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Noncovalent Interactions between Volatile Anesthetics (Enflurane, Isoflurane) and Dimethyl Ether. Spectroscopic Demonstration of Trimer Formation

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Abstract—The IR spectra of solutions of mixtures of volatile anesthetics (enflurane, isoflurane) and dimethyl ether were studied by cryospectroscopy in the temperature range 120–160 K. The formation of complexes has been observed: dimers at lower concentrations and trimers at higher concentrations. The results of quantum-chemical calculations are in qualitative agreement with the results of measurements.

Keywords: volatile anesthetics, cryospectroscopy, hydrogen bonding, dimers, trimers

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INTRODUCTION

Many volatile hydrocarbons and ethers exhibit strong analgesic and anesthetic effects. Some of them are used in modern invasive surgery. In particular, these are the isomers of enflurane ($CHFCl–CF_2–O–CHF_2$) and isoflurane ($CF_3–CHCl–O–CHF_2$). A characteristic feature of these halogen-containing ethers is the presence of two CH groups, which can act as weak CH donors under certain conditions during interactions with target molecules possessing acceptor properties [1–5]. One of the simplest acceptors that simulates the reversible nature of the anesthetic effect is dimethyl ether (DME). Its characteristic feature is the presence of an oxygen atom with a lone electron pair. In the present work, main attention is paid to the study of noncovalent interactions between these isomers and DME. Weak complexes were detected by cryospectroscopy. The measurements were performed in cryosolutions in liquefied krypton (Kr) at temperatures T ~ 120–160 K in the range ~800–4000 cm^{-1} using a Nicolet-6700 Fourier transform infrared spectrometer with a resolution of 0.5 cm^{-1}. The information was mainly obtained from the CH stretching vibration bands of the isomers (~3100–2800 cm^{-1}) and the region of the CD stretching vibrations of DME (~2200–1800 cm^{-1}), where the formation of complexes led to noticeable changes in the spectroscopic parameters of the donor and acceptor bands.

In addition to spectroscopic measurements, quantum-chemical calculations were performed to search for stable conformers and complexes. The results were obtained in the MP2 second order perturbation theory using the Pople basis sets including polarization and diffuse functions. The final level of calculations (MP2/6-311++G(*df*,*pd*)) was determined by the availability of computer resources.

EXPERIMENTAL

The isomers are characterized by a variety of possible conformer structures. Conformational analysis for both enflurane and isoflurane was performed previously [4, 5]. It follows from it that at the temperatures of this experiment, the IR spectrum of the anesthetics under study is mainly determined by the most stable conformers: enflurane and isoflurane, presented in Figs. 1a and 1b. These conformers contain two oppositely oriented CH groups, which are potentially weak proton donors during the formation of a hydrogen bond (HB).

The IR spectra were recorded on a Nicolet-6700 Fourier transform infrared spectrometer with a resolution of 0.5 cm^{-1}. To study the cryosolutions, a homemade optical cryostat was used, which was cooled by dosing liquid nitrogen. The temperature was measured both according to the vapor pressure above liquid krypton and using a thermocouple built in the body of the cell. The optical length of the low-temperature liquid cell was 1 cm. The effect of the overlap of the CH stretching vibration bands of the anesthetic and target was eliminated by using the fully deuterated form of DME ($(CD_3)_2O$). The concentrations of anesthetics and DME in liquefied Kr were varied widely (~10^{-5}–10^{-3} mole fractions). The signs of complex formation (dimers, trimers) were detected during the tempera-

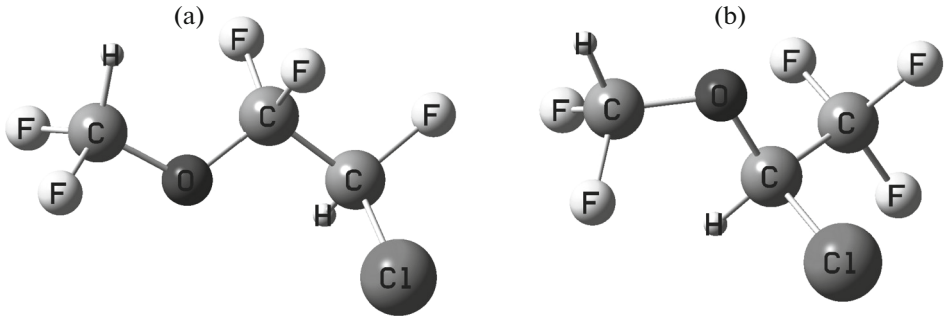

Fig. 1. Structures of isomers: (a) enflurane and (b) isoflurane.

ture measurements (T ~ 120–160 K) in mixtures with a varied DME content.

The equilibrium geometry, interaction energies, harmonic frequencies, and thermodynamic parameters were calculated using the GAUSSIAN 16 Rev. A.03 package [6]. The results were obtained using available computer resources in the second-order approximation of the Møller-Plesset (MP2) perturbation theory [7] with the Pople basis set including polarization and diffuse functions: 6-311++G(*df*,*pd*). The results were corrected for the basis set superposition error (BSSE) using the generally accepted method implemented in the package [8, 9]. The found structures of the complexes had all positive (real) wave numbers.

RESULTS AND DISCUSSION

The results for isoflurane with DME were obtained previously [10]. With a tenfold excess of DME, the spectrum showed new intense bands, which were attributed to the trimer complexes with two CH donor groups of isoflurane, interacting with a pair of DME acceptors. The experimental observations are confirmed by calculations.

In the case of enflurane, the changes in the spectrum in a mixture with DME are presented in Fig. 2. The bands of the complexes were isolated using the standard method, by subtracting the bands of monomers (enflurane and DME) from the spectrum of the mixture with optimum selection of their intensities. During the formation of dimers, the most appreciable changes are expected for the stretching vibration band of CH whose hydrogen atom is directly involved in hydrogen bonding with the DME oxygen acceptor. It is natural to believe that for the other CH band with an inactive H atom, the spectroscopic changes will be minimum. When two types of dimers are formed with participation of the H atom or the F_2CH or ClFCH groups having comparable concentrations, up to four new bands can appear. Finally, under conditions of a large excess of trimers, only a couple of new intense bands may be detected in the region of the CH stretching vibration bands of enflurane.

From Figs. 2a and 2b, showing the result for equal concentrations of enflurane and DME, it follows that the low-frequency band belonging to the vibrations of the CH group of FClCH significantly increased in intensity and slightly shifted in frequency relative to the band of the monomer. Two relatively weak high-frequency bands can be attributed to the vibrations of the CH group of FFCH of the two above-mentioned types of dimers, namely, with FClCH···O and FFCH···O hydrogen bonds, respectively. The absence of the fourth band may be associated with the low intensity of the band of the CH group of FClCH, which is not involved in hydrogen bonding. As the temperature increases, the band intensity of the complex decreases, while that of the monomer increases.

When the concentration of DME is significantly higher than that of enflurane (Figs. 2c and 2d), only two intense bands are recorded, which can be attributed to two vibrations of the CH groups of FClCH and FFCH, whose H atoms are involved in the formation of trimers. As the temperature increases, the qualitative picture approaches the case with a low DME concentration. Note that the observed temperature changes in the spectrum of the mixtures were reversible. The CD stretching vibration bands of dimethyl ether experienced a slight high-frequency shift, which is typical for complexes with HBs [10, 11]. This effect was practically independent of the type of the complex formed and was not considered in detail.

Figure 3 presents the result of fitting of the bands of the complexes for different DME concentrations at 120 K, which allows us to estimate both the relative intensity of the high- and low-frequency components and the frequency of the maximum of these bands. The results are shown in Fig. 3.

Figure 4 shows the optimized structures of two dimers, D_1 and D_2, and the trimer, corresponding to the real minima on the potential energy surface (PES). The enflurane dimers with DME are denoted as D_1 for the complex with FClCH···DME hydrogen bonds and as D_2 for the complex with F_2CH···DME hydrogen bonds, respectively. The table presents some parame-

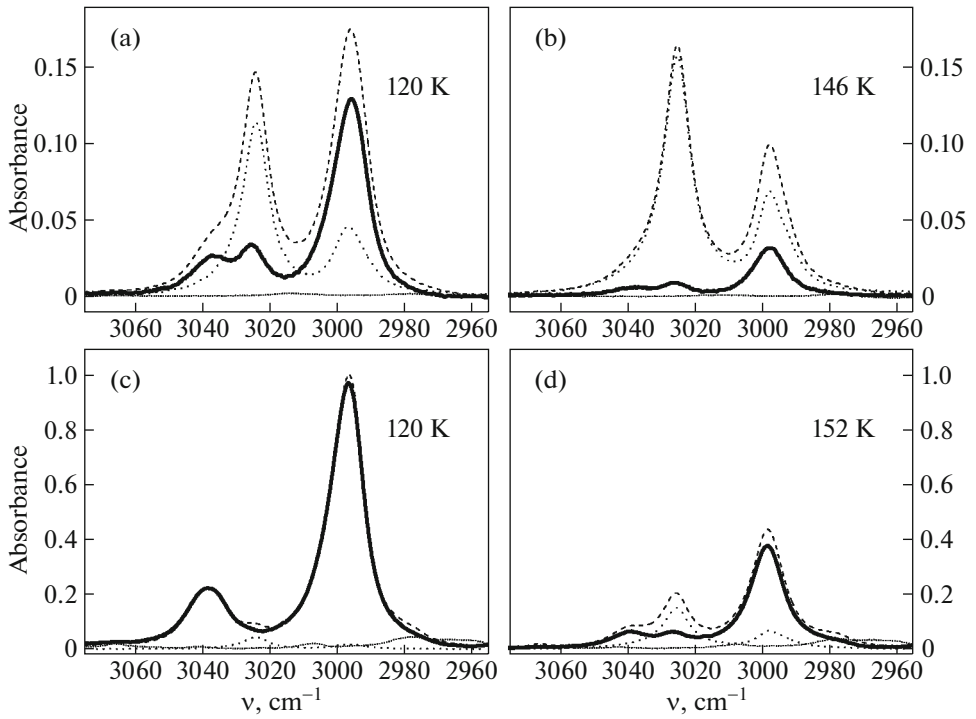

Fig. 2. IR spectra of the mixtures of enflurane and DME in liquefied krypton; (a, b) enflurane ~5×10^{-5} mole fractions, DME ~5×10^{-5} mole fractions; (c, d) enflurane ~5×10^{-5} mole fractions, DME ~5×10^{-4} mole fractions. Dashed line: mixture, dotted lines: monomers (enflurane, DME (short dotted line)), solid thick line: complex.

ters of the complexes. The calculation (MP2/6-311++G(*df*,*pd*)) showed that the first dimer is slightly more stable than the second (−4.95 and −4.55 kcal/mol with CP2 correction, respectively). The trimer is almost twice more stable (−9.41 kcal/mol). The maximum (almost sixfold) increase in intensity is predicted for the ν_2 band for the formation of the D_1 dimer and trimer. At the same time, the intensity of the ν_1 band practically does not change. Both results are in agreement with the experimental observations.

The changes in the position of the bands are reproduced much worse. For the ν_1 band, there is at least qualitative agreement between the calculations and measurements, while the ν_2 band should be blue-shifted according to calculations, whereas in the experiment the shift is minimum and almost absent. This discrepancy is not surprising and can be explained by neglect of anharmonic effects in the harmonic approximation, as well as the influence of the solvent (liquid krypton), which reduces the blue shift [12]. When the DME concentration substantially increases, only two intense bands are observed in the spectrum, which are mainly determined by trimers. The content of dimers is small and practically does not affect the form of the observed spectrum.

From the analysis of intensities it can be assumed that at a ratio of ~1 : 1, dimers of two types are formed, D_1 being the dominant dimer, for which the intensity of the low-frequency CH band, as would be expected, substantially increases. Among the two high-frequency components, one belongs to D_1, and the other, to D_2. They have comparable intensities both in experiment and in calculations. The absence of the low-frequency component for D_2 may be explained by its low calculated intensity. At significantly higher concentrations of the DME target (1 : 10), the band intensities of the complex significantly increase, especially for the low-frequency CH band, and slightly shift toward high frequencies. Importantly, the spectrum is simplified, namely, only one band is recorded in the high-frequency region, but not two, as in the case of comparable concentrations of the anesthetic and target. According to calculations, this result corresponds to the spectrum of the trimer. With increasing temperature, as the trimers are destroyed, the spectrum becomes similar to the case of the 1 : 1 ratio.

The above interpretation of the experimental data can be supported by thermodynamic evaluation of the relative concentrations of the dimers and trimer. The calculated standard Gibbs free energies for dimers D_1, D_2 and trimers taken from the output files of the GAUSSIAN program were used to estimate the equilibrium constant [13, 14]:

$$K_i = \exp\left(\frac{-\Delta G_i^0}{RT}\right), \quad (1)$$

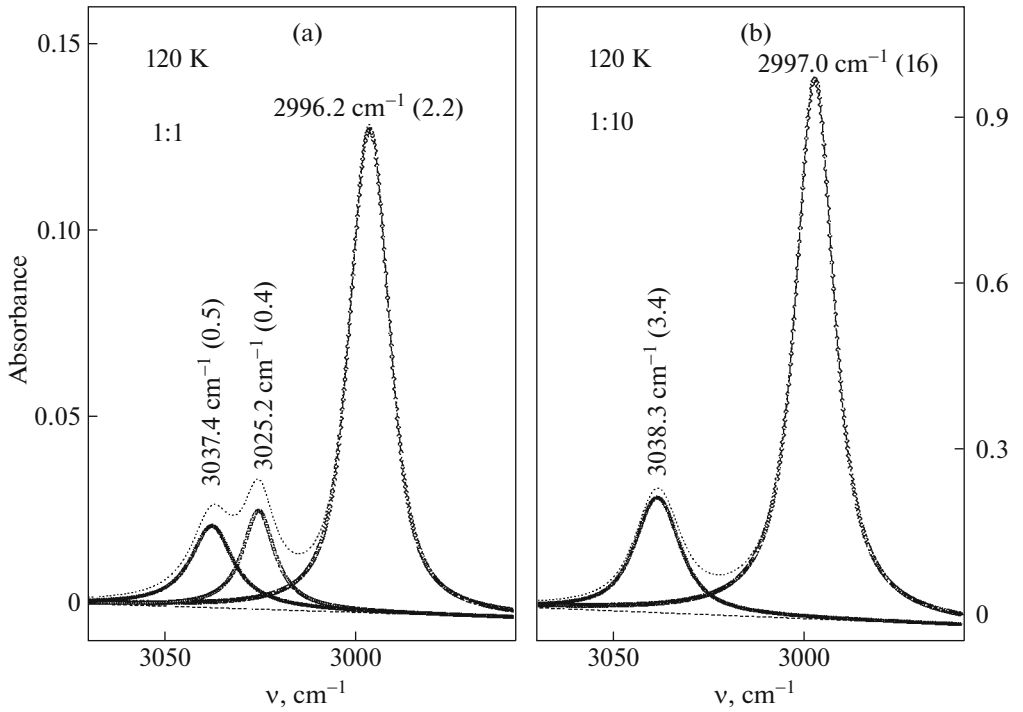

Fig. 3. Result of fitting of the bands of the complex. The wave numbers of maxima are indicated; the areas of the bands are indicated in parentheses; (a) equal concentrations of enflurane and DME, (b) the DME concentration is 10 times higher.

where i denotes D_1, D_2, and trimer; and R = 1.987 cal/(K mol) is the universal gas constant. Using the GAUSSIAN program gives the results for the reaction in the gas phase under standard conditions (the standard pressure p^0 =1 bar); then the equilibrium constant K_i^{liq} of the monomers (a is enflurane, and b is DME) and complexes dissolved in an inert solvent (krypton), is recorded as [15]

$$K_i^{\text{liq}} = K_i \frac{V_m^{\text{gas}} T}{T^0 V_m^{\text{liq}}(T)}, \tag{2}$$

where $V_m^{\text{gas}} = 22.4 \times 10^3$ cm^3 is the molar volume of the ideal gas under standard conditions; T^0 = 273.15 K; and $V_m^{\text{liq}}(T)$ is the molar volume of liquid krypton at a temperature T [16]. The equilibrium constant K_i^{liq} can be expressed in terms of the mole fractions C_i of the components involved in the formation of the dimers (D_1, D_2) and trimer (T):

$$K_{a\text{D1}}^{\text{liq}} = \frac{C_{a\text{D1}}}{C_a C_{\text{DME}}}, \tag{3}$$

$$K_{a\text{D2}}^{\text{liq}} = \frac{C_{a\text{D2}}}{C_a C_{\text{DME}}}, \tag{4}$$

$$K_{a\text{T}}^{\text{liq}} = \frac{C_{a\text{T}}}{C_a C_{\text{DME}}^2}. \tag{5}$$

By solving the system of Eqs. (3)–(5) using the estimated equilibrium constant, one can obtain the concentration of the dimers, trimer, and monomers in mole fractions. Figure 5 shows the temperature dependences of the concentrations of the enflurane dimers, trimer, and monomer in the mixture at different tem-

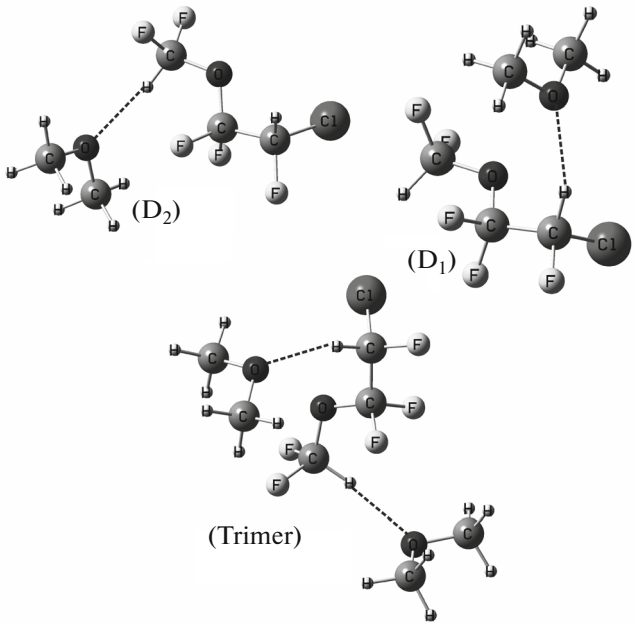

Fig. 4. Predicted structures of the dimers (D_1, D_2) and trimer.

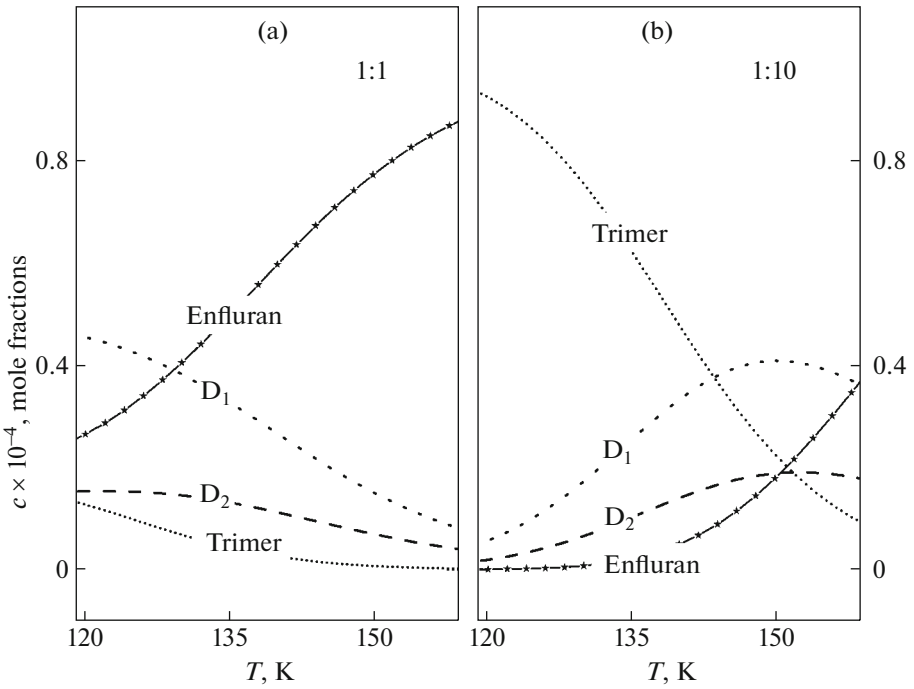

Fig. 5. Temperature dependences of the concentrations of the dimers (D_1, D_2), trimer (mole fractions), and free enflurane; (a) equal enflurane and DME concentrations in the initial mixture, (b) the DME concentration is ten times higher.

peratures. It can be seen that at low and identical concentrations of the donor and acceptor, the trimer content is low even at a minimum temperature of 120 K. The maximum concentration is obtained for the most stable dimer D_1. The concentration of D_2 is evidently greatly underestimated. An increase in the temperature leads to an increase in the concentration of free enflurane (and ether) and a decrease in the concentrations of all complexes. The calculation agrees with the results of measurements, at least qualitatively, except for the underestimated D_2 content. When the DME content is significantly higher (right side of Fig. 5), the concentration of trimers is much higher than that of dimers and unbound enflurane at 120 K. However, as in the experiment, an increase in temperature leads to a decrease in the content of trimers in favor of dimers and monomers.

The disadvantage of the above estimations is the use of the electronic energy of the components (Gibbs free energy), obtained from the results of the gas-phase calculation. Inclusion of the solvent effect, for example, within the framework of the reactive field model, can level out the difference in the values for the dimers D_1 and D_2, thereby reducing the gap in the content of these complexes.

CONCLUSIONS

The IR cryospectra of enflurane and its isomer isoflurane in mixtures with dimethyl ether (DME)

Table 1. Calculated energies and spectroscopic parameters of enflurane and its complexes with DME (MP2/6-311++G(*df*,*pd*))

Compound	$-\Delta E_e^{SR}$, kcal/mol	r_1(CH), Å	ν_1, cm^{-1}	A_1,km/mol	r_2(CH), Å	ν_2, cm^{-1}	A_2, km/mol
Monomer	—	1.0904	3172.7	13.6	1.0905	3161.7	5.4
D_1 dimer	4.95	1.0904	3172.5	14.8	1.0905	3167.4	30.5
D_2 dimer	4.55	1.0907	3177.1	14.5	1.0904	3162.7	5.4
Trimer	9.41	1.0906	3177.3	13.8	1.0905	3167.1	30.3

ΔE_e^{SR} is the energy (absolute value) of complex formation with a BSSE correction; r_1(CH), ν_1, and A_1 are the CH bond length, wave number, and intensity of the CH stretching band of F_2CH of enflurane, respectively; r_2(CH), ν_2, and A_2 are the same for the FClCH group.

showed the signals of the formation of dimers; with a large excess of DME and at the minimum temperature (120 K) of their solution in krypton, trimers were found. The results of calculations performed at the MP2/6-311++G(*df*,*pd*) level agree with the experimental data, at least qualitatively. The formation of trimers involving an isomer (isoflurane, enflurane) and two DME molecules was predicted. In this case, both CH bonds of the anesthetic act as HB donors.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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