The Exciton Chirality Method in Vibrational Circular Dichroism

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Supporting Information Placeholder

**ABSTRACT:** The interaction of two IR chromophores yields a strong vibrational circular dichroism couplet whose sign reflects the absolute configuration of the molecule. We present a method to determine absolute configuration of a chiral molecule based on this couplet without need of theoretical calculation. Not only can this method analyze various molecules whose absolute configuration is difficult to determine by other spectroscopic methods, but also it can significantly enhance VCD signals.

Chirality plays fundamental roles in numerous biological and nonbiological phenomena. The determination of absolute configuration of chiral molecules is an essential step in various research fields including pharmacological science, drug development, biosynthesis, asymmetric reaction, total synthesis and supramolecular chemistry. Chiroptical spectroscopy is the sole technique that can nonempirically determine molecular chirality without need of crystallization. One of the most widely used is the exciton chirality method using electronic circular dichroism (ECD), developed by Harada and Nakanishi, for its high sensitivity and the ease of spectral interpretation; however, the requirement for two or more appropriate UV-Vis chromophores with proper orientation restricts its applicability. In the past decade, vibrational circular dichroism (VCD) spectroscopy using *ab initio* theoretical calculation has been established as a reliable and convenient approach. Although its application to middle-sized molecules and even peptides and nucleic acids could be possible in successful cases, VCD technique has been hampered by the low sensitivity of vibrational absorption and by the computational demand. In exploration of a more universal, sensitive method, we envisioned the potential of an exciton coupling approach in VCD, also classically known as a coupled oscillator model. So far, no study has reported its use for the assignment of absolute configuration; a stark contrast with the well-established ECD exciton chirality method. Here we demonstrate the utility of the VCD exciton coupling approach as a versatile method to determine absolute configuration through a systematic study on small molecules.

The through-space interaction of two electric transition moments yields a split-type bisignate CD signal that reflects the absolute sense of the twist of the two moments: the positive twist generates a positive first Cotton effect (Δε1, lower in wavenumber) and a negative second Cotton effect (Δε2, higher in wavenumber), and vice versa (Supporting Figure S1). The carbonyl functional groups are promising chromophores for the VCD exciton coupling approach because of their strong, sharp, isolated absorption band at around 1650-1800 cm⁻¹ and because of their well-localized C=O stretching vibrational mode that gives rise to electric transition moments whose direction is virtually parallel to the C=O bond. Moreover, carbonyl groups can be routinely installed to a desired part of the molecule, e.g. by esterification of a hydroxyl group. The exciton approach based on C=O stretching has been successfully applied in VCD studies of biomacromolecules.  

**Figure 1.** Comparison of VCD spectra of mono- and biscarbonyl compounds. The VCD (top) and IR (bottom) spectra and the arrangement of the electric transition moments (red arrows parallel to C=O bonds) of (a) α-substituted lactones 1 and (b) mannose derivatives 2. Each spectrum was measured using CDCl₃ (c = 0.05 M, l = 100 μm) and corrected by a solvent spectrum obtained under the identical measurement condition. The ester carbonyls are represented as syn to the methine hydrogen and the ester group is in s-trans orientation. The orientations of two carbonyl groups...
seen from one carbonyl carbon to the other are presented in Supporting Figure S2.

To test the feasibility of this approach in determining absolute configuration, we examined the VCD spectra of chiral α-hydroxylactone 1a, a common structural motif found in natural products such as ginkgolides,4 and its derivatives 1b and 1c (Figure 1a). Each sample was dissolved in DCl3 at a concentration of 0.05 M and placed in a 100-µm CaF2 cell. IR and VCD spectra were measured for 2 and 90 mins, respectively. The monocarbonyl (S)-1a and (S)-1b showed a strong IR absorption band at around 1780 cm⁻¹ with no significant VCD features in the C=O stretching region, while a simple introduction of an acetate group ((S)-1c) resulted in a sharp bisignate VCD signals whose intensity was amplified by more than a factor of 25 (Table 1). A similar phenomenon was observed for mannose derivatives 2. As shown in Figure 1b, the bisacetoate derivative 2c exhibited a VCD couplet that is more than ~20 times stronger than the signals of monoaecate derivatives 2a and 2b. The comparison of the VCD spectra of 2a-2e suggests that the observed couplets were not the sum of the signals from each C=O group but should be ascribed to a through-space and/or through-bond interaction of the two carbonyl chromophores. Importantly, the signs of these couplets are consistent with the absolute twist of the two C=O bonds (defined by the sign of the dihedral angle θ) exhibited a positive-negative couplet (a positive value), which is expectedly all compounds with a clockwise twist (0° < θ < 180°) were well approximated by the sum of the component bischromophoric combinations 2c, 2d and 2e (Supporting Figure S3). Although the degree of the contributions from the through-space (excitonic) and through-bond interactions to the origin of the VCD couplet is yet to be discussed, this approach shares the same features (1)-(4) with the ECD exciton chirality method.1 This regard, we feel it appropriate to call this method as VCD exciton chirality method.

Figure 2. The structures of the biscarbonyl compounds prepared and measured in this study.

Furthermore, the set in Table 1 was designed to evaluate the influence of the spatial arrangement and the nature of the chromophores on the amplitude A. Although a precise correlation of these factors could be obscured by the presence of other conformers that contributed to the observed A value, these data suggested some practical aspects of this approach. (1) An increase in the energy difference between two chromophores lowered the A value (1c, 1d and 1e, and 2c and 2f). It is striking that two chromophores that differ by over 100 cm⁻¹ yielded a couplet (1e). (2) A dihedral angle close to 0° and 180° resulted in a decrease in A (e.g., 2d and 5). (3) A longer interchromophoric distance, R, attenuated the coupling (e.g., 6 and 7). A coupleting over as far as 11 Å can be detectable unless intrinsic VCD signals interfere, as seen in 8. In contrast, two carbonyls in the close vicinity (~3 Å) in 9 exhibited a huge VCD couplet that reached to the Δε value of ±1. Lastly, (4) the additivity rule1b may be applied: the spectral shape of the couplet in a trischromophoric system 2g was well approximated by the sum of the component bischromophoric combinations 2c, 2d and 2e (Supporting Figure S3). The degree of the contributions from the through-space (excitonic) and through-bond interactions to the origin of the VCD couplet is yet to be discussed5b-7c; this approach shares the same features (1)-(4) with the ECD exciton chirality method.1 In this regard, we feel it appropriate to call this method as VCD exciton chirality method.

Not only can the VCD exciton chirality method be used as conveniently as the ECD method, but also it can analyze molecules that are outside of the coverage of ECD and other spectroscopic techniques. For example, spirobicyclic compounds such as 2,2'-spirobiindane-1,1'-dione (9), azaspirene and biyuyanagins,8 may be categorized to such a class. This advantage was further pronounced in our next study on biologically and therapeutically important molecules that include α-hydroxyketone, α-amidolactam and dilactone – difficult targets by other methods (Figure 3). N-Tetradecanoyl homoserine lactone 10 (a signaling molecule in bacterial quorum sensing), picrotoxinin 11 (a GABAₐ receptor chloride channel blocker), diltiazem 12 (an antianginal and antiarrhythmic drug) exhibited a bisignate VCD signal with its sign corresponding to their structures. Such a couplet was also recognized in the VCD spectrum of penicillin G 13 (Supporting Figure S4). The couplets in 12 and 13 were not perturbed by other chromophores. In the case of taxifolin 14 (a flavonol with a potential chemopreventive effect), an acetate chromophore was strategically introduced to observe a VCD coupling with the pre-existing ketone chromophore, which led to a couplet consistent with their clockwise chromophoric orientation. Such bisignate strong signals were seen also in previous DFT-based VCD studies on natural products, although no attempt was made to correlate the spectral shape and their molecular structure without computation. Structural determination using the VCD exciton chirality method does not require theoretical calculation, and therefore it should be amenable to the analysis of further bigger, more complex systems, which is in due course.

The utility of this method as a signal intensifier has not escaped our interest. Indeed, 1c exhibited a clearly observable VCD couplet at a concentration of 2.5 mM (180-min accumu-
lation, \( l = 100 \mu m \)), where less than 20 \( \mu g \) of the sample was used, or within a 2-min VCD accumulation (\( c = 0.05 \ M, \ l = 100 \mu m \)) (Supporting Figure S5). Such measurement would be impossible for the unmodified 1a.

It should be reminded that a VCD coupling phenomenon is not limited to carbonyl groups, although C=O stretching vibration is by far easier to analyze than absorption in a lower frequency region. Properly used, other chromophores such as C-O groups (data not shown) could offer useful stereostuctural information. It is intriguing to consider any of a propitious pair of electric transition moments associated with up to 3\( N - 6 \) fundamental vibrational modes (where \( N \) is the number of the atoms in the molecule) could be used for the exciton approach in VCD. (data not shown).

### Table 1. VCD couplet by two carbonyl chromophores.

<table>
<thead>
<tr>
<th>( \Delta \varepsilon_1 ) (M(^{-1}) cm(^{-1}))</th>
<th>( \Delta \varepsilon_2 ) (M(^{-1}) cm(^{-1}))</th>
<th>( A )</th>
<th>( \theta )</th>
<th>( R ) [( \AA )]</th>
</tr>
</thead>
<tbody>
<tr>
<td>((S)-1a) (R = OH)</td>
<td>-0.011</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>((S)-1b) (R = OMe)</td>
<td>-0.19</td>
<td>+0.28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-1d) (R = OAc)</td>
<td>-0.12</td>
<td>+0.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-1e) (R = OAc)</td>
<td>-0.041</td>
<td>+0.075</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-1f) (R = OAc)</td>
<td>+0.17</td>
<td>-0.27</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((R)-1c) (R = OH)</td>
<td>+0.17</td>
<td>+0.44</td>
<td>+99°</td>
<td>3.7</td>
</tr>
<tr>
<td>((R)-1f) (R = OAc)</td>
<td>-0.016</td>
<td>+0.044</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-2a) (R(^1) = R(^2) = Me, R(^3) = Me)</td>
<td>N.D.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-2b) (R(^1) = Me, R(^2) = OAc)</td>
<td>-0.40</td>
<td>+0.42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-2d) (R(^1) = Me, R(^2) = Ac, R(^3) = Me)</td>
<td>-0.072</td>
<td>+0.13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-2f) (R(^1) = Ac, R(^2) = Me, R(^3) = Me)</td>
<td>-0.016</td>
<td>+0.044</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-2g) (R(^1) = Ac, R(^2) = Me, R(^3) = Ac)</td>
<td>-0.35</td>
<td>+0.37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-3i) (R = Ac)</td>
<td>-0.30</td>
<td>+0.41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-4a) (R = Ac)</td>
<td>-0.11</td>
<td>+0.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((S)-4b) (R = Bz)</td>
<td>+0.14</td>
<td>-0.062</td>
<td>+60°</td>
<td>4.7</td>
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<tr>
<td>((S)-5i) (R = Ac)</td>
<td>+0.044</td>
<td>-0.045</td>
<td>+176°</td>
<td>4.4</td>
</tr>
</tbody>
</table>

VCD measurement condition: 45 or 90 min accumulation, in CDCl\(_3\), \( c = 0.025 \ M \) (for 2f) or 0.05 M (others). Calculation condition to obtain the most stable conformer: MMFF94 MonteCarlo Search or DFT optimization at B3LYP/6-311+g(d,p) or B3LYP/6-31g(d). \( \Delta \varepsilon_1 - \Delta \varepsilon_2 \) Amplitude of the VCD couplet, \( \Delta \varepsilon_1 \) - \( \Delta \varepsilon_2 \). Dihedral angle defined by the two C=O of the most stable conformer. \( \Delta \varepsilon \) Interchromophoric distance of the most stable conformer. Only monosignate signal was detected. \( \theta \) No significant signal was detected. \( \theta \) DFT/B3LYP/6-311+g(d,p). \( \theta \) DFT/B3LYP/6-31g(d). \( \theta \) MMFF94.

**Figure 3.** The VCD (top) and IR (bottom) spectra and the arrangement of two carbonyl chromophores of natural products and...
drugs. The IR and VCD spectra were measured for 2 and 90 mins, respectively, in CDCl₃ (l = 100 μm) at a concentration of 0.075 M (10 and 12), 0.05 M (11 and 14). Each spectrum was corrected by a solvent spectrum obtained under the identical measurement condition. Each wavenumber at the extrema is labeled in italic. The alkyl chain in the model of 10 is omitted for clarity. The derivatization scheme of 14 is shown in (d).

In summary, we present a new approach for the analysis of chiral molecules based on the bisignate VCD couplet originating from two IR chromophores. This technique can analyze molecules whose absolute configuration would otherwise be difficult to determine. Moreover, it can significantly enhance the signals by a factor of ~20 in the case of 1 and 2, while an even stronger signal was observed for 9. This property would redeem the low-sensitivity of VCD spectroscopy. Supported by the recent development of more sensitive VCD instruments, this method should find various usages in future, e.g., analysis of minuscule molecules with or without using theoretical calculation or time-dependent VCD measurement.

ASSOCIATED CONTENT

Selected experimental and theoretical spectra, procedures for experiment and calculation, synthesis and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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