

Vibrational Circular Dichroism, Absolute Configuration, and Predominant Conformations of Volatile Anesthetics: Desflurane

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Vibrational absorption and circular dichroism spectra of desflurane have been measured in chloroform solution in the 2000–900 cm^{-1} region. These spectra are compared with the ab initio predictions of absorption and VCD spectra obtained with density functional theory using B3LYP/6-31G* and B3PW91/6-311G(2d) basis sets for different conformers of desflurane. These results confirm the assignment of the (R) configuration to (–)-desflurane and suggest that three different conformers of desflurane are responsible for the observed spectral features in the solution phase.

Introduction

There has been an increased interest¹ in the commercialization of enantiomerically pure chemicals for medicinal use because the two enantiomers of chiral compounds in some cases have significantly different pharmaceutical effects. Volatile chiral anesthetics are one class of compounds that have attracted much attention.² Fluorinated ethers are being investigated for their role as anesthetic agents.² To understand or model the molecular basis of anesthetic action, the determination of absolute configuration and predominant conformations of a given chiral anesthetic is necessary. While traditional methods such as electronic circular dichroism³ have widely been used for determining the absolute configuration of chiral compounds, the experimental and ab initio optical rotations have also been used⁴ in recent years for this purpose. Vibrational optical activity (VOA) is another chiroptical method that has been recently developed and holds promise for determining complete molecular stereochemistry in the solution phase. There are two forms of VOA: infrared vibrational circular dichroism (VCD)⁵ and vibrational Raman optical activity (VROA).⁶ These two techniques benefit from a large number of vibrational transitions that are accessible for stereochemical elucidation. The absolute configuration and predominant conformations of two anesthetics, isoflurane⁷ and 1,2,2,2-tetrafluoroethyl methyl ether,⁸ and of bromochlorofluoromethane⁹ were suggested by comparing the experimental VOA observations for a given enantiomer with those predicted using ab initio theoretical methods for a given configuration and different conformations.

Desflurane, another anesthetic, has been investigated¹⁰ before for determining its absolute configuration and predominant conformations using VCD. In the first report,^{10a} the absolute configuration was assigned as (S)-(–), but later when it was discovered that the labels on (+)- and (–)-enantiomer samples were interchanged, the assignment of the absolute configuration

was corrected^{10b} as (R)-(–). This later conclusion is in agreement with the absolute configuration assignment based on the optical rotations⁴ and X-ray studies.¹¹ The question of predominant conformations of desflurane in the solution phase is yet to be firmly answered. In the previous investigation, ab initio calculations based on the 6-31G* basis set results were used to suggest the predominant conformers. Much more accurate levels of theory can now be employed to address this issue. Ab initio applications using density functional theory (DFT),¹² which provide vibrational frequencies and intensities that are comparable to the post-SCF calculations employing electron correlation, have become state-of-the-art in recent years. The DFT theory has also been extended to the VCD intensity calculations.¹³ On the experimental side, improvements in VCD instrumentation have made it possible to obtain the VCD spectra with enhanced signal-to-noise ratios.

In light of these developments, we have remeasured the VCD of desflurane with improved signal quality and undertaken the state-of-the-art ab initio theoretical VCD investigations using B3LYP/6-31G* and B3PW91/6-311G(2d) basis sets. These results are used to suggest the predominant conformations, and to confirm the absolute configuration, of desflurane.

Procedures

The (–)-desflurane sample was supplied by Anaquest Inc. Negative optical rotation was observed for this sample in CDCl_3 solvent. The infrared and VCD spectra were recorded on a commercial Fourier transform VCD spectrometer, Chiralir (Bomem-BioTools, Canada) with a ZnSe beam splitter, BaF_2 polarizer, optical filter (transmitting below 2000 cm^{-1}), and 2 mm \times 2 mm HgCdTe detector. One difference from the standard Chiralir instrument is that the photoelastic modulator used was a PEM-80 model (Hinds Instruments) without AR coating on the ZnSe optical element. The VCD spectra were

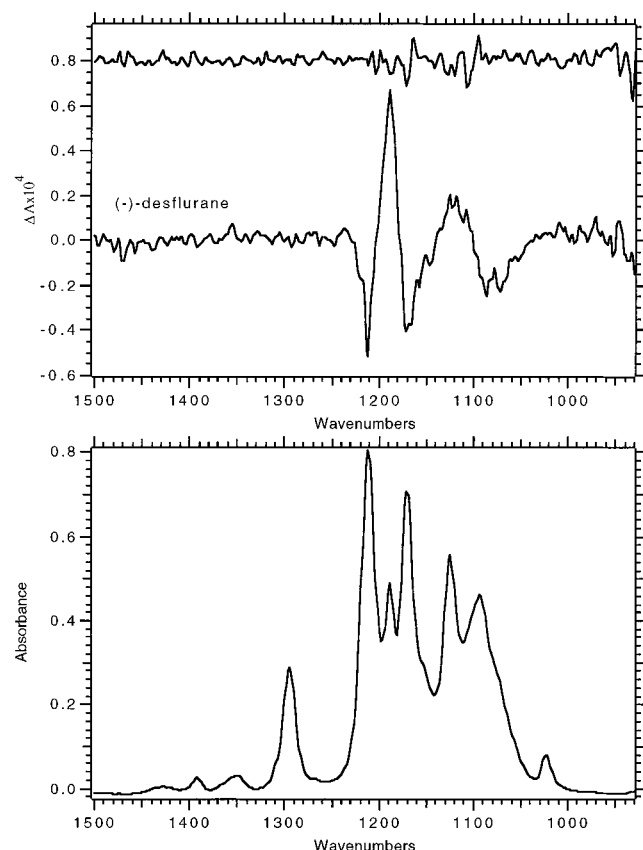


Figure 1. Vibrational absorption (bottom panel) and VCD (top panel) spectra for (–)-desflurane in CDCl_3 solvent. The solvent absorption was subtracted out. The uppermost trace in the top panel shows the noise level in VCD.

recorded, using the supplied Chiralir software, with 1 h data collection time (two sets of 1247 AC scans and 138 DC scans) at 4 cm^{-1} resolution. The absorption spectra were obtained from 138 DC scans and the same number of background scans. The transmission properties of the optical filter and BaF_2 substrates used in the instrument restrict the range of measurements to $2000\text{--}900\text{ cm}^{-1}$. Spectra were measured for the (–)-enantiomer in CDCl_3 solvent. As a result of the volatile nature of desflurane, the concentration of the sample dissolved in CDCl_3 could not be established accurately, but based on the previous absorption measurements,¹⁰ the concentration is estimated to be $\sim 0.3\text{ M}$. The sample was held in a variable path length cell with BaF_2 windows at a path length of $\sim 50\text{ }\mu\text{m}$. In the absorption spectrum presented (bottom panel in Figure 1), the solvent absorption was subtracted out. In the VCD spectrum presented (bottom trace in the top panel of Figure 1), the raw VCD spectrum of the solvent was subtracted from that of the (–)-enantiomer.

The ab initio vibrational frequencies, absorption, and VCD intensities for (R)-desflurane were calculated using the Gaussian 98 program¹⁴ on a Pentium II 300 MHz PC. Two sets of calculations were undertaken, both employing the density functional theory (DFT). One set of calculations used the B3LYP functional^{12,14,15} and 6-31G* basis set,¹⁶ while the other used the B3PW91 functional^{12,14,17,18} and 6-311G(2d) basis set.^{16,18} The vibrational band positions predicted with these methods are usually higher than the experimental values, so the frequencies obtained with the B3LYP/6-31G* method were multiplied by 0.97 and those obtained with B3PW91/6-311G(2d) were multiplied by 0.985. The procedure for calculating the VCD intensities using DFT theory is due to Cheeseman et al.¹³ as implemented in Gaussian 98 program.¹⁴

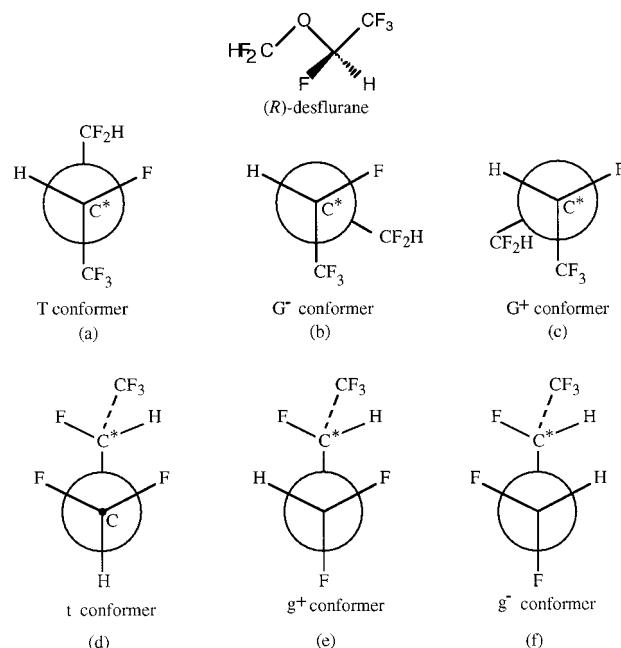


Figure 2. Conformations of desflurane: (a) trans $\text{C}-\text{O}-\text{C}^*-\text{C}$ conformer; (b) gauche minus $\text{C}-\text{O}-\text{C}^*-\text{C}$ conformer; (c) gauche plus $\text{C}-\text{O}-\text{C}^*-\text{C}$ conformer; (d) trans $\text{H}-\text{C}-\text{O}-\text{C}^*$ conformer; (e) gauche plus $\text{H}-\text{C}-\text{O}-\text{C}^*$ conformer; (f) gauche minus $\text{H}-\text{C}-\text{O}-\text{C}^*$ conformer.

Results and Discussion

Different conformations are possible for desflurane (see Figure 2). These conformations are labeled with two letters. The first (upper case) letter represents the dihedral angle of $\text{C}-\text{O}-\text{C}^*-\text{C}$ segment as trans (T), gauche plus (G^+), or gauche minus (G^-). The standard definitions of dihedral angles for the trans, gauche plus, and gauche minus conformers are $\sim 180^\circ$, $\sim +60^\circ$, and $\sim -60^\circ$ respectively. However, the “trans” designation is used more liberally in this manuscript, as the same designation is used for dihedral angles as different as $+145^\circ$ and $+155^\circ$. The second letter (lower case) represents the $\text{H}-\text{C}-\text{O}-\text{C}^*$ dihedral angle. For example, the designation (T, g^+) represents the trans orientation of $\text{C}-\text{O}-\text{C}^*-\text{C}$ and the gauche-plus orientation of $\text{H}-\text{C}-\text{O}-\text{C}^*$. For geometry optimizations with B3LYP/6-31G*, 12 different starting values for these dihedral angles were used, but only 6 stable conformers, namely, (T, t), (T, g^+), (T, g^-), (G^-, g^-), (G^-, t), and (G^-, g^+), were found. For geometry optimizations with the B3PW91/6-311G(2d) basis set, seven different starting values for the dihedral angles were used and five stable conformations, namely, (T, t), (T, g^+), (T, g^-), (G^-, g^-), and (G^-, t), were found. The (G^-, g^+) conformation, although stable in the B3LYP/6-31G* calculation, is found not to be stable in the B3PW91/6-311G(2d) calculation as the (G^-, g^+) conformation converged to the (G^-, g^-) conformation. The converged $\text{C}-\text{O}-\text{C}^*-\text{C}$ and $\text{H}-\text{O}-\text{C}^*-\text{C}$ dihedral angles, optimized energies, and relative populations based on the Gibbs energies are listed in Table 1. It may be noted that the gauche plus orientation for the $\text{C}-\text{O}-\text{C}^*-\text{C}$ segment does not appear to be stable, as this orientation converged to the trans orientation probably because the gauche plus conformer does not have a well-defined potential energy minimum. In a related molecule, 1,2,2,2-tetrafluoroethyl methyl ether, the G^+ orientation of the $\text{C}-\text{O}-\text{C}^*-\text{C}$ segment was also found⁸ to converge to the trans orientation.

The ab initio energies (Table 1) suggest that desflurane exists predominantly ($\sim 76\text{--}78\%$) in the (T, t) conformation with (T, g^+) and (T, g^-) as the second ($\sim 15\text{--}17\%$) and third

TABLE 1: Conformations and Energies of Desflurane

no.	starting geometry (deg) ^c		converged geometry (deg) ^c		energy ^d		label ^e	ΔE^f	population (%) ^g
	C—O—C*—C	H—C—O—C*	C—O—C*—C	H—C—O—C*	electronic	Gibbs			
B3LYP/6-31G*									
1 ^a	+148	+174	+145	+176	−789.781799	−789.754267	T,t	0.0	78.5
	−145	+180	+145	+176					
	+60	+180	+145	+176					
2 ^a	+178	+64	+173	+61	−789.779896	−789.752725	T,g ⁺	0.97	15.3
	−145	+60	+173	+61					
	+60	+60	+173	+61					
3 ^b	+156	−56	+155	−54	−789.777951	−789.751339	T,g [−]	1.84	3.5
	−145	−60	+155	−54					
	+60	−60	+155	−54					
4	−60	+180	−54	−165	−789.776935	−789.748265	G [−] ,t	3.76	0.1
5	−60	−60	−65	−27	−789.779112	−789.750889	G [−] ,g [−]	2.12	2.2
6	−60	+60	−57	+55	−789.776754	−789.749163	G [−] ,g ⁺	3.20	0.3
B3PW91/6-311G(2d)									
1	+60	+180	+146	+176	−789.746591	−789.719380	T,t	0.0	76.3
2	+60	+60	+168	+55	−789.744825	−789.717962	T,g ⁺	0.89	17.0
	+173	+61	+169	+56	−789.744821				
3	+60	−60	+159	−38	−789.743154	−789.716987	T,g [−]	1.50	6.0
4	−54	−165	−55	−165	−789.739530	−789.711170	G [−] ,t	5.15	0
5	−65	−27	−66	−21	−789.742449	−789.714938	G [−] ,g [−]	2.79	0.7
	−57	+55	−66	−21					

^a Starting from MP2/6-31G* optimized geometry. ^b Starting from 6-31G* optimized geometry. ^c Dihedral angles. ^d In hartrees. ^e The uppercase letters T,G⁻ and G⁺ represent the orientation of the C—O—C*—C dihedral angle; lower case letters t, g⁻, and g⁺ represent the orientation of the H—C—O—C* dihedral angle. (T or t: trans orientation; G⁺ or g⁺: gauche—clockwise orientation; G⁻ or g⁻: gauche—counterclockwise orientation). ^f Gibbs energy difference (kcal/mol) relative to the lowest energy conformer. ^g Based on Gibbs energies.

(3–6%) most abundant conformations. The populations of gauche minus C—O—C*—C conformers are negligibly small. These conclusions are not very much different from the lower level Hartree–Fock calculations, using the 6-31G* basis set, reported earlier,¹⁰ where only the trans orientation of C—O—C*—C was investigated. The (T,t), (T,g⁺), and (T,g⁻) conformers correspond respectively to the conformers 1, 2, and 3 in the notation of the earlier paper.¹⁰

The vibrational frequencies, absorption intensities, and VCD intensities were calculated for the optimized conformations of desflurane, again using the B3LYP/6-31G* and B3PW91/6-311G(2d) basis sets. The absorption and VCD spectra simulated with 15 cm⁻¹ half-widths and Lorentzian band shapes are presented in Figures 3 and 4. These theoretical spectra can be compared to the experimental spectra of (–)-desflurane (in Figure 1) to determine the predominant conformations and absolute configuration.

The experimental absorption spectrum contains moderate to strong bands at ~1295, 1211, 1188, 1170, 1124, 1093, and 1023 cm⁻¹. The intensities of the 1211, 1170, 1124, and 1093 cm⁻¹ bands decrease approximately linearly from high frequency to low frequency. Weaker bands at 1152 and 1074 cm⁻¹ appear as shoulders, while those at ~1349, 1393, and 1428 cm⁻¹ appear as weak resolved bands. The VCD spectrum shows three sharp bands: a negative band at 1211 cm⁻¹, a positive band at 1188 cm⁻¹, and a negative band at 1170 cm⁻¹. In addition to these three VCD bands, which have corresponding absorption band maxima at the same frequencies, the VCD spectrum also has two somewhat broader bands: a positive VCD band at ~1124 cm⁻¹ and a negative VCD band with maxima in the 1085–1072 cm⁻¹ region. The overall VCD sign pattern observed in the 1300–1000 cm⁻¹ region for (–)-desflurane is (–,+,–,+,–), which forms the basis for determining the absolute configuration and predominant conformations. The absorption and VCD spectra obtained here are in agreement with those reported earlier, except that the (+)-desflurane label in an earlier paper^{10a} should have been (–)-desflurane, due to mislabeling as pointed out already.^{10b}

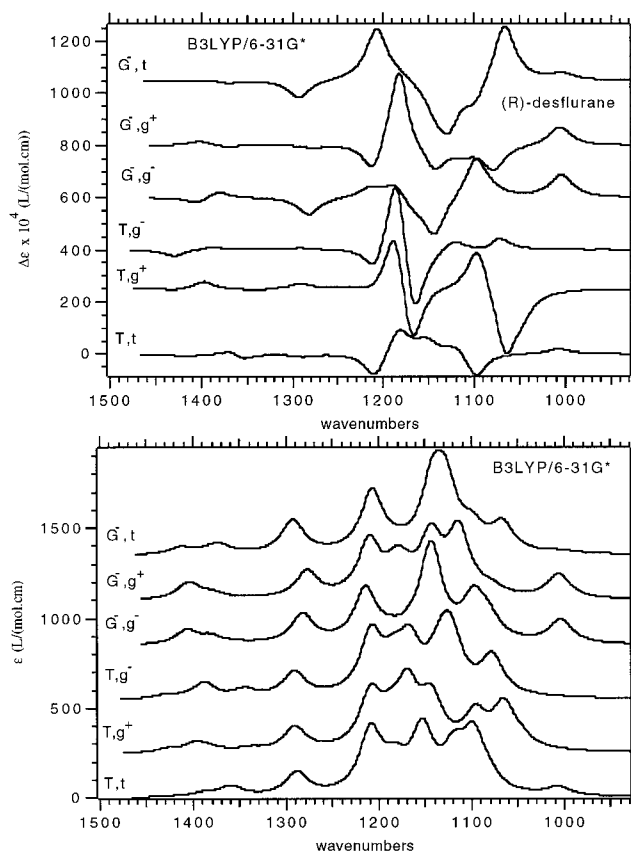


Figure 3. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for six conformers of (R)-desflurane obtained with the B3LYP/6-31G* basis set. The spectra were simulated with Lorentzian band shapes and 15 cm⁻¹ half-widths, and frequencies were multiplied by 0.97.

The predicted absorption and VCD spectra for none of the conformers by themselves match well with the experimental spectra. This is true in both B3LYP/6-31G* (Figure 3) and B3PW91/6-311G(2d) (Figure 4) calculations. Since the ab initio

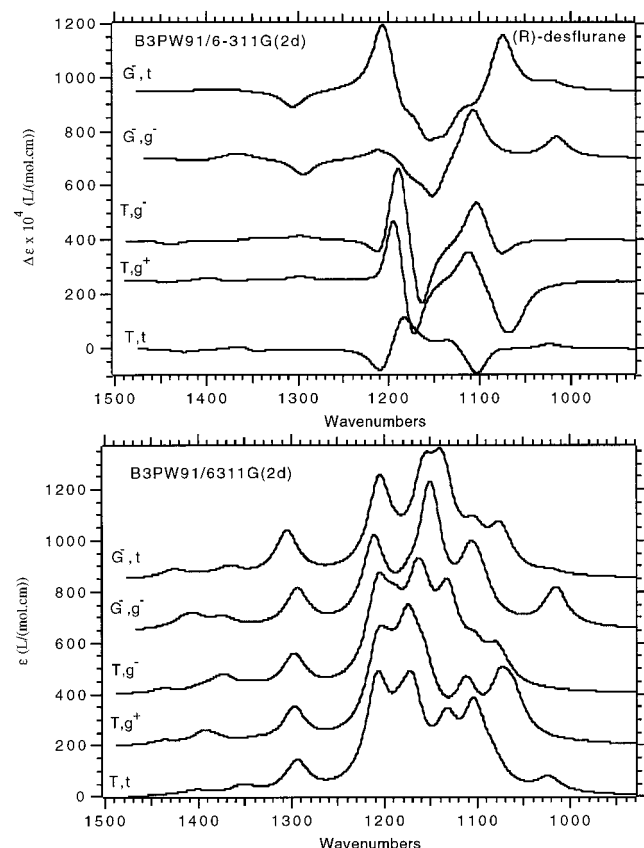


Figure 4. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for the five conformers of (*R*)-desflurane obtained with the B3PW91/6-311G(2d) basis set. The spectra were simulated with Lorentzian band shapes and 15 cm⁻¹ half-widths, and frequencies were multiplied by 0.985.

energies predict the (T,t) conformer to be the predominant one (76–78%), it is appropriate to see how different, or close, the observed absorption and VCD features are from those predicted for this conformer. The experimental absorption band at 1295 cm⁻¹ has a corresponding band in the simulated absorption spectra for all of the conformers, at or around ~1290 cm⁻¹ in the B3LYP/6-31G* spectra and at or around ~1295 cm⁻¹ in the B3PW91/6-311G(2d) spectra. The experimental absorption band at 1023 cm⁻¹ however has a corresponding band at or around ~1004 cm⁻¹ in the simulated absorption spectra only for the (T,t), (G⁻,g⁻), and (G⁻,g⁺) conformers in the B3LYP/6-31G* calculation and at or around ~1024 cm⁻¹ in the simulated absorption spectra only for the (T,t) and (G⁻,g⁻) conformers in B3PW91/6-311G(2d) calculation. Since (G⁻,g⁻) and (G⁻,g⁺) conformations are predicted to have negligible population, the experimental absorption band at 1023 cm⁻¹ can thus be attributed to the (T,t) conformer. Between the two absorption bands discussed above, the experimental absorption spectrum shows four strong bands at 1211, 1170, 1124, and 1093 cm⁻¹ in decreasing order of intensity, a weaker band at 1188 cm⁻¹, and a shoulder at 1074 cm⁻¹. In the simulated absorption spectrum obtained in the B3LYP/6-31G* calculation, there are four peaks at 1209, 1153, 1116, and 1100 cm⁻¹, all with approximately the same intensity, a weaker band at 1184 cm⁻¹, and a shoulder ~1081 cm⁻¹. The intensity pattern predicted for the 1209, 1153, 1116, and 1100 cm⁻¹ bands does not match the observed intensity pattern for the corresponding observed bands at 1211, 1170, 1124, and 1093 cm⁻¹. The intensity pattern predicted for the (T,t) conformer in the simulated absorption spectrum obtained in the B3PW91/

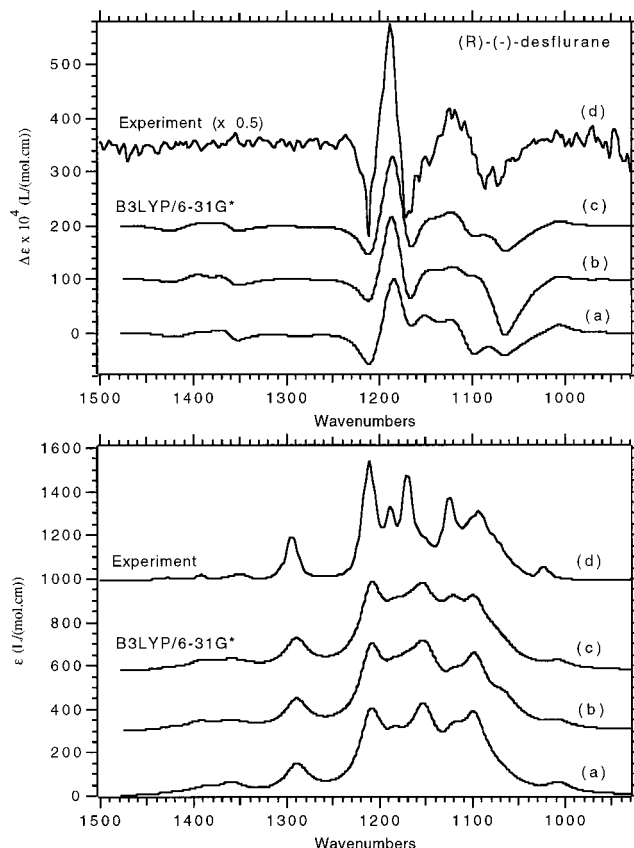


Figure 5. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for the mixed conformers of (*R*)-desflurane obtained with the B3LYP/6-31G* basis set: (a) compositions predicted by B3LYP/6-31G* energies (see Table 1); (b) 60% (T,t) + 40% (T-,g⁺); (c) 60% (T,t) + 20% (T-,g⁺) + 20% (T-,g⁻); (d) experimental spectrum. The calculated spectra were simulated with Lorentzian band shapes and 15 cm⁻¹ half-widths, and frequencies were multiplied by 0.97. The experimental VCD intensities were multiplied by 0.5.

6-311G(2d) calculation, however, appears somewhat closer to the experimental spectrum. This is because in the simulated spectrum the two peaks at 1207 and 1172 cm⁻¹ have larger intensities than the peaks at 1132 and 1104 cm⁻¹, a pattern that is closer to that seen in the experimental spectrum for the bands at 1211, 1170, 1124, and 1093 cm⁻¹. Nevertheless, in this calculation, there is no visible appearance for a band corresponding to that of 1188 cm⁻¹ experimental band. Also the calculated VCD spectrum for the (T,t) conformer does not match with the experimental VCD spectrum in either the B3PW91/6-311G(2d) or B3LYP/6-31G* calculation. In both calculations, a (-,+,+,-) VCD sign pattern was predicted for the (T,t) conformer in place of a (-,+,-,+,-) sign pattern observed in the experimental spectrum.

The negative VCD missing in the middle of the predicted VCD pattern for the (T,t) conformer could be coming from another conformer. In particular the (T-,g⁺) and (T-,g⁻) conformers are predicted to have large negative VCD at ~1170 cm⁻¹, a place where the negative VCD was missing in the predicted spectrum for the (T,t) conformer. Thus, it is necessary to consider the possibility that a mixture of conformations might be present for desflurane in the solution phase. The population of conformers predicted from Gibbs energies of isolated molecules provide a starting point for considering the contributions from different conformers. The absorption and VCD obtained for the mixture of conformers with the compositions obtained from Gibbs energies (see Table 1) are displayed in Figures 5 and 6, as trace a. In both B3LYP/6-31G* and

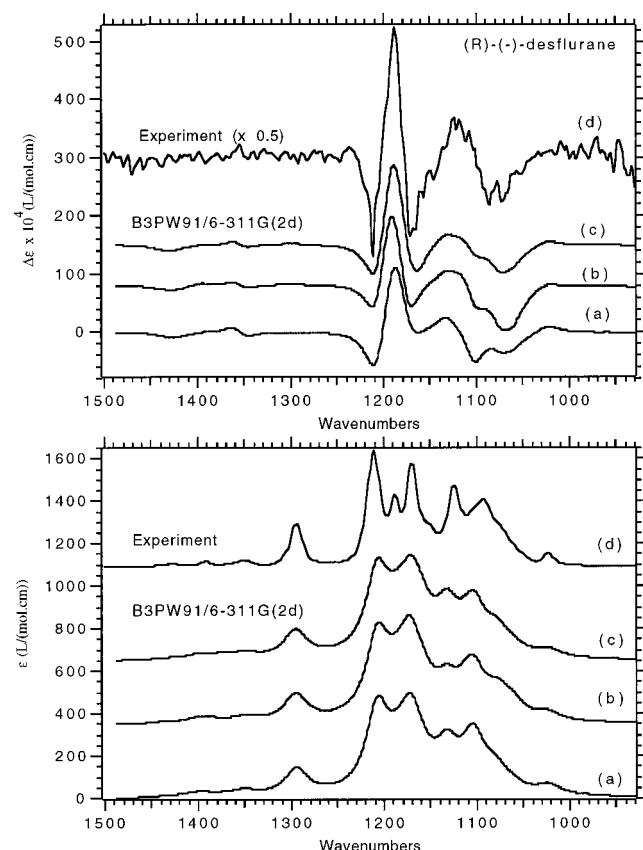


Figure 6. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for the mixed conformers of (*R*)-desflurane obtained with the B3PW91/6-311G(2d) basis set: (a) compositions predicted by B3PW91/6-311G(2d) energies (see Table 1); (b) 60% (*T,t*) + 40% (*T,g*⁺); (c) 60% (*T,t*) + 20% (*T,g*⁺) + 20% (*T,g*[−]); (d) experimental spectrum. The calculated spectra were simulated with Lorentzian band shapes and 15 cm^{−1} half-widths, and frequencies were multiplied by 0.985. The experimental VCD intensities were multiplied by 0.5.

B3PW91/6-311G(2d) calculations the VCD sign pattern predicted is (−,+,+,−), which differs from the observed sign pattern (−,+,−,+,−). Also, the predicted absorption spectral pattern with this composition does not match the experimental absorption spectral pattern. Thus, it appears that the population of conformers predicted for an isolated desflurane molecule differs from that for desflurane in the condensed phase.

Analysis of VCD spectra for individual conformers suggests that the negative VCD band corresponding to the one at 1170 cm^{−1} in the experimental spectrum can be seen in the simulated spectra if we increase the population of (*T,g*⁺) and/or (*T,g*[−]) conformers. So the spectra simulated with 60%(*T,t*) + 40%(*T,g*⁺) composition are obtained for B3LYP/6-31G* and B3PW91/6-311G(2d) calculations and displayed in Figures 5 and 6, as trace b. Although a (−,+,−,+,−) VCD sign pattern, matching the experimental pattern, is obtained with this composition, the relative magnitude of negative VCD predicted in the simulated spectra at ~1070 cm^{−1} is considerably larger than that observed at 1085 cm^{−1}. To correct for this discrepancy, a different composition, 60%(*T,t*) + 20%(*T,g*⁺) + 20% (*T,g*[−]), is investigated (see trace c in Figures 5 and 6). With this composition, not only does the predicted VCD sign pattern, (−,+,−,+,−), match the observed sign pattern but the relative intensity pattern also is closer to the observed pattern in both calculations. Furthermore, the absorption spectral pattern obtained with this composition is closer to the observed absorption spectral pattern, more so in the B3LYP/6-31G* calculation than

in the B3PW91/6-311G(2d) calculation. Thus, the composition of conformers of desflurane in CDCl₃ solution can be deduced to be approximately 60% (*T,t*), 20% (*T,g*⁺), and 20% (*T,g*[−]). This composition is somewhat different from a composition of 50% (*T,t*) and 50% (*T,g*⁺), which was deduced in an earlier VCD investigation from lower level ab initio calculations.¹⁰

Although the composition of conformers had to be adjusted to obtain an agreement between the calculated and observed spectra, inspection of the calculated VCD spectra in Figures 3 and 4 indicates that the observed VCD sign pattern for (−)-desflurane cannot be reproduced by the conformers with (*S*) configuration. Since the experimentally observed VCD sign pattern for (−)-desflurane can only be reproduced by the conformers of (*R*)-desflurane, the absolute configuration of (−)-desflurane is assigned as (*R*). This assignment is in agreement with that obtained from earlier VCD investigation,^{10b} X-ray studies,¹¹ and optical rotation.⁴

Summary

The comparison of experimental and ab initio predicted absorption and VCD spectra indicate that (a) the absolute configuration of (−)-desflurane is (*R*); (b) the composition of conformers obtained for isolated desflurane molecule, from Gibbs energies in B3LYP/6-31G* and B3PW91/6-311G(2d) calculations, is different from that in CDCl₃ solution; (c) the simulated absorption and VCD spectra with a composition of 60% (*T,t*), 20% (*T,g*⁺), and 20% (*T,g*[−]) is found to compare well with the corresponding experimental spectra in CDCl₃ solution, so this composition appears to represent the solution-phase composition of desflurane in CDCl₃.

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