Multinuclear NMR studies of gaseous and liquid sevoflurane

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Abstract

For the first time, a small amount of sevoflurane $((CF_3)_2CHOCH_2F)$ in carbon dioxide and xenon as the gaseous solvents has been studied using ^{19}F and ^1H NMR spectra. Density-dependent ^{19}F and ^1H nuclear magnetic shielding was observed when the pressure of each solvent was increased. After extrapolation of the results to the zero-density limit it was possible to determine the appropriate shielding constants free from intermolecular interactions, $\sigma_0(F)$ and $\sigma_0(H)$. Similar procedure has also been applied for the investigation of fluorine-proton spin–spin couplings and the $^2J_0(FH)$ and $^3J_0(FH)$ constants of an isolated $(CF_3)_2CHOCH_2F$ molecule were also obtained. Additionally, high-resolution ^1H, ^{13}C, ^{17}O and ^{19}F NMR spectra of pure liquid sevoflurane were also recorded and all the $^1H–^{13}C$, $^1H–^{19}F$ and $^{19}F–^{13}C$ spin–spin coupling constants and NMR chemical shifts were measured. It is shown that the experimental NMR parameters are suitable for comparison with the results of recent quantum-chemical calculations.
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1. Introduction

Sevoflurane (2,2,2-trifluoro-1-(trifluomethyl) ethyl ether, $(CF_3)_2CHOCH_2F$), also called fluoromethyl, is a new efficient agent used for induction and general maintenance of anesthesia. It is applied as a volatile drug for inhalation, mixed at various concentrations with nitrous oxide and oxygen. Sevoflurane is relatively nonirritant and rapid-acting anesthetic [1,2]. Increasing applications of the new medicine require better understanding of its physicochemical and molecular properties. Sevoflurane has already been studied by theoretical means of ab initio calculations and details of its electronic structure were given by Tang et al.[3]. Harmonic vibrations and isotropic shielding constants of magnetic nuclei in a $(CF_3)_2CHOCH_2F$ molecule were also calculated and compared with experimental results obtained for a pure liquid sevoflurane [4]. The latter comparison of shielding constants cannot be satisfactory because it completely neglects the influence of intermolecular interactions and may lead to misunderstandings. Moreover shielding calculations for small molecules are relatively easy, and can be routinely carried out at the SCF or DFT level providing fairly accurate results [5] but molecules

containing fluorine atoms still provide a challenge to theoreticians. It is obvious that in this case reliable experimental results are needed for the verification of previous and future theoretical predictions.

NMR spectroscopy in the gas phase is used to monitor chemical shifts and spin–spin coupling constants as functions of density. After extrapolation to the zero-density limit it allows the determination of spectral parameters free from intermolecular interactions [6] and such parameters are more suitable for comparison with quantum-chemical results obtained for an isolated molecule [7]. The present work has been designed to investigate selected NMR spectral parameters of sevoflurane in the gas phase. ^1H and ^{19}F chemical shifts of sevoflurane were monitored as a function of density of gaseous solvents (i.e. Xe and CO_2) when their densities were changed in a wide range. The addition of these inert gases helped us to obtain the well-resolved NMR spectra with narrow lines and allowed the determination of appropriate shielding parameters free from intermolecular interactions. Low concentration of solute compound was absolutely necessary in this study but it permitted only the observation of proton and fluorine-19 NMR signals. The $^2J(HF)$ and $^3J(HF)$ spin–spin coupling constants were also observed from both the ^1H and ^{19}F NMR spectra. The detailed examination of our results revealed that these coupling constants were practically independent of density. Additionally, high-resolution ^1H, ^{13}C, ^{17}O and ^{19}F NMR spectra of pure liquid sevoflurane were also recorded. We have made the precise measurements of all the chemical shifts and the $^1H–^{19}F$,

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^{1}H–^{13}C and ^{19}F–^{13}C spin–spin coupling constants in liquid sevoflurane. The latter ^{1}H and ^{19}F results reveal the influence of intermolecular interactions in the liquid phase on appropriate shielding and spin–spin coupling constants when they are compared with the parameters obtained for an isolated molecule in the gas phase.

2. Experimental

Standard one-dimensional NMR spectra were acquired on a Varian UNITYplus-500 FT spectrometer at the 500.62 MHz transmitter frequency for the ^{1}H nuclei, 471.04 MHz for ^{19}F, 125.877 MHz for ^{13}C and 67.864 MHz for ^{17}O. The FID acquisition time was set to 2 s for the ^{1}H nuclei, 1.2 s for ^{19}F, 1.3 s for ^{13}C and 0.01 s for ^{17}O. The spectral width was varied from 1500 to 20 kHz. Gaseous and liquid samples in 4 mm o.d. glass tubes were fitted into the standard 5 mm o.d. thin-walled NMR tubes (Wilmad 528-PP) with liquid benzene-d_6 in the annular space. Benzene-d_6 was applied for the deuterium lock system, its constant frequency (76.8465 MHz) allowed us to preserve the same B_0 for all measurements. ^{1}H and ^{13}C NMR chemical shifts were measured relatively to external liquid TMS as described earlier [8]. The absolute ^{1}H and ^{13}C magnetic shielding data of liquid TMS (32.775 and 186.37 ppm, respectively; in a cylindrical tube parallel to external magnetic field) [9] were used to convert the NMR chemical shifts into the absolute shielding constants of ^{1}H and ^{13}C nuclei in sevoflurane. ^{19}F and ^{17}O chemical shifts were determined relatively external liquid CFCl$_3$ and H$_2$O, respectively. The absolute shielding values of latter standards are equal to 192.7 ppm for CFCl$_3$ [10,11] and 287.4 ppm for liquid water [12,13].

Gas samples were prepared by condensation of sevoflurane vapor and pure solvent gas (Xe or CO$_2$) from the calibrated part of vacuum line as described in our previous papers [8,9]. Sevoflurane (Abbott, Great Britain) from a glass container and xenon (99.9%, Messer Duisburg, Germany) or carbon dioxide (99.8%, Aldrich) from lecture bottles were used to prepare samples without further purification. In gaseous mixtures the solute gas (sevoflurane) has been used at a low constant density ($\sim$ 0.0035 mol/L, pressure $\sim$ 65 Torr) and mixed with various quantities of the gaseous solvents: Xe or CO$_2$ (approx. from 0.2 to 1.6 mol/L). Liquid samples contained neat sevoflurane or the standard liquids in 4 mm o.d. NMR tubes (Wilmad 406 PP). NMR measurements were performed at 300 K unless stated otherwise.

3. Results and discussion

For a binary mixture of gas A, containing the nucleus X whose shielding $\sigma(X)$ is of interest, and gas B as the solvent, it can be written according to the RBB approximation [14]:

$$\sigma(X) = \sigma_0(X) + \sigma_{AA}(X)\rho_A + \sigma_{AB}(X)\rho_B + \cdots \quad (1)$$

where ρ_A and ρ_B are the densities of A ((CF$_3$)$_2$CHOCH$_2$F) and B (Xe or CO$_2$), respectively and $\sigma_0(X)$ is the shielding at the zero-density limit. The coefficients $\sigma_{AA}(X)$ and $\sigma_{AB}(X)$ contain the bulk susceptibility corrections ((σ_A)$_b$ and (σ_B)$_b$) and the terms taking account of intermolecular interactions during the binary collisions of A–A and A–B molecules are ($\sigma_{(A-A)}(X)$ and $\sigma_{(A-B)}(X)$), respectively. It is worth noting that the shielding parameters in Eq. (1) are temperature dependent and for this reason all the present measurements have been performed at the constant temperature of 300 K. Moreover, in this work the density of A has been kept sufficiently low to simplify Eqs. (1):

$$\sigma(X) = \sigma_0(X) + \sigma_{AB}(X)\rho_B \quad (2)$$

According to Eq. (2) the measurements of nuclear magnetic shielding linearly depend on solvent density and the extrapolation of results to the zero-density limit allows the determination of a $\sigma_0(X)$ parameter. It is certainly important to use at least two different gaseous solvents in order to verify the final result of $\sigma_0(X)$; within the limit of experimental error every chemically inert solvent should give the same value.

Fig. 1 displays the dependence of proton magnetic shielding in (CF$_3$)$_2$CHOCH$_2$F on the density of solvent gases (Xe or CO$_2$) when the solute compound has been used at low and constant pressure (approx. 65 Torr). The plots in Fig. 1 describe shielding of two magnetically nonequivalent protons: (CF$_3$)$_2$CHOCH$_2$F and (CF$_3$)$_2$CHOCH$_2$F, respectively. Each group of protons gives a signal which is linearly dependent on solvent density. It proves that the approximation expressed by Eqs. (1) and (2) is valid and allows the determination of the $\sigma_0(^1H)$, $\sigma_{AB}(^1H)$ and $\sigma_{(A-B)}(^1H)$ shielding parameters, as shown in Table 1. The absolute ^{1}H shielding constants of an isolated (CF$_3$)$_2$CHOCH$_2$F molecule are equal to 26.489(3) ppm (for –CH= proton) and 25.462(4) ppm (for –CH$_2$– protons) when xenon gas is used as a solvent. It is important that the other set of measurements, obtained for carbon dioxide as a solvent, gives the same $\sigma_0(H)$ results within the experimental error: 26.429(9) and 25.467(9) ppm, respectively. The absolute shielding of sevoflurane protons has been determined assuming that the $\sigma_0(^1H)$ value for liquid TMS is equal to 32.775 ppm [9]. Table 1 also reveals that all the intermolecular effects for

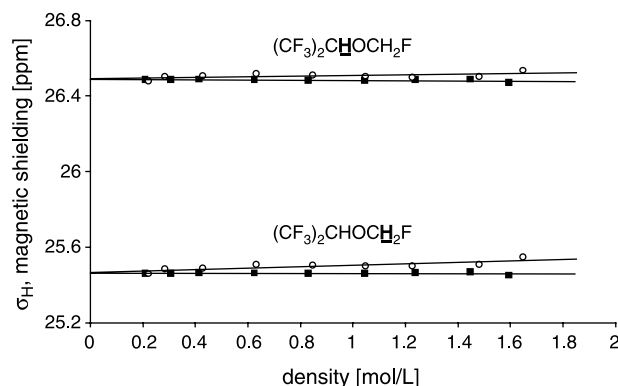Fig. 1. The dependence of ^{1}H magnetic shielding in sevoflurane on the density of solvent gases (xenon, Xe (■) and carbon dioxide, CO$_2$ (○)) at 300 K. The solute compound has been observed at low and constant density (approx. 3.5 × 10^{-3} molL^{-1}). The results are not corrected for bulk susceptibility effects and the real intermolecular effects ($\sigma_{(A-B)}$) are all negative, cf. Table 1.

Table 1
[1]H and ^{19}F nuclear magnetic shielding and spin–spin coupling constants of gaseous sevoflurane and their dependence on density in binary mixtures with Xe and CO_2 at 300 K. The other multinuclaer NMR measurements refer to liquid sevoflurane at the same temperature

Parameter[a]	Gas solvent (B)		Liquid[b]
	Xe	CO_2	
Nuclear magnetic shielding			
σ_0 ((CF$_3$)$_2$**CH**OCH$_2$F) (ppm)	26.489(3)	26.492(9)	28.791(1)
σ_0 ((CF$_3$)$_2$CHOC**H**$_2$F) (ppm)	25.462(4)	25.467(9)	27.835(1)
σ_0 ((**C**F$_3$)$_2$CHOCH$_2$F) (ppm)	269.874(4)	269.884(7)	269.224(1)
σ_0 ((CF$_3$)$_2$CHOCH$_2$**F**) (ppm)	353.073(7)	353.074(8)	349.610(1)
σ ((**C**F$_3$)$_2$CHOCH$_2$F) (ppm)			65.370(2)
σ ((**C**F$_3$)$_2$CHOCH$_2$F) (ppm)			112.053(2)
σ ((CF$_3$)$_2$**CH**OCH$_2$F) (ppm)			83.421(2)
σ ((CF$_3$)$_2$CHOCH$_2$**F**) (ppm)			243.13(1)
σ_{AB} ((CF$_3$)$_2$**CH**OCH$_2$F) (ppm mL mol^{-1})	−1(3)	37(9)	
σ_{AB} ((CF$_3$)$_2$CHOC**H**$_2$F) (ppm mL mol^{-1})	−6(3)	16(9)	
σ_{AB} ((**C**F$_3$)$_2$CHOCH$_2$F) (ppm mL mol^{-1})	−495(4)	−205(7)	
σ_{AB} ((CF$_3$)$_2$CHOCH$_2$**F**) (ppm mL mol^{-1})	−721(7)	−501(7)	
$(\sigma_B)_b$ (ppm mL mol^{-1})[c]	191	87	
$\sigma_{(A-B)}$ ((CF$_3$)$_2$**CH**OCH$_2$F) (ppm mL mol^{-1})	−192(3)	−50(9)	
$\sigma_{(A-B)}$ ((CF$_3$)$_2$CHOC**H**$_2$F) (ppm mL mol^{-1})	−197(3)	−71(9)	
$\sigma_{(A-B)}$ ((**C**F$_3$)$_2$CHOCH$_2$F) (ppm mL mol^{-1})	−686(4)	−292(7)	
$\sigma_{(A-B)}$ ((CF$_3$)$_2$CHOCH$_2$**F**) (ppm mL mol^{-1})	−912(7)	−588(7)	
Spin–spin coupling			
$^2J_0$ ((CF$_3$)$_2$**CH**OCH$_2$**F**) (Hz)	53.58(9)	53. 56(11)	53.7(2)
$^3J_0$ ((CF$_3$)$_2$**CH**OC**H**$_2$F) (Hz)	5.65(3)	5.68(3)	5.8(2)
^1J ((**C**F$_3$)$_2$CHOCH$_2$F) (Hz)			258.2(2)
^1J ((CF$_3$)$_2$**CH**OCH$_2$F) (Hz)			147.3(2)
^2J ((**C**F$_3$)$_2$**CH**OCH$_2$F) (Hz)			33.8(2)
^3J ((CF$_3$)$_2$**CH**OC**H**$_2$F) (Hz)			7.0(2)
^1J ((CF$_3$)$_2$CHO**C**H$_2$F) (Hz)			178.4(2)
^1J ((CF$_3$)$_2$CHOC**H**$_2$**F**) (Hz)			223.7(2)
^3J ((CF$_3$)$_2$**CH**OCH$_2$**F**) (Hz)			6.4(2)

Magnetic shielding parameters were measured relative to external liquid standards assuming the absolute shielding of reference compounds as follows: TMS for [1]H (32.775 ppm [9]), TMS for [13]C (186.37 ppm [9]), water for [17]O (287.4 ppm [12,13]) and CFCl$_3$ for [19]F (192.7 ppm[10,11])

[a] σ_0 and J$_0$ refer only to the results obtained for gases and extrapolated to the zero-density points according to Eqs. (1) and (2).

[b] Measurements for liquid sevoflurane contain intermolecular effects; shielding constants given without a bulk susceptibility correction.

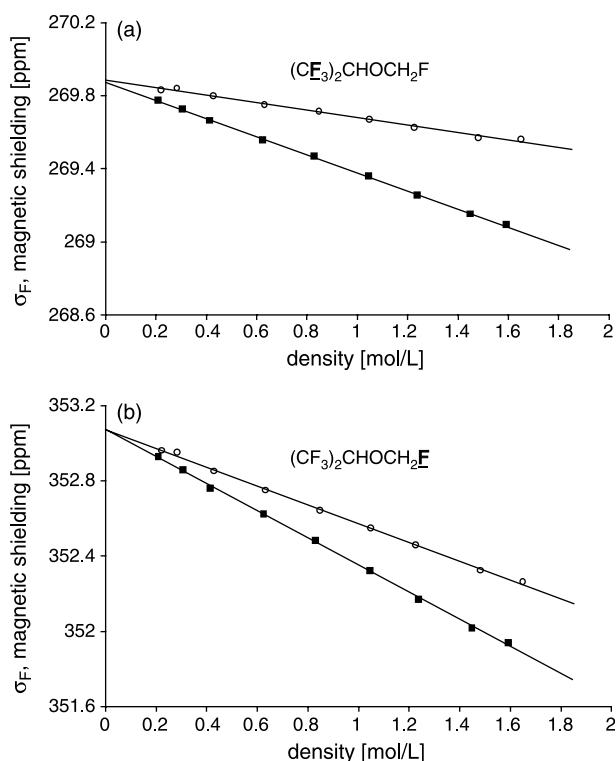[c] $(-4\pi/3)\chi_M$, where χ_M is the molar susceptibility of a solvent gas [15].

Fig. 2. The ^{19}F nuclear magnetic shielding in –CF$_3$ groups (a) and in a –CH$_2$F group (b) of sevoflurane as a function of density at 300 K when xenon (Xe (■)) and carbon dioxide (CO_2 (○)) are used as the solvent gases. The solute compound has been observed at constant low density (approx. 3.5×10^{-3} molL^{-1}). The results are not corrected for bulk susceptibility effects.

353.073(7) ppm, respectively) were determined taking into account the absolute shielding of fluorine nuclei in liquid CFCl$_3$ (192.7 ppm) [10,11]. Intermolecular interactions diminish the fluorine shielding constant much more efficiently than it is observed for protons. All the intermolecular effects ($\sigma_{(A-B)}$(^{19}F) and $\sigma_{(A-B)}$(^{1}H)) are negative and more efficient when xenon gas is used as the solvent. Table 1 also contains the measurements of $^2J_0$(^{19}F,[1]H) and $^3J_0$(^{19}F,[1]H) spin–spin coupling constants in the gas phase, their values have been fairly constant and independent of density within experimental error. It is worth to note that these coupling constants practically remain unchanged also when sevoflurane is condensed to the liquid phase, cf. the results for pure liquid sevoflurane in Table 1.

The present NMR measurements were carried out for microscopic samples of sevoflurane mixed with gaseous solvents. It permitted us to avoid solute–solute interactions present in Eq. 1 but the concentration of sevoflurane in our samples was too small for the observation of ^{13}C and ^{17}O NMR signals at the natural abundance of these isotopes. It was obviously possible to observe the carbon and oxygen NMR signals for pure liquid sevoflurane and the appropriate parameters are shown in the last column of Table 1. All the shielding parameters of liquid (CF$_3$)$_2$CHOCH$_2$F contain an unknown bulk susceptibility correction, its value (($4\pi/3)\chi_M$, where χ_M is the molar susceptibility of liquid sevoflurane) can be estimated using Pascal's constants for approx. +2.6 ppm

protons ($\sigma_{(A-B)}$(^{1}H)) are negative and it is normal for proton shielding. Fig. 1 shows that the slops for carbon dioxide are positive but it is only the bulk susceptibility effect (($\sigma_B)_b$) which covers the real influence of intermolecular interactions in the gas phase, cf. Table 1.

Similar NMR measurements have also been performed for the shielding of fluorine nuclei in sevoflurane, as illustrated by plots in Fig. 2a and b. The plots allow the determination of ^{19}F shielding parameters: σ_0(^{19}F), σ_{AB}(^{19}F) and $\sigma_{(A-B)}$(^{19}F), their values are given in Table 1. The absolute ^{19}F shielding constants of –CF$_3$ and –CH$_2$F groups (269.874(4) and

Table 2
Theoretical and experimental shielding constants of sevoflurane [ppm]

Atom	RHF [4]	B3PW91 [4]	B3LYP [4]	σ_o at 300 K	Liq. σ at 300 K[a]
(**CF$_3$**)$_2$CHOCH$_2$F	89.65	57.36	51.58		65.370(2)
(**CF$_3$**)$_2$CHOCH$_2$F	128.84	110.37	104.98		112.053(2)
(**CF$_3$**)$_2$CHOCH$_2$F	108.20	84.12	78.82		83.421(2)
(**CF$_3$**)$_2$CHOCH$_2$F	304.06	248.08	242.84	269.874(4)	269.224(1)
(CF$_3$)$_2$CHOCH$_2$**F**	379.33	333.87	327.76	353.073(7)	349.610(1)
(CF$_3$)$_2$CH**O**CH$_2$F	289.42	238.34	229.01		243.13(1)
(CF$_3$)$_2$**C**HOCH$_2$F	28.71	27.65	27.71	26.489(3)	28.791(1)
(CF$_3$)$_2$CHOC**H**$_2$F	27.60	26.34	26.37	25.462(4)	27.835(1)

[a] Without the bulk susceptibility correction $((-4\pi/3)\chi_M$, where χ_M is the molar susceptibility of liquid sevoflurane), its value can be estimated using Pascal's constants for approx. $+2.6$ ppm [16]. The results in this column are artificially enlarged due to the susceptibility correction.

[16]. It explains that all the $\sigma_0(^1H)$ and $\sigma_0(^{19}F)$ shielding constants for an isolated (CF$_3$)$_2$CHOCH$_2$F molecule are larger than appropriate shielding parameters measured for liquid sevoflurane. Table 1 also gives all the spin–spin coupling constants which can be measured for pure liquid (CF$_3$)$_2$-CHOCH$_2$F compound.

Finally we can use the new shielding constants for the verification of recent quantum-chemical calculations [4]. Table 2 shows the results of restricted Hartree-Fock (RHF) and density-functional theory (DFT, B3PW91 and B3LYP functionals) calculations performed for the shielding constants of sevoflurane and the best present results of NMR measurements. General agreement between the theoretical and experimental data is well seen in Table 2 though some details are really important here. Firstly, the real shielding constants (σ_0's) are available only for protons and fluorine nuclei, the shielding of other nuclei (^{13}C and ^{17}O) are known only for pure liquid sevoflurane and the latter results contain negative contributions from intermolecular interactions. It can safely be assumed that the real ^{13}C and ^{17}O shielding constants of an isolated molecule will be larger. Secondly, the calculations were completed for the equilibrium structure of a (CF$_3$)$_2$CHOCH$_2$F molecule. It means that temperature effects are not included and the final results of calculations consequently exhibit much higher shielding of heavier nuclei (^{13}C, ^{17}O and ^{19}F) than it can be observed for an isolated molecule at 300 K. As shown in Table 2 the DFT calculations predict too small shielding for carbon and oxygen nuclei, for the fluorine shielding constants the discrepancy is so obvious that in our opinion the DFT results are not much better than the RHF data. It is consistent with a general rule given by Auer et al. [17] that density-functional theory calculations of nuclear magnetic shielding constants are less accurate than other modern advanced methods of theoretical chemistry. However, a new functional can always make the DFT calculations of shielding much more efficient in near future.

4. Conclusions

The present NMR study has yielded experimental results for the ^{19}F and ^1H magnetic shielding and ^{19}F –^1H spin–spin coupling constants of sevoflurane in the gas phase. We have found distinct density dependences of nuclear magnetic shielding and the appropriate parameters for an isolated (CF$_3$)$_2$CHOCH$_2$F molecule have been determined with high accuracy. In contrast the $^2J(^{19}F,^1H)$ and $^3J(^{19}F,^1H)$ spin–spin coupling constants were independent of density within the limit of experimental error, they also remained unchanged when sevoflurane was condensed to the liquid phase. All the other shielding and spin–spin coupling constants were available only for a pure liquid compound and consequently the effects of intermolecular interactions remained unknown for ^{13}C and ^{17}O nuclear magnetic shielding in this case. Our new results permitted us to judge the quality of quantum-chemical calculations of NMR parameters for sevoflurane.

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