Cryospectroscopic and ab initio studies of noncovalent interactions between sevoflurane and selected acceptor-targets.

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Introduction.

Sevoflurane ((CF_3)$_2$-CH-O-CH$_2$F) belongs to the most safety anesthetics for purposes of invasive surgery (except very expensive Xe). This compound poses CH and CH$_2$ groups which can act as weak CH donor in interactions with targets of acceptor property [1-3]. In the present report, the attention focuses on the features of noncovalent interactions between sevoflurane and such targets as dimethyl ether (DME) and acetone (ACT). A homemade optical cryostat was used for preparation of the species and temperature spectroscopic measurements. The mixtures of sevoflurane and DME or ACT were dissolved in liquefied noble gases (Kr (~120-165 K) or Xe (~170-185 K)). The FTIR spectra of cryosolutions in liquefied noble gases were studied in the frequency domain of c.a. 800 ÷ 4000 cm^{-1} using a Nicolet Fourier Transform spectrometer, with a resolution of 0.5 cm^{-1}.

1. Calculations.

Ab initio calculations (MP2/6-311++G(d,p)) were performed to obtain geometric and spectroscopic parameters of sevoflurane, and stable forms of sevoflurane + B (DME, ACT) heterodimers. **Figure 1** presents **2** stable structures of sevoflurane + DME. The energy of formation achieves ΔE^e = -25 kJ/mol in the case of complex *a*. (Zero point corrected energy is ΔE^0 ~ -23 kJ/mol). Complex *b* is markedly weaker (ΔE^e ~ -15 kJ/mol). Relative population P_a : P_b estimated on the basis of the known thermodynamic equations for Gibbs energy comprises 1 : 10^{-5} at T ~ 120 K . Thus only the most stable complex *a* contributes to the IR spectra recorded.

In the case of sevoflurane + ACT *three* stable structures were predicted – **Figure 2.** ΔE^e = -26, -23 and -19 kJ/mol for the structures 1, 2 and 3. Thermodynamics led to conclusion that the **structure 2** prevails at T > 170 K.
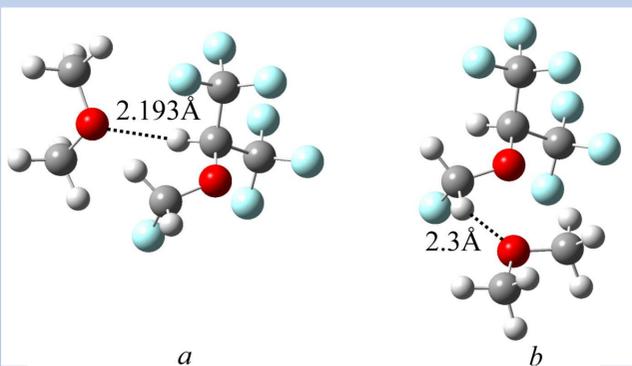

a   *b*

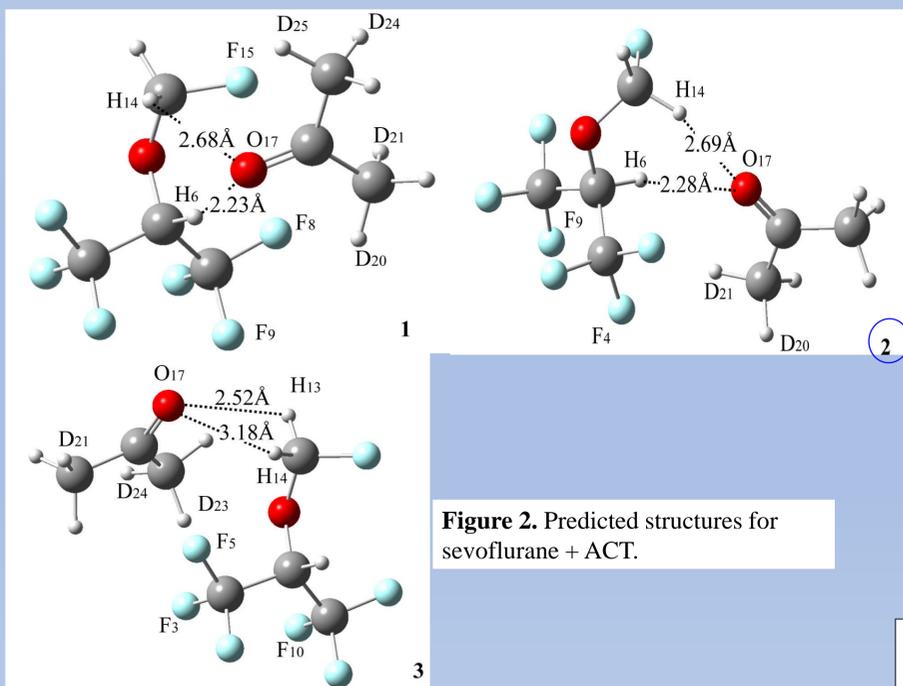**Figure 1**. Predicted structures for sevoflurane + DME.

Figure 2. Predicted structures for sevoflurane + ACT.

References:
[1] S.M. Melikova, K.S. Rutkowski. Opt. and Spectrosc., 2021, 129(4), 493–500.
[2] K.S. Rutkowski, S.M. Melikova, M. Rospenk J. Molec. Struct. 2020, 1221, 128852.
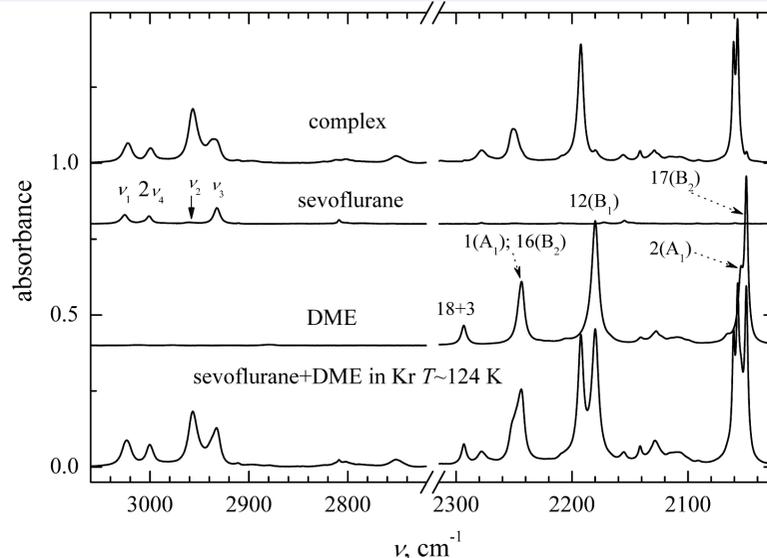[3] K.S. Rutkowski, S.M. Melikova, M. Rospenk. Spectrochim. Acta A, 2017, 184, 163–168.

Figure 3

Table 3. Measured and calculated (MP2/6-311++G(d,p)) selected spectroscopic parameters of sevoflurane…DME.

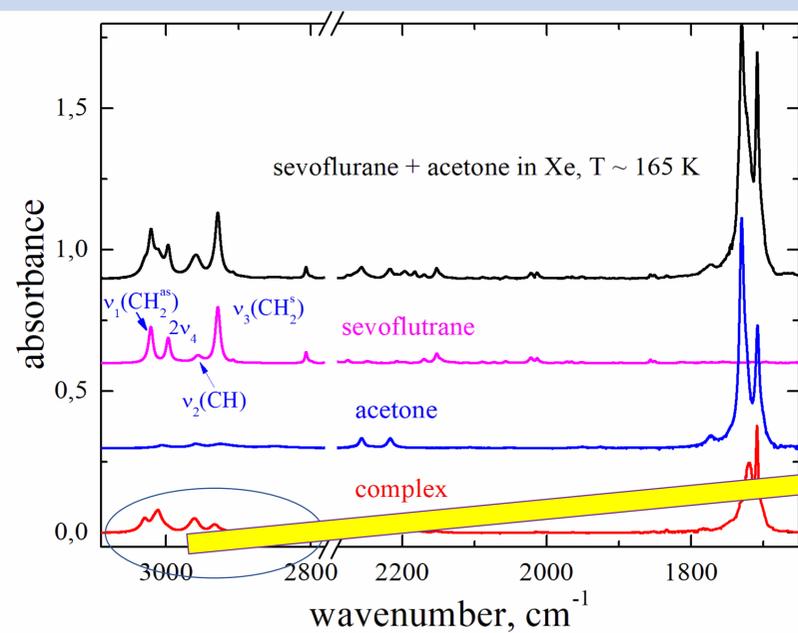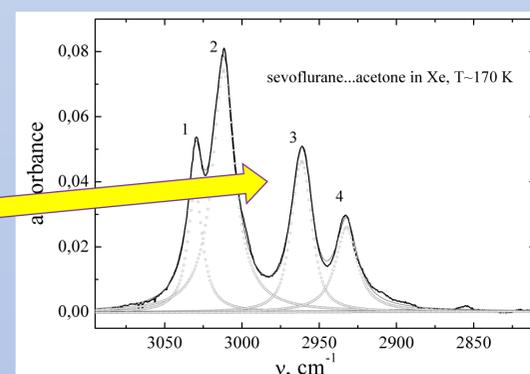| Assignment	Kr$_{liq}$; 124 K			harmonic			anharmonic		
	ν,	$\Delta \nu^{c-m}$	I_{rel}	$\nu (A)$	$\Delta \nu^{c-m}$	I_{rel}	$\nu (A)$	$\Delta \nu^{c-m}$	I_{rel}
ν_1^c(CH$_2$^{as})	3023.0	**-2.5**	1	3226.1 (14)	+0.7	1	3086.7 (15)	**+0.7**	1
ν_2^c(CH)	2956.4	**-4.3**	3	3117.1 (55)	**-12.8**	4	2995.1 (41)	**-5.1**	3
ν_3^c(CH$_2$^{s})	2934.5	**+1.5**	1.3	3132.7 (25)	**+9.1**	1.8	2973.6 (23)	**-3.1**	1.5
$2\nu_4^c$	2999.1	**-2**	0.6	-	**-**	-	3057.3 (10)	**-5**	0.7
$2\nu_5^c$	~2813	**+4.8**	0.1	-	**-**	-	2860.5 (5)	**+7.8**	0.3

2. Measurements.

Figure 3. presents an example of the extraction of the bands ascribed to a complex in the region of CH stretching vibrations of sevoflurane and DME. Note, that ν(C-D) modes of DME undergo blue shift due to complex formation. **Table 3** collects measured and calculated (MP2/6-311++G(d,p)) selected spectroscopic parameters (ν and $\Delta \nu^{c-m}$, cm^{-1}, I, km/mol, I_{rel}= $I(\nu_i)/I(\nu_1)$ – relative intensity of band ν_i). Anharmonic analysis was performed with the help of single point calculations, considering a set of Fermi resonances between first order stretching and second order bending vibrations ($\nu_2/\nu_3/2\nu_4/2\nu_5$). Darling-Dennison resonance between first order (ν_2/ν_3) CH states of sevoflurane was also taken into account.

Figure 4 shows the results- for sevoflurane + ACT in liquefied Xe (ACT do not dissolves properly in Kr). Also the anharmonic analysis is desired to interpret the experimental results. Selected data are collected in **Table 4**. The results obtained for conformer **2** describe experimental finding quite satisfactorily. Four bands are predicted in the CH stretching region. They are slightly blue shifted in comparison with respective bands of monomer. It should be recognized that intensity of ν_2 is overestimated. The case of ACT-target is complicated by diversity of structures and by non zero action of Xe. More refined anharmonic analysis could be needed with numerous resonances included.

Figure 4

Table 4. Calculated selected spectroscopic parameters of Sevofluran...ACT. ω -harmonic wave number, ν - anharmonic wave number.

	monomer	1	2
$\omega_1(I)$	3225.4 (13)	3224.5 (14.5)	3223.9 (14)
$\omega_2(I)$	3129.9 (4)	3113.7 (57)	3134.7 (31)
$\omega_3(I)$	3123.6 (31)	3127.8 (22)	3130.7 (33)
ω_4 (δ CH$_2$)	1552.4	1548.4	1551.1
ω_5 (δ CH$_2$)	1476.0	1477.2	1479.2
ν_4	1513.6	-	-
$\nu_1 (I)$	3086.0 (13)	3085.1 (14.5)	3084.5 (14)
$2\nu_4 (I)$	3062.3 (12)	3055.3 (8)	3063.7 (10)
$\nu_2 (I)$	3000.2 (2)	2989.8 (45)	3005.7 (26)
$\nu_3 (I)$	2976.7 (13)	2973.3 (17)	2977.3 (20)

Conclusions.

1. Interactions between sevoflurane and B (DME, ACT) result in reversible complex formation stabilized by H bond of C-H…O type predominantly. Additionally the complexes are stabilized by weaker van der Waals interactions. Complex formation results in noticeable changes in IR spectra of sevoflurane.

2. MP2/6-311++G(d,p) ab initio calculations are in line with experimental observations on qualitative level of comparison.

3. The Fermi resonances between the first order and second order transitions modify noticeably the IR spectrum in the region of CH and CH$_2$ symmetric stretching vibrations of sevoflurane.