

Complementarity of Electronic and Vibrational Circular Dichroism Spectroscopy in Structure Determination of *Vic*-Amino Alcohols

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Editorial

There is no doubt that determination of the absolute configuration of isolated natural products or synthesized compounds remains one of the most important tasks in all fields of chemistry, biochemistry, structural biology and medicinal chemistry. This is unquestionably due to the fact that biological activity is closely related to the stereostructure of bioactive compounds. Therefore, access to methods allowing simple and primarily unequivocal determination of their absolute configuration (AC) and/or conformation is of particular significance. Such a role is at present fulfilled by chiroptical techniques. In the last two decades chiroptical spectroscopy has been one of the most rapidly developing areas of chiral analysis due to the availability of modern, highly specialized and dedicated to particular chiroptical techniques commercial instruments. Recent progress in *ab initio* simulations of chiroptical properties has also significantly contributed to the increase of the use of chiroptical spectroscopy as a stereochemistry probe [1]. It is generally accepted that combined experimental and theoretical analysis opens much broader application opportunities for chiroptical spectroscopy by giving theoretical basis to experimental results [1-4]. Moreover, utilization of multiple (at least two) chiroptical techniques increases the confidence level of the stereochemical assignment and is nowadays considered by many authors to be the best practice [1-5].

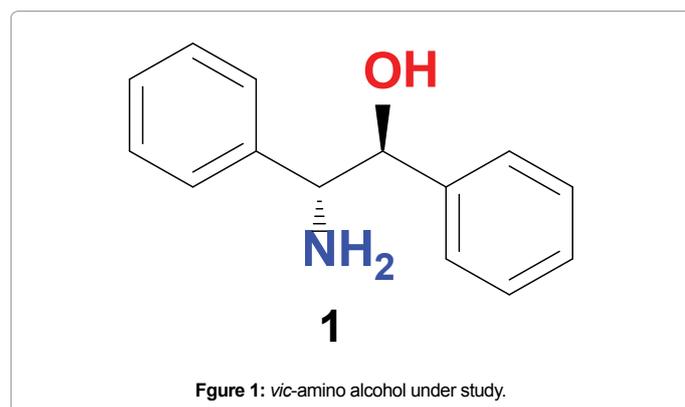
In this Editorial, we will focus on such a combined experimental and theoretical approach of electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) to determine the absolute configuration and conformation. We intend to demonstrate that both these chiroptical techniques are well cooperating and mutually complementary. Moreover, we want to show that the concerted use of the two methods clearly provides more definitive ACs although in many cases stereochemistry can be determined by using only a single chiroptical property. As a model compound for this study (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1**) with formula shown here below and representing *vic*-amino alcohols was chosen (Figure 1).

Information obtained through ECD concerns chromophore and its nearest surroundings whereas the data from VCD covers the whole molecule. Therefore, in the case of ECD the acquired information is

restricted to the chromophore unit and its nearest surroundings. Consequently, the assignment of AC can be easily achieved by semi-empirical and empirical rules known as sector and helicity rules supported by quantum mechanics calculations. In contrast to ECD, the advantage of VCD spectroscopy comes mainly from the presence of numerous well-resolved vibrational transitions from the skeleton of the whole chiral molecule. Thus, high information content about vibrations of the electronic ground state is provided. Since the functional groups responsible for vibrations are distributed over the entire skeleton of the molecule, the VCD contains information on the geometry of the whole structure. Therefore, in this case, the calculations are not additional data but the information necessary to assign AC.

To effectively use the concerted experimental-theoretical methodology in AC determination, all contributing conformers must be known. This is particularly relevant for conformationally flexible molecules. In this case, the AC determination increases in complexity due to the large number of existing conformers. Consequently, the prediction of chiroptical properties requires averaging the contributions of the all duly populated molecular conformations thus implying that careless conformational analysis may result in an incorrect assignment.

Since amino alcohol **1** is a relatively flexible molecule, a complete conformational analysis was carried out to obtain the multiple possible conformations. A systematic and thorough conformational search using the MMFF94s molecular mechanics force field identified nine conformers of **1** within a 3 kcal/mol energy window. The lowest energy and thus the most populated conformers 1a and 1b differ principally concerning the position of substituents at C1 carbon atom associated with the rotation about the C1-C2 bond (Figure 2, left). Full geometry optimization of the MMFF94s conformations obtained was then completed in the framework of density functional theory (DFT) using B3LYP exchange-correlation functional at the aug-cc-pVDZ basis set level. Next, the appropriate chiroptical properties (ECD, VCD) were simulated by using Gaussian09 program package [6]. In all calculations the polarizable continuum model (PCM) was adopted to consider solvent effects using the dielectric constant of solvents employed in the measurements. Structures of all conformers of **1** resulting from conformational analysis, i.e., conformers 1a-1i, together with experimental and simulated ECD and UV spectra of *vic*-amino alcohol



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1 are depicted respectively in Figure 2 left and right. The assignment of the AC at the stereogenic center in **1** was made on the basis of comparison of experimental and simulated spectra for arbitrarily chosen AC, in this case (1*S*,2*R*). As can be seen in Figure 2 right, the agreement between both ECD curves is satisfactory, thereby confirming a predetermined AC. However, due to the diastereoisomeric relation associated with the presence of two stereogenic centers unambiguous assignment of AC may require verification.

Corroboration of the (1*S*,2*R*) assignment was provided by the so-called dirhodium method with dirhodium tetraacetate acting as auxiliary chromophore [7-9]. In this methodology the *in situ* formation of chiral complexes results from mixing optically active *vic*-amino alcohols with the achiral $[Rh_2(OAc)_4]$. The measured ECD spectra of the chiral complexes formed *in situ* allow the assignment of the AC of the amino alcohol unit directly from the spectrum based on a sign sequence of Cotton effects (CEs) [10-13]. The determining is strictly

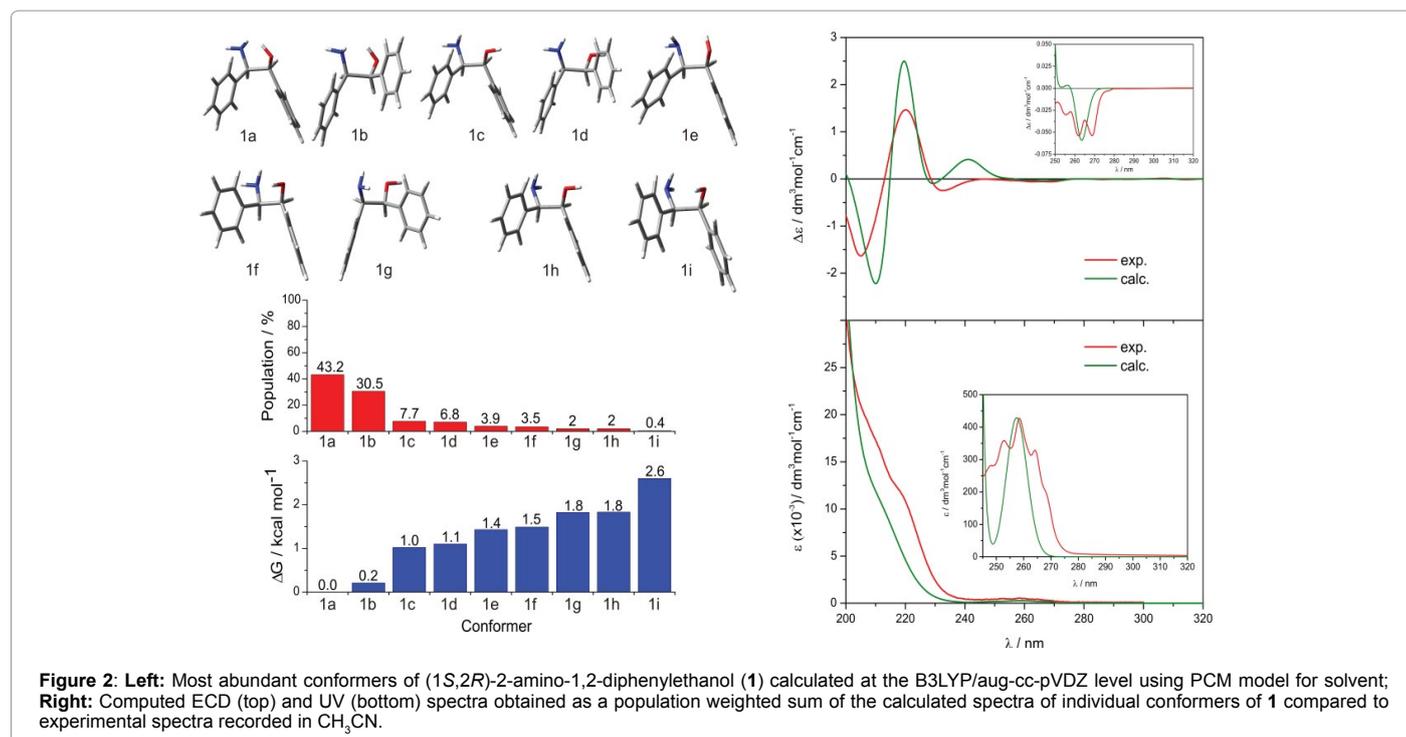


Figure 2: Left: Most abundant conformers of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1**) calculated at the B3LYP/aug-cc-pVDZ level using PCM model for solvent; Right: Computed ECD (top) and UV (bottom) spectra obtained as a population weighted sum of the calculated spectra of individual conformers of **1** compared to experimental spectra recorded in CH_3CN .

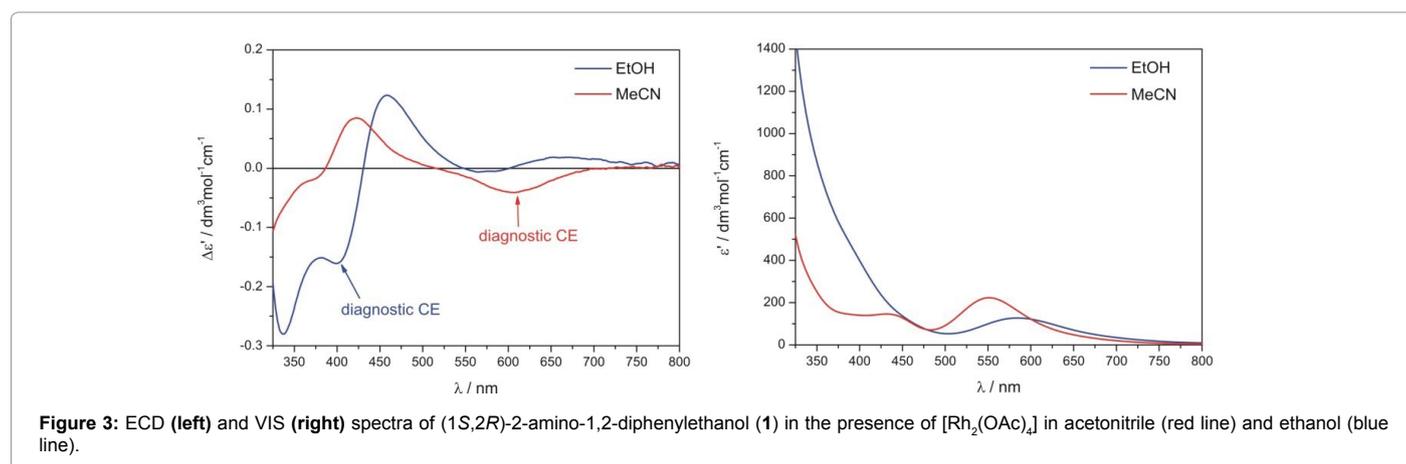


Figure 3: ECD (left) and VIS (right) spectra of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1**) in the presence of $[Rh_2(OAc)_4]$ in acetonitrile (red line) and ethanol (blue line).

associated with the dependence of the signs of CEs occurring within the d-d absorption bands of the Rh_2 -core solely upon the chirality of the 1,2-amino alcohol ligands. In the case of **1** the positive (incompletely developed in the spectrum to a real maximum), negative, positive sign sequence of CEs in the 350-500 nm spectral range occurring in its ECD spectrum with Rh_2 -core recorded in ethanol is in agreement with the previous literature data for (1*S*,2*R*)-2-amino-1,2-diphenylethanol (Figure 3) [11]. In the acetonitrile solution, in turn, the negative sign

of the decisive CE arising at ~600 nm is in agreement with the sector rule formulated for such kind of complexes [12,13]. On this basis, the effected assignment can be considered as being safe.

According to the current trend towards confirming stereochemical assignment by at least two independent chiroptical methods, we decided to apply an additional technique, namely VCD. The population-weighted VA and VCD spectra of the nine most stable conformers were compared to the experimental spectra as shown in Figure 4. The overall

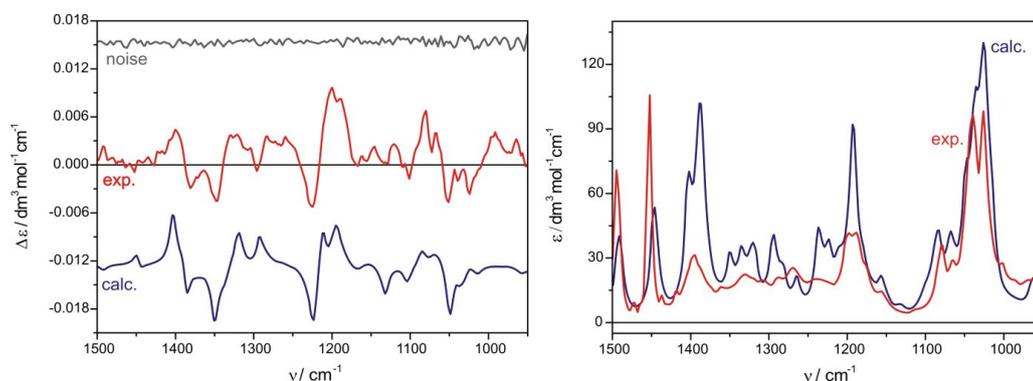


Figure 4: Comparison of the experimental VA (right) and VCD (left) spectra of **1** with the corresponding population weighted spectra of **1** based on the solution phase (CHCl_3) PCM simulations.

agreement of the predicted and experimental VA and VCD spectra support the same assignment of the AC of **1** as obtained above with the ECD method. Moreover, according to the CompareVOA™ program the confidence level of the achieved assignment in both cases equals 100% [14]. Thus, it can be concluded that the pre-assignment performed using the ECD is confirmed by the VCD results. Based on this, we can confirm that the assignment of absolute configuration of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1**) was done in a reliable manner.

In conclusion, we have shown in this Editorial that the application of concerted chiroptical spectroscopic methods in combination with *ab initio* calculations can be profitably applied to reliably determine the AC of *vic*-amino alcohols characterized by a considerable degree of conformational freedom. Such approach to assigning AC has great applicability for compounds or their derivatives which:

- Do not provide the appropriate crystals for single crystal X-ray analysis
- Are structurally complex - at present DFT calculations may still not give a conclusive answer due to e.g. difficulties of assigning the most abundant pool of conformers in the equilibrium
- Manifest a strong solvent effect on chiroptical spectra - standard protocols of calculations could fail because of difficulties with a proper description of the solvent contribution

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