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Regional Susceptibility in VCD Spectra to Dynamic Molecular Motions: The Case of a Benzyl α -Hydroxysilane**

Yiyin Xia⁺,^[a] Mark A. J. Koenis⁺,^[a] Juan F. Collados,^[b] Pablo Ortiz,^[b] Syuzanna R. Harutyunyan,^[b] Lucas Visscher,^[c] Wybren J. Buma,^[a] and Valentin P. Nicu^{*,[a, d]}

Experimental and theoretical studies of the vibrational circular dichroism (VCD) spectrum of 3-methyl-1-(methyl-diphenylsilyl)-1-phenylbutan-1-ol, whose absolute configuration is key to elucidating the Brook rearrangement of tertiary benzylic α -hydroxysilanes, are presented. It is found that the entire OH-bending region in this spectrum—a region that provides important marker bands—cannot be reproduced at all by standard theoretical approaches even though other regions are well described. Using a novel approach to disentangle contributions to the rotational strength of these bands, internal coordinates are identified that critically influence the appearance of this part of the spectrum. We show that the agreement between experiment and theory is greatly improved when structural dynamics along these coordinates are explicitly taken into account. The general applicability of the approach underlines its usefulness for structurally flexible chiral systems, a situation that is more the rule rather than the exception.

Vibrational circular dichroism (VCD) spectroscopy has developed over the past decades into one of the most accurate techniques for assigning the absolute configuration (AC) of chiral molecules.^[1–4] To determine the AC of a compound, experimentally obtained VCD spectra are compared with theoretical spectra computed for one of the enantiomers and on the

basis of their similarity the AC is assigned.^[1–4] Although in theory such a procedure appears quite straightforward, its practical application is hindered by conformational heterogeneity and the fact that band frequencies and intensities in experimental and theoretical spectra do not completely match up. As a result, it is not uncommon that situations arise in which Boltzmann-averaged VCD spectra appear to indicate one assignment in certain spectral regions of the VCD spectrum but the opposite assignment in other regions.

Such ambiguities may have far-reaching consequences. As a case in point we consider in the present study the Brook rearrangement of tertiary benzylic α -hydroxysilanes.^[5,6] One of the key questions for elucidating the reaction mechanism is whether the reaction proceeds with or without inversion of configuration. As yet, the available experimental material was inconclusive and hinged upon the determination of the absolute configuration of the starting material, 3-methyl-1-(methyl-diphenylsilyl)-1-phenylbutan-1-ol (Figure 1), henceforth referred

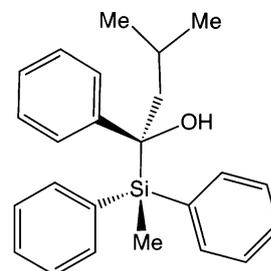


Figure 1. Structure of S-3-methyl-1-(methyl-diphenylsilyl)-1-phenylbutan-1-ol.

to as silyl-alcohol.^[6] Outside the OH-bending region experimental and theoretical VCD spectra suggest an S configuration of the employed compound, but for the OH-bending region large discrepancies are observed. These discrepancies cannot be ignored as the OH-bending bands are predicted to be the most intense bands in the spectrum. Moreover, the hydroxyl group is connected directly to the chiral centre and the OH-bending bands are therefore expected to provide key signatures for the AC.

We have recently introduced the Generalized Coupled Oscillator (GCO) model and have shown that this provides a powerful method to analyze contributions to the rotational strength of vibrational transitions.^[7–9] From this work it has become clear that the ‘static molecule’ picture that is normally used to analyze VCD spectra may very well lead to incorrect conclu-

[a] Y. Xia,⁺ M. A. J. Koenis,⁺ Prof. Dr. W. J. Buma, Dr. V. P. Nicu
Van't Hoff Institute for Molecular Sciences
University of Amsterdam
Science Park 904, 1098 XH Amsterdam (The Netherlands)
E-mail: vp.nicu@gmail.com

[b] Dr. J. F. Collados, Dr. P. Ortiz, Prof. Dr. S. R. Harutyunyan
Stratingh Institute for Chemistry
University of Groningen, Nijenborgh 4
9747 AG Groningen (The Netherlands)

[c] Prof. Dr. L. Visscher
Amsterdam Center for Multiscale Modeling
Section Theoretical Chemistry, Faculty of Sciences
Vrije Universiteit Amsterdam
De Boelelaan 1083, 1081 HV Amsterdam (The Netherlands)

[d] Dr. V. P. Nicu
Lucian Blaga University of Sibiu
Faculty of Agricultural Sciences
Food Industry and Environmental Protection
7–9 Ioan Ratiu Street, 550012 Sibiu (Romania)

[⁺] These authors contributed equally to this work

[**] VCD: Vibrational Circular Dichroism

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sions on their interpretation. In real life, molecules are dynamic and experience varying interactions with neighbouring solvent molecules. As a result, the molecule probes effectively a much larger structural phase space than one normally would take into account. Here we will show that a GCO analysis of modes for which the experimental rotational strength is apparently at odds with theoretical predictions allows one to directly identify internal coordinates that strongly affect magnitude and sign of the bands. Subsequent linear transit (LT) calculations in which VCD spectra are calculated as a function of these coordinates are then shown to be able to rationalise the differences between the experimentally obtained and the theoretical "static molecule" spectra, thus allowing for an unambiguous stereochemical analysis.

In the present study, 23 low-energy silyl alcohol conformers have been considered that were found to be within a 2 kcal mol⁻¹ energy window. Figure 2 compares measured vibrational absorption (VA) and VCD spectra with simulated spectra that have been obtained as Boltzmann-averages over the considered conformers. As far as the VA spectra are concerned, quite a nice agreement is observed between experiment and simulation. The simulated VCD spectrum, on the other hand, shows a very good agreement in the frequency intervals from 950–1160 cm⁻¹ and 1380–1700 cm⁻¹, but exhibits very intense bands in the frequency interval between 1160–1380 cm⁻¹ that are absent in the experiment. Since the experimental spectra of the two enantiomers display a good mirror image at these frequencies (see Figure S1 in the SI) one must conclude that

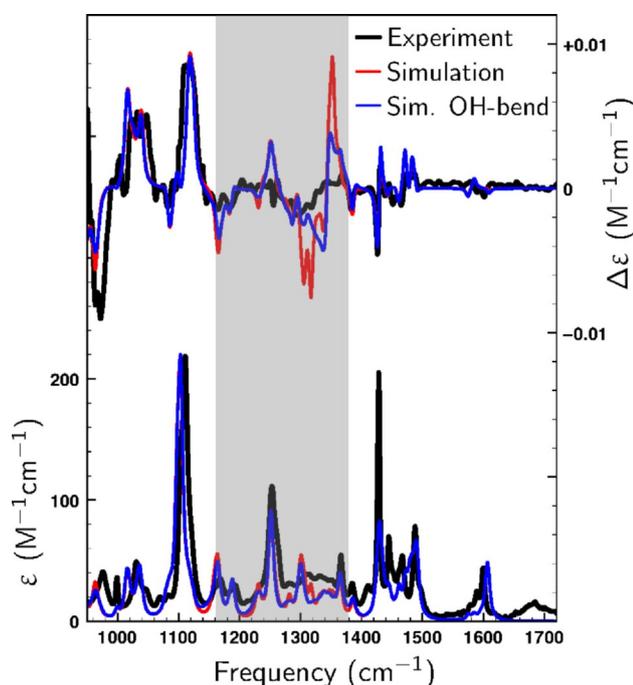


Figure 2. Comparison between the experimental and simulated VA (bottom) and VCD (top) spectra of S-silyl-alcohol. Black traces correspond to the experimental spectra, red traces to Boltzmann-weighted simulated spectra without taking structural dynamics into account, blue traces to Boltzmann-weighted simulated spectra in which structural dynamics along the OH-bending internal coordinate have been incorporated.

this discrepancy originates from the simulation. Further support for this conclusion is provided by an analysis of the robustness of the VCD spectrum in the problematic region using the vibrational dissymmetry factor (VDF) criterion proposed by Covington and Polavarapu^[10] which shows that the experimental spectral region between 1280 to 1380 cm⁻¹ (where the largest discrepancies between experiment and calculations are found) is robust. Next, we have performed VCD DFT calculations with five different sets of computational parameters (including the COSMO^[11,12] solvation model and the D3-BJ^[13] dispersive correction for DFT). However, at all levels of theory intense bands are predicted in the 1160–1380 cm⁻¹ frequency interval which are not observed experimentally (see Figure S2 in the SI). Finally, the discrepancy between the experimental and simulated VCD spectra has been quantified^[14–16] by computing spectra similarities using the method proposed by Shen and co-workers.^[14] The value of 0.46 obtained for the associated SimVCD^[14,16] index suggest a decent, though not ideal, agreement between the experimental and simulated VCD spectra.

To find the underlying reason for the differences observed between the VCD spectra, a GCO analysis^[8] of the fingerprint modes has been performed for all conformers. This analysis shows that, in contrast to the rest of the fingerprint bands, the rotational strengths of the intense bands in 1160–1380 cm⁻¹ spectral region are determined almost entirely by the coupling between the OH-bending and CH-bending motions via the GCO mechanism (see Table S1 in the SI). As previously shown,^[8] the sign and magnitude of the VCD intensity of such GCO bands depends sensitively on the relative orientation of the interacting fragments and on their involvement in the normal mode motion. The high sensitivity of these GCO bands on the orientation of the coupling fragments is illustrated in Figure 3 where we compare the VCD spectra of conformers 2, 8 and 17. These three conformers differ primarily in the orientation of the OH group but their VCD spectra show large variations in the 1160–1380 cm⁻¹ frequency interval. The same holds for conformers 4, 10 and 12 (see Figure S3 in the SI), which also differ only in the orientation of the OH group.

Following the procedure proposed in refs. [7, 17, 18] we have employed LT calculations to explore the effect of motions along internal coordinates involving the relative orientation of the OH group and the CH bonds that are important for the exciton-coupling. Motions that are accompanied by small energy changes are in this respect natural choices as one expects this part of the structural phase space to be explored under room-temperature solution conditions. Therefore, besides altering the orientation of the OH bond (the main contributor to the GCO intensity), additional LT parameters have been identified by analysing the movements associated with low-frequency modes. An overview of all LT calculations performed is shown in Figure S4 in the SI. Most LT calculations have only been run for conformers 8 and 10. These two conformers are the dominant conformers, each with a predicted weight of 17% and account for the intense VCD bands in the 1160–1380 cm⁻¹ spectral interval. Only the LT calculation with the largest effect on the simulated spectrum, i.e., bending of the OH group, has been performed for all 23 low energy conformers.

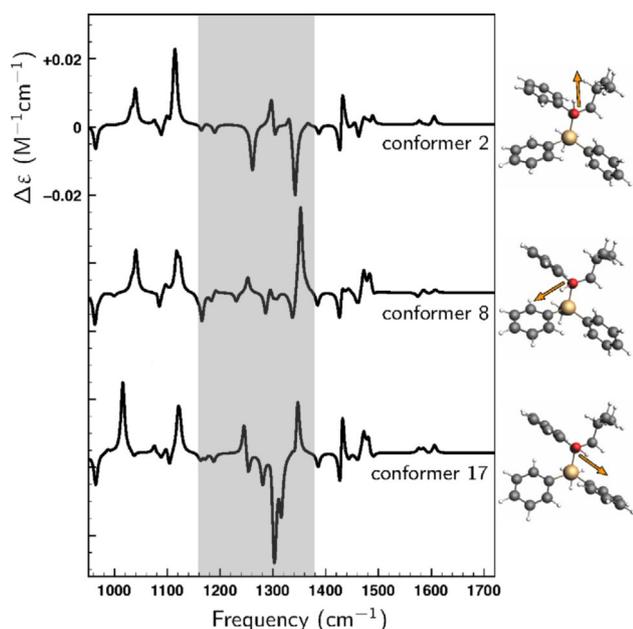


Figure 3. Comparison of the VCD spectra computed for conformers 2, 8 and 17 which differ primarily in the orientation of the OH-bond.

Although most LT calculations lead to changes in the 1160–1380 cm^{-1} spectral interval of the individual VCD spectra, only one LT calculation results in a significant effect on the total Boltzmann-weighted spectra, namely the OH-bending LT calculation in which the C–O–H angle is changed. Figure 4 shows the dependence of the VCD spectra of conformers 8 and 10 on this C–O–H angle. Even though this angle can only be changed by a few degrees without large energy changes, the individual spectra show dramatic variations in both intensity and frequency of bands in the 1160–1380 cm^{-1} interval. Equally important is the fact that the VCD bands outside this interval are not affected. As a result, the intense bands in the problematic region are broadened and reduced in size, which improves the agreement with the experimental spectrum (see Figure 2). This improvement is reflected by the SimVCD index which increases from 0.46 to 0.51.

Interestingly, we find that among the ineffective LT calculations is the rotation of the OH group which a priori would appear to be important.^[7,19,20] Although the OH bond can be rotated by $\pm 15^\circ$ without significantly increasing the energy, this rotation is not sufficient to induce significant changes in the magnitude of the intense VCD bands. The reason for this is

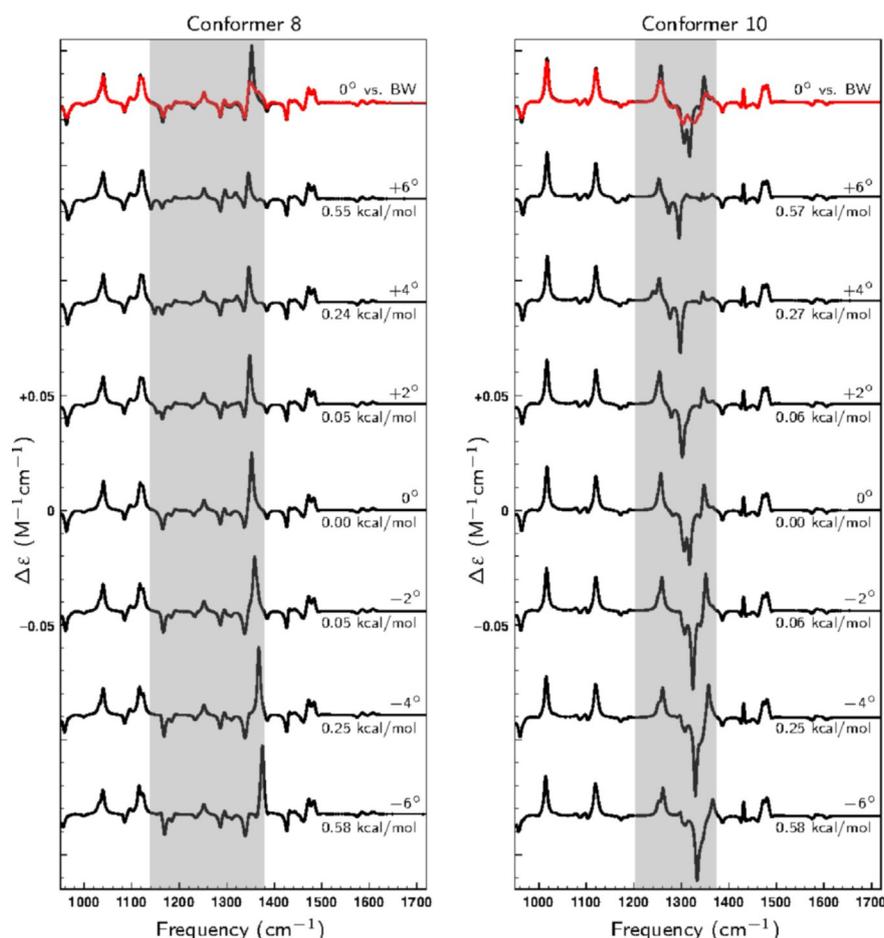


Figure 4. VCD spectra associated with the linear transit (LT) calculation along the bending coordinate of the OH group in conformers 8 and 10. Red: Simulated spectrum obtained as a Boltzmann average of the VCD spectra computed for the LT structures. Black: VCD spectra computed for the individual LT structure. The variation in the COH angle with respect to the equilibrium structure (0°) and the corresponding energy are indicated at the right side of each spectrum. Only LT structures within an energetic window of 1 kcal mol^{-1} have been considered.

threefold. Rotation of the OH group: 1) does not influence the involvement of the OH bond in the intense modes, 2) does not induce shifts in their frequencies, and 3) is too small to change the relative orientation of the interacting electric dipole transition moments as the electric dipole transition moment associated with OH-bending modes are roughly perpendicular to the OH bond. Changing the C–O–H angle, on the other hand, modifies the hybridisation of the oxygen atom. This, in turn, addresses effectively all three points mentioned previously and results in large changes in the position and intensity of the problematic VCD bands. Having thus rationalised the apparent disagreement between experimental and simulated VCD spectra, we can confidently assign the AC of the sample as being S.

In the present study we have employed linear transit calculations to simulate the conformational dynamics of a molecule under “real-life” conditions. This approach appears to capture the relevant physics involved quite well as it broadens the problematic GCO VCD bands while leaving the VA bands intact. It is important to notice that simply broadening the bands in the problematic interval using Lorentzian functions with larger half-width values does improve the agreement between the experimental and simulated VCD spectra but at the same time deteriorates the agreement between the VA spectra, and is therefore not an acceptable solution (see Figure S5 in the SI). Finally, we need to recognise that although this approach has been quite successful in accounting for the observed differences between the experimental VCD spectrum and the simulated spectrum as is standardly predicted, Figure 2 makes clear that there is still room for further improvement. In particular, one would like to “unbias” molecular motions and take the entire explored structural phase space into account. Molecular Dynamics calculations are in this respect an attractive path to pursue.^[21,22] Such calculations are indeed presently being explored by us.

In conclusion, we have reported on studies in which the standard approach used to compute VCD spectra leads to an apparent disagreement between theoretically predicted and experimentally obtained VCD spectra for an entire spectral region. We have shown that this regional susceptibility is caused by the GCO mechanism in combination with the dispersion of the normal mode contribution of the main coupling group over many modes. This makes the VCD spectrum very sensitive to changes due to small motions of this group. Similar complications have also been encountered previously,^[7] and the present study in fact suggests that one can expect it to occur in the analysis of the VCD spectra of many other molecules. At the same time, we have demonstrated that a GCO analysis is a powerful means to unravel the underlying origin for the discrepancies and account for them. As a result, we have been able to show for the case of silyl-alcohol that considering the motion along the OH bending coordinate greatly improves the agreement between experiment and theory, and that it allows us to unambiguously determine the absolute configuration of the molecule even though initially the agreement would have been concluded to be rather poor in the OH-bending region.

Computational Methods

Experimental details and more extensive computational details are given in the Supporting Information. The low-energy conformers have been generated using two independent software packages, MacroModel from the Schrödinger software suite and RDKit embedded in the Amsterdam Density Functional (ADF) suite.^[23–26] In both software packages 10 000 conformers were quasi-randomly generated and optimized with molecular mechanics using, respectively, the MMFF and UFF force fields.^[27,28] Geometry optimizations have been performed using the QUILD optimization routines in the ADF software suite.^[29–31] For the conformers within a energy window of 2 kcal mol⁻¹ from the lowest energy structure, the VCD spectrum was calculated^[32] and the resulting spectra were combined by means of Boltzmann weighting. The linear transit calculations have been performed in ADF. Starting from the energy minimum the angles and dihedral angles were changed in both directions in steps of 1° and 5° respectively. For linear transit structures within 1 kcal mol⁻¹ the VCD spectrum was computed. The resulting spectra from the linear transit calculation were Boltzmann weighted for each conformer separately. Most DFT calculations have been performed at the BP86/TZP level of theory.^[33–35] Additional calculations have been performed using the OLYP, PBE functionals, using the COSMO solvation model for chloroform and the DFT-D3-BJ dispersion correction.^[11–13,36–38]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: configuration determination • conformations analysis • density functional theory • vibrational circular dichroism • vibrational spectroscopy

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