Towards the limits of vibrational circular dichroism spectroscopy: VCD spectra of some alkyl vinylethers

Abstract: Three alkyl vinylethers from our collection of chiral samples were investigated through VCD spectroscopy, in combination with DFT calculations. Despite the simplicity of the compounds, reproducing all the spectra features is an involved task, since the many significantly populated conformers contribute to the total VCD spectrum with bands which often have opposite signatures. Nevertheless, we show that certain bands can be satisfactorily reproduced by calculation and therefore they may be employed for the determination of absolute configuration in these and similar compounds, for which no simple alternative method is available.

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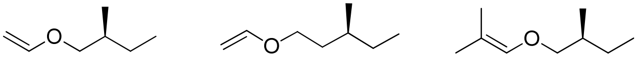
Keywords: VCD, DFT calculations, chiroptical spectroscopy, cryptochirality, absolute configuration, infrared spectroscopy, conformational analysis, Fermi resonance

Introduction

Determination of absolute configuration with direct methods of non-chromophoric and low molecular weight molecules may reveal particularly challenging. In these cases, electronic circular dichroism (ECD), probably the most widely used chiroptical method to accomplish this task,[1] cannot be of any aid. An obvious case are alkanes[2,3] and non-conjugated alkenes.[4] Although several methods exist based on chromophoric derivatives and/or supramolecular approaches,[5-7] they are based on chemical derivatization and require at least one reactive functional group such as alcohol, amine, carboxylic acid, etc. Quite often, small non-chromophoric molecules show weak or negligible optical rotation, making also the use of this technique challenging.[8] Moreover, some molecules may be CD silent and display very little or no optical rotation[3,9] even in the presence of chromophores.[10-12] This phenomenon is indicated as cryptochirality. When such situations occur, vibrational circular dichroism (VCD) may prove a powerful and relatively easy tool to assess absolute configurations and even support relative configurations determined with other methods. Successful applications of VCD in this field are, among others,[13] absolute configuration determination of alkanes,[14] terpenes[15,16] and glycerophospholipids.[17]

Taking advantage of our relatively vast collection of chiral molecules spanning several classes of organic compounds, we decided to undertake a chiroptical analysis of vinyl ethers. These compounds are used as monomers for the preparation of chiral polyvinylethers, that is polyethylenes appended with chiral ether pendants.[18-21] To the best of our knowledge, no VCD investigation has been reported so far for this class of compounds.

We chose to analyze three alkyl vinyl ethers **1-3** (Scheme) in which chirality is brought about by a methyl-ethyl difference at the stereogenic center. In two cases out of three the asymmetric carbon is in position 2 with respect to the oxygen ((*S*)-2-methyl butyl vinylether **1** and (*S*)-2-methyl butyl isobutenylether **3**), while in one case it is in position 3 ((*S*)-3-methyl pentyl vinylether **2**). These three compounds are interesting since they display no significant ECD signal associated with the only accessible electronic transition (π→π* at 200 nm) (see Supporting Information), moreover their optical rotation is quite weak ($[\alpha]_D^{25}$ =+6.65°, +7.36°, +1.17° for compound **1**,**2** and **3** respectively),[22] therefore one cannot rely on these data when trying to assign absolute configurations. Conversely, these compounds display weak but significant VCD spectra in the fingerprint region, which in principle can be satisfactorily employed for their stereochemical characterization. However, as we will show below, VCD calculations are not straightforward, since these compounds – despite their apparent structural simplicity– are endowed with a wealth of conformational possibilities.



1 **2** **3**

Scheme 1 The three alkyl vinyl ethers investigated in this work.

Materials and Methods

NMR spectra were measured with a Bruker Avance DRX 400 instrument. VCD spectra were recorded using a Jasco FVS 6000 VCD spectrometer (6000-8000 scans). The instrument performance was checked using CCl_4 solutions of (+) and (-)-camphor and (+) and (-)-limonene, used as standards,[23,24] just before measuring the samples. The samples were measured in CCl_4 solution (0.6 and 0.3 M) in a 100 μm KBr cell. At least three different measurements were performed on each sample to check consistency. The spectra displayed in Figure 1 were obtained by subtracting the CCl_4 spectrum recorded in the same conditions to the raw spectrum.

(S)-2-methyl butyl vinylether **1**: ^{1}H NMR (400 MHz, chloroform-d_3, δ): 6.50 (dd, *J* = 7 Hz; 1H), 4.80 (dd, *J* = 2, 14 Hz; 1H), 3.98 (dd, *J* = 2, 7 Hz; 1H), 3.57 (dd, *J* = 6 , 10 Hz, 1H); 3.48 (dd, *J* = 6, 10 Hz; 1H), 1.75 (oct, *J* = 7; 1H), 1.50 (sep, *J* = 7; 1H), 1.21 (sep, *J* = 7; 1H), 0.96 (d, *J* = 7; 3H), 0.93 (t, *J* = 7; 3H).

(S)-3-methyl pentyl vinylether **2**: ^{1}H NMR (400 MHz, chloroform-d_3, δ): 6.49 (dd, *J* = 7 Hz; 1H), 4.19 (dd, *J* = 2, 14 Hz; 1H), 3.99 (dd, *J* = 2, 7 Hz; 1H), 3.73 (m; 2H), 1.73 (m; 1H), 1.52 (m; 1H), 1.39 (m; 2H), 1.21 (m; 1H), 0.91 (m; 6H).

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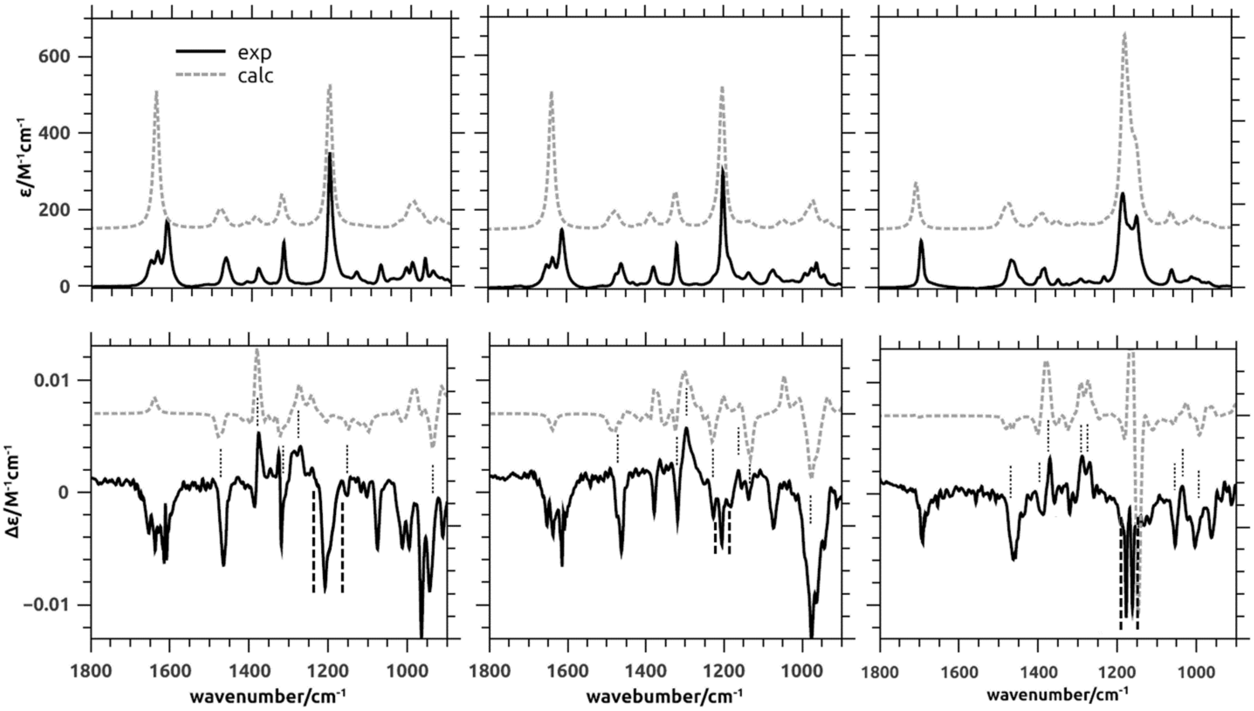


Figure 1: Calculated (dashed line) and experimental (continuous line) IR (top) and VCD (bottom) spectra for compounds **1** (left), **2** (centre) and **3** (right). Calculated spectra are shown with a vertical offset for clarity. The region around 1200 cm^{-1} enclosed by dashed vertical lines was measured on diluted samples.

(S)-2-methyl butyl isobutenylether **3**: ^1H NMR (400 MHz, chloroform-d_3, δ): 5.80 (m; 1H), 3.54 (dd, *J* = 6, 10 Hz; 1H), 3.45 (dd, *J* = 7, 10 Hz; 1H), 1.69 (m; 1H), 1.63 (s; 3H), 1.56 (s; 3H), 1.48 (m; 1H), 1.18 (m; 1H), 0.93 (m; 6H).

MMFF calculations were run with Spartan'14 (Wavefunction, Inc., Irvine CA, 2014), with standard parameters and convergence criteria. DFT calculations were run with Gaussian'09,[25] with default grids and convergence criteria. Conformational searches were run with the Monte Carlo algorithm implemented in Spartan'14 using Merck molecular force field (MMFF). All structures thus obtained were optimized with DFT method using B3LYP functional and 6-31G+(d,p) or 6-311G++(2p,2d) basis sets in vacuo. Frequency calculations were run at the same level of theory on all conformers with a Boltzmann population >1% at 300K. IR and VCD spectra were obtained as sums of Lorentzian functions with a half-width at half height of 8 cm^{-1}, and a frequency scale factor of 0.98, and Boltzmann-averaged at 300K using internal energies. Average spectra were generated with the software Specdis, v. 1.63.[26]

Results and Discussion

Compounds **1-3** were synthesized by Salvadori and Lardicci[22] in 1964, they also assigned the absolute configuration through chemical correlation and reported their optical rotations. The samples were conserved in sealed glass vial under inert atmosphere in the dark, and their purity was re-checked through ^1H-NMR shortly before the VCD analysis. Since ^1H-NMR data for these compounds are not available in the literature, we report them in the Materials and Methods section and the spectra in the Supporting Information.

The IR and VCD spectra of compounds **1-3** are reported in Figure 1 (solid lines). We focused our VCD investigation in the 850-2000 cm^{-1} region. In this region the IR spectra show several prominent features: =CH out-of-plane deformation (960 cm^{-1}), =C-O-C symmetric (1070 cm^{-1}) and asymmetric stretching (1200 cm^{-1}), =CH, $=CH_2$, -CH, $-CH_2$ and $-CH_3$ in-plane deformation (1320-1460 cm^{-1}) and a rather strong C=C stretching (1610-1650 cm^{-1}).

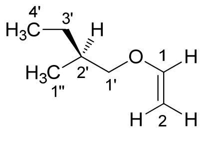
The two other bands found experimentally above 1650 cm^{-1} for compounds **1** and **2** are often encountered in IR spectra of vinyl ethers and, noteworthy, they are not reproduced by calculations (Figure 1, dotted lines). The older literature[27] explained them as the C=C stretching of less populated rotamers or as overtones of $=CH_2$ out-of-plane deformations, enhanced by Fermi resonance mixing with the strong C=C stretching. Our DFT calculations (see below), carried out on all relevant populated conformers, yielded only one band at almost the same frequency for the C=C stretching of all low-energy structures, ruling out the contribution by different conformers to this spectral feature. This led us to conclude that the overtone explanation may be the most suitable to rationalize the observed bands above 1650 cm^{-1}. Moreover this explanation is also consistent with the single band observed in this region for isopropenyl ether **3**, since the two $=CH_2$ hydrogen are replaced with two methyl groups and therefore they cannot contribute to overtones at these wavenumbers. It is also noteworthy that in the calculated IR spectra all the intensities match fairly well the experimental ones with the only exception of the band associated with the C=C stretching, this can be explained taking into account that the actual intensity of this band is reduced as an additional effect of the Fermi resonance mixing. In compound **3**, where no mixing occurs, the experimental and calculated intensities of this band do not differ significantly. The effects of Fermi resonance are also seen in VCD spectra[28,29] of **1** and **2**, where the rotational strength of the fundamental vibration at 1610 cm^{-1} is redistributed within the overtone bands at higher frequencies, giving a multiplet of bands with the same sign (negative for both **1** and **2**, Figure 1).

The experimental VCD spectra show several bands in all the investigated region, most of them with a dissymmetry factor *g* ($\Delta\varepsilon/\varepsilon$) of the order of 10^{-4}-10^{-5}, or 10-100 ppm. Thus, most bands satisfy Góbi and Magyarfalvi criterion[30] for the reliability of VCD measurements, that is ζ_2 = R/D = *g*/4 > 10 ppm, where R is the rotational strength and D the dipole strength. The use of *g*-factor is a consolidated method to estimate the match between calculated and experimental VCD spectra.[31,32] Therefore, we tried to reproduce the VCD spectra through DFT calculations. Despite the simplicity of the compounds, this task is involved due to the high number of populated conformers, contributing with opposite signature to the total spectrum (Supporting Information). We screened the different conformers by means of a systematic conformational search run with molecular mechanics (MMFF force field), followed by DFT geometry optimizations at B3LYP/6-31G+(d,p) level. Considering only the conformers with at least 1% Boltzmann population at 300K, they amount to 12, 14 and 21 for **1**, **2** and **3**, respectively. In this way, these conformers account for at least 99, 90, and 99% of the overall population, respectively. All the conformers for compound **1**, and the 4 most populated ones for compounds **2** and **3**, are shown in the Supporting Information. Structural details in terms on relevant dihedral angles are given for the first eight conformers of compound **1** in Table 1. All of them share the expected s-*cis* conformation around the =C–O bond, namely the O-C1' bond is eclipsed with the C=C double bond, and the *anti* arrangement around the O-C1' dihedral (Scheme 2). This is in fact the preferred conformation of the parent ethyl vinyl ether.[33] A similar situation is found for **2**, while in compound **3** the favored conformation around the =C–O bond is s-*trans* because of the sterical hindrance of the methyl group *cis* to the oxygen (see Supporting Information).

TABLE 1 Descriptors of dihedral angles and relative energies for the lowest energy conformers of compound (*R*)-**1** calculated at B3LYP/6-31G+(p,d) level.

#	C1-O [a]	O-C1' [a]	C1'-C2' [a]	C2'-C3' [a]	Energy [b]
1	c	a	g–	a	0
2	c	a	a	a	+0.047
3	c	a	g+	g+	+0.252
4	c	a	a	g+	+0.255
5	c	a	g+	a	+0.387
6	c	a	g–	g–	+0.765
7	c	a	a	g–	+0.992
8	c	a	g–	g+	+1.251

[a] Rotamerism around the bond; see Scheme 2 for atom numbering. Legend: c, s-*cis*; a, *anti*; g+, *gauche* plus; g–, *gauche* minus.
[b] Relative internal energy in kcal/mol.



Scheme 2 Most stable conformation of (*S*)-2-methyl butyl vinylether (**1**) and atom numbering used in Table 1.

Frequency calculations were carried out on **1-3** at the same B3LYP/6-31G+(p,d) level. The effect of the basis set was investigated carrying out the same calculation for compound **1** with a larger basis (6-311G++(2p,2d)). The IR and VCD calculated spectra thus obtained were almost coincident with the ones calculated with the smaller basis set (see Supporting Information).

It may be appreciated from Figure 1 that the calculations reproduce fairly well several features of the VCD spectra in all the compounds (see vertical dashed lines). In particular, the following bands offer a useful signature which would allow one to assign the absolute configuration in similar compounds:=CH out-of-plane deformation (960 cm^{-1}); in-plane deformations and skeletal vibrations (1250-1460 cm^{-1}). In particular, the manifold associated with =CH_2 In-plane deformations (around 1320 cm^{-1}) and the rather strong negative band associated with CH_3 deformations (around 1460 cm^{-1}), are well reproduced by the calculations in all the cases.

On the other hand, several other bands are not satisfactorily reproduced by the calculations, most likely because of the great variation in the calculated VCD spectra for the individual conformers (see Supporting Information), which introduces a severe source of error in the computations. Among the problematic bands, it is worth noticing that the =C-O-C asymmetric stretching at 1200 cm^{-1} is not robust according to Góbi and Magyarfalvi criterion,[30] since the calculated ζ_2 (for the most populated conformer) is ~6 ppm for **1** and ~3 ppm for **2** and **3**, below the 10 ppm threshold. Similarly, for the C=C stretching at 1620 cm^{-1} the calculated ζ_2 for the most populated conformer of **1** is ~1 ppm, well below the 10 ppm threshold. Therefore this band should be disregarded. Obviously, a correct prediction of the region around 1600 cm^{-1}, including overtones and Fermi resonance, requires an anharmonic computational approach.[34]

Finally it is interesting to note that compounds **1** and **2** which bear chirality in position 2 and 3 respectively, and share otherwise a similar skeleton and the same configuration, should in principle lead to an odd-even effect such as that observed by Nafie et al.[35] for chiral alcohols. However, most VCD bands, in either the experimental or calculated spectra, have the same sign for **1** and **2**, demonstrating that in the present case no odd-even effect is evident.

Conclusion

We have shown that simple chiral alkyl vinyl ethers can be conveniently characterized only through VCD spectroscopy, but not ECD or optical rotation. However, many conformers are significantly populated at room temperature, and each of them gives a different contributions to the total VCD spectrum with bands displaying opposite sign and variable intensity. Thus, special care should be taken in interpreting calculation results and comparing them with the experiment. Nevertheless some bands, and most notably the signals associated with the deformations in the 1300-1460 cm^{-1} region, could offer a useful fingerprint to solve absolute configuration problems for this class of compounds and similar ones.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website. It contains: VCD spectra calculated for **1** with different basis sets; UV and ECD spectra of **1-3**; VCD spectra calculated for different conformers of **1-3**; structures and relative energies of low-energy conformers of **1-3**; ^{1}H NMR spectra of **1-3**.

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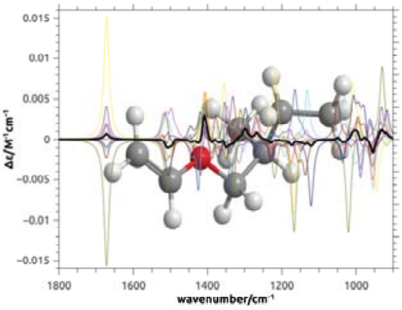
Graphical Abstract



Alkyl vinylethers display zero ECD signal and very weak optical rotations, making vibrational circular dichroism an almost essential tool to solve absolute configuration problems. However, given the many conformational possibilities leading to completely different spectral features, the DFT calculations are not straightforward. Nevertheless, we found that certain bands could be reliably employed as a fingerprint for these and similar compounds.