Conformational Spaces and Absolute Configurations of Chiral Fluorinated Inhalation Anaesthetics. A Theoretical Study

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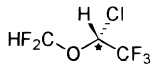
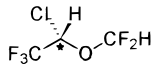
The results of an ab initio DFT study of the conformational spaces of the chiral fluorinated inhalation anaesthetics Isoflurane and Desflurane and their theoretical VCD spectra using the hybrid density functional B3LYP and 6-311++G** GIAO basis functions are reported. In each case six conformers were characterized by analytical frequencies. At room temperature conformers 1 and 2 of Isoflurane account for 71% and 27% of the population, respectively, and conformers 1 and 2 of Desflurane account for 82% and 16% of the population, respectively. Each of the six conformers of (*R*)-Isoflurane and (*R*)-Desflurane gives rise to a clearly distinct VCD spectrum with different vibrational frequencies and rotatory strengths. The less populated conformers 2 of (*R*)-Isoflurane and of (*R*)-Desflurane give rise to vibrational modes with much higher rotational strength than the corresponding conformers 1. In studies of conformational equilibria and absolute configurations based on VCD spectroscopy, Boltzmann weights rather than arbitrarily selected relative weights are recommended. In view of the ambiguities and shortcomings of the previous calculated and experimental VCD spectra of Isoflurane and Desflurane, the results of the present theoretical VCD study may serve together with future independent experimental VCD spectra as a basis for an unequivocal determination of the absolute configurations of Isoflurane and Desflurane.

The chiral inhalation anaesthetics Isoflurane (2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane) and Desflurane ((2-difluoromethoxy)-1,1,1,2-tetrafluoroethane) are clinically administered as synthetic racemic mixtures.[1,2]



(*R*)-Isoflurane



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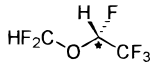
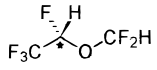


(*R*)-Desflurane



(*S*)-Desflurane

Isoflurane is a successful second generation halogenated anaesthetic, while Desflurane, a third generation anesthetic, is considered the current state-of-the-art in marketed anaesthetic agents.[1] It combines the desirable properties of good anaesthetic syndrome, nonflammability, negligible metabolism, and fast recovery time.[3] The search for an ideal anaesthetic agent may lead to the use of enantiomerically pure Isoflurane or Desflurane with clinical advantages over the currently available racemates.[3−6] The enantiomers of Isoflurane and Desflurane were first prepared at the Anaquest Division of the BOC Group (later Ohmeda Pharmaceutical Products Division, now Baxter Pharmaceutical Products, Inc., Liberty Corner, NJ).[3] In two consecutive 1992 US patents, (*R*)-Isoflurane and (*R*)-Desflurane (US Patent A 5114714) as well as (*S*)-Isoflurane and (*S*)-Desflurane (US Patent A 5114715) were claimed to induce and maintain anaesthesia and to be associated with less adverse effects than the corresponding racemates.[7,8] According to the abstract of a 1994 US patent, the highly purified (+)-enantiomer of Desflurane is advantageous over the (−)-enantiomer or the racemate.[9] Calculations based on shape similarity suggest that Isoflurane is likely to show more difference in anaesthetic potency between enantiomers than Desflurane, Enflurane, and Halothane.[10] The evaluation of the anesthetic potencies of single enantiomers of Isoflurane and Desflurane is still in its infancy.[11−21]

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The absolute configurations of Isoflurane and Desflurane were first determined by Polavarapu et al., using vibrational circular dichroism (VCD) spectroscopy in the infrared in combination with ab initio calculations at the HF/6-31G* level.[22,23] The following assignments were reported:

(+)-Isoflurane = (*S*)-Isoflurane;[22]

(−)-Isoflurane = (*R*)-Isoflurane;[22]

(+)-Desflurane = (*R*)-Desflurane;[23]

(−)-Desflurane = (*S*)-Desflurane.[23]

Thus, the (+)- and (−)-enantiomers of Isoflurane and Desflurane possess opposite absolute configurations, respectively. These assignments by Polavarapu, in particular the relative configurations of (+)-Isoflurane vs (+)-Desflurane, have raised doubts among the practitioners of chirality as to the absolute configurations of (+)- and (−)-Desflurane. These doubts emanated from an accumulation of circumstantial evidence[24] including signs of optical rotation, gas chromatographic elution order,[25,26] direction in ^{1}H NMR spectroscopic low field chemical shifts (in the presence of a γ-CD derivative),[27,28] the expected stereochemical course of the halogen exchange of the enantiomers of Isoflurane into the enantiomers of Desflurane, and of the decarboxylation of (+)-(*R*)-1-methoxytetrafluoropropanoic acid to (−)-1,2,2,2-tetrafluoroethyl methyl ether.[29] Schurig et al. have recently determined the absolute configurations of single crystals of (+)-Isoflurane and (+)-Desflurane by anomalous dispersion of X-rays at cryogenic temperatures.[5,6,24] According to these assignments, both (+)-enantiomers possess the (*S*)-configuration. Thus, Polavarapu's original VCD assignment of (+)-(*R*)-Desflurane[23] should be reversed to (+)-(*S*). However, even Schurig et al. considered this new assignment as "somewhat ambiguous".[24] "Due to the absence of heavy atoms [...], the determination of the absolute configuration for Desflurane is clearly linked with some ambiguity".[5]

The new assignment by Schurig et al.,[24] prompted Polavarapu et al. to publish in February 1997 the following correction:[30] "The labels on the enantiomer samples of Desflurane supplied were found to be interchanged. Thus (+)-Desflurane in this paper[23] should be read as (−)-Desflurane and vice versa. We thank Drs. Minnie Park (Vanderbilt University) and Leo Rozov (Ohmeda Inc.) for measuring the optical rotations in chloroform solution and as neat liquid."[30] This belated correction is inadequate and unsatisfactory. The reader is left with a vague, ambiguous picture. Very recently Polavarapu reported the calculated ab initio optical rotations of the two most stable conformers of (*R*)-Isoflurane and of (*R*)-Desflurane, using HF/4-31G and HF/6-31G* and compared them to the experimental values.[31] The comparisons were consistent with Schurig's assignments[5,6,24] of the absolute configurations.[31]

Polavarapu et al. calculated the VCD spectra of the enantiomers of Isoflurane and Desflurane using the ab initio HF/6-31G* level and field-independent basis functions (FIAOs).[22,23] The limitations of HF/SCF and FIAOs in VCD have since been recognized.[32−36] "It was clear a long time ago that SCF force fields are insufficiently accurate to provide useful predictions of VCD spectra."[32] Furthermore, Polavarapu et al. characterized only the global minimum (conformer 1) and the second most stable conformer (conformer 2) of Isoflurane and of Desflurane. Other, less stable conformers were not taken into account. According to these calculations, the relative populations of conformer 1 and conformer 2 are 85:15 and 80:20 (at HF/6-31G*) for Isoflurane[22] and Desflurane,[23] respectively. Despite these uneven ratios, Polavarapu used in the HF/FIAO calculations of the VCD spectra, in each case, a 1:1 ratio of the two conformers. He argued that "because a better comparison between the experimental and theoretical relative intensities is obtained with equal populations, it is assumed that the two conformations have equal populations".[23]

The ambiguities and shortcomings surrounding the determinations of the absolute configurations of the enantiomers of Isoflurane and Desflurane call for a new, independent experimental as well as a theoretical definitive study. Infrared vibrational circular dichroism spectroscopy (VCD), a component of vibrational optical activity (VOA),[37] has emerged as a powerful tool for the determination of absolute configurations of chiral molecules.[32−39] The method consists of a combination of the VCD experiment and predicted theoretical VCD spectrum obtained by high level ab initio calculations. There has been limited experience in applying the VCD method to conformational analyses of chiral organic

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Table 1. Ab Initio Total Energies, Relative Energies, Torsion Angles, and Dipole Moments of (*R*)-Isoflurane Conformers at B3LYP/6-311++G**

	E_{tot}[a]	E_{rel}[b]	population[c]	H−C−O−C[d]	C−O−C−C[d]	O−C−C−F[d]	dipole[e]
1	−1150.39987	0.00	70.8	179.3	138.8	−179.5	1.57
2	−1150.39896	0.57	27.0	60.3	165.1	−179.5	2.06
3	−1150.39617	2.32	1.4	−36.7	148.2	−179.5	2.77
4	−1150.39563	2.66	0.8	−20.9	−66.0	−171.6	1.63
5	−1150.39111	5.49	0.007	−168.5	−56.0	−166.5	2.41
6	−1150.39099	5.57	0.006	164.3	−78.3	−155.3	2.11

[a] In hartree. [b] In kcal/mol. [c] Percentages at 298 K. [d] In degrees. [e] In Debye.

molecules.[39] We report here the results of an ab initio DFT study of the conformational spaces of Isoflurane and Desflurane[40] and their theoretical VCD spectra, using the hybrid density functional B3LYP and the 6-311++G** basis set with gauge-invariant atomic orbitals (GIAOs). Recently it was demonstrated that the B3LYP density functional and magnetic field-dependent basis functions (GIAOs) considerably improve the correlation of the theoretical mid-IR frequencies and rotatory strengths with the experimental spectra.[32,33,35] In fact, results obtained with hybrid density functionals such as B3LYP and B3PW91 are much more accurate than HF/SCF results.[32,34−36,39] Hybrid density functionals in combination with basis sets larger than 6-31G* have been shown to give more accurate VCD spectra.[33,35,36]

Methods

The conformational spaces of Isoflurane and Desflurane, spanned by rotation about the C_2-O and $O-C_{1'}$ single bonds, were systematically searched using a two-dimensional grid. All local minima were fully optimized using Becke's three-parameter hybrid density functional[41] with the nonlocal correlation functional of Lee, Yang, and Parr,[42,43] B3LYP, and the triple split valence basis set augmented with diffuse functions and polarization functions on all atoms (6-311++G**). The conformations were characterized as minima by calculation of analytical frequencies. Geometries were optimized using Gaussian 94, Revision D1.[44] Vibrational frequencies, dipole strengths and VCD rotational strengths were calculated at B3LYP/6-311++G** with magnetic field-dependent basis functions (GIAOs) using Gaussian 98.[34,45] Dipole strengths are reported in 10^{-40} esu^2 cm^2 and rotational strengths in 10^{-44} esu^2 cm^2. Vibrational modes were assigned by analysis of the normal coordinates. The VCD spectra were simulated using unscaled frequencies and Lorentzian band shapes with a half-width at half-height of 8 cm^{-1}. The individual spectra of the conformers were weighted according to the Boltzmann distribution at 298 K calculated from the B3LYP/6-311++G** ab initio total energies.

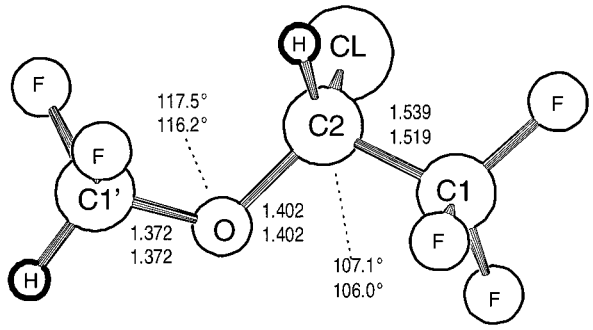

Figure 1. (*R*)-Isoflurane B3LYP/6-311++G** 3D structure of conformer 1 and selected calculated (top) and experimental (X-ray, below) bond lengths and bond angles.

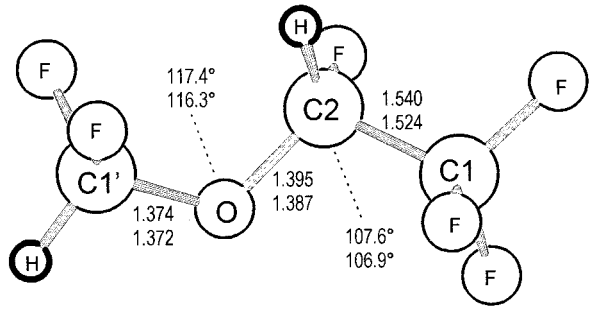

Figure 2. (*R*)-Desflurane B3LYP/6-311++G** 3D structure of conformer 1 and selected calculated (top) and experimental (X-ray, below) bond lengths and bond angles.

Results and Discussion

Figure 1 and Figure 2 give the calculated B3LYP/6-311++G** 3D structures of the global minimum of (*R*)-Isoflurane and (*R*)-Desflurane, respectively, along with selected calculated and experimental (X-ray[24]) bond lengths and bond angles.

Table 1 and Table 2 give the calculated total energies, relative energies, percentages, torsion angles $C_2-O-C_{1'}-H_{1'}$, $C_1-C_2-O-C_{1'}$, and $F_{1a}-C_1-C_2-O$ and dipole moments of the six conformers of (*R*)-Isoflurane and the six conformers of (*R*)-Desflurane, respectively, at B3LYP/6-311++G**.

The conformers 1−3 of (*R*)-Isoflurane are characterized by an extended "backbone" (torsion angle $C_1-C_2-O-C_{1'} \cong 150°$). They differ by rotation of the CHF_2 group about the C−O bond. Conformers 4−6 have a (−) gauche conformation of the backbone ($C_1-C_2-O-C_{1'} \cong -65°$). No (+) gauche conformers were found for (*R*)-Isoflurane. At

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Table 2. Ab Initio Total Energies, Relative Energies, Torsion Angles, and Dipole Moments of (*R*)-Desflurane Conformers at B3LYP/6-311++G**

	E_{tot}[a]	E_{rel}[b]	population[c]	H−C−O−C[d]	C−O−C−C[d]	O−C−C−F[d]	dipole[e]
1	−790.05146	0.00	81.6	177.4	145.1	179.7	1.74
2	−790.04992	0.97	15.9	59.3	169.5	177.8	1.92
3	−790.04791	2.23	1.9	−32.5	158.7	177.9	2.99
4	−790.04690	2.86	0.6	−16.2	−67.2	−175.4	1.48
5	−790.04309	5.25	0.012	−166.6	−56.1	−168.8	2.52
6	−790.04254	5.60	0.006	171.6	−103.6	−175.2	2.16

[a] In hartree. [b] In kcal/mol. [c] Percentages at 298 K. [d] In degrees. [e] In Debye.

room temperature the global minimum, conformer 1, accounts for ca. 71%, conformer 2 for ca. 27% of the population. Conformers 3 and 4 contribute ca. 1.4% and 0.8%, respectively. The torsion angles found in the X-ray structure of (*S*)-Isoflurane, $C_2-O-C_{1'}-H_{1'} = 179.9°$, $C_1-C_2-O-C_{1'} = -133.5°$, and $F_{1a}-C_1-C_2-O = -174.9°$, closely resemble the values for the mirror image of our calculated conformer 1 of (*R*)-Isoflurane. Thus, the conformation of the molecule found in the crystal structure corresponds to the global minimum conformation.

The conformations of (*R*)-Desflurane (Table 2) are similar to those of (*R*)-Isoflurane. Again, no (+) gauche conformers were found for (*R*)-Desflurane. However, the population of the global minimum, conformer 1, is even higher (82%), while the population of conformer 2 is lower (16%). In the X-ray structure of (*S*)-Desflurane torsion angles $C_2-O-C_{1'}-H_{1'} = -170.0°$, $C_1-C_2-O-C_{1'} = -142.7°$, and $F_{1a}-C_1-C_2-O = -169.9°$ were observed, similar to those corresponding to the mirror image of the calculated global minimum conformation 1 of (*R*)-Desflurane.

Figure 3 gives the calculated B3LYP/6-311++G** VCD spectra of the six conformers of (*R*)-Isoflurane and the superposition of these spectra. The spectrum of conformers 1−6 corresponds to the Boltzmann distributed population at 298 K calculated from the ab initio energies. For comparison, the theoretical VCD spectrum of a 71:27 and a 1:1 mixture of conformers 1 and 2 are also shown.

Figure 4 gives the calculated B3LYP/6-311++G** VCD spectra of the six conformers of (*R*)-Desflurane and the superposition of these spectra, including a 82:16 and a 1:1 combination of conformers 1 and 2.

Each conformer of Isoflurane and Desflurane has 30 ($3n - 6$) vibrational frequencies. Frequencies, dipole strengths, and sign and magnitude of the rotational strengths are different for each vibration of each conformer/compound. Each conformer of Isoflurane and of Desflurane has two C−H bond stretching vibrations in the range 3075−3165 and 3055−3166 cm^{-1}, respectively. The C−H bond stretching vibrations have weak dipole strengths (<53) and weak rotational strengths (abs value < 20). The C−H vibrations are not shown in the spectra (Figure 3 and Figure 4). Four H−C−X (X = C, O, F, Cl) bending vibrations were found in the regions 1298−1428 cm^{-1} and 1357−1445 cm^{-1} for each conformer of Isoflurane and Desflurane. The H−C−X bending vibrations have weak to medium dipole strengths (<200 for Isoflurane and <53 for Desflurane) and low rotational strengths (−40 to +65 for (*R*)-Isoflurane and −12 to +14 for (*R*)-Desflurane). Each conformer of Isoflurane and Desflurane has one vibration in the ranges 1260−1276 cm^{-1} and 1288−1303 cm^{-1}, respectively. The corresponding normal modes include stretching of the C−C bond as a major component with contributions from C−F stretching (*anti*-phase). The dipole strength is medium (370 to 660). However, the rotational strength of this vibration is low: −86 to −44 for the (*R*)-Isoflurane conformers and −45 to +35 for the (*R*)-Desflurane conformers. Note that all conformers of (*R*)-Isoflurane show negative rotational strengths for this mode. The vibrations with highest dipole strengths and rotational strengths were identified as C−F and/or C−O bond stretching modes. (*R*)-Desflurane has seven such vibrational modes for each conformer with wavenumbers in the range 999−1188 cm^{-1}, dipole strengths up to 2020 and rotational strengths of −404 to +471. At 848−891 cm^{-1}, Desflurane conformers have one vibrational mode composed from an in-phase combination of C−F and C−C bond stretching. This vibration has relatively low dipole strengths (<180) and low rotational strengths (−30 to +10 for the conformers of (*R*)-Desflurane). Each conformer of (*R*)-Isoflurane has six C−F and C−O bond stretching modes in the range 986−1186 cm^{-1} with dipole strengths up to 1945 and rotational strengths ranging from −428 to +310. There is one vibration in the range 844−877 cm^{-1} for each conformer. This mode is an in-phase combination of C−C and C−F bond stretching. The corresponding dipole strengths range from 94 to 344, and the rotational strengths are relatively low (−50 to +19 for (*R*)-Isoflurane). The C−Cl bond stretching vibration at 778−833 cm^{-1} has medium dipole strengths (218 to 532) and low rotational strengths (−4 to +47 for (*R*)-Isoflurane conformers). Vibrations of Isoflurane and Desflurane with lower wavenumbers correspond to various bending and deformation modes. They also include three internal rotations about single bonds (formal harmonic wavenumbers < 120 cm^{-1}). The bending and deformation modes have low dipole strengths and low rotational strengths.

It is interesting to note that the sign (and magnitude) of the rotational strength of corresponding vibrational modes may change from conformer to conformer giving rise to characteristic patterns in the VCD spectra of each conformer of Isoflurane and of Desflurane. Furthermore, the total magnitudes of the VCD spectra of each conformer are quite different. In particular, it should be noted that for (*R*)-Isoflurane, conformer 2 has rotational strengths up to −428, more than twice the magnitude of the strongest VCD in conformer 1. For conformer 2 of (*R*)-Desflurane rotational strengths up to +470 were calculated, more than 6 times the highest magnitude computed for conformer 1. In fact, for Isoflurane, as well as for Desflurane, conformers 1 with torsion angles $C_2-O-C_{1'}-H_{1'}$ and $C_1-C_2-O-C_{1'}$ close to *anti* show the weakest VCD spectrum of all conformers (Figure 3 and Figure 4). Thus in the Boltzmann-weighted VCD spectrum of Desflurane, conformer 2 makes a contribution comparable to that of conformer 1, despite its lower population. The same holds true in the case of Isoflurane. This effect has to be kept in mind in calculations of

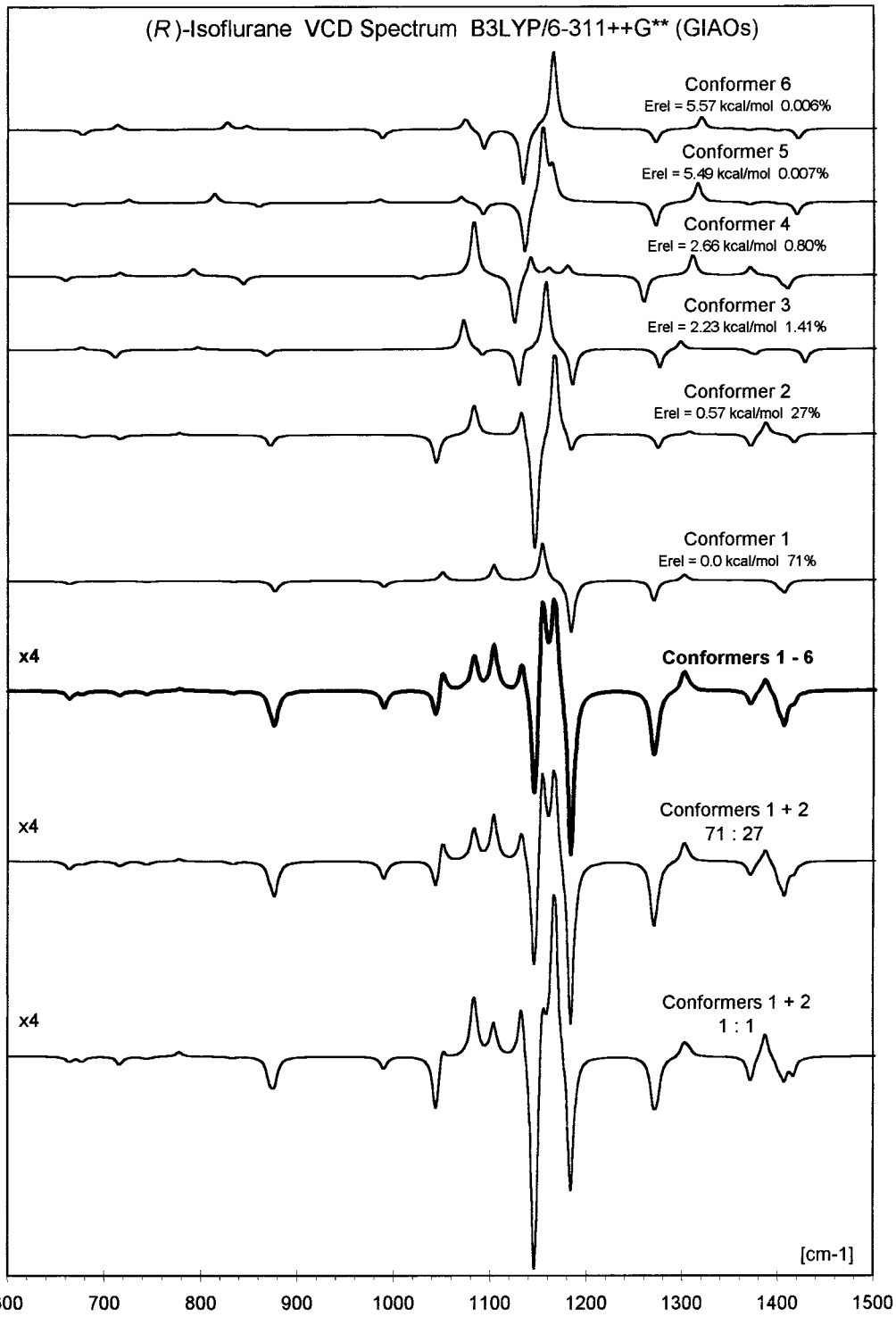

Figure 3. Calculated B3LYP/6-311++G** (GIAOs) VCD spectra of the six conformers of (*R*)-Isoflurane and the superposition of these spectra.

theoretical VCD spectra of conformationally flexible compounds. The superposition of the spectra of the conformers 1 and 2 in their Boltzmann-weighted ratio results in a spectrum very similar to the superposition of all conformers. However a 1:1 superposition is unacceptable, resulting in a distorted spectrum (Figure 3 and Figure 4).

The vibrational modes with the highest rotational strengths share the following common pattern: two noncoplanar C−F bonds (or one C−F and one C−O bond) contributing stretching vibrations with comparable amplitudes. The two C−F bonds involved, are located at the opposite ends of the molecule, in the CF_3 and CHF_2 groups, respectively.

A comparison of our calculated B3LYP/6-311++G** (GIAOs) VCD spectra of Isoflurane (Figure 3) with the published[22] calculated HF/6-31G* (FIAOs) spectra shows that our spectrum of (*R*)-Isoflurane corresponds to the enantiomer of the published[22] calculated spectrum of (*S*)-Isoflurane. However, note the improved correlation of our calculated spectrum with the experimental spectrum. In particular, our spectrum shows a strong negative, a

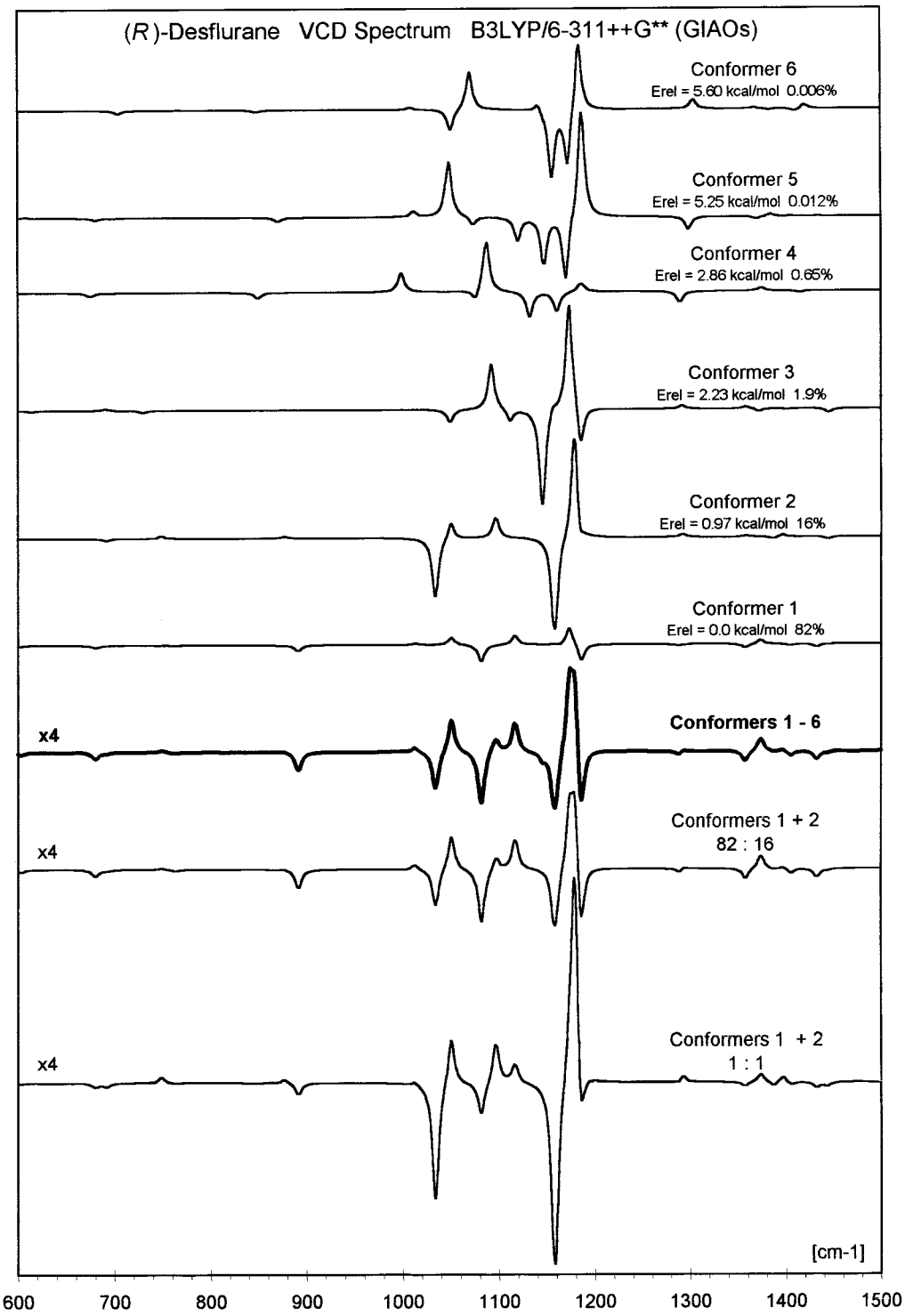

Figure 4. Calculated B3LYP/6-311++G** (GIAOs) VCD spectra of the six conformers of (*R*)-Desflurane and the superposition of these spectra.

double positive and another very strong negative peak in the range of 1140−1200 cm^{-1}, while the (inverted) published[22] spectrum shows only one weak negative peak and one relatively strong positive peak in this range. Also note that the medium strong negative peak at ∼875 cm^{-1} corresponds well to the inverted experimental spectrum,[22] while the only comparable peak in the HF/FIAO calculated spectrum[22] is at ∼770 cm^{-1}. Comparing our calculated spectrum for (*R*)-Desflurane (Figure 4) with the published[23] calculated spectrum of (*R*)-Desflurane shows notable differences in the region of 1000−1150 cm^{-1}. Our DFT/GIAO spectrum shows a strong positive peak at 1050 cm^{-1} which has no correspondence in the HF/FIAO[23] spectrum. Furthermore, by far the strongest negative peak in the HF/FIAO[23] spectrum at ∼1080 cm^{-1} corresponds to a medium strong peak at 1081 cm^{-1} in our spectrum.

A comparison of the theoretical VCD spectra of individual conformers of Isoflurane and of Desflurane at B3LYP/6-311++G** (this work) with the respective HF/6-31G*[22,23] results indicates significant frequency shifts in the range of 1150−1250 cm^{-1}. We focus on the spectra of conformers 2, which give the strongest VCD signals. The strongest (negative) peak of conformer 2 of (*R*)-

Isoflurane computed by the B3LYP/6-311++G** at 1146 cm^{-1} corresponds to a small positive peak at ~1140 cm^{-1} in the published[22] spectrum of (*S*)-Isoflurane. On the other hand, the strongest positive peak in the HF/FIAO[22] spectrum (at ~760 cm^{-1}) may correspond either to the very weak positive peak at 777 cm^{-1} or to the weak negative peak at 716 cm^{-1} in our DFT/GIAO spectrum. In our VCD spectrum of conformer 2 of (*R*)-Desflurane, the vibrations at 1159 and 1157 cm^{-1} with very negative rotational strengths give rise to a single negative peak. In the published[23] spectrum of (R)-Desflurane, conformer 2, the two negative peaks are clearly separated (~1145 and ~1160 cm^{-1}). The HF/FIAO[23] spectrum shows a strong positive peak at ~1110 cm^{-1} and a very strong negative peak at ~1080 cm^{-1}, while our spectrum has only one weak positive peak at 1097 cm^{-1} in this range. On the other hand, the B3LYP/6-311++G** spectrum has a strong negative peak at 1034 cm^{-1} and a weak positive peak at 1050 cm^{-1} which correspond to only one weak negative peak at ~1040 cm^{-1} in the HF/FIAO[23] spectrum.

The differences in the theoretical VCD spectra calculated at B3LYP/6-311++G** (GIAOs) with respect to the HF/6-31G* (FIAOs) spectra[22,23] illustrate the progress in the theoretical methods.[32−36,39]

In previous studies of conformational equilibria based on VCD spectroscopy and ab initio calculated rotational strengths it was not uncommon to use arbitrarily selected relative weights of the conformations rather than Boltzmann weights.[39] The results reported here indicate that such an arbitrary approach may be treacherous. The criterion of a good agreement with experiment at the expense of ignoring Boltzmann weighting is unjustified.

In conclusion, the results of the present theoretical VCD study may serve, together with future independent experimental VCD spectra, as a basis for an unequivocal determination of the absolute configurations of Isoflurane and Desflurane.

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Supporting Information Available: The results of the VCD calculations of the six conformers of (*R*)-Isoflurane and the six conformers of (*R*)-Desflurane are listed in Table S1 and Table S2. Figures S1 and S2 give the calculated IR spectra of the Isoflurane conformers and of the Desflurane conformers (4 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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