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The conformation equilibrium study in halothane–methyl fluoride system by the methods of IR cryospectroscopy and quantum chemistry

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IR absorption spectra of mixtures of the halothane ($C_2HBrClF_3$) and methyl fluoride (FCD_3) in liquefied krypton were obtained and analyzed. The band of the stretching vibration CH of halothane reveals noticeable high frequency shift and broadens perceptually at complex formation with methyl fluoride engaged. The complexation enthalpy formation has been evaluated in the series of temperature measurements. The *ab initio* calculations, performed with the help of GAUSSIAN 16 program, suggest the formation of several conformers, characterized by close spectroscopic parameters and complexation energy. The calculations are in line with the experimentally observed effects.

Keywords: IR spectra of cryosolutions, liquid Kr, halothane, methyl fluoride, hydrogen bond, *ab initio* calculations.

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Introduction

Having proton donor properties, a CH group of individual molecules may be involved in complex formation with a weak hydrogen bond (HB) when interacting with acceptors. In some cases, such complexes exhibit unusual spectroscopic and geometrical properties: high-frequency shift of the CH stretching band and CH bond contraction. Pronounced nonlinearity of the forming HB is also typical. Such molecules primarily include fluoroform (HCF_3) with a negative derivative of the dipole moment with respect to CH bond stretch [1–3] and chloroform ($HCCl_3$) with a positive, but close-to-zero first derivative [4,5]. The above-mentioned unusual properties disappear in interactions with strong proton acceptors, for example, with trimethylamine, transition to HB with typical spectroscopic properties takes place — low-frequency shift and increase in CH stretching band intensity [6–8]. There is reason to believe that Halothane ($C_2HBrClF_3$), an effective inhalation anesthetic, has similar properties [9–13].

This study uses infrared (IR) absorption spectra of cryosolutions in krypton and *ab initio* quantum chemical calculations to analyze the aspects of complex formation with the involvement of halothane as a CH donor and a target — methyl fluoride (FCD_3) containing so-called organic fluorine with weak proton acceptor properties. The experiments were performed with considerable methyl fluoride additives providing significant concentrations of complexes. According to the calculations, four conformers with various geometries, but close energy and spectroscopic properties, can be involved in complex formation.

1. Experimental and calculation procedure

Measurements were carried out by the cryospectroscopy method using a Fourier transform IR spectrometer (Nicolet 6700). The main measurement parameters are: interval 4000–1000 cm^{-1}, resolution 0.5 cm^{-1}, number of scans 64. Primary focus was made on the CH stretching regions of halothane and methyl fluoride as the most informative for identification of complex formation. Overlapping of these bands was avoided by using deuterated methyl fluoride (FCD_3).

An original optical cryostat was used that was cooled by metering liquid nitrogen into reservoir 1 cm length cell through a copper cold holder BaF_2 windows are sealed with metallic indium. Temperature was estimated with an accuracy of 3 °C by the saturated vapor pressure above the cryosolution. Temperature variation range is: 120–155 K. Krypton (Kr) was used as a solvent for halothane, methyl fluoride and their mixtures. Concentrations of solution components were $10^{17} - 10^{18}$ molec/cm^3. Most measurements were carried out with multiple excess of methyl fluoride.

Enthalpy of ΔH_T complex formation was estimated by the temperature measurements of integrated intensities of the absorption bands assigned to the monomers and complex. This included a correction for variation of krypton density with temperature equal to ~ 0.6 kJ/mol [14].

The calculations were performed in GAUSSIAN 16 software package Rev. A.03 [15]. The results were obtained in the second-order Møller-Plesset perturbation theory (MP2) [16] using the Pople split-valence basis set, including the polarization and diffuse functions: 6–311++G(df,pd).

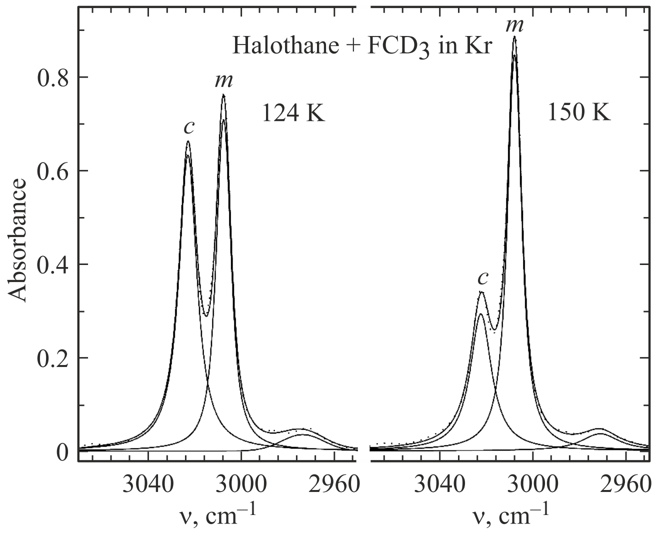

Figure 1. Infrared spectrum of the $C_2HBrClF_3-CD_3F$ mixture in liquid Kr at 124 K (left) and 150 K (right). Dashed line — measured spectrum, solid lines — simulated data. A band at $\sim 2960\,\mathrm{cm}^{-1}$ is assigned to a high-order band of CD_3F.

The method and basis set were chosen from a compromise between the repeatability of the identified spectroscopic effects and available computer resources.

Geometry, interaction energy and frequencies of normal vibration of the complex conformers were obtained considering the basis set superposition error (BSSE) using the option CP = 2 implemented in GAUSSIAN 16 [17,18].

2. Measurement data

Figure 1 shows the mixture spectra in the CH halothane stretching region with typical temperature variations. On the high-frequency side of the CH band of the halothane monomer, there is a band whose intensity decreases as the temperature rises. It may be assigned to the CH band of the halothane-methyl fluoride complex. It follows from a series of temperature and concentration measurements that the stretching band intensity ν_1(CH) of halothane increases during complex formation. Broadening of this band (from $7.6\,\mathrm{cm}^{-1}$ to $9.5\,\mathrm{cm}^{-1}$ at $T \sim 120\,\mathrm{K}$) and peak shift towards high frequencies by $\Delta\nu^{\text{c-m}} \sim +15\,\mathrm{cm}^{-1}$ are also identified. Absolute shift value slightly decreases as the liquid krypton solution temperature rises. stretching bands of CD methyl fluoride undergo a minor high-frequency shift during complex formation (they are located at $2000-2200\,\mathrm{cm}^{-1}$ and are not shown).

The temperature measurements of the integrated fundamental band intensities of the monomers and halothane-methyl fluoride complex in liquid krypton ($T \sim 120-155\,\mathrm{K}$) were used to build the Van 't Hoff plots $\ln K = -\Delta H_T/RT + \Delta S/R$, R is the universal gas constant, ΔS is the entropy change in complex formation, K is the ratio between the halothane band area in the complex and the product of monomer band areas (CD_3F and halothane). The slope of the $\ln K(1/T)$ line allows the complex formation enthalpy ΔH_T to be estimated. Such plot is illustrated in Figure 2. A value derived from the slopes of individual plots considering the change in liquid density with temperature is $(-6)-(-7)$ kJ/mol in liquid krypton. A mean value with respect to a series of temperature measurements is -6.5 ± 0.5 kJ/mol.

3. Calculation results and discussion

MP2/6−311++G(df,pd) calculations were performed in GAUSSIAN 16 software package. Several stable dimer structures were found with some important parameters summarized in Table 1, 2 and geometry shown in Figure 3. Two weakest structures (*5, 6*) may be assigned to dimers with a so-called halogen bond Hal...FCD_3. Absolute complex formation energy is a little higher than 4.2 kJ/mol, and the predicted CH stretching frequency shift of halothane is close to zero and equal to $\sim -1\,\mathrm{cm}^{-1}$. These structures don't appear in the experiment. Conformers No. *1−4* shown in Figure 3 with close complex formation energies (12.1−11.3 kJ/mol) and high-frequency CH stretching shift of halothane $(+18)-(+22)\,\mathrm{cm}^{-1}$ are of interest. These are non-linear structures stabilized by CH...F bonds and additionally by D...Hal (Hal = F, Cl) contacts.

Calculated formation energies of the most stable structures are not very much different from the measured complex formation enthalpy. Thus, it is suggested that all these conformers make a comparable contribution to the formation and additional broadening of the complex's CH band. As known, due to an increase in the moment of inertia, weak complexes may exhibit slight narrowing of the CH band followed by broadening when the dimer strength increases [19]. Relative content of the found structures

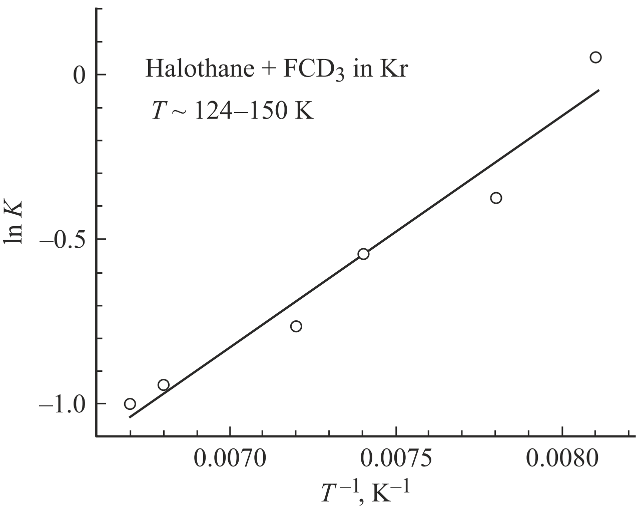

Figure 2. Van't Hoff plot $\ln K = -\Delta H_T/RT + \Delta S/R$, R is the universal gas constant, ΔS is the entropy change in complexing, K is the ratio between the halothane band are in the complex and the product of monomer band areas (CD_3F and halothane).

Table 1. Calculated (MP2/6−311++G(df,pd), CP = 2) geometrical parameters of the halothane–methyl fluoride complex conformers

Conformer	ΔE^e, kJ/mol	R(CH...F*), Å	∠(CH...F*), deg	R(CD...F*), Å	∠(CD...F*), deg
1	−12.16	2.280	146.5	2.880	123.4
2	−12.05	2.291	149.1	3.137 3.138	103.5 108.5
3	−12.0.0	2.293	144.5	3.165	94.99
4	−11.34	2.298	139.0	R(CD...Cl) 3.668	∠(CD...Cl) 103.9
5	−5.77	R(CBr...F*) 3.162	∠(CBr...F*) 170.4	R(CD...F**) 4.659	∠(CD...F**) 145.0
6	−4.22	R(CCl...F*) 3.220	∠(CCl...F*) 162.9	R(CD...F**) 3.887	∠(CD...F**) 152.8

Note: ΔE^e is the complex conformer formation energy, F^* is the methyl fluoride fluorine atom, F^{**} is the halothane fluorine atom.

Table 2. Measured and calculated (MP2/6−311++G(df,pd)) stereoscopic parameters of individual bands (c, m, Figure 1) of conformers *1*–*6* (Figure 3) of the $CD_3F...HC_2BrClF_3$ complex

Assignment	Experiment Solution in liquid Kr,$T \sim 124$ K					Calculation MP2/6−311++G(df,pd), CP = 2				
	ν^m	nu^c	$\Delta\nu^{c\text{-}m}$	$2\Gamma^m$	$2\Gamma^c$	ω^m	A^m	ω^c	A^c	$\Delta\omega^{c\text{-}m}$
$C_2HBrClF_3$	3007.5	3022.8	+15.3	7.6	9.5	3172.9	0.61			
1								3192.6	22.7	19.6
2								3194.9	22.6	+21.9
3								3192.8	24.9	+19.9
4								3190.1	24.3	+17.2
5								3171.7	3.45	−1.2
6								3171.8	3.55	−1.1
FCD_3	2084.7	2086.7	+2.0	6.8	4	2201.3	27.8			
1								2206.9	23.7	+5.6
2								2207.4	26.1	+6.1
3								2206.9	24.7	+5.6
4								2205.7	22.8	+4.4
5								2203.4	26.6	+2.1
6								2202.6	25.5	+1.3

Note: $\nu^{m,c}$ ($\omega^{m,c}$) is the wave number (ω — harmonic) of the monomer vibration band at maximum (in cm $^{-1}$), $2\Gamma^{m,c}$ is the full width at half maximum (in cm $^{-1}$), A is the absolute intensity (in km/mol).

may be found from thermodynamic considerations using the calculation results obtained in GAUSSIAN 16.

Relative concentrations of four conformers were calculated using the following equation:

$$P_i = \frac{\exp\left(\frac{\delta G_i}{kT}\right)}{\sum\limits_{i-1}^{4} \exp\left(\frac{\delta G_i}{kT}\right)}, \tag{1}$$

where δG_i is the Gibbs free energy of the i-th complex counted from the energy of a complex with the minimum electron energy ($i = 1$): $\delta G_i = \Delta G_i - \Delta G_1$.

$$\Delta G_i = \Delta E_i^{el} + \Delta H_i - \Delta ST, \quad i = 1 - 4,$$

where ΔE_i^{el} is the electron bond energy calculated considering the basis set superposition error [17,18]. At 120 K, relative concentrations of four conformers are as follows:$P_1 = 0.25$, $P_2 = 0.27$, $P_3 = 0.13$, $P_4 = 0.35$.

Resultant band of the complex simulated for such concentration ratio is shown in Figure 4. At the calculated relative concentrations and the chosen width of Lorentzian bandshapes of conformers at half maximum $2\Gamma = 4\,\text{cm}^{-1}$, the obtained band appears to be close to the experimentally

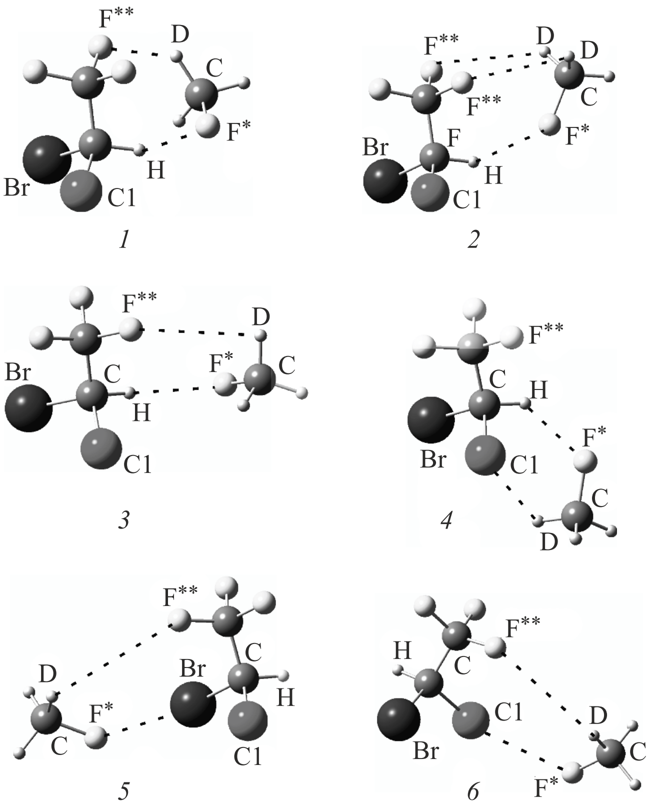

Figure 3. Equilibrium geometry of six complex conformers found in MP2(FC)/6−311++G(df,pd), CP = 2, calculations.

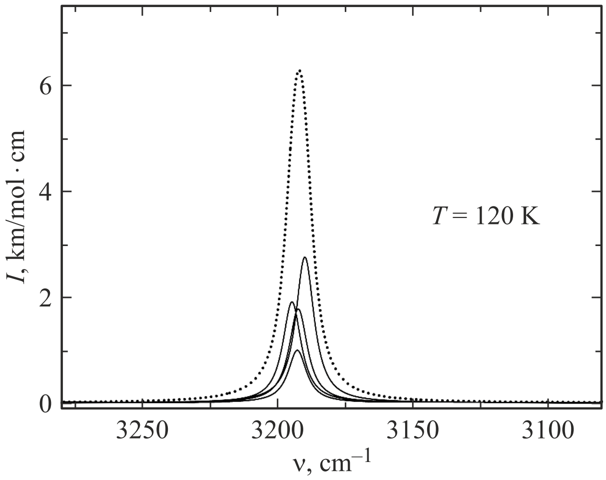

Figure 4. Reconstruction of the complex band considering four complex conformers. Solid lines — bands of four conformers with calculated relative concentrations and Lorentzian bandshapes with $2\Gamma = 4\,\mathrm{cm}^{-1}$. Dashed lines — addition result, $2\Gamma = 9.6\,\mathrm{cm}^{-1}$.

observed one and has the width $2\Gamma \sim 9.6\,\mathrm{cm}^{-1}$. A somewhat larger difference in conformer band positions is predicted for the region of frequencies corresponding to halothane CH bending vibration $\sim 1200 - 1300\,\mathrm{cm}^{-1}$

Note that changes in concentrations within the experiment temperature range ($\sim 120 - 155$ K) are not too large. Even at the maximum temperature $T \sim 155$ K, $P_1 = 0.23$, $P_2 = 0.25$, $P_3 = 0.13$, $P_4 = 0.39$.

The origin of high-frequency shift of the CH stretching band in some donors during complex formation with a hydrogen bond was considered earlier in terms of the symmetry-adapted perturbation theory (SAPT) by decomposing the donor-target interaction energy E_{int} into physically distinct components [20]. These are electrostatic, induction, dispersion and exchange components. Only the last of them always has a repulsive nature and contributes to the high-frequency shift of the donor stretching vibration. Other interactions at distances close to the equilibrium position are responsible for a larger or smaller low-frequency shift.

The band shift is estimated using the expression derived in terms of the perturbation theory:

$$\Delta\omega_1 \approx \frac{1}{2}\frac{\partial^2 E_{\mathrm{int}}}{\partial Q_1^2} - \frac{3\alpha_{111}}{\omega_1}\frac{\partial E_{\mathrm{int}}}{\partial Q_1} + \cdots, \tag{2}$$

where Q_1 is the dimensionless normal coordinate for stretching ν_1(CH). For halothane, the cubic constant $\alpha_{111} = -324\,\mathrm{cm}^{-1}$ was derived in calculation with the „anharm“ option in GAUSSIAN 16, harmonic frequency $\omega_1 = 3173\,\mathrm{cm}^{-1}$.

From the previous estimates it follows that, for the proton donors forming „blue“ hydrogen bonds with the weak acceptors, a slight high-frequency band shift $\Delta\omega_1$ of CH stretching takes place already at large distances where the energy E_{int} is substantially the electrostatic energy [20]. This means that the signs and absolute value of the first and second electrostatic energy derivatives are such that equation (2) gives a positive $\Delta\omega_1$. A reasonable estimate of the electrostatic energy at large distances may be obtained in point dipole approximation. The result generally depends on the mutual arrangement of dipole moments of the donor and acceptor. By arranging the halothane CH (A) and methyl fluoride CF (B) bonds collinearly (along the z axis), which corresponds to formation of a linear hydrogen bond, and using the expressions for the dipole-dipole interaction energy E_{dd}, first and second derivatives, the sign of frequency shift may be estimated:

$$E_{dd} = -\frac{2}{R^3}\mu_z(A)\mu_z(B), \tag{3}$$

$$\frac{\partial E_{dd}}{\partial Q_1} = -\frac{2}{R^3}\frac{\partial \mu_z(A)}{\partial Q_1}\mu_z(B), \tag{4}$$

$$\frac{\partial^2 E_{dd}}{\partial Q_1^2} = -\frac{2}{R^3}\frac{\partial^2 \mu_z(A)}{\partial Q_1^2}\mu_z(B). \tag{5}$$

According to the calculation, the dipole moment of methyl fluoride is $\mu_z(B) = 1.96$ D. The halothane dipole moment projection on the CH bond direction is $\mu_z(A) = 1.138$ D. Projections of the first and second derivatives of the halothane dipole moment on the same direction are $\mu_z'(A) = 0.016$ D, $\mu_z''(A) = -0.010$ D. When these values are applied to equations (4), (5), then the frequency shift is a small positive value $\sim +2/R^3$.

Note that the value and, in some cases, sign of thus estimated shift depend on the mutual arrangement of the donor and acceptor. As mentioned above, orientation corresponding to the start of formation of the linear HB CH...FC was chosen.

Comparison with the previous similarly obtained estimates for fluoroform, chloroform and propyne [4,20] suggest that formation of complexes with blue HB is fostered by a nonstandard nature of the dependence of the dipole moment function on a normal coordinate corresponding to donor CH bond stretching. Thus, for fluoroform with two, first, and second, negative dipole moment derivatives, the high-frequency CH band shift in complex formation with methyl fluoride is maximum. Chloroform with positive first and negative second derivatives exhibits a smaller high-frequency shift. Both the dipole moment function and halothane CH band shift have the same behavior. Finally, propyne (CH_3CCH) has a standard growing dipole moment function with small, but positive derivatives. A low-frequency shift of the CH band continuously growing during convergence to an equilibrium distance is predicted for all types of acceptors.

Conclusion

The behavior of IR absorption spectrum in liquid krypton shows that halothane with methyl fluoride, similar to chloroform (that also has low positive dipole moment derivative with respect to a normal coordinate of CH stretching), forms complexes with weak HB characterized by a moderate high-frequency shift and increase in the absolute intensity of this vibration. In interactions with halothane, even when weak complexes are formed, broadening of the donor CH stretching band is observed and may be attributed to formation of four complex conformers having similar spectroscopic and energy parameters. Besides these four conformers, the calculation predicts possible formation of very weak dimers with a halogen bond that are not observed experimentally.

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Conflict of interest

The authors declare that they have no conflict of interest.

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