Chapter 2

Non-bonded Halogen bonding interaction and the influence of the stereoelectronic effect

2.1. Investigation of X-ray crystallographically observed O···Br-Br halogen bonding interactions with \textit{ab initio} calculations

2.1.1. Introduction

In this section, a systematic study of halogen bonding interactions has been performed on a series of dimeric complexes formed between bromine molecules and several oxygen containing electron donors. The \textit{ab initio} quantum chemical calculations and complete basis set method have been applied to examine the nature and directionality of the bromine molecules towards the sp$^3$ and sp$^2$ hybridized oxygen atoms.

Weak intermolecular interactions play important roles in many chemical phenomena, such as molecular recognition, conformational transformation, and molecular packing in crystals.\textsuperscript{1} Hence, a great effort has been made to understand how these interactions participate in protein folding, ligand binding, and enzymatic catalysis. Hydrogen bonding is the most frequently used tool to assemble organic molecules in solid, liquid, or in gas-phases.\textsuperscript{2} However, there are other kinds of non-bonded (non-covalent) interactions such as cation-\(\pi\), lone pair-\(\pi\), \(\pi\)-\(\pi\) stacking, anion-\(\pi\), CH-\(\pi\) are also investigated as those steering physical and chemical processes.\textsuperscript{3} Halogen bonding has also been studied recently to understand the importance in chemistry, biology and solids. It is also treated as the competitive interaction to the typical hydrogen bonding. Halogen bonding is often defined as the interaction of halogen atom acting as the Lewis acid with the Lewis base possessing at least one lone pair.\textsuperscript{4} Halogen bonding may involve dihalogens \(X_2\) and interhalogens X-Y as well as organic halides. The interhalogen molecules with larger dipole moments (FBr > FCl > ClBr) and dihalogens with higher polarizability (Br$\textsubscript{2}$ > Cl$\textsubscript{2}$ > F$\textsubscript{2}$) shows the significant interaction energies with respect to a given Lewis base.\textsuperscript{5} By virtue of their strength, selectivity, and directivity, halogen bonds have proved to be a useful tool for designing new functional materials and may hold considerable promise in medicinal chemistry.\textsuperscript{5,7}

The existence of the halogen bonds is surprising and counterintuitive, because both halogen atoms and halogen bond acceptors are electronegative and are typically viewed as being negatively charged. However, recent studies of the electrostatic potentials of halogen-containing molecules by Brinck et al.,\textsuperscript{8a} Auffinger et al.,\textsuperscript{7a} and Politzer et al.\textsuperscript{4b,8b} show that the larger halogens bound to carbon (and some other elements) often have a region of positive potential. The region of positive potential on a halogen’s surface is often described as a positive \(\sigma\)-hole,\textsuperscript{8c} and has
also been termed the electropositive crown.\textsuperscript{7a} This positive region exist on the extension of the covalent bond to the halogen atom, that is, on the side of the halogen. The remainder of the halogen normally has also a negative region of the potential, forming a ring around its lateral sides.\textsuperscript{8b} The halogen bonding originates from the electrostatic attraction between the σ-hole and the negative Lewis base.

In 1954, the first x-ray crystallographic study of a molecular addition compound containing bromine molecule and an electron donor molecule 1,4-dioxane was carried out by Hassel and Hvoslef’s.\textsuperscript{9} The most significant feature of this complex structure is a short intermolecular interaction between the oxygen atoms of dioxane and the bromine atoms of molecular bromine. The O...Br distance in the crystal is found equal to 2.72 Å, which is much smaller than the sum of the van der Waals radii of oxygen and bromine (3.35 Å).\textsuperscript{10} The crystal structures show that the electron donor molecules form endless chains by the help of linear halogen bridges. Hassel and co-workers have studied the interaction of molecular bromine with different organic molecules to examine the unexpected features of non-bonded interactions.\textsuperscript{11} Such linear halogen bridges are also found in the 1:1 addition compound between acetone and molecular bromine.\textsuperscript{11d} The x-ray results show that the carbonyl oxygen atom is linked by two halogen bridges (Figure 1C). Theoretical studies of halogen bonding have been undertaken to characterize the geometric and energetic properties of halogen bonds in recent years.\textsuperscript{12,13} The studies mainly focused with inter-halogen compounds and organic halides to characterize the halogen bond strengths\textsuperscript{12b-j,13c-e} and the dihalogen interactions with Lewis bases are scarce in the literature.\textsuperscript{5,12a,13j}

In this section, a systematic computational study has been performed of C-O\textsuperscript{-}Br-Br interactions on a series of dimeric complexes formed between bromine molecule and several oxygen containing electron donors. The sp\textsuperscript{3} and sp\textsuperscript{2} hybridized molecules such as methanol (1), dimethyl ether (2), 1,4-dioxane (3), 1,3-dioxane (4), acetone (5) and formaldehyde (6) have been explored to examine the O\textsuperscript{-}Br-Br interactions in this study (Scheme 1). The \textit{ab initio} quantum chemical calculations on some of the systems can be directly taken for a comparison with the observed x-ray structures and their nature of interactions with molecular bromine, whereas, the other model systems have been considered to substantiate the study.
Both sp\(^3\) and sp\(^2\) hybridized molecules such as dimethyl ether and acetone have lone pairs that can be described in two equivalent ways: two equivalent sp\(^2\) like orbitals (A) or as a combination of a p-type orbital and an \(\sigma\)-type orbital with high s-character (B) (Scheme 2).\(^{14}\) Such a description of lone pairs can be extended to other systems as well. The description of lone pairs and their interactions with Lewis acids is even more relevant to the stereoelectronic effects such as anomeric and gauche effects, that are found with oxygen.\(^{15}\) The Cambridge Structural Database (CSD) analysis concerning intermolecular contacts between (Cl, Br, and I) atoms and electronegative (O and N) atoms suggests that a highly directional, and attractive interaction exists in such cases.\(^{12b}\) The directionality of bromine molecules has also been examined towards the sp\(^3\) and sp\(^2\) hybridized oxygen atoms and analyzed their relative stabilities with molecular electrostatic isopotential surface and AIM methods.

\[
\text{Scheme 2:}
\]

2.1.2. Computational Methods

The geometries of organic molecules and their complexes with Br\(_2\) molecule were fully optimized at MP2/6-311+G\(^*\)\(^{16a}\) and CBS-QB3\(^{16b}\) levels of theory with Gaussian 03.\(^{17}\) The harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. The interaction energy for the intermolecular O\(^-\)-Br-Br interactions was calculated using the following equation:
E_{\text{(interaction energy)}} = E_{\text{(complex)}} - E_{\text{(molecule 1)}} - E_{\text{(molecule 2)}} \quad (1)

The calculated interaction energies were corrected by the basis set superposition error (BSSE). The standard counterpoise procedure of Boys and Bernardi was used for single point BSSE correction at MP2/6-311+G* level of theory without further optimization of the geometries. The ‘atoms in molecules’ (AIM) theory of Bader was also applied here to find critical points and to analyze them in terms of electron densities and their Laplacians. Molecular electrostatic potential (MESP) calculations have been performed at the MP2/6-311+G* level of theory.

2.1.3. Results and Discussion

(I) Single crystal x-ray structural analysis:

The single x-ray crystal structures for the adduct of bromine molecules with methanol, 1,4-dioxane and acetone were reported. These crystal structures were retrieved from crystallographic structure database (CSD).

![Figure 1](A) Unit cell of methanol:Br₂ adduct with a = 16.07 Å, b = 11.16 Å, c = 8.16 Å and α=γ = 90°, β= 92.31° (Ref. 11c); (B) Unit cell for 1,4-dioxane:Br₂ adduct with a = 9.65 Å, b = 9.05 Å, c = 4.25 Å and α=γ = 90°, β= 91.4° (Ref. 9); (C) Unit cell for acetone:Br₂ adduct with a = 7.12 Å, b = 7.48 Å, c = 12.9 Å and α=γ = 90°, β= 111.5° (Ref. 11d). Weak intermolecular interactions between the oxygen atom and bromine molecules are shown with dashed lines in A, B and C.

The crystal structure observed for methanol bromine adduct showed that the O•Br-Br distance is 2.78 Å and the Br•O-C angle is 109.0°. The bromine molecule is bridged between the methanol molecules (Figure 1A). The observed torsion angle for the O•Br-Br•O arrangement is 177.0°, which is close to linearity. The reported data suggest that each oxygen atom is tetrahedrally surrounded by its methyl group and by three bridges linking it neighboring oxygen atoms. Two of these bridges are ordinary hydrogen bridges, the third one is the bromine molecular bridge. Going to the 1,4-dioxane bromine adduct, shorter O•Br-Br distance (2.72 Å) is observed compared to the methanol system. In this case also, the bromine molecule is bridged between the dioxane molecules (Figure 1B). The observed O•Br-Br•O arrangement is also linear (180.0°) in this case. The torsion angle for the Br•O-C₂-C₃ was found to
be 170.0° (Figure 1B). The crystal structure of acetone bromine adduct is slightly different than methanol and 1,4-dioxane. The two carbonyl oxygen lone pairs interact with two bromine molecules (Figure 1C).\textsuperscript{11d} The observed O–Br–Br distances are 2.82 Å. The angle between the two O–Br–Br–O lines meeting in a particular oxygen atom is 110.0°. The Br–O–C bond angle is 125.0°.

The observed O–Br distances in these crystal structures are shorter than the sum of the corresponding van der Waals radii.\textsuperscript{10} These single x-ray crystal analyses suggest that the structure of molecules Figure 1A, 1B and 1C seem to be stabilized by the C–O–Br–Br interaction, therefore, it was interesting to characterize them by means of quantum-chemical methods. In an earlier work, Dance showed that the distance criterion need not always be indicative of the presence of attractive forces between the atoms.\textsuperscript{22} The close contact between the atoms may be energetically destabilizing, but when forced by several stronger interactions may yield a net gain in stability.

To understand the non-bonded attractive interactions between the oxygen atoms and bromine molecules, \textit{ab initio} quantum chemical calculations have been performed at different levels of theory. Besides the crystal structures obtained of methanol, 1,4-dioxane and acetone--dimethyl ether, formaldehyde and 1,3-dioxane have also been considered as model systems in the present study. To analyze the interaction between these organic systems and molecular bromine, MP2/6-311+G* and CBS-QB3 levels of theory were employed in each case. The geometries were fully optimized at these levels of theory. The interaction of molecular bromine with the oxygen atoms was modeled with different situations in each case. The bromine molecule was interacted with (a) the σ-type lone pair of oxygen atom followed by (b) the p-type lone pair in each case (Scheme 2B). No symmetry constraints were imposed in such calculations and the bromine molecule was allowed to maximize the interaction with the oxygen atoms.

\textbf{(II) Molecular electrostatic isopotential surface:}

Wiberg and co-workers have examined the effective location of lone pairs at the oxygens of sp\textsuperscript{2} and sp\textsuperscript{3} hybridized molecules and concluded that they are essentially featureless.\textsuperscript{14b} However, the CSD structural studies discussed the directional approach of halogen bonds.\textsuperscript{12b} Initially, the molecular electrostatic isopotential surface (MESP), which has proved itself an effective tool for quantitatively assessing various non-covalent interactions, such as hydrogen bonding and cation-π interactions, has been explored in this study.\textsuperscript{23}
Figure 2: Molecular electrostatic isopotential surfaces of oxygen containing compounds at -49.89 kcal/mol (-0.0795 au). The minimum electrostatic potentials of oxygen atom are given in kcal/mol. Here the yellow colour represents the electropositive region and the red colour represents the electronegative region. The calculated $V_{\text{min}}$ is shown with black dots in each case.

The Molecular electrostatic isopotential surfaces of all the electron donor molecules are presented in Figure 2. The electron rich regions are shown by highly negative MESP whereas electron deficient regions are characterized by positive MESP.\textsuperscript{24} The most negative valued points ($V_{\text{min}}$) have been located at the oxygen atom in each case (Figure 2).\textsuperscript{25} For the isosurface, the value -49.89 kcal/mol (-0.0795 au) is chosen because it can show the progressive decrease in the negative character of the MESP when going from more electron dense centre to the less electron dense centre. Further, the molecular electrostatic isopotential surface of Br$_2$ has been measured and it was found that an electropositive crown was formed around Br-Br axis (yellow region in Figure 3).\textsuperscript{8} An electroneutral ring (white surface in Figure 3) was formed surrounds the crown and an electronegative belt exist around the circumference of the Br atom (red region in Figure 3). The $V_{S,\text{max}}$ has been located on the bromine atom along the extension of its Br-Br bond. The angle Br-Br-\(V_{S,\text{max}}\) is 178.6°, confirming that the $V_{S,\text{max}}$ is essentially on the extension of the Br-Br bond (Figure 3). The $V_{S,\text{max}}$ calculated for Br$_2$ is 31.2 kcal/mol, which is in good agreement with the previous report (31.8 kcal/mol) by Zheng et al.\textsuperscript{26} The MESP surface suggests that the halogen bonding can occur through a halogen's electropositive crown and an electronegative oxygen atom. The headon interaction of the C-X unit (X = halogen) with an electronegative atom suggested in the CSD study seems to be in accord to the derived MESP of Br$_2$ molecule.\textsuperscript{12b} These MESP results suggest that the donors do not show any obvious directionality of lone pairs and in the accord to the description of rabbit ears.\textsuperscript{14} The $V_{\text{min}}$ located for 3 and 4 shows a
different picture compared to the other donor systems. The location of \( V_{\text{min}} \) in the case of 3 is in between the axial and equatorial lone pairs, however, in the case of 4 it is located near the axial lone pair (Figure 2).

![Illustration of molecular electrostatic isopotential surfaces of Br\(_2\) in two orientation at -4.08 kcal/mol (-0.0065 au). It represents the crown-ring-belt structure of Br\(_2\). Here the yellow region represents the electropositive crown, the white region represents the electroneutral region and the red region represents the electronegative belt. The maximum electrostatic potential (\( V_{\text{S,max}}, \text{kcal/mol} \)) of bromine atom for Br\(_2\) molecule is also shown. [Distances are in Å and angle in degree]

**Figure 3:**

**(III) MP2/6-311+G* calculated results:**

The qualitative picture drawn from the MESP analysis prompted to examine the interaction of donor molecules with the Br\(_2\) molecule. The MP2/6-311+G* optimized molecular structures of the complexes under investigation were depicted in Figure 4. The approach of Br\(_2\) molecule to the \( \sigma \)-type and p-type orbitals of donor oxygens was optimized in all cases. The converged complexes for the \( \sigma \)-type interactions of Br\(_2\) with methanol, dimethyl ether, acetone and formaldehyde were all saddle points (Figure 5). In the true minimum structures, the O…Br intermolecular distances are substantially shorter than the sum of the van der Waals radii of the O and Br atoms (Figure 4).\(^\text{10}\) In the case of methanol, the calculated O…Br non-bonded distance was found to be slightly shorter compared to the observed x-ray results (Figure 4). Further, the calculated Br…O-C angle for 1 is 113.4°, which is slightly higher than the observed angle in the x-ray crystal structure (109.0°). The calculated O…Br-Br angle is in excellent agreement with the observed x-ray structure (Figure 4). The calculated directionality of Br\(_2\) addition to the methanol is slightly different than that of observed in the crystal structure.\(^\text{11c}\) The analysis of the crystal packing of the methanol bromine addition complex suggests that the Br\(_2\) is aligned in a headon fashion to the oxygen atom (Figure 6). The mean plane angle calculations suggest that the bromine molecule approaches at an angle of 1.8° to the methanol plane, whereas, the mean plane angle calculated for the optimized complex is 43.5°. The
headon approach of Br₂ to the methanol oxygen was found to be a saddle point though energetically similar to the minimum energy complex (Figure 4, 5 and Table 1). These results suggest that the halogen bonding found in the x-ray crystal structure for methanol-Br₂ complex may be controlled by crystal forces. It is to note that formaldehyde is also present in the unit cell of methanol-Br₂ complex and possibly play a role in orienting the Br₂ in the observed crystal structure. The MESP analysis does not show the discrete lone pairs (Scheme 2B) for dimethyl ether, which has been reflected in the complexed geometry with the bromine molecule (Figure 4). The mean plane angle calculations suggest that the bromine molecule approaches at an angle of 48.9° to the C-O-C plane. The calculated O···Br distance (2.631 Å) was slightly shorter than the methanol O···Br non-bonded distance and Br·O-C angles were found to be very similar to that obtained for methanol system (Figure 4). The calculated O…Br-Br angle for (2) with Br₂ is also similar to that obtained with (1). The interaction energy reported for Br₂...OH₂ complex at MP2 level is ~3.0 kcal/mol, which is lower than the computed O…Br₂ interaction energies for methanol and dimethyl ether (~4.0 kcal/mol) (Table 1). This might be attributed due to the electron donating groups present in the methanol and dimethyl ether systems compared to the water molecule. The MP2 calculations reported that the complexes of Br₂ with FH, CO and HCCH, can be formed, however much weaker compared to ammonia and water molecules.

![Figure 4](image-url)  
**Figure 4:** MP2/6-311+G* optimized geometries for methanol, dimethyl ether, 1,4-dioxane, 1,3-dioxane, acetone and formaldehyde with bromine molecule.[Experimental values are given in parenthesis( )] [Distances are in Å and angles are in degrees] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]
Figure 5: MP2/6-311+G* optimized geometries of σ-type interaction for methanol, dimethyl ether, acetone and formaldehyde with bromine molecule. [Distances are in Å] [BSSE corrected binding energies given in kcal/mol] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]

Figure 6: Different geometries of methanol, 1,4-dioxane, acetone and formaldehyde with bromine molecule taken from x-ray crystal structure. [Distances are in Å] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]

Table 1: MP2/6-311+G* calculated binding energies (BSSE corrected) in kcal/mol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Binding Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-4.0</td>
</tr>
<tr>
<td>2</td>
<td>-4.4</td>
</tr>
<tr>
<td>3_{eq}</td>
<td>-4.5</td>
</tr>
<tr>
<td>3_{ax}</td>
<td>-4.5</td>
</tr>
<tr>
<td>4_{eq}</td>
<td>-4.2</td>
</tr>
</tbody>
</table>
The stereoelectronic effects have been observed due to the axial and equatorial lone pairs of oxygen atoms in 1,4-dioxane molecule.\textsuperscript{15,28} Two different geometries were obtained for 1,4-dioxane with bromine molecule at MP2/6-311+G* level (Figure 4). In one case, bromine molecule approaches to the axial lone pair, whereas in the other case, it is in the equatorial side of 1,4-dioxane molecule. The BSSE corrected interaction energy is similar in both cases i.e., 4.5 kcal/mol (Table 1). The computed O...Br non-bonded distances were found to be slightly shorter in these cases compared to the observed x-ray results (Figure 4). The calculated bond angles (O...Br-Br) in the halogen complexes are in good agreement with the x-ray crystal structure (Figure 4). The small deviations in the structural parameters observed between calculations and the x-ray results is expected as other crystal forces are absent while modeling the small parts of crystal geometry. The single x-ray crystal structure showed that the formation of halogen bridge is propagated in the equatorial direction of the 1,4-dioxane molecule.\textsuperscript{9} The MESP calculations performed with the bromine complexed 1,4-dioxane showed the significant $V_{S,max}$ value on the free bromine atom, which supports the formation of halogen bridge in 1,4-dioxane molecules (Figure 7).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure7.png}
\caption{The maximum electrostatic potentials ($V_{S,max}$, kcal/mol) of bromine atom for 1,4-dioxane:Br$_2$ and acetone:Br$_2$ complexes. The distances are given in Å. [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]}
\end{figure}

Similar type of geometries were predicted for 1,3-dioxane with bromine molecule. The calculated O...Br distances and Br...O-C angles for both type of interactions were found to be very similar to that obtained for 1,4-dioxane system
The interaction energies for the 1,3-dioxane:Br$_2$ complexes showed that the attraction between 1,3-dioxane and Br$_2$ in axial position is higher compared to the equatorial position (Table 1). It is expected from the stereoelectronic theory that the equatorial lone pair should be involved in hyperconjugative interaction with antiperiplanar C-O $\sigma^*$ orbital and hence should be less available for the complexation with the bromine molecule. The interaction energies indicate that the axial lone pair is more available for the Br$_2$ complexation and more stabilizing compared to the equatorial lone pair. Further, the $V_{\text{min}}$ calculated for 1,3-dioxane also supports the approach of bromine molecule from the axial direction (Figure 2). However, such Stereoelectronic effects were not seen in the case of 1,4-dioxane molecule with the Br$_2$ molecule. Moving from sp$^3$ hybridized oxygen centers to sp$^2$ centers, the calculated acetone:Br$_2$ complexed structure is similar to that obtained from the single x-ray crystal structure (Figure 4). The computed bond angle for p-type interaction (128.8°) is similar to the observed x-ray structure (125.0°). The calculated bond angle (O…Br-Br) in the acetone:Br$_2$ complex is in good agreement with the x-ray crystal structure (Figure 4). The mean plane calculation performed with the optimized complex shows that the acetone and bromine lies almost in the same plane (2.5°), however, in the observed x-ray structure the bromine molecule is deviated by 15.3° with respect to the acetone plane. In the x-ray crystal structure of acetone:Br$_2$ addition, both the carbonyl oxygen lone pairs are involved in bridging with the bromine molecules. Therefore, the interaction of the second bromine molecule is also examined with the carbonyl oxygen lone pair (Figure 8). A significant change was noticed in the mean plane deviation of the bromine molecules with respect to the acetone plane. The mean plane angle increased to 6.4° as compared to the previous single Br$_2$ interaction with the acetone molecule, which suggests that the multiple complexation with the same donor molecule can perturb the crystal geometry significantly. As observed in the case of 1,4-dioxane donor molecules, the $V_{S,\text{max}}$ value on the free bromine atom is also significantly higher (17.0 kcal/mol) in the acetone:bromine complex supports the bridge formation (Figure 7). The modeled formaldehyde complex with Br$_2$ molecule also showed p-type interaction as observed in the case of acetone molecule. The calculated O…Br non-bonded distance (2.815Å) was found to be slightly shorter compared to the observed x-ray results (Figure 4). Further, the computed Br…O-C angle for 6 is 114.0°, which is slightly lower than the observed angle in the x-ray crystal structure (118.9°). The calculated O…Br-Br angle is linear and is in good agreement with the observed x-ray structure (Figure 4). Further, the crystal packing analysis of the formaldehyde bromine addition complex retrieved from the methanol:Br$_2$ complexed x-ray structure suggests that the
Br$_2$ is aligned in a side-wise fashion to the oxygen atom (Figure 6). Comparing the interaction energies calculated for 5 and 6, it appears that the methyl groups present in the 5 enhances the attraction between acetone and Br$_2$ molecule (Table 1).

![Figure 8: MP2/6-311+G* optimized bridging geometry of acetone with bromine molecule. [Distances are in Å] [Binding energies (BSSE corrected) are in kcal/mol] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]

The interaction energies calculated at MP2 level correlate well with intermolecular distance between oxygen and bromine atoms (Figure 9). This plot shows that the interaction energies of the halogen complexes enhance with decrease in intermolecular O...Br distances.

![Figure 9: Correlation between the O...Br intermolecular distance and the interaction energy of halogen complexes.

(IV) CBS-QB3 calculated results:

To examine the reliability of MP2 calculated results, CBS-QB3 calculations have also been performed for both σ-type and p-type interactions of Br$_2$ with oxygen donor molecules. The converged complexes for the σ-type interactions of Br$_2$ with methanol, dimethyl ether and formaldehyde were all saddle points similar as observed in MP2 calculation (Figure 10). The O⁻⁻Br-Br non-bonded interactions appeared to be stronger upon incorporating the complete basis set method.
compared to MP2 calculated results (Table 1 & Table 2). The O…Br interaction energies predicted up to ~5.0 kcal/mol, which is comparable to the typical O-H…O and O-H…N hydrogen bond strengths. The stronger interactions obtained at CBS-QB3 are reflected in the optimized structural parameters (Figure 11). The O…Br non-bonded distances are slightly shorter and the Br-Br distances are longer compared to the MP2/6-311+G* and X-ray crystal structures (Figure 4 and Figure 11). Such changes can be attributed to the transfer of electron density from the electron donor oxygen atom to the Br-Br σ* orbitals. CBS-QB3 predicted the similar directionality of Br₂ addition to donor molecules as observed with MP2 results.

![Figure 10: CBS-QB3 optimized geometries of σ-type interaction for methanol, dimethyl ether and formaldehyde with bromine molecule. [Distances are in Å][Binding energies are in kcal/mol] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]

Table 2: CBS-QB3 calculated binding energies in kcal/mol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Binding Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.6</td>
</tr>
<tr>
<td>2</td>
<td>-4.8</td>
</tr>
<tr>
<td>3_{eq}</td>
<td>-5.2</td>
</tr>
<tr>
<td>3_{ax}</td>
<td>-5.3</td>
</tr>
<tr>
<td>4_{eq}</td>
<td>-4.9</td>
</tr>
<tr>
<td>4_{ax}</td>
<td>-5.1</td>
</tr>
<tr>
<td>5</td>
<td>-4.6</td>
</tr>
<tr>
<td>6</td>
<td>-3.2</td>
</tr>
</tbody>
</table>
Figure 11: CBS-QB3 optimized geometries for methanol, dimethyl ether, 1,4-dioxane, 1,3-dioxane, acetone and formaldehyde with bromine molecule. [Experimental values are given in parenthesis ( )] [Distances are in Å and angles are in degrees] [Gray = carbon; white = hydrogen; red = oxygen; dark red = bromine]

The computed interaction energies for the non-bonded O·Br-Br systems studied here at more reliable MP2 and CBS-QB3 level is in the order of ~4-5 kcal/mol (Table 1 & 2). Further, the sp³-hybridized oxygens prefer to interact more strongly compared to the sp²-hybridized oxygens. It is to note that the mode of interaction of bromine molecule with the σ-type vs. p-type lone pairs of oxygen atom does not lead to a general conclusion and is basis set dependent. In general, the mode of interactions of bromine molecules with oxygen atoms was found to be in agreement between the x-ray results and calculations, which, however is to some extent fortuitous. In the absence of the crystal forces, perturbations have been noticed in the calculated results.

(V) Topological Analysis.

Topological analysis of the electron density supports the existence of halogen bonds in all of the complexes. A bond critical point (BCP) exists in a bond path between the two interacting atom (O and Br). The local properties calculated at O...Br bond critical points (BCPs, critical points with two negative curvatures, λ₁ and λ₂, and the remaining one, λ₃ being positive) in the halogen complexes are given in Table 3. The properties at the BCPs are analyzed in terms of the two parameters: the electron density \(\rho(rₜ)\) and its Laplacian \(\nabla^2 \rho(rₜ)\). The Laplacian of the electron density provides a
measure of the local curvature of \( \rho \) and indicates whether the electron density is locally concentrated, \( \nabla^2 \rho (r_c) < 0 \) or depleted \( \nabla^2 \rho (r_c) > 0 \) at a given point in the space. Table 3 shows the AIM results for all the complexes examined in this work. The value of electron density, \( \rho (r_c) \), is relatively low; the ratio of the perpendicular contractions of \( \rho (r_c) \) to its parallel expansion \( |\lambda_1|/\lambda_3 \) was <1, and the Laplacian of the electron density \( \nabla^2 \rho (r_c) \) is positive. It indicates that the electronic charge is depleted in the internuclear region and shows the properties of closed-shell interactions. It can be seen that the values of \( \rho (r_c) \) are calculated to be a range of 0.0167-0.0258 au, whereas the value of \( \nabla^2 \rho (r_c) \) are all positive, ranging from 0.0627 to 0.0955, which correlates well with the values reported for halogen bonding.

Table 3: AIM parameters for all the complexes calculated at MP2/6-311+G* level\(^a\).

|                | \( \rho (r_c) \) | \( \nabla^2 \rho (r_c) \) | \( |\lambda_1|/\lambda_3 \) |
|----------------|------------------|------------------|------------------|
| **Methanol:Br\(_2\)** |                  |                  |                  |
| 1              | 0.1476           | 0.0226           | 0.0856           |
| **Dimethyl ether:Br\(_2\)** |                  |                  |                  |
| 2              | 0.1532           | 0.0250           | 0.0929           |
| **1,4 Dioxane:Br\(_2\)** |                  |                  |                  |
| 3\(_{eq}\)    | 0.1532           | 0.0258           | 0.0955           |
| 3\(_{ax}\)    | 0.1513           | 0.0244           | 0.0911           |
| **1,3 Dioxane:Br\(_2\)** |                  |                  |                  |
| 4\(_{eq}\)    | 0.1506           | 0.0234           | 0.0868           |
| 4\(_{ax}\)    | 0.1499           | 0.0225           | 0.0842           |
| **Acetone:Br\(_2\)** |                  |                  |                  |
| 5              | 0.1388           | 0.0186           | 0.0719           |
| **Formaldehyde:Br\(_2\)** |                  |                  |                  |
| 6              | 0.1466           | 0.0167           | 0.0627           |

\(^a\)Topological properties at O…Br bond critical points are in au.

In Figure 12, plots of the electron densities and their Laplacians versus the interaction energies for the complexes are linear. The correlation coefficients amount to 0.93 and 0.94, respectively. It shows that the electron densities and their Laplacians are good indications of the strength of halogen bonding interactions.
Figure 12: (a) Correlation between the electron density at O…Br critical point and the interaction energy of halogen complexes. (b) Correlation between the Laplacian of electron density at O…Br critical point and the interaction energy of halogen complexes.

### 2.1.4. Conclusions

In this section, the oxygen bromine non-bonded interactions observed in the x-ray crystal structures of methanol, 1,4-dioxane and acetone have been examined with MP2 and CBS-QB3 calculations. The study has been extended with dimethyl ether, 1,3-dioxane and formaldehyde. The molecular electrostatic isopotential surface analysis showed that the description of oxygen lone pairs is not discrete or featureless. The approach of bromine molecule to the methanol oxygen seems to be controlled by crystal forces. The accurate CBS-QB3 calculations predicted the O…Br interactions in the order of 3-5 kcal/mol. The AIM analysis supports the existence of halogen bonding interactions in the complexes, and the topological properties of halogen bond critical points (BCPs), such as the electron density $\rho(r_c)$ and its Laplacian $(\nabla^2 \rho(r_c))$ are shown to correlate with the interaction energy for these systems. The MP2 and CBS-QB3 calculations showed that the axial oxygen lone pair is energetically slightly more favored for the interaction with $\text{Br}_2$ molecule compared to the equatorial lone pair of oxygen of 1,3-dioxane. However, such stereoelectronic differentiation of oxygen lone pairs was not observed in the case of 1,4-dioxane.
molecule. The quantum chemical calculations using the molecular model systems have in general explained the propagation of bridging interaction between the bromine molecule and the donor systems as observed in the x-ray structures, however, the importance of crystal forces overriding the molecular forces has also been noticed.
Chapter 2.1

References


[21] (a) CSD version 5.2.7 Nov 2005. (b) Mercury 1.4.1 supplied with CSD.


2.2. The halogen bonding interactions with anomeric systems using quantum chemical \textit{ab initio} calculations

2.2.1. Introduction

In this section, non-covalent halogen bonding interactions have been examined on a series of dimeric complexes formed between inter-halogen compounds (such as BrF, BrCl and BrI) and several oxygen containing electron donors. The \textit{ab initio} quantum chemical calculations have been applied to study both the nature and directionality of the halogen molecules towards the sp³ oxygen atoms as well as the stereoelectronic nature of the donor molecules.

Intermolecular halogen bonding interactions are highly directional and exhibits applications in crystal engineering, materials chemistry, drug discovery and solid state synthesis of organic molecules in the field of supramolecular chemistry. Such attractive interactions occur from the terminal positive electrostatic potential (ESP), known as σ-hole, of covalently bound halogens along the direction of the R-X bonds. Halogen bonds can be considered as short range R-X···YZ type of interaction, where X is a halogen (typically chlorine, bromine, or iodine) that is part of the molecule RX and YZ is a Lewis base (where Y is typically oxygen, nitrogen, or sulfur). The strength of the R-X···YZ halogen bond is related to the group adjacent with X. This non-covalent interaction is enhanced when the X atom is joined with an electron-withdrawing atom or group and Y atom is connected with an electron-donating atom or group. The electron-withdrawing nature of the substituent group (R) enhances the magnitude of $V_{S,max}$ (the most positive electrostatic potential at the σ-hole). Halogen bonding may occur with dihalogens X₂ and interhalogens X-Y as well as organic halides. The inter-halogen compounds with higher polarizability demonstrate the significant interactions energies with respect to a specific donor molecule.

In this section, second-order Möller-Plesset perturbation theory (MP2) calculations and coupled cluster method including singles, doubles and triples term (CCSD(T)) were employed on a series of O···X halogen bonds between O-containing donor molecules and Br-containing inter-halogen compounds. The possibility of the formation of halogen bonding has been examined through both sides of the interhalogen compounds (FBr, ClBr and IBr) with a given donor. Two oxygen containing electron donor molecules, tetrahydro-1,3-oxazine and 1,3-dioxane, have been taken in this study. The stereoelectronic effects have been observed due to the presence of axial and equatorial lone pairs of oxygen atoms in these electron donor
molecules. The stereoelectronic behavior of X-C-Y containing systems (X, Y = OR, NR₂, Hal), known as the anomeric effect, has been widely studied in the literature. Generally, the magnitude of anomeric effect is only a few kcal/mol and thus comparable to the strength of conventional hydrogen bonds. The anomeric effect refers to the thermodynamic preference of glycopyranosyl derivatives with electronegative (polar) substituents adjacent to the endocyclic oxygen atom in an axial position (α anomer) rather than an equatorial position (β anomer) in the chair conformation. In many chemical reactions and carbohydrate chemistry, the anomeric effect ubiquitously exists. It is widely assumed that both steric and electronic interactions create contributions to the conformational preferences, although their exact roles are controversial. Currently, the popular explanation for the anomeric effect is hyperconjugation model, where the electron delocalization occur from the lone pair of electron donor atom to the vacant antibonding orbital σ*ₜᵢ₅ (Scheme 1). As a result various structural parameters are found to be changed e.g., shorter or longer anomeric bonds and larger anomeric bond angles. Another explanation for the anomeric effect is the electrostatic model, which was originally from antiparallel arrangement of the two local dipoles in the axial conformer stabilizes the molecule (Scheme 1).

Scheme 1: Schematic representation of Hyperconjugation and electrostatic model.

In this section, a systematic computational study has been performed of C-O⋯X-R interactions on a series of dimeric complexes formed between halogen atom and tetrahydro-1,3-oxazine or 1,3-dioxane. Tetrahydro-1,3-oxazines can be regarded as unsymmetrical 1,3-heteroanalogs of cyclohexane. Two different geometries are obtained, in one case interhalogen compound approaches to the axial lone pair, whereas in the other case, it is in the equatorial side of the donor molecules (Scheme 2).
Scheme 2: Axial and equatorial lone pair sides of tetrahydro-1,3-oxazine and 1,3-dioxane.

2.2.2. Computational Methods

The geometries of organic molecules and their complexes with BrF, BrCl, BrI molecules were fully optimized at MP2/aug-cc-pVDZ\textsuperscript{11} level of theory with Gaussian 09.\textsuperscript{12} LANL2DZ basis set was used for iodine in this study. The harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. The interaction energy for the intermolecular O⋯X interactions was calculated using the following equation:

\[ E_{\text{interaction energy}} = E_{\text{complex}} - E_{\text{molecule 1}} - E_{\text{molecule 2}} \] (1)

The calculated interaction energies were corrected by the basis set superposition error (BSSE). The standard counterpoise procedure of Boys and Bernardi was used for single point BSSE correction at MP2/aug-cc-pVDZ level of theory without further optimization of the geometries.\textsuperscript{13} Single point calculations are performed at CCSD(t)/aug-cc-pVDZ level of theory with the optimized complex geometries. The electrostatic potentials were computed with Multiwfn program\textsuperscript{14} on the 0.001 au surface of the molecules electron density.\textsuperscript{15} Subsequently, the noncovalent interaction (NCI) index calculations were also performed with Multiwfn program\textsuperscript{14} and visualized using the VMD program.\textsuperscript{16}

2.2.3. Results and Discussion

Molecular electrostatic potentials, Geometries and halogen-bonded interaction energies

The molecular electrostatic isopotential surfaces (MESP) of the interhalogen compounds are computed and presented in Figure 1. The molecular electrostatic isopotential surface (MESP), provides an effective tool for quantitatively measuring various non-covalent interactions, such as hydrogen bonding and cation-π
interactions.\textsuperscript{17} The electropositive regions (\(\sigma\)-hole) are present on the outer surface of the X (X= Cl, Br, I) atom along the extension of the R-X bond. The presence of electron-withdrawing substituent can enhance the size of the \(\sigma\)-hole. For a given halogen atom (Br), the \(V_{S,max}\) value decreases in the consequence of decreasing electron withdrawing nature of R (F>Cl>I) (Figure 1). The most positive electrostatic potentials of the \(\sigma\)-hole are found to be associated with bromine atom of FBr. Further, it is observed that \(V_{S,max}\) value correlates with the halogen polarizibility (mass number of the atom). In the presence of same substituent groups \(V_{S,max}\) value follows the order Cl < I (Figure 1).

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {Br};
\node (2) at (1,0) {F};
\node (3) at (2,0) {Cl};
\node (4) at (3,0) {Br};
\node (5) at (4,0) {I};
\node (6) at (1.5,0.5) {V_{S,max}(Br) = 48.4}
\node (7) at (1.5,-0.5) {V_{S,max}(Br) = 34.5}
\node (8) at (1.5,-1.5) {V_{S,max}(Br) = 19.0}
\node (9) at (3.5,0.5) {V_{S,max}(Cl) = 21.5}
\node (10) at (3.5,-0.5) {V_{S,max}(I) = 47.2}
\end{tikzpicture}
\end{center}

\textbf{Figure 1}: The maximum electrostatic potential (\(V_{S,max}\) kcal/mol) of halogen atom for BrF, BrCl and BrI molecules.[dark red = bromine; cyan = fluorine; dark violet = chlorine; indigo = iodine]

All possible geometric configurations on the potential energy surface (PES) of Tetrahydro-1,3-oxazine and interhalogen complexes were optimized and the optimized geometries of the complexes are shown in Figure 2. The unsubstituted tetrahydro-1,3-oxazine was reported to exist mainly as chair conformer with axial N–H bond.\textsuperscript{18} The earlier studies have been demonstrated that there is fairly strong similarity between geometric parameters of tetrahydro-1,3-oxazine and 1,3-dioxane, in particular dihedral angles in the carbon and heteroatom fragments in the ring.\textsuperscript{18} The halogen-bonded interaction is examined with chair conformer of tetrahydro-1,3-oxazine with axial N–H bond.

The qualitative picture drawn from the MESP analysis provoked to examine the interaction of interhalogen compound with the donor molecules. The approach of R-X molecule to the axial and equatorial position of donor oxygens was optimized in all cases. The converged complexes for the interactions of tetrahydro-1,3-oxazine with FBr, ClBr and IBr were all local minima on their potential energy surfaces (Figure 2). In the true minimum structures, the O…Br intermolecular distances are substantially shorter than the sum of the van der Waals radii of the O and Br atoms (Figure 2).\textsuperscript{19}
the case of FBr, the calculated O...Br-F angle is approximately 180°, which indicates that the halogen bonding is highly directional (Figure 2). The calculated O...Br non-bonded distance was found to be similar in both cases (Figure 2). The interaction energy calculated for 1$_{eq}$ complex at CCSD(t) level is -13.8 kcal/mol, which is lower than the computed O...Br interaction energy for 1$_{ax}$ (-14.4 kcal/mol) (Table 1). These calculated results indicate that the bromine atom of FBr can interact preferentially with the axial lone-pair of donor oxygen in tetrahydro-1,3-oxazine than the equatorial lone-pair. This might be attributed due to the anomeric effect of tetrahydro-1,3-oxazine, in which the equatorial lone pair should be involved in hyperconjugative interaction with antiperiplanar C-N σ* orbital and hence should be less available for the complexation with the FBr molecule.

Similar type of geometries were predicted for tetrahydro-1,3-oxazine with BrCl molecule. The calculated O...Br distances and O...Br-Cl angles for both type of interactions were found to be very similar to that obtained for tetrahydro-1,3-oxazine:BrF system (Figure 2). The interaction energies for the tetrahydro-1,3-oxazine:BrCl complexes showed that the attraction between tetrahydro-1,3-oxazine and BrCl in axial position is higher compared to the equatorial position (Table 1).

The stereoelectronic effects have also been observed in tetrahydro-1,3-oxazine and BrI complexes due to the axial and equatorial lone pairs of oxygen atoms. Two different geometries were obtained for tetrahydro-1,3-oxazine with BrI molecule at MP2/aug-cc-pVDZ level of theory (Figure 2). The computed O^-Br-I bond angle was found to be slightly larger in axial cases compared to the equatorial approach (Figure 2). There is a small deviations in the structural parameters observed between axial and equatorial complexes of tetrahydro-1,3-oxazine with BrI. The preferential binding of BrI towards axial position of donor oxygen is also observed compared to the equatorial position (Table 1).
**Figure 2:** MP2/aug-cc-pVDZ optimized geometries for tetrahydro-1,3-oxazine with BrF, BrCl and BrI. [Distances are in Å and angles are in degrees] [Green = carbon; white = hydrogen; red = oxygen; dark blue = nitrogen; dark red = bromine; cyan = fluorine; dark violet = chlorine; indigo = iodine]

**Table 1:** The calculated binding energies of the halogen-bonded complexes in kcal/mol. In parenthesis, the binding energies are calculated in which it is assumed that in complex geometry there is no structural change of monomers.

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>CCSD(t)/aug-cc-pVDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BSSE corrected</td>
</tr>
<tr>
<td>1eq:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1ax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2eq:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2ax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3eq:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3ax:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Further, the study has been extended for halogen-bonded interaction with tetrahydro-1,3-oxazine and substituted groups of interhalogen compounds. Similar type of geometries were predicted for tetrahydro-1,3-oxazine with BrCl and BrI molecules (Figure 3). The computed O–Cl–Br bond angle was found to be slightly larger in axial cases compared to the equatorial approach (Figure 3). The small deviations in the structural parameters observed between axial and equatorial complexes with BrI also. The interaction energies for the tetrahydro-1,3-oxazine:ClBr complexes showed that the attraction between tetrahydro-1,3-oxazine and ClBr in axial position is higher compared to the equatorial position (Table 2). The preferential binding of BrI towards axial position of donor oxygen is also observed compared to the equatorial position.
Figure 3: MP2/aug-cc-pVDZ optimized geometries for tetrahydro-1,3-oxazine with ClBr and IBr. [Distances are in Å and angles are in degrees] [Green = carbon; white = hydrogen; red = oxygen; dark blue = nitrogen; dark red = bromine; cyan = fluorine; dark violet = chlorine; indigo = iodine]

Table 2: The calculated binding energies of the halogen-bonded complexes in kcal/mol. In parenthesis, the binding energies are calculated in which it is assumed that in complex geometry there is no structural change of monomers.

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>CCSD(t)/aug-cc-pVDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSSE corrected</td>
<td></td>
</tr>
<tr>
<td>2'. X=Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2' eq</td>
<td>-3.9 (-4.1)</td>
<td>-5.8</td>
</tr>
<tr>
<td>2' ax</td>
<td>-4.4 (-4.6)</td>
<td>-6.4</td>
</tr>
<tr>
<td>3'. X=I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3' eq</td>
<td>-6.6 (-7.7)</td>
<td>-14.1</td>
</tr>
<tr>
<td>3' ax</td>
<td>-7.0 (-8.2)</td>
<td>-15.2</td>
</tr>
</tbody>
</table>
Decomposition of binding energies

To get a better insight on the nature of halogen bonding, it is important to decompose the noncovalent halogen-bonded interaction into various "components" and to quantify their contributions to the binding energy. Various procedures have been introduced for partitioning the binding energy into different subsets like electrostatics, dispersion, charge transfer, polarization, exchange repulsion, induction, orbital interaction, Pauli repulsion and distortion, etc.\textsuperscript{21} In this section, localized molecular orbital energy decomposition analysis (LMO-EDA) has been utilized for energy decomposition analysis.\textsuperscript{22} LMO-EDA method as implemented in the quantum chemistry software GAMESS is carried out to examine the factors contributing to such interaction energies.\textsuperscript{23} The earlier studies have been demonstrated that the halogen bonds are stabilized primarily by electrostatics and dispersion.\textsuperscript{24} Several normal halogen bonding and other $\sigma$-hole interactions are adequately and fully explained by electrostatics/polarization and dispersion as the principle attractive components.\textsuperscript{24} The calculated results show that the stabilities of the O$\cdots$Br and O$\cdots$Cl halogen bonds are attributed mainly to electrostatic and dispersion forces (Table 3). The total interaction energies calculated in LMO-EDA method are similar to the BSSE corrected interaction energies calculated with Gaussian 09 program (Table 1 and 2). In the presence of electron-withdrawing substituents, the halogen bonding interactions become stronger and more electrostatic in nature. The LMO-EDA analysis suggests that the electrostatic forces in tetrahydro-1,3-oxazine:FBr complexes are larger than other interhalogen complexes (Table 3). Further, the larger size of the halogen atom influences to increase the strength of the halogen bonding interaction by enhancing the electrostatic forces in the halogen bonded complexes.

\textbf{Table 3:} LMO-EDA decomposed energy terms in kcal/mol at MP2/aug-cc-pVDZ level of theory.

<table>
<thead>
<tr>
<th></th>
<th>$1_{eq}$</th>
<th>$1_{ax}$</th>
<th>$2_{eq}$</th>
<th>$2_{ax}$</th>
<th>$2'_{eq}$</th>
<th>$2'_{ax}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrostatic</td>
<td>-31.45</td>
<td>-33.28</td>
<td>-21.84</td>
<td>-23.44</td>
<td>-9.60</td>
<td>-10.68</td>
</tr>
<tr>
<td>Repulsion</td>
<td>89.56</td>
<td>96.27</td>
<td>68.22</td>
<td>74.31</td>
<td>34.23</td>
<td>38.08</td>
</tr>
<tr>
<td>Polarization</td>
<td>-17.73</td>
<td>-18.61</td>
<td>-10.78</td>
<td>-11.44</td>
<td>-4.11</td>
<td>-4.45</td>
</tr>
<tr>
<td>Dispersion</td>
<td>-6.78</td>
<td>-7.60</td>
<td>-7.35</td>
<td>-8.31</td>
<td>-5.55</td>
<td>-6.30</td>
</tr>
</tbody>
</table>
Noncovalent Interactions (NCI) index of the halogen bond

The noncovalent interaction (NCI) index is based on the relationship between the electron density and the reduced density gradient. Such approach has been taken in recent times to detect noncovalent interactions in real space, based on the electron density and its derivatives. This analysis provides a rich representation of van der Waals interactions, hydrogen bonds, and steric repulsion in small molecules, molecular complexes, and solids.

The reduced density gradient is expressed as,

\[ s = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla \rho|}{\rho^{4/3}} \]

The reduced density gradient can be useful to identify the noncovalent interactions and covalent interactions in real space. Therefore, the NCI index becomes useful tool to distinguish and visualize different types of noncovalent interactions in real space. In QTAIM, the value of \( \rho \) indicates the strength of the noncovalent interactions. The sign of the Laplacian of the density, \( \nabla^2 \rho \), is mainly used to distinguish between different types of strong interactions. For better understanding the bonding, the Laplacian is often decomposed into a sum of contributions along the three principal axes of maximal variation, such that \( \nabla^2 \rho = \lambda_1 + \lambda_2 + \lambda_3 \). The analysis of these components has been widely applied to chemical bonding. \( \rho \) and \( \text{sign}(\lambda_2) \), the sign of \( \lambda_2 \) are accomplished of distinguishing the type and strength of the interactions. Therefore, it is considered that large value of \( \rho \) and negative sign of \( \text{sign}(\lambda_2) \) indicates the attractive interaction, whereas large value of \( \rho \) and positive sign of \( \text{sign}(\lambda_2) \) suggest that the interaction is nonbonding. Figure 4 shows the \( s(\rho) \) vs \( \text{sign}(\lambda_2)\rho \) in the halogen-bonded complexes with the low density, low-gradient spike lying at negative values indicative of stabilizing interactions of halogen bonding. In the internuclear region between halogen atom and donor oxygen atom of the halogen-bonded complexes, there is a presence of bonding isosurface (Figure 4). The color code of these bonding isosurfaces is from blue to green, which indicates that the halogen bond interactions are becoming weaker in the sequence of tetrahydro-1,3-oxazine:BrF, tetrahydro-1,3-oxazine:BrCl, tetrahydro-1,3-oxazine:BrI (Figure 4).
Figure 4: Plots of the reduced density gradient versus the electron density multiplied by the sign of the second Hessian eigen value and bonding isosurfaces were generated.

To have a further insight into the halogen bonding, the changes in electron density that arises during the formation of the complexes were analysed. Total electron density maps have been shown to accurately determine electron density shifts.\textsuperscript{27} The electron density shifts that occur in tetrahydro-1,3-oxazine:BrF complexes are shown in Figure 5. These maps were generated by subtracting the sum of the electron densities of the isolated subsystems frozen in the optimized structure of the complex from the electron density in the complex. Red regions indicate increased electron density, whereas dark blue regions represent decreased electron density. Increased electron density is observed at the inter-nuclear position of the halogen-bonded complexes (Figure 5).

![Figure 5: Electron density shifts in the Halogen-bonded complexes upon the formation of each complex. Red regions indicate increased density, dark blue regions indicate decreased density. Contours are shown at the 0.001 au level.](image)

Further, the study has been extended with 1,3-dioxane, the symmetrical 1,3 analogs of tetrahydro-1,3-oxazine. The converged complexes for the axial and equatorial-type interactions of 1,3-dioxane with BrF, BrCl and BrI were all local minima similar as observed with tetrahydro-1,3-oxazine (Figure 6). The O...Br-R non-bonded interactions appeared to be slightly weaker with 1,3-dioxane compared to tetrahydro-1,3-oxazine (Table 1, 2, 4 and 5). The O...Br interaction energies suggest that the preferential binding of interhalogen compounds towards axial position of donor oxygen becomes less compared to the equatorial position (Table 4 and 5). To examine the weakening of anomeric effect in 1,3-dioxane: interhalogen complexes, the study has been extended with charge model calculations, where the anomeric oxygen in 1,3-dioxane is replaced by its charge. The calculated results show that
there is a greater preference of halogen-bonded interactions in the axial position of 1,3-dioxane with the inter-halogen compounds compared to the equatorial one and further suggests the effect of the anomeric oxygen to diminish the stereo-electronic effect.

**Figure 6**: MP2/aug-cc-pVDZ optimized geometries for 1,3-dioxane with BrF, BrCl and BrI. [Distances are in Å and angles are in degrees] [Green = carbon; white =
hydrogen; red = oxygen; dark red = bromine; cyan = fluorine; dark violet = chlorine; indigo = iodine]

**Table 4:** The calculated binding energies of the halogen-bonded complexes in kcal/mol. In parenthesis, the binding energies are calculated in which it is assumed that in complex geometry there is no structural change of monomers.

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>CCSD(t)/aug-cc-pVDZ //MP2/aug-cc-pVDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4. X=F</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>-10.0 (-11.0)</td>
<td>-12.4</td>
</tr>
<tr>
<td>4&lt;sub&gt;ax&lt;/sub&gt;</td>
<td>-9.9 (-10.7)</td>
<td>-12.3</td>
</tr>
<tr>
<td><strong>5. X=Cl</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>-6.4 (-6.9)</td>
<td>-9.1</td>
</tr>
<tr>
<td>5&lt;sub&gt;ax&lt;/sub&gt;</td>
<td>-6.6 (-7.0)</td>
<td>-9.3</td>
</tr>
<tr>
<td><strong>6. X=I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>-3.0 (-3.1)</td>
<td>-8.1</td>
</tr>
<tr>
<td>6&lt;sub&gt;ax&lt;/sub&gt;</td>
<td>-3.2 (-3.3)</td>
<td>-8.2</td>
</tr>
</tbody>
</table>

The interactions of substituted groups of inter-halogen compounds are also examined with 1,3-dioxane. Two different geometries were obtained for 1,3-dioxane with interhalogen molecules at MP2/aug-cc-pVDZ level (Figure 7). The interaction energies for the 1,3-dioxane:ClBr complexes showed that the attraction between 1,3-dioxane and ClBr in axial position is higher compared to the equatorial position (Table 5). The preferential binding of IBr towards axial position of donor oxygen is also observed compared to the equatorial position.
Figure 7: MP2/aug-cc-pVDZ optimized geometries for 1,3-dioxane with ClBr and IBr. [Distances are in Å and angles are in degrees] [Green = carbon; white = hydrogen; red = oxygen; dark red = bromine; cyan = fluorine; dark violet = chlorine; indigo = iodine]

Table 5: The calculated binding energies of the halogen-bonded complexes in kcal/mol. In parenthesis, the binding energies are calculated in which it is assumed that in complex geometry there is no structural change of monomers.

<table>
<thead>
<tr>
<th></th>
<th>MP2/aug-cc-pVDZ</th>
<th>CCSD(t)/aug-cc-pVDZ //MP2/aug-cc-pVDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSSE corrected</td>
<td></td>
</tr>
<tr>
<td>5\textsuperscript{'} X=Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5\textsuperscript{'}\textsubscript{eq}</td>
<td>-3.4 (-3.6)</td>
<td>-5.3</td>
</tr>
<tr>
<td>5\textsuperscript{'}\textsubscript{ax}</td>
<td>-3.6 (-3.8)</td>
<td>-5.4</td>
</tr>
<tr>
<td>6\textsuperscript{'} X=I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6\textsuperscript{'}\textsubscript{eq}</td>
<td>-5.4 (-6.2)</td>
<td>-12.6</td>
</tr>
<tr>
<td>6\textsuperscript{'}\textsubscript{ax}</td>
<td>-5.7 (-6.4)</td>
<td>-12.8</td>
</tr>
</tbody>
</table>
Decomposition of binding energies

The localized molecular orbital energy decomposition analysis (LMO-EDA) shows that halogen bonds are attributed mainly to electrostatic and dispersion forces (Table 6). The effects of halogen atoms and the presence of electron-withdrawing groups also follow the same trend as observed in the case of halogen complexes of tetrahydro-1,3-oxazine.

**Table 6:** LMO-EDA decomposed energy terms in kcal/mol at MP2/aug-cc-pVDZ level of theory.

<table>
<thead>
<tr>
<th></th>
<th>$4_{eq}$</th>
<th>$4_{ax}$</th>
<th>$5_{eq}$</th>
<th>$5_{ax}$</th>
<th>$5'_{eq}$</th>
<th>$5'_{ax}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repulsion</td>
<td>79.36</td>
<td>73.23</td>
<td>56.70</td>
<td>53.01</td>
<td>28.83</td>
<td>27.98</td>
</tr>
<tr>
<td>Polarization</td>
<td>-15.16</td>
<td>-13.82</td>
<td>-8.43</td>
<td>-7.86</td>
<td>-3.21</td>
<td>-3.22</td>
</tr>
<tr>
<td>Dispersion</td>
<td>-6.34</td>
<td>-6.21</td>
<td>-6.57</td>
<td>-6.62</td>
<td>-4.97</td>
<td>-5.14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>-11.04</strong></td>
<td><strong>-10.77</strong></td>
<td><strong>-6.95</strong></td>
<td><strong>-7.07</strong></td>
<td><strong>-3.63</strong></td>
<td><strong>-3.79</strong></td>
</tr>
</tbody>
</table>

The scatter plots of reduced gradient are also examined to characterise the non-covalent interactions (Figure 8). The low density, low-gradient spike in the negative region for both equatorial and axial interactions suggest the presence of weak halogen bonding interactions. The reduced gradient isosurface also agrees with the analysis of the scatter plots. The color coding of the bonding isosurfaces is changed from blue to green, which indicates the decrease of halogen bond strength in the sequence 1,3-dioxane:BrF, 1,3-dioxane:BrCl and 1,3-dioxane:BrI (Figure 8). The shift of electron density is also occurring at the middle region of the halogen and donor oxygen atom (Figure 9).
Figure 8: Plots of the reduced density gradient versus the electron density multiplied by the sign of the second Hessian eigen value and bonding isosurfaces were generated.

Figure 9: Electron density shifts in the Halogen-bonded complexes upon the formation of each complex. red regions indicate increased density, dark blue regions indicate decreased density. Contours are shown at the 0.001 au level.

2.2.4. Conclusions

In this section, the oxygen halogen non-bonded interactions have been examined with MP2 and CCSD(t) calculations. The halogen bonding interactions have been examined with electron donor molecules such as tetrahydro-1,3-oxazine and 1,3-dioxane and interhalogen compounds like FBr, BrCl and BrI. The molecular electrostatic isopotential surface analysis showed that the presence of positive electrostatic potential region on the extension of X-R bond. The electron-withdrawing nature of substituents can increase the maximum positive electrostatic potential ($V_{s,max}$), which is further responsible for strengthens the halogen bonding. The MP2 and CCSD(t) calculations showed that the axial oxygen lone pair is more available for the interaction with halogen atom compared to the equatorial lone pair of oxygen of tetrahydro-1,3-oxazine and 1,3-dioxane. The calculated localized molecular orbital energy decomposition analysis (LMO-EDA) shows that the stabilities of the O·Br and O·Cl halogen bonds are attributed mainly to electrostatic and dispersion forces. The electron-withdrawing substituents enhance the halogen bonding interactions by increasing the electrostatic force of the interactions. The non-covalent interaction (NCI) index of the halogen bond has been analysed to visualize the non-covalent halogen bonding interactions in real space. The low-gradient isosurfaces with low densities indicates the stabilizing interactions of halogen bonding. The changes in electron density during the formation of the complexes are analysed by considering the electron density shifts in the complex structures.
References


[14] Lu, T. Multiwfn: A Multifunctional Wavefunction Analyzer, Version 3.0.1, 

[15] Politzer, P.; Truhlar, D. G. Chemical Applications of Atomic and Molecular 


(b) Lukin, O.; Leszczynski, J. J. Phys. Chem. A, 2002, 106, 6775; (c) Joubert, 


[20] (a) Murray, J. S.; Politzer, P. Chem. Phys. Lett., 1988, 152, 364; (b) Haeberlein, 
M.; Murray, J. S.; Brinck, T.; Politzer, P. Can. J. Chem., 1992, 70, 2209; (c) 
2011, 111, 2597; (b) Grabowski, S. J. J. Phys. Chem. A, 2001, 105, 10739; (c) 
Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. J. Am. Chem. Soc., 2000, 122, 
10405.


P.; Beratan, D. N.; Yang, W. J. Chem. Theory Comput., 2011, 7, 625; (b) 
Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. 
J.; Yang, W. J. Am. Chem. Soc., 2010, 132, 6498; (c) Contreras-Garcia, J.; 
