Cl showing that polarization is more significant for Br compared with Cl.[17]

The use of an interaction in crystal engineering demands as full an understanding of its chemical nature as possible. Since the early 1990s, our group has examined halogen···halogen contacts ($X_1 \cdots X_2$; $X_1 = X_2$ and $X_1 \neq X_2$) in molecular crystals to ascertain the nature of these interactions. Is the type I and type II classification merely geometric taxonomy or does it have a chemical basis? The early literature holds that these preferred type I and type II geometries are due to either specific attractive forces in certain directions leading to weak bonding or nonspherical shapes arising from polar flattening. The first model corresponds to increased attraction,[18] whereas the second corresponds to decreased repulsion;[19] it was very difficult to distinguish between these alternatives using the computational techniques that were prevalent 30 years ago. Looking back, this ambiguity could have arisen because of the lack of a statistical number of crystal structures that were examined. However, in a paper published in 1994,[20] we showed that as the polarizability of X increases (Cl < Br < I), type II contacts become more significant than type I contacts and an X···X interaction can be more nearly considered to arise from specific attractive forces between X atoms. Unsymmetrical contacts ($X_1 \neq X_2$) have two possibilities for type II contacts, and these are shown in Figure 5a. A type II contact in which bending (θ_1) occurs at the lighter halogen atom is distinctly favored compared with the situation where bending occurs at the heavier halogen atom, in accord with an electrostatic model for type II and concurring with drawing a parallel between halogen bonds and hydrogen bonds; the halogen atom is considered as an electrophile in the polar region. Accordingly, we see an analogy between halogen, ethynyl, and hydroxyl groups (Figure 5b).[21]

By the late 1990s, it was evident that halogen atom interactions could be used as robust design elements in crystal engineering. In a intriguing example, a cluster of four Br atoms tetrahedrally disposed to each other is a good mimic for a molecule of CBr_4 in that the diamond based crystal structures of tetrakis(4-bromophenyl)methane and of the 1:1 cocrystal of tetraphenylmethane and CBr_4 are very similar.[22] That molecular and supramolecular synthons are interchangeable is also seen in the crystal structure of *trans*-1,5-dichloro-9,10-diethynyl-9,10-dihydroanthracene-9,10-diol, a symmetrical molecule that does not lie on a crystallographic inversion center in a centrosymmetric space group because the Cl_4 supramolecular synthons occupy such a position (Figure 6).[23] Synthons and molecules in effect fulfill equivalent roles in crystal packing.[24]

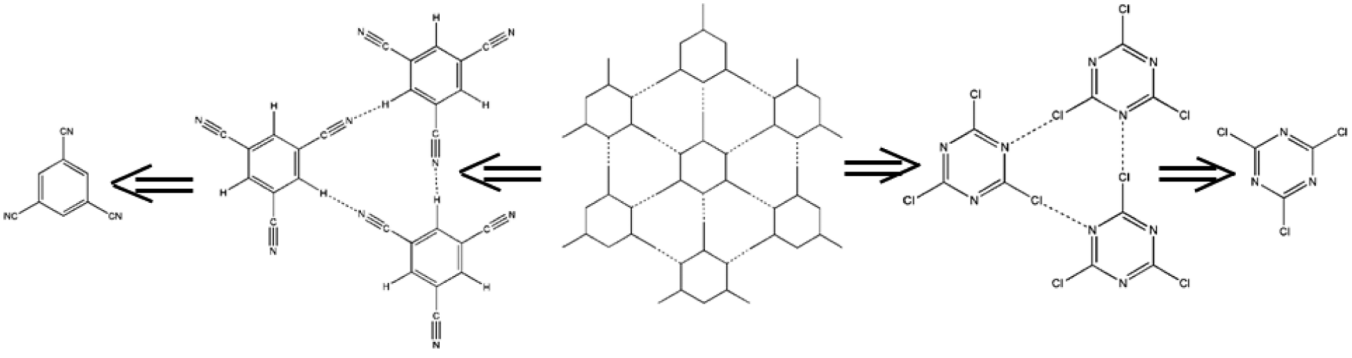


Figure 2. Similar topological pattern generated in the crystal structures of 1,3,5-tricyanobenzene (in its 1:1 cocrystal with hexamethylbenzene) and cyanuric chloride, showing the equivalence of C≡N···H—C and N···Cl interactions.

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514−2524

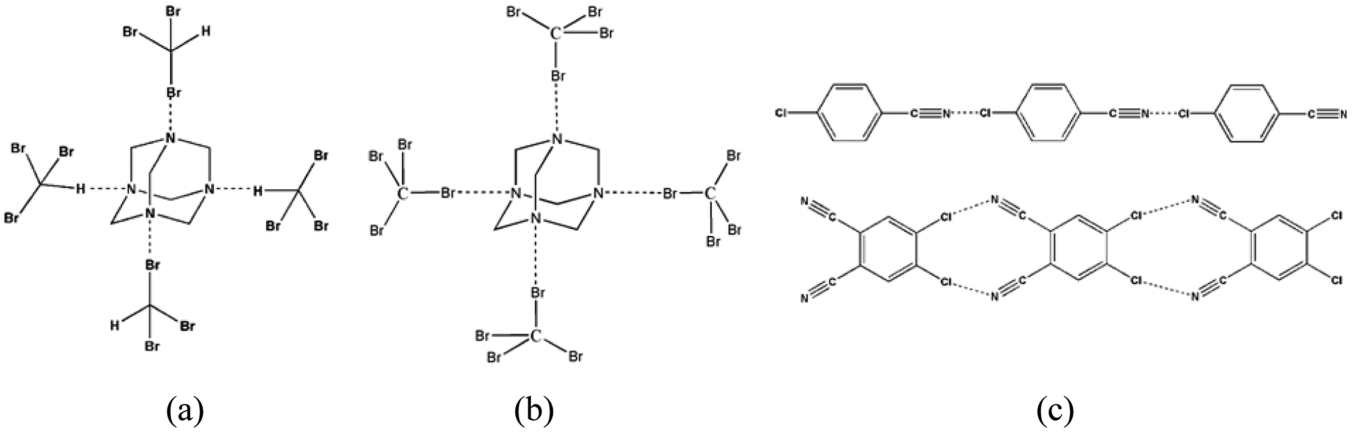


Figure 3. (a) A 2:1 adduct of bromoform and urotropin showing Br···N and C−H···N interaction. (b) Cocrystal of carbon tetrabromide and urotropin showing Br···N interaction. (c) Linear chain and molecular tapes using C≡N···Cl interactions.

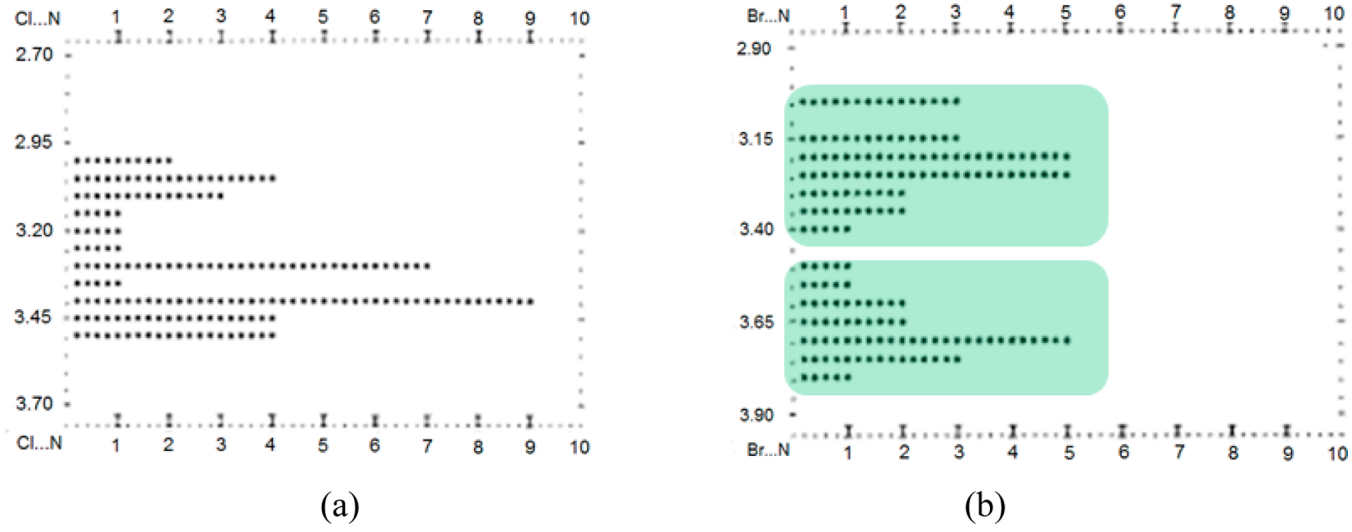


Figure 4. CSD Data, 1989. (a) Histogram of C≡N···Cl contacts. (b) Histogram of C≡N···Br contacts. The polarization and van der Waals contacts for the latter are well demarcated (shaded green).

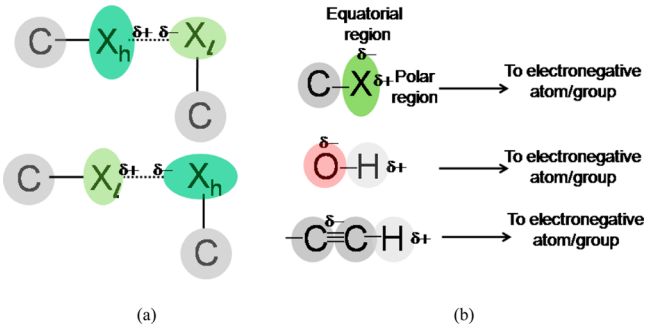


Figure 5. (a) Two possibilities for heterohalogen contacts, $X_l \cdots X_h$ where $X_l \neq X_h$: (top) bending at the lighter halogen, X_l; (bottom) bending at heavier halogen, X_h. The first possibility is preferred because the heavier halogen is more polarizable. (b) Similarity between halogen bonds and hydrogen bonds.

Around this time, Metrangolo and Resnati suggested the name *halogen bond*.[25,26] This name focused research in this area, and many systematic attempts in crystal engineering using halogen bonds appeared. We present here recent examples from our group where one builds up from previous knowledge on X···X contacts, using the modern definition of a halogen bond, to characterize the interaction in more detail and generate more diverse examples in crystal engineering.

DISTINGUISHING BETWEEN TYPE I AND TYPE II HALOGEN···HALOGEN INTERACTIONS

Chemical Effects Probed with the CSD

A statistical approach, employing crystallographic databases like the CSD, is important in the study of weak intermolecular interactions. Such data mining extracts chemical information from crystallographic data. A number of CSD studies pertaining to $X_1 \cdots X_2$ interactions appeared subsequent to our papers in 1989 and 1994.[5,20] Very recently, we revisited the whole issue in two papers[27,28] where we considered both symmetrical ($X_1 = X_2$) and unsymmetrical ($X_1 \neq X_2$) contacts. A histogram, at 5° intervals, of the difference in the angle $|\theta_1 - \theta_2|$ is given for I···I interactions (Figure 7). Similar histograms are obtained for Cl···Cl and Br···Br. A clear demarcation is observed between types I and II. The $|\theta_1 - \theta_2| = 0–5°$ region has the highest frequency per interval. A number of further conclusions may be drawn. (1) There is a clear geometric and chemical distinction between type I and type II X···X interactions. Type I is a geometry-based contact that arises from close packing and is found for all halogens. It is not a halogen bond. Type II is a

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514−2524

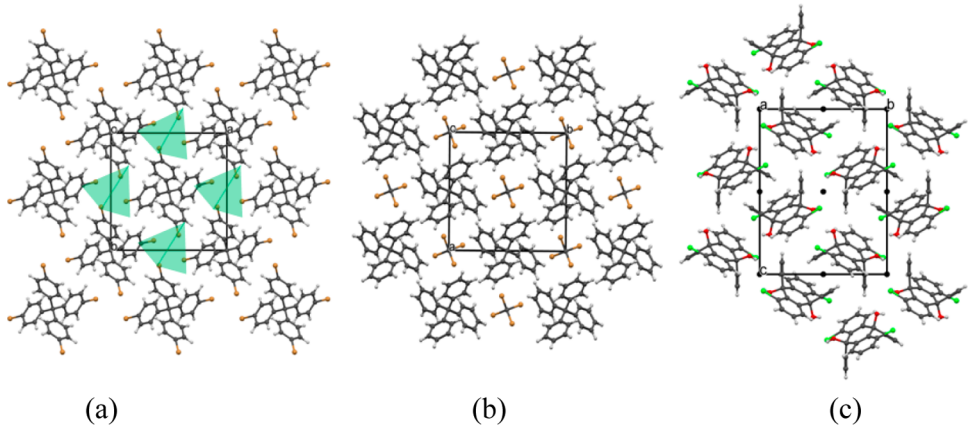


Figure 6. (a) Br_4 synthon in tetrakis(4-bromophenyl)methane, (b) cocrystal of CBr_4 and tetraphenylmethane showing that Br_4 in panel a is replaced with CBr_4, and (c) crystal structure of *trans*-1,5-dichloro-9,10-diethynyl-9,10-dihydroanthracene-9,10-diol wherein the molecule does not lie on a crystal inversion center. This position is occupied by a Cl_2 supramolecular synthon.

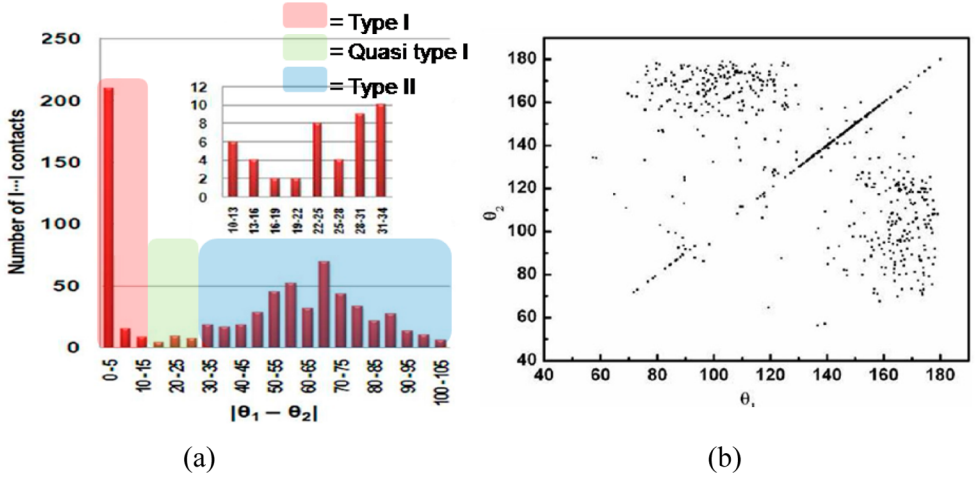


Figure 7. (a) Histogram of I···I contacts and assignment of type I and type II regions. (b) Scattergram for I···I contacts.

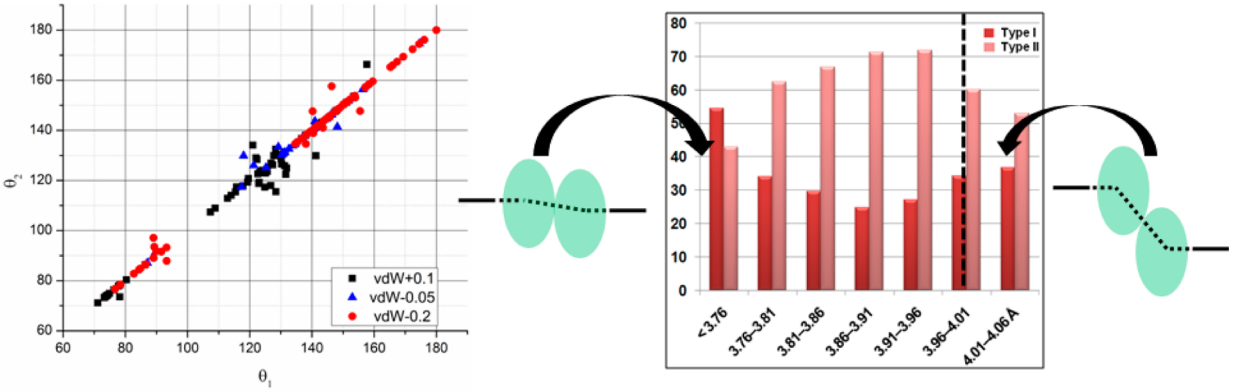


Figure 8. Scattergrams and histograms for I···I contacts. The scattergram shows the angular distribution of type I contacts at two extremes whereas the histogram shows the variation of type I and type II contacts with increasing I···I separation (vdW shown as a dashed line). Type I I···I geometries at shorter distances are more linear, while at longer distances they are bent.

halogen bond and arises from an electrophile−nucleophile pairing. It is favored in I, less so in Br, and the least in Cl. In unsymmetrical type II contacts, there is a continuous increase in the ratio of $N_{\theta 1>\theta 2}/N_{\theta 2>\theta 1}$, as the difference in electronegativity increases between the two interacting halogens, as might be expected. (2) There are a small proportion of contacts that appear between type I and type II, which may be termed as quasi-type I/type II. These quasi contacts are relatively more numerous for Cl, less so for Br, and the least for I. (3) The halogen atom in an X···X contact behaves both as an atom of a certain size and as an atom of a certain polarizability. These are, respectively, the geometric and chemical manifestations of molecular recognition. Because the size of the halogen atom is

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514−2524

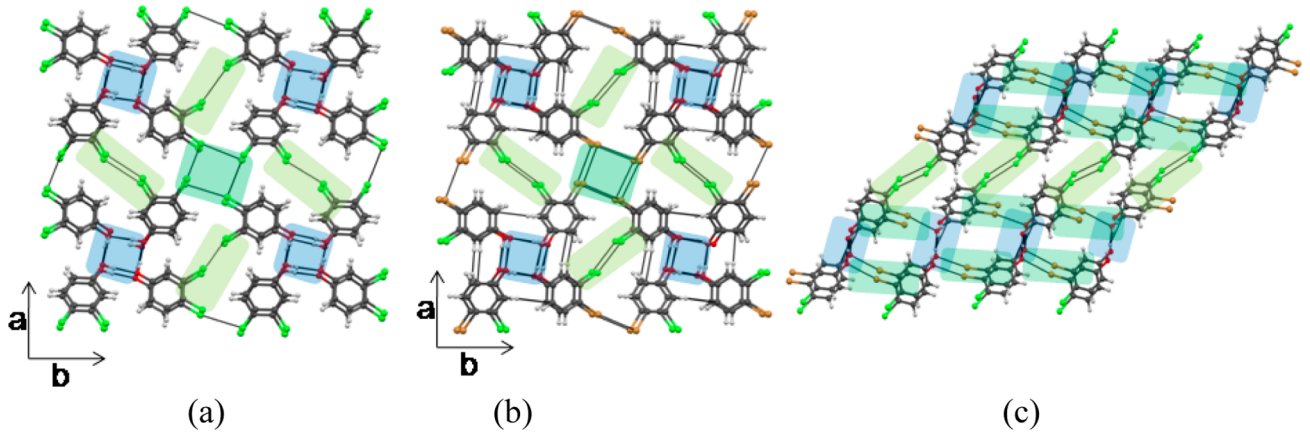


Figure 9. Crystal structures of (a) 3,4-dichlorophenol, (b) 4-bromo-3-chlorophenol, (c) 3-bromo-4-chlorophenol. Note the Cl/Br equivalence in panels a and b.

much larger than that of a hydrogen atom, the analogy between halogen bonds and hydrogen bonds cannot be taken too far.

Considering all this together, the following criteria for classification of type I and type II contacts are suggested: (1) contacts with $0° \leq |\theta_1 - \theta_2| \leq 15°$ are type I; (2) contacts with $30° \leq |\theta_1 - \theta_2|$ are type II; (3) contacts with $15° \leq |\theta 1 - \theta 2| \leq 30°$ are quasi-type I/type II.

Geometric Effects Probed with the CSD

The size of the hydrogen atom in a hydrogen bond does not normally need to be considered. In contrast, the size of a halogen atom in a halogen bond has implications for the interaction. Polarization in the large I atom results in distinct electropositive and electronegative regions within the atom. The bigger size of the halogens makes the geometric model more important for halogen bonded structures. It is probably this polarization-with-size effect that makes X···X contacts so common in crystal structures. Despite the ubiquitous presence of the H atom in molecular peripheries, short $H^{\delta+}\cdots H^{\delta-}$ interactions, the so-called dihydrogen bonds, are an infrequent occurrence because it is difficult to polarize the very small H atom appropriately except in "loaded" systems.

Type I and type II I···I contacts when analyzed as a function of interaction distance (Figure 8) show that at distances less than vdW, type I predominates at shortest distances, while type II is more frequent closer to vdW. This is because the electrostatic nature of type II contacts allows them to be viable at longer distances, whereas type I contacts being vdW operate at short distances. However, at separations greater than vdW, type I is again favored. Analysis of the angular preferences of type I I···I contacts show that while larger θ_1 ($= \theta_2$) is preferred at shortest distances (vdW − 0.2), smaller θ is observed at the longest I···I separations (vdW + 0.1). This is rationalized by invoking anisotropic vdW radii, which leads to higher θ at short separations and lower θ at long separations. Lower θ type I contacts could even have some electrostatic character, allowing them to be viable at long separations.[29] This size effect is practically absent for Cl···Cl type I interactions, Cl being much less anisotropic, while Br···Br contacts furnish a complex intermediate case.

Geometric effects in a halogen···halogen contacts can also be assessed by studying Cl/Br exchange. Substitutional isostructurality arises from a combination of chemical and geometric factors. Cl/Me isostructurality is the most well-known.[30] Not well-studied is Cl/Br isostructurality. Among the 1867 pairs of molecules in the CSD that contain identical molecular scaffolds save for the Cl/Br replacement, 152 contain X···X interactions (X = halogen). Of these, 95 pairs are isostructural with regard to Cl···Cl and Br···Br replacement. Of these, 64 (67.4%) have type I Cl···Cl and Br···Br interactions, while 31 (32.6%) have type II. A parallel study showed that type II comprises 41.6% of all Cl···Cl contacts in the CSD, whereas type I Br···Br contacts constitute 42.5% of the global sample. These statistics show that formation of type II contacts by Cl diminishes considerably (41.6% to 32.6%) in moving from the global sample to the limited set of 95 isomorphous pairs. Type I Br···Br contacts, in contrast, increase from 42.5% of the global to 67.4% in the isostructural set. This difference in isostructural and global sets clearly shows that Cl/Br isostructurality follows from shape/size matching, or geometric factors, rather than any chemical similarity between Cl and Br. If the reason for Cl/Br isostructurality were chemical, the proportion of type II Cl···Cl contacts in the isostructural pairs would have been higher than the global value of 41.6% (the same is true for type I Br···Br).[28]

3,4-Dichlorophenol. A Unique Crystal Structure

This tetragonal structure offers a platform for many interesting studies of halogen bonding because it contains both type I and type II Cl···Cl contacts (Figure 9). The 3-substituent forms a type I interaction while the 4-substituent forms a type II. Because type I and type II interactions are chemically different, this crystal structure lends itself well to their calibration. We investigated the crystal structures of 3-chloro-4-bromophenol and 3-bromo-4-chlorophenol in the expectation that the structural consequences of these substitutional changes would allow an assessment of chemical and geometric factors in Cl···Cl contacts.[28] If geometric effects are key to the packing, both test structures should be isostructural to the original compound. We found that while 4-bromo-3-chlorophenol is isostructural with 3,4-dichlorophenol, 3-bromo-4-chlorophenol is not and crystallizes in the space group $P2_1/c$ with an entirely different packing. More tellingly, the structure is sustained with a type I Cl···Cl contact and a type II Br···O interaction. We concluded that instead of being directed by their positioning in the molecule, Cl and Br behave in accordance with their chemical nature. A small chemical perturbation (3-Cl → 3-Br) upsets the structure of 3,4-dichlorophenol completely.

A subsequent variable temperature crystallography study (VT study) was performed to examine differences between type I

dx.doi.org/10.1021/ar5001555 | Acc. Chem. Res. 2014, 47, 2514−2524

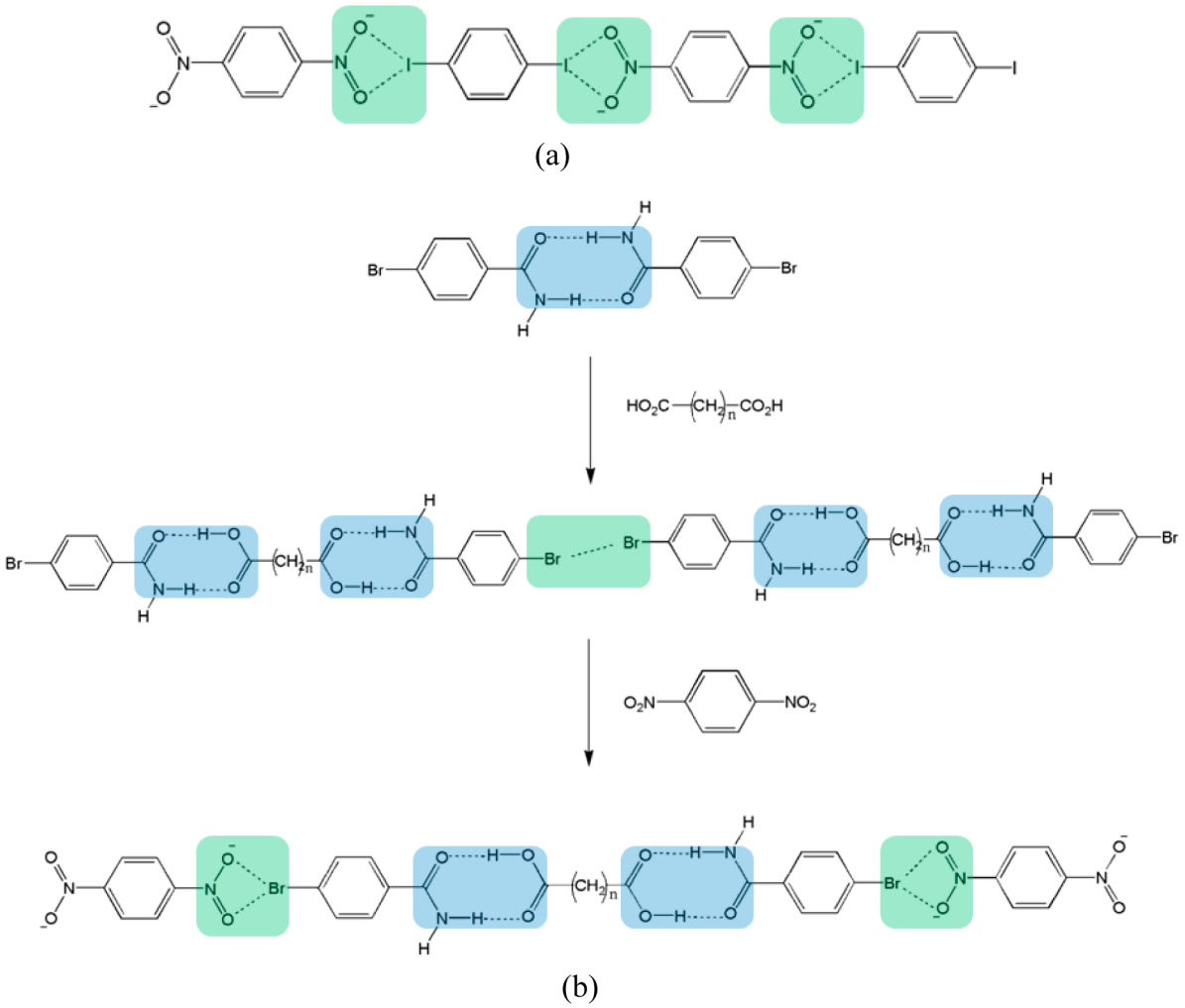


Figure 10. (a) Cocrystal of 1:1 1,4-dinitrobenzene and 1,4-diiodobenzene. Note the halogen bonded I···O_2N synthon. (b) Graded halogen and hydrogen bonds in the ternary cocrystal.

and type II contacts. 3,4-Dichlorophenol with its potential for internal calibration is a suitable compound. The percentage increase in the X···X distances with increasing temperature is more prominent for type II than for type I. The type II Cl···Cl distance increases smoothly by 1.8%, when the temperature rises from 150 to 296 K, whereas the type I contact increases by only 1.0%. The electrostatic type II contacts are viable at longer distances and can lengthen more easily when temperature is increased. However, type I contacts are more vdW in nature and so do not lengthen so much with temperature increase. The corresponding type II Br···Br contact in the isostructural 4-bromo-3-chlorophenol increases more as expected. These VT effects are seen in other halogenated crystals, and this is surely a promising method to identify type I and type II contacts, and also the quasi-type I/type II.

It may be concluded at this point that (i) type II X···X contacts are true halogen bonds while type I contacts arise because of close packing in the molecular crystals, (ii) unsymmetrical $X_1 \cdots X_2$ ($X_1 \neq X_2$) contacts are always type II and are similar to heteroatom···halogen contacts where halogen interacts noncovalently with other electronegative atoms (O, N, S), and (iii) the halogen bond, while analogous to hydrogen bond from a purely electrostatic viewpoint, is different when the size of halogens is considered.

DESIGNING TERNARY COCRYSTALS WITH HALOGEN BONDS

Cocrystals have assumed major importance in crystal engineering because they are of sufficient diversity and complexity as synthetic targets. While logic driven retrosynthesis based on heterosynthons is well developed for binary cocrystals, the design of ternary cocrystals, in which three neutral solid compounds are present in a single crystal structure, is very challenging.[31]

An early example of retrosynthesis with halogen bonds for a binary cocrystal was furnished by Thalladi et al., who reported the 1:1 cocrystal of 1,4-dinitrobenzene and 1,4-diiodobenzene.[32] This structure is based on the I···O_2N synthon and contains the I···O halogen bond (Figure 10). The similarity of this halogen bond to a hydrogen bond in similar cocrystals is unmistakable. This approach was extended by Nangia, who used hydrogen bonds (acid···pyridine) and halogen bonds (I···O_2N) together in binary design. The synthon energies of halogen bonds were estimated and compared with hydrogen bonds (I···O_2N, 2.5 kcal mol^{-1}; iodo···pyridine, 3.4 kcal mol^{-1}; acid···pyridine, 9.9 kcal mol^{-1}; acid···acid 7.8 kcal mol^{-1}).[33] Note that the halogen bond is intermediate in energy terms between strong and weak hydrogen bonds.

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514−2524

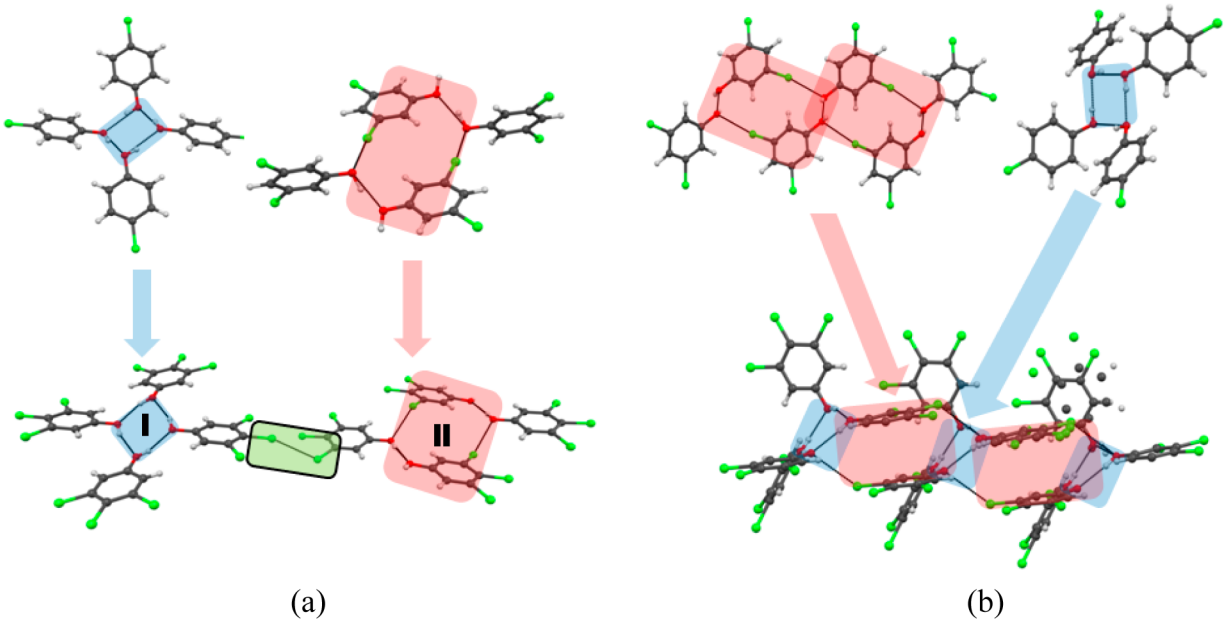


Figure 11. (a) Structural modularity in 3,4,5-trichlorophenol. Module **I** (blue) is seen in 4-chlorophenol, whereas module **II** (red) is seen in 3,5-dichlorophenol. **I** and **II** are connected with a halogen bond (green). (b) Binary disordered cocrystal of 1:9 2,3,4-trichlorophenol and 3,4,5-trichlorophenol showing the presence of conjoined hydrogen bonded domains **I** and **II**.

Any cocrystallization is difficult because crystallization is inherently a purifying technique that favors single-component outcomes. Crystallization of a ternary cocrystal such as $M_1\cdots M_2\cdots M_3$ is hard because there are many possibilities: single-component M_1, M_2, or M_3; binary cocrystals $M_1\cdots M_2$, $M_1\cdots M_3$, or $M_2\cdots M_3$, solvated cocrystals, or polymorphs of single component crystals. To address this problem, we considered a selection of graded interactions. If there are molecules M_1, M_2, and M_3 where the interaction $M_1\cdots M_2$ (e.g., a hydrogen bond) is stronger than the interaction $M_2\cdots M_3$ (e.g., halogen bond), then one may expect that initial formation of $M_1\cdots M_2$ in solution can direct crystallization to the association of M_3 to give an $M_1\cdots M_2\cdots M_3$ aggregate leading to a ternary cocrystal. However, $M_1\cdots M_2$ should not be too strong or the resulting binary cocrystal too insoluble; then it will be preferentially isolated. A fine balance of interaction strength and solubilities is needed to get a ternary cocrystal. The intermediate energy ranking of a halogen bond between strong and weak hydrogen bonds makes them especially relevant to such design strategies.

This approach was successful. We began with binary cocrystals formed by 4-bromobenzamide with aliphatic dicarboxylic acids using the well-known propensity for the formation of the acid···amide heterosynthon (Figure 10).[27] The resulting Br···Br halogen bond is a helpful add-on in that it provides the necessary $M_2\cdots M_3$ "hook" for ternary design. When 1,4-dinitrobenzene is taken along with acid and amide in the cocrystallization, borrowing from the approach of Thalladi et al., a ternary cocrystal is obtained. Similarly, 1,4-diiodobenzene/4-nitrobenzamide/dicarboxylic acid and 1,4-dinitrobenzene/4-iodobenzamide/dicarboxylic acid ternary cocrystals were isolated.[34] The halogen bond is strong enough to maintain synthon robustness, but it is weak enough so that a binary cocrystal of the type $M_2\cdots M_3$ is not formed. It is the distinctiveness of halogen bonds and hydrogen bonds that permits this synthetic strategy.

STRUCTURAL MODULARITY

Successful design strategies in crystal engineering depend on synthon *insulation*. As synthons become larger, it becomes increasingly difficult to obtain such insulation. *Structural modularity* in which an entire crystal structure may be defined as a combination of different crystal structures is therefore extremely rare because it implies insulation of large synthons. We observed such modularity in 3,4,5-trichlorophenol where there are two synthons, **I** and **II** (Figure 11), that are connected to one another by a short (quasi) type II Cl···Cl contact (3.352 Å).[35] Synthon **I**, which is also seen in 4-chlorophenol, is a cooperative hydrogen bonded tetramer. The Cl-atoms in the 3- and 5-positions of 3,4,5-trichlorophenol are vestigial and the 4-chloro substituent assumes the same role as it does in 4-chlorophenol. It is almost as if the packing of this tetramer module is "blind" to the 3- and 5-chloro substituents. Intriguingly, a complementary modularity is seen in the packing of synthon **II** units where the construction of the synthon and its extension into the infinite ladder resembles the molecular assembly in 3,5-dichlorophenol. The packing of this segment of the structure is "blind" to the 4-chloro substituent. In the context of the long-range synthon aufbau module (LSAM, see next section for definition), the connecting halogen bond links two LSAMs.

From the viewpoint of crystallization pathways it can be hypothesized that both synthons, **I** and **II**, are present in solution during the early stages of crystallization. These hydrogen bonded modules come together with a Cl···Cl halogen bond, in line with the fact that O–H···O and O···Cl are stronger than Cl···Cl. Once again, the relative weakness of the Cl···Cl halogen bond with respect to the O–H···O hydrogen bond permits this type of sequential molecular association. The binary 1:9 cocrystal of 3,4,5-trichlorophenol and 2,3,4-trichlorophenol also shows a similar modularity with the presence of both synthon **I** and synthon **II**, but unlike pure 3,4,5-trichlorophenol, these two synthons are coupled in the cocrystal structure like Siamese twins (Figure 11b).

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514–2524

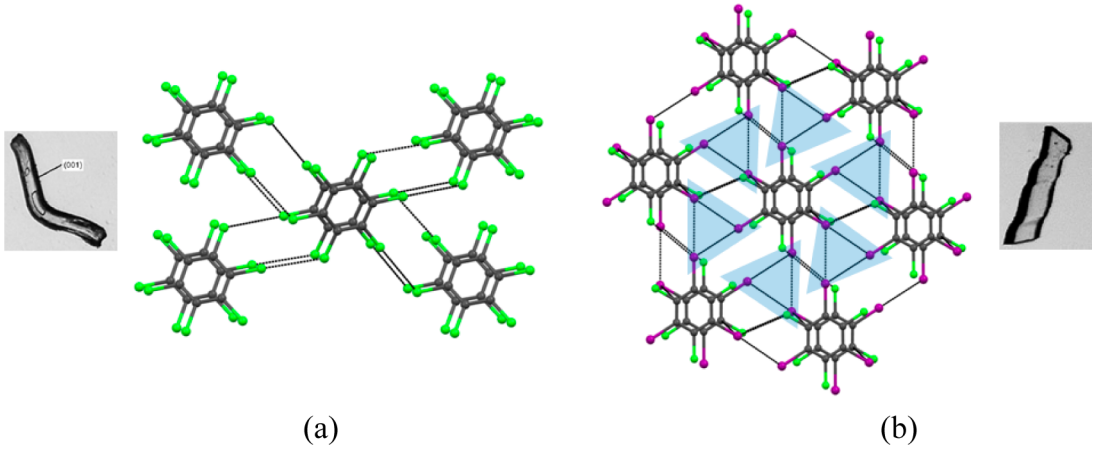


Figure 12. Structural variability in hexahalogenated benzenes: (a) C_6Cl_6 is monoclinic and shows plastic bending, while (b) 1,3,5-trichloro-2,4,6-triiodobenzene is triclinic and shows shearing along layers.

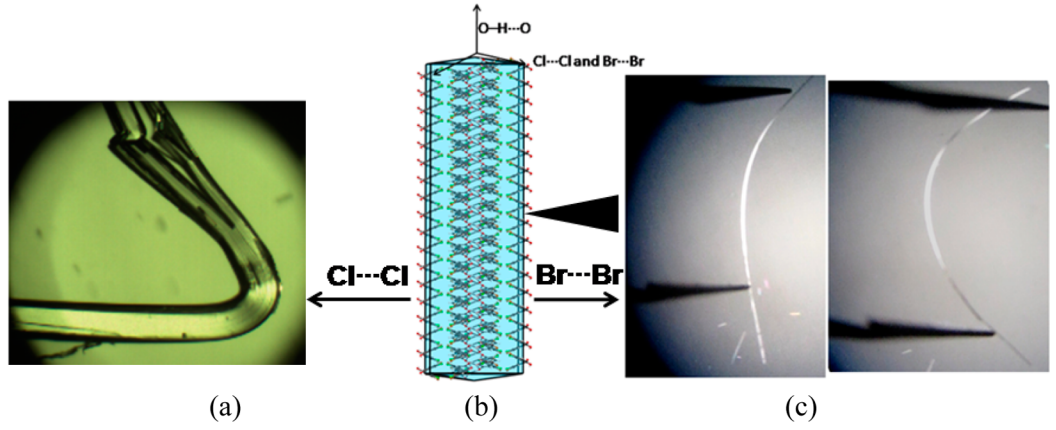


Figure 13. (a) Plastic bending in 3,4-dichlorophenol, (b) BFDH morphology of 3,4-dichlorophenol explaining the basis of bending, and (c) elastic bending in 4-bromo-3-chlorophenol.

■ ORTHOGONALITY AND INSULATION: MECHANICAL PROPERTIES

The graded strength of halogen bonds make them well suited for the *structural insulation* that is required for any target oriented design strategy. However, this is often precluded by stronger interactions in the structure. One way to tackle this problem is to choose systems that have halogen bonds orthogonal to stronger interactions thereby accentuating insulation. In this regard, we studied mechanical properties of hexahalogenated benzenes.[36] These compounds crystallize in monoclinic and triclinic packings. The former is observed in C_6Cl_6, whereas the layered triclinic packing (pseudohexagonal) is observed when different halogens alternate in 1,3,5 and 2,4,6 positions, for example, *sym*-$C_6Cl_3I_3$. These two structural classes show different response to mechanical stress (Figure 12).

The monoclinic C_6Cl_6 shows plastic bending along (001) that results from the presence of $\pi\cdots\pi$ stacking and weak orthogonal Cl···Cl interactions. The anisotropic plastic bending shows that $\pi\cdots\pi$ stacking is stronger than Cl···Cl interactions. Triclinic $C_6Cl_3Br_3$ and $C_6Cl_3I_3$, however, show shearing. This change in mechanical properties can be explained on the basis of formation of intralayer I···I interactions, specifically I_3 synthons. The triangular I_3 synthon is comparable in strength to $\pi\cdots\pi$ stacking interactions and reduces the anisotropy in the orthogonal directions. This is manifested in the shearing property in the triclinic crystals. In 3,4-dichlorophenol (Figure 9a), the bending directions are facilitated by weak Cl···Cl interactions. However, these directions [100] and [010] are symmetry related. Therefore, the crystals bend with equal ease on both the equivalent faces (010) and (100) into a variety of irregular shapes.[37] 4-Bromo-3-chlorophenol, unlike 3,4-dichlorophenol, exhibits elastic bending.[28] This observation is rationalized from the strength of the Br···Br interaction relative to Cl···Cl, which reduces the anisotropy in the orthogonal directions to the extent that the stress induced deformation is elastic (Figure 13).

■ HALOGEN BONDS AS STRUCTURAL GLUE: ASSEMBLY OF LSAMs

One is tempted to ask: How much can one exploit orthogonality? Can more complexity be achieved with the rational use of halogen bonds?

There have been some attempts to engineer crystals with specified interactions in all three perpendicular directions.[38] This would seem to be a difficult, even unrealistic goal. However, a beginning can be made if three chemically distinct types of interactions are used. The natural choices would seem to be hydrogen bonding, halogen bonding, and $\pi\cdots\pi$ stacking. In this context, we recently reported on some cocrystals of halogen substituted phenols and anilines. Earlier studies

dx.doi.org/10.1021/ar5001555 | *Acc. Chem. Res.* 2014, 47, 2514−2524

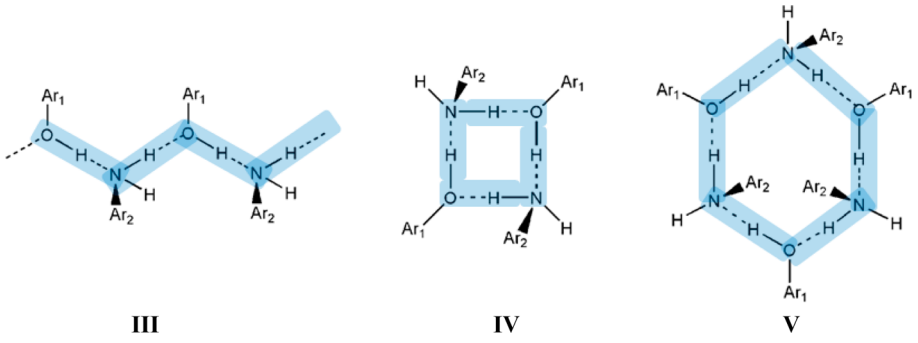


Figure 14. Synthon possibilities in aminophenols. Notice the cooperative hydrogen bonds.

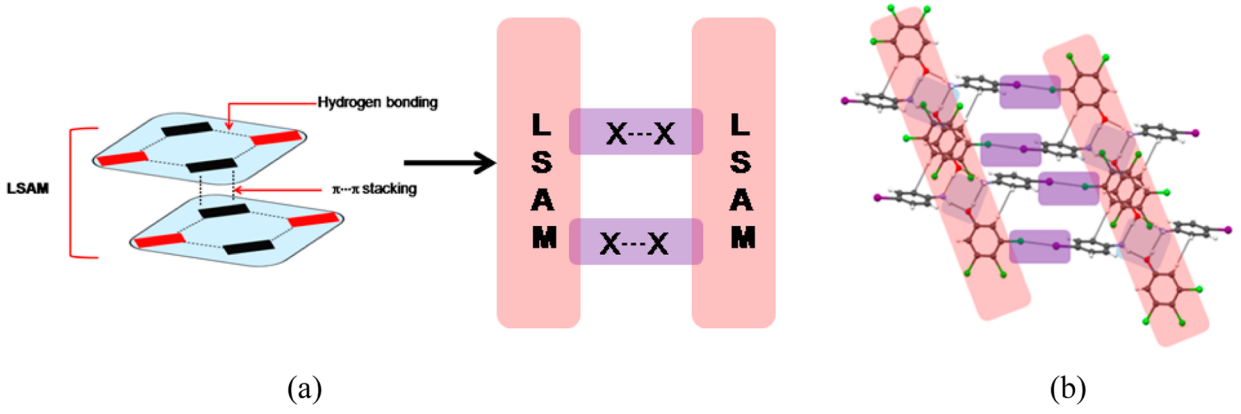


Figure 15. (a) Construction of LSAMs and their organization with halogen bonds and (b) a 1:1 cocrystal of 3,4,5-trichlorophenol and 4-iodoaniline showing the organization of LSAMs through an I···O halogen bond.

indicated that there are three possible synthons in this group of compounds (Figure 14).[39]

The cocrystal design strategy involves the orthogonal positioning of two synthons, namely synthon **IV** and $\pi\cdots\pi$ stacking between two trichlorophenol rings, and this combination resulted in an LSAM or large synthon (Figure 14). The LSAM attempts to combine two different viewpoints namely Kitaigorodskii's aufbau principle and Desiraju's supramolecular synthon.[40] According to this visualization, short-range synthons are combined to form long-range aufbau modules, which lead to the final 3D structure. Accordingly, LSAMs may be defined in all crystal structures. From the viewpoint of crystallization pathways, LSAM, being a higher order aggregate, appears at the later stages in the nucleation process and therefore contains more geometric and chemical information than smaller supramolecular synthons. The advantage of the LSAMs over smaller synthons is they can be used to tune the finer details of crystal structures. We found that because of the modular nature of the LSAMs in these aniline phenol cocrystals, two unit cell dimensions can be predicted (from hydrogen bonding and $\pi\cdots\pi$ geometries) while the third dimension is of variable lengths depending on the interactions present in that direction (halogen bonding).[41] The observed crystal structures show that the *c*-axis length varies within a small range; the interactions that operate in this direction are also predictable (Br···O, I···O, and I···O) (Figure 15). In this regard, the halogen bond is a good alternative to provide the third dimensional control.

CONCLUSIONS

Although halogen bonds have been hitherto used in analogy with hydrogen bonds, there are differences that arise due to the size of the halogens. The clear distinction between type I and type II interactions and Cl/Br isostructurality point to the geometric factors inherent to these interactions. Chemical factors are also important; the intermediate strength of halogen bonds and their directionality provides a clear edge over weak hydrogen bonds in terms of orthogonality or organization of LSAMs. Yet, in a chameleon like way, they are similar to hydrogen bonds and can compete with them.[42−44] These similarities and differences make halogen bonds a special tool in the crystal engineer's toolbox.

Where does one go? Introduction of experimental techniques such as force microscopy[45] or charge density analysis[46] may increase our understanding of this interaction, while studies in solution[47] may shed light on its aggregation behavior. Other questions need attention too: (i) Are F···F contacts chemically relevant? (ii) Can the HSAB principle be applied in crystal engineering to halogen bonds? (iii) Can the gradation among *different* halogen···halogen contacts be exploited in crystal design? (iv) Can similar chalcogen or pnicogen bonds be used in *conjunction* with halogen bonds?[48] With a formal definition in place, the halogen bond, which is strong enough, directional enough, and modular enough yet distinctive enough from a hydrogen bond, has come of age as an appropriately modulated interaction in crystal engineering.

AUTHOR INFORMATION

Corresponding Author

*E-mail: desiraju@sscu.iisc.ernet.in.

Notes

The authors declare no competing financial interest.

Biographies

Arijit Mukherjee was born in 1985 and received his B.Sc. (Honours) degree from Calcutta University and an M.Sc. from the Indian Institute of Technology, Guwahati, both in chemistry. He has just completed his Ph.D. under the supervision of Professor Desiraju, working on halogen bonding, especially in phenols.

Srinu Tothadi obtained his M.Sc. degree from Sri Venkateswara Univesity, Tirupati, and joined the Indian Institute of Science, Bangalore, for his Ph.D. degree in 2009 with Professor Desiraju, focusing on the design of organic ternary cocrystals in crystal engineering.

Gautam R. Desiraju served on the editorial advisory board of *Accounts of Chemical Research* between 1998 and 2005 and as consulting editor between 2005 and 2009. He has published in *Accounts* in 1986, 1991, 1996, and 2002.

■ ACKNOWLEDGMENTS

A.M. and S.T. thank I.I.Sc. for research fellowships. G.R.D. thanks DST for a J. C. Bose fellowship. We thank Dr. Sumy Joseph for several CSD searches reported in this Account.

■ REFERENCES

(1) Desiraju, G. R.; Ho, P. S.; Kloo, L.; Legon, A. C.; Marquardt, R.; Metrangolo, P.; Politzer, P.; Resnati, G.; Rissanen, K. Definition of the halogen bond (IUPAC Recommendations 2013). *Pure Appl. Chem.* **2013**, *85*, 1711−1713.

(2) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. Definition of the hydrogen bond (IUPAC Recommendations 2011). *Pure Appl. Chem.* **2011**, *83*, 1637−1641.

(3) Collin, R. L. The crystal structure of solid chlorine. *Acta Crystallogr.* **1952**, *5*, 431−432.

(4) Sakurai, T.; Sundaralingam, M.; Jeffrey, G. A. A nuclear quadrupole resonance and X-ray study of crystal structure of 2,5-dichloroaniline. *Acta Crystallogr.* **1963**, *16*, 354−363.

(5) Desiraju, G. R.; Parthasarathy, R. The nature of halogen···halogen interactions - Are short halogen contacts due to specific attractive forces or due to close packing of nonspherical atoms. *J. Am. Chem. Soc.* **1989**, *111*, 8725−8726.

(6) Metrangolo, P.; Resnati, G. Type II halogen···halogen contacts are halogen bonds. *IUCrJ* **2014**, *1*, 5−7.

(7) Bent, H. A. Structural chemistry of donor−acceptor interactions. *Chem. Rev.* **1968**, *68*, 587−648.

(8) Hassel, O. Structural aspects of interatomic charge-transfer bonding. *Science* **1970**, *170*, 497−502.

(9) Blackstock, S. C.; Lorand, J. P.; Kochi, J. K. Charge-transfer interactions of amines with tetrahalomethanes. X-ray crystal structures of the donor-acceptor complexes of quinuclidine and diazabicyclo [2.2.2]octane with carbon tetrabromide. *J. Org. Chem.* **1987**, *52*, 1451−1460.

(10) Schmidt, G. M. J. Photodimerization in the solid state. *Pure Appl. Chem.* **1971**, *27*, 647−678.

(11) Sarma, J. A. R. P.; Desiraju, G. R. The role of Cl···Cl and C−H···O interactions in the crystal engineering of 4-Å short-axis structures. *Acc. Chem. Res.* **1986**, *19*, 222−228.

(12) Kitaigorodskii, A. I. *Molecular Crystals and Molecules*; Academic Press: New York, 1973.

(13) Desiraju, G. R. Midsummer madness. *Nature* **2004**, *431*, 25−25.

(14) Thomas, N. W.; Desiraju, G. R. An investigation into the role of chloro-substituents in hydrogen-bonded crystals: The crystal structures of the dichlorophenols. *Chem. Phys. Lett.* **1984**, *110*, 99−102.

(15) Reddy, D. S.; Craig, D. C.; Rae, A. D.; Desiraju, G. R. N···Br mediated diamondoid network in the crystalline complex carbon tetrabromide: hexamethylenetetramine. *J. Chem. Soc., Chem. Commun.* **1993**, 1737−1739.

(16) Reddy, D. S.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. Molecular tapes based on C≡N···Cl interactions. *J. Chem. Soc., Chem. Commun.* **1993**, 661−662.

(17) Desiraju, G. R.; Harlow, R. L. Cyano-halogen interactions and their role in the crystal structures of the 4-halobenzonitriles. *J. Am. Chem. Soc.* **1989**, *111*, 6757−6764.

(18) Williams, D. E.; Hsu, L. Y. Transferability of nonbonded Cl···Cl potential-energy function to crystalline chlorine. *Acta Crystallogr.* **1985**, *A41*, 296−301.

(19) Nyburg, S. C. Intermolecular forces and space group of solid chlorine. *J. Chem. Phys.* **1964**, *40*, 2493−2501.

(20) Pedireddi, V. R.; Reddy, D. S.; Goud, B. S.; Craig, D. C.; Rae, A. D.; Desiraju, G. R. The nature of halogen halogen interactions and the crystal structure of 1,3,5,7-tetraiodoadamantane. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2353−2360.

(21) Dey, A.; Desiraju, G. R. Supramolecular equivalence of ethynyl, chloro, bromo and iodo groups. A comparison of the crystal structures of some 4-phenoxyanilines. *CrystEngComm* **2004**, *6*, 642−646.

(22) Reddy, D. S.; Craig, D. C.; Desiraju, G. R. Supramolecular synthons in crystal engineering. 4. Structure simplification and synthon interchangeability in some organic diamondoid solids. *J. Am. Chem. Soc.* **1996**, *118*, 4090−4093.

(23) Banerjee, R.; Desiraju, G. R.; Mondal, R.; Batsanov, A. S.; Broder, C. K.; Howard, J. A. K. Dilemmas in crystallization. The 'unusual' behavior of trans-1,5-dichloro-9,10-diethynyl-9,10-dihydroanthracene-9,10-diol and the more 'normal' behavior of its pseudopolymorphs with dipolar aprotic solvents. *Helv. Chim. Acta* **2003**, *86*, 1339−1351.

(24) Thallapally, P. K.; Chakraborty, K.; Katz, A. K.; Carrell, H. L.; Kotha, S.; Desiraju, G. R. Matching of molecular and supramolecular symmetry. An exercise in crystal engineering. *CrystEngComm* **2001**, *3*, 134−136.

(25) Metrangolo, P.; Resnati, G. Halogen bonding: A paradigm in supramolecular chemistry. *Chem.—Eur. J.* **2001**, *7*, 2511−2519.

(26) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. Halogen bonding based recognition processes: A world parallel to hydrogen bonding. *Acc. Chem. Res.* **2005**, *38*, 386−395.

(27) Tothadi, S.; Joseph, S.; Desiraju, G. R. Synthon modularity in cocrystals of 4-bromobenzamide with n-alkanedicarboxylic acids: Type I and type II halogen···halogen interactions. *Cryst. Growth Des.* **2013**, *13*, 3242−3254.

(28) Mukherjee, A.; Desiraju, G. R. Halogen bonds in some dihalogenated phenols: applications to crystal engineering. *IUCrJ* **2014**, *1*, 49−60.

(29) Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. The nature of halogen···halogen synthons: Crystallographic and theoretical studies. *Chem.—Eur. J.* **2006**, *12*, 8952−8960.

(30) Desiraju, G. R.; Sarma, J. A. R. P. The chloro-methyl exchange rule and its violations in the packing of organic molecular solids. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1986**, *96*, 599−605.

(31) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. "Total Synthesis" supramolecular style: Design and hydrogen-bond-directed assembly of ternary supermolecules. *Angew. Chem., Int. Ed.* **2001**, *40*, 3240−3242.

(32) Thalladi, V. R.; Goud, B. S.; Hoy, V. J.; Allen, F. H.; Howard, J. A. K.; Desiraju, G. R. Supramolecular synthons in crystal engineering. Structure simplification, synthon robustness and supramolecular retrosynthesis. *Chem. Commun.* **1996**, 401−402.

(33) Saha, B. K.; Nangia, A.; Jaskolski, M. Crystal engineering with hydrogen bonds and halogen bonds. *CrystEngComm* **2005**, *7*, 355−358.

(34) Tothadi, S.; Desiraju, G. R. Designing ternary cocrystals with hydrogen bonds and halogen bonds. *Chem. Commun.* **2013**, *49*, 7791−7793.

(35) Mukherjee, A.; Desiraju, G. R. Halogen bonding and structural modularity in 2,3,4- and 3,4,5-trichlorophenol. *Cryst. Growth Des.* **2011**, *11*, 3735−3739.
(36) Reddy, C. M.; Kirchner, M. T.; Gundakaram, R. C.; Padmanabhan, K. A.; Desiraju, G. R. Isostructurality, polymorphism and mechanical properties of some hexahalogenated benzenes: The nature of halogen center dot center dot center dot halogen interactions. *Chem.—Eur. J.* **2006**, *12*, 2222−2234.
(37) Reddy, C. M.; Gundakaram, R. C.; Basavoju, S.; Kirchner, M. T.; Padmanabhan, K. A.; Desiraju, G. R. Structural basis for bending of organic crystals. *Chem. Commun.* **2005**, *0*, 3945−3947.
(38) Wells, K. E.; Weatherhead, R. A.; Murigi, F. N.; Nichol, G. S.; Carducci, M. D.; Selby, H. D.; Mash, E. A. Organic crystal engineering with 1,4-Piperazine-2,5-diones. 8. Synthesis, crystal packing, and thermochemistry of piperazinediones derived from 2-Amino-4,7-dialkoxyindan-2-carboxylic Acids. *Cryst. Growth Des.* **2012**, *12*, 5056−5068.
(39) Vangala, V. R.; Bhogala, B. R.; Dey, A.; Desiraju, G. R.; Broder, C. K.; Smith, P. S.; Mondal, R.; Howard, J. A. K.; Wilson, C. C. Correspondence between molecular functionality and crystal structures. Supramolecular chemistry of a family of homologated aminophenols. *J. Am. Chem. Soc.* **2003**, *125*, 14495−14509.
(40) Ganguly, P.; Desiraju, G. R. Long-range synthon aufbau modules (LSAM) in crystal structures: systematic changes in $C_6H_{6-n}F_n$ ($0 \leq n \leq 6$) fluorobenzenes. *CrystEngComm* **2010**, *12*, 817−833.
(41) Mukherjee, A.; Dixit, K.; Sarma, S. P.; Desiraju, G. R. Aniline−phenol recognition. From solution through supramolecular synthons to cocrystals. *IUCrJ* **2014**, in press.
(42) Corradi, E.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G. Halogen bonding versus hydrogen bonding in driving self-assembly processes. *Angew. Chem., Int. Ed.* **2000**, *39*, 1782−1786.
(43) Aakeröy, C. B.; Fasulo, M.; Schultheiss, N.; Desper, J.; Moore, C. Structural competition between hydrogen bonds and halogen bonds. *J. Am. Chem. Soc.* **2007**, *129*, 13772−13773.
(44) Brammer, L.; Espallargas, G. M.; Libri, S. Combining metals with halogen bonds. *CrystEngComm* **2008**, *10*, 1712−1727.
(45) Boterashvili, M.; Shirman, T.; Cohen, S. R.; Evmenenko, G.; Dutta, P.; Milko, P.; Leitus, G.; Lahav, M.; van der Boom, M. E. Interfacial halogen bonding probed using force spectroscopy. *Chem. Commun.* **2013**, *49*, 3531−3533.
(46) Bui, T. T. T.; Dahaoui, S.; Lecomte, C.; Desiraju, G. R.; Espinosa, E. The nature of halogen···halogen interactions: A model derived from experimental charge-density analysis. *Angew. Chem., Int. Ed.* **2009**, *48*, 3838−3841.
(47) Erdelyi, M. Halogen bonding in solution. *Chem. Soc. Rev.* **2012**, *41*, 3547−3557.
(48) Scheiner, S. The pnicogen bond: Its relation to hydrogen, halogen, and other noncovalent bonds. *Acc. Chem. Res.* **2012**, *46*, 280−288.