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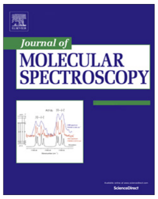

Overtone spectra of fluorinated ether anesthetics at 4 and 5 quanta of C–H stretch

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ABSTRACT

We present laser photoacoustic spectra for three fluorinated ether anesthetics (enflurane CHF_2OCF_2CHF, isoflurane $CF_3OCHClCHF_2$, and desflurane $CF_3OCHFCHF_2$) at the third and fourth C–H stretch overtones. Each fluorinated ether possesses two C–H bonds, and we attempt to use conformer-specific local-mode calculations to assign the observed peaks. Experimental spectra capture C–H stretches for enflurane's four conformers, and are limited to the spectral range predicted for the two lowest energy conformers of isoflurane and desflurane. These later two anesthetics show multiple peaks towards higher frequency, where calculations predict the lowest-energy conformer's terminal C–H overtone to appear. While a full Fermi-resonance analysis is beyond the scope of this work, adding Fermi resonance between the C–H stretch and H–C–O bend lends more plausibility to the simulations.

1. Introduction

Volatile halogenated anesthetics are used for medical, veterinary, and research purposes, with annual global use estimated on the order of 10 kilotons per year [1]. Because 80% of these anesthetics are exhaled, in the absence of recycling systems, the majority find their way into the atmosphere [2]. Such anesthetics include fluorinated methyl ethyl ethers, which were developed during the 1960 as alternatives halothane ($CF_3CHClBr$) [3]. Given their long atmospheric lifetimes (8.2 years for enflurane [1], 3.2 years for isoflurane [4,5], and 14 years for desflurane [5]), several groups have investigated the spectroscopic properties of volatile halogenated anesthetics, to determine their contribution to ozone depletion [1,2] and global warming [1,5,6]. Spectroscopic investigations have also established gas-phase conformations, with the goal of better understanding their mechanism of action. Key spectroscopic studies along this vein include gas electron diffraction (GED) [7,8], vibrational circular dichroism (VCD) in $CDCl_3$ or CCl_4 [9–11], and infrared spectroscopy (IR) [12] in an argon matrix.

While UV wavelengths dominate atmospheric photochemistry, vibrational overtone excitation in the near-IR and visible regions can have influence at times when UV light is scarce [13,14]. A proposed mechanism is enhanced photolysis or bimolecular reactions for molecules with several quanta of C–H stretch, as has been observed in the laboratory. While the probability of C–H overtone-induced chemistry in the atmosphere is complicated by low absorption cross sections, IVR, and collisional deactivation, spectroscopic studies of C–H stretch overtones may have some potential to contribute to atmospherically-relevant molecular characterization. Spectroscopy of C–H stretch overtones is also sensitive to local chemical environments [15]. For example, halogenation tends to increase C–H stretch frequencies compared to non-halogenated analogs [16]. Overtone spectroscopy has been used to distinguish individual C–H bonds and specific conformers [15].

Here we present laser photoacoustic spectra at four and five quanta of C–H stretch for three fluorinated ether anesthetics, along with conformer-specific frequency and local-mode cross section calculations. We compare our overtone spectra with spectral predictions, and attempt identification of prominent features in the C–H stretch overtone regions.

2. Materials and methods

Samples of gaseous anesthetics came from Synquest (desflurane and enflurane) and from Primal Healthcare (isoflurane). Because water absorbs in the wavelength regions of interest, liquid samples were stored under vacuum with molecular sieves. Vapors were passed over molecular sieves before reaching the photoacoustic cell. While molecular sieves reduced interference by water absorption, sharp water lines still appeared in several spectra.

Our experimental setup for photoacoustic spectroscopy is described in more detail elsewhere [17]. Briefly, 10-ns pulses from

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a dye laser (Sirah Cobra Stretch pumped by 532 nm from a Spectra Physics LAB150 at 10 Hz) enters a home-built glass cell containing ~100 Torr of sample. A microphone (Knowles EK3132) detects pressure waves generated when the sample absorbs light. Monitoring a gated signal peak while stepping the dye laser (laser dyes LDS698, 750, 751, 821, 867, and 925) generates spectra. The reported spectra are normalized for fluctuations in dye laser power.

3. Calculations

GAUSSIAN09 calculations are at the B3LYP/6-311++G (3d,2p) level. For each optimized conformer, energies and dipole moments were obtained for C–H bond stretches/compressions ±0.3 Å from the potential minimum, in 0.05 Å steps. The energies for each C–H bond stretch/compression yield frequencies (ω) and anharmonicites (ωx) via a non-linear least squares fits of the Morse parameters *a* and *D* to the energies, as in previous work [18]. Transition energies are those for a Morse oscillator with the parameters ω and ωx. Transition intensities come from the standard expression, here given in units of cm^2 molecule^{-1},

$$\sigma = \frac{fe^2}{4m_e c^2 \varepsilon_0} \tag{1}$$

where *f* is the unitless oscillator strength for a transition,

$$f_{e \leftarrow g} = 4.70165 \times 10^7 [\text{cm D}^{-2}] \underset{e \leftarrow g}{\tilde{v}} |\mu_{e \leftarrow g}|^2 \tag{2}$$

for each vibrational transition from ground (g, here $v = 0$) to excited state (e, here $v = 4$ or 5). The transition moment is evaluated as

$$\mu_{e \leftarrow g} = \sum_{i=6}^{6} \left\langle \psi_e(q) \middle| q^i \frac{1}{i!} \left(\frac{d^i \mu(q)}{dq^i} \right)_{q=0} \middle| \psi_g(q) \right\rangle \tag{3}$$

using Morse wavefunctions as a function of C–H bond displacement from the potential minimum (q) and dipole derivatives from seven-term polynomial fits.

Simulations of overtone absorption spectra combine the calculated transition energies and intensities with conformational populations, and Gaussian functions that approximate the vibrational band shapes. Conformation populations used here assume the calculated relative electronic free energies at 298 K. Gaussian widths are arbitrarily chosen at 40 cm^{-1}, to resemble experimental spectra. Overtone literature for similarly sized molecules find FWHM line widths on the order of tens and up to over a hundred wavenumbers, often showing increases in widths at higher overtones [16,19–21]. Unlike more sophisticated studies of C–H stretch overtones in the literature for similarly-sized, fluorinated molecules [20,22], simulations presented here do not take into account Fermi resonance [23–26] due the interaction between C–H stretch and bend.

4. Results and discussion

4.1. Lowest-energy conformers

Figs. 1–3 show the four lowest energy conformations for each fluorinated ether, using notation from previous works [10,12] that have already established the conformations for enflurane [7,9,12], isoflurane [8,11,27], and desflurane [8,10,28]. For enflurane, the first letter denotes the orientation of the chlorine atom relative to the O atom (Cl–C3*–C2–O dihedral), the second the C1–O–C2–C3* backbone, and the third the H atom on C1 in relation to C2 (H–C1–O–C2 dihedral). Isoflurane and desflurane require only the last two letter designations. The uppercase letter denotes the C1–O–C2–C3* orientation, while the lower case refers to the positioning of the H attached to C1 in relation to C2. The most stable conformers for all three anesthetics share a C1–O–C2–C3 backbone in a trans orientation, as denoted by the uppercase T. Enflurane, however, is distinct in that all four conformations (Fig. 1) share a C2–O–C1–H dihedral that is gauche. As a result, its conformers differ primarily on the rotation of the CHFCl group, as reflected in the first g$^-$/t/g$^+$ designation. The gauche C2–O–C1–H dihedral in enflurane differs from the trans orientation featured in the lowest-energy configurations of isoflurane (Fig. 2) and desflurane (Fig. 3), which sends the H on C1 facing away from the rest of the molecule. As pointed out in previous studies, this difference in C2–O–C1–H configuration is due to the presence of two fluorines on C2 in enflurane, allowing for favorable interactions when the H on C1 comes in close proximity to both F atoms on C2 [12,29,30].

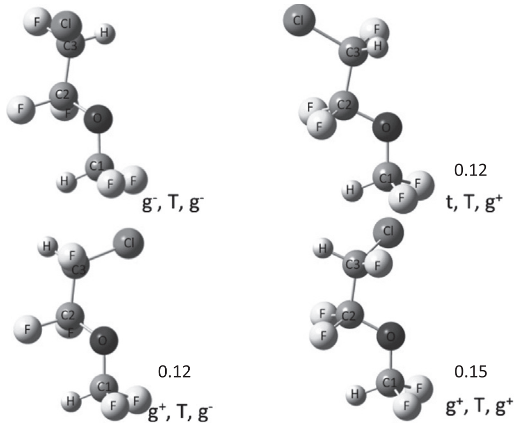

Fig. 1. *S*-enflurane in its four most stable conformers (t, T, g$^+$; g$^-$, T, g$^+$; g$^-$, T, g$^-$; g$^+$, T, g$^+$) with relative B3LYP 6-311++G(3d,2p) free energies above the lowest energy conformer in kcal mol^{-1}. Conformer notation follows Michalska [12]. The first letter (lower case) describes the positioning of the Cl atom relative to the O atom: trans (t) ~180°, gauche minus (g$^-$) ~−60°, or gauche plus (g$^+$) ~60°. The second letter (capital) describes the C1–O–C2–C3* backbone. The third letter (lower case) denotes the positioning of the H attached to C1 in relation to C2.

Because our spectral simulations require relative conformer populations, we compare our predicted Boltzmann populations for the four lowest conformers at room temperature with previous works (Fig. 4). Tabulated energies are in Supplementary information (Tables S1–S3).

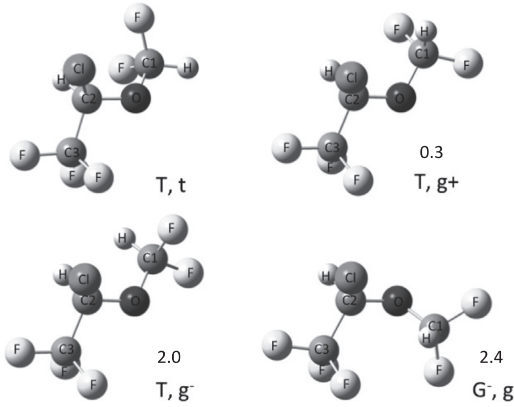

Fig. 2. *R*-isoflurane in its four most stable conformers (T, t; T, g$^+$; T, g$^-$; G$^-$, g$^-$) with relative B3LYP 6-311++G(3d,2p) free energies above the lowest energy conformer in kcal mol^{-1}. Conformer notation follows Polavarapu [10]. The first letter (capital) denotes the dihedral angle of the C1–O–C2*–C3 backbone: trans (T) ~180°, gauche minus (G$^-$) ~−60°, or gauche plus (G$^+$) ~60°. The second letter (lower case) denotes the H–C1–O–C2 dihedral.