Halogen bonded complexes between volatile anaesthetics (chloroform, halothane, enflurane, isoflurane) and formaldehyde: a theoretical study

Wiktor Zierkiewicz, a Robert Wieczorek, b Pavel Hobza c,d and Danuta Michalska a

Received 8th October 2010, Accepted 12th January 2011
DOI: 10.1039/c0cp02085k

The structures and intermolecular interactions in the halogen bonded complexes of anaesthetics (chloroform, halothane, enflurane and isoflurane) with formaldehyde were studied by ab initio MP2 and CCSD(T) methods. The CCSD(T)/CBS calculated binding energies of these complexes are between −2.83 and −4.21 kcal mol$^{-1}$. The largest stabilization energy has been found for the C–Br···O bonded halothane···OCH$_3$ complex. In all complexes the C–X bond length (where X = Cl, Br) is slightly shortened, in comparison to a free compound, and an increase of the C–X stretching frequency is observed. The electrostatic interaction was excluded as being responsible for the C–X bond contraction. It is suggested that contraction of the C–X bond length can be explained in terms of the Pauli repulsion (the exchange overlap) between the electron pairs of oxygen and halogen atoms in the investigated complexes. This is supported by the DFT-SAPT results, which indicate that the repulsive exchange energy overcompensates the electrostatic one. Moreover, the dispersion and electrostatic contributions cover about 95% of the total attraction forces, in these complexes.

1. Introduction

Anaesthesia is a reversible phenomenon and general anaesthetics act by perturbing weak intermolecular interactions without breaking or forming covalent bonds. Despite the fact that volatile anaesthetics, such as chloroform, halothane, enflurane and isoflurane, have been used clinically, the mechanism of their action is still not fully understood. They may act by a direct bonding to neuroreceptors. 1–6 Sandorfy 7 reported that they can form weak van der Waals hydrogen bonds or intermolecular hydrogen bonds, and the strength of these interactions is in the range between 1.0 and 2.2 kcal mol$^{-1}$. Investigation of the halogen bonds and hydrogen bonds may help to explain anaesthetic properties of polyhalogenated alkanes and ethers. 7–9 A number of experimental and theoretical evidences confirm that the halogen bond plays an important role in a wide variety of biological phenomena such as protein–ligand complexion.10–15 Eckenhoff and coworkers16 reported the crystal structure of the halothane/apoferritin and isoflurane/apoferritin complexes.

For the halothane complex it has been shown that in the binding pocket the distance between the bromine atom of halothane and the carbonyl oxygen atom of leucine (3.11 Å) is smaller than the sum of the corresponding van der Waals radii (3.37 Å).

Studies of the electrostatic potentials of the halogen bonded systems show that the lone electron pairs of the halogen atom bonded to the carbon atom form a belt of negative electrostatic potential around its central part leaving the outermost region positive, the so-called σ-hole.17,18 The halogen bonding was explained as a noncovalent interaction between a covalently bound halogen on one molecule and a negative site of another.7,19–21 Recently, it has been shown that the interaction energy in these complexes is dominated by the dispersion and electrostatic contributions.22–24 Halogen bonds are similar to hydrogen bonds in many respects. Therefore, they may collaborate or compete with each other.25–30

The aim of this work is to elucidate the nature of interactions in the chloroform, halothane, enflurane and isoflurane complexes with formaldehyde using ab initio MP2 and CCSD(T) methods. The studies on the halogen bond interactions between anaesthetics and amino acids are important for understanding their mechanism of action, in biological systems. Therefore, the complexes investigated in this work can serve as the models for such studies.

The structures, binding energies and harmonic frequencies of these complexes are discussed. The C–X (X = Cl, Br) bond in anaesthetics becomes shorter and stronger upon formation of a complex with formaldehyde. The possible explanation of this phenomenon is presented.
2. Theoretical methods

Full geometry optimizations of the isolated anaesthetic molecules (chloroform, halothane, enflurane, isoflurane) and their halogen bonded complexes with formaldehyde were performed by the \textit{ab initio} second order Møller–Plesset perturbation (MP2) method\cite{31} using the 6-311++G(d,p) basis set.\cite{32,33} The counterpoise CP-corrected gradient optimization has been used.\cite{34} Subsequently, vibrational harmonic frequencies and infrared intensities have been calculated for all species considered in this work.

To elucidate the relativistic effects for the halothane···formaldehyde complex with the C–Br···O halogen bond, we have performed additional calculations using the LanL2DZdp pseudopotential basis set\cite{35} for the bromine atom and the 6-311++G(d,p) basis set for the other atoms. Moreover, the geometry of the halothane···formaldehyde complex has been optimized at the MP2/cc-pVTZ level. Further, the interaction energy has been calculated using both the aug-cc-pVTZ basis set\cite{36,37} on all atoms and mixed aug-cc-pVTZ-PP basis set\cite{38} on the bromine atom and aug-cc-pVTZ on other atoms.

The CCSD(T) complete basis set (CBS) limit interaction energies have been obtained as a sum of the MP2/CBS interaction energies and the CCSD(T) correction term, which is defined as a difference between the MP2 and CCSD(T) interaction energies determined in a smaller basis set (6-31G*).\cite{39,40}

The CBS limit energies were evaluated by an extrapolation of the Hartree–Fock energy and the MP2 correlation energy from the cc-pVTZ and cc-pVQZ basis sets.\cite{36,37} The two-point extrapolation methods of Helgaker \textit{et al.} were used.\cite{41,42}

To get a detailed insight into the nature of bonding in these complexes, the symmetry adapted perturbation theory DFT-SAPT\cite{43} calculations were carried out at the PBE0/aug-cc-pVTZ level.\cite{44} The SAPT method determines the total interaction energy as the sum of the first- and second-order perturbation terms. The favorable performance of the method is due to a combination of the DFT treatment for monomers and SAPT treatment for interaction between monomers. A natural bond orbital (NBO) analysis\cite{45} was performed at the MP2/6-311++G(d,p) level of theory. To calculate the positive sigma hole potentials, the electrostatic potential surface maxima on halogen atoms of isolated σ-hole donors have been computed at the B3PW91/6-31G(d,p) level using the WFA (Wavefunction Analysis Program).\cite{36}

All calculations were carried out with the GAUSSIAN 09\cite{47} or MOLPRO 2006\cite{48} programs.

3. Results and discussion

3.1 Structures

Fig. 1 shows the structures of the chloroform···OCH$_2$ and halothane···OCH$_2$ complexes optimized at the MP2/6-311++G(d,p) level. It should be mentioned that the most stable conformer of halothane has been selected for investigations.\cite{39,52} As is seen from this figure, two structural isomers of the halothane···formaldehyde complex have been found. The (A) complex with the C–Br···O halogen bond is more stable, by 0.44 kcal mol$^{-1}$, than the (B) complex with the C–Cl···O bond.

Fig. 2 illustrates the structures of the formaldehyde complexes with the most stable conformers of enflurane\cite{53,56} and isoflurane. In the case of the isoflurane···OCH$_2$ complex, the MP2 calculations have revealed the presence of two structural isomers, (A) and (B), where (A) is more stable by 0.16 kcal mol$^{-1}$. The formation of these two isomers can be explained as a consequence of the weak secondary interaction between the hydrogen atom of formaldehyde and the fluorine atom of isoflurane.

Tables 1 and 2 list the selected geometrical and vibrational parameters for the investigated complexes. As follows from Table 1, the C$1$–X$_2$ bond (where X = Cl, Br) is contracted upon complexation. In the chloroform and isoflurane complexes the C$1$–Cl$_2$ bond length is contracted by $-0.003$ Å, while the smallest change ($-0.001$ Å) is observed in the halothane···OCH$_2$ (A) complex. As follows from Table 2, a
contraction of the C1−X2 bond is concomitant with a small (up to 4 cm⁻¹) increase of the C−X stretching frequency (blue-shift). For the enflurane−OCH2 complex, the infrared intensity of the corresponding mode decreases by −15 km mol⁻¹. In other complexes the decrease of the IR intensity is smaller (from 0 to −5 km mol⁻¹).

Recently, van der Veken and coworkers⁵⁷ have confirmed experimentally the small (+1.7 cm⁻¹) blue-shift of the υ(C−Cl) stretching frequency in the trifluorochloromethyl dimethyl ether complex containing the C−Cl−O halogen bond. The MP2/6-311+G(d,p) calculated contraction of the C−Cl bond was −0.006 Å.

As shown in Table 1, upon complexation, the C3−O4 bond is elongated by 0.001 Å, in all complexes. This is accompanied by a small (up to 2 cm⁻¹) red-shift of the υ(C3−O4) stretching frequency and the decrease of the infrared intensity of this mode, by about −11 km mol⁻¹ in all complexes, except for the halothane−formaldehyde (A) complex, where the IR intensity decreases only by −1 km mol⁻¹ (Table 2).

The sum of the van der Waals radii of the chlorine−oxygen and the bromine−oxygen atoms is 3.27 and 3.37 Å, respectively.⁵⁸ As follows from Table 1, in the chloroform and halothane (A) and (B) complexes, the intermolecular X2−C−O distances are smaller than the corresponding sum of the vdW radii.

In the enflurane−OCH2 and isoflurane−OCH2 complexes the Cl2−O distance is equal to (or is slightly larger than) the sum of the vdW radii. Despite this fact, the theoretical methods have predicted that these complexes are stable.

Auffinger et al.⁴⁵ on the basis of the Protein Data Basis (PDB) survey have reported that the average Br−O distance (3.15 Å) is longer, by 0.09 Å, than the average Cl−O distance. However, in the halothane−formaldehyde (A) complex the MP2 calculated Br−O distance (3.14 Å) is shorter (by 0.06 Å) than the Cl−O distance in the (B) complex, as shown in Table 1. A similar effect was reported for the complexes of hypohalous acids with formaldehyde⁵⁹ and for the F3CCBr−OCH2 and F3CCI−OCH2 complexes.⁶⁰ On the other hand, calculations performed at the MP2/6-311+G(d,p) level for the F3CCBr and F3CCI complexes with dimethyl ether predicted the same Br−O and Cl−O atom distances (2.89 Å), whereas MP2 calculations of the halothane−dimethyl ether predicted a longer Br−O distance than Cl−O, by about 0.05 Å.⁶¹ This comparison shows that the intermolecular Br−O and Cl−O distances are different, in various systems.

The sum of the van der Waals radii of the chlorine−hydrogen and bromine−hydrogen atoms is 2.95 and 3.05 Å, respectively.⁵⁸ In the CHCl3−OCH2, CHClBrCF3−OCH2 (A), CHClBrCF3−OCH2 (B), enflurane−OCH2, isoflurane−OCH2 (A) and isoflurane−OCH2 (B) complexes, the shorter distance between the H atom of OCH2 and the halogen atom is equal: 3.29, 3.53, 3.29, 2.99, 3.91 and 3.39 Å, respectively. All these distances are larger than the corresponding sum of the vdW radii. Nevertheless, some weak secondary interactions may also occur in these complexes. Especially, in the enflurane−OCH2 complex, where the closest H−F distance is only slightly larger (0.04 Å) than the sum of the vdW radii.

In biological molecules with the halogen bond, the average C−X−O and X−O−C angles are 160°−180° and about 90°, respectively.⁴⁵ The results collected in Table 1 show that the C1−X2−O4 angles in the C−Cl−O bonded complexes are smaller than the C−Br−O angle in the halothane (A) complex.

### Table 1: Selected structural parameters of the anaesthetic−formaldehyde complexes (distances r, d, in Å, angle θ in °). Results from the MP/6-311++G(d,p) and the MP/6-311++G(d,p)/LanL2DZdp calculations

<table>
<thead>
<tr>
<th>Compound</th>
<th>r(C1−X2)</th>
<th>r(C1−O4)</th>
<th>d(X2−O4)</th>
<th>θ(C1−X2−O4)</th>
<th>θ(X2−O4−C3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform−OCH2</td>
<td>1.762</td>
<td>1.214</td>
<td>3.23</td>
<td>166.9</td>
<td>101.2</td>
</tr>
<tr>
<td>(−0.003)⁶⁷</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane−OCH2 (A)</td>
<td>1.930</td>
<td>1.214</td>
<td>3.14</td>
<td>171.1</td>
<td>110.8</td>
</tr>
<tr>
<td>(−0.001)⁶⁸</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane−OCH2 (A)⁹</td>
<td>1.934</td>
<td>1.214</td>
<td>3.13</td>
<td>171.1</td>
<td>110.6</td>
</tr>
<tr>
<td>(−0.001)⁹</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane−OCH2 (B)</td>
<td>1.758</td>
<td>1.214</td>
<td>3.20</td>
<td>164.5</td>
<td>101.8</td>
</tr>
<tr>
<td>(−0.002)⁹</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enflurane−OCH2</td>
<td>1.750</td>
<td>1.214</td>
<td>3.30</td>
<td>154.1</td>
<td>97.3</td>
</tr>
<tr>
<td>(−0.002)⁹</td>
<td></td>
<td>(+ 0.001)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Isoflurane−OCH2 (A)</td>
<td>1.764</td>
<td>1.214</td>
<td>3.27</td>
<td>160.5</td>
<td>98.3</td>
</tr>
<tr>
<td>(−0.003)⁹</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
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<tr>
<td>Isoflurane−OCH2 (B)</td>
<td>1.764</td>
<td>1.214</td>
<td>3.28</td>
<td>158.6</td>
<td>97.8</td>
</tr>
<tr>
<td>(−0.003)⁹</td>
<td></td>
<td>(+ 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁶⁷ In parentheses are shown differences between the values in the complex and in the isolated molecule. ⁶⁸ Results from the MP2 calculations with the LanL2DZdp basis set for the bromine atom and the 6-311++G(d,p) basis set for the other atoms.

### Table 2: Selected vibrational parameters of the anaesthetic−formaldehyde complexes (vibrational frequency ν, in cm⁻¹, infrared intensity I, in km mol⁻¹). Results from the MP/6-311++G(d,p) calculations

<table>
<thead>
<tr>
<th>Compound</th>
<th>ν(C1−X2)</th>
<th>I(C1−X2)</th>
<th>ν(C1−O4)</th>
<th>I(C1−O4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform−OCH2</td>
<td>588 (+4)⁷</td>
<td>1 (0)</td>
<td>1760 (−1)</td>
<td>64 (−10)</td>
</tr>
<tr>
<td>Halothane−OCH2 (A)</td>
<td>739 (+1)</td>
<td>14 (−5)</td>
<td>1759 (−2)</td>
<td>73 (−1)</td>
</tr>
<tr>
<td>Halothane−OCH2 (A)⁹</td>
<td>741 (+2)</td>
<td>13 (−5)</td>
<td>1758 (−3)</td>
<td>72 (−2)</td>
</tr>
<tr>
<td>Halothane−OCH2 (B)</td>
<td>849 (0)</td>
<td>70 (−5)</td>
<td>1760 (−1)</td>
<td>64 (−10)</td>
</tr>
<tr>
<td>Enflurane−OCH2</td>
<td>862 (+2)</td>
<td>45 (−15)</td>
<td>1759 (−2)</td>
<td>63 (−11)</td>
</tr>
<tr>
<td>Isoflurane−OCH2 (A)</td>
<td>764 (0)</td>
<td>28 (−1)</td>
<td>1760 (−1)</td>
<td>63 (−11)</td>
</tr>
<tr>
<td>Isoflurane−OCH2 (B)</td>
<td>764 (+1)</td>
<td>26 (−3)</td>
<td>1760 (−1)</td>
<td>63 (−11)</td>
</tr>
</tbody>
</table>

⁷ In parentheses are shown differences between the values in the complex and in the isolated molecule. ⁹ Results from the MP2 calculations with the LanL2DZdp basis set for the bromine atom and the 6-311++G(d,p) basis set for the other atoms.
The deviation of the C₁–X₂–O₄ angles from 180° can be attributed to the secondary weak interaction between the hydrogen atom of formaldehyde and halogen atom or atoms of the halogen donor. The biggest deviation (25.9°) of this angle has been found in the enflurane···OCH₂ complex. It should be mentioned that the H···O distance (2.97 Å) between the H atom of formaldehyde and O atom of enflurane is larger, by 0.25 Å, than the sum of the corresponding vdW radii.

The Cl₁···O₂–C₃ angles are in the range 97.3°–101.8°, and all are smaller than the Br···O₂–C₃ angle (110.8°) in the halothane (A) complex. A similar effect was reported earlier for the halomethane···formaldehyde complexes, and it was attributed to the difference in the dispersion energy in the Cl···O interaction.²³

To answer the question whether the relativistic effects are important in the halothane···formaldehyde complex (A) with the C–Br···O halogen bond, the additional MP2 calculations have been performed using the LanL2DZdp pseudopotential basis set for the bromine atom and the 6-311++G(d,p) basis set for the other atoms. A similar method was used by Michelsen et al.⁶⁴ The results are presented in Tables 1 and 2. As follows from Table 1 the use of the LanL2DZdp basis set for Br leads to an elongation of the C₁–Br bond by 0.004 Å, and a shortening of the Br···O₄ distance by 0.01 Å. The stabilization energies of this complex calculated at the MP2/6-311++G(d,p) and MP2/6-311++G(3,p)/LanL2DZdp levels are 2.00 and 2.03 kcal mol⁻¹, respectively. Thus, the difference between the binding energies is only 1.5%, which indicates that the relativistic effects are negligible for the halothane···formaldehyde complex with the C–Br···O bond. However, it should be mentioned that, in the case of the H₃CBr···OCH₂ complex, the relativistic effects evaluated at different levels of theory were slightly higher, the MP2 interaction energy of this complex calculated with the aug-cc-pVTZ-PP basis set on the bromine atom and aug-cc-pVTZ on all other atoms was larger by 4.2% than that calculated using the aug-cc-pVTZ on all atoms.²³ We have performed calculations on the same level of theory for the halothane···formaldehyde complex (A) and the results are very similar, the difference between the two interaction energies is 4.5%. Thus, the relativistic effects in the investigated system are rather small.

In order to make the comparison between formaldehyde and formamide as the σ-hole acceptors, the chloroform···formamide complex has also been studied (Fig. 3).

In the latter, the shortening of the C₁–Cl₂ bond caused by complexation (−0.005 Å) is larger than that in the chloroform···formaldehyde complex (−0.003 Å). Contraction of the C₁–Cl₂ bond is concomitant with an increase of the C–Cl stretching frequency (+4 cm⁻¹). The infrared intensity of the corresponding mode increases by +7 km mol⁻¹. The Cl₂···O₄ distance in the chloroform···OCH₃H₂ complex is shorter (by 0.08 Å) than in the chloroform···formaldehyde complex. The C₁–Cl₂···O₄ angle (170.2°) is larger by 3.3° despite the fact that the shorter distance between the H atom of OCH₃H₂ and the halogen atom (3.29 Å) is the same as that in the formaldehyde complex.

### 3.2 NBO analysis

The selected NBO data are listed in Table 3. As follows from this table, the halogen atom shows the largest change of the atomic charge, upon complexation. The charge on X₂ increases in the range between 0.012 and 0.018 e (halothane···OCH₂ (A) complex).

Examination of occupancies of the bonding σ(C₁–X₂) and antibonding σ*(C₁–X₂) orbitals indicates that the change in the electron density on these orbitals is negligible (smaller than ±0.002 e), upon complexation.

### Table 3 Charges (q in e) on selected atoms, charge transfer (CT in e) in anaesthetic···formaldehyde complexes calculated at the MP2/6-311++G(d,p) level

<table>
<thead>
<tr>
<th></th>
<th>C₁</th>
<th>X₂°</th>
<th>O₄</th>
<th>C₃</th>
<th>CT^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform···OCH₂</td>
<td>−0.310</td>
<td>0.052</td>
<td>−0.469</td>
<td>0.287</td>
<td>0.002</td>
</tr>
<tr>
<td>Halothane···OCH₂ (A)</td>
<td>−0.402</td>
<td>0.131</td>
<td>−0.473</td>
<td>0.290</td>
<td>0.007</td>
</tr>
<tr>
<td>Halothane···OCH₂ (B)</td>
<td>−0.008</td>
<td>0.018</td>
<td>−0.009</td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td>Enflurane···OCH₂</td>
<td>−0.397</td>
<td>0.065</td>
<td>−0.470</td>
<td>0.287</td>
<td>0.002</td>
</tr>
<tr>
<td>Isoflurane···OCH₂ (A)</td>
<td>−0.007</td>
<td>0.036</td>
<td>−0.472</td>
<td>0.286</td>
<td>0.002</td>
</tr>
<tr>
<td>Isoflurane···OCH₂ (B)</td>
<td>−0.006</td>
<td>0.012</td>
<td>−0.005</td>
<td>0.000</td>
<td>0.002</td>
</tr>
</tbody>
</table>

ₐ X₂ means the bromine atom in the halothane···OCH₂ (A) complex and chlorine atoms in all other complexes. ᵇ Charge transfer from formaldehyde to a σ-hole donor. ° In parentheses are shown the changes of the charges caused by complexation, calculated as differences between the values in the complex and in the isolated molecule.
As follows from the last column of Table 3, the charge transfer (CT) from formaldehyde to halothane (A complex) is equal to 0.007 e, while in the remaining complexes it is about twice smaller. It is worth to mention that the values of CT are similar to those found for weak hydrogen bonds.\(^\text{62}\) The NBO analysis has been performed also for the chloroform · · · formamide complex. These results have revealed that the change of the charge on the chlorine atom caused by complexation equals +0.023 e, which is much larger than that in the chloroform · · · formaldehyde complex (+0.013 e).\(^\text{63}\) This fact can be explained as a consequence of different charges on the O4 atoms in the σ-hole acceptors. The charges on the oxygen atoms in formaldehyde and formamide are −0.464 and −0.564 e, respectively. The larger the electron density (ED) on the oxygen atom, the larger the decrease of ED on the chlorine atom.

3.3 Contraction of the C–X2 bond

Recently, it has been suggested that in the halogen bonded complexes with weak hyperconjugative interaction, the electrostatic interaction is responsible for contraction of the Y–X bond (where Y = C, N, Si and X = Cl, Br).\(^\text{63}\) Thus, we have also investigated the role of electrostatic and polarization effects in chloroform and its complex with formaldehyde. The Merz–Kollman charges of formaldehyde atoms (obtained from the complex) were placed at the positions of the respective atoms. In this treatment, the geometry changes were caused by both electrostatic and polarization interactions between chloroform and the inhomogenous electric field. According to these calculations, the C1–Cl2 bond of chloroform was only slightly elongated (by 0.0002 Å) upon the electric field of the proton acceptor. In addition, geometry optimization of the isolated halogen donors was performed in the uniform electric field parallel to the C1–Cl2 bond. These results have shown that in the homogenous electric field (in the range from 0.004 to 0.024 au) the C1–Cl2 bond length is elongated. This excludes the electrostatic interaction as being responsible for the contraction of the C1–Cl2 bond length.

To examine the Hermansson\(^\text{64}\) and the Qian/Krimm\(^\text{65}\) models for predicting contraction or elongation of the C1–X2 bond (blue-shifting or red-shifting complexes, respectively) we calculated the derivatives of the permanent dipole moments (\(\partial \mu / \partial R_{\text{C1–X2}}\)) and their directions for each anaesthetic, see Table 4. According to these models the change in the frequency of the C1–X2 bond should be related to the magnitudes and directions of the derivatives \(\partial \mu / \partial R_{\text{C1–X2}}\), and \(\partial \mu^{\text{ind}}/ \partial R_{\text{C1–X2}}\), where \(\mu^{\text{ind}}\) is the dipole moment induced by the electric field of the σ-hole acceptor. Since \(\partial \mu^{\text{ind}}/ \partial R_{\text{C1–X2}}\) is in the direction of the electric field, it always supports an elongation of the C1–X2 bond.\(^\text{66}\)

As is seen from Table 4 only in the case of halothane (X2 = Br) the \(\partial \mu^{\text{ind}}/ \partial R_{\text{C1–X2}}\) has a negative value. This indicates that the negative dipole gradient for the C1–X2 bond is not the necessary condition for the blue-shift of the C1–X2 stretching vibration.

In the last column of Table 4 the values of angle between the dipole moment and the bond from C1 to X2 are collected. An angle of 180° correlates with a contraction of this bond (blue-shifting complexes), while an angle of 0° indicates possibility of an elongation of the bond (red-shifting complexes).\(^\text{66}\)

As follows from this table only in the case of enfurane the value of this angle (150°) is nearest to 180°. In the other molecules the dipole derivatives are more or less perpendicular to the uniform electric field. Thus, it is impossible to derive the definite conclusions regarding the nature of contraction of the C1–X2 bond on the basis of these results.

In the case of the blue-shifted hydrogen bonded complexes Schlegel\(^\text{67}\) suggested that the Pauli repulsion between two fragments is responsible for the contraction of the X–H bond. Now, the question arises: can the analogous Pauli repulsion (the exchange overlap) effect explain the changes of the C–X bond length in the investigated complexes?

The halogen atom has three electron pairs which form a belt of negative electrostatic potential around the central part of this atom, leaving the outermost region positive (σ-hole).\(^\text{17,18}\) The oxygen atom of formaldehyde has two lone pair orbitals LP(1)O4 and LP(2)O4. The LP(2)O4 orbital is involved in the formation of the halogen bond, and it overlaps with the σ*(C1X2) orbital of the investigated anaesthetic. This orbital interacts with the halogen atom through the σ-hole. Simultaneously, electrons of the LP(1)O4 orbital can repulse the electron pairs on the halogen atom. In our opinion, this repulsion is responsible for pushing the halogen atom towards the carbon atom, which makes the C1–X2 bond shorter.

Fig. 4 illustrates the contours of the selected orbital amplitudes in the plane passing through the C1, C2 and O4 atoms, in the CHCl3 · · · OCH32 complex. The overlap of LP(2)O4 with the σ*(C1Cl2) orbitals is shown in Fig. 4A, while the overlap of LP(1)O4 with LP(1)Cl2 and overlap of LP(1)O4 with LP(2)Cl2 are depicted in Fig. 4B and C, respectively. It should be mentioned that the contour of the third electron pair orbital of the Cl atom (LP(3)Cl2) is not seen in the selected plane.

If the suggested idea of repulsion is responsible for this effect, then in the case of a halogen acceptor with only one electron pair (for instance the N atom), the contraction of the C–X bond should be smaller (in comparison to the O atom acting as the halogen acceptor) or elongation of this bond should be observed.

In the C–X · · · O halogen bonded complexes of F3C–X with dimethyl ether, the C–X bonds (X = Cl, Br, I) were contracted by −0.005, −0.006 and −0.004 Å, respectively. On the other hand, in the C–X · · · N halogen bonded complexes of F3C–X with trimethylamine, the C–X bonds (X = Br, I) were elongated by 0.005 and 0.015 Å, respectively, or negligibly contracted (by −0.001 Å for X = Cl).\(^\text{60,68}\) Analogous results

| Table 4: Derivatives of the permanent dipole moments of anaesthetics \((\partial \mu/ \partial R_{\text{C1–X2}})\) in D Å\(^{-1}\) and the angle between the dipole moment and the bond from C1 to X2 (angles in °). Calculations performed at the MP2/6-311++G(d,p) level |
|----------------|-----------|
| Anaesthetic \((X_2 = \text{Cl})\) | \((\partial \mu/ \partial R_{\text{C1–X2}})\) | Angle |
| Chloroform | 0.30 | 108 |
| Halothane \((X_2 = \text{Br})\) | −0.35 | 84 |
| Halothane \((X_2 = \text{Cl})\) | 0.02 | 93 |
| Enflurane \((X_2 = \text{Cl})\) | 2.12 | 150 |
| Isoflurane \((X_2 = \text{Cl})\) | 1.13 | 106 |

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energy is larger, by about 31%, than that in the halothane···OCH_{2} (B) complex (C–Cl···O bond), as revealed by the CCSD(T)/CBS calculations. A similar effect was reported for the H_{2}CBr···OCH_{2} and H_{2}CCl···OCH_{2} complexes, calculated at the same level of theory (CCSD(T)/CBS), the former complex had a stronger binding energy (by about 32%) than the latter.23 Moreover, for two halothane···dimethyl ether complexes, that with the C–Br···O bond had a larger interaction energy (−3.82 kcal mol\(^{-1}\)) than the other, with the C–Cl···O bond (−2.58 kcal mol\(^{-1}\)).61

The CCSD(T) correction terms (calculated as differences between ΔE_{CCSD(T)/CBS} and ΔE_{HF/CBS}) are about 60–70% of the total interaction energies. This indicates that dispersion is very important in the formation of these complexes.

For the chloroform···formamide complex the calculated CCSD(T)/CBS, MP2/CBS and HF/CBS binding energies are −3.42, −3.48 and −1.13 kcal mol\(^{-1}\), respectively. Thus, the chloroform···OCHNH_{2} complex is more stable than chloroform···OCH_{2} by ~0.53 kcal mol\(^{-1}\).

It was shown that the positive surface potential maxima \(V_{s,max}\) correlate with the interaction energies, in the bromo-benzene and bromopyridine complexes with acetone.24 To check this idea, the positive sigma hole potentials for isolated anaesthetics have been calculated. The most positive values of \(V_{s,max}\) on the chlorine and bromine atoms in anaesthetics investigated are listed in Table 6.

For the chlorine atoms, the values of \(V_{s,max}\) range from 8.8 kcal mol\(^{-1}\) (isoflurane) to 14.3 kcal mol\(^{-1}\) (halothane) while for the bromine atom in halothane \(V_{s,max}\) is 20.8 kcal mol\(^{-1}\). Trogdon et al.9 calculated the \(V_{s,max}\) values on the chlorine and bromine atoms in the same anaesthetics at the HF/6-31* level of theory. They obtained slightly larger values: 14.5, 22.3, 15.3, 13.0, 14.1 kcal mol\(^{-1}\) for chloroform, halothane (Br), halothane (Cl), enfurane and isoflurane, respectively.

In the series of anaesthetics investigated in this work we have found the linear relationship between the interaction energies ΔE_{CCSD(T)/CBS} and the \(V_{s,max}\) with a correlation coefficient of 0.77. A rather poor correlation clearly indicates that the electrostatic term is not the dominant one and the dispersion and polarization energy terms contribute to a stabilization of the halogen bond as well.

### 3.5 Decomposition of interaction energies

The DFT symmetry adapted perturbation theory (DFT-SAPT) analysis has been performed at the PBE0/aug-cc-pVTZ level of theory. The results are collected in Table 7. The DFT-SAPT interaction energies vary between −2.58 and −3.92 kcal mol\(^{-1}\). In all Cl···O–H halogen bonded complexes considered in this

### Table 6

| \(V_{s,max}\) (in kcal mol\(^{-1}\)) on X_{2} (X_{2} = Cl or Br) atoms for isolated anaesthetics calculated at the B3PW91/6-31Gi(d,p) level |
|---|---|---|---|---|
| Chloroform (X_{2} = Cl) | 13.8 |
| Halothane (X_{2} = Br) | 20.8 |
| Halothane (X_{2} = Cl) | 14.3 |
| Enfuran (X_{2} = Cl) | 11.1 |
| Isoflurane (X_{2} = Cl) | 8.8 |
work, the dispersion $E_D^{(2)}$ energy is the dominant attraction component representing about 50% of the total attraction forces, while the electrostatic $E_{el}^{(1)}$ forces account for about 40–45% of the total energy. In the Br–O halogen bonded complex of halothane (A), $E_D^{(1)}$ contributes 51%, while $E_D^{(2)}$ contributes 38% to the total energy. Similar results were obtained for the halomethane–formaldehyde complexes. In the chloroform–formamide complex, electrostatic and dispersion energies contribute about 45% each to the total energy. For all complexes investigated, the repulsive exchange energy $E_{ex}^{(1)}$ overcompensates $E_{el}^{(1)}$, thus the first-order energies $E^{(1)}$ are repulsive by less than 0.70 kcal mol$^{-1}$. The magnitude of the repulsive exchange energy supports the conclusion that the Pauli repulsion (the exchange overlap) effect is responsible for the contraction of the C–X bond in the anaesthetics upon complexation.

The contribution of the induction $E_i^{(2)}$ energy to the total attraction energy is about 5%. These results show that the dispersion and electrostatic contributions cover about 95% of the total attraction forces, in these complexes.

### 3.6 Comparison of the halogen bond and hydrogen bond

Both types of the intermolecular interactions share several characteristics such as strength or the hyperconjugation between antibonding orbital of the C–X bond (X = Cl, Br) and the electron pair of the oxygen atom. In this work we would like to point out the different mechanisms responsible for the contraction of the C–H bond (in the blue-shifted hydrogen bonded complexes) and the C–X bond (in the complexes considered in this work). In both cases the oxygen atom is the acceptor for the H or X atoms. In the former complexes the electrostatic interaction plays the crucial role, while in the latter complexes the repulsion between the electron pairs of the oxygen and halogen atoms is the driving force. In both cases the contraction of the C–H or C–X bonds is accompanied by an increase of the C–H or C–X stretching frequencies (blue-shift).

### 4. Conclusions

In this work the structures and binding energies of the halogen bonded complexes of anaesthetics (chloroform, halothane, enflurane and isoflurane) with formaldehyde were studied using ab initio MP2 and CCSD(T) methods. The understanding of the halogen bond interaction between anaesthetics and amino acids is important for elucidation of their mechanism of action, in biological systems. Thus, the complexes investigated in this work can serve as the models for such studies. The most important conclusions are the following:

1. All anaesthetics studied in this work make stable complexes with formaldehyde through the Cl–O halogen bonding. In addition, halothane also forms the Br–O halogen bonded complex (B). According to the MP2 method, the halothane–OCH$_2$ complex with the C–Br–O halogen bond is more stable, by 0.44 kcal mol$^{-1}$, than the other one. In the case of the isoflurane–OCH$_2$ complex, the MP2 calculations have revealed the presence of two structural isomers, which differ in energy by 0.16 kcal mol$^{-1}$.

2. Binding energies calculated by the CCSD(T) complete basis set (CBS) limit method for six halogen bonded anaesthetic–formaldehyde complexes vary between −2.83 and −4.21 kcal mol$^{-1}$. The largest $\Delta E_{CCSD(T):CBS}$ has been found for the C–Br–O halogen bonded halothane–OCH$_2$ (A) complex, while the smallest binding energy has been obtained for the isoflurane–OCH$_2$ (B) complex.

3. The C–X bond lengths (where X = Cl, Br) are contracted upon complexation. It is suggested that the main reason for contraction of the C–X bond is a repulsion between the lone electron pair orbitals (the exchange overlap) of the oxygen and halogen atoms.

4. In the chloroform and two halothane complexes with formaldehyde, the intermolecular (X–O) distance is smaller than the sum of the corresponding van der Waals radii. In the enflurane–OCH$_2$ and isoflurane–OCH$_2$ complexes the intermolecular distance is equal to or slightly longer than the sum of the corresponding vdW radii. However, all the calculations performed in this work predict these complexes to be stable.

5. The DFT-SAPT results show that the dispersion and electrostatic contributions cover about 95% of the total attraction forces, in these complexes. In the Cl–O halogen bonded complexes, the dispersion is the dominant attraction component representing about 50% of the total attraction forces, while the electrostatic forces account for about 40–45% of the total energy. In the Br–O halogen bonded complex of halothane, the electrostatic and dispersion terms contribute 51% and 38%, respectively, to the total attraction forces.

6. According to the DFT-SAPT results for all complexes investigated, the repulsive exchange energy overcompensates the electrostatic one. This supports our conclusion that the Pauli repulsion (the exchange overlap) effect is responsible for...
the contraction of the C-X bond in the anaesthetics upon complexation.

(7) Calculations performed for the chloroform - formamide and chloroform - formaldehyde complexes at the CCSD(T)/CBS level of theory have revealed that the former is more stable by \(-0.53\) kcal mol\(^{-1}\).

Acknowledgements

The authors are indebted to Wroclaw University of Technology for financial support, Grant No. 344113. The generous computer time from the Poznan Supercomputer and Networking Center as well as Wroclaw Supercomputer and Networking Center is acknowledged. This work was a part of the research project No. Z40550506 of the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic and it was also supported by Grants No. LC512 and MSM6198959216 from the Ministry of Education, Youth and Sports of the Czech Republic. The support of Praemium Academiae, Academy of Sciences of the Czech Republic, awarded to PH in 2007 is also acknowledged.

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