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PAPER

On the weakly C–H... π hydrogen bonded complexes of sevoflurane and benzene[†]

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A vibrational assignment of the anaesthetic sevoflurane, (CF₃)₂CHOCH₂F, is proposed and its interaction with the aromatic model compound benzene is studied using vibrational spectroscopy of supersonic jet expansions and of cryosolutions in liquid xenon. *Ab initio* calculations, at the MP2/cc-pVDZ and MP2/aug-cc-pVDZ levels, predict two isomers for the 1 : 1 complex, one in which the *near-cis*, *gauche* conformer of sevoflurane is hydrogen bonded through its isopropyl-hydrogen atom, the other in which the same conformer is bonded through a bifurcated hydrogen bond with the fluoromethyl hydrogen atoms. From the experiments it is shown that the two isomers are formed, however with a strong population dominance of the isopropyl-bonded species, both in the jet and liquid phase spectra. The experimental complexation enthalpy in liquid xenon, $\Delta H^\circ(\text{LXe})$, of this species equals $-10.9(2) \text{ kJ mol}^{-1}$, as derived from the temperature dependent behaviour of the cryosolution spectra. Theoretical complexation enthalpies in liquid xenon were obtained by combining the complete basis set extrapolated complexation energies at the MP2/aug-cc-pVXZ (X = D,T) level with corrections derived from statistical thermodynamics and Monte Carlo Free Energy Perturbation calculations, resulting in a complexation enthalpy of $-11.2(3) \text{ kJ mol}^{-1}$ for the isopropyl-bonded complex, in very good agreement with the experimental value, and of $-11.4(4) \text{ kJ mol}^{-1}$, for the fluoromethyl-bonded complex. The Monte Carlo calculations show that the solvation entropy of the isopropyl-bonded species is considerably higher than that of the fluoromethyl-bonded complex, which assists in explaining its dominance in the liquid phase spectra.

1. Introduction

The working principle of anaesthetics has been in the focus of vigorous research for many decades, always with the intention of improving and understanding their remarkable medical applications. The investigations have shown that they selectively interact with membrane proteins.¹ Model systems for these, *i.e.* reference proteins with specifically designed binding locations, have been developed and have been intensively studied with X-ray methods and spectroscopic techniques such as infrared and Raman, fluorescence and high resolution NMR.^{2–4}

The results point in the direction of direct binding *via* weak hydrogen bonds and van der Waals interactions to specific protein targets. The anaesthetics were found to bind preferentially to

aromatic side chains, for instance the indole part of tryptophan.² In a major calculational effort to simulate that kind of interactions, molecular dynamics calculations are being carried out^{2,5,6} that employ force fields which lead to binding strengths of the formed complexes in the range of $10\text{--}15 \text{ kJ mol}^{-1}$.⁷ This, from a dynamical point of view, amounts to average lifetimes of the complexes of $10\text{--}100$ picoseconds.⁵ Lifetimes in that order allow vibrational spectroscopy to observe the complexes as well-defined separate species. We have, therefore, initiated a vibrational study of the complexes of anaesthetics with simple model systems that are the building blocks of the real world biological materials, aiming at providing thermodynamic data from which, amongst others, the molecular dynamics can be validated.

For the present study, we have concentrated on sevoflurane, (CF₃)₂CHOCH₂F, one of the prevalent anaesthetics,^{7–9} and its interactions, in view of the above, with the ultimate aromatic model compound benzene, using supersonic jet and cryosolutions infrared and Raman spectroscopic techniques. The supersonic jet experiments allow the study of weakly bonded complexes, amplifying their concentration due to the low temperatures, without the complications of solvent influences. These complexes

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survive at the higher temperatures of the solutions in liquid xenon (LXe), where they can be studied under conditions of thermodynamic equilibrium, allowing the stoichiometry and complexation enthalpy to be determined.

2. Experimental and computational details

Samples of benzene (99.9%) and sevoflurane (1,1,1,3,3,3-hexafluoroisopropyl fluoromethyl ether, 99.98%) were purchased from Aldrich and Abbott, respectively, and were used without further purification. The sample of 1,1,1,3,3,3-hexafluoroisopropyl methyl- d_3 ether was prepared using 1,1,1,3,3,3-hexafluoroisopropanol (Aldrich, >99.0%), $DMSO_4-d_6$ (Aldrich, >99.0%) and NaOH, in a procedure similar to the one described by Baker *et al.*,¹⁰ followed by purification on a low-temperature, low-pressure fractionation column. The solvent gas xenon, used for the cryosolutions, has a stated purity of >99.995% and was supplied by Air Liquide. The helium used as a carrier gas in the supersonic jet experiments had a stated purity of 99.996% and was supplied by Linde.

Infrared spectra of the cryosolutions were recorded on a Bruker IFS 66v Fourier transform spectrometer. For the mid-infrared spectra, a Globar source was used in combination with a Ge/KBr beamsplitter and a LN_2 -cooled broad band MCT detector. For the far-infrared spectra, a 6 micron Mylar beamsplitter and a LHe-cooled bolometer were used. The interferograms were averaged over 500 scans, Blackman–Harris three-term apodized and Fourier transformed to yield spectra with a resolution of 0.5 cm^{-1} . The experimental set-up used to investigate the solutions in liquid noble gases has been described before.^{11–13} Liquid cells equipped with wedged Si windows with pathlengths of 0.6 and 10.0 mm were used to record the spectra.

Raman spectra of the cryosolutions were recorded using a Trivista 557 spectrometer consisting of a double $f = 50\text{ cm}$ monochromator equipped with a 2000 lines mm^{-1} grating, a $f = 70\text{ cm}$ spectrograph equipped with a 2400 lines mm^{-1} grating, and a back-illuminated LN_2 -cooled CCD detector. The 514.5 nm line of a 2017-Ar S/N 1665 Spectra-Physics argon ion laser was used for Raman excitation. The power of the incident laser beam was set to 0.8 W, and plasma lines were removed using an appropriate interference filter. Frequencies were calibrated using neon and mercury emission lines, and are expected to be accurate to $0.25\text{--}0.50\text{ cm}^{-1}$, depending on the frequency range. The full widths at half height of the most intense Ne lines studied typically are in the order of 0.5 to 0.6 cm^{-1} . A home-built liquid cell equipped with four quartz windows at right angles was used to record the spectra.^{11,14}

The Raman scattering set-up used for the jet-measurements was described previously.^{15,16} The gas mixtures were obtained by premixing 0.2% to 0.3% of the studied compounds with pure helium. The chamber was evacuated by a $250\text{ m}^3\text{ h}^{-1}$ and a $500\text{ m}^3\text{ h}^{-1}$ Roots pump backed by a $100\text{ m}^3\text{ h}^{-1}$ rotary vane pump. During the measurements the gas mixtures were collected in a 4.7 L Teflon coated reservoir and expanded through a homebuilt $2.5 \times 0.2\text{ mm}^2$ or $4 \times 0.15\text{ mm}^2$ slit nozzle into the chamber, with the stagnation pressure in the reservoir set to 700 and 1000 mbar. A frequency doubled continuous Nd:YVO₄ laser (532 nm, Coherent Verdi V18, $P = 18\text{ W}$)

serving as a light source was focused on the jet expansion at a distance of 2 mm from the nozzle exit. The 90° scattered light was filtered by a Raman edge filter (L.O.T., $\varnothing = 25\text{ mm}$, OD 6.0, $T > 90\%$, 535.4–1200 nm), dispersed by a McPherson Model 2051 monochromator ($f/8.6$, $f = 1000\text{ mm}$) and detected by a back-illuminated liquid N_2 cooled CCD camera (PI Acton, Spec-10:400 B/LN, $1340 \times 400\text{ pixel}$). The spectra represent averages over three to six jet measurements, each with a duration of 300 s. Cosmic ray signals were removed iteratively by comparing successive measurement blocks.

The infrared set-up in the jet-experiments has previously been described.^{17–19} Pure helium was used as carrier gas flowing through thermostated glass saturators which contained the studied compounds. The obtained gas mixture was collected in a 0.06 m^3 reservoir before being dumped into the jet chamber at a flow rate of about 2 mol s^{-1} through 6 pulsed magnetic valves (Parker) feeding the slit nozzle. The core 100 ms section of the gas pulse is sampled by an 80 kHz FTIR scan which provides a spectral resolution of 2 cm^{-1} . The attenuation of the modulated IR beam caused by the pulsed gas absorption is monitored with InSb or MCT detectors through KBr or CaF_2 optics and is referenced against the IR spectrum prior to the gas pulse. In this way, transient natural absorbances of less than 10^{-4} can be routinely detected.

Accurate *ab initio* energy calculations for weak complexes containing an aromatic moiety are somewhat problematic because they require quite sophisticated levels of calculation.²⁰ For the present complexes the required CCSD(T) calculations at the aug-cc-pVDZ level^{21–24} turn out to be beyond reasonable computational efforts. As a compromise, therefore, in this study we will discuss energies at the MP2/aug-cc-pVXZ level extrapolated to the complete basis set (CBS) limit, as the energies at that level appear to satisfactorily reproduce the experimentally determined complex stability. Harmonic and anharmonic force field calculations were performed at the MP2/cc-pVDZ level. The calculations were made using Gaussian03, Gaussian09²⁵ and Molpro2009.²⁶ Corrections for BSSE were accounted for using CP-corrected gradient techniques.

Corrections for zero-point vibrational and thermal influences were performed using standard statistical thermodynamics.²⁷ Solvation Gibbs energies for the monomers and for the complexes were derived from Monte Carlo Free Energy Perturbation simulations, using a modified version of BOSS 4.1.²⁸ They were calculated for a solution in LXe at temperatures between 177 and 217 K. The entropies and enthalpies of solvation were extracted using the expressions $\Delta_{\text{sol}}S = -(\partial\Delta_{\text{sol}}G/\partial T)_p$ and $\Delta_{\text{sol}}H = \Delta_{\text{sol}}G + T\Delta_{\text{sol}}S$.

3. Results and discussion

3.1 Monomer sevoflurane

The conformational landscape of sevoflurane was recently studied using a combined *ab initio*/microwave approach, by Lesarri *et al.*²⁹ These authors identified two stable conformers that differ in their values of the dihedral angles $\tau_1(F_5-C_4-O_3-C_2)$ and $\tau_2(C_4-O_3-C_2-H_1)$, collected in Table 1. Their global minimum at the MP2/6-311++G(2df,p) level

Table 1 Comparison of the geometrical properties and standard Gibbs energy differences with the global minimum of the conformers of sevoflurane

SEV1		SEV2		SEV3	
Lesarri <i>et al.</i>	MP2/cc-pVDZ	Lesarri <i>et al.</i>	MP2/cc-pVDZ	Lesarri <i>et al.</i>	MP2/cc-pVDZ
$\tau_1(\text{F}_5\text{--C}_4\text{--O}_3\text{--C}_2)$	$\pm 68^\circ$	$\pm 65.3^\circ$	$\pm 89^\circ$	$\pm 86.3^\circ$	$\pm 179.0^\circ$
$\tau_2(\text{C}_4\text{--O}_3\text{--C}_2\text{--H}_1)$	$\mp 15^\circ$	$\mp 15.6^\circ$	$\mp 171^\circ$	$\mp 169.9^\circ$	$\mp 8.8^\circ$
$\Delta G^{298}/\text{kJ mol}^{-1}$	0.0	0.0	16.4	15.4	15.9

has the following values (τ_1, τ_2) for these angles: ($-68^\circ; +15^\circ$), with an equivalent mirror image at ($+68^\circ; -15^\circ$). A higher-energy conformer was found with values [$(-89^\circ; +171^\circ); (+89^\circ; -171^\circ)$]. We have re-investigated the *ab initio* conformational landscape, using correlation-consistent basis sets. The choice for the latter was necessary in order to avoid problems with the benzene moiety of the complexes, as it is known that Pople-type basis sets cause basis set incompleteness errors^{30,31} for the planar configuration of that moiety.³² At the MP2/cc-pVDZ level we have identified three pairs of equivalent conformers that, as was the case with the previous investigation,²⁹ differ in the values of τ_1 and τ_2 . The values obtained have been collected in Table 1. Obviously, the global minimum, SEV1, in our calculations is identical to the one arrived at by Lesarri *et al.*, while our second conformer, SEV2, corresponds to their second one as well. SEV3 was not identified by Lesarri *et al.*²⁹ as a local minimum as it is in this study, but as a saddle point between two SEV1 minima, most likely as a consequence of the coarseness of the grid used to construct their conformational map.

Table 1 also contains the Gibbs energy difference ΔG^{298} , between the higher energy conformers and the global minimum, calculated at 298 K, using *ab initio* energies, rotational constants and harmonic frequencies. The values for the latter can be seen to be $+15.4$ and $+15.8$ kJ mol^{-1} for SEV2 and SEV3, respectively. These values force the conclusion that even at room temperature the conformational landscape of sevoflurane is largely, if not completely, dominated by the *near-cis*, *gauche* conformer SEV1. This conclusion appears to be supported by the microwave experiments reported by Lesarri *et al.*,²⁹ who were able to identify a single conformer only.

The *ab initio* harmonic frequencies and infrared intensities of the three conformers are given in Table S1 of the ESI.† A systematic study of the vibrations of sevoflurane appears not to have been published before. Therefore, we have paid some attention to the assignments of the observed bands, in particular to see if the spectra support the occurrence of a single conformer in the fluid phases.

Sevoflurane has three C–H bonds. Each of them can engage in a C–H $\cdots\pi$ bond with benzene, and it will be shown below that indeed two different types of complexes have been found, one in which the interaction takes place *via* the isolated C–H bond of the isopropyl moiety, while the other interacts *via* the CH_2 grouping of the fluoromethyl moiety. The complexation influences the strength of the C–H bonds involved, which makes that the C–H stretching region of the spectra of sevoflurane is of particular interest for the present study. That region in the infrared and Raman spectra of the vapour phase and of a solution in liquid xenon is shown in Fig. 1. Inspection shows the clear presence of six transitions, three of which must be assigned as C–H stretches. It follows from the

Fig. 1 Vibrational spectra in the C–H stretching region of sevoflurane. Vapour phase spectra are given in the top panels. The bottom panels give the corresponding spectra of a solution of sevoflurane in liquid xenon at 173 K containing mole fractions of 3×10^{-3} (infrared) and 2.5×10^{-2} (Raman). Infrared spectra are given in transmission mode in the traces *a*, Raman spectra are given in the traces *b*.

significant relative intensity of two of the remaining bands that resonance enhancement of overtones or combination bands is active.

As a first step, the C–H stretch of the isolated C–H bond of the hexafluoroisopropyl group was identified. We have done so by comparing the vapour phase infrared spectra, in the region involved, of sevoflurane and hexafluoroisopropyl methyl- d_3 ether. In the latter, it is straightforward to assign the C–H stretch to the single band in this region, at 2934.6 cm^{-1} . The corresponding vibration in sevoflurane is, however, not expected to be found at exactly the same frequency, because of the small difference in the bond length of the C–H bonds in the two molecules. From a calculation of the relaxed structure of the ether it is found that the equilibrium bond length is 0.0028 Å longer than in sevoflurane, so that the C–H stretch in the latter must be expected at higher frequency than in the deuterated ether. Assuming the difference in r_0 values is not significantly different from the above difference in r_e values, the relation between isolated C–H stretching frequencies and r_0 bond lengths by McKean *et al.*³³ shows that in sevoflurane the C–H stretching mode is expected to occur 27.4 cm^{-1} above the value in the ether, *i.e.* at 2962 cm^{-1} . Therefore, there is little doubt that we have to assign that stretching to the band at 2966 cm^{-1} in the vapour phase spectrum. Some circumstantial evidence supports this assignment: the vapour phase contour of the 2966 cm^{-1} band has a barely visible rotational structure, much less pronounced than the other modes in the same region, as can be appreciated from Fig. 1. This suggests that the 2966 cm^{-1} band is strongly broadened due to the presence of thermally excited states of vibrations localised in nearby groups. The two CF_3 groups attached to the same carbon atom have the required number of low-frequency deformation modes to provide the thermally excited states, while the single fluorine atom in the vicinity of the CH_2 group of sevoflurane does not provide similar conditions, and, therefore, should give rise to more clearly visible rotational structures. Further evidence comes from the increased relative intensity of this band in the Raman spectrum, which matches theoretical predictions. Finally, this band is most strongly red-shifted when moving to the liquid state (not shown), which already indicates its involvement in intermolecular interactions.

The other bands in the C–H stretching region remain to be assigned to the CH_2F -moiety of sevoflurane. It appears evident to assign the two most intense ones to the CH_2 stretches ν_1 and ν_3 . As can be seen in Fig. 1, the vapour phase contour of the former is predominantly type C, while that of the latter is predominantly type A. This difference in contour supports their assignment to an antisymmetric and a symmetric vibration of the same grouping, in this case the C–H stretches, ν_1 and ν_3 , of the fluoromethyl moiety. The bands with the weaker intensities, at 3008 , 2918 and 2814 cm^{-1} in the vapour phase then must be due to overtones and/or combination bands. As the deformation δCH_2 , ν_4 , and wagging ωCH_2 , ν_5 , are assigned (*vide infra*) in the vapour phase at 1502 and 1419 cm^{-1} , the weaker bands are assigned, in order of descending frequency, as $2\delta\text{CH}_2$, $\delta\text{CH}_2 + \omega\text{CH}_2$ and $2\omega\text{CH}_2$, the relative intensities at least of the two overtones suggesting significant resonance with the fundamentals. The relative intensities as well as the proposed assignments

of these CH_2 modes are consistent with, for instance, those of fluoromethyl methyl- d_3 ether.³⁴

In an attempt to gain insight into the resonances in the C–H stretching region, anharmonic frequencies at the MP2/cc-pVDZ level were calculated for sevoflurane, and also for fluoromethyl methyl- d_3 ether. Despite the similarity in the infrared intensities of the CH_2 multiplets in both compounds, these calculations resulted in the incongruent result that for fluoromethyl methyl- d_3 ether the main contribution to the highest, and more intense, component of the CH_2 multiplet is due to the fundamental ν_1 , but is due to the overtone $2\nu_4$ in sevoflurane, and *vice versa* for the less intense second component. The reason for this unexpected result is the second order perturbation calculation of the anharmonic frequencies as implemented in Gaussian,²⁵ which does not properly handle the significant resonances between ν_3 and the ν_4 and ν_5 overtone and combination levels. This is not a real surprise, as the stretch-bend resonances of C–H bonds go beyond the validity range of simple perturbation theory.³⁵ The problem was avoided by deleting the contributions due to the cubic force constants k_{344} , k_{355} and k_{345} from the second order perturbation calculation and by treating their influence *via* a separate local perturbation matrix. Because the harmonic frequency differences of ν_1 with $2\nu_4$ and $2\nu_5$ are much higher than those of ν_3 with the same overtones, and because the force constants k_{144} and k_{155} are significantly smaller than k_{344} and k_{355} , the second order perturbation procedure in Gaussian leads to reliable anharmonic corrections due to k_{144} and k_{155} . Therefore, there is no need to include ν_1 in the local perturbation matrix treatment of the Fermi resonances. Thus, the correct assignments for ν_3 , $2\nu_4$, $2\nu_5$ and $\nu_4 + \nu_5$ of sevoflurane were obtained by diagonalising a 4×4 matrix A , the diagonal elements of which were the partially anharmonic frequencies derived from second order perturbation theory without the contributions due to k_{344} , k_{355} , and k_{345} , these being used to construct the non-zero non-diagonal matrix elements. Using the Nielsen notation, the values of these cubic force constants as derived from the *ab initio* calculations are $k_{344} = -84.52\text{ cm}^{-1}$, $k_{355} = -130.06\text{ cm}^{-1}$ and $k_{345} = -4.67\text{ cm}^{-1}$. The diagonal elements obtained from the calculations, *i.e.* the *ab initio* Fermi deperturbed frequencies, have been collected in Table 4 under the heading ν_{ai} . It is rather evident that they are unreliable estimates of the real values: for instance, diagonalizing the above perturbation matrix in which they are used leads to an anharmonic value for $2\nu_4$ of 3058.3 cm^{-1} , while the corresponding mode in the experimental spectrum appears at 3008 cm^{-1} . In contrast, it is the experience that at the level of computation used here, *ab initio* cubic force constants are acceptable approximations to the real values.¹⁴ Better values for the Fermi deperturbed frequencies were, therefore, derived in the following iterative procedure. In the first step the eigenvalue problem defined using the *ab initio* data was solved: $A = LAL^{-1}$. Then, using the same expression, a new matrix, A' , is constructed using the eigenvector matrix L of A , and the diagonal matrix A_{exp} containing the experimentally observed frequencies ν_{exp} , collected in the last column of Table 4. This matrix is subsequently transformed into a new perturbation matrix A'' by replacing its non-diagonal elements by those of A . This matrix A'' is then used to start the next iteration step.

In the first few steps the convergence of this procedure is fast, but then slows down to produce, after 20 steps, the anharmonic frequencies ν_{calc} given in Table 4. They can be seen to be in very good agreement with the observed frequencies. The Fermi deperturbed frequencies, appearing as the diagonal elements of the 20th A'' matrix, are collected in Table 4 as the ν_{ft} . Comparison of the latter with the ν_{exp} shows that the Fermi resonance significantly affects the highest and lowest members of the quadruplet, while the inner ones, ν_3 and $\nu_4 + \nu_5$, are hardly shifted. This obviously is the consequence of the fact that their downward shift due to the resonance with $2\nu_4$ is as good as compensated by their upward shift due to the resonance with $2\nu_5$.

From the comparison of the observed infrared and Raman spectra in liquid xenon and in the jets with the calculated frequencies the assignment of the fundamentals ν_4 to ν_{38} is straightforward. With one exception these fundamentals appear as singlets in the liquid xenon spectra. The data in Table S1 (ESI†) indicate that for a significant number of these fundamentals conformational frequency shifts of more than

5 cm^{-1} are predicted. Hence, the observation of singlets does not support the presence of a second conformer. The exception is ν_{27} , which appears at 523.3 cm^{-1} . In the liquid xenon spectra this band shows a clear low frequency shoulder near 518 cm^{-1} , while SEV2 and SEV3 are predicted to show shifts of -3.3 and -21.4 cm^{-1} . The anharmonic frequency calculations, however, predict a Fermi resonance between ν_{27} and the combination level $\nu_{28} + \nu_{37}$, with the component closest to the fundamental appearing on the high frequency side. We, therefore, favor the assignment of this doublet as due to a Fermi resonance rather than as an indication for the presence of a second conformer.

At this point it is worth noting that for the transitions in the fingerprint region the harmonic MP2/cc-pVDZ frequencies agree rather well with the experimental values: the Root Mean Square (RMS) deviation for the modes $\nu_{19} - \nu_{38}$, situated between 1000 and 50 cm^{-1} , is 9.4 cm^{-1} . As most of the calculated frequencies in the region concerned are slightly overestimated, an improvement of the RMS deviation must

Table 2 Characteristic frequencies, in cm^{-1} , and vibrational assignments for jet expansions of sevoflurane and for solutions in liquid xenon at 173 K, in comparison with harmonic and anharmonic MP2/cc-pVDZ and MP2/aug-cc-pVDZ vibrational frequencies, in cm^{-1} . Infrared intensities, in km mol^{-1} , and Raman scattering activities (RSA), in $\text{\AA}^4 \text{ amu}^{-1}$, for the global minimum conformer, SEV1

Assignment	Experimental frequencies				MP2/cc-pVDZ				MP2/aug-cc-pVDZ	
	IR (LXe) ν	Raman (LXe) ν	IRjet ν	Raman jet ν	Harmonic			Anharmonic ν	Harmonic	
					ν	Int(IR)	RSA		ν	Int(IR)
ν_1	3021	3021	3032	3031	3220.2	25.0	73.0	3077.8	3225.5	10.2
ν_2	2956	2956	2968	2966	3143.0	2.2	51.2	3016.2	3120.8	15.7
ν_3	2929	2929	2939	2938	3119.5	42.3	78.4	3029.2	3116.2	16.1
ν_4	1497.7	1496.9	—	—	1538.2	2.7	8.0	1540.4	1524.4	0.7
ν_5	1415.9	1415.9	—	1414.3	1465.3	21.6	2.5	1453.7	1431.1	8.8
ν_6	1380.5	—	—	—	1438.3	134.8	1.9	1404.0	1413.9	86.0
ν_7	1370.0	1370.3	—	1370.9	1416.4	55.6	3.1	1383.9	1392.1	56.1
ν_8	1299.7	1297.8	—	1302.0	1348.9	329.8	2.6	1321.0	1311.8	191.1
ν_9	1291.6	—	—	1290.3	1321.5	32.4	1.7	1293.7	1293.1	20.2
ν_{10}	1280.1	1279.3	—	1278.1	1311.1	22.4	4.1	1279.2	1281.3	42.6
ν_{11}	1270.3	—	—	1270.1	1283.2	458.2	1.2	1259.3	1219.3	522.4
ν_{12}	1233.0	—	—	1234.9	1257.5	215.5	3.1	1231.4	1207.6	245.8
ν_{13}	1213.7	1212.1	—	1212.5	1215.2	50.1	0.6	1191.0	1188.4	64.2
ν_{14}	1182.9	—	—	1182.5	1211.1	101.0	1.0	1184.7	1152.0	12.2
ν_{15}	1130.4	1129.7	—	1130.2	1166.0	171.9	2.3	1138.4	1138.7	144.4
ν_{16}	1111.5	1110.7	—	1111.5	1145.3	173.4	1.6	1122.7	1098.1	159.0
ν_{17}	1032.2	1031.3	1038.5	1035.4	1091.5	128.8	2.1	1064.4	1042.8	42.7
ν_{18}	1021.6	1020.0	1027.9	1026.9	1060.8	27.0	3.2	1036.0	1012.7	161.5
ν_{19}	905.3	906.0	910.6	—	928.3	50.3	0.8	914.6	906.1	56.7
ν_{20}	879.1	879.9	882.8	—	902.1	20.2	4.4	888.3	880.7	19.6
ν_{21}	742.6	742.5	744.8	743.3	749.3	7.4	3.9	740.7	726.1	5.7
ν_{22}	690.9	690.3	692.3	690.5	697.0	49.4	0.5	689.9	674.8	43.9
ν_{23}	—	602.8	603.4	603.0	611.0	6.7	2.3	604.6	592.2	9.2
ν_{24}	567.4	566.2	—	566.2	582.9	5.8	1.2	575.0	559.1	4.5
ν_{25}	548.5	—	—	—	556.1	2.0	0.5	551.8	535.0	1.7
ν_{26}	537.2	536.6	—	536.7	542.5	3.6	0.6	537.9	519.5	3.0
ν_{27}	523.3	—	—	522.2	526.3	11.5	1.5	523.0	504.9	9.9
ν_{28}	444.1	442.9	—	443.5	452.8	2.2	0.8	447.1	439.1	1.8
ν_{29}	358.9	358.9	—	358.9	366.9	4.7	1.2	361.1	361.4	5.2
ν_{30}	329.3	328.8	—	327.1	336.2	1.3	1.6	333.0	326.8	1.4
ν_{31}	298.3	298.2	—	298.4	297.9	1.9	0.8	293.8	292.2	2.5
ν_{32}	294.4	294.6	—	293.5	295.6	1.7	0.5	291.5	288.7	0.8
ν_{33}	224.3	224.0	—	219.5	225.1	2.0	0.4	223.3	220.3	1.9
ν_{34}	193.8	193.2	—	—	191.2	0.3	0.2	187.7	190.6	0.2
ν_{35}	161.7	—	—	—	166.2	4.4	0.0	160.3	163.1	3.9
ν_{36}	106.4	—	—	—	111.4	4.5	0.1	106.9	103.1	5.0
ν_{37}	71.8	—	—	—	70.7	0.5	0.0	65.3	69.4	0.9
ν_{38}	54.7	—	—	—	54.8	1.1	0.0	49.7	51.3	1.6
ν_{39}	—	—	—	—	31.0	0.0	0.0	24.3	34.0	0.0

be expected when anharmonicities are corrected for. The anharmonic data in Table 2 confirm this, the RMS deviation being reduced to 6.4 cm^{-1} . To see if an expansion of the basis set to MP2/aug-cc-pVDZ would result in an improvement, the harmonic frequencies at that level were also calculated: the results are also given in Table 2, the RMS deviation for the same range of frequencies being 8.3 cm^{-1} , *i.e.* marginally better than the MP2/cc-pVDZ values. However, it can also be seen that most of the harmonic frequencies are predicted at values below the experimentally observed transitions, so that corrections for anharmonicity would only worsen the RMS deviation. Therefore, MP2/aug-cc-pVDZ calculations of frequencies, neither for monomers nor for complexes, were further pursued.

3.2 Sevoflurane homo-dimers and larger clusters

The isolated C–H bonds of sevoflurane can act as Lewis acids, and its oxygen atom is a Lewis base. This allows the possibility to form homo-complexes of various complexities. As an example, the *ab initio* homo-dimers are given in Fig. 2. Indications that dimers and higher clusters do form are found in the jet spectra. This can be illustrated with the spectra in Fig. 3, which give the Raman, top panel, and infrared, bottom panel, jet spectra of mixtures of the carrier gas helium and sevoflurane. It is clear from the traces that the monomer ν_3^{sevo} band at 2918 cm^{-1} is accompanied by a series of blue shifted bands with decreasing intensity, and that these bands decrease in relative intensity for the less concentrated mixtures shown in traces b, confirming that they originate in composite species of sevoflurane that contain not only the dimers of Fig. 2, but also trimers and higher clusters. Similar bands have been observed in the neighbourhood of other sevoflurane bands. The complexity in the number of oligomer bands, and the problem of the possibility of forming different isomeric species, makes that the exact nature of the individual weak bands is presently not fully understood. They, therefore, will form the subject of a separate study in which the observed features will be investigated in combination with similar bands detected in the jet spectra of other anaesthetics, such as isoflurane and desflurane.³⁶ It is clear from Fig. 3, however, that they have sufficiently been documented to prevent them from being mistaken as bands due to complexes formed between sevoflurane and benzene.

3.3 Sevoflurane/benzene complexes: infrared and Raman spectra

Structural information on the interactions between sevoflurane and benzene was obtained from MP2/cc-pVDZ and MP2/aug-cc-pVDZ *ab initio* calculations. For both basis sets the

Fig. 2 The isopropyl-bonded (left) and fluoromethyl-bonded (right) dimers of sevoflurane.

Fig. 3 The top panel gives Raman jet spectra of the C–H stretching region of sevoflurane at different concentrations. Trace *a* was recorded from a mixture of 700 mbar with 0.3% of sevoflurane in the reservoir, trace *b* was recorded from a mixture of 200 mbar 0.3%. Infrared jet spectra for the same region are given in the bottom panel, with trace *a* recorded from a mixture with a higher stagnation pressure of sevoflurane than that shown in trace *b*.

Fig. 4 The 1 : 1 complexes of sevoflurane with benzene. The isopropyl-bonded complex is shown on the left hand side, the fluoromethyl-bonded complex is shown on the right hand side.

geometry optimizations involving the dominant *near-cis*, *gauche* conformation lead to two different isomers. In the most stable structure, shown on the left in Fig. 4, sevoflurane binds towards benzene through the hydrogen atom in the isopropyl moiety. In the second isomer, presented on the right in Fig. 4, the two C–H bonds in the fluoromethyl group simultaneously bind to the aromatic ring, forming a so-called bifurcated structure. The MP2/cc-pVDZ and MP2/aug-cc-pVDZ harmonic vibrational frequencies and complexation shifts for monomer sevoflurane and for the complexes with benzene are summarized in Tables S2 and S3 of the ESI.†

Experimental information on the different complexes of sevoflurane with benzene was obtained by recording infrared and Raman spectra of a series of mixtures in LXe, and by recording the spectra of mixtures of both gases in helium jets. In the following paragraphs the main spectral features of the

Table 3 Experimental vibrational frequencies of the sevoflurane/benzene complexes, $\nu_{\text{compl}}^{\text{exp}}$, observed in supersonic jets (jet) and in liquid xenon (LXe), and corresponding calculated frequencies for monomers, $\nu_{\text{mono}}^{\text{calc}}$, and for the isopropyl-bonded (i) and fluoromethyl-bonded (f) complexes, and experimental, $\Delta\nu_{\text{exp}}$, and calculated, $\Delta\nu_{\text{calc}}$, complexation shifts. All frequencies and frequency shifts are in cm^{-1} .

	$\nu_{\text{compl}}^{\text{exp}}(\text{jet})$	$\nu_{\text{compl}}^{\text{exp}}(\text{LXe})$	$\nu_{\text{mono}}^{\text{calc}}$	$\nu_{\text{compl}}^{\text{calc}}(\text{i})$	$\nu_{\text{compl}}^{\text{calc}}(\text{f})$	$\Delta\nu_{\text{exp}}(\text{jet})$	$\Delta\nu_{\text{exp}}(\text{LXe})$	$\Delta\nu_{\text{calc}}(\text{i})$	$\Delta\nu_{\text{calc}}(\text{f})$
Sevoflurane									
ν_1	3024	3016	3220.2	3211.1	3237.0	−7	−5	−9.1	16.8
ν_2	2962	2950	3143.0	3137.5	3141.0	−3	−5.3	−5.5	−2.0
ν_3	2932.5	—	3119.5	3111.1	3125.8	−5.5	—	−8.4	6.3
Benzene									
$\nu_4(\text{i})$	682	681.5	686	692.5	690.2	7	6.5	6.5	4.2
$\nu_4(\text{f})$	—	678	686	692.5	690.2	—	3	6.5	4.2
$2\nu_{13}$	2952	2944	—	—	—	—	−5.9	—	—

Table 4 *Ab initio* Fermi deperturbed frequencies, ν_{ai} , iterated Fermi-deperturbed frequencies, ν_{it} , calculated Fermi perturbed frequencies, ν_{calc} , and experimental vapor phase frequencies, ν_{exp} , of the fluoromethyl moiety vibrations in the C–H stretching region of sevoflurane. All frequencies are in cm^{-1} .

	ν_{ai}	ν_{it}	ν_{calc}	ν_{exp}
$2\nu_4$	3012.5	2967.5	3009.6	3008
ν_3	2995.7	2940.4	2935.3	2937
$\nu_4 + \nu_5$	2945.9	2918.1	2918.0	2918
$2\nu_5$	2879.6	2851.0	2814.1	2814

mixed solutions will be discussed. We will use the Herzberg number and symmetry label for the modes of the monomers as well as for the corresponding modes in the complex.

The presence of a complex in the spectra of mixtures of the two monomers must be derived from the appearance of new bands that are not present in the spectra of either monomer. Inspection shows that in a limited number of cases such bands have indeed been found. Relevant data on them have been collected in Table 3. As a general remark it may be pointed out that in some cases the band frequencies measured in the jet spectra differ significantly from those in solution. These differences are not due to calibration errors but are due to solvent influences and also to temperature effects, as was shown recently.²⁰ We will return to this point later.

A spectral region from which not only the formation of a complex can be seen but which also allows the identification of the isomer formed is shown in Fig. 5, giving the 2975–2915 cm^{-1} ν_2^{sevo} , ν_3^{sevo} and $2\nu_{13}^{\text{benz}}$ region of the spectra. The Raman jet spectra of sevoflurane/benzene mixtures, traces *a* and *b* in the top left panel, show the presence of a prominent new band at 2932.5 cm^{-1} , red shifted by 5.5 cm^{-1} from the monomer ν_3^{sevo} . Inspection of Table S2 (ESI†) shows that the predicted shifts for that mode are 6.3 cm^{-1} to the blue and 8.4 cm^{-1} to the red for the fluoromethyl- and isopropyl-bonded complexes, respectively. The quality of the predicted complexation shifts is such³⁷ that from the red shift of the observed 2932.5 cm^{-1} band can be concluded with confidence that it is due to the isopropyl-bonded complex. The absence of a blue-shifted complex band in the same traces further shows that under the circumstances used the concentration of the fluoromethyl-bonded isomer must be significantly less. The infrared jet spectra in the bottom left panel confirm the conclusion and at the same time illustrate that as the benzene concentration is increased, the ν_3^{sevo} sevoflurane/benzene band increases in relative intensity, while the intensities of the sevoflurane homopolymer

Fig. 5 The left hand panels show jet Raman, top panel, and jet infrared spectra, bottom panel, of mixtures of sevoflurane and benzene in the 2975–2915 cm^{-1} C–H stretching region. In these panels, trace *a* gives the spectrum of a mixture with a higher concentration of benzene than that used for trace *b*. Traces *c* and *d* are monomer spectra of sevoflurane and benzene, respectively. The right hand side panels give the corresponding region of the Raman, top panel, and infrared spectra, bottom panel, of solutions of sevoflurane and benzene in liquid xenon. Traces *a* give the spectrum of a sevoflurane/benzene mixture, traces *b* and *c* are rescaled monomer spectra of sevoflurane and benzene, respectively, and traces *d* give the spectrum of the complexes as obtained by subtracting the monomer spectra from that of the mixture.

bands decrease, suggesting there is competition between the two phenomena.

The same panels show further monomer bands, due to $2\nu_{13}^{\text{benz}}$ near 2956 cm^{-1} and due to ν_2^{sevo} near 2965 cm^{-1} . The former mode in the complex is assigned to the low frequency shoulder which is most clearly visible in trace *a*. Its shift is in line with expectations, *i.e.* a red shift of twice the predicted value for ν_{13}^{benz} of 1.3 cm^{-1} . In trace *c* of the Raman jet spectra, top left panel of Fig. 5, homopolymer bands are easily detected on the high frequency side, near 2970 cm^{-1} , of monomer ν_2^{sevo} , while in trace *a* these are largely replaced by a low-frequency complex band, red shifted by approximately 3 cm^{-1} , in reasonable agreement with the predicted shift of −5.5 cm^{-1} for the isopropyl-bonded complex. With $2\nu_{13}^{\text{benz}}$ not showing up in the 2975–2940 cm^{-1} region of the infrared jet spectra, bottom left panel, only weak, diffuse bands can be detected, which must be interpreted as due to ν_2^{sevo} , but the lack of resolution in this region prevents a detailed analysis.

The panels on the right hand side of Fig. 5 contain the corresponding Raman and infrared spectra of the species in cryosolutions. The subtraction-experiments leading to the spectrum of the complex in trace *d* of the Raman spectra, top right panel, show no evidence for a ν_3^{sevo} band in the complex. Complex bands do clearly show up, however, for ν_2^{sevo} and $2\nu_{13}^{\text{benz}}$. Their complexation shifts are -5.3 and -5.9 cm^{-1} . In the infrared spectra, lower right panel, the only features that show up in the difference spectrum of the complex, trace *d*, are some very weak intensities on either side of the band maximum of the monomer ν_3^{sevo} and a very weak low-frequency shoulder on ν_2^{sevo} . It is tempting to associate the former intensities with the presence of homopolymers or a complex with benzene, but it is felt as more likely that its presence is due to minor temperature differences between the solutions used to record traces *a* and *b*, and/or to minor differences in the solvent influences on monomer sevoflurane between the two solutions. The frequency shift of the low frequency shoulder on ν_2^{sevo} , -5.5 cm^{-1} , correlates very well with the ν_2^{complex} transition which was clearly identified in the Raman spectrum.

The only further region of the spectra where clear evidence is found for the presence of complex bands is the $\nu_{22}^{\text{sevo}}/\nu_4^{\text{benz}}$ region, $695\text{--}670$ cm^{-1} , shown in Fig. 6, with the results in LXe shown in the upper panel and those for the jet spectra in the lower one. In both panels a prominent new band

Fig. 6 The ν_{22}^{sevo} and ν_4^{benz} region of infrared spectra in liquid xenon, top panel, and in the jet, bottom panel, of sevoflurane and benzene. Traces *a* are the spectra of the sevoflurane/benzene mixture and traces *b* and *c* give the monomer benzene and sevoflurane spectra, respectively. The mole fractions of sevoflurane and benzene in the mixture are 5×10^{-3} and 3×10^{-3} , respectively.

is seen in the spectra of the mixtures near 682 cm^{-1} , approximately midway between ν_{22}^{sevo} , in the cryosolution at 690.5 cm^{-1} , and the out-of-plane A_{1u} ν_4^{benz} , in the cryosolution at 675.0 cm^{-1} . The predicted complexation shifts, at the two levels of calculation, for the isopropyl-bonded isomer of the complex in Tables S2 and S3 (ESI†) show that the ν_{22}^{sevo} in the complex must be red shifted, by 1.0 or 1.2 cm^{-1} , from the monomer band, while for ν_4^{benz} it is expected to be blue shifted, by 6.5 or 8.9 cm^{-1} . With the 682 cm^{-1} band red shifted by some 9 cm^{-1} from the monomer ν_{22}^{sevo} and blue shifted by 6.5 cm^{-1} from monomer ν_4^{benz} , its assignment as ν_4^{benz} is much more likely, and is adapted here. A second new feature, much less intense than the first one, can be seen in the top panel near 679 cm^{-1} , while there is indication that it is also present as a high frequency shoulder on the homo-dimer ν_4^{benz} band at 677 cm^{-1} in the lower panel. The predicted frequencies make it highly unlikely that it is due to ν_{22}^{sevo} in the isopropyl-bonded complex. It is, therefore, more likely to originate in the less stable fluoromethyl-bonded complex. The distance of the feature from monomer ν_{22}^{sevo} , 12.5 cm^{-1} , is significantly larger than the predicted complexation shift of ν_{22}^{sevo} , -0.8 or -0.6 cm^{-1} , while its distance from ν_4^{benz} , 3 cm^{-1} , agrees much better with the predicted complexation shift of ν_4^{benz} , 4.2 or 6.7 cm^{-1} . We therefore, assign it to the latter mode. In view of the similar *ab initio* infrared intensities of the ν_4^{benz} modes in the two isomers of the complex, Tables S2 and S3 (ESI†), the relative intensity of the weak band, which can be estimated to differ by at least an order of magnitude from that of the 682 cm^{-1} band, is sufficiently small to not contradict the absence of a ν_3^{sevo} band of the fluoromethyl-bonded isomer in the 2925 cm^{-1} region.

3.4 Sevoflurane/benzene complexes: stoichiometry and complexation enthalpy

From the above it is clear that the complexes formed between sevoflurane and benzene are dominated by the isopropyl-bonded isomer, with a minor fraction of the fluoromethyl-bonded isomer. The 682 cm^{-1} band in the cryosolutions due to the more abundant species is well defined and allows quantitative analysis. In the first place the stoichiometry of the isopropyl-bonded complex was determined, using data from an isothermal concentration study of the cryosolutions. The mole fractions used vary between 1.0×10^{-3} and 4.0×10^{-3} for benzene and 1.5×10^{-3} and 6.5×10^{-3} for sevoflurane. The integrated intensity of the 682 cm^{-1} band was plotted *versus* products of the monomer intensities $(I_{\text{sevo}})^n \times (I_{\text{benz}})^m$ with *n* and *m* being 1, 2 and 3. As monomer intensities the integrated intensities of the ν_4^{sevo} band at 1497 cm^{-1} and the $\nu_4^{\text{benz}} + \nu_{11}^{\text{benz}}$ band at 1520 cm^{-1} were used. The plots are shown in Fig. S2 of the ESI†. The χ^2 values of the linear regression lines clearly support the 1 : 1 stoichiometry of the complex.

The standard complexation-enthalpy difference of the isopropyl-bonded complex was determined using the van't Hoff relation²⁰ which establishes a linear relation, with a slope related to $\Delta H^\circ(\text{LXe})/R$, between the inverse temperature $1/T$ and the natural logarithm of the intensity product $I_{\text{compl}}/(I_{\text{sevo}} \times I_{\text{benz}})$. To exploit this relation, infrared spectra of mixed solutions were recorded at temperatures between 169 and 213 K. The resulting van't Hoff plots, obtained by again using the areas of the 682 cm^{-1} , 1497 cm^{-1} and

1520 cm⁻¹ bands, are shown in Fig. S1 of the ESI.† The slopes of the regression lines were corrected for the temperature variations of the density of the solution³⁸ and yield an average standard complexation enthalpy $\Delta H^\circ(\text{LXe})$ of $-10.9(2)$ kJ mol⁻¹.

In view of the weakness and the poor resolution of the 679 cm⁻¹ band, no attempts were made to either confirm the stoichiometry or measure the complexation enthalpy.

3.5 Sevoflurane/benzene complexes: discussion

Table 5 contains the *ab initio* complexation energies ΔE for both complexes, calculated at a few different levels of theory. It also contains the main statistical thermodynamic quantities, calculated at 196 K, the central temperature in the range used for solutions in LXe. The thermodynamic quantities include the zero point and thermal contributions to the vapour phase standard complexation enthalpy, $\Delta_T H$, the solvation contributions to the same quantity, $\Delta_{\text{sol}} H$ and the standard complexation enthalpy in liquid xenon, $\Delta_{\text{calc}} H^\circ(\text{LXe})$, calculated using the MP2_{CBS}/aug-cc-pVXZ energies. The table further contains the calculated vapour phase standard entropy difference, $\Delta S^\circ(\text{vap})$, the solvation contributions to the entropy difference, $\Delta_{\text{sol}} S$, and the standard complexation entropy difference in liquid xenon, $\Delta S^\circ(\text{LXe})$.

It is clear that at the level selected for further use, MP2_{CBS}/aug-cc-pVXZ, the predicted complexation energy of the isopropyl-bonded complex is larger by at least 1.8 kJ mol⁻¹ than for the other levels. It can further be seen in Table 5 that this value eventually leads to a calculated standard complexation enthalpy in liquid xenon equal to $-11.2(3)$ kJ mol⁻¹, which is in very good agreement with the experimental value of $-10.9(2)$ kJ mol⁻¹. This supports our preference for the chosen level, as it is evident that selection of one of the others would result in a poorer agreement of calculation with experiment.

It can also be seen in Table 5 that the *ab initio* calculations predict a clear difference in the stability of both types of complexes, with the isopropyl-bonded complex more stable by 4.7–7.6 kJ mol⁻¹. The zero point and thermal corrections that translate the energies into vapour phase enthalpies hardly affect the relative stabilities, but the Monte Carlo solvation destabilization is much more important for the isopropyl-bonded complex than for the other complex. The result is that the predicted standard complexation enthalpies are very close, with in fact the fluoromethyl-bonded complex slightly more

stable. It is clear that in order to reconcile this result with the relative intensities in the observed spectra, where the bands due to the isopropyl complex are considerably more intense than those of the fluoromethyl complex, the entropic contributions to the standard Gibbs energy difference must tip the balance in favor of the isopropyl-bonded complex. The results in Table 5 confirm this, at least in part. Although the rotational constants and vibrational frequencies for both complexes are slightly different, their entropic contributions are very similar, resulting in almost identical values for the vapor phase standard entropy difference, as is clear from Table 5. However, the solvation contributions to the entropy are significantly larger for the isopropyl-bonded complex than for the other. At 196 K this results in a difference in the standard Gibbs complexation energy of some 2.1 kJ mol⁻¹ between the complexes, and this leads to a concentration ratio of the complexes of 3.75 in favor of the isopropyl-bonded complex. Thus, the relative concentrations are in the right direction, but a rough estimate of the relative intensity of the 679 cm⁻¹ in comparison with that of the 682 cm⁻¹ band shows that the calculated ratio is too small by a factor of at least 5. The causes of that may be multiple, but it cannot be excluded that the difference in the *ab initio* complexation energy between the two complexes is somewhat underestimated, which most likely would be the consequence of the compromise, discussed above, about the level at which the present *ab initio* calculations had to be made.

Recently, we have discussed the complexes of another anaesthetic, halothane, CF₃CHBrCl, with benzene.²⁰ At identical levels, the *ab initio* complexation energy of the 1 : 1 halothane complex differs by not more than 1 kJ mol⁻¹ from that of the isopropyl-bonded sevoflurane complex, and the complexation enthalpy of the former, in liquid krypton, $-9.8(2)$ kJ mol⁻¹, is close to the value of $-10.9(2)$ kJ mol⁻¹ for the sevoflurane complex. This suggests that both complexes are held together by very similar hydrogen bonds. The jet spectra result in a complexation shift of the halothane C–H stretching of $+5.5$ cm⁻¹, changing to -0.5 cm⁻¹ at the lowest temperature, and -3.4 cm⁻¹ at the highest temperature in liquid krypton, and -7.7 cm⁻¹ in the room temperature vapour phase spectrum. That evolution was explained by the dependence of the halothane C–H stretching frequency on the van der Waals vibrations of the complex. That frequency tends to decrease with increasing excitation of the van der Waals modes, so that the significant increases in the relative populations of the latter with increasing temperature cause a remarkable downward shift of the observed C–H stretching band. With an estimated vibrational temperature of 50 K, the jet spectra, therefore, must be regarded as giving the best approximation to the ground state complexation shift. For the sevoflurane complex the corresponding shift is that of ν_2^{sevo} , which, as was shown above, equals -3 cm⁻¹. Thus, despite the resemblance of complexation energies and enthalpies, the C–H bonds in halothane and in the isopropyl moiety of sevoflurane have a different aspect, with the one in the sevoflurane complex showing a red shift, compared to a blue shift for the halothane complex. The shift of ν_2^{sevo} increases to -5.3 cm⁻¹ in liquid xenon, *i.e.* the mode shifts in the same direction as for the halothane complex. Taking into account the higher temperature

Table 5 *Ab initio* complexation energies, in kJ mol⁻¹, statistical thermodynamic enthalpic quantities, in kJ mol⁻¹, and statistical thermodynamic entropic quantities, in kJ mol⁻¹ K⁻¹, for the two types of complexes of sevoflurane with benzene

	Isopropyl-bonded complex	Fluoromethyl-bonded complex
$\Delta E(\text{MP2/aug-cc-pVDZ})$	-27.8	-20.2
$\Delta E(\text{MP2/aug-cc-pVTZ})$	-30.1	-24.1
$\Delta E(\text{MP2}_{\text{CBS}}/\text{aug-cc-pVXZ})$	-31.9	-27.2
$\Delta_T H$	6.4(3)	6.6(4)
$\Delta_{\text{sol}} H$	14.3(3)	9.2(2)
$\Delta_{\text{calc}} H^\circ(\text{LXe})$	-11.2(4)	-11.4(4)
$\Delta S^\circ(\text{vap})$	-0.1275	-0.1272
$\Delta_{\text{sol}} S$	0.0309	0.0189
$\Delta S^\circ(\text{LXe})$	-0.0966	-0.1083

of the LXe solution, it is clear, however, that the shift per unit temperature for the halothane complex is larger than in the sevoflurane case. This reflects the lesser sensitivity of ν_2^{sevo} to excitation of the van der Waals modes than for the C–H stretching of halothane, and it confirms the different aspects of both C–H bonds involved. Unfortunately, all attempts to observe ν_2^{sevo} of the complex in room temperature vapor phase spectra have failed up to now, so that it cannot be confirmed if this trend persists at higher temperatures.

4. Conclusions

An assignment of the observed vibrational fundamentals of sevoflurane has been proposed and a detailed analysis of the bands in the C–H stretching region has been made, allowing the identification of the Fermi resonances active in this region.

The interaction of sevoflurane with the aromatic model compound benzene has been studied using vibrational spectroscopy of supersonic jet expansions and cryosolutions in liquid xenon. The experimental data show that sevoflurane interacts with the electron rich π -system of the aromatic model system, either through the isolated C–H bond in the isopropyl group or through the C–H bonds in the fluoromethyl group, the former giving rise to the more abundant complex. The *ab initio* complexation energies at the MP2_{CBS}/aug-cc-pVXZ level for these complexes are $-31.9(3)$ and $-27.2(4)$ kJ mol⁻¹, respectively. When corrected for zero-point vibrational and thermal influences, and for solute–solvent interactions, these energies translate into calculated complexation enthalpies in liquid xenon, $\Delta_{\text{calc}}H^\circ(\text{LXe})$ of $-11.2(3)$ and $-11.4(4)$ kJ mol⁻¹. The former, for the isopropyl-bonded complex, compares favourably with the experimental complexation enthalpy of $-10.9(2)$ kJ mol⁻¹, derived from the temperature dependent behaviour of the spectra.

The experimental observation of intermolecular complexes formed between sevoflurane and benzene, and the spectroscopic and thermodynamical properties derived are in line with results previously obtained for halothane–benzene complexes,²⁰ and confirm that the binding of anaesthesia with neuroreceptors is possible, even at room temperature, *via* a direct C–H $\cdots\pi$ type hydrogen bonding^{39–41} involving a polarized C–H bond in the anaesthetic and an aromatic site in the neuroreceptor. Hereby we emphasize that the term “hydrogen bonding” reflects the structural characteristics of the C–H $\cdots\pi$ interaction and not its electronic properties, which are rather different from those in a “classical” hydrogen bond.^{42,43}

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