

A theoretical investigation on the conformation and the interaction of CHF₂OCF₂CHF₂ (desflurane II) with one water molecule

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Abstract The conformation and the interaction of CHF₂OCF₂CHF₂ (desflurane II) with one water molecule is investigated theoretically using the ab initio MP2/aug-cc-pvdz and DFT-based M062X/6-311++G(d,p) methods. The calculations include the optimized geometries, the harmonic frequencies of relevant vibrational modes along with a natural bond orbital (NBO) analysis including the NBO charges, the hybridization of the C atom and the intra- and intermolecular hyperconjugation energies. In the two most stable conformers, the CH bond of the F₂HCO- group occupies the *gauche* position. The hyperconjugation energies are about the same for both conformers and the conformational preference depends on the interaction between the non-bonded F and H atoms. The deprotonation enthalpies of the CH bonds are about the same for both conformers, the proton affinity of the less stable conformer being 3 kcal mol⁻¹ higher. Both conformers of desflurane II interact with water forming cyclic complexes characterized by CH...O and OH...F hydrogen bonds. The binding energies are moderate, ranging from -2.4 to -3.2 kcal mol⁻¹ at the MP2 level. The origin of the blue shifts of the $\nu(\text{CH})$ vibrations is analyzed. In three of the complexes, the water molecule acts as an electron donor. Interestingly, in these cases a charge transfer is also directed to the non bonded OH group of the water molecule. This effect seems to be a property of polyfluorinated ethers.

Keywords CHF₂OCF₂CHF₂ · Frequency shift · Hydrogen bonding · M062X · MP2 · NBO analysis · Water

Introduction

Halogenated methyl ethers or methyl ethyl ethers such as desflurane, enflurane, isoflurane, sevoflurane have been known for many years to possess anaesthetic properties [1–8]. The significant role of hydrogen bonding in anaesthetic properties of these molecules has been studied in many recent works [9–16]. The study of fluorinated ethers has drawn more attention because of their less toxicity as compared to their chlorinated counterparts. Furthermore, hydrofluoroethers (HFEs) are considered to be a third generation replacement for the chlorofluorocarbons (CFCs) because of their shorter lifetime in the atmosphere resulting from the reaction with OH radical. Further, they do not possess ozone depletion potential. The kinetics and mechanism of the reactions between HFEs and OH radical have been studied in several recent works [17–24]. The formation of the hydrogen bonds in the pre- and post-reaction complexes plays an important role in these reactions. Indeed, HFEs possess several CH bonds which can act as proton donors and one O which can potentially act as a proton acceptor. The interaction of enflurane (CHFClOCF₂CHF₂) [25] and desflurane (CHF₂OCHF₂CF₃) [26] with one water molecule has been investigated in recent works. In the present work, the conformation and hydrogen bond ability of CHF₂OCF₂CHF₂, an isomer of desflurane (designated as Desflurane II) are discussed by using quantum chemical methods. As far as we know, no experimental or theoretical data are available for this molecule.

The arrangement of the present work is as follows. In the first part, the geometrical properties and acidity and basicity of the two most stable conformers of CHF₂OCF₂CHF₂ are discussed. In the second part of our work, the interaction of CHF₂OCF₂CHF₂ with one water molecule is discussed. The

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binding energies of the complexes are calculated. The results are supported by NBO data (hybridization, delocalization and orbital occupancies) in the isolated molecules as well as in the complexes. Special attention is paid to the variation of the parameters in the complexed H₂O molecule.

Computational methodology

The geometries of isolated CHF₂OCF₂CHF₂ and their complexes with one water molecule have been optimized using the MP2/aug-cc-pvdz and the DFT-based M062X [27] method with 6-311++G(d,p) basis set. The M062X functional is designed to obtain reliable results for hydrogen bonding and non-covalent interactions. The harmonic frequencies have been calculated using the same method and the same basis set. The natural bond orbital (NBO) population scheme [28] was used in order to discuss important parameters such as charges on individual atom, hybridization, orbital occupancies, inter and intramolecular hyperconjugation energies. The NBO analysis was carried out using M062X/6-311++G(d,p) method. The hydrogen bonding interaction energies of the complexes were calculated by using the usual definition [29] where the energies of the isolated molecules E_A and E_B are subtracted from the total energy E_{AB} of the complex

$$E_{\text{HB}} = E_{\text{AB}} - E_{\text{A}} - E_{\text{B}} \quad (1)$$

In this definition the hydrogen bonding energy is implicitly assumed to be equal to the total interaction energy between the two molecules forming the H-bond. It should be mentioned that empirical formula based on shift in stretching frequency of the proton donor bond or value of local potential energy at the bond critical point has also been used to estimate the strength of the H-bonding energy [30, 31]. The hydrogen bond energies include the zero point energy (ZPE) and the basis set superposition energy (BSSE) corrections computed by the counterpoise method [32]. The proton affinity (PA) of the O atom and the deprotonation enthalpy of the CH bonds (DPE) of desflurane II were calculated assuming the standard conditions in the gas phase reaction. The whole set of calculations were carried out using Gaussian 09 suite of program [33]. The

ultrafine grid was used for all DFT calculations. The M062X results are mainly discussed here unless mentioned otherwise.

Results and discussion

Conformation of CHF₂OCF₂CHF₂

Various possible conformers of CHF₂OCF₂CHF₂ were optimized. The structures of the two most stable conformers **SC1** and **SC2** are shown in Fig. 1 and the optimized parameters are listed in Table 1. The energies of other conformers are more than 1.2 kcal mol⁻¹ higher than the **SC1** conformer indicating that the **SC1** and **SC2** conformers are largely predominant at 298 K. The two conformers differ mainly in the orientation of the C4-H10 bond relative to the COCC framework. The dihedral angle O2C3C4H10 is -58° for **SC1** and 180° for **SC2**, whereas the dihedral angle H5C1O2C3 is almost the same for both conformers (25° in **SC1** and 26° in **SC2**). In the two structures, the C1H5 bond is in a *gauche* position as in enflurane [34, 35]. This is in contrast with desflurane where the CF bonds are in *gauche* position [26]. Let us briefly notice that the conformation of several fluorinated dimethyl ethers has been analyzed and it has been shown that the CF bonds adopt the *gauche* conformation owing to the greater σ*(CF) acceptability as compared with the σ*(CH) one [36, 37]. In the present case, however, the **SC1** conformer is slightly more stable, by 0.37 kcal mol⁻¹, than the **SC2** conformer. The energy difference is only 0.17 kcal mol⁻¹ at the MP2 level. The interconversion between the two conformers is related to the torsional motion about the C-C bond of the ethyl group. Therefore, it is important to check from the torsional barrier height and the ZPE value corresponding to the torsional vibration whether these two conformers are dynamically stable [38]. The barrier height for torsional motion about the C-C bond is found to be 3.6 kcal mol⁻¹ at the M062X level whereas the ZPE value for the torsional vibration is only 0.1 kcal mol⁻¹, indicating that the two conformers are dynamically stable. This is also the case of enflurane where the energy differences between the conformers are very small and depend on the level of calculations [34, 35]. In recent works, the conformational preference of isoflurane (CHF₂OCHClCF₃) [39] and desflurane

Fig. 1 Optimized structures of the two conformers of CHF₂OCF₂CHF₂ (desflurane II) as obtained from M062X calculations. The values in parentheses correspond to the MP2 results. Bond lengths and angles are in Å and degrees, respectively

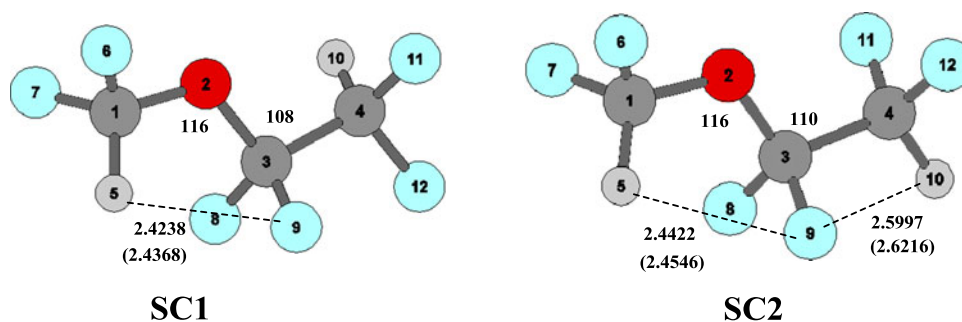


Table 1 Relevant parameters in the SC1 and SC2 conformers of CHF₂OCF₂CHF₂ (distances in Å, angles in degrees, dipole moment in D, vibrational frequencies in cm⁻¹). In parenthesis are the data calculated at the MP2/aug-cc-pvdz level

	SC1	SC2
r(C1H5)	1.0900 (1.0964)	1.0902 (1.0967)
r(O2C3)	1.3618 (1.3744)	1.3551 (1.3667)
r(C1F7)	1.3404 (1.3607)	1.3392 (1.3595)
r(C3F9)	1.3453 (1.3649)	1.3528 (1.3741)
r(C4H10)	1.0911 (1.0985)	1.0920 (1.0990)
H5C1O2C3	25	26
C1O2C3C4	177	176
O2C3C4H10	-58	180
μ	0.71	2.58
ν(C1H5)	3167	3165
ν(C4H10)	3151	3139

[26] has been investigated by theoretical methods and it has been suggested that in both cases, the most stable conformer is stabilized by larger hyperconjugation effects.

In the present systems, the delocalization effects are very large because they involve the lone pairs (LPs) of the O and all the F atoms to the different antibonds of the molecule. The second-order interaction energies involving the hyperconjugation from the O2 or F LPs to the σ*(C1H5) and σ*(C4H10) antibonds are indicated in Table 2. The sum of these energies is nearly the same for both conformers (38.4 kcal mol⁻¹). The same remarks also

Table 2 Relevant NBO parameters in the SC1 and SC2 conformers of CHF₂OCF₂CHF₂ (NBO charges in e, occupation of orbitals (e), hyperconjugation energies to σ*(C1H5) and σ*(C4H10) (in kcal mol⁻¹))

	SC1	SC2
q(C1)	0.8753	0.8761
q(O2)	-0.5867	-0.5762
q(C4)	0.5848	0.5854
q(H5)	0.1411	0.1384
q(H10)	0.1589	0.1551
σ*(C1H5)	0.0437	0.0442
σ*(C4H10)	0.0360	0.0358
%sC1(H5)	30.40	30.30
%s C4(H10)	28.40	28.05
HYPE		
LPO2→σ*(C1H5)	4.21	4.32
LPF6→σ*(C1H5)	8.38	8.45
LPF7→σ*(C1H5)	7.97	8.09
LPF9→σ*(C4H10)	0.53	
LPF11→σ*(C4H10)	8.69	8.78
LPF12→σ*(C4H10)	8.63	8.75
ΣHYPE→σ*(C1H5)	20.56	20.86
ΣHYPE→σ*(C4H10)	17.85	17.53

holds when considering the second-order interaction energies involving all the bonds which is on the order of 281 kcal mol⁻¹ for both conformers (S.I.1). Let us notice that in desflurane, the difference in delocalization energies between the two most stable conformers is equal to 4 kcal mol⁻¹ [26] which indicates a net conformational preference, in contrast with the present systems.

It can thus be concluded that when the O atom in ether bears a CF₂ group like in enflurane or in the present molecule, the CH bond in the -OCHF₂ moiety prefers to be in *gauche* position. The conformer is stabilized by a relatively short intramolecular H5...F9 bond (H5...F9=2.424 Å). A C1F7 bond in *gauche* position should lead to a repulsion between the F7 and F8 atoms. In contrast, when the O2 atom bears a C3H8F9 group as in desflurane, the C1F7 bond is in *gauche* position and molecule is stabilized by an intramolecular F7...H8 interaction. The conformational preference is larger in this case, as previously mentioned.

The proton affinity (PA) of O atom and the deprotonation enthalpy (DPE) of CH bonds of CHF₂OCF₂CHF₂ calculated for both conformers are indicated in Table 3. The basicity of the O atom is by 3 kcal mol⁻¹ larger in the SC2 conformer than in the SC1 one. The acidity of the C1H5 and C1H10 are almost the same for both conformers. But let us notice that in both conformers, the C1H5 bond is more acidic than the C4H10 one by 2–3 kcal mol⁻¹. This may result from a strong hyperconjugation between the O lone pair and the σ*(C1H5) bond which is absent for the C4H10 bond. As a result of this strong hyperconjugation, the σ*(C1H5) population is markedly larger than the σ*(C4H10) one. This is clearly indicated in Table 2 which shows that in both conformers of desflurane II, the σ*(C1H5) population is about 8 me larger than the σ*(C4H10) one.

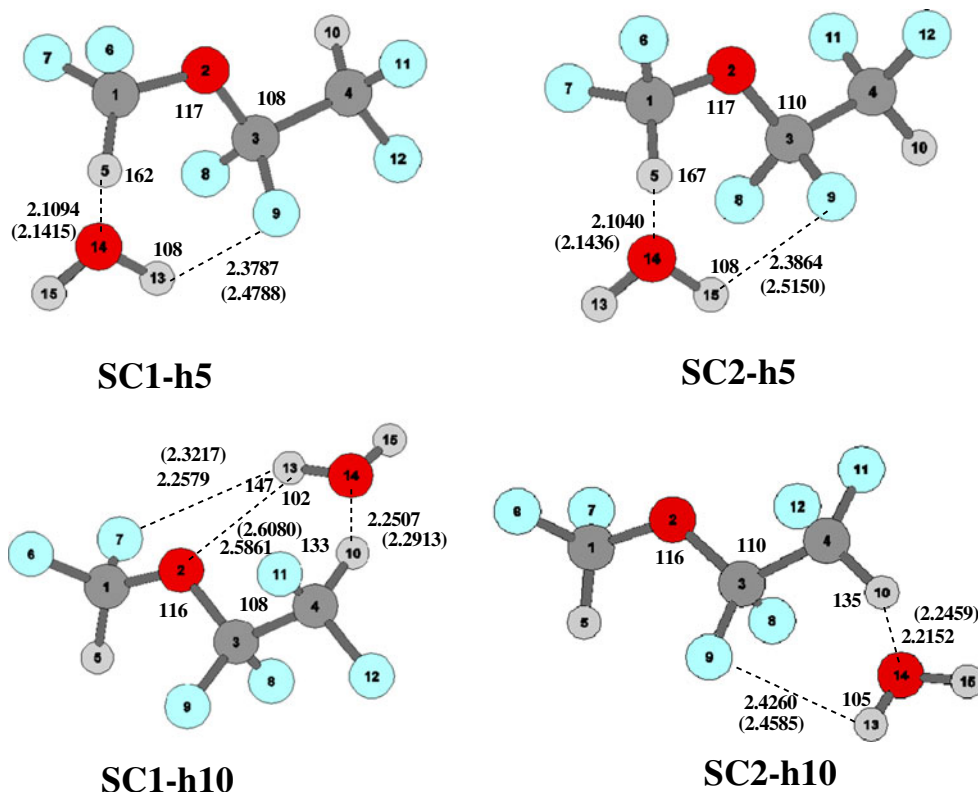
Interaction of desflurane II with one water molecule

The structure of the complexes between the SC1 and SC2 conformers of desflurane II and one water molecule is illustrated in Fig. 2. Each conformer interacts with water by forming stable SC1-h5 and SC2-h5 or SC1-h10 and SC2-h10 structures. The interaction with water results in small changes of the dihedral angles. The H5C1O2C3 angle is reduced by 4° and the C1O2C3C4 angle is reduced by 6° in the SC1-h10 complex. These variations will not be considered hereafter.

Table 3 Proton affinity (PA) of the O atom and deprotonation enthalpy (DPE) of the CH bonds in the SC1 and SC2 conformers of CHF₂OCF₂CHF₂ (in kcal mol⁻¹)

	SC1	SC2
PA	146.5	149.3
DPE (C1H5)	362.7	363.2
DPE (C4H10)	365.7	365.2

Fig. 2 Optimized structures of the four hydrogen bonded complexes of the two conformers of desflurane II with H₂O as obtained from M062X calculations. The values in parentheses correspond to the MP2 results. Bond lengths and angles are in Å and degrees, respectively



Desflurane II and water molecule primarily interact by forming C1H5...O or C4H10...O hydrogen bond, the corresponding intermolecular distances ranging from 2.104 to 2.251 Å (M062X level). The complexes are also stabilized by secondary interaction between the F9 or F7 atoms and one of the OH bonds of water. This is indicated by the relatively weak H...F distances ranging between 2.26 and 2.59 Å. A weak charge transfer between the LPs of the F atoms and the water moiety also indicates this interaction. In the case of the **SC1-h10** system, we have also noticed a weak charge transfer from the O2 atom to the water molecule. This is the only complex where the O2 atom of desflurane II participates to the interaction. This will be discussed more in detail in the last section dealing with the NBO analysis.

The hydrogen bond energies reported in Table 4 are moderate and range between -3.4 and -4.7 kcal mol⁻¹ (M062X/6-311++G(d,p) level). The interaction energy is the largest for the **SC1-h10** hydrogen bonded system and this may result from the multiple interactions as previously outlined.

The interaction of desflurane II with one water molecule results in a significant variation of several intramolecular distances. When the F atom of a CF bond is involved in the interaction with water, this CF bond is elongated. In the **SC1-h5**, **SC2-h5** and **SC2-h10** complexes where the F9 atom participates in the interaction with water, the C3F9 bond is elongated by 6.1, 11.1 and 6.5 mÅ, respectively. Whereas in

the **SC1-h10** complex, where the F7 atom is involved in the interaction with water, the C1F7 bond is elongated by 13.3 mÅ, the variation of the other CF bond lengths being much smaller. The variations of the other intramolecular distances are indicated in Table S.I.2 as supplementary information and will not be discussed hereafter, the present work been aimed to discuss in more detail the variation of the CH and OH distances along with the corresponding vibrational frequencies.

The CH distances and $\nu(\text{CH})$ vibrational frequencies are reported in Table 5. Let us at first notice that the interaction with water does not result in a variation of the conformation of desflurane II, the different dihedral angles remain almost

Table 4 Hydrogen bonding energies (including BSSE) for the interaction of the SC1 and SC2 conformers of desflurane II with one water molecule calculated at the M062X/6-311++G(d,p) level (in kcal mol⁻¹)

System	E_{HB}^{a}	$E_{\text{HB}}(\text{ZPE})^{\text{b}}$
SC1-h5	-5.54	-3.97 (-2.87)
SC1-h10	-6.35	-4.71 (-3.19)
SC2-h5	-5.05	-3.50 (-2.60)
SC2-h10	-5.01	-3.37 (-2.42)

^a without ZPE correction

^b The values in parentheses indicate the MP2/aug-cc-PVDZ results

Table 5 $r(\text{CH})$ distances (Å), dihedral angle (degree) and $\nu(\text{CH})$ vibrational frequencies (cm^{-1}) in the complexes between $\text{CHF}_2\text{OCF}_2\text{CHF}_2$ and one water molecule. M062X/6-311++G(d, p) calculations. Values in parentheses indicate the variations from the monomer. Variation in C-H bond length is given in mÅ

	SC1-h5	SC1-h10	SC2-h5	SC2-h10
$r(\text{C1H5})$	1.0897 (−0.3)	1.0895 (−0.5)	1.0898 (−0.4)	1.0902 (0)
$r(\text{C4H10})$	1.0909 (−0.2)	1.0891 (−2)	1.0921 (+0.1)	1.0893 (−2.7)
H5C1O2C3	23 (−2)	21 (−4)	24 (−2)	25 (−1)
C1O2C3C4	175 (−2)	171 (−6)	174 (−2)	175 (−1)
O2C3C4H10	−58 (0)	−58 (0)	180 (0)	179 (−1)
$\nu(\text{C1H5})$	3184 (+17)	3175 (+8)	3188 (+23)	3163 (−2)
$\nu(\text{C4H10})$	3148 (−3)	3181 (+30)	3138 (−1)	3192 (+53)

unchanged. The calculations show that the interaction with water induces a contraction of the CH bonds at the exception of the C4H10 bond in the SC2-h5 system which shows a small elongation. In agreement with the variation of the CH bond lengths, the shift of the $\nu(\text{C4H10})$ vibration in the SC2-h5 system is negligible and takes a maximum value of $+53 \text{ cm}^{-1}$ for the $\nu(\text{C4H10})$ vibration in the SC2-h10 system, where the contraction is the largest (2.7 mÅ). Similar shortening of CH bond length was observed for MP2 calculated data which ranges from 0.1 to 2.5 mÅ and as a result a blue shift is predicted ranging between 4 and 39 cm^{-1} . Let us note a discrepancy for the C4H10 bond in the SC1-h5 system where a small red shift of 3 cm^{-1} is predicted from M062X results despite the small contraction of 0.2 mÅ of this bond whereas MP2 calculated data shows a blue shift of 8 cm^{-1} . The variation of the CH distances and the frequency shifts of the $\nu(\text{CH})$ vibration are linearly correlated [40]. The IR intensities for the C-H stretching vibrations do not change significantly upon complex formation except for the C4H10 bond in SC1-h10 and SC2-h10 complexes, where the intensity decreases by 10 and 12 km mol^{-1} , respectively. The E_{HB} is not seen to be linearly correlated with $\Delta\nu(\text{CH})$, although such correlation has been observed in many cases [41]. This may be due to

the fact that hydrogen bonding angle varies significantly among the complexes studied here and also secondary interactions are involved in all the complexes. The bending modes of the CH bond are strongly coupled and do not reflect the strength of the interaction. It may be worthwhile to note the change in frequency for the torsional motion of the $-\text{CHF}_2$ in ethyl group about the C-C bond while going from the free molecule to the complex. In SC1-h10 and SC2-h10, where ethyl C4-H10 is bonded to H_2O , the frequency for torsional vibration increases by 6 and 12 cm^{-1} , respectively, whereas the frequency decreases by almost 5 cm^{-1} in SC1-h5 and SC2-h5 complexes.

Relevant NBO data for the CH bonds (NBO charges, $\sigma^*(\text{CH})$ occupation, hybridization status of the C atom bonded to the H, intra- and intermolecular hyperconjugation energies) are reported in Table 6. Interestingly, the negative charge on the O2 atom increases in the SC1-h5 and SC2-h5 complexes; is negligible in the SC2-h10 system but slightly decreases in the SC1-h10 system. This can be explained by the energy associated with a small charge transfer of $0.21 \text{ kcal mol}^{-1}$ taking place from the LPO2 to the $\sigma^*(\text{O14H15})$ orbital and this confirms the existence of a weak interaction between the O2 atom of desflurane II and the HO bond of water which was

Table 6 NBO data for the CH bonds in water complexes. NBO charges in e, variation of NBO charge in me, $\sigma^*(\text{CH})$ occupation in e, variation of σ^* occupation in me, ΣHYPE in kcal mol^{-1}

	SC1-h5	SC1-h10	SC2-h5	SC2-h10
q(C1)	0.8528 (−22.5)	0.8741 (−1.2)	0.8542 (−22.9)	0.8764 (+0.3)
q(H5)	0.1849 (+43.8)	0.1449 (+3.8)	0.1826 (+44.2)	0.1351 (−3.3)
q(O2)	−0.5890 (−2.3)	−0.5855 (+1.2)	−0.5787 (−2.7)	−0.5757 (+0.5)
q(C4)	0.5850 (+0.2)	0.5699 (−14.9)	0.5863 (+0.9)	0.5688 (−16.6)
q(H10)	0.1585 (−0.6)	0.1954 (+36.5)	0.1513 (−3.9)	0.1929 (+37.8)
$\sigma^*(\text{C1H5})$	0.0433 (−0.5)	0.0428 (−0.9)	0.0435 (−0.7)	0.0446 (+0.4)
$\sigma^*(\text{C4H10})$	0.0359 (−0.1)	0.0345 (−1.5)	0.0361 (+0.2)	0.0341 (−1.7)
%s C1(H5)	32.12 (+1.72)	30.57 (+0.17)	32.04 (+1.74)	30.20 (−0.1)
%s C4(H10)	28.39 (−0.01)	29.67 (+1.26)	27.95 (−0.1)	29.41 (+1.36)
$\Sigma \text{HYPE} \rightarrow \sigma^*(\text{C1H5})$	17.74 (−2.82)	20.42 (−0.14)	17.97 (−2.89)	21.79 (+0.93)
$\Sigma \text{HYPE} \rightarrow \sigma^*(\text{C4H10})$	18.29 (+0.44)	15.55 (−2.3)	17.58 (+0.05)	15.57 (−1.96)
LPO14 $\rightarrow \sigma^*(\text{C1H5})$	5.63	0	5.72	0
LPO14 $\rightarrow \sigma^*(\text{C4H10})$	0	2.46	0	2.61'

Table 7 Sum of the NBO charges on the H₂O molecule and $\sigma^*(\text{OH})$ population (me), OH distances (Å), $\nu(\text{OH})$ frequencies (cm⁻¹) and hyperconjugation energies (kcal mol⁻¹) for the complexes of CHF₂OCF₂CHF₂ with water. The variations of the OH bond length are indicated in mÅ.^a

	SC1-h5	SC1-h10	SC2-h5	SC2-h10
$\Sigma q(\text{H}_2\text{O})$	+6.1	-0.8	+6.0	+2.2
$r(\text{O14H13})$	0.9608 (+1.7)	0.9619 (+2.8)	0.9604 (+1.3)	0.9605 (+1.4)
$r(\text{O14H15})$	0.9596 (+0.5)	0.9596 (+0.5)	0.9595 (+0.4)	0.9595 (+0.4)
$\nu^{\text{asym}}(\text{OH})$	3986 (-12)	3978 (-20)	3990 (-8)	3988 (-10)
$\nu^{\text{sym}}(\text{OH})$	3881 (-11)	3875 (-17)	3885 (-7)	3883 (-9)
$\sigma^*(\text{O14H13})$	0.6	2.8	0.5	0.5
$\sigma^*(\text{O14H15})$	1.1	1.1	1.2	1.1
$\Sigma\text{HYPE} \rightarrow \sigma^*(\text{O14H13})$	0.14	1.02	0.18	0.13
$\Sigma\text{HYPE} \rightarrow \sigma^*(\text{O14H15})$	0.45	0.38	0.48	0.43

^a In isolated H₂O, $r(\text{OH})=0.9591$ Å, $\nu^{\text{asym}}(\text{OH})=3998$ cm⁻¹, $\nu^{\text{sym}}(\text{OH})=3892$ cm⁻¹ (17), $\sigma^*(\text{OH})=0$

suggested previously by the short H...O2 intermolecular distance. Let us also notice that this charge transfer takes place to the external O14H15 bond.

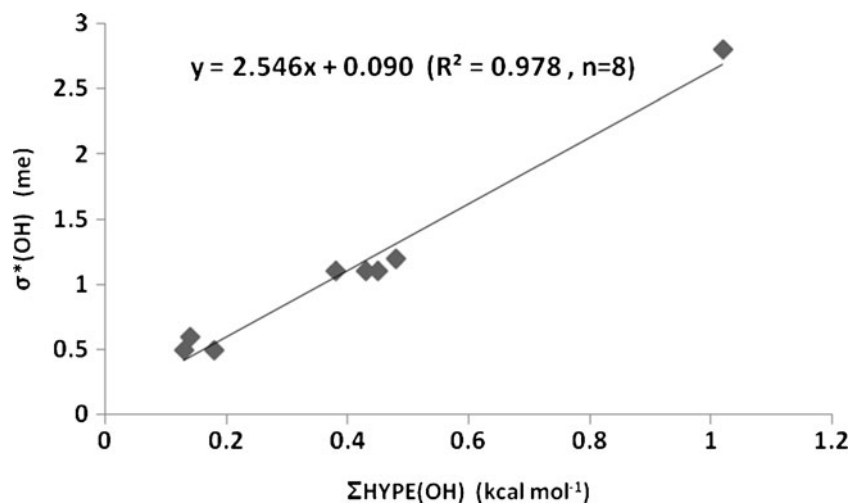
As discussed in several works [42–44], the contraction of the CH bond and the corresponding blue shift in a hydrogen-bonded system is related to the decrease of the $\sigma^*(\text{CH})$ occupation and to the increase of the %sC(H) character. For the C1H5 bonds, the decrease in $\sigma^*(\text{C1H5})$ occupation amounts to 0.5–0.9 me and the increase in %sC1(H5) character 0.17–1.74. For the C4H10 bonds, our calculations predict a decrease of $\sigma^*(\text{C4H10})$ occupation by 0.1–1.7 me and an increase in %sC4(H10) by 1.26–1.36. It should also be noticed, that the interaction with water results in a non-negligible decrease of the intramolecular hyperconjugation energies. As indicated in Table 6, the decrease of these energies is equal to 2.82–2.89 kcal mol⁻¹ for the SC1-h5 and SC2-h5 complexes and from 1.96 to 2.3 kcal mol⁻¹ for the SC1-h10 and SC2-h10 complexes. In the four complexes, the formation of the CH...O14 hydrogen bond implies a charge transfer from the LPO14 of water to the corresponding $\sigma^*(\text{CH})$ orbital. The charge transfer energies are equal to 5.63 and 5.72 kcal mol⁻¹ for the C1H5...O14 interaction and 2.46–2.61 kcal mol⁻¹ for the C4H10...O14 interaction. This indicates that the decrease of the intramolecular

hyperconjugation which results in a contraction of the CH bonds is more important than the intermolecular charge transfer which results in an elongation of the CH bonds. These effects have been discussed for other hydrogen bonds [45, 46].

Finally we would like to discuss the changes in the properties of the water molecule when it forms a complex with desflurane II. Important properties such as OH bond lengths, $\nu(\text{OH})$ stretching frequencies and NBO parameters are listed in Table 7. As in numerous systems, the interaction with water results in a moderate elongation of the OH bond which is somewhat larger for the O14H13 bond involved in the interaction than for the external O14H15 bond. The largest elongation (2.8 mÅ) is predicted for the O14H13 bond in the SC1-h10.H₂O complex.

An interesting difference among the four complexed systems is that the sum of the NBO charges ($\Sigma q\text{H}_2\text{O}$) on water clearly indicates that water acts as an electron acceptor in the SC1-h10 system and as an electron donor in the other systems. This was already suggested by the fact that the negative charge on the O2 atom of desflurane II slightly decreases in this complex. This can be further explained by the fact that the hyperconjugation energy from the F atom to the $\sigma^*(\text{O14H13})$ is larger in this system (Table 7).

Fig. 3 Plot of antibonding OH orbital population of water against total hyperconjugation energy



More intriguing is the fact that in the **SC1**-h5, **SC2**-h5 and **SC2**-h10 systems, the $\sigma^*(\text{O14H15})$ occupation of the external OH bond is larger than the $\sigma^*(\text{O14H13})$ occupation of the bonded OH group. We have tried to explain these results by considering the sum of the hyperconjugation energies to the $\sigma^*(\text{O14H13})$ and $\sigma^*(\text{O14H15})$ antibonds. It should be noticed that the $\Sigma(\text{HYPE})$ values reported in Table 7 involve only the LPs of the F atoms, but for **SC1**-h5, **SC2**-h5 and **SC2**-h10 complexed with water, some weak charge is transferred from the $\sigma(\text{C1H5})$ or $\sigma(\text{C4H1O})$ bonds. This is not the case for the **SC1**-h10 complex where, as previously mentioned, the charge transfer goes in the reverse direction.

The following correlation illustrated in Fig. 3 between $\sigma^*(\text{OH})$ occupation (me) and second-order hyperconjugation energies to the $\sigma^*(\text{OH})$ bond (kcal mol^{-1}) can be established, considering the external as well the bonded OH groups:

$$\sigma^*(\text{OH}) = 2.54 \Sigma \text{HYPE}(\text{OH}) + 0.09 (r = 0.989) \quad (2)$$

A similar correlation (slope=2.43) has been calculated recently for complexes involving polyfluorinated ethers or desflurane complexed with one water molecule [26]. The charge transfer to the external OH bond seems to be a specific property of polyfluorinated ethers complexed with one water molecule. Let us notice that although the variations of the parameters are relatively small they are systematic and reliable.

Finally, it must be mentioned that the elongation of the OH bond usually results in a decrease of the frequency of the $\nu(\text{OH})$ vibrations of H_2O along with an increase in IR intensity. This is the case for all the hydrogen bonded complexes of **SC1** and **SC2** complexed with one water molecule. The M062X results show a red-shift of 7–20 cm^{-1} for the $\nu(\text{OH})$ vibrations of H_2O due to complex formation with desflurane II. Similar type of observations were noticed with the MP2 calculated data which predicts a red shift of 6–7 cm^{-1} for both the $\nu^{\text{as}}(\text{OH})$ and $\nu^{\text{s}}(\text{OH})$ vibrations. As usual, the red-shift is seen to be correlated to the lengthening of the O-H bond of water. The IR intensity for the $\nu^{\text{s}}(\text{OH})$ increases in the range of 6–18 km mol^{-1} , whereas the same for $\nu^{\text{as}}(\text{OH})$ increases by 27–52 km mol^{-1} upon complex formation with desflurane II.

Conclusions

The present work deals with a theoretical investigation of the conformation, acidity/basicity and the interaction of desflurane II ($\text{CHF}_2\text{OCF}_2\text{CHF}_2$) with one water molecule. The most important conclusions of the work are the following:

1. The two most stable conformers of desflurane II are characterized by a *gauche* position of the CH bond of the $\text{F}_2\text{HC-O}$ group. The sum of the hyperconjugation energies involving the delocalization of the LPs of the O

and F atoms is similar for both conformers, suggesting that the conformational preference depends on interaction between the non-bonded H and F atoms.

2. The PA of the O atom is slightly larger for the less stable conformer. The DPE of the CH bonds is the same for both conformers.
3. Both conformers of desflurane II interact with water, the binding energies ranging between -3.4 and $-4.7 \text{ kcal mol}^{-1}$ at the M062X/6-311++G(d,p) level and between -2.4 and $-3.2 \text{ kcal mol}^{-1}$ at the MP2/aug-cc-pvDZ level. The structure of the complexes is cyclic and characterized by CH...O and OH...F hydrogen bonds.
4. The interaction with water results in most of the complexes, in a contraction of the CH bond and a blue shift of the corresponding $\nu(\text{CH})$ vibration. The decrease of the intramolecular hyperconjugation energies to the $\sigma^*(\text{CH})$ bond is a more important factor than the intermolecular charge transfer to this antibond.
5. In three of the complexes, water acts as an electron donor. In these complexes, the charge transfer to the $\sigma^*(\text{OH})$ bond and the corresponding $\sigma^*(\text{OH})$ occupation is larger for the external than for the bonded OH group. This unusual behavior has also been observed for desflurane and aliphatic fluorinated ethers complexed with water and seems to depend on the number of F atoms implanted on the ether derivative.

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