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Molecular mechanical perspective on halogen bonding

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Abstract The nature and strength of halogen bonding in halo molecule–Lewis base complexes were studied in terms of molecular mechanics using our recently developed positive extra-point (PEP) approach, in which the σ-hole on the halogen atom is represented by an extra point of positive charge. The contributions of the σ-hole (i.e., positively charged extra point) and the halogen atom to the strength of this noncovalent interaction were clarified using the atomic parameter contribution to the molecular interaction (APCtMI) approach. The molecular mechanical results revealed that the halogen bond is electrostatic and van der Waals in nature, and its strength depends on three types of interaction: (1) the attractive electrostatic interaction between the σ-hole and the Lewis base, (2) the repulsive electrostatic interaction between the negative halogen atom and the Lewis base, and (3) the repulsive/attractive van der Waals interactions between the halogen atom and the Lewis base. The strength of the halogen bond increases with increasing σ-hole size (i.e., magnitude of the extra-point charge) and increasing halogen atom size. The van der Waals interaction's contribution to the halogen bond strength is most favorable in chloro complexes, whereas the electrostatic interaction is dominant in iodo complexes. The idea that the chloromethane molecule can form a halogen bond with a Lewis base was revisited in terms of quantum mechanics and molecular mechanics. Although chloromethane does produce a positive region along the C–Cl axis, basis set superposition error corrected second-order Møller–Plesset calculations showed that chloromethane–Lewis base complexes are unstable, producing halogen–Lewis base contacts longer than the sum of the van der Waals radii of the halogen and O/N atoms. Molecular mechanics using the APCtMI approach showed that electrostatic interactions between chloromethane and a Lewis base are unfavorable owing to the high negative charge on the chlorine atom, which overcomes the corresponding favorable van der Waals interactions.

Keywords Halogen bond · Noncovalent interaction · σ-Hole · PEP approach · APCtMI approach

This article is dedicated to Prof. T. Clark and P. Politzer.

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Introduction

Quantum mechanical (QM) and experimental studies of halogen atoms in crystal structures have revealed the dual nature of halogens: they act as a Lewis acid (bond donor) in halogen-bond formation and as a Lewis base (bond acceptor) in hydrogen-bond formation [1–5]. This dual behavior of halogens is attributed to the anisotropic distribution of the electron density around the halogen atom. Highly negative charge accumulation occurs in the equatorial area, forming an area of charge depletion along the covalent bond axis, called a σ-hole; see Fig. 1 [2, 6, 7]. This σ-hole has been observed by means of molecular electrostatic potential calculations on covalently bonded chlorine, bromine, and iodine atoms, and its size increases in the order Cl<Br<I [2, 6]. Consequently, the strength of the halogen bond increases as the size of the halogen atom increases [2, 8, 9]. It is worth mentioning that fluorine can also be polarized, and can therefore act as a halogen-bond donor [10, 11].
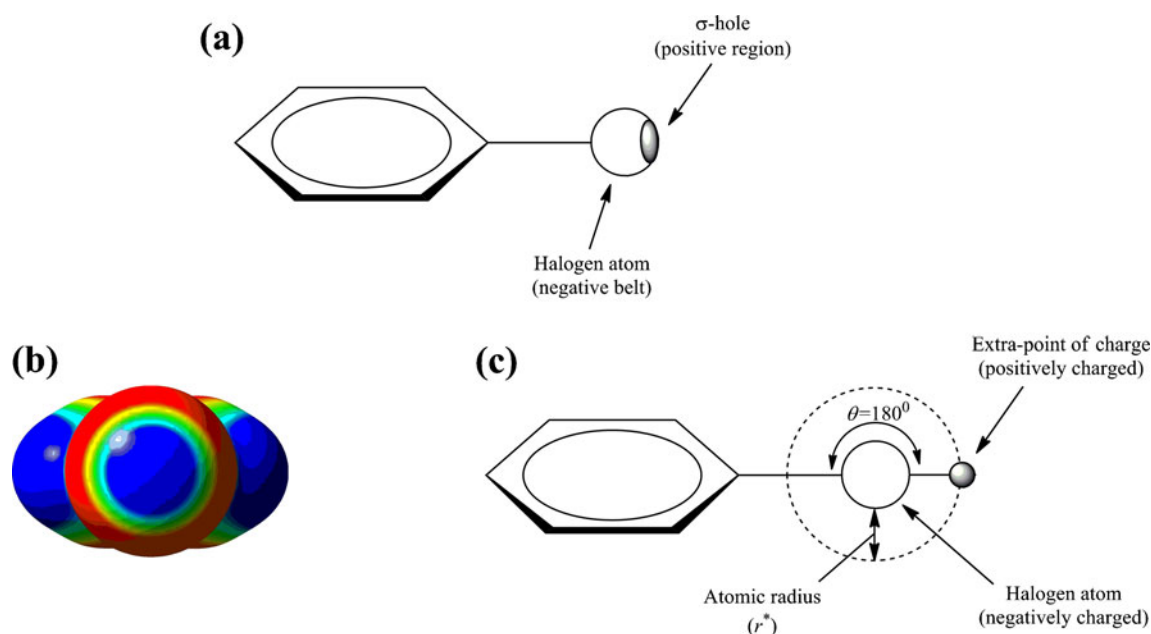
Fig. 1a–c Schematic representation of halobenzene molecule, indicating the charge polarization on the halogen atom. b Ab initio molecular electrostatic potential surface of bromobenzene (positive potential in blue; negative potential in red). c Schematic representation of the molecular mechanical positive extra-point (PEP) approach

The nature of the halogen bond is still the source of debate [1]. An analysis of halogen-bond-forming complexes based on the quantum theory of atoms in molecules showed that the nature of the bond is basically electrostatic in weakly halogen-bonded complexes and more covalent in strongly halogen-bonded complexes [12, 13]. Symmetry-adapted perturbation theory was used to determine that the halogen bond involves electrostatic and dispersive interactions; the electrostatic contribution increases with increasing size of the halogen atom, becoming dominant in the case of iodine [14]. Using the Kohn–Sham molecular orbital approach, it was found that the halogen bond has significant covalent characteristics, and that the stabilizing energy for complexation is contributed primarily by HOMO/LUMO charge transfer and polarization [9].

Until recently, the halogen bond was poorly described in terms of molecular mechanics (MM) owing to the inability of conventional force fields to describe the anisotropic charge density distribution on the halogen atom [15, 16]. This bottleneck has been overcome by the author and, for the first time, an extra point of positive charge was used to represent the σ-hole on the halogen atom. This is called the positive extra-point (PEP) approach and is illustrated schematically in Fig. 1 [16]. Interestingly, it has been shown that the PEP approach describes the halogen bond better than semiempirical methods, including the recent halogen-bond-corrected PM6 (PM6-DH2X) method [17, 18]. The PEP approach also gave promising results in

describing other noncovalent halogen interactions, such as the C–X···H and C–X···π-system interactions [17].

With the aid of our PEP approach, the first MM–molecular dynamics (MM-MD) study of inhibitors that form a halogen bond with a receptor was performed for tetrahalobenzotriazole inhibitors complexed to cyclin-dependent protein kinase 2 (CDK2) [16]. When the PEP approach was used, the calculated MM–generalized Born surface area (MM-GBSA)// MM-MD binding energies for halobenzimidazole and halobenzotriazole inhibitors complexed with protein kinase CK2 were found to correlate well with the corresponding experimental data, with correlation coefficients R^2 of greater than 0.90 [17, 18].

In the present study, the nature and strength of halogen bonding in small halo molecule–Lewis base complexes are studied and discussed from the MM perspective. First, the effect of the halogen–extra point distance on the predicted halogen bond length and energy in the halobenzene–formaldehyde complex is discussed. Second, the correlation between the size of the σ-hole (i.e., the magnitude of the extra-point charge) and the halogen bond strength is investigated in halobenzene–formaldehyde complexes. In addition, we propose the use of the atomic parameter contribution to the molecular interaction (APCtMI) approach to study the individual contributions of the σ-hole (i.e., a positively charged extra point) and the halogen atom (i.e., a negatively charged halogen atom) to the halogen bonding strength. Finally, the idea that the chloromethane molecule can form a halogen bond with a Lewis base is revisited and discussed using MM and QM methods.

Methods

The properties of halogen bonds in halo molecule–Lewis base complexes were studied. The geometrical structures of the halo molecules and Lewis bases were first optimized by the second-order Møller–Plesset (MP2) method [19] with the aug-cc-pVDZ-PP [20, 21] basis set for the Br and I atoms and the aug-cc-pVDZ [20] basis set for all other atoms. The structures were then kept frozen during the rest of study. This protocol was used previously, and yielded an ~0.02 kcal mol^{-1} difference in interaction energy from the fully optimized complex [8]. This was confirmed in the current study, where the differences in halogen bond energy and length between the fully and partially MM optimized complexes were only ~0.03 kcal mol^{-1} and ~0.01 Å, respectively. The potential energy surfaces (PESs) for halogen-bond dissociation in halo molecule–Lewis base complexes were then generated at the MM level and compared to those generated at the corresponding basis set superposition error (BSSE) corrected MP2/aug-cc-pVDZ level (with PP functions used for the Br and I atoms). The BSSE was corrected using the Boys and Bernardi counterpoise method [22]. The C–X⋯O/N and X⋯O–C angles in the studied halo complexes were held at 180° during the study to decrease any possible noncovalent interactions between the halogen atom and the other Lewis base atoms. The QM calculations were performed using the Gaussian 03 software package [23], whereas the MM calculations were realized using the MM standalone program implemented in the Gaussian 09 software package [24].

The PEP approach was applied in the MM calculations, and an extra point of charge was placed on the halogen atom. The general AMBER force field (GAFF) [25] was used to describe the studied complexes, and the corresponding parameters for the extra point were taken from our previous study [16]. For partial charge calculation, the electrostatic potentials of the studied molecules were first generated at the HF/6−31G* level (treating bromine and iodine atoms with the aug-cc-pVDZ-PP basis set), and then the atomic charges were assigned using the restrained electrostatic potential (RESP) [26] approach. We introduce the APCtMI approach in the current study. The contribution of an atomic parameter to the MM interaction energy between two monomers that form a noncovalent complex is given by

$$E_{interaction} = E_{complex} - E_{monomer,1} - E_{monomer,2}$$

$$= \frac{1}{2} \sum_{j=n} \sum_{i=m} E_j^{AP(i)} \qquad (1)$$

where

$$E_j^{AP(i)} = E_{interaction} - E_{interaction}^{(for\ j, AP(i)=0)} \qquad (2)$$

AP is an atomic parameter such as the atomic charge or van der Waals parameter; n is the total number of atoms in the

complex, and m is the number of atomic parameters studied. Thus, the contribution of AP to the molecular interaction can be defined as the total interaction energy of the two monomers minus the corresponding interaction energy calculated when AP was neglected (i.e., equal to zero). The factor of ½ is necessary because AP is counted twice during the overall summation of the atomic parameter energies (E^{AP}).

Despite the simplicity of the APCtMI approach, it has not been proposed previously (as far as we are aware). The APCtMI approach was used in this study to split the contributions of the σ-hole (i.e., a positively charged extra point) and the negative belt around the halogen atom (i.e., a negatively charged halogen atom) to the halogen bond strength. The approach was also applied to estimate the contribution of each atom to the molecular interaction.

Results and discussion

Molecular mechanical approach

We developed the PEP approach in our previous work to describe the anisotropic distribution of the charge density on a halogen atom in the framework of classical force fields [16]. The σ-hole on the halogen atom was represented by an extra point of charge, and the corresponding partial charges on the extra point and the other atoms (including the halogen atom) were determined using the RESP approach. The required parameters of the extra point were developed so as to give the correct description of the halogen bond in a halobenzene molecule that forms a halogen bond with a formaldehyde molecule, compared to the corresponding QM data. The optimum halogen–extra point (X–EP) distance was found to equal the r^* value of the corresponding halogen atom, where $r^* = \sqrt[6]{2}\,\sigma$ (σ is the van der Waals radius of the atom), i.e., 2.35, 2.22, and 1.95 Å for I, Br, and Cl, respectively, as shown in Fig. 1c. The rationality of the generated parameters was also investigated by studying the properties of the halogen bonds in various halogen-bond-forming complexes [16]. Moreover, including the PEP approach was found to improve the description of the charge on halo molecules, yielding more accurate solvation free energies and dipole moments when compared to the experimental and QM data, respectively [16].

Because the X–EP bond length is a crucial factor when predicting the molecular charge description, the correlation between the X–EP distance and the extra point and halogen atom charges in the iodobenzene molecule was studied, as shown in Fig. 2i. In addition, to assess the effect of the X–EP length on the halogen bond properties, the PESs for halogen-bond dissociation in halobenzene–formaldehyde complexes were calculated for X–EP bond lengths ranging from 1.2 Å to 2.4 Å. At lengths >2.4 Å, a conflict between
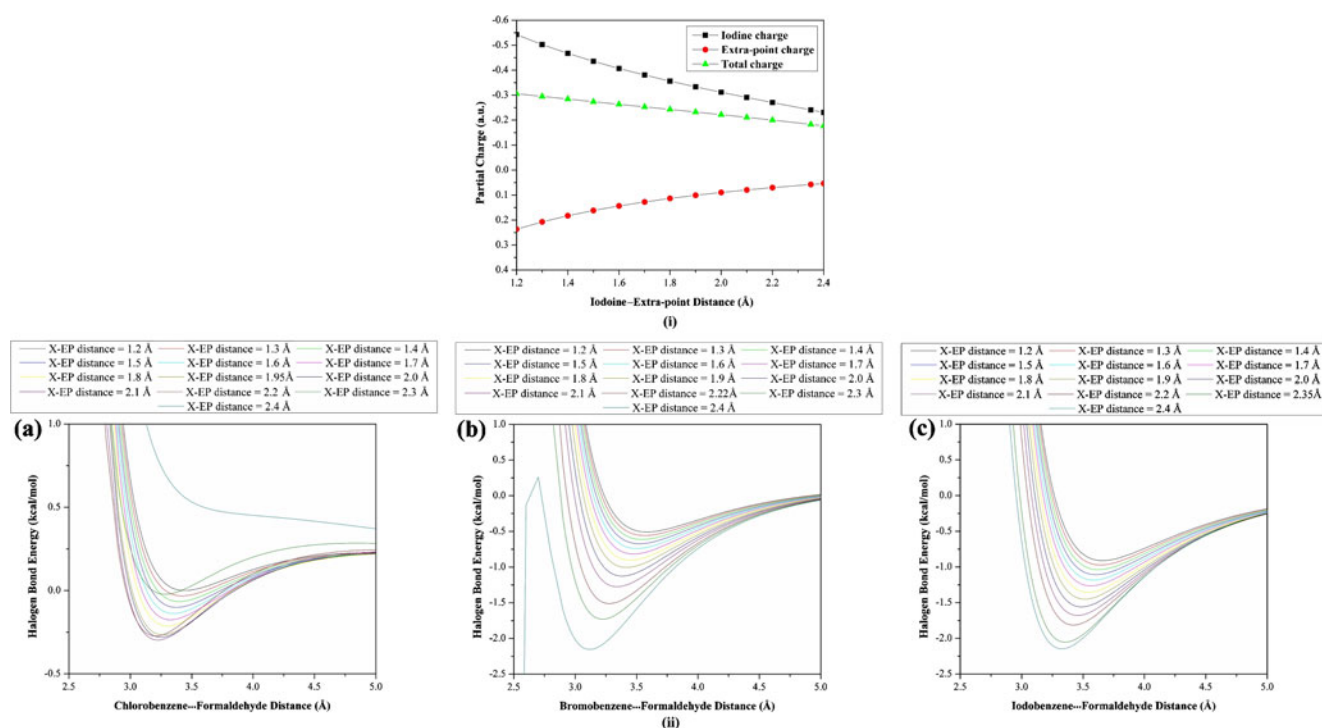
Fig. 2a–c Effect of the halogen–extra point (X–EP) distance on **i** the halogen and extra-point charges in an iodobenzene molecule, and **ii** the halogen bond energies in **a** chloro-, **b** bromo-, and **c** iodobenzene–formaldehyde complexes

the Lewis base and the extra point could exist at a short halo molecule⋯Lewis base distance. The generated PESs are plotted in Fig. 2ii. The calculated halogen bond lengths and the energies of the corresponding local minima are given in Table 1. The corresponding properties of halogen bonds calculated at the BSSE-corrected MP2/aug-cc-pVDZ level (with PP functions used for the Br and I atoms) are also supplied for comparison.

As seen in Fig. 2i, the X–EP distance has a considerable effect on the atomic partial charges of the molecular system, which in turn affects the solvation energy of and the noncovalent interactions exhibited by the halo molecule. Indeed, the magnitudes of the extra-point and halogen-atom charges decrease as the X–EP distance increases. Therefore, an accurate X–EP distance is needed in order to correctly describe the halo molecule's noncovalent interactions.

In addition, the bond dissociation curves in Fig. 2ii show that the halogen bond length decreases, and thus the bond strength increases, as the X–EP distance increases. However, the effect of the X–EP distance is smaller in the chloro complex than in the bromo and iodo complexes. This is because the charge on the extra point on the chlorine atom is smaller in magnitude than those on the bromine and iodine atoms; moreover, the halogen bond in the chloro complex is dominated by the van der Waals interaction, as discussed below.

Placing the extra point on the halogen atom at a distance r^* yielded results that agreed well with the MP2 data. The

performance of the X–EP parameter ($= r^*$) was assessed in our previous study; the total RMS error values for halogen bond length and energy were 0.18 Å and 0.49 kcal mol^{-1}, respectively, when compared to those obtained at the BSSE-corrected MP2/aug-cc-pVDZ level (with PP functions used for the Br and I atoms) in 12 halogen-bond-forming complexes [17]. Better results could be obtained by increasing the X–EP length. Because the MP2 method overestimates the halogen bond strength compared to the CCSD(T) method [14–16], and a long X–EP would result in a conflict between the extra point and the Lewis base, especially in MD, as in the bromobenezene–formaldehyde complex with Br–X equal to 2.40 Å (Fig. 2ii and Table 1), the X–EP distance of r^* value would be optimum to correctly describe the halogen bonding.

Nature of the halogen bond

In this work, the nature of the halogen bond was studied from the MM perspective. The PESs for halogen bond dissociation in six halobenzene–Lewis base complexes (chloro-, bromo-, and iodobenzene molecules complexed to formaldehyde and ammonia molecules) were generated at the MM level and compared to the corresponding BSSE-corrected MP2 data. The halogen bond lengths and energies for the corresponding local minima are given in Table 2. The MM energy components are also supplied to gain a better understanding of the nature of the halogen bond.

Table 1 Effect of the halogen–extra point (X–EP) distance on the predicted properties of the halogen bonds in halobenzene–formaldehyde complexes

X–EP distance (Å)	Chlorobenzene–formaldehyde complex		Bromobenzene–formaldehyde complex		Iodobenzene–formaldehyde complex	
	Halogen bond length (Å)	Halogen bond energy (kcal mol^{-1})	Halogen bond length (Å)	Halogen bond energy (kcal mol^{-1})	Halogen bond length (Å)	Halogen bond energy (kcal mol^{-1})
1.20	3.44	0.00	3.58	−0.51	3.66	−0.91
1.30	3.42	−0.03	3.57	−0.56	3.64	−0.97
1.40	3.40	−0.07	3.54	−0.61	3.62	−1.04
1.50	3.37	−0.10	3.52	−0.67	3.60	−1.11
1.60	3.35	−0.14	3.50	−0.74	3.58	−1.18
1.70	3.33	−0.18	3.48	−0.82	3.56	−1.27
1.80	3.30	−0.21	3.45	−0.90	3.54	−1.35
1.90	3.26[a]	−0.27[a]	3.42	−1.00	3.51	−1.45
2.00	3.25	−0.28	3.38	−1.13	3.49	−1.56
2.10	3.22	−0.30	3.34	−1.28	3.46	−1.68
2.20	3.21	−0.27	3.28[b]	−1.51[b]	3.42	−1.81
2.30	3.28	−0.02	3.22	−1.73	3.35[c]	−2.05[c]
2.40	5.00[d]	0.37	2.50[d]	−15.96	3.33	−2.15
MP2 data[e,f]	3.21	−0.53	3.18	−1.14	3.27	−1.72

[a] Data correspond to an X–EP bond length of 1.95 Å

[b] Data correspond to an X–EP bond length of 2.22 Å

[c] Data correspond to an X–EP bond length of 2.35 Å

[d] Minimum/maximum halobenzene–formaldehyde scanned bond length

[e] MP2 data correspond to the BSSE-corrected MP2/aug-cc-pVDZ level (with PP functions used for the Br and I atoms)

[f] Taken from our previous study [17]

As seen in Table 2, the MM level of theory that includes the PEP approach accurately describes the halogen bonding in the studied complexes, giving RMS errors for the calculated halogen bond lengths and energies of 0.09 Å and 0.37 kcal mol^{-1}, respectively, relative to the MP2 level.

On the other hand, an examination of the MM energy components revealed that in chloro complexes, the van der Waals interaction (E_{vdw}) contributes to the halogen bond strength and dominates the bond energy in the chlorobenzene–formaldehyde complex, where the calculated E_{vdw} was −0.29 kcal mol^{-1} out of

Table 2 Calculated halogen bond lengths and energies of halobenzene molecules complexed to formaldehyde and ammonia molecules

Complex	Halogen bond length (Å)		Halogen bond energy (kcal mol^{-1})			
	MP2[a,b]	MM	MP2[a,b]	MM		
				Electrostatic interaction	van der Waals interaction	Total energy
Chlorobenzene–formaldehyde	3.21	3.26	−0.53	0.03	−0.29	−0.27
Chlorobenzene–ammonia	3.33	3.34	−0.71	−0.36	−0.09	−0.44
Bromobenzene–formaldehyde	3.18	3.28	−1.14	−1.78	0.27	−1.51
Bromobenzene–ammonia	3.21	3.31	−1.83	−2.70	0.89	−1.82
Iodobenzene–formaldehyde	3.27	3.35	−1.72	−2.59	0.54	−2.05
Iodobenzene–ammonia	3.22	3.38	−3.03	−3.66	1.29	−2.37
RMS error[c]		0.09				0.37

[a] MP2 data correspond to the BSSE-corrected MP2/aug-cc-pVDZ level (with PP functions used for the Br and I atoms)

[b] Data taken from our previous study [17]

[c] RMS error was calculated with respect to the MP2 level

a total interaction energy of −0.27 kcal mol^{-1}. However, the electrostatic interaction (E_{elec}) is unfavorable in the latter complex, in which E_{elec} equals 0.03 kcal mol^{-1}. For the bromo and iodo complexes, the contribution of the van der Waals interaction to the halogen bond was found to be unfavorable, yielding a positive E_{vdw}, and the halogen bond strength was dominated by electrostatic interactions, which ranged from −1.78 kcal mol^{-1} in the bromobenzene–formaldehyde complex to −3.66 kcal mol^{-1} in the iodobenzene–ammonia complex. In addition, electrostatic interactions are stronger in the iodo complexes than in their bromo analogs owing to the higher positively charged extra point on (and the lower negative charge of) the iodine atom compared to that on (and that of) the bromine atom.

Interestingly, the inexpensive MM results agree well with the costly high-level QM data, producing a similar interpretation of the halogen bond—that it is electrostatic and van der Waals in nature, and showing that the van der Waals interaction effectively contributes to the chlorine halogen bond, while the electrostatic interaction dominates the halogen bond strength in the iodo complexes [14].

Why does the van der Waals interaction contribute favorably to the chlorine halogen bond, while the bromine and iodine halogen bonds are dominated by the electrostatic interactions between the halo molecule and the Lewis base? This can be answered from the MM perspective by studying the van der Waals interaction in an uncharged diatomic halogen-Lewis base molecule; the "O" GAFF oxygen atom type was taken as an example for the Lewis base. The correlation between the halogen⋯oxygen distance and the van der Waals interaction of the diatomic molecule is plotted in Fig. 3. For numerical comparison, the van der Waals interaction energies at certain halogen⋯oxygen distances are given in Table 3.
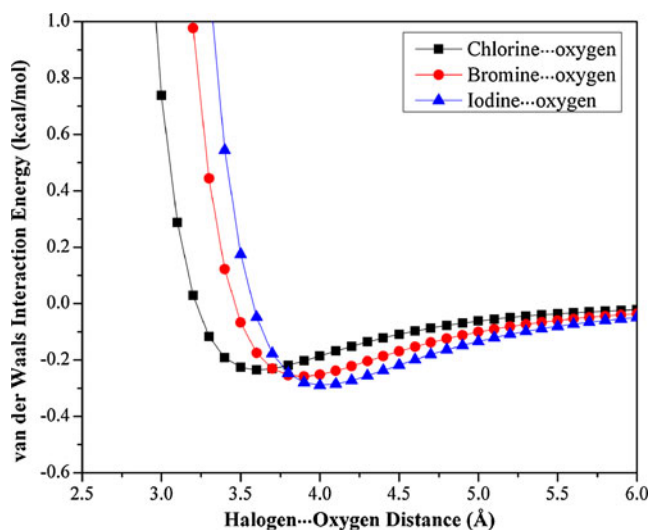

Fig. 3 Correlation between the molecular mechanical van der Waals interaction energy and the halogen⋯Lewis base distance in an uncharged diatomic system. The "O" GAFF oxygen atom type was taken as an example for the Lewis base

Table 3 Calculated molecular mechanical van der Waals interaction energies for uncharged halogen⋯Lewis base diatomic systems at particular separation distances[a]

Halogen⋯Lewis base distance (Å)	van der Waals interaction energy (kcal mol^{-1})		
	Cl⋯O	Br⋯O	I⋯O
3.0	0.74	3.27	6.15
3.2	0.03	0.98	2.11
3.5	−0.23	−0.07	0.17
4.0	−0.19	−0.25	−0.29
6.0	−0.02	−0.04	−0.05
Σvdw radii[b]	−0.09	0.20	0.17

[a] The "O" GAFF oxygen atom type was taken as an example for the Lewis base

[b] Σvdw distance equals 3.27, 3.37, and 3.50 Å for chloro, bromo, and iodo molecules, respectively

Figure 3 shows that the most favorable van der Waals interactions between the halogen and oxygen atoms occur at 3.6, 3.9, and 4.0 Å for chloro, bromo, and iodo molecules, respectively, with interaction energies of −0.24, −0.26 and −0.29 kcal mol^{-1}, respectively. Therefore, the van der Waals interaction increases with increasing size of the halogen atom (i.e., Cl<Br<I) at long-range distances (≥ 3.8Å). The van der Waals interaction approaches zero at distances >6.0 Å. In contrast, the van der Waals interaction is more unfavorable at short-range distances (≤ 3.7Å) in the order Cl<Br<I, giving interaction energies of −0.12, 0.44, and 1.15 kcal mol^{-1} for chloro, bromo, and iodo molecules, respectively, at an halogen⋯oxygen distance of 3.3 Å (Table 3). The magnitude of the unfavorable van der Waals interaction increases with decreasing halogen⋯oxygen distance (at distances≤3.5 Å, see Table 3). The latter observations highlight that, at the halogen bond distance (i.e., at a distance equal to or shorter than the sum of the van der Waals radii of the halogen atom and the Lewis base), the van der Waals interaction between the halogen atom and the Lewis base is favorable and contributes to the total interaction energy in the case of the chloro complex, but for the bromo and iodo complexes, the van der Waals interaction is unfavorable, and the favorable electrostatic interaction between the σ-hole and the Lewis base must be larger in magnitude than the corresponding unfavorable van der Waals interaction to form a halogen bond. The latter favorable electrostatic interaction must be larger in the case of the iodo complex than in the corresponding bromo analog because the van der Waals interaction becomes increasingly unfavorable in the same order (i.e., Br<I).

It is worth mentioning that the above observations are based on the van der Waals interaction between the halogen atom and oxygen atom in an uncharged diatomic molecule. However, in a halo molecule–Lewis base complex, the long-range van der Waals and electrostatic interactions among all of the atoms will contribute to the total interaction energy,

and the van der Waals interaction between the halogen atom and the Lewis base increases as the atomic number of the Lewis base increases, in the order N<O<S.

Halogen bond strength

As noted in the "Introduction," the strength of the halogen bond is correlated with the size of the halogen atom, and increases in the order Cl<Br<I; the size of the σ-hole increases in the same order. In this study, the correlation between the halogen bond strength and the size of the σ-hole was investigated from an MM perspective. Here, the size refers to the magnitude of the extra-point charge on the halogen atom. The correlation was studied in chloro-, bromo-, and iodobenzene molecules complexed to a formaldehyde molecule. The charge on the extra point was scaled from 0.000 a.u. to 0.100 a.u. at intervals of 0.005 a.u., and the partial atomic charges on the other halo molecule atoms (i.e., the X, C, and H atoms) were subsequently refitted. Note that free optimization of the halo complexes was conducted in this part of the study, and the X–EP distance was kept constant according to the PEP parameters regardless of the magnitude of the extra-point charge. The effect of the extra-point charge on each halogen's atomic charge, bond length, and bond energy was investigated and is plotted in Fig. 4.

As shown in Fig. 4a, the atomic partial charge of the halogen atom is well correlated with the magnitude of the extra-point charge (i.e., the σ-hole); as the positive charge on the extra point increases, the negative charge on the halogen increases in magnitude. Note that this correlation between the extra-point and halogen-atom charges has no physical meaning, because a restraint was applied on the extra-point charge during the RESP-charge fitting stage. For the same magnitude of extra-point charge, the magnitude of the negative charge on the halogen follows the halogen's electronegativity (i.e., Cl>Br>I).

Figure 4b shows the correlation between the magnitude of the extra-point charge and the halogen bond length in the studied halobenzene complexes. The halogen bond length decreases with increasing positive charge on the extra point.

It should be mentioned that the existence of a positive charge on the halogen atom does not a guarantee the formation of a halogen bond, because the halogen bond is not purely an attractive electrostatic interaction between the σ-hole and the Lewis base; that is, the repulsive electrostatic and van der Waals interactions between the negative halogen atom and the Lewis base also contribute to the halogen bond strength, as seen below for the case of chloromethane complexes.

Assuming that there is a bond between two atoms when the distance between them is equal to or shorter than the sum of their van der Waals radii, a halogen bond formed in the halobenzene–formaldehyde complex when the positive charge on the extra point was equal to or greater than 0.040 a.u. in the iodo and bromo complexes and 0.035 a.u. in the chloro complex. The latter observation shows that correct charge descriptions of the extra point and the halogen atom are necessary to correctly describe the halogen bond. Despite the fact that the negative charge on chlorine is higher than the corresponding charges on bromine and iodine atoms, a smaller extra-point positive charge was needed to form the halogen bond. This is attributed to the earlier observation that the van der Waals interaction dominates the halogen bond in the chlorobenzene–formaldehyde complex.

Regarding the correlation between the magnitude of the extra-point charge and the halogen bond energy, as expected, the halogen bond strength increases as the positive charge on the extra point increases (Fig. 4c), as seen in terms of the halogen bond length. This agrees well with the QM observations [2, 8, 9].

Here, two points should be discussed. First, the correlation between the extra-point charge and the bond energy in the chloro complex differs slightly from that seen for the bromo and iodo complexes, as was also observed in the effect of the X–EP distance on the halogen bond energy (Fig. 2ii). This is attributed to the fact that the van der Waals
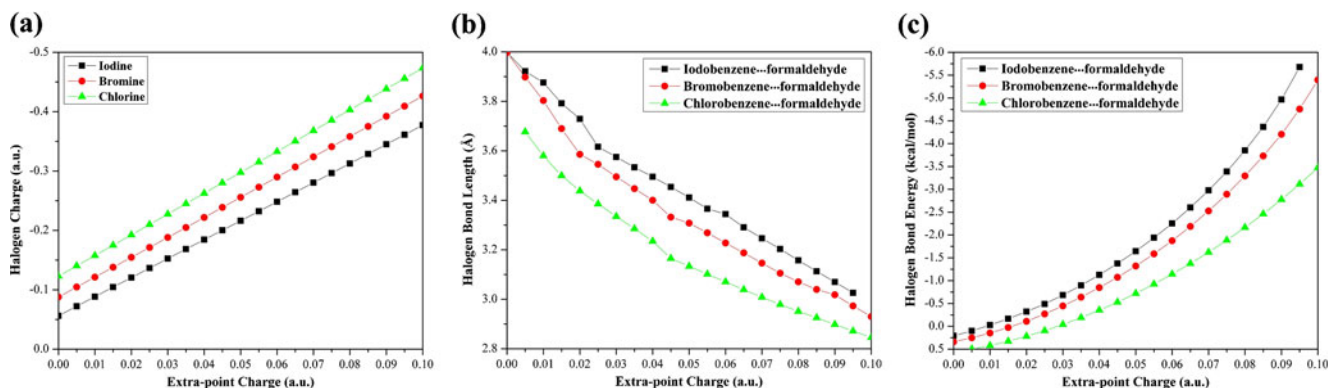

Fig. 4a–c Effect of the extra-point charge on **a** the charge on the halogen in a halobenzene molecule, **b** the length of the halogen bond, and **c** the halogen bond energy of the halobenzene–formaldehyde complex

interaction heavily contributes to the halogen bond energy in the chloro analog, whereas it is unfavorable in the bromo and iodo analogs. Second, assuming that bond formation occurs between two molecules when the interaction energy is negative, a negative interaction between the halobenzene molecule and formaldehyde exists when the positive charge of the extra point is equal to or greater than 0.030, 0.020, and 0.010 a.u. in the chloro, bromo, and iodo complexes, respectively. These values are well correlated with the magnitude of the negative charge on the halogen atom, which is highest for chlorine and lowest for iodine. To better understand this point, the contributions of the charges on the halogen and extra point to the molecular interaction was calculated using the APCtMI approach. Data were generated for iodo-, bromo-, and chlorobenzene molecules complexed to formaldehyde, with positive charges on the halogen extra point of 0.010 and 0.030 a.u., as shown in Table 4.

The data in Table 4 indicate that when the extra-point charge is less than 0.030, a halogen bond does not form between the halobenzene and formaldehyde, where the total halogen···Lewis base interaction energy is positive. In addition, the van der Waals interaction is favorable, and the electrostatic interaction is unfavorable and dominates the molecular interaction, yielding a net positive interaction energy. The electrostatic interaction is generally more favorable in the order Cl<Br<I, because the magnitude of the negative charge on the halogen atom decreases in the order Cl>Br>I. When the extra-point charge equals 0.030 a.u., the attractive electrostatic interaction between the positive extra point and the Lewis base overcomes the repulsive electrostatic interaction between the negative halogen atom and the Lewis base, resulting, when combined with the favorable van der Waals interaction, in net negative interaction energies of −0.68 and −0.45 kcal mol^{-1} for iodine and bromine complexes, respectively. In contrast, the higher

negative charge on the chlorine atom overcomes the attractive electrostatic interaction for chlorine, yielding a net positive electrostatic interaction of 0.32 kcal mol^{-1}. However, in the latter complex, the favorable van der Waals interaction of −0.36 kcal mol^{-1} overcomes the unfavorable electrostatic interaction, resulting in a net negative interaction energy of −0.04 kcal mol^{-1}.

Chloromethane–Lewis base complex

The ability of chloromethane to form a halogen bond with a Lewis base is still a dogma. A molecular electrostatic potential study of the chloromethane molecule showed that the chlorine's surface is completely negative, with a most positive electrostatic potential, $V_{S,max}$, value of −1.5 kcal mol^{-1} [1, 2]. The absence of a positive σ-hole makes it impossible for chloromethane to form a halogen bond with Lewis bases such as formaldehyde and ammonia [2]. However, coupled cluster [CCSD(T)/aug-cc-pVTZ] calculations showed that chloromethane forms a halogen bond of strength −1.05 kcal mol^{-1} with a formaldehyde molecule [14]. Because it is important to understand the behavior of chloromethane and its ability to form halogen bonds, chloromethane–Lewis base complexes were revisited in terms of quantum mechanics and molecular mechanics.

Existence of the σ-hole

The molecular electrostatic potential of chloromethane was quantitatively analyzed by Politzer and co-workers on a 0.001 a.u. electron density envelope [1, 2], and it was found that chloromethane has a $V_{S,max}$ value of −1.5 kcal mol^{-1} along the C–Cl axis. In contrast, the RESP charge calculation for chloromethane showed that the extra point of charge on the chlorine atom at a distance of 1.95 Å retains a

Table 4 Atomic parameter contributions to the halogen bond strengths in halobenzene–formaldehyde complexes with positive extra-point charge magnitudes of 0.010 and 0.030 a.u.[a]

Complex	Halogen···Lewis base contact (Å)	Electrostatic interaction (kcal mol^{-1})				Van der Waals interaction (kcal mol^{-1})				Total interaction energy (kcal mol^{-1})
		σ-Hole	X	Rest[b]	Total	σ-Hole	X	Rest[b]	Total	
Extra-point charge=0.010 a.u.										
Chlorobenzene–formaldehyde	3.58	−0.41	1.74	−0.51	0.82	0.00	−0.32	−0.08	−0.40	0.42
Bromobenzene–formaldehyde	3.80	−0.42	1.20	−0.21	0.56	0.00	−0.36	−0.06	−0.42	0.14
Iodobenzene–formaldehyde	3.88	−0.45	0.85	0.02	0.42	0.00	−0.40	−0.05	−0.45	−0.03
Extra-point charge=0.030 a.u.										
Chlorobenzene–formaldehyde	3.33	−1.57	2.84	−0.95	0.32	0.00	−0.26	−0.10	−0.36	−0.04
Bromobenzene–formaldehyde	3.50	−1.78	2.16	−0.55	−0.17	0.00	−0.20	−0.08	−0.28	−0.45
Iodobenzene–formaldehyde	3.58	−1.89	1.69	−0.25	−0.45	0.00	−0.17	−0.06	−0.23	−0.68

[a] Data were taken from the free optimization of halobenzene–formaldehyde complexes

[b] $E_{Rest} = E_{total} - E_{\sigma-hole} - E_X$

positive charge of 0.0200 a.u. To better understand this, the electrostatic potential on the chloromethane surface was quantitatively re-examined on 0.001 and 0.002 a.u. electronic density contours at the B3PW91/aug-cc-pVDZ and B3PW91/6-31 G(d,p) levels using the Wavefunction Analysis (WFA v1.0) program [27]. These two values of contours are recommended by Bader et al. [28], and are large enough to embrace ~96 % of the molecule's electronic charge. The calculated $V_{S,max}$ values for chlorine in the chloromethane molecule are listed in Table 5.

Table 5 shows that chloromethane does not produce a positive region on the chlorine atom when the electrostatic potential is computed on the 0.001 electronic density envelope, and the most positive electrostatic potential along the C–Cl axis equals −0.73 and −1.38 kcal mol^{-1} at the B3PW91/aug-cc-pVDZ and B3PW91/6-31 G(d,p) levels of theory, respectively. However, when the 0.002 a.u. electronic density envelope was used for the electrostatic potential calculation, a weakly positive region appeared on the chlorine atom, with $V_{S,max}$ values of 3.96 and 2.90 kcal mol^{-1} at the B3PW91/aug-cc-pVDZ and B3PW91/6-31 G(d,p) levels of theory, respectively.

In summary, the PEP approach and quantitative analysis of the electrostatic potential of the chloromethane molecule showed that chloromethane produces a positive region on the chlorine atom, and the use of the 0.002 a.u. electronic density envelope is recommended over the corresponding 0.001 a.u. envelope to achieve a better qualitative analysis of the molecular electrostatic potential.

Potential-energy surface calculations

To examine the ability of chloromethane to form stable halogen-bond-forming-complexes with Lewis bases, the PESs of chloromethane complexed to formaldehyde and ammonia were generated along the C–X···O/N axis at the BSSE-corrected MP2/aug-cc-pVDZ and MM levels. As discussed in section on the methodology, the C–X···N/O and X···O–C angles were kept constant at 180° to decrease the possibility of any further interactions between the Lewis base and the halo molecule, rather than halogen bonding. The generated potential energy curves are plotted in Fig. 5, and the corresponding halogen bond properties are given in Table 6.

The MP2 PESs in Fig. 5a show that chloromethane–Lewis base complexes are unstable; the interaction energies between the chloromethane and Lewis bases are only −0.04 and −0.12 kcal mol^{-1} for the formaldehyde and ammonia complexes, respectively. The corresponding halogen···Lewis base contact distances in chloromethane–formaldehyde/ammonia complexes are 3.32/3.45 Å, respectively, which are longer than the sum of the van der Waals radii of Cl and O and of Cl and N, respectively. The long Cl···O/N contacts reveal the unstable nature of the chloromethane–Lewis base complexes. The small negative interaction energies for chloromethane complexes can be attributed to other long-range noncovalent interactions between the chloromethane and Lewis base molecules, such as the dispersion interaction, which is overestimated by the MP2 method [29, 30], rather than to halogen bonding. This was verified by investigating the dissociation curves for the studied chloro complexes at the HF/aug-cc-pVDZ level (Fig. 5b). As shown in Fig. 5b, the calculated HF interaction energies between the chloromethane and the Lewis bases are positive. The positive HF interaction energies confirm that the dispersion interaction is the source of the small negative MP2 energies, which is absent at the HF level.

On the other hand, the calculated MM PESs showed that no halogen bond formed between chloromethane and the Lewis base molecules (Fig. 5c), although the RESP calculations assigned a positive charge to the extra point placed on the chlorine atom. To better understand this, free optimization of the chloromethane complexes was performed at the MM level with a C–X···Lewis base bond angle of 180°. The results were then compared to the corresponding data for the chlorobenzene complex. Furthermore, the individual atomic parameter contributions of the σ-hole (i.e., positively charged extra point) and the negatively charged halogen atom to the molecular interactions were calculated and analyzed using the APCtMI approach. All of the data are given in Table 7. Indeed, the MM results produced by the APCtMI approach revealed that the repulsive electrostatic interaction between the negative halogen atom and the Lewis base in chloromethane complexes is approximately three times greater than the attractive electrostatic interaction between the σ-hole and the Lewis base, which is only ~1.5 times in the chlorobenzene complex. This is attributed to the magnitudes of the partial charges of the σ-hole and chlorine atom in chloro molecules, which are 0.0200 and −0.2356 a.u. for the chloromethane molecule and 0.0382 and −0.2561 a.u. for the chlorobenzene molecule, respectively. Although the van der Waals interaction between the chlorine atom and the Lewis base is more favorable in the chloromethane complexes than in the chlorobenzene complexes, the total magnitude of the unfavorable electrostatic interaction in

Table 5 The most positive electrostatic potentials $V_{S,max}$ on the 0.001 and 0.002 a.u. surfaces of chlorine in the chloromethane molecule

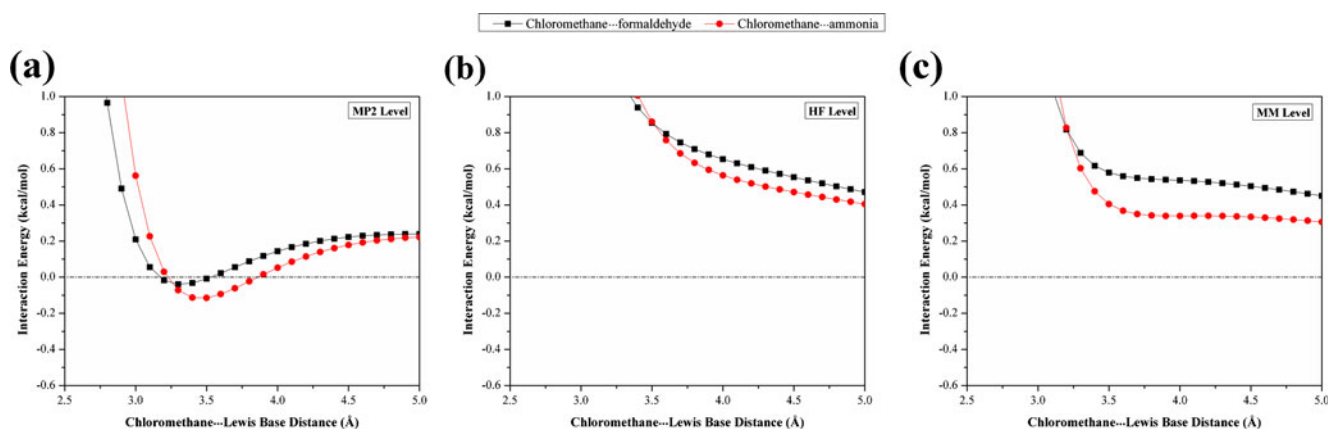| Theoretical level	Electronic density (a.u.)	$V_{S,max}$ (kcal mol^{-1})
B3PW91/aug-cc-pVDZ	0.001	−0.73
	0.002	3.96
B3PW91/6-31 G(d,p)	0.001	−1.38 (−1.5[a])
	0.002	2.90

[a] Taken from [1, 2]

Fig. 5a–c Potential-energy surface along the Cl···Lewis base axis for a chloromethane molecule complexed to formaldehyde and ammonia molecules, calculated at the **a** BSSE-corrected MP2/aug-cc-pVDZ level, **b** BSSE-corrected HF/aug-cc-pVDZ level, and **c** MM level

chloromethane complexes overcomes the favorable van der Waals interaction, making the chloromethane–Lewis base complexes unstable.

Regarding the reported CCSD(T) interaction energy of -1.05 kcal mol^{-1} in the chloromethane–formaldehyde complex, the measured C–Cl···O and Cl···O–C bond angles in the chloromethane complex were reportedly 166.8° and 91.3°, respectively. Therefore, the given interaction energy can be attributed to noncovalent interactions such as the C–X···H/C interaction between the chloromethane and the Lewis base molecules, but not to halogen bonding. It is worth mentioning that the C–X···H interaction would reduce the highly negative charge on the chlorine atom, resulting in the formation of a stable halogen-bonded chloromethane–formaldehyde complex.

Effect of the Cl···O–C bond angle

To better understand the effect of the Cl···O–C angle on the chloromethane···formaldehyde interaction energy, the PES along the Cl···O–C angle from 90° to 180° was calculated at the BSSE-corrected MP2/aug-cc-pVDZ and MM levels. In

the latter calculation, the Cl···O contact was kept constant at 3.17 Å, which is 0.10 Å less than the sum of the van der Waals radii of Cl and O. The generated PESs are plotted in Fig. 6.

Figure 6 shows the correlation between the Cl···O–C angle and the interaction energy difference ($\Delta E = E_{\theta°} - E_{180°}$) in the chloromethane–formaldehyde complex. Interestingly, the PES generated at the MM level is compatible with the corresponding PES generated at the MP2 level, both of which indicate that the complex with a Cl···O–C angle of 95° is the most stable, with a 0.21 kcal mol^{-1} energy difference between the two surfaces. The corresponding energies are given in Table 8.

The differences between the calculated MM and MP2 interaction energies are 0.66 and 0.87 kcal mol^{-1} for chloro complexes with Cl···O–C angles of 95° and 180°, respectively. The latter difference shows that the energy difference can be mainly attributed to the overestimation of either the repulsive Cl···O electrostatic interaction at the MM level or the attractive Cl···O noncovalent interaction at the MP2 level. This energy difference would not affect the interpretation of the higher stability of the chloro complex with a Cl···O–C angle of 95° over that with a Cl···O–C angle of 180°.

Furthermore, APCtMI analysis of the contributions of formaldehyde's atomic parameters to the interaction energy was performed on chloro complexes with Cl···O–C angles of 95° and 180°. The data are given in Table 9.

The APCtMI results can be summarized as follows. (1) The atomic contribution of the oxygen atom is the same at both studied angles because its position is the same, resulting in unfavorable electrostatic and van der Waals interactions of 3.14 and 0.04 kcal mol^{-1}, respectively, with the chloromethane molecule. (2) The electrostatic and van der Waals interaction contributions of the hydrogen atoms H_a and H_b (see Fig. 6 for atom numbering) to the interaction energy are the same for an angle of 180° due to the

Table 6 Calculated halogen bond lengths and energies of chloromethane–Lewis base complexes[a]

Complex	Halogen bond length (Å)			Halogen bond energy (kcal mol^{-1})		
	MP2[b]	HF[c]	MM	MP2[b]	HF[c]	MM
Chloromethane–formaldehyde	3.32	-[d]	-[d]	−0.04	-[d]	-[d]
Chloromethane–ammonia	3.45	-[d]	-[d]	−0.12	-[d]	-[d]

[a] C–Cl···O/N and Cl···O–C angles in the studied chloro complexes were held at 180°

[b] MP2 data correspond to the BSSE-corrected MP2/aug-cc-pVDZ level

[c] HF data correspond to the BSSE-corrected HF/aug-cc-pVDZ level

[d] No local minima were observed; see Fig. 5

Table 7 Comparison of the atomic parameter contributions in chloromethane–Lewis base and chlorobenzene–Lewis base complexes[a]

Complex	Halogen bond length (Å)	Halogen bond energy (kcal mol^{-1})								
		Electrostatic interaction				van der Waals interaction				Total
		σ-hole	X	Rest[b]	Total	σ-hole	X	Rest[b]	Total	
Chloromethane–formaldehyde	3.70	−0.73	2.45	−0.85	0.87	0.00	−0.31	−0.04	−0.35	0.53
Chloromethane–ammonia	3.78	−0.65	1.75	−0.53	0.58	0.00	−0.23	−0.03	−0.26	0.31
Chlorobenzene–formaldehyde	3.26	−2.18	3.33	−1.15	0.00	0.00	−0.18	−0.11	−0.29	−0.29
Chlorobenzene–ammonia	3.33	−2.14	2.48	−0.75	−0.41	0.00	0.02	−0.09	−0.07	−0.47

[a] Data were taken from the free optimization of halo molecule–Lewis base complexes

[b] $E_{Rest} = E_{total} - E_{\sigma-hole} - E_X$

symmetrical positions of the two hydrogen atoms. However, for an angle of 95°, the favorable electrostatic contribution of the H_a atom is greater than that of the H_b atom (−0.16 and −0.08 kcal mol^{-1}, respectively), because H_a is closer to the chloromethane molecule and exhibits an Cl⋯H electrostatic interaction. (3) The electrostatic contributions of the carbon atom are −2.84 and −2.02 kcal mol^{-1} at angles of 95° and 180°, respectively. On the other hand, its van der Waals contributions were quite similar, −0.09 and −0.12 kcal mol^{-1}, at angles of 95° and 180°, respectively.

The greater stability of the chloro complex with a Cl⋯O–C angle of 95° can be attributed to the more favorable electrostatic interaction between formaldehyde's hydrogen and carbon atoms and the chloromethane molecule compared to the corresponding data at 180°.
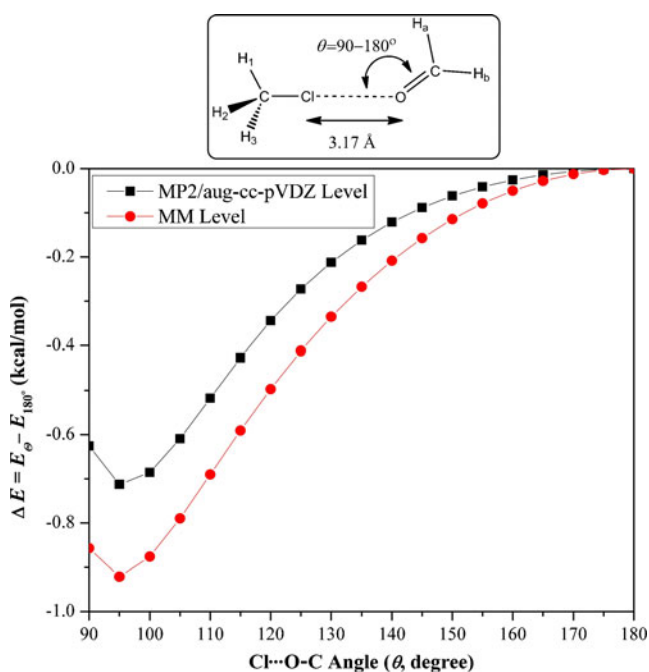

Fig. 6 Effect of the Cl⋯O–C angle, θ, on the interaction energy difference ($\Delta E = E_{\theta} - E_{180°}$) in the chloromethane–formaldehyde complex

Overall, because the MM electrostatic interaction exhibited by the oxygen is highly unfavorable (3.14 kcal mol^{-1}) and overcomes the other favorable interactions between the chloromethane and formaldehyde molecules, the net MM interaction energy is only −0.05 kcal mol^{-1} in the chloro complex with a Cl⋯O–C angle of 95°.

When the Cl⋯O–C angle in the chloro complex is 90°, formaldehyde's hydrogen (H_a) atom exhibits unfavorable van der Waals contact with the chlorine atom, giving a positive van der Waals interaction energy (Table 9). The latter unfavorable van der Waals interaction overcomes the corresponding favorable Cl⋯H_a electrostatic interaction, resulting in a total interaction energy which is lower than that in the corresponding chloro complex with a Cl⋯O–C angle of 95°, see Table 9. The latter explains why the chloromethane complex with a Cl⋯O–C angle of 95° is more stable than that with a Cl⋯O–C angle of 90°.

Lone-pair alignment effect

Our MM results regarding the effect of the Cl⋯O–C angle on the halogen bond strength are in good agreement with those obtained by Riley and Merz, who found via quantum mechanics that the preferred X⋯O–C angle in halobenzene–

Table 8 Calculated interaction energies for chloromethane–formaldehyde complexes with Cl⋯O–C angles of 95° and 180° and a Cl⋯O distance of 3.17 Å[a]

Complex	Interaction energy		Energy difference ($\Delta E = E_{95°} - E_{180°}$)	
	MP2[b]	MM	MP2[b]	MM
Chloromethane–formaldehyde (θ=180°)[c]	0.00	0.87		
Chloromethane–formaldehyde (θ=95°)[c]	−0.71	−0.05	−0.71	−0.92

[a] Energies are given in kcal mol^{-1}

[b] MP2 data correspond to BSSE-corrected MP2/aug-cc-pVDZ level

[c] θ refers to the corresponding Cl⋯O–C angle in the chloro complex

Table 9 Atomic parameter contributions of the formaldehyde atoms to the molecular interaction in chloromethane–formaldehyde complexes with Cl⋯O–C angles of 180°, 95°, and 90°[a]

Complex	Interaction energy (kcal mol^{-1})[a]										Total
	Electrostatic interaction					van der Waals interaction					Total
	H_a	H_b	C	O	Total	H_a	H_b	C	O	Total	
Chloromethane–formaldehyde ($\theta=180°$)[b]	−0.07	−0.07	−2.02	3.14	0.97	−0.01	−0.01	−0.12	0.04	−0.10	0.87
Chloromethane–formaldehyde ($\theta=95°$)[b]	−0.16	−0.08	−2.84	3.14	0.05	−0.03	−0.02	−0.09	0.04	−0.10	−0.05
Chloromethane–formaldehyde ($\theta=90°$)[b]	−0.18	−0.09	−2.96	3.14	−0.09	0.08	−0.02	0.00	0.04	0.10	0.02

[a] For the H_a and H_b numbering system, see Fig. 6

[b] θ refers to the corresponding Cl⋯O–C angle in the chloro complex

formaldehyde complexes ranges from 95° to 115° [8]. Riley and Merz suggested that the preferred angle can be attributed to the orientation of the halogen atom with respect to that of the lone pair on the oxygen atom.

To assess the effect of the alignment of the lone pair on the interaction energy in terms of MM, two lone pairs ("lps"; i.e., negatively charged extra points) were placed on the oxygen atom of the formaldehyde molecule. The parameters for the lone pairs were taken from the literature [31]. The PES along the Cl⋯O–C angle was then re-generated with and without the lone pairs. In the case with no lone pairs on the oxygen atom, the atomic partial charges were taken from the corresponding molecule with the lone pair, and the extra-point charges were added to the oxygen atom. This was done so that we could assess the effect of the lone pair under equivalent conditions. The generated PESs are plotted in Fig. 7.

The two generated PESs at the MM level (those obtained with and without the inclusion of the negative oxygen's lone pairs, Fig. 7) indicate that the complex with a Cl⋯O–C angle of 95° is the most stable, and that the orientation of the chloromethane with respect to the lone pair on oxygen has a non-negligible effect on the interaction energy; the energy difference $\Delta\Delta E$ ($\Delta\Delta E = \Delta E_{\text{with lp(O)}} - \Delta E_{\text{without lp(O)}}$) is −0.17 kcal mol^{-1}. The energy difference $\Delta\Delta E$ can be attributed to the difference in the Cl⋯O electrostatic interaction between the two studied systems. In addition, the favorable Cl⋯H_a and Cl⋯C electrostatic interactions heavily contribute to the stabilization energy of the chloro complex with a Cl⋯O–C angle of 95°. It is worth pointing out that if the alignment of the lone pair on oxygen with respect to the chlorine atom dominates the stabilization energy of the chloromethane complex, the local minimum should be located at a Cl⋯O–C angle of ~120°, which is not the case here. This reveals that other noncovalent interactions overcome the lone-pair alignment factor and bend the formaldehyde molecule to produce a Cl⋯O–C angle of 95°.

The contribution of the Cl⋯H_a noncovalent interaction to the total interaction energy in the chloromethane–formaldehyde complex with a Cl⋯O–C angle of 95° can be proven by performing second-order perturbation analysis of the studied systems as implemented in the natural bond orbital (NBO) method [32]. This type of analysis examines and estimates all
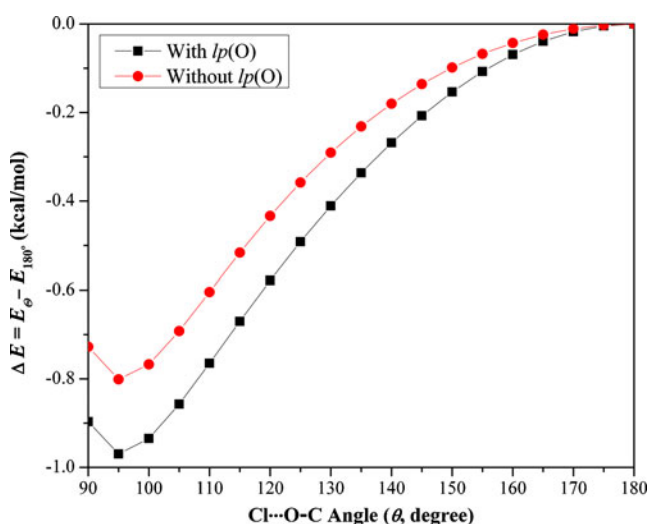

Fig. 7 Effect of the carbonyl oxygen's lone pair on the MM correlation between the Cl⋯O–C angle, θ, and the interaction energy difference ($\Delta E = E_\theta - E_{180°}$) in the chloromethane–formaldehyde complex

Table 10 The most important donor/acceptor NBO interactions in chloromethane–formaldehyde complexes with Cl⋯O–C angles of 180° and 95° and a Cl⋯O distance of 3.17 Å

Cl⋯O–C angle (θ in °)	Donor/acceptor NBOs	$E(2)$[a]
$\theta=180°$	LP(O)/BD*(C–Cl)	0.24
$\theta=95°$	LP(Cl)/BD*(C–H_a)[b]	0.37[c]
	LP(Cl)/BD*(C–H_b)[b]	0.06
	LP(O)/BD*(C–Cl)	0.39

[a] Stabilization energy in kcal mol^{-1}

[b] For numbering system, see Fig. 6

[c] Data correspond to the sum of the chlorine's lone-pair interactions

possible interactions between donor and acceptor Lewis-type NBOs. Therefore, natural bond orbital analysis of chloromethane–formaldehyde complexes with Cl···O–C angles of 95° and 180° were performed at the HF/aug-cc-pVDZ level using the Gaussian03 software package. The most important interactions between the NBOs are given in Table 10.

The data in Table 10 confirm the MM results in which the noncovalent Cl···H interaction contributes to the molecular stabilization of the chloromethane complex with a Cl···O–C angle of 95°. On the other hand, in the chloromethane complex with a Cl···O–C angle of 180°, no Cl···H orbital interaction was observed.

Last but not least, it is well known that the optimum A–X···Lewis base bond angle is 180° in small halogen-bond-forming complexes [1]. The current results for the participation of the formaldehyde hydrogen atom in the noncovalent C–X···H interaction with the chlorine atom explain why the reported CCSD(T) halogen bond angles in halomethane–formaldehyde complexes are less than 180° (166.8°, 171.2°, and 172.9° for chloro-, bromo-, and iodomethane complexes, respectively). These deviated angles reflect the competition between the C–X···H hydrogen bond and the C–X···O halogen bond in the studied halomethane complexes; the halogen bond strength increases in the order chloro<bromo<iodo complexes, so the halogen bond angle gets closer to 180° in the same order.

Conclusions

The MM approach to halogen bonding that we have developed, PEP, in which an extra point of positive charge is used to represent the σ-hole on the halogen atom, accurately describes the halogen bonding in halobenzene–Lewis base complexes. The MM perspective revealed that the halogen bond is electrostatic and van der Waals in nature. Estimating the atomic parameter contributions to halogen bonding using the APCtMI approach revealed that the halogen bond strength is a function of (i) the attractive electrostatic interaction between the Lewis base and the positive σ-hole on the halogen atom, (ii) the repulsive electrostatic interaction between the Lewis base and the negative charge on the halogen atom, and (iii) the repulsive/attractive van der Waals interaction between the halogen atom and the Lewis base. The strength of the halogen bond increases as the size of the σ-hole (i.e., the magnitude of the positive charge on the extra point) increases. Qualitative analysis of the electrostatic potential of the chloromethane surface showed a positive region on the chlorine surface. MM calculations for chloromethane–Lewis base complexes showed that chloromethane cannot form halogen bonds due to the excessive negative charge on the chlorine atom, resulting in an unfavorable electrostatic interaction that is larger than the

favorable halogen van der Waals interaction. The large reported CCDS(T) interaction energy of −1.05 kcal mol^{-1} is not due to pure halogen bonding but to other electrostatic interactions between the chloromethane and formaldehyde molecules, such as C–X···H/C interactions. Consequently, the results presented in the CCDS(T) study [14] should be reconsidered. MM using simple approaches such as PEP and APCtMI can help researchers to examine interactions that cannot be studied by costly QM methods; for example, they can be used to differentiate the contributions of the σ-hole on and the negative belt around the halogen atom to the halogen bond strength.

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