

# Revisiting Vibrational Circular Dichroism Spectra of (S)-(+)-Carvone and (1S,2R,5S)-(+)-Menthol Using SimIR/VCD Method

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## Supporting Information

**ABSTRACT:** The VCD spectra of (S)-(+)-carvone and (1S,2R,5S)-(+)-menthol are recalculated using the DFT method with extended conformation and configuration spaces. The calculated individual and averaged spectra are compared against observed ones using the previously reported similarity index,  $S_V$ . It is found that the  $S_V$  population forms approximately two normal distributions, depending on whether a spectrum matches the observed one or not. This statistical character can be used to estimate the error in absolute configuration (AC) assessments. To avoid erroneous AC assignments and incomplete conformation searching, it is advisable to employ a minimum  $|S_V|$  of 0.2 and maximize it using conformation averaging. It is demonstrated that this approach is suitable and robust for flexible chiral molecules.

## 1. INTRODUCTION

Vibrational circular dichroism (VCD) spectroscopy<sup>1–4</sup> has been used to determine the absolute configurations (ACs) of many chiral pharmaceuticals and natural products. On the basis of the model–observation agreement, the AC determination of a stereoisomer is to find a calculated spectrum that resembles the observed spectrum. If the degree of resemblance is acceptable, the hypothesized AC in the calculation is assigned to the stereoisomer. For a nonrigid stereoisomer, the calculated spectra of several conformers are averaged with proper weightings to obtain the best match. Relying heavily on the visual identification of matched bands at various frequencies, the VCD spectrum comparison poses a great challenge due to the approximations in the theoretical models, the conformation sampling, the spectrum dependency on chirality and conformation, etc. The resulting AC assignments often lack quantitative error assessments unless the tedious band-to-band correlation analysis<sup>2</sup> or an emerging automatic method is applied.

We proposed a VCD spectrum similarity index,  $S_V$ , and a spectrum comparison method, SimIR/VCD,<sup>5</sup> which are among several methods<sup>6–9</sup> including CompareVOA for quantifying the model–observation agreement. Whether in practice or in publication, these methods start to play an important role in AC determination using VCD. For the past two years, we continued to focus on unmet needs in using SimIR/VCD. While an  $|S_V|$  of 0.2 or greater was found to be predictive for correct AC assignments, the fundamental basis of the prediction and the differentiation of  $S_V$  with respect to conformation and configuration have not been systematically studied. The lack of this knowledge casts doubts on the applicability of  $S_V$  for a wide range of chiral molecules. In addition, the use of  $S_V$  as a quantitative confidence measure has not been well established. This statistical measure is essential for an unbiased judgment on accepting a matched spectrum and its associated AC.

Aiming to explore the characteristics of  $S_V$  and its reliability in AC assessments, we carried out VCD studies for two natural products, (S)-(+)-carvone and (1S,2R,5S)-(+)-menthol. They were chosen in this study for their manageable number of conformations and small molecular size, which made the calculation fast. Although both molecules have been subjected to several VCD studies,<sup>10–14</sup> only low energy conformers with known configurations were rigorously modeled. In contrast, we treated both stereoisomers as undetermined samples to test whether  $S_V$  is a reliable parameter for identifying a correct AC. Together with more calculated conformers, the new study sampled enough  $S_V$  for statistical inference. The performances of several DFT functionals were also evaluated for VCD spectrum fitness based on  $S_V$  values. We demonstrate that  $S_V$  is not only a reliable index for AC determination but also a quantitative indicator of confidence assessment.

## 2. METHOD AND CALCULATION

The experimentally observed IR and VCD spectra of (S)-(+)-carvone (1.05 M in  $\text{CCl}_4$ ) and (1S,2R,5S)-(+)-menthol (1.33 M in  $\text{CCl}_4$ ) were measured with a path length of 73  $\mu\text{m}$  and a resolution of 2  $\text{cm}^{-1}$ . The conformation search was carried out using MCMC/low-mode in Maestro 8.5 (Schrödinger, LLC). For all diastereomers associated with (+)-menthol, an energy cutoff of 5 kcal/mol and an RMSD of 1.0 Å were used to generate starting conformers for the subsequent DFT calculations. Gaussian 03 (Gaussian Inc.)<sup>15</sup> was used for all DFT (optimization + VCD) calculations with the 6-31G(d) basis set and several functionals including PBEPBE,<sup>16</sup> B3LYP, and B3PW91. The IR and VCD spectra were generated using a Lorentzian half-width of 8  $\text{cm}^{-1}$ . The conformer population is calculated on the basis of the Gibbs

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Table 1. Spectrum Similarity Values of Carvone Conformers Using B3PW91<sup>a</sup>

conformer	D (deg) <sup>b</sup>	S <sub>I</sub>	S <sub>V</sub>	E (B3PW91) <sup>c</sup>	E (kcal/mol)	population (%)
CE1	57	0.68	0.45	−464.52253	0	51
CE2	−169	0.77	0.32	−464.52214	0.25	23
CE3	−68	0.75	0.38	−464.52202	0.32	23
CA1	−69	0.80	−0.17	−464.51925	2.06	1
CA2	−174	0.84	−0.15	−464.51961	1.83	1
CA3	64	0.76	−0.21	−464.51913	2.13	1
<CE> <sup>d</sup>		0.73	0.63			

<sup>a</sup>6-31G(d) basis set was used. <sup>b</sup>Dihedral angle is defined by the four connecting carbons from the methyl of isopropylene to the CH<sub>2</sub> next to the carbonyl, see ref 14. <sup>c</sup>For comparison with ref 14. <sup>d</sup>52%CE1 + 24%CE2 + 24%CE3.

free energy of Gaussian 03 output. Unless noted, the default parameters were used.

The spectrum comparison and alignment were carried out using the SimIR/VCD protocol implemented in Scitegic PipelinePilot 8.0 (Accelrys Inc.). Briefly, the two similarities between calculated (c) and observed (o) IR and VCD spectra are defined as

$$S_I = \frac{I_{co}}{I_{cc} + I_{oo} - I_{co}} \quad (1)$$

$$S_V = \frac{I_{co}}{I_{cc} + I_{oo} - |I_{co}|} \quad (2)$$

where  $I_{ij}$  are the self and overlap integrals of spectra  $i$  and  $j$ ,

$$I_{ij} = \int F_i(\nu) F_j(\nu) d\nu \quad (3)$$

The sign of  $S_V$  indicates whether the model and the sample have the same AC (+) or if they are an enantiomeric pair (−).  $S_I$  and  $S_V$  can be computed directly according to eqs 1 and 2 or optimized as described previously<sup>3</sup> and briefly in the following. The calculated IR spectrum is first divided into a number of bands. Each band is then shifted locally to maximize  $S_I$ . Such frequency shifts are then applied to each corresponding band of the calculated VCD spectrum to yield an optimized  $S_V$ . The strengths of the measured and calculated IR and VCD spectra were normalized to [0 to 1] and [−1 to 1] ranges, respectively, in the processing and plotting. For conformation averaging, the selected spectra were added together with their corresponding Boltzmann weighting.<sup>3</sup>

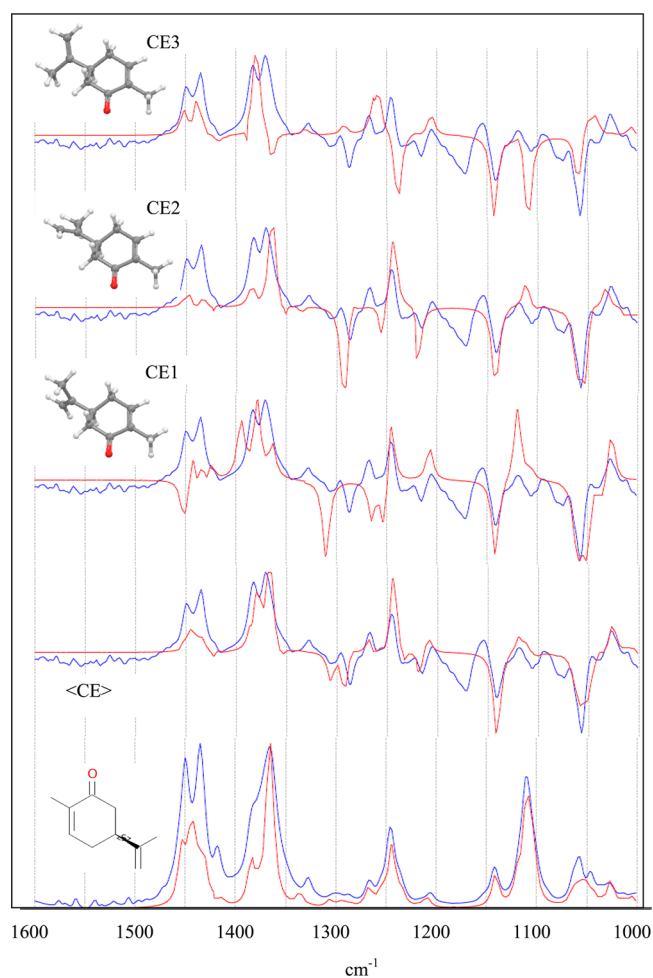
### 3. RESULTS

**3.1. (S)-(+)-Carvone.** (S)-(+)-carvone is known to have six stable conformers generated by the combination of two positions (equatorial or axial) and three rotamers of the isopropylene. The three equatorial conformers (CE1–3) are more stable than the axial ones (CA1–3), as shown in Table 1. The optimized geometries and energies for CE1–3 agree with Hoffmann's study<sup>14</sup> (<1° in the torsion and <0.01 kcal/mol in energy).

The energy and geometry of antigauche(+) conformer CA1 are identical to those obtained by Hoffmann. However, contrary to the previous study, CA2, an antigauche(−) conformer, is the most stable structure among the axial conformers with an energy 0.23 kcal/mol lower than CA1. In fact, Hoffmann<sup>14</sup> did not fully optimize CA2 and CA3 (a syn-gauche conformer) and deemed them unfavorable in energies based on the conformation-constrained calculations. The better stability of CA2 is probably due to the electrostatic interaction between the ethylene proton and the oxygen ( $d = 2.8$  Å). The

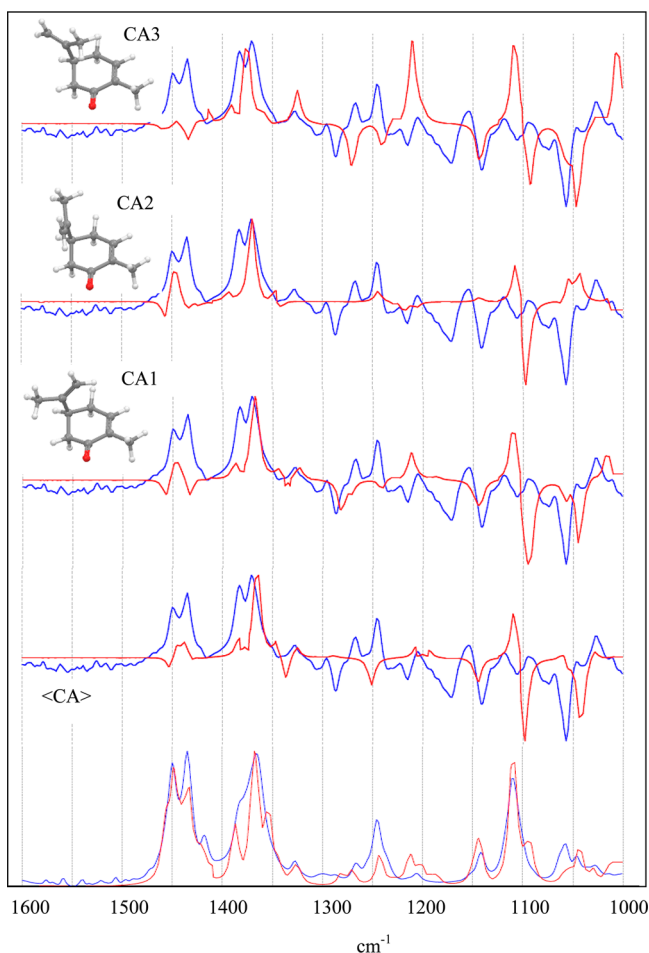
high energy of CA3 is likely caused by the unfavorable steric interaction between the isopropylene methyl and the ring. Interestingly, the corresponding syn-gauche conformer CE1 has the lowest energy. Compared with CA3, CE1 has its ring bent in the opposite direction. This conformational change reduces the contact surface area between the methyl and the ring by 4 Å<sup>2</sup>, thereby lowering the steric energy.

Also listed in Table 1 are the optimized  $S_I$  and  $S_V$ , as well as the calculated population for all six conformers. It appears that the lower the energy, the higher the  $S_V$ . The observed and the calculated spectra of CEs and CAs are shown in Figures 1 and



**Figure 1.** Aligned IR (bottom) and VCD spectra (top 4) for three equatorial conformers of (S)-carvone with blue for the experiment and red for the calculation (B3PW91). <CE> = 52%CE1 + 24%CE2 + 24%CE3 for both IR and VCD spectra shown.

2, respectively. The conformation averaging of CE spectra ( $\langle CE \rangle$ ) yields a  $S_V$  of 0.63. As shown in Figure 1, the averaged



**Figure 2.** Aligned IR (bottom) and VCD spectra (top 4) for three axial conformers of (*S*)-carvone with blue for the experiment and red for the calculation (B3PW91). The calculated VCD spectra are inverted in sign for comparison.  $\langle CA \rangle = 43\%CA2 + 30\%CA1 + 27\%CA3$ .

spectrum indeed resembles the observed VCD spectrum better than any individual spectrum. In contrast, the averaging of CA spectra ( $\langle CA \rangle$ ) did not improve the averaged  $S_V$ .

Similar spectrum calculations were also carried out using functionals B3LYP and PBEPBE. The resulting geometries and energy ranks shown in Tables 2 and 3 are very similar to those using B3PW91. In terms of the  $S_V$  value of  $\langle CE \rangle$ , B3PW91

**Table 2. Spectrum Similarity Values of Carvone Conformers Using B3LYP<sup>a</sup>**

conformer	$S_I$	$S_V$	$E$ (kcal/mol)	population (%)
CE1	0.68	0.41	0	50
CE2	0.69	0.33	0.30	24
CE3	0.74	0.33	0.35	23
CA1	0.75	−0.17	2.10	1
CA2	0.76	−0.06	1.85	1
CA3	0.76	−0.20	2.13	1
$\langle CE \rangle^b$	0.72	0.51		

<sup>a</sup>6-31G(d) basis set was used. <sup>b</sup>51%CE1 + 25%CE2 + 24%CE3.

**Table 3. Spectrum Similarity Values of Carvone Conformers Using PBEPBE<sup>a</sup>**

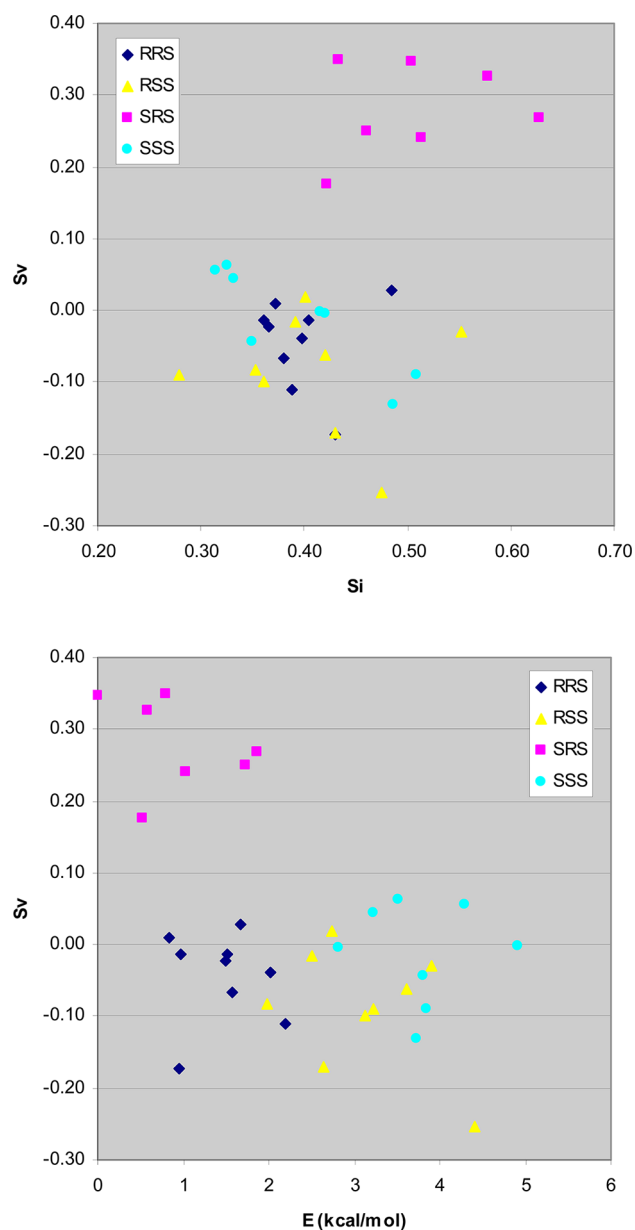
conformer	$S_I$	$S_V$	$E$ (kcal/mol)	population (%)
CE1	0.69	0.44	0	48
CE2	0.74	0.35	0.27	24
CE3	0.75	0.35	0.27	24
CA1	0.70	−0.10	1.97	1
CA2	0.75	−0.14	1.68	2
CA3	0.71	−0.15	1.88	1
$\langle CE \rangle^b$	0.78	0.57		
$\langle CA \rangle^c$	0.72	−0.13		
$\langle CE+CA \rangle^d$	0.75	0.54		

<sup>a</sup>6-31G(d) basis set was used. <sup>b</sup>50%CE1 + 25%CE2 + 25%CE3. <sup>c</sup>43%CA2 + 30%CA1 + 27%CA3. <sup>d</sup>48%CE1 + 24%CE2 + 24%CE3 + 2%CA2 + 1%CA1 + 1%CA3.

appears to be the best followed by PBEPBE and B3LYP. All three averaged CE spectra match the observed spectrum very well. On the basis of the positive sign of  $S_V$  and the visual examination of spectra, the AC of the sample is (*S*).

**3.2. (1*S*,2*R*,5*S*)-(+)-Menthol.** This exercise was designed to conduct a blind test on a diastereomer with three chiral centers. Because the ACs of an enantiomeric pair can be identified by the sign of  $S_V$ , four menthol-associated nonenantiomeric diastereomers were calculated. They are designated as RRS, RSS, SRS, and SSS according to the chiralities at the 1, 2, and 5 positions. To quickly identify matched stereoisomer and associated conformers, the direct  $S_I$  and  $S_V$  were calculated and compared in Figure 3. The  $S_I$  and  $S_V$  values span from 0.28 to 0.63 and −0.25 to 0.35, respectively. Only SRS conformers can be separated from the rest. It appears that conformers with the same chirality are somewhat clustered in the  $S_V$ -energy space. In addition to  $S_V$  differences, larger energy differences among the diastereomers separate the associated conformer sets from each other. It is also observed that the  $S_V$  distribution (Figure 4a) has two peaks, a head and a shoulder, maximized at about 0 and 0.3, respectively. Furthermore, the two peaks fit approximately two normal distributions: the head N1 with a mean value of 0 and the shoulder N2 with a mean value of 0.3. Both have a standard deviation of 0.08. It is also remarkable that N2 contains only the SRS conformers and N1 contains the rest.

Several large  $|S_V|$  values of SRS conformers in Figure 3 indicate that the associated spectra resemble the observed spectrum the most. The geometries and energies of the eight SRS conformers are compared with the results of McCann et al.'s study<sup>13</sup> in Table 4. The small deviations in torsions are due to the different functionals used. In terms of energy ranking, the use of functional PBEPBE only affects two conformers, SRS85 and SRS81, which reverse their order in the B3LYP calculation. It is worth noting that their energy difference, 0.05 kcal/mol, is the smallest among the conformers. The aligned spectra of low energy conformers are shown in Figure 5 with the optimized  $S_V$ . These  $S_V$  values are greater than the corresponding ones in Table 4 due to the better spectrum band overlap generated by the frequency shifting. Figure 6 shows that the direct  $S_V$ , by and large, correlates with the optimized  $S_V$ , which validates the use of direct  $S_V$  for fast spectrum screening. The conformation-averaged spectrum,  $\langle SRS \rangle$ , further improves the  $S_I$  and the  $S_V$  to 0.83 and 0.71, respectively. Again, the positive sign of the optimized  $S_V$  and the aligned spectra provide unambiguous



**Figure 3.**  $S_V$  vs  $S_I$  and  $S_V$  vs energy for conformers of four stereoisomers.

evidence that the AC of (1*S*,2*R*,5*S*)-(+)-menthol and of the SRS conformers is identical.

The head–shoulder pattern in Figure 4a and our observation of other VCD calculations suggest that the probability of  $S_V$  forms two normal distributions: one fits the observed spectrum and the other does not. To prove the assertion, we added the spectra of 32 higher energy SRS conformers. The direct  $S_V$  distribution of all 40 nonredundant conformers is compared with a standard Gaussian curve in Figure 4b. Indeed, most  $S_V$  values fall into a normal distribution N3 with a mean value of 0 and SD of 0.1. The  $S_V$  shoulder on the positive side corresponds to the same SRS conformers that fit the observed spectrum well, as shown in Table 4 and Figure 4a. Therefore, it can be described by the normal distribution N2.

#### 4. DISCUSSIONS

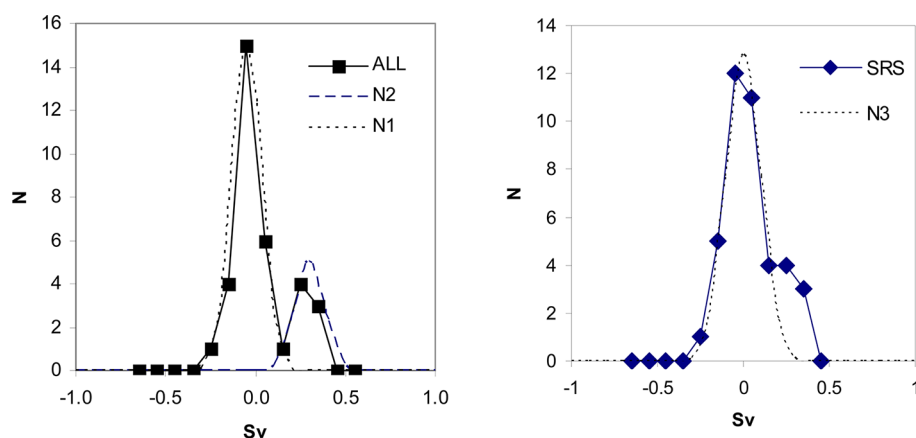
By definition,  $S_V$  is a property with inputs from both experiments and theory. Therefore, its value can be influenced by many variables, including the quality of observed spectra, bandwidth of simulated spectra, and frequency shifts. It also depends on molecule structures, solvents, methods, and parameters used in the calculation. Despite these uncertainties,  $S_V$  appears to be a normal random variable with different characteristic probabilities for two groups of calculated VCD spectra: one that matches the observation and the other that does not. The corresponding conformers can be called the spectrum-fit (SF) conformers and the spectrum-unfit (SU) conformers, respectively. Here the definition of SF or SU is more conceptual than concrete because there is no clear division between SF and SU. The parameters of  $S_V$  distribution for SF conformers are usually difficult to evaluate due to the small number of conformers. In contrast,  $S_V$  distribution for SU conformers can be easily characterized with a sufficient number of samplings, which are mostly SU conformers.

We know from this study that the  $S_V$  population of SU conformers approximates a normal distribution centered at zero with an SD of about 0.1. This phenomenon has been observed for all (more than 20) chiral molecules we studied, including very flexible ones with a number of sampled conformers of as many as 150. The character of  $S_V$  distribution can be used as a null hypothesis for selecting a matched VCD spectrum. For example, we will reject a spectrum with an  $|S_V|$  of 0.05 because the associated conformer has a greater than 60% of chance being an SU conformer. But we will accept a spectrum with an  $|S_V|$  of 0.25 because the associated conformer has only a 0.2% of a chance of being an SU conformer. Therefore, the conformer is considered an SF conformer, and the associated AC should be very reliable. Now, the approach has converged with our previous requirement of  $|S_V| > 0.2$  for reliable AC determinations. Statistically, the empirical rule can now be written as  $|S_V| > 2SD$ . In other words, an AC assignment based on such an  $S_V$  has a confidence level (CL) of greater than 95%.

This approach is different from CompareVOA by Debie et al.,<sup>9</sup> where a CL is estimated by comparing another similarity value with those of the fit (good) spectra of well-determined chiral molecules. In contrast, our method in principle uses the unfit (bad) spectra of the same molecule to derive the distribution parameters for estimating the rejection region of  $S_V$  and the CL. Practically, all conformers can be counted as the statistics because the number of SF conformers is usually much less than that of SU conformers. In many cases, the two methods for CL estimation produce similar results. For example, we submitted three calculated spectra of Otamixaban, an fXa inhibitor with two chiral centers, for CompareVOA calculation. The CLs are 86%, 86%, and 100%, which correspond to 91%, 99%, and 100%, respectively, using our method.

Although the  $S_V$  statistics of each stereoisomer differ, the minimum  $|S_V|$  requirement ( $>0.2$  or  $2SD$ ) is quite stringent for most stereoisomers we have studied. Two exceptions caught our attention in this work and led us to re-examine the criteria:  $S_V$  values of CA3 (Table 1) in carvone and one of the RSS conformers (Figure 3) in menthol are  $-0.21$  and  $-0.25$ , respectively. Both satisfy the minimum  $|S_V|$  of 0.2 but would result in wrong ACs if CE conformers or SRS conformers had been missed. These hypothetical errors, however, are totally





**Figure 4.**  $S_V$  distribution for menthol conformers. (a) All (34) low energy RRS, RSS, SRS, and SSS conformers and two simulated normal distributions N1 ( $\mu = 0.05$ ,  $\sigma = 0.08$ ) and N2 ( $\mu = 0.30$ ,  $\sigma = 0.08$ ). (b) All 40 conformers of SRS and the simulated normal distributions N3 ( $\mu = 0.0$ ,  $\sigma = 0.10$ ).  $N$  is the number of conformers binned with an interval of  $0.1 S_V$ .

**Table 4.** Spectrum Similarities, Geometry, and Energy for SRS Conformers<sup>a</sup>

conformer ID	$S_I$	$S_V^b$	hydroxyl D (deg) <sup>c</sup>	isopropyl D (deg)	$E$ (kcal/mol)	population (%)	B3LYP rank <sup>d</sup>
SRS82	0.50	0.35	−178.3	69.4	0	43	1
SRS85	0.42	0.18	178.8	−78.5	0.53	18	3
SRS81	0.58	0.33	−64.2	65.8	0.58	16	2
SRS83	0.43	0.35	53.1	62.5	0.80	11	4
SRS84	0.51	0.24	−64.3	−82.2	1.04	7	5
SRS88	0.46	0.25	−178.7	163.1	1.72	2	6
SRS86	0.63	0.27	49.3	−82.6	1.86	2	7
SRS87	0.59	0.26	−65.1	156.5	2.43	1	8

<sup>a</sup>PBEPBE with 6-31G(d) basis set was used. <sup>b</sup> $S_I$  and  $S_V$  are not optimized. <sup>c</sup>Dihedrals are defined in ref 13. <sup>d</sup>Taken from ref 13.

avoidable by appropriate conformation and configuration samplings.

The population of three higher energy CA conformers of carvone is simply too low for a statistics-based test or a CL estimate. Fortunately, a complete conformation sampling can be carried out for carvone or similar stereoisomers with limited flexibility. The AC is then determined by the sign of the best  $S_V$ . While missing all three CE conformers of carvone is very unlikely in practice, the importance of thorough conformation searches for relatively rigid stereoisomers should not be overlooked.

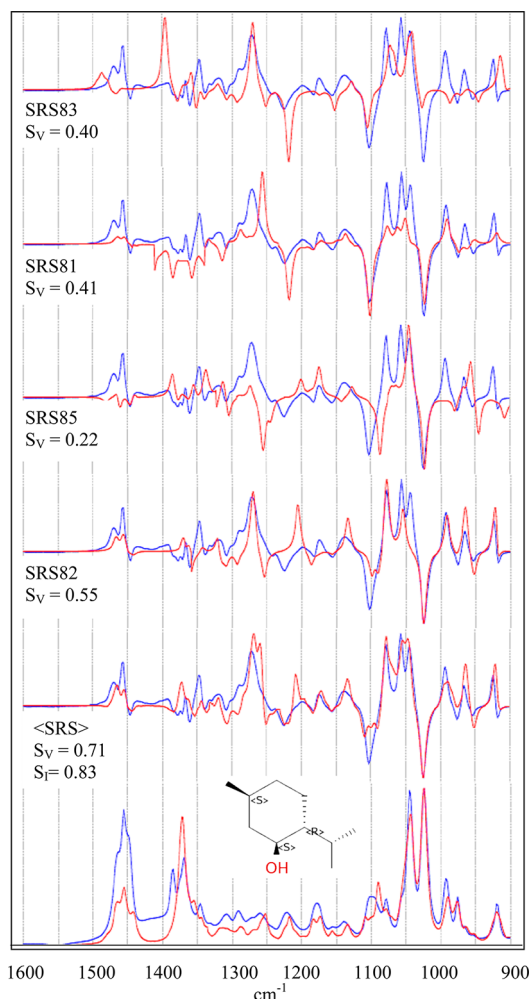
The reason for the high  $|S_V|$  of the RSS conformer is different. The negative sign of the  $S_V$  indicates that the spectrum of its enantiomer with the (1*S*,2*R*,5*R*) configuration matches the observed spectrum. Because two of three chiral centers have configurations identical to (1*S*,2*R*,5*S*)-(+)-menthol, it is not surprising that the calculated spectrum bears some similarities to the observed one. In addition, a flexible molecule rarely appears as a single conformer in a solution state. Together with the high similarities of multiple SRS spectra, the possibility of the (1*S*,2*R*,5*R*) configuration should be ruled out.

Besides the adequate conformation sampling with the minimum  $|S_V|$  requirement, the commonly used conformation averaging provides a second measure to ensure the accuracy of the AC assessments. An averaged  $|S_V|$  should be significantly greater than any individual  $|S_V|$ . This is valid for flexible molecules because the observed spectrum is a measurement of a collection of conformations at equilibrium. Many studies, including this one, have shown visually that a conformation-averaged spectrum resembles the corresponding experimental spectrum more closely.

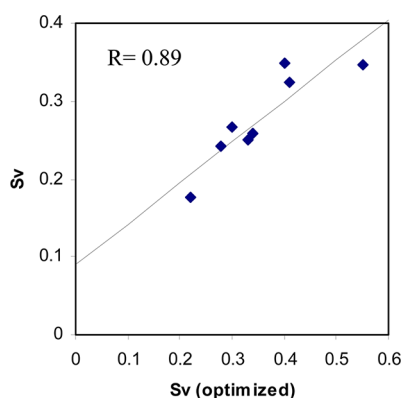
Applying the second measure has been demonstrated in the two cases. For example, the averaged  $S_V$  of carvone is 0.63, which is ~40% greater than the largest  $S_V$  of CE1. Similarly, the averaged  $S_V$  of menthol is 0.71, which is ~30% greater than 0.55, the largest individual  $S_V$  of SRS conformers. In contrast, the averaged spectrum of three higher energy CA conformers of carvone only increases the  $|S_V|$  by a marginal 10% to 0.23. By the second measure, the associated (*R*) configuration is questionable, and further conformation sampling would be warranted. Similarly, the conformation averaging of RSS spectra did not improve the  $|S_V|$  beyond 0.25 (the highest in RSS), which rules out the associated AC.

Although we used Boltzmann distribution for conformation averaging in this study, one would probably notice in Figure 3 that  $S_V$  is not correlated to the energy, which means there are cases where the lowest energy conformer is not the best fit. In fact, slightly changing the population ratio could result in a higher  $S_V$ , thereby providing a better-matched spectrum. This is generally true because the calculation is done *in vacuo* without solvent, which could significantly alter the energetic ranking of conformers. Several studies<sup>17–19</sup> tried to incorporate solvents in VCD calculations. In contrast, optimizing averaged  $S_V$  may provide another population estimate backed by VCD observations. More studies need to be done in this direction with the consideration of other errors.

The better performance of functionals PBEPBE over B3LYP for simulating VCD spectra agrees with our previous study.<sup>5</sup> Although PBEPBE is not widely used in VCD/IR calculation, a few studies found it is useful in vibration analysis.<sup>20,21</sup> Functional B3PW91 appears equal to or slightly better than PBEPBE but consumes ~25% more CPU time, which could



**Figure 5.** Aligned IR (bottom) and VCD spectra (top 5) for (1S,2R,5S)-(+)-menthol with blue for the experiment and red for the calculation.  $\langle \text{SRS} \rangle = 49\% \text{ SRS82} + 20\% \text{ SRS82} + 18\% \text{ SRS85} + 13\% \text{ SRS81}$ . Each  $S_V$  is optimized with the corresponding IR spectrum.



**Figure 6.** Relation between direct  $S_V$  and optimized  $S_V$  for eight SRS conformers with a regression line.

become a limiting factor for sizable molecules. Another advantage of using PBEPBE is the calculation of a direct  $S_V$  without frequency scaling and shifting. In fact, in the strong VCD band (1000–1400  $\text{cm}^{-1}$ ) region, the calculated bands usually match the observed ones quite well with deviations of a few wave numbers. Because the direct  $S_V$  can be calculated much faster without any human interference, it has been

routinely used to screen all calculated spectra for selecting better-matched ones before  $S_V$  optimization and the spectrum alignment.

## 5. CONCLUSION

The revisiting of VCD spectra of (S)-(+)-carvone and (1S,2R,5S)-(+)-menthol shows that the SimIR/VCD method is suitable and robust for flexible stereoisomers. The statistical character of the similarity index  $S_V$  provides a simple measure of confidence level in VCD-determined AC. The error in AC determination using VCD can be analyzed within the framework of normal distribution statistics. To avoid erroneous AC assignments and incomplete conformation searching, it is advisable to employ a minimum  $|S_V|$  of 0.2 and to maximize it using the conformation averaging. DFT with the PBEPBE functional is suitable for VCD spectrum calculation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Measured and calculated IR and VCD spectral data as well as Cartesian coordinates of optimized structures are available free of charge via the Internet at <http://pubs.acs.org/> or <http://www.simvcd.net/>.

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### Notes

The authors declare no competing financial interest.

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