Amplified vibrational circular dichroism

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AMPLIFYING VIBRATIONAL CIRCULAR DICHROISM BY MANIPULATION OF THE ELECTRONIC MANIFOLD

Vibrational circular dichroism is a powerful technique to study the stereochemistry of chiral molecules, but often suffers from small signal intensities. In this chapter, electrochemical modulation of the energies of the electronically excited state manifold is demonstrated to lead to an order-of-magnitude enhancement of the differential absorption. Quantum-chemical calculations show that increased mixing between ground and excited states is at the origin of this amplification.

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5.1 INTRODUCTION

The development of tools to unambiguously assign the absolute configuration of naturally occurring and synthetic chiral molecules is of major importance for biochemical and pharmaceutical research. Vibrational Circular Dichroism (VCD), the infrared circular dichroism associated with vibrational transitions of chiral molecules, is a powerful spectroscopic method for this purpose since it makes it possible to determine the absolute configuration and conformation (or distribution of conformations) of a molecule without reference to any previous empirical rules. However, in many cases VCD measurements are difficult because of the small signal magnitudes (the differential absorption being typically $10^{-5}$ of the absorption itself). Such small intensities can be measured routinely nowadays, but at the expense of long measuring times. Strategies that would enhance VCD signals and thereby improve the ability of accurately differentiating between optical isomers by means of their vibrational signatures could therefore be of substantial importance.

It has been reported previously that molecular systems with low-lying electronically excited states can exhibit strongly enhanced VCD signals [68, 69, 70]. The origin of this enhancement can be understood from the expression for the vibrational magnetic-dipole transition moment derived in the vibronic coupling theory for VCD [14, 25]. The theoretical arguments that sustain this phenomenon are explained in chapter 2. In this chapter, we present a novel approach to amplify VCD signals by modulation of the energies of the excited-state manifold in a controlled way using spectroelectrochemistry (SEC) [71, 72, 73]. For this purpose we performed VCD–SEC measurements on two enantiomeric compounds, henceforth to be designated as (R)–1 and (S)–1 (1 = methyl 2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propanoate, Fig. 19). The experimental apparatus developed for this kind of measurements is described in detail in Chapter 3 (section 3.2).
5.2 SYNTHETIC METHODS AND EXPERIMENTAL PROCEDURES

A mixture of 2.50 g of 1,8-naphthalic anhydride and 2.0 g of L-alanine methyl ester hydrochloride (Aldrich) and 4 ml of triethylamine (TEA) in 150 ml of methanol under Ar was refluxed for 15 h. After approximately 1 hour of reflux a clear solution was obtained. The brown solution was concentrated with a rotavap to give a pale brown solid residue. Standing at room temperature a precipitate is formed. After cooling in ice the precipitate was filtered off, washed with cold methanol and dried in vacuum. Yield: 1.772 g, mp.156-8°C (needles). The procedure was repeated with D-alanine methyl ester hydrochloride (Aldrich). The optical rotation of (R)-1 and (S)-1 was measured using the Sodium D line: \( \alpha_D^{20}=0.131^\circ \) (concentration: 2.7mg/mL, CH\(_3\)CN) and \( \alpha_D^{20}=-0.123^\circ \) (concentration 2.6mg/mL, CH\(_3\)CN), respectively. For the spectroelectrochemical measurements, tetrabutylammonium hexafluorophosphate (Bu\(_4\)NPF\(_6\), Sigma Aldrich) was used as supporting electrolyte. Dry deuterated acetonitrile (CD\(_3\)CN) was used as the standard solvent in all the experiments. All samples were prepared under a N\(_2\) atmosphere. Fourier-transform infrared (FTIR) and VCD spectra were recorded on a Bruker Vertex 70 FTIR spectrometer in combination with a PMA 50 module (with 2 cm\(^{-1}\) and 4 cm\(^{-1}\) spectral resolution, respectively). UV-Vis absorption spectra were obtained with a HP 8453 UV-Vis Spectrophotometer.
5.3 RESULTS AND DISCUSSION

5.3.1 VCD enhancement in electrochemically generated radical anions

To investigate the effect of electrochemical reduction on the VCD response, we measured IR and VCD spectra of compounds (+)-1 and (−)-1 (Fig. 19) both in their neutral and radical anion forms.

The FTIR spectrum of neutral (−)-1 is shown in Fig. 20B (blue curve). In the 1500-1780 cm\(^{-1}\) frequency range four dominant vibrational modes (\(A_1 - A_4\)) can be identified and assigned by comparison with literature [74]. The FTIR spectrum of the radical anion (red curve in Fig. 20B), was obtained upon complete reduction of a 35 mM solution of (−)-1 in CD\(_3\)CN (10\(^{-1}\)M Bu\(_4\)NPF\(_6\)) at 293 K, using an OTTLE cell [39, 75]. The thin-layer (TL) cyclic voltammogram (CV) for (−)-1 shows a completely reversible cathodic wave (see Fig. 20A). The observed reduction potential (\(E_{1/2} = -1.3\) V vs. Fc/Fc\(^+\)) is in good agreement with previously reported values for similar systems. [74] Intermediate spectra were recorded in small potential steps across the cathodic wave, and IR spectral changes were monitored at each step (Fig. 20B).

Comparison of the IR spectra of neutral and anionic (−)-1 shows that the IR bands \(A_2\) and \(A_3\) of the neutral at 1704 cm\(^{-1}\) and 1667 cm\(^{-1}\), assigned to the symmetric and asymmetric C=O stretching modes of the naphthalimide moiety, are red-shifted in the radical anion to 1615 cm\(^{-1}\) (\(A_2^\leftrightarrow\)) and 1562 cm\(^{-1}\) (\(A_3^\leftrightarrow\)), respectively. The naphthalimide aromatic C=C stretching mode (\(A_1\)) observed in neutral (S)-1 at 1589 cm\(^{-1}\) is red-shifted to 1525 cm\(^{-1}\) (\(A_1^\leftrightarrow\)) in the radical anion. The methyl ester C=O stretching mode of the amino-acid moiety (\(A_4\)) at 1750 cm\(^{-1}\) is red-shifted to 1740 cm\(^{-1}\) (\(A_4^\leftrightarrow\)) in the radical anion.

The VCD spectra of 7 mM solution of neutral and radical anion (+)-1 and (−)-1 are displayed in Fig. 20C. Spectra for both enantiomers have been obtained by averaging three consecutive sets of 20 min. scans (for the neutral) and three sets of 2 min. scans from independent but consecutive CV cycles. For neutral (+)-1 and (−)-1, three features \(R_2\), \(R_3\) and \(R_4\) can be observed in the VCD spectra. These bands are red-shifted for the radical anion of (+)-1 and (−)-1 to the features \(R_2^\leftrightarrow\), \(R_3^\leftrightarrow\) and \(R_4^\leftrightarrow\), respec-
tively. Moreover, the spectra show another band \( R_1^- \) that is not visible in the spectrum of the neutral. Importantly, we find that the VCD signals are enhanced up to one order of magnitude compared to the neutral species. As will be argued in the following, this enhancement is due to a strong vibronically induced mixing of low-lying electronic excited states with the ground state in the electrochemically generated radical anion species.
5.3.2 Low-lying electronically excited states

The peak intensities in VCD spectra are proportional to the rotational strength, given by: [76]

\[ R = \text{Im}[\langle \psi_i | \hat{\mu}_e | \psi_f \rangle \cdot \langle \psi_f | \hat{\mu}_{\text{mag}} | \psi_i \rangle] \]  \hspace{1cm} (55)

where \( \hat{\mu}_e \) and \( \hat{\mu}_{\text{mag}} \) are the electric and magnetic dipole moment operators, respectively, and \( |\psi_i\rangle \) and \( |\psi_f\rangle \) are the total wave functions for the initial and final states. It has been shown previously [77] that within the Born-Oppenheimer (BO) approximation, the electronic contribution to the vibrational magnetic transition dipole moment \( \hat{\mu}_{\text{mag}} \) is identically zero, and that VCD can be described only if vibronically induced mixing of the BO wave functions of the electronically excited states and the ground state is taken into account. [14, 15] In particular, it can be shown that when a molecule is in an electronic state \( |\psi_0\rangle \), the electronic contribution to the magnetic transition dipole moment of a transition between the \( \nu = 0 \) and \( \nu = 1 \) levels of a vibrational mode is given to first order by: [14, 15]

\[ \langle \psi_f | \hat{\mu}_{\text{mag}}^e | \psi_i \rangle = \langle \chi_{\nu=0} | \sum_{K \neq G} \frac{\langle \psi_0 | \hat{\mu}_{\text{mag}}^e | \psi_K \rangle}{W_K - W_0} \left( \langle \psi_K | T_{\text{nucl}} | \psi_0 \rangle - \langle \psi_0 | T_{\text{nucl}} | \psi_K \rangle \right) | \chi_{\nu=1} \rangle \] \hspace{1cm} (56)

where \( |\chi_{\nu=0}\rangle \) and \( |\chi_{\nu=1}\rangle \) are the nuclear wave functions of the \( \nu = 0 \) and \( \nu = 1 \) states in the electronic ground state \( |\psi_0\rangle \), and \( T_{\text{nucl}} \) is the nuclear kinetic energy operator. \( \hat{\mu}_{\text{mag}}^e \) is the electronic magnetic transition dipole moment, \( |\psi_0\rangle \) and \( |\psi_K\rangle \) are the BO electronic wave functions for the ground state and the \( K^{th} \) electronically excited state, with energies \( W_0 \) and \( W_K \), respectively.

For large energy gaps between ground and electronically excited states, the coefficients in the perturbation expansion, \( \langle \psi_0 | \hat{\mu}_{\text{mag}}^e | \psi_K \rangle / (W_K - W_0) \) (see Eq. 56), are small due to large energy denominators. As a consequence, the VCD signals are very small. This is the case for nearly all closed-shell organic molecular systems.
In open-shell species, on the other hand, the first electronically excited states are generally at much lower energies. Equation 56 shows that this leads to a strong increase in the magnetic-transition dipole moments, and thus in the VCD amplitudes. Indeed, the UV-Vis absorption spectrum of the radical anion displayed in Fig. 21 shows absorption bands at much longer wavelengths than the corresponding spectrum of the neutral system. We have confirmed the presence of these low-energy states and identified their electronic characteristics using time-dependent density functional theory (TD-DFT) calculations on the most stable conformer of the radical anion. The low-energy nature of these excited states induces mixing of their wave functions into the ground state, increasing the total number of adiabatic electronic states contributing to the vibrational eigenfunctions, and leading to strongly enhanced VCD signals, as confirmed by our experimental results.

From the TD-DFT calculations we can assign two almost degenerate electronic states, D$_1$ and D$_2$, contributing to the absorption band at 822 nm in Fig. 21. Interestingly, we find that the electronic magnetic transition-dipole moment $\langle \Psi_0 | \mu_{\text{mag}}^e | \Psi_2 \rangle$ between the ground state and
Figure 22: Difference density plots (isovalue 0.004) for the first (left) and second (right) excited states (D₁ – D₀) and (D₂ – D₀), respectively, from a TD-DFT (B3LYP/6-31G(d,p)) calculation on the radical anion of (S)-1, where blue color represents negative (lost ground-state) density and the yellow color positive (gained excited-state) density.

D₂ is one order of magnitude larger than for any other of the first ten electronically excited states. Equation 56 thus tells us that D₂ will be a dominant contributor to the vibrational magnetic transition dipole moment, not only because of the relatively small energy gap (W₂ – W₀), but also because of the large value of the $\langle \psi_0 | \vec{\mu}_{\text{mag}}^c | \psi_2 \rangle$ matrix element. It will therefore magnify the vibrational magnetic transition dipole moment, and thus the VCD intensity. The difference density plot between D₂ and the ground state D₀ shows that the electron density on the naphthalimide carbonyl groups is noticeably different in D₂ and D₀, while the electron density on the carbonyl group near the methyl ester is the same in the two states. The dominant role of D₂ in the expansion of the vibrational magnetic transition moment (Eq. 56) makes one there-

Table 1: Electronic magnetic transition-dipole moments between the ground and Kᵗʰ electronically excited state (arbitrary units).

<table>
<thead>
<tr>
<th>K</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\langle \psi_0</td>
<td>\vec{\mu}_{\text{mag}}^c</td>
<td>\psi_K \rangle$</td>
<td>0.07</td>
<td>1.61</td>
<td>0.01</td>
<td>0.10</td>
<td>0.18</td>
<td>0.05</td>
<td>0.08</td>
<td>0.35</td>
</tr>
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</table>
fore expect that the VCD of the naphthalimide C=O-stretching modes would be affected in particular. Our experimental results nicely confirm this expectation: we observe maximum VCD enhancement (one order of magnitude) for the symmetric naphthalimide C=O-stretching mode. It is satisfying to note that our observations are internally consistent in other respects, as well. From a purely energetic point of view, $D_1$ might also be expected to make a significant contribution to the vibrational magnetic transition dipole moment. Difference density plots between $D_1$ and $D_0$ show, however, that the electron density on the naphthalimide carbonyl groups is hardly different in $D_1$ and $D_0$ (Fig. 22). A dominant contribution of $D_1$ in Eq. 56 would thus be at odds with an enhancement of the naphthalimide C=O-stretching modes. Indeed, the influence of $D_1$ is greatly reduced in the end on account of the small electronic magnetic transition dipole moment from the ground state (Table 1).

5.3.3 Conformational analysis

In the previous sections of this chapter we have shown that modulation of the electronic excitation energies can be used advantageously to enhance VCD signals. Here, we will be concerned with the absolute configuration and conformation of the compounds used in the present study. To this purpose four different conformers were identified at the AM1 semi-empirical level for both the neutral and the anionic species. The geometries of these conformations served as a starting point for further optimization at the DFT level of theory using the B3LYP functional and the 6-31G(d) and 6-31+G(d,p) basis sets for neutral and radical anion species, respectively. All calculations were performed with Gaussian 03 [78]. The final structures that were thus obtained for the neutral molecule are displayed in Fig. 23. For the radical anion the same conformations were obtained with only minor changes in geometrical parameters.

Conformers 1a and 1b were found to have the lowest energy in both the neutral and anionic forms. For the neutral conformer, 1b has the lowest energy with conformer 1a being 0.7 kcal/mol higher in energy, for the anion the energies of the two conformers are within 0.01 kcal/mol.
Figure 23: Equilibrium geometries obtained at the B3LYP/6-31G(d) DFT level of theory, for the four conformations of (S)-1, ordered from lower to higher energy a–d.

Such energy differences are far smaller than the accuracy of the calculation. We therefore have to assume that both conformers can in principle contribute to the observed IR and VCD spectra. Neutral (anionic) conformers 1c and 1d, on the other hand, have energies that are 13.9 (13.0) and 10.4 (10.5) kcal/mol higher than the lowest energy conformer, and can thus safely be ruled out as being present under the employed experimental conditions.

At each of the optimized geometries harmonic force fields were calculated. From the calculated dipole and rotational strengths IR and VCD spectra were simulated assuming Lorentzian band shape with a width
of 2 and 4 cm\(^{-1}\), respectively, and scaling the computed frequencies with a factor of 0.97. In Fig. 24 we show the observed and calculated IR and VCD spectra for the neutral species of (S)-1. From comparison of the observed spectra in Fig. 24 and calculated spectra for the (S) configuration, we assign the absolute configuration as (−)-(S)-1. In general, good agreement is observed between the experimental spectra and the predicted spectra of conformations that are expected to be dominantly present. The sign pattern and intensities predicted for the VCD spectra of conformers 1c and 1d are irreconcilable with the experimentally ob-

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**Figure 24:** Observed and calculated IR (upper-panel) and VCD (lower-panel) spectra for the neutral (left) and radical anion (right) species of (−)-(S)-1. All spectra are scaled and normalized for clear comparison.
served patterns, confirming their absence under employed experimental conditions. A more detailed comparison of the spectra predicted for conformers 1a and 1b with the experimental spectra rapidly leads to the conclusion that the IR spectrum is not sensitive enough to distinguish the subtle geometrical differences between 1a and 1b, and therefore cannot provide a means to access their configuration to the experimental spectrum. The VCD spectrum has in that respect much more resolving power. Inspection of the 1400–1800 cm\(^{-1}\) region shows that the experimental spectrum — and in particular the sign pattern — is in significantly better agreement with the predicted spectrum of conformer 1a than of 1b. Nevertheless, the oppositely predicted sign of the band at 1700 cm\(^{-1}\) and the intensity of the 1750 cm\(^{-1}\) band remains at odds with the observed spectrum.

Recently, the concept of robust normal modes has been introduced.\(^{[79]}\) Such modes have been defined as modes for which the angles between the electronic and magnetic transition dipole moments differ by at least 30° from 90° and have rotational strengths of significant magnitude. In that study it was concluded that preferably only robust modes should be employed for configurational and conformational assignments as other modes are too sensitive to the finer details of the calculations. Analysis of the modes of (S)-1 in the 1400–1800 cm\(^{-1}\) region shows that in the present case none of the modes can be marked as robust. In fact, we find for the modes at 1700 cm\(^{-1}\) and 1750 cm\(^{-1}\) angles that are close to 90°, rationalizing the discrepancies between experiment and theory observed for these two modes.

In Fig. 24 we show the observed and calculated IR and VCD spectra for the radical anion species of (−)-(S)-1. Again, we find very good agreement between experimental and calculated IR spectra, but no distinct markers that would enable us to rule out one or more conformers. However, as was argued for the neutral species, the absence of spectral signatures of 1c and 1d in the VCD spectrum of the radical anion indicates that these conformers are not present. It is considerably more difficult to determine in which ratio conformers 1a and 1b are present. Comparison of the experimental VCD spectrum with the predicted spectra for 1a and 1b in the spectral region where the experimental spectrum
has relevant intensity shows a fair agreement, but the only mode that appears to be truly distinctive is the one at 1750 cm\(^{-1}\). We recall that the two conformers are predicted to have similar energies. Indeed, analysis of the experimental spectrum in terms of varying contributions of the predicted spectra for 1a and 1b indicates that it is rather plausible that both conformers contribute to the experimental spectrum.

5.4 FINAL REMARKS

We have observed a strong enhancement of VCD signals upon the electrochemical reduction of a closed-shell organic compound in solution: the conversion from neutral molecule to radical anion increases the VCD signals by up to one order of magnitude. Such intensity-enhanced VCD arising from the presence of electrochemically “created” low-lying electronic states should be a general phenomenon in organic compounds. As such, electrochemical VCD can be a valuable tool for amplifying signals in molecules that have small VCD amplitudes, or that can be studied only at low concentrations (see Chapter 8).