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The study of noncovalent interactions between sevoflurane and acetone in liquefied Xe by the method of IR spectroscopy

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The IR spectra of sevoflurane + acetone mixtures in liquefied Xe were studied at $T \sim 165-190$ K. Complex formation stabilized by noncovalent interactions of weak H-bond type has been identified on the basis of changes found at selected bands of both components. Quantum-chemical calculations made on MP2/6-311++G(d,p) level, show that the spectrum in the region of stretching vibrations of CH and CH_2 groups is formed due to anharmonic effects, specifically Fermi resonances.

Keywords: cryospectroscopy, sevoflurane, acetone, complex, noncovalent interactions, quantum-mechanical calculations.

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Introduction

At present, along with gaseous xenon (Xe), such a halogen-substituted ether as sevoflurane $(CF_3)_2$-CH-O-CH_2F) is most often used in invasive surgery as a widely used inhalation anesthetic. This is due to the rather high efficiency of this volatile compound with its relatively low nephro- and hepatotoxicity [1–3]. Its main metabolite is hexafluoroisopropanol (1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)), which is excreted from the body almost unchanged. Sevoflurane has been widely used for more than a decade. However, the nature of the mechanisms of the anesthetic effect is still not clear.

The simplest working hypothesis, supported by a number of experimental data, is that inhalational anesthetics act by binding to specific targets, such as proteins, thereby disrupting their normal functioning [4,5]. Such binding must be reversible so that the anesthetic effect disappears quickly after the agent flow is discontinued. This can be realized if the interaction of the anesthetic with the target will be of a non covalent nature H-bond [6,7] primarily belongs to this type of interactions. Sevoflurane, like a number of other halogen substituted ethers, has from one to several CH groups, which can act as weak proton donors in interactions with acceptor target molecules. Acceptors are, in particular, molecules containing an oxygen atom with lone electron pair. For example, this is dimethyl ether [8]. Acetone also belongs to this type of target, which, similarly to dimethyl ether, can form complexes when interacting with a number of halogen-substituted ethers [9–13].

In this work, using the method of IR cryospectroscopy and quantum-mechanical calculations, one studied the features of interactions between sevoflurane and acetone, the natural metabolite of the human body. Test calculations were carried out using the GAUSSIAN package, confirming the possibility of the formation of weak complexes in the system under consideration. The geometric and spectroscopic parameters of the monomers and complexes are obtained. Interpretation of the characteristic changes in the IR spectrum related with the formation of complexes is proposed. Conformational analysis for this volatile anesthetic was performed earlier [8,14].

Experimental and calculation procedure

The experimental setup unit used in this work for spectroscopic measurements in low-temperature liquid solutions does not fundamentally differ from the setup units described earlier [8–11]. Cryostat with a cell sealed in the body of a copper radiator was cooled by metered dosed supply of liquid nitrogen into a stainless steel vessel. The temperature was determined by the vapour pressure over the liquid cryo-solution, additional control was carried out using a thermocouple The optical length of the cell was 1 cm, i.e. value sufficient for quantitative measurements at component concentrations $\sim 10^{17}-10^{18}$ molec/cm^3. To prevent overlapping of the CH stretching bands of the donor and acceptor, a fully deuterated acetone sample $(OC(CD_3)_2)$ was used. Liquefied xenon Xe was used as a solvent. This choice was justified both by the good solubility of acetone in the absence of signs of its self-association, and by the fact that Xe, as the safest in invasive surgery, but extremely expensive inhalation anesthetic, is increasingly being used in mixtures with sevoflurane. It should be noted that with their „inertness“ the interactions of xenon with a number of molecules are not so weak and they have the nature of van der Waals interactions. Estimates made in the framework of quantum-mechanical calculations lead to the conclusion that in some cases the energy of formation of complexes with Xe reaches two to three kcal/mol [15].

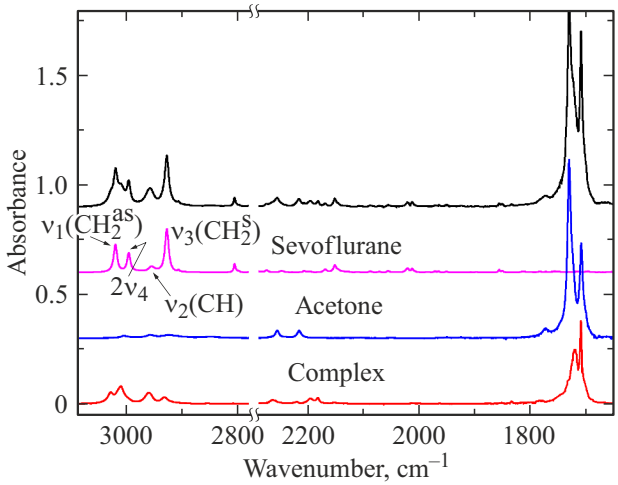

Figure 1. Infrared spectrum of a mixture of sevoflurane with acetone in liquid Xe. The result of selecting the bands of the complex is shown in the lower panel. $T \sim 165$ K.

Temperature measurements were carried out in the range of 165–190 K. The spectra were recorded in the range ~ 800–3500ċm^{-1} by Nicolet 6700 Fourier spectrometer with resolution of 0.5ċm^{-1}. The ranges of CH stretching vibrations of sevoflurane, as well as CD and CO stretching vibrations of acetone, were selected as the spectral regions most informative for identifying the formation of complexes, since the most noticeable changes are observed during the formation of complexes in these regions.

The calculations were carried out using the Gaussian16, Revision A.03 package [16]. The search for minima in the potential energy of the complexes was carried out using several initial configurations (the interaction between the donor CH groups of sevoflurane and the oxygen atom of acetone was taken as the main contact). The found local minimum was optimized at the level of second-order perturbation theory Möller–Plesset (MP2) with the frozen core (FC) [17] option. The calculations were carried out using the three-exponential Pople basis 6-311++G(d,p), which satisfactorily describes the features of the IR spectrum in the region of the main stretching vibration bands of CH- and CH_2-groups of sevoflurane. Equilibrium geometry, interaction energy, wavenumbers of harmonic vibrations and thermodynamic parameters of the complexes were obtained taking into account the correction for the incompleteness of the basis set in the framework of the gradient correction technique CP [18,19]. The desired structures corresponded to local minima with absence of imaginary wave numbers. The calculations with the „freq=anharm“ option were tested in order to analyze the possibility of their application to take into account anharmonic effects, especially the Fermi resonance, for the spectra of sevoflurane and complexes.

Measurement results

Sevoflurane ($(CF_3)_2$-CH-O-CH_2F) has three CH groups that can be candidate donors for non covalent interactions with target molecules having acceptor properties. Three bands of the first order of different intensity belong to these groups. The infrared spectrum of sevoflurane was previously recorded in the gas phase and cryo-solutions [8,20]. In this work, the main attention is paid to obtaining and analyzing the IR spectrum of the components and the complex in liquefied Xe in the regions indicated in the previous section. Fig. 1 shows the IR spectrum of a mixture of sevoflurane with acetone (according to $\sim 3 \cdot 10^{17}$ molec/cm^3) in Xe, as well as the result of separation of the bands assigned to the complex ($T \sim 170$ K). In the region of CH stretching vibrations of sevoflurane, in addition to the three bands of the fundamental vibrations, an additional band of noticeable intensity is observed. As shown earlier, the appearance of this relatively strong second-order band $2\nu_4$ is due to anharmonic resonance interactions [8].

It follows from the result of separation of the bands of the complex (lower part of Fig. 1) that the position and intensity of the stretching bands of the CH donor, as well as the CD and CO bands of the acceptor (acetone) change noticeably. The CO band doublet has an anharmonic resonance nature For weak CD bands, a weak high-frequency, so-called blue shift [9,21–23] is noted, and for CO the low-frequency shift is noted. It should be noted that the intensities of these bands decrease with increase in the temperature of the solution, which corresponds to a relative decrease in the content of complexes in the solution.

Calculation results and discussion

Conformational analysis was previously performed for sevoflurane [14,20]. The main result of this analysis is the conclusion that, under conditions typical for this experiment ($T < 190$ K), only the most stable conformer can be detected in the solution. The structure of this conformer obtained at the MP2/6-311++G(d,p) level is shown in Fig. 2. The next stable structure is located much higher on the potential energy surface (~ 14 kJ/mol) and does not manifest in the IR spectrum. The found geometric parameters were found to be close to the data given in the literature, and therefore are not presented here.

It follows from the analysis of spectroscopic measurements that the IR spectrum of sevoflurane noticeably changes due to anharmonic effects. The result of the effect of vibrational resonances is a shift and a change in the intensity of stretching vibration bands, as well as the appearance of new, relatively strong, second-order bands. Table 1 shows the experimental data for some bands of sevoflurane and acetone, both monomers and in the complex. If for the target, i.e., acetone, interpretation is not difficult, then in the case of sevoflurane, additional analysis is necessary. From the results of fitting the spectrum of

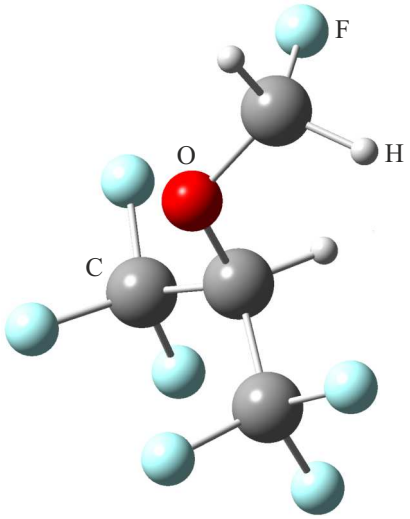

Figure 2. The most stable structure of sevoflurane obtained as a result of MP2/6-311++G(d,p) calculation.

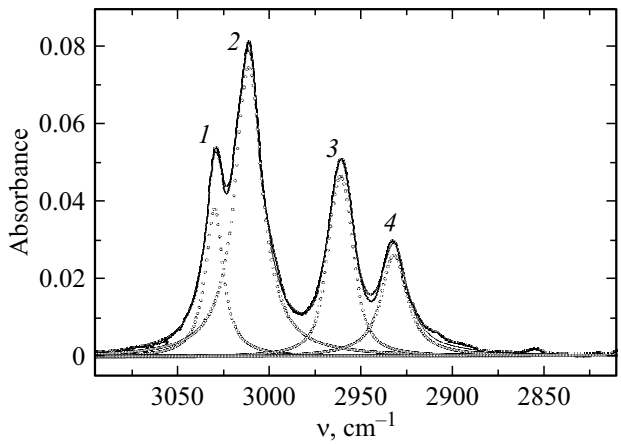

Figure 3. Band fitting in the IR spectrum of the complex of sevoflurane with acetone in liquid Xe using the ORIGIN application software. The Voigt profile was chosen as the model contour. $T \sim 170$ K.

the complex in the range of CH stretching vibrations of sevoflurane, shown in Fig. 3, it can be seen that it consists of four noticeably broadened bands. Assuming that the order of the bands of the complex as in the monomer is preserved, the numbers in Fig. 3 correspond to the bands $\nu_1(CH_2^{as})$, $2\nu_4$, ν_2(CH), and ν_3 (CH_2^s). All of them exhibit a slight high-frequency shift, and the band 2 assigned to the $2\nu_4$ overtone is unexpectedly characterized by its maximum intensity.

From the calculations performed in the Gaussian software environment, it follows that sevoflurane with acetone can form at least three stable (absence of imaginary frequencies) conformers. Fig. 4 shows the result obtained at the MP2/6-311++G(d,p) level. Table 2 lists the energy of formation of complexes, the dipole moment, and the distances between individual atoms of sevoflurane and acetone involved in hydrogen bonds (HB) and additionally stabilizing the complex due to van der Waals interactions.

Within the framework of the MP2 perturbation theory, the spectroscopic parameters were obtained for all three structures of the complex in the harmonic approximation. Some of them are presented in Table 3. The relative population of structures 1, 2, 3 estimated within the framework of the thermodynamic relation for the Gibbs energy in the harmonic approximation at a temperature of 170 K is $\sim 0.3 : 0.69 : 0.01$. Thus, one can restrict the consideration by to considering two structures. Moreover, the contribution of the second structure becomes predominant with increasing temperature.

It follows from a comparison of the measurement results (Table 1) and the harmonic calculation (Table 3) that none of the structures even has a qualitative agreement with the experiment. The harmonic calculation does not reproduce even the required (4) number of bands. As noted earlier, to interpret the spectrum of the sevoflurane monomer, it is necessary to proceed to an anharmonic analysis, namely, to solve the block of the secular equation for vibrational resonances $\nu_2/\nu_3/2\nu_4/2\nu_5$, which are observed in the region

Table 1. Measured spectroscopic parameters of separate bands (ν and $\Delta\nu^{c-m}, \text{cm}^{-1}$) of free sevoflurane ($m$) and sevoflurane in a complex with acetone (c) in solution in liquefied Xe at a temperature of 170 K. $I_{\text{rel}} = I(\nu_i)/I(\nu_1)$ is relative band intensity ν_i.

Vibration	ν_m	I_{rel}	ν^c	$\Delta\nu^{c-m}$	I_{rel}
$\nu_1(CH_2^{as})$	3021.3	1	3030.6	+9.3	1
ν_2(CH)	2956.0	0.3	2961.2	+5.2	1.4
$\nu_3(CH_2^s)$	2928.6	1.6	2932.3	+3.7	1
$2\nu_4$	2997.0	0.7	3011.9	+14.9	2.9

Note. The bands of the complex are numbered for convenience in the same way as the bands of the monomer.

Table 2. The geometric parameters of the three found structures of the sevoflurane + acetone complex obtained as a result of the MP2/6-311++G(d,p) calculation

Structure	1	2	3
ΔE^e_{CP2}, kcal/mol	−6.3	−5.6	−4.6
μ, D	4.44	5.25	2.04
$R(O_{17}\ldots H_6)$, Å	2.229	2.276	–
$R(O_{17}\ldots H_{14})$, Å	2.680	2.693	3.185
$R(O_{17}\ldots H_{13})$, Å	–	–	2.519
$R(F_a\ldots D_{20})$, Å	3.234	3.594	–
$R(F_b\ldots D_{21})$, Å	3.209	3.283	3.616
$R(F_c\ldots D_{24})$, Å	3.486	3.643	–
$R(F_d\ldots D_{21})$, Å	–	–	–
$R(F_e\ldots D_{23})$, Å	–	–	2.974
$R(F_{10}\ldots D_{23})$, Å	–	–	3.359

Note. $a, b = 8$ for structure 1; $c = 15$ for 1; $a, b = 4$ for structure 2; $c = 9$ for 2; $e = 3$ for structure 3, $b = 5$ for 3.

Table 3. Harmonic wave numbers (ω, cm^{-1}) and (in brackets) intensities (I, km/mol) of separate normal vibrations of sevoflurane and structures 1, 2, 3. MP2/6-311++G(d,p) calculation results

Vibrations	Monomer	1	2	3
$\omega_1(CH_2^{as})$	3225.4 (13.3)	3224.5 (14.5)	223.6 (14.8)	3253.6 (4.1)
$\omega_2(CH)$	3129.9 (4.0)	3113.7 (57)	3133.6 (28)	3127.1 (6.6)
$\omega_3(CH_2^s)$	3123.6 (30.6)	3127.8 (22)	3130.0 (33.8)	3135.2 (18.6)
$\omega_4(\delta CH_2)$	1552.4 (0.75)	1548.4 (3.1)	1551.1 (0.32)	1553.8 (0.28)
$\omega_5(\delta CH_2)$	1475.9 (12)	1477.2 (9.8)	1479.3 (13.4)	1472.2 (6.7)

Table 4. Parameters of $v_2/v_3/2v_4/2v_5$ Fermi and $v2/v3$ Darling–Dennison resonances (in units of wave numbers, cm^{-1}) and the result of the diagonalization of the secular equation for sevoflurane and structures 1 and 2 (see text). The intensities of the resonance multiplet components in km/mol are given in brackets

Parameter	Monomer	1	2
ν_1^0	3086.0	3085.1	3084.5
ν_2^0	3004.2	2988.0	3009.0
ν_3^0	2978.2	2982.4	2985.3
$2\nu_4^0$	3025.5	3017.5	3022.9
$2\nu_5^0$	2883.9	2886.3	2890.3
W_{23}	8.9	(8.9)	(8.9)
W_{244}	16	5	12.5
W_{255}	26	5	23
W_{344}	39	44	42
W_{355}	57	59	55
Solution			
ν_1	3086.0(13)	3085.1(14.5)	3084.5(14)
$2\nu_4$	3062.3(12)	3055.3(8)	3063.7(10)
ν_2	3000.2(2)	2989.8(45)	3005.7(26)
ν_3	2976.713	2973.3(17)	2977.3(20)
$2\nu_5$	2852.7(6)	2855.8(4)	2860.9(5)

of CH stretching vibrations. The resonance parameters for free sevoflurane and two structures of the complex are given in Table 4. The unperturbed frequencies ν^0 and the interaction matrix elements of the Fermi resonance W_{ikk} and Darling–Dennison resonance W_{ik} for the monomer were obtained within the framework of the Gaussian16, Revision A.03 package [16] with option„freq=anharm“. In the case of complexes, due to limited computer resources, a number of simplifications were made.

a) To estimate the unperturbed anharmonic frequencies ν_i^{c0} of fundamental vibrations i, one used the anharmonic frequency shifts of the monomer ($\Delta\nu_i^m = \nu_i^{m0} - \omega_i^m$): $\nu_i^{c0} \sim \omega_i^c + \Delta\nu_i^m$. For example, for the ν_1 vibration of a monomer, the shift is $\Delta\nu_1^m = 3086.0 - 3225.4 = -139.4\,cm^{-1}$. For the harmonic frequency $\omega_1^c = 3224.5\,cm^{-1}$ of the structure 1, the estimate of the unperturbed anharmonic frequency is $\nu_1^{c0} = 3224.5 - 139.4 = 3085.1\,cm^{-1}$.

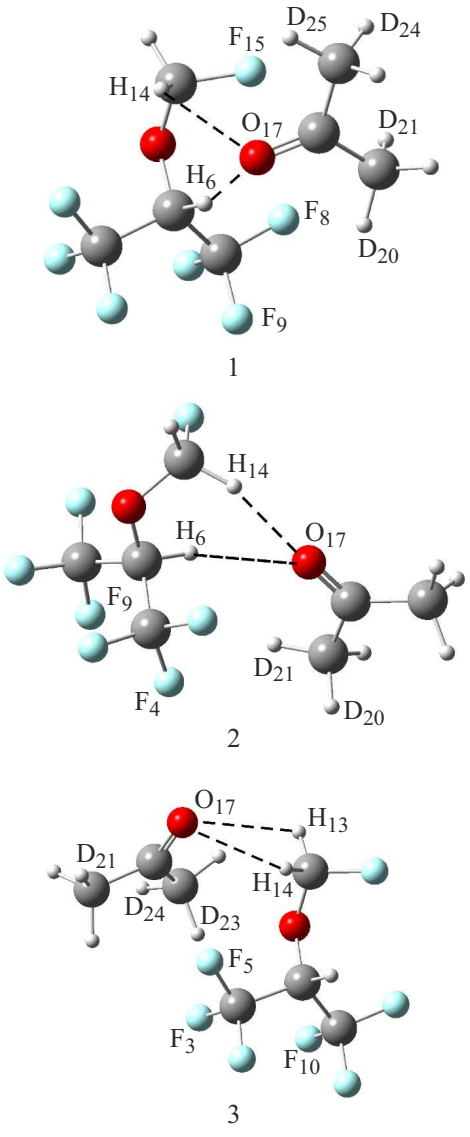

Figure 4. Structures 1, 2, 3 of the sevoflurane-acetone complex predicted by MP2/6-311++G(d,p) calculations.

b) The unperturbed overtone frequencies of bending vibrations were determined as the sum of the overtone frequency for the monomer and the doubled difference between the harmonic frequencies of the com-

plex and the monomer. For example, for structure 1: $2\nu_4^0 = 3025.5 + 2(1548.4 - 1552.4) = 3017.5\,\mathrm{cm}^{-1}$.

c) The interaction matrix element of the Darling–Dennison resonance W_{23} was assumed to be the same for the monomer and the complex.

d) Matrix elements of the interaction of Fermi resonances were obtained in a series of pointwise calculations of the potential energy surface for pairs of point by step calculations Q_2Q_4, Q_2Q_5, Q_3Q_4, Q_3Q_5 for the found structures of the complex.

From a comparison of the estimates obtained for the monomer and structures 1, 2 (Table 4), it follows that the calculation results for structure 2 are closer to the experimental observations (Table 1). Namely, most of the bands of this structure experience a slight high-frequency shift (with the exception of the practically unshifted band of the antisymmetric CH_2 vibration ν_1). However, it is not possible to reproduce the nature of the change in the intensities of the quartet bands ν_1, $2\nu_4$, ν_2, ν_3 is the intensity of the CH band ν_2 increases strongly and turns out to be noticeably higher than the intensity of the other bands. To obtain a better agreement with experiment, a more rigorous account of anharmonic effects is required. The analysis shows that the result of the anharmonic analysis strongly depends not only on the level of calculations, but also on the wideness of the used basis set [8]. The nonzero nature of the interactions of the system under consideration with Xe can, in principle, affect the change in the spectral characteristics. However, estimates made within the framework of self-consistent reactive field (SCRF) models indicate that the effects are insignificant, and they do not lead to qualitative changes.

Conclusion

In the IR spectra of solutions of sevoflurane with acetone in liquefied Xe, reversible changes were found, demonstrating the formation of complexes with a weak HB.

According to calculations performed at the MP2/6-311++G(d,p) level, sevoflurane can interact with an oxygen-containing target : the acetone, forming several (3) structures. The stabilization of the most stable structures occurs with the participation of non covalent interactions between the H atom of the CH group of sevoflurane and the O atom of acetone. Additional stabilization is associated with contacts between the D and F atoms of acetone and sevoflurane, respectively. The spectroscopic predictive performance of calculations is low, especially in the harmonic approximation.

Accounting for resonance effects of anharmonic nature significantly improves the situation. In this case, the result obtained for the most populated structure 2 is at least qualitatively close to the data of experimental observations.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

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