



Vibrational circular dichroism study for natural bioactive schizandrin and reassignment of its absolute configuration



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ABSTRACT

Bioactive natural product (+)-schizandrin was assigned as (7*S*,8*S*) using NMR. Recently, we obtained (+)-schizandrin from TCM *Schisandra sphenanthera* Rehd. et Wils. Its planar structure was well established using NMR and HR-MS including the reported references. Its absolute configuration is assigned using vibrational circular dichroism (VCD). By careful VCD investigation of (7*S*,8*S*) and (7*S*,8*R*) using B3LYP/6-311+G(d) methods, absolute configuration of (+)-schizandrin is assigned as (7*S*,8*R*). Electronic circular dichroism (ECD) was used for the discussion too and it gave the same conclusion.

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More and more natural products have been identified using vibrational circular dichroism (VCD) technology,^{1–5} which now has played an important role in absolute configuration (AC) determination for chiral compounds. Schizandrin has wide bioactivity, such as antihepatotoxic, anti-HIV, and antitumor,^{6–8} and it has become a research hot point recently (Fig. 1). Its AC was assigned as (7*S*,8*S*).^{9,10} On the other hand, syntheses of (+)-schizandrin **1** (optical rotation (OR) of +86 to +92) and (+)-isoschizandrin **2** (near +110°) were reported,^{9d} including biosynthesis of schizandrins.¹¹ It is worthy to discuss the relationship between VCD and its structure. In this study, we report the unexpected results that the early reported AC for (+)-schizandrins is not correct using VCD methods.¹² The corrected AC for (+)-schizandrin is (7*S*,8*R*).

The whole dried fruits of *Schisandra sphenanthera* Rehd. et Wils. (5 kg) were used in extraction using EtOH (95%) at room temperature. The middle polar extractions were used for purification using column chromatography repeatedly to afford schizandrin (135 mg), its purity is over 98% analyzed by HPLC. Its optical rotation is from +81 to +91 in chloroform when different concentrations were used in measurement. This is close to the reported optical rotation of +86 to +92 in chloroform.^{9d,10a} The isoschizandrin has optical rotation of about +110. Combined with NMR data

(including comparing them to the reported NMR data) and HRMS (found: 432.2146 for C₂₄H₃₂O₇, calcd: 432.2148), its planar structure was identified as **1** including its AC.^{7,9}

As mentioned above, this chiral compound is a good example for VCD study since it has one axial chirality and two standard *sp*³ stereogenic centers. Conformational searches for (7*S*,8*S*)-**1** were performed first using FFMM94S force field. Totally 63 conformations were found. The obtained geometries were then optimized at the B3LYP/6-31G(d) level in the gas phase, all were used for VCD computations at the same level using Gaussian 03 package.¹³ The predicted VCD and infrared spectroscopy (IR) for (7*S*,8*S*)-**1** are illustrated in Figure 2. The VCD was measured in CDCl₃ at room temperature. The comparison of both VCDs is superimposed in Figure 2.

Both VCD spectra look similar in some places, including their IR spectra. The major difference between the predicted and experimental VCD is that a strong negative signal appeared near 1400 cm⁻¹ in calculated VCD as well as about 1480 cm⁻¹ in experiments as we pointed as dash circle Figure 2. It may be caused by the use of low basis sets in computations. Therefore, a higher level of B3LYP/6-311+G(d)//B3LYP/6-311+G(d) was used for its VCD computations. Total electronic energy (TEE) and Gibbs free energy (GFE) were used for the VCD and IR simulations, respectively. Unfortunately, the predicted VCD and IR look similar to those obtained at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level. The computed VCD and IR spectra are illustrated in Figure 3.

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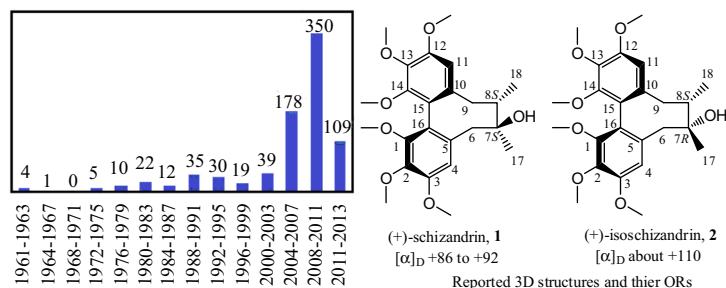


Figure 1. The research reports searched by 'schizandrin' and 3D structures for (+)-schizandrin and (+)-isoschizandrin (the deadline for searching is May of 2013).

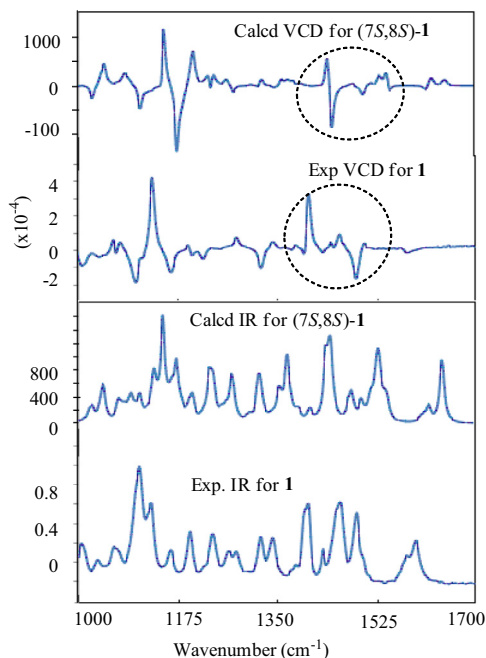
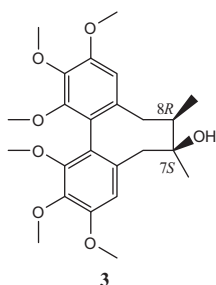


Figure 2. The calculated IR and VCD for (7*S*,8*S*)-**1** and comparison of both VCDs. The measurement of VCD is at room temperature with a concentration of 50 mg/mL.

Obviously, from the frequency computations, the bond vibrational manners (e.g., stretching vibration, swing vibration) can be seen by the corresponding window viewer, for example, Gauss-View. It was found that the frequency near 1400–1500 cm^{-1} in VCD majorly is responding to different stretching vibrations of bonds near the stereogenic centers C-7 and C-8. The different VCD structures in this range may hint different AC for (+)-**1**. Therefore, compound **3** with (7*S*,8*R*) AC was considered in further VCD study.



After the conformational search using MMFF94S force field as used for (7*S*,8*S*)-**1**, all the geometries were used for optimizations at the B3LYP/6-31G(d) level in the gas phase first. Then conformers

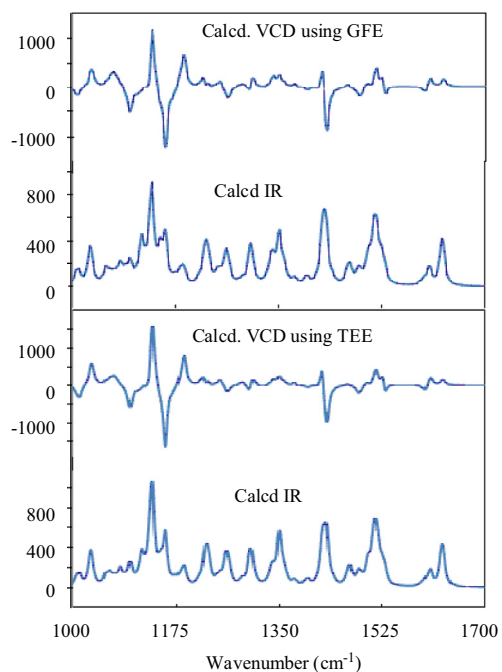


Figure 3. Predicted VCD and IR spectra for (7*S*,8*S*)-**1** using GFE, and TEE, respectively, at the B3LYP/6-311+G(d) level in the gas phase.

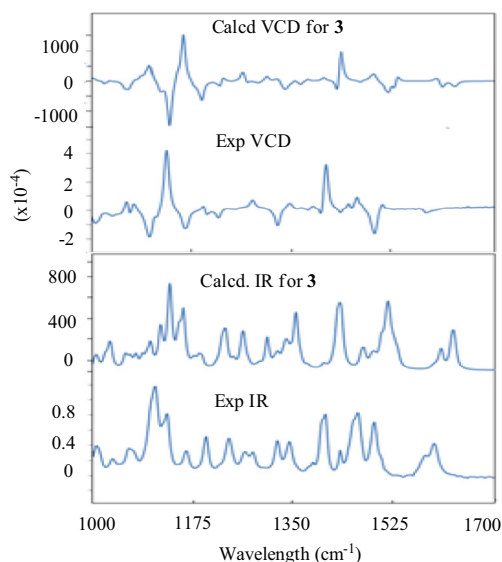


Figure 4. Comparison of both experimental and computed VCDs and IRs.

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