



Vibrational circular dichroism, absolute configuration and predominant conformations of volatile anesthetics: 1,2,2,2-tetrafluoroethyl methyl ether

Prasad L. Polavarapu,^{a,*} Chunxia Zhao^a and Keith Ramig^b

^aDepartment of Chemistry, Vanderbilt University Nashville, TN 37235, USA

^bDepartment of Natural Sciences, Baruch College/CUNY, 17 Lexington Avenue, New York, NY 10010, USA

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Abstract

Vibrational absorption and circular dichroism spectra of (–)-1,2,2,2-tetrafluoroethyl methyl ether have been measured in CCl₄ 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 (R)-1,2,2,2-tetrafluoroethyl methyl ether. The results suggest that the *trans*-conformer of 1,2,2,2-tetrafluoroethyl methyl ether is predominant in the solution phase and that the (–)-enantiomer has the *R*-configuration. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, there has been an increased interest¹ in the commercialization of enantiomerically pure chemicals for medicinal use because the enantiomers in some cases have significantly different pharmaceutical effects. Volatile chiral anesthetics are one class of compounds that have attracted much attention.² Chiral fluorinated ethers are being investigated for their role as anesthetic agents.² To understand or model the molecular basis of anesthetic action, determination of absolute configuration and predominant conformations of a given chiral anesthetic is necessary. While traditional methods such as electronic circular dichroism³ have been widely 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 recently been developed and holds promise for determining complete molecular stereochemistry in the solution phase. There are two forms of VOA: one is infrared vibrational circular dichroism (VCD)⁵ and the other is

* Corresponding author. E-mail: polavapl@ctrvax.vanderbilt.edu

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, isoflurane^{7a} and desflurane,^{7b,c} and the absolute configuration of bromochlorofluoromethane^{7d} 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 conformation. Recently, the geometrical structure and conformational properties of the anesthetic enflurane have been studied by electron diffraction and quantum chemical methods.⁸

The 1,2,2,2-tetrafluoroethyl methyl ether is an important intermediate in the synthesis⁹ of chiral anesthetic desflurane and is also an anesthetic itself.¹⁰ Based on the synthetic route used for its preparation, the (*R*)-absolute configuration has been assigned to (–)-1,2,2,2-tetrafluoroethyl methyl ether.¹¹ However, it is not clear which of the three possible conformations for this molecule are predominant in the solution phase. In this paper we report the experimental and ab initio theoretical VCD results for 1,2,2,2-tetrafluoroethyl methyl ether and based on these results, the absolute configuration and predominant conformations of this molecule are suggested.

2. Procedures

The (–)-enantiomer [97% (–)-enantiomer] and racemic samples of 1,2,2,2-tetrafluoroethyl methyl ether were synthesized by decarboxylation of (*R*)-(+)-1-methoxytetrafluoropropionic acid¹¹ and (*R,S*)-1-methoxytetrafluoropropionic acid,⁹ respectively. The optical rotation of the (–)-enantiomer was measured by dissolving 25 μ l of sample in 2 mL of CCl₄. Assuming a density of 1.5 g/cc, the specific rotation was found to be $[\alpha]_D = -37.9$ (20°C). The infrared and VCD spectra were recorded on a commercial Fourier transform VCD spectrometer, Chiralir (Bomem-BioTools, Canada) with a ZnSe beamsplitter, BaF₂ polarizer, optical filter (transmitting below 2000 cm⁻¹) and a 2×2 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 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 BaF₂ substrates used in the instrument restrict the range of measurements to 2000–900 cm⁻¹. Spectra were measured for the (–)-enantiomer and racemic samples in CCl₄ solvent (at a concentration of ~25 μ L per mL of CCl₄). In the absorption spectrum presented (bottom panel in Fig. 1) the solvent absorption was subtracted out. In the VCD spectrum presented (lower trace in the top panel of Fig. 1), the raw VCD spectrum of the racemic sample was subtracted from that of the (–)-enantiomer. The noise level in the VCD spectrum, shown as the top trace in the top panel of Fig. 1, is obtained as the difference between the VCD obtained from two 30 min data collections.

The ab initio vibrational frequencies, absorption and VCD intensities were calculated using the Gaussian 98 program¹² 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 B3LYP functional^{12–14} and 6-31G* basis set,¹⁵ while the other used B3PW91 functional^{8,12,13,16} and 6-311G(2d) basis set.^{12,15,8} These B3LYP and B3PW91 functionals were shown^{14,16} to satisfactorily reproduce the experimental VCD. The procedure for calculating the VCD intensities using DFT theory is due to Cheeseman et al.¹⁷ as implemented in the Gaussian 98 program.¹²

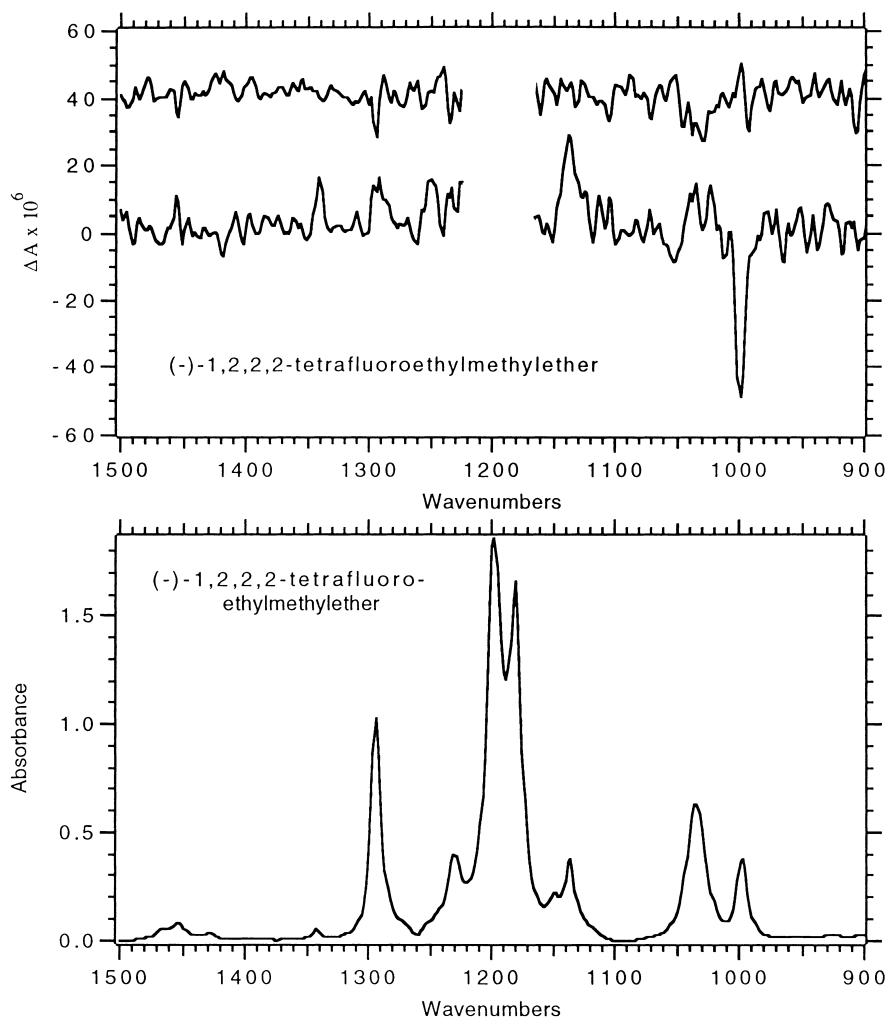
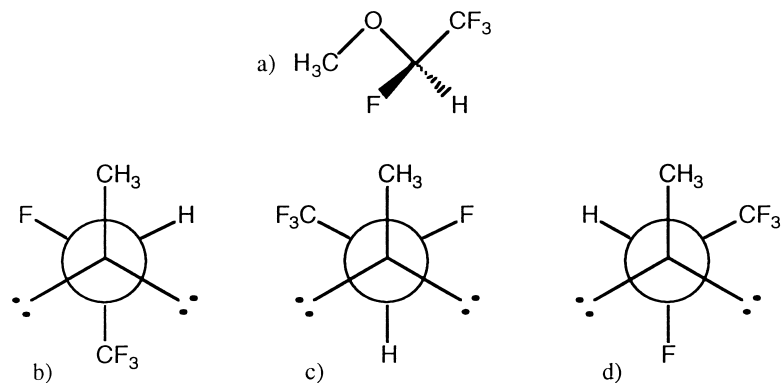


Figure 1. Vibrational absorption (bottom panel) and VCD (top panel) spectra for (-)-1,2,2,2-tetrafluoroethyl methyl ether (concentration=25 μL in 1 mL of CCl_4 ; pathlength=100 μm). Noise level in the VCD spectrum (top trace of the top panel) is obtained as the difference between two 30 min collected VCD spectra. The solvent absorption is subtracted out. Due to excessive absorbance, VCD in the 1220–1180 cm^{-1} region is not reliable and has been cut out

3. Results and discussion

There are three possible conformations for 1,2,2,2-tetrafluoroethyl methyl ether, labeled as *trans*, gauche plus (g^+) and gauche minus (g^-), which differ in the dihedral angle of C–O–C*–C segment (Scheme 1). This dihedral angle is $\sim 180^\circ$ for the *trans*-conformer, $\sim +60^\circ$ for the g^+ conformer and $\sim -60^\circ$ for the g^- -conformer. Using these starting values, the geometries were optimized with B3LYP/6-31G* and B3PW91/6-311G(2d) basis sets. While stable energy minima were found for the *trans*- and g^- -conformers, the g^+ -conformer converged to the *trans*-conformer in both methods of calculations, probably because the g^+ conformer does not have a potential energy minimum. The converged C–O–C*–C dihedral angles, optimized energies and relative populations based on the Gibbs energies are listed in Table 1. These results suggest that 1,2,2,2-tetrafluoroethyl methyl ether exists only in two different

conformations, *trans* and g^- , with the *trans*-conformer being the dominant one ($\sim 78\%$ at B3LYP level and 90% at B3PW91 level).



Scheme 1. Conformers of 1,2,2,2-tetrafluoroethyl methyl ether. (a) (*R*)-1,2,2,2-Tetrafluoroethyl methyl ether, (b) *trans*-conformer, (c) g^- -conformer, (d) g^+ -conformer

The vibrational frequencies, absorption intensities, and VCD intensities were calculated for the two optimized conformations of (*R*)-1,2,2,2-tetrafluoroethyl methyl ether, 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 Figs. 2 and 3. These theoretical spectra can be compared to the experimental spectra of (*-*)-1,2,2,2-tetrafluoroethyl methyl ether (in Fig. 1) to determine the predominant conformations and absolute configuration.

The predicted absorption spectra with B3LYP/6-31G* (Fig. 2) and B3PW91/6-311G(2d) (Fig. 3) basis sets for the *trans*-conformer match closely with the experimental spectrum (Fig. 1). The two strong bands in the experimental absorption spectrum at 1198 and 1180 cm^{-1} correspond to the two strong bands at ~ 1234 and 1218 cm^{-1} in the simulated spectrum of B3LYP/6-31G* calculation, and at ~ 1216 and 1207 cm^{-1} in the simulated spectrum of B3PW91/6-311G(2d) calculation. The moderately strong

Table 1
Conformations and energies of 1,2,2,2-tetrafluoroethyl methyl ether

No.	Starting geometry ^a	Converged geom ^a	Energy ^b		Label ^c	ΔE^d	pop ^e
			Electronic	Gibbs			
B3LYP/6-31G*							
1	+173°	+172°	-591.299023	-591.25414	<i>trans</i>	0.0	78%
2	+60°	+172°					
3	-60°	-61°	-591.298411	-591.25296	g^-	0.74	22%
B3PW91/6-311G(2d)							
1	+172°	+169.6°	-591.265987	-591.22150	<i>trans</i>	0.0	90%
2	+60°	+169.6°					
3	-61°	-60.6°	-591.264340	-591.21936	g^-	1.34	10%

^adihedral angles

^bin Hartrees

^cthe label represents the orientation of C-O-C*-C dihedral angle. (*trans*:*trans* orientation; g^- : counterclockwise *gauche* orientation)

^drelative energy difference (in Kcal/mol)

^epopulation based on Gibbs energies

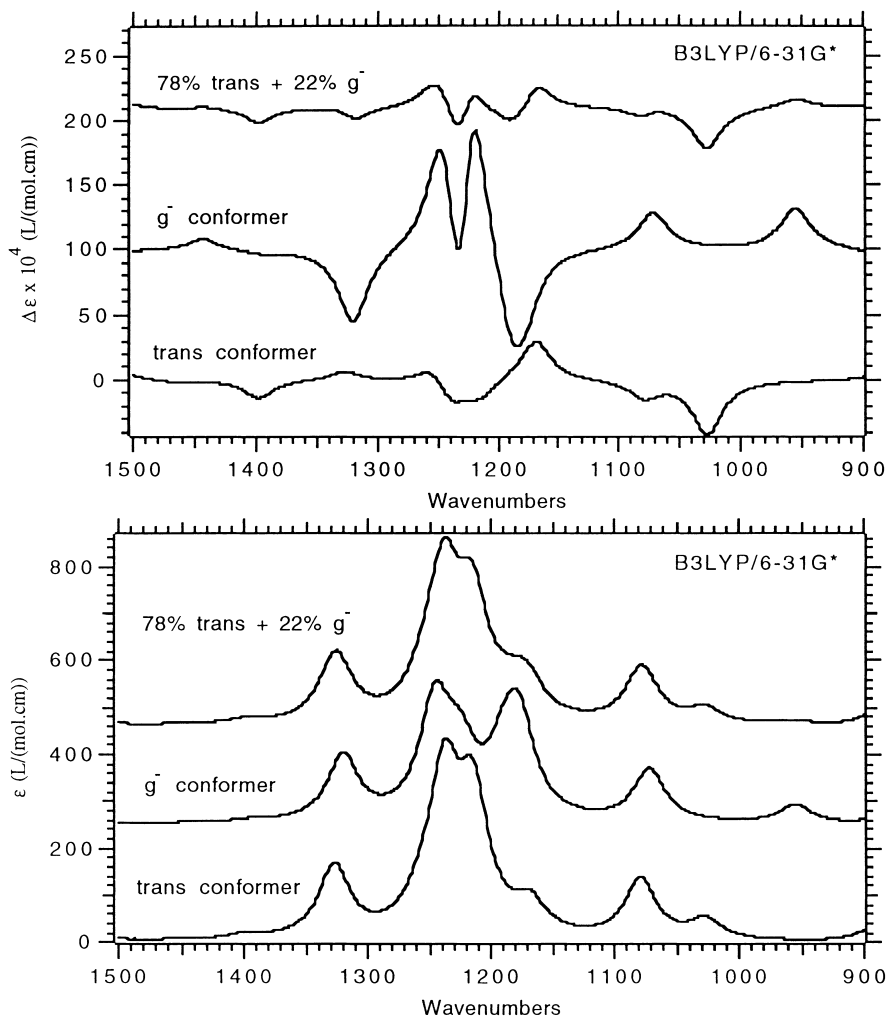


Figure 2. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for the *trans* and g^- -conformers of (*R*)-1,2,2,2-tetrafluoroethyl methyl ether obtained with B3LYP/6-31G* basis set. The spectra were simulated with Lorentzian band shapes and 15 cm^{-1} half-widths

absorption bands in the experimental spectrum at 1293 , 1136 , 1034 and 997 cm^{-1} correspond to the moderately strong bands at ~ 1327 , 1171 , 1078 and 1028 cm^{-1} in the simulated spectrum of B3LYP/6-31G* calculation, and at ~ 1313 , 1167 , 1066 and 1038 cm^{-1} in the simulated spectrum of B3PW91/6-311G(2d) calculation. The band corresponding to the experimental band at 1229 cm^{-1} is not resolved in the simulated spectrum of B3LYP/6-31G* calculation, but is clearly seen at $\sim 1250\text{ cm}^{-1}$ in the simulated spectrum of B3PW91/6-311G(2d) calculation. The absorption spectrum predicted for g^- -conformer is significantly different from that of the *trans*-conformer and from that of the experimental absorption spectrum. So the experimental and predicted absorption spectra suggest that, as concluded above from the energies of the conformers, the *trans*-conformer of 1,2,2,2-tetrafluoroethyl methyl ether is predominant in the solution phase.

The experimental VCD spectrum (Fig. 1) of (*-*)-1,2,2,2-tetrafluoroethyl methyl ether is very weak with only two bands that are above the noise level: one positive VCD band at 1138 cm^{-1} and one negative VCD band at 999 cm^{-1} . The strong absorption bands in the experimental spectrum at 1198 and 1180

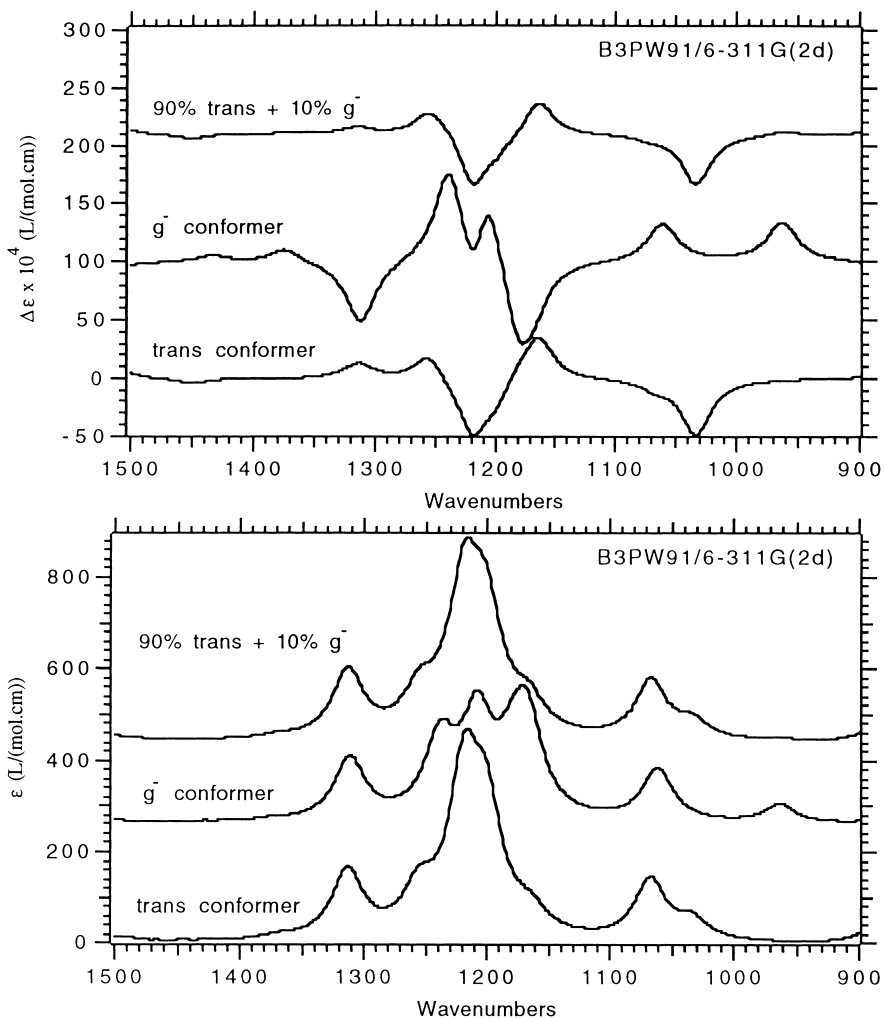


Figure 3. Ab initio vibrational absorption (bottom panel) and VCD (top panel) spectra for the *trans* and g^- -conformers of (*R*)-1,2,2,2-tetrafluoroethyl methyl ether obtained with B3PW91/6-311G(2d) basis set. The spectra were simulated with Lorentzian band shapes and 15 cm^{-1} half-widths

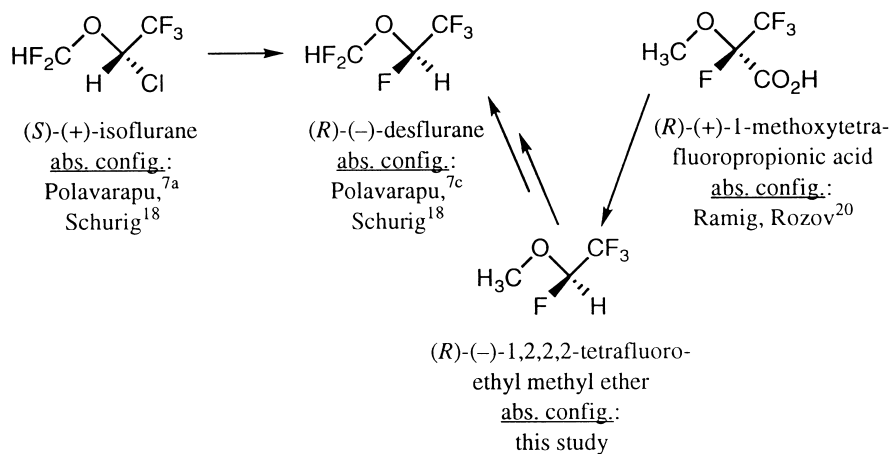
cm^{-1} do not exhibit measurable VCD. In both calculations (see Figs. 2 and 3) the *trans*-conformer is predicted to have much weaker VCD signals than the g^- -conformer and the VCD spectral pattern predicted for the *trans*-conformer is close to the experimental VCD spectrum. Thus, the VCD spectrum of (*-*)-1,2,2,2-tetrafluoroethyl methyl ether is dominated by the weak VCD of the *trans*-conformer. The presence of a small amount of g^- -conformer actually reduces the overall VCD signal, as the opposite signed VCD signals from the g^- -conformer cancel some of the already weak signals of *trans*-conformer. This can be seen from the comparison of the VCD spectra of individual conformers with that of the mixed conformers in Figs. 2 and 3. The simulated theoretical VCD spectrum (Fig. 2) for the *trans*-conformer of the (*R*)-enantiomer obtained with the B3LYP/6-31G* basis set predict positive VCD at $\sim 1168\text{ cm}^{-1}$ and negative VCD at 1027 cm^{-1} , which correspond to the experimental VCD bands at 1138 and 999 cm^{-1} , with matching VCD signs. The corresponding peak positions in the simulated VCD spectrum (Fig. 3) of B3PW91/6-311G(2d) calculation are 1165 and 1033 cm^{-1} .

While both B3PW91/6-311G(2d) and B3LYP/6-31G* calculations predict very similar VCD spectra,

the experimental absorption spectrum (especially the band at 1229 cm^{-1}) is better reproduced by the simulated spectrum obtained with B3PW91/6-311G(2d) than by that obtained with B3LYP/6-31G* calculation. For this reason, the predictions of B3PW91/6-311G(2d) calculation might be preferable.

Since the predicted VCD spectra for the *trans*- and *g*⁻-conformers are very different and the experimental VCD spectra are closer to the predicted spectra for the *trans*-conformer, the predicted VCD intensities for individual conformers also confirm earlier conclusions, based on the Gibbs energies and absorption intensities, that the *trans*-conformer is the predominant one. Moreover, since the VCD signs predicted for the (*R*)-enantiomer match those observed for the (–)-enantiomer, the absolute configuration of (–)-1,2,2,2-tetrafluoroethyl methyl ether can be assigned as *R*. This assignment of absolute configuration is supported by earlier studies based on optical rotations⁴ and the synthetic route.¹¹

These results, along with those of Schurig et al.,¹⁸ put to rest the controversy over the absolute configurations of 1,2,2,2-tetrafluoroethyl methyl ether, desflurane, and isoflurane. Earlier data,^{7b} where mislabeling of (+)- and (–)-enantiomers of desflurane was not recognized, led to the conclusion that isoflurane and desflurane had opposite absolute configurations. Since then, several reports have appeared that provide evidence that this conclusion was incorrect. Firstly, it was disclosed that the conversion of isoflurane to desflurane proceeded with retention of configuration, despite an apparent S_N2-type process.¹⁹ Later, it appeared that the highly stereoselective reaction which produced an enantiomer of 1,2,2,2-tetrafluoroethyl methyl ether resulted in an unprecedented stereochemical course, namely nearly complete inversion of configuration for a C–C bond-breaking process.²⁰ In those studies, the absolute configuration of the product 1,2,2,2-tetrafluoroethyl methyl ether was deduced by correlation with that of desflurane, using the original assignment.^{7b} All these studies suggest that the original assignment of the (*R*)-configuration to (+)-desflurane is in error; the original assignment has since been corrected.^{7c} The current study corroborates the corrected configurational assignments of 1,2,2,2-tetrafluoroethyl methyl ether, desflurane, and indirectly, the configurational assignment of isoflurane. Scheme 2 shows the revised stereochemical outcomes of the two stereoselective reactions in question.



Scheme 2. Corrected stereochemical outcomes for two stereoselective reactions

4. Summary

A comparison of the experimental vibrational absorption and VCD spectra of 1,2,2,2-tetrafluoroethyl methyl ether with those predicted for the *trans*- and *g*⁻-conformers suggests that the *trans*-conformer of

1,2,2,2-tetrafluoroethyl methyl ether is predominant in the solution phase. Furthermore, the VCD signs observed for (–)-1,2,2,2-tetrafluoroethyl methyl ether match those predicted ab initio for (R)-1,2,2,2-tetrafluoroethyl methyl ether, so the absolute configuration of the (–)-enantiomer can be assigned as R.

Acknowledgements

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