

Halogen bonding and the design of new materials: organic bromides, chlorides and perhaps even fluorides as donors

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Abstract In some halides RX, the halogen X has a region of positive electrostatic potential on its outermost portion, centered around the extension of the R–X bond. The electrostatic attraction between this positive region and a lone pair of a Lewis base is termed halogen bonding. The existence and magnitudes of such positive potentials on some covalently bonded halogens, and the characteristic directionality of the interaction, can be explained in terms of the degree of *sp* hybridization and polarizability of X and the electronegativity of R. Halogen bonding increases in strength in the order Cl < Br < I; fluorine is frequently said to not form halogen bonds, although a notable result of the present study is computational evidence that it does have the capability of doing so, if R is sufficiently electron withdrawing. An increasingly important application of halogen bonding is in the design of new materials (e.g., crystal engineering). In this paper, we present the calculated energies of a series of halogen-bonding interactions that could be the basis for forming linear chains, of types X---X---X--- or X---Y---X---Y---. We focus upon chlorides and bromides, and nitrogen bases. The B3PW91/6-311G(3df,2p) and MP2/6-311++G(3df,2p) procedures were used. We show how the computed electrostatic potentials (B3PW91/6-31G**) can provide guidance in selecting appropriate halide/base pairs.

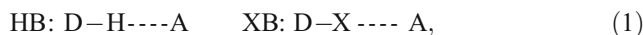
Keywords Electrostatic potentials · Halogen bonding · Noncovalent interactions · Crystal engineering

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Introduction

There is now a growing awareness of the importance of halogen bonding, an attractive noncovalent interaction that is (or can be) a significant factor in areas ranging from crystal engineering [1, 2] to biological recognition processes [2, 3]. Like the much more familiar hydrogen bonding, halogen bonding involves sharing an atom (a halogen rather than a hydrogen) between a donor molecule DX and an acceptor A. Thus, the two interactions can be depicted as



where HB represents hydrogen bonding and XB represents halogen bonding.

In Eq. 1, X is usually Cl, Br or I; most often it is one of the last two. A key feature of halogen bonding is its directional character; the angle between the D–X and X–A bonds is always close to 180°.

Experimentally, it has been found that the strength of halogen bonding increases in the order Cl < Br < I. In the past, it has sometimes been said that fluorine does not form halogen bonds, but we shall present evidence indicating that it could do so on occasion, although probably rarely. In both hydrogen bonding and halogen bonding, the donor D tends to be electron-withdrawing, of high electronegativity; the acceptor A is usually a Lewis base, with an available pair of electrons.

While several different types of donors can halogen-bond, our focus will be on organic halides. Early reviews and discussions of the analogies between halogen bonding and hydrogen bonding were presented by Bent [4] and by Hassel [5], although the first use of the term “halogen bonding” that we have found was by Dumas et al. [6]. An important step in providing a sound experimental basis for the concept of halogen bonding was the analysis of large

numbers of crystal structures, which revealed anomalously short intermolecular distances between some halogens and nucleophiles such as oxygens and nitrogens [7–9]. For a recent overview of halogen bonding, see Politzer et al. [10].

Origins of halogen bonding

A covalently bonded halogen atom, as in an organic halide RX, is typically negative in character. Why then does it interact attractively with a lone pair on the acceptor A? It was suggested some time ago by us [11, 12], and more recently by others [3], that the explanation lies in a rather surprising feature of many covalently bonded halogens: a region of positive electrostatic potential on the outermost portion of the halogen atom, centered around the extension of the R–X bond. We attribute the formation of halogen bonds to the attractive electrostatic interaction between this positive potential and a lone pair of the acceptor.

The key to this interpretation is the electrostatic potential $V(\mathbf{r})$ on the molecular surface of the halide RX. $V(\mathbf{r})$ is defined rigorously by

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}') d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|}, \quad (2)$$

where Z_A is the charge on nucleus A, located at \mathbf{R}_A , and $\rho(\mathbf{r})$ is the molecule's electronic density. $V(\mathbf{r})$, the electrostatic potential that is created at any point \mathbf{r} by the molecule's nuclei and electrons, is a physical observable; it can be determined experimentally, by diffraction techniques [13, 14], as well as computationally. Our interest is in $V(\mathbf{r})$ on the molecular surface, which we take to be the 0.001 electrons/bohr³ contour of $\rho(\mathbf{r})$, as suggested by Bader et al. [15]. $V(\mathbf{r})$ computed on this surface is designated as $V_S(\mathbf{r})$.

For organic molecules in general, $V_S(\mathbf{r})$ is typically weakly positive over much of the surface, with local maxima, $V_{S,\max}$, near the hydrogens [16, 17]. The negative regions tend to be smaller, but are often stronger, especially those associated with the lone pairs of electronegative atoms.

$V_S(\mathbf{r})$ has been shown to be an effective means of analyzing and predicting noncovalent interactions [17–20]. Of particular relevance in the present context is the fact that its most positive and most negative values, $V_{S,\max}$ and $V_{S,\min}$, have been found to correlate quantitatively with hydrogen bond donating and accepting tendencies, respectively [21].

In earlier reports, [10–12] we presented figures showing the computed electrostatic potentials on the molecular surfaces of a series of alkyl halides. In CH₃F, CH₃Cl and CF₄, the halogens are—as anticipated—completely negative. This can also be seen in Fig. 1 for CH₃CH₂Cl; we computed the latter at the density functional B3PW91/6-

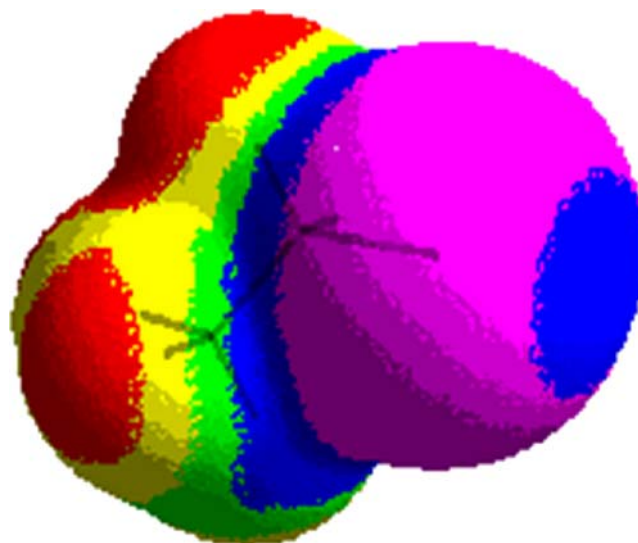


Fig. 1 Computed B3PW91/6-31G** electrostatic potential of CH₃CH₂Cl on the molecular surface defined by the 0.001 electrons/bohr³ contour of the electronic density. The chlorine is at the right. Color scale (kcal/mol): red is more positive than 10; yellow is between 5 and 10; green is between 0 and 5; blue is between –10 and 0; purple is more negative than –10. The chlorine surface is completely negative

31G** level. The unexpected feature appears in proceeding to CH₃Br [10] or CH₃CH₂Br (Fig. 2). In each case, the bromine, despite being nearly as electronegative as chlorine, has a small region of positive potential on its outer side, at the intersection with the C–Br axis. (Even in CH₃CH₂Cl, Fig. 1 shows that the outermost part of the chlorine surface is less negative than the remainder.)

In Table 1 are listed the most positive electrostatic potentials, the $V_{S,\max}$, on the halogen surfaces of 27 organic halides. The $V_{S,\max}$ are all located at the intersections of the surfaces with the C–X axes, as in Fig. 2. Also included in Table 1 are the most negative potentials, the $V_{S,\min}$, associated with the nitrogens of four Lewis bases. Halogen bonding can be understood in terms of the electrostatic attraction between such positive (halogen) and negative (base) potentials.

Table 1 shows that chlorine does have the capacity for developing a positive surface region, if the remainder of the molecule is sufficiently electron withdrawing. Thus, replacement of hydrogens by fluorines in CH₃Cl gives the chlorine an increasingly positive region, reaching $V_{S,\max} = 16.3$ kcal/mol for F₃C–Cl. Other electron-withdrawing groups are even more effective; note, for example, NC–Cl and NC–C≡C–Cl. For each comparable chloride/bromide pair, however, the more polarizable bromine has the higher $V_{S,\max}$.

The case of fluorine is particularly interesting. Until recently, we had never found a positive potential associated with it. Now Table 1 shows that the strongly electron withdrawing CN group is able to produce a significantly

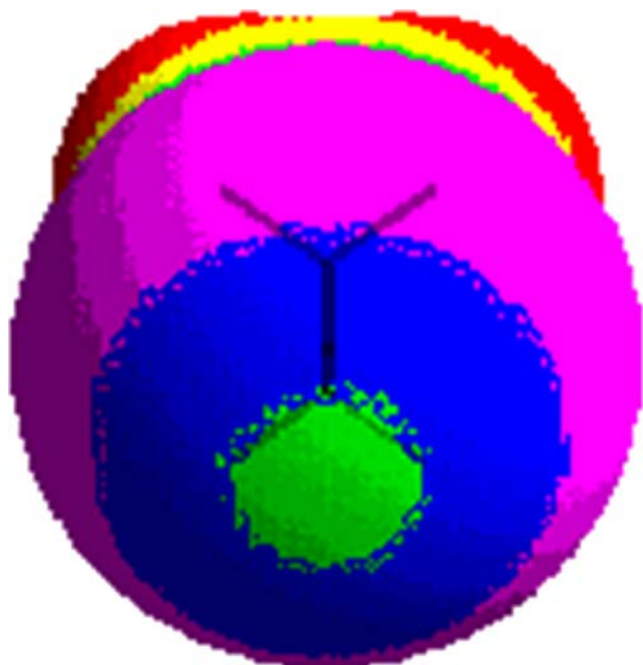


Fig. 2 Computed B3PW91/6-31G** electrostatic potential of $\text{CH}_3\text{CH}_2\text{Br}$ on the molecular surface defined by the 0.001 electrons/ bohr^3 contour of the electronic density. The bromine is facing the reader. Color scale (kcal/mol): red is more positive than 10; yellow is between 5 and 10; green is between 0 and 5; blue is between -10 and 0; purple is more negative than -10. The bromine has a small positive (green) region centered around the intersection of the C-Br axis with the surface, the maximum being 2.9 kcal/mol

positive $V_{S,\text{max}}$ of more than 16 kcal/mol. We will return to this shortly.

What determines whether a halogen in a given molecule RX will develop a positive potential on its outermost portion, and how strong will it be? This has been analyzed by Clark et al. [22]. We have already seen the importance of the electronegativity of R and the polarizability of the halogen. Another factor is the degree of sp hybridization of the halogen's unshared s valence electrons.

A free, neutral ground-state halogen atom has a spherically symmetric s^2p^5 valence configuration, in which each p orbital has, on average, $5/3$ electrons. When the atom forms an R-X bond along, say, the z -axis, the p_x and p_y orbitals become doubly occupied, and their total of four electrons contribute a negative potential around the central part of the halogen atom. The remaining half-filled p_z orbital may hybridize to varying extents with the s orbital. Consider two extremes. If there is no sp hybridization, then the s charge remains spherically symmetrical around the nucleus, while the lone p_z electron interacts with R. There is then a deficiency of electronic charge in the outer lobe of the p_z orbital, creating what was termed a "sigma hole" along the R-X axis [22] and resulting in a positive surface region. This $s^2p_x^2p_y^2p_z^1$ configuration produces an anisotropic charge distribution around the atom X, which has in fact

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

Halide, R-X	$V_{S,\text{max}}$ (X)	X,N molecules	$V_{S,\text{max}}$ (X)	$V_{S,\text{min}}$ (N)	Nitrogen bases	$V_{S,\text{min}}$ (N)
$\text{H}_3\text{C-F}$	-21.0	$\text{N}\equiv\text{C-F}$	16.4	-30.8	NH_3	-46.3
$\text{H}_3\text{C-Cl}$	-1.5 ^a	$\text{N}\equiv\text{C-Cl}$	34.9	-30.7	$\text{N}\equiv\text{C-C}\equiv\text{N}$	-19.6
$\text{H}_2\text{FC-Cl}$	3.5 ^a	$\text{N}\equiv\text{C-Br}$	42.1	-32.0	$\text{N}\equiv\text{C-C}\equiv\text{C}\equiv\text{N}$	-23.4
$\text{HF}_2\text{C-Cl}$	8.9 ^a	$\text{N}\equiv\text{C-C}\equiv\text{C-F}$	16.9	-33.7	Pyrazine (1,4-diazine)	-31.3
$\text{F}_3\text{C-Cl}$	16.3 ^a	$\text{N}\equiv\text{C-C}\equiv\text{C-Cl}$	35.0	-33.4		
		$\text{N}\equiv\text{C-C}\equiv\text{C-Br}$	41.6	-34.0		
$\text{H}_3\text{C-Br}$	5.9 ^a					
$\text{F}_3\text{C-Br}$	21.3 ^a					
$\text{CH}_3\text{CH}_2\text{-Cl}$	-3.7					
$\text{CH}_3\text{CH}_2\text{-Br}$	2.9					
$\text{HC}\equiv\text{C-F}$	2.3					
$\text{HC}\equiv\text{C-Cl}$	20.4					
$\text{HC}\equiv\text{C-Br}$	27.0					
$\text{FC}\equiv\text{C-F}$	1.8					
$\text{ClC}\equiv\text{C-Cl}$	22.4					
$\text{BrC}\equiv\text{C-Br}$	28.7					
$\text{HOCH}_2\text{CH}_2\text{-Cl}$	-1.1 ^a					
$\text{HOCH}_2\text{CH}_2\text{-Br}$	5.9 ^a					
$\text{O}_2\text{NCH}_2\text{CH}_2\text{-Cl}$	7.8 ^a					
$\text{O}_2\text{NCH}_2\text{CH}_2\text{-Br}$	14.8 ^a					
<i>trans</i> - $\text{ClFC}=\text{CF-Cl}$	17.9					
$\text{BrC}_6\text{F}_4\text{-Br}$ (1,4-dibromotetrafluorobenzene)	23.6					

^a From [10]

been observed experimentally in halogen-bonded systems [23–25]. It is the sigma hole that gives halogen bonding its directional character.

On the other hand, if there is complete *sp* hybridization, one half-filled *sp* will interact with R to form the R–X bond, while the other, containing two electrons, will be concentrated along the R–X axis in the direction away from R. There is in this case no sigma hole and the halogen would *not* be expected to have a positive outer portion.

Clark et al. [22] assessed the hybridization of the halogen X in the series of trifluoromethyl halides F₃C–X, where X is F, Cl, Br and I. Natural bond order (NBO) analyses were carried out. They showed that the highest level of *sp* hybridization of X is when X is F, double that when X is Cl, which in turn is more than when X is Br or I.

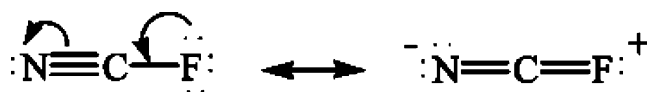
With respect to electronegativity and polarizability, the more electron-withdrawing is R relative to X, and the greater is the polarizability of X, the more will be enhanced the development of a positive region on the latter. Halogen electronegativities increase and their polarizabilities decrease on going from iodine to fluorine. Thus, if the results of the NBO studies of the F₃C–X series are valid in general, at least qualitatively, then both the hybridization and the electronegativity/polarizability factors indicate that the likelihood of having significant positive surface regions is least for fluorines, intermediate for chlorines, and greatest for bromines and iodines. This is consistent with the experimental observation that halogen-bonding capability increases in the same order.

Since the extent of *sp* hybridization, relative electronegativity and polarizability all tend to work against fluorine having a significant positive surface region, why does this occur in NC–F and NC–C≡C–F, in which fluorine achieves $V_{S,max} \approx 17$ kcal/mol (Table 1)? We addressed the hybridization issue via NBO analyses of H₃C–F and H₃C–Cl, in which the halogen surfaces are entirely negative, and NC–F and NC–Cl, in which they have positive regions (Table 1). This was done at the B3PW91/6-31G** level, the same as the calculation of the $V_{S,max}$ in Table 1.

Fluorine was found to have essentially the same degree of *sp* hybridization in both molecules. This is also true of chlorine; however, the *sp* hybridization is considerably less.

In the C–F bonds, for example, the fluorine had 26 and 28% 2*s* character in H₃C–F and NC–F respectively, compared with 16 and 18% 3*s* for chlorine in the C–Cl bonds in H₃C–Cl and NC–Cl. These results are similar to what was obtained by Clark et al. [22] for the F₃C–X series. They show that the development of a positive potential on fluorine in NC–F does not reflect a marked change in *sp* hybridization. The key to the positive $V_{S,max}$ is apparently

the very strong electron-attracting power of the CN substituent, both through resonance,



and inductively; the inductive constant σ_I is 0.613 for CN, greatly exceeding the 0.364 for F [26]. This results in the fluorine surface being completely positive (Fig. 3).

Strengths of halogen bonds

The most extensive experimental data concerning the strengths of halogen bonds of which we are aware are for perfluorocarbon iodides with various nitrogen bases [1]. Interaction energies are reported to be in the range –5 to –8 kcal/mol. The N–I distances are intermediate between the typical N–I covalent bond and the sum of the N and I van der Waals radii.

There have been a number of computational treatments of halogen bonding [10, 24, 27–32], involving different halogen donors RX and a variety of bases, including NH₃, H₂O, H₂CO, nitrogen heterocycles, metal hydrides, Br[–] and others. The interaction energies for forming a single donor–acceptor complex R–X–base become more negative as the electron-withdrawing capacity of R increases and, for a given R, on going from X is F to Cl to Br to I. Among the most negative computed ΔE were –11.74 kcal/mol for F₂N–Cl–Br[–] and –10.61 kcal/mol for F₃C–Br–Br[–] (MP2/6-311++G** [30]), –7.81 kcal/mol for F₃C–I–ON(CH₃)₃ (BP86/frozen core, extended

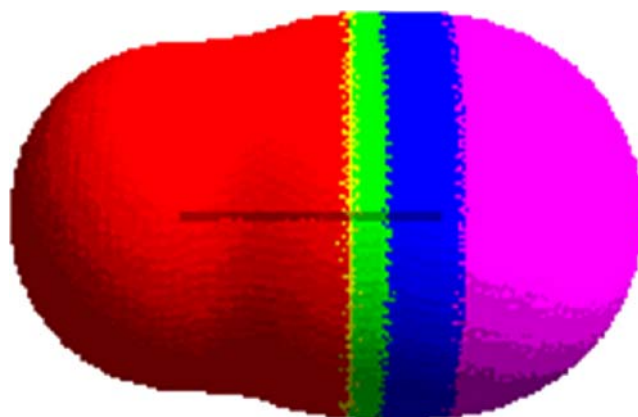


Fig. 3 Computed B3PW91/6-31G** electrostatic potential of FCN on the molecular surface defined by the 0.001 electrons/bohr³ contour of the electronic density. The fluorine is at the left. Color scale (kcal/mol): red is more positive than 10; yellow is between 5 and 10; green is between 0 and 5; blue is between –10 and 0; purple is more negative than –10. The fluorine surface is completely positive, with a maximum of 16.4 kcal/mol

Slater-type orbital valence basis set [28]) and -6.4 kcal/mol for $F_3C-I \cdots NH_3$ (BP86/DZVP [27]). This is all in accord with the earlier discussion and with experimental observations. No stable interactions were found for H_3C-F and H_3C-Cl [10, 24].

Given the similarities between halogen bonding and hydrogen bonding, it is natural to ask if the two are competitive, and in particular, can halogen bonding interfere with hydrogen bonding? Both answers are yes. This was demonstrated more than 30 years ago by Bernard-Houplain and Sandorfy [33] and Di Paulo and Sandorfy [34, 35], for solutions of organic bases. They showed that IR peaks due to solute–solute hydrogen bonding were considerably diminished when co-solutes capable of halogen bonding to the bases were introduced; this was interpreted as indicating some disruption of hydrogen bonds.

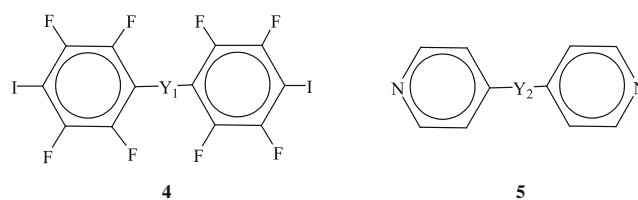
More recently, working with crystals, Corradi et al. [36] provided striking examples of halogen bonding actually dominating over hydrogen bonding. These involved a diamine or diazine **1** that was known to co-crystallize via halogen bonding with an X donor **2**, $\cdots 1 \cdots 2 \cdots 1 \cdots 2 \cdots$, and via hydrogen bonding with a H donor **3**, $\cdots 1 \cdots 3 \cdots 1 \cdots 3 \cdots$. When **1**, **2** and **3** were simultaneously dissolved in an appropriate solvent, crystallization produced, in each instance, only $\cdots 1 \cdots 2 \cdots 1 \cdots 2 \cdots$, the H donor being left in solution.

It has been suggested that halogen interference with hydrogen bonding may help to explain the anesthetic activities of certain polyhalogenated alkanes and ethers [2, 37–39], such as halothane, $CF_3CHBrCl$ and methoxyflurane, $CH_3OCF_2CHCl_2$. It has been proposed that these may interfere with the normal functioning of key brain proteins, perhaps by disrupting their hydrogen-bond structures by means of the positive potentials associated with some of the hydrogens, bromines and/or chlorines on the anesthetic molecule.

Halogen bonding and crystal engineering

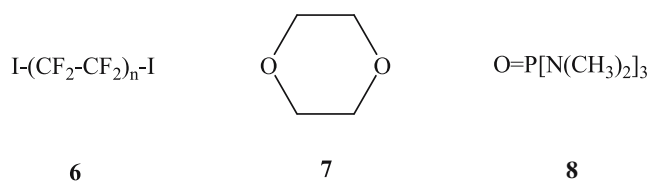
The study of halogen bonding versus hydrogen bonding by Corradi et al. [36] that was mentioned in the last section was in the context of crystal engineering, a very active area in which designed halogen bonding is playing an increasing role [1, 2]. We refer in particular to the self-assembly of co-crystals, driven by halogen bonding between the components. Existing and potential applications include molecular conductors, superconductors, nonlinear optical materials, coatings, etc. Among the advantages of halogen bonding in crystal engineering, as pointed out by Guardigli et al. [1], are its strength, specificity and directionality, which allow reliable prediction of the topology of the resulting co-crystal.

Numerous examples of the formation of halogen-bonded co-crystals are available in the literature; many of these are cited and discussed by Metrangolo et al. [2]. For instance, Guardigli et al. [1] co-crystallized X donors with acceptors of the types **4** and **5** from appropriate solvents such as chloroform to produce co-crystals composed of linear chains $\cdots 4 \cdots 5 \cdots 4 \cdots 5 \cdots$.

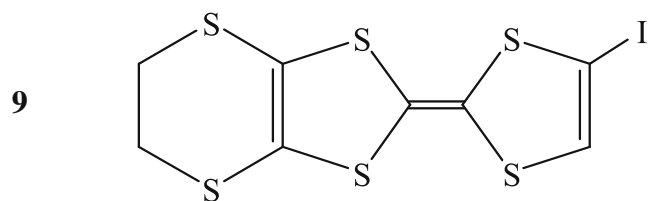


Y_1 and Y_2 were various linking groups, e.g., $N(CH_3)$ or $(CH_2)_2$.

While the $I \cdots N$ interaction is the most common basis for halogen-bonded co-crystals, there are certainly other possibilities. Chu et al. [40] produced co-crystals of perfluorinated diiodoalkanes **6** with 1,4-dioxane, **7**, and also with hexamethylphosphoramide, **8**.

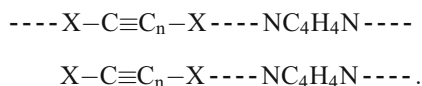


XB-based ionic co-crystals can also be prepared. This was demonstrated by Imakubo et al. [41], who combined the monoiodide donor **9** with salts containing various anions such as $Ag(CN)_2^-$, Cl^- and Br^- . This led to ionic systems in which the negative ions were iodide:anion complexes in ratios of 2:1.

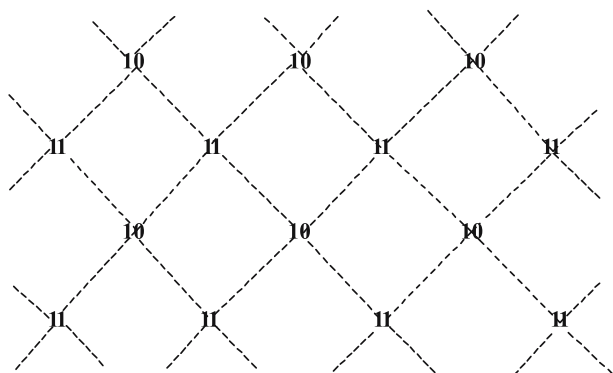
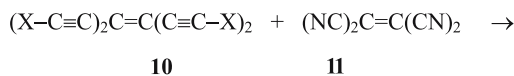


As the preceding discussion indicates, iodides have been the most widely used donors in crystal engineer-

ing based on halogen bonding. We have been interested in exploring the feasibility of bromides or even chlorides serving as donors. One can envision co-crystals composed of linear chains having, for example, $X-(C\equiv C)_n-X$, where $X=Cl$ or Br , combined with $NC-(C\equiv C)_m-CN$ or pyrazine (1,4-diazine, NC_4H_4N), e.g.,



More ambitious would be a two-dimensional network formed by the two ethylene derivatives **10** and **11**.

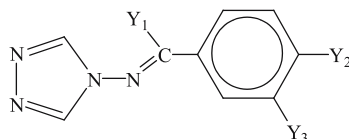


Our proposed donors and acceptors are selected such that the co-crystal would have extensive multiple bonding, to promote potential conducting and nonlinear optical activity. In the next section, we shall report results of preliminary calculations intended as initial tests of such possible XB interactions.

Computed interaction energies for some possible crystals

Rather than proceeding directly to co-crystals with two components, we will first consider polymeric systems having a single repeating monomer that is capable of being both a halogen bond donor and acceptor. Berski et al. have recently synthesized three compounds of this type, and analyzed them both crystallographically and computationally [29].

The monomers were the triazole derivatives **12–14**, and they were linked by $Br\cdots N$ interactions.



- 12:** $Y_1=H, Y_2=Br, Y_3=H$
13: $Y_1=H, Y_2=H, Y_3=Br$
14: $Y_1=CH_3, Y_2=Br, Y_3=H$

For the formation of dimers of **12–14**, Berski et al. obtained ΔE of -1.2 to -1.3 kcal/mol (B3LYP/LANL2DZ) [29].

We have chosen to begin with smaller molecules, in order to be able to work at a higher computational level and to more easily identify factors involved in the interactions. We used the B3PW91/6-311G(3df,2p) and MP2/6-311++G(3df,2p) procedures. The B3PW91-optimized geometries were utilized for the MP2 calculations. These large basis sets should minimize any basis set superposition error, which was not explicitly taken into account.

In Table 2 are given the computed B3PW91 and MP2 energy minima, $E_{\min}(0\text{ K})$, and the B3PW91 enthalpies, $H(298\text{ K})$, for 22 molecules and halogen-bonded complexes. From these were obtained the $\Delta E_{\min}(0\text{ K})$ and the $\Delta H(298\text{ K})$ for the formation of the complexes; these are in Table 3. Two general observations can be made from the results in Table 3:

1. The MP2 $\Delta E_{\min}(0\text{ K})$ are invariably more negative than the B3PW91, sometimes by as much as 3 kcal/mol. This may reflect the larger MP2 basis set and/or a greater capability on the part of MP2 for taking account of dispersion effects.
2. The B3PW91 $\Delta H(298\text{ K})$ are generally slightly less negative than the B3PW91 $\Delta E_{\min}(0\text{ K})$, usually by 1–2 kcal/mol.

Discussion and summary

First, we want to note the interesting point that FCN does form stable halogen bonds, as might have been inferred from the significant positive potential on the fluorine, $V_{S,\max}=16.4$ kcal/mol (Table 1). In addition to the two examples in Table 3, we also found a stable interaction between FCN and NH_3 , giving $H_3N\cdots FCN$ with $\Delta E_{\min}(0\text{ K}) = -1.3$ kcal/mol at the MP2/6-311++G(3df,2p) level. These are the first instances of fluorine halogen bonding of which we are aware.

With regard to forming linear chains of halogen-bonded molecules, Table 3 suggests that this may be easier when they involve just a single repeating monomer that is both a

Table 2 Computed energies and enthalpies

Molecule or complex	B3PW91/6-311G(3df,2p)		MP2/6-311++G(3df,2p)
	$E_{\min}(0\text{ K})$	$H(298\text{ K})$	$E_{\min}(0\text{ K})$
FCN	-192.62514	-192.61103	-192.35719
ClCN	-552.98069	-552.96777	-552.35177
BrCN	-2,666.93823	-2,666.92579	-2,665.19116
CIC≡CCI	-996.45845	-996.44155	-995.35886
BrC≡CBr	-5,224.37191	-5,224.35599	-5,221.03727
NC–CN	-185.63010	-185.60897	-185.32320
NC–C≡C–CN	-261.77718	-261.74390	-261.31997
Pyrazine (1,4-diazine)	-264.29329	-264.21141	-263.78490
1,4-Dibromotetrafluorobenzene	-5,776.19638	-5,776.13686	-5,772.11121
FCN---FCN	-385.25173	-385.22394	-384.71651
FCN---FCN---FCN	-577.87859	-577.83711	-577.07622
CICN---CICN	-1,105.96524	-1,105.93791	-1,104.70964
CICN---CICN---CICN	-1,658.95068	-1,658.90894	-1,657.06910
BrCN---BrCN	-5,333.88163	-5,333.85526	-5,330.39012
BrCN---BrCN---BrCN	-8,000.82637	-8,000.78605	-7,995.59044
NC–CN---CIC≡CCI	-1,182.08954	-1,182.05008	-1,180.68501
NC–C≡C–CN---BrC≡CBr	-5,486.15107	-5,486.10042	-5,482.36172
BrC≡CBr---NC–C≡C–CN---BrC≡CBr	-10,710.52482	-10,710.45680	-10,703.40334
BrC≡CBr---NC–C≡C–CN---BrC≡CBr---NC–C≡C–CN	-10,972.30377	-10,972.20103	–
Pyrazine---CIC≡CCI	-1,260.75464	-1,260.65437	–
Pyrazine---BrC≡CBr	-5,488.66981	-5,488.57045	-5,484.83005
NC–C≡C–CN---1,4-dibromotetrafluorobenzene	-6,037.97492	–	-6,033.43544

donor and an acceptor. Compare, for example, the MP2 $\Delta E_{\min}(0\text{ K})$ for BrCN---BrCN and NC–C≡C–CN---BrC≡CBr. This is readily understandable; when a molecule contains both donor and acceptor portions, they strengthen each other. In BrCN, for example, the CN withdraws electronic charge from the Br, making the latter more positive and the former more negative, and promoting their electrostatic interactions with other BrCN molecules. In NC–C≡C–CN, on the other hand, the two acceptor groups compete with each other for the polarizable charge of the triple bond.

An interesting feature of the complexes having a single repeating monomer can be seen by comparing the interaction energies in Table 3 for the systems XCN---XCN and XCN---XCN---XCN, where X is F, Cl or Br. In each case, the magnitude of $\Delta E_{\min}(0\text{ K})$ for the latter is more than twice that for the former. Thus, the overall interactions are strengthened in going from two to three units. These may be examples of the “cooperativity effect” mentioned by Grabowski et al. [31, 42]. The results for the complexes involving NC–C≡C–CN and BrC≡CBr (Table 3) suggest

Table 3 Computed interaction energies and enthalpies

Halogen-bonded complex	B3PW91/6-311G(3df,2p)		MP2/6-311++G(3df,2p)
	$\Delta E_{\min}(0\text{ K})$	$\Delta H(298\text{ K})$	$\Delta E_{\min}(0\text{ K})$
FCN---FCN	-0.91	-1.2	-1.3
FCN---FCN---FCN	-2.0	-2.5	-2.9
CICN---CICN	-2.4	-1.5	-3.8
CICN---CICN---CICN	-5.4	-3.5	-8.7
BrCN---BrCN	-3.2	-2.3	-4.9
BrCN---BrCN---BrCN	-7.3	-5.4	-10.6
NC–CN---CIC≡CCI	-0.62	0.28	-1.9
NC–C≡C–CN---BrC≡CBr	-1.2	-0.33	-2.8
BrC≡CBr---NC–C≡C–CN---BrC≡CBr	-2.4	-0.58	-5.5
BrC≡CBr---NC–C≡C–CN---BrC≡CBr---NC–C≡C–CN	-3.5	-0.78	–
Pyrazine---CIC≡CCI	-1.8	-0.88	–
Pyrazine---BrC≡CBr	-2.9	-1.9	-4.9
NC–C≡C–CN---1,4-dibromotetrafluorobenzene	-0.85	–	-2.7

that this effect may not operate when different molecules act as donor and acceptor.

In considering potential co-crystals, a judicious choice of both donor and acceptor is required. Computed electrostatic potentials can provide some guidance. Thus, Table 1 shows that the nitrogen $V_{S,\min}$ of pyrazine are significantly more negative than are those of $\text{NC}-\text{C}\equiv\text{C}-\text{CN}$, which suggests that a halogen-bond donor should interact more favorably with the former. This is confirmed in Table 3; compare the interaction energies for pyrazine--- $\text{BrC}\equiv\text{CBr}$ and $\text{NC}-\text{C}\equiv\text{C}-\text{CN}$ --- $\text{BrC}\equiv\text{CBr}$. With regard to the donor, it is interesting that the bromine $V_{S,\max}$ are somewhat more positive in $\text{BrC}\equiv\text{CBr}$ than in 1,4-dibromotetrafluorobenzene (Table 1), despite the presence of four electronegative fluorines in the latter. Their inductive effect is evidently partially cancelled by resonance donation to the aromatic ring. Table 3 indicates that the interaction of 1,4-dibromotetrafluorobenzene with $\text{NC}-\text{C}\equiv\text{C}-\text{CN}$ is slightly weaker than is that of $\text{BrC}\equiv\text{CBr}$.

Overall, the computed electrostatic potentials in Table 1 and interaction energies in Table 3 do offer some encouragement concerning the feasibility of preparing co-crystals with bromide, chloride and perhaps even fluoride donors. Indeed the possibility of the last of these, suggested by the examples of $\text{NC}-\text{F}$ and $\text{NC}-\text{C}\equiv\text{C}-\text{F}$, is a notable feature of Tables 1 and 3.

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