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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,[1] 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.[2] Although its application to middle-sized molecules[3] and even peptides and nucleic acids[4] 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.[5] So far, no study has reported its use for the assignment of absolute configuration; a stalk 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:[6] the positive twist generates a positive first Cotton effect ($\Delta\varepsilon_1$, lower in wavenumber) and a negative second Cotton effect ($\Delta\varepsilon_2$, higher in wavenumber), and *vise verse* (Supporting Figure S1).[1] 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.[4b,7]

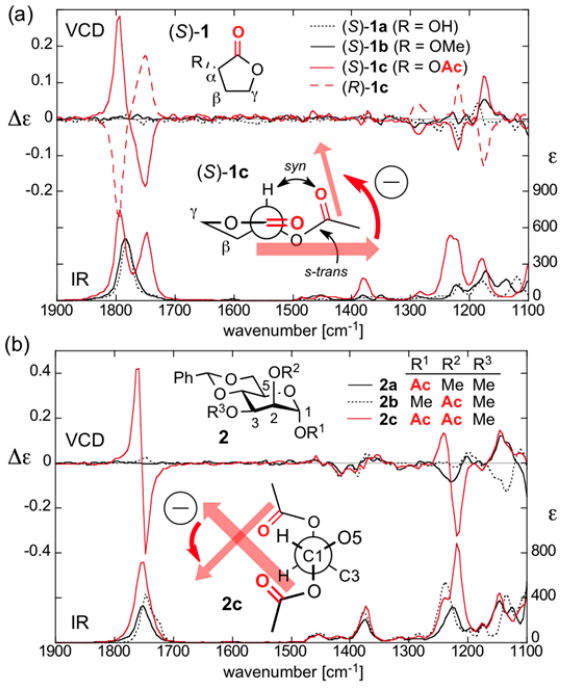

Figure 1. Comparison of VCD spectra of mono- and biscarbonyl compounds. The VCD (top) and IR (bottom) spectra and the arrangement of the electric transition moments (red arrows parallel to C=O bonds) of (a) α-substituted lactones **1** and (b) mannose derivatives **2**. Each spectrum was measured using $CDCl_3$ (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,[8] and its derivatives **1b** and **1c** (Figure 1a). Each sample was dissolved in $CDCl_3$ at a concentration of 0.05 M and placed in a 100-μm CaF_2 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 bisacetate derivative **2c** exhibited a VCD couplet that is more than ~20 times stronger than the signals of monoacetate derivatives **2a** and **2b**. The comparison of the VCD spectra of **2a**-**2c** 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 of two C=O groups, see Supporting Figure S1) estimated from the *s*-trans conformation of the ester groups and the *syn* relationship between the ester carbonyl and the methine hydrogen.[1] Namely, negative-positive (from lower to higher frequency) signals were observed for (*S*)-**1c** and **2c**, both of which display a counterclockwise chromophoric orientation (Figure 1). Density functional theory (DFT) calculation of **1c** and **2c** at the B3LYP/6-311G+(d,p) level well reproduced the observed VCD couplets, including their signs (Supporting Figure S2).

To bolster the generality of the relationship between the chromophoric orientation and the sign of the couplets, we prepared a series of biscarbonyl compounds (Figure 2) and measured their VCD spectra. Table 1 lists the observed values of $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$, the amplitude of the couplet *A* (defined as $\Delta\varepsilon_1 - \Delta\varepsilon_2$) and θ of the most stable conformers of each compound calculated either by MMFF94 MonteCarlo search or by DFT optimization (see the Supporting Information for details). Expectedly, all compounds with a clockwise twist ($0° < \theta < +180°$) exhibited a positive-negative couplet (a positive *A* value), while a counterclockwise screw sense ($-180° < \theta < 0°$) showed a negative-positive signal (a negative *A* value), probing the reliability of this methodology for determination of absolute configuration.

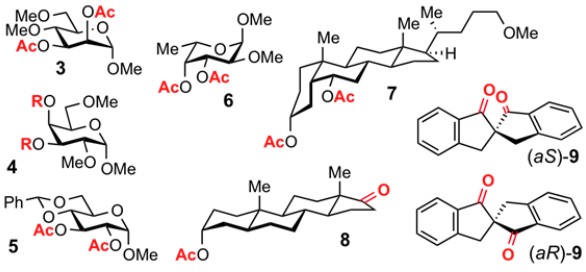

Figure 2. The structures of the biscarbonyl compounds prepared and measured in this study.

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 coupling 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 rule[1b] 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). 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,[5b,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, spirobicarbonyl compounds such as 2,2'-spirobiindane-1,1'-dione (**9**), azaspirene and biyouyanagins,[9] 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-amidelactam and dilactone – difficult targets by other methods (Figure 3). *N*-tetradecanoyl homoserine lactone **10** (a signaling molecule in bacterial quorum sensing), picrotoxinin **11** (a $GABA_A$ 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 flavanonol 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,[8b,10] 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 μm), where less than 20 μg of the sample was used, or within a 2-min VCD accumulation (c = 0.05 M, l = 100 μm) (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 stereostructural information. It is intriguing to consider any of a propitious pair of electric transition moments associated with up to $3N - 6$ 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.

	$\Delta\varepsilon_1$ [a] (ν [cm^{-1}])	$\Delta\varepsilon_2$ [a] (ν [cm^{-1}])	A [a,b]	θ [c]	R [d] [Å]
(*S*)-**1a** (R = OH)	+0.011 (1782) [e]		-	-	-
(*S*)-**1b** (R = OMe)	N.D. [f]		-	-	-
(*S*)-**1c** (R = O**Ac**) [g]	-0.19 (1751)	+0.28 (1794)	-0.47	-99°	3.7
(*S*)-**1d** (R = O**Bz**) [h]	-0.12 (1728)	+0.15 (1794)	-0.27	-135°	4.1
(*S*)-**1e** (R = NH**Ac**) [g]	-0.041 (1678)	+0.075 (1782)	-0.12	-152°	4.3
(*R*)-**1c** [g]	+0.17 (1751)	-0.27 (1794)	+0.44	+99°	3.7
2a (R^1 = **Ac**, R^2 = Me, R^3 = Me)	N.D. [f]		-	-	-
2b (R^1 = Me, R^2 = **Ac**, R^3 = Me)	+0.025 (1747) [e]		-	-	-
2c (R^1 = Me, R^2 = **Ac**, R^3 = **Ac**) [g]	-0.40 (1747)	+0.42 (1759)	-0.82	-113°	5.6
2d (R^1 = Me, R^2 = **Ac**, R^3 = **Ac**) [i]	-0.072 (1736)	+0.13 (1751)	-0.20	-60°	4.8
2e (R^1 = **Ac**, R^2 = Me, R^3 = **Ac**) [i]	-0.016 (1736)	+0.044 (1747)	-0.06	-150°	6.3
2f (R^1 = **Bz**, R^2 = **Ac**, R^3 = Me) [i]	-0.35 (1732)	+0.37 (1751)	-0.72	-83°	5.1
2g (R^1 = **Ac**, R^2 = **Ac**, R^3 = **Ac**)	-0.30 (1747)	+0.41 (1763)	-0.71	-	-
3 [i]	-0.11 (1732)	+0.12 (1747)	-0.23	-61°	4.8
4a (R = **Ac**) [i]	+0.11 (1740)	-0.088 (1751)	+0.20	+60°	4.7
4b (R = **Bz**) [i]	+0.14 (1720)	-0.062 (1732)	+0.20	+60°	4.7
5 [i]	+0.044 (1736)	-0.045 (1755)	+0.09	+176°	4.4
6 [h]	-0.15 (1736)	+0.19 (1751)	-0.34	-61°	3.7
7 [i]	-0.020 (1712)	+0.083 (1736)	-0.10	-59°	7.3
8 [i]	-0.015 (1717)	+0.058 (1736)	-0.07	-120°	11.0
(*aS*)-**9** [g]	-1.01 (1697)	+0.75 (1724)	-1.76	-100°	3.1
(*aR*)-**9** [g]	+1.00 (1697)	-0.73 (1724)	+1.73	+100°	3.1

VCD measurement condition: 45 or 90 min accumulation, in $CDCl_3$, l = 100 μm, 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). [a] In M^{-1} cm^{-1}. [b] Amplitude of the VCD couplet, $\Delta\varepsilon_1 - \Delta\varepsilon_2$. [c] Dihedral angle defined by the two C=O of the most stable conformer. [d] Interchromophoric distance of the most stable conformer. [e] Only monosignate signal was detected. [f] No significant signal was detected. [g] DFT/B3LYP/6-311+g(d,p). [h] DFT/B3LYP/6-31g(d). [i] MMFF94.

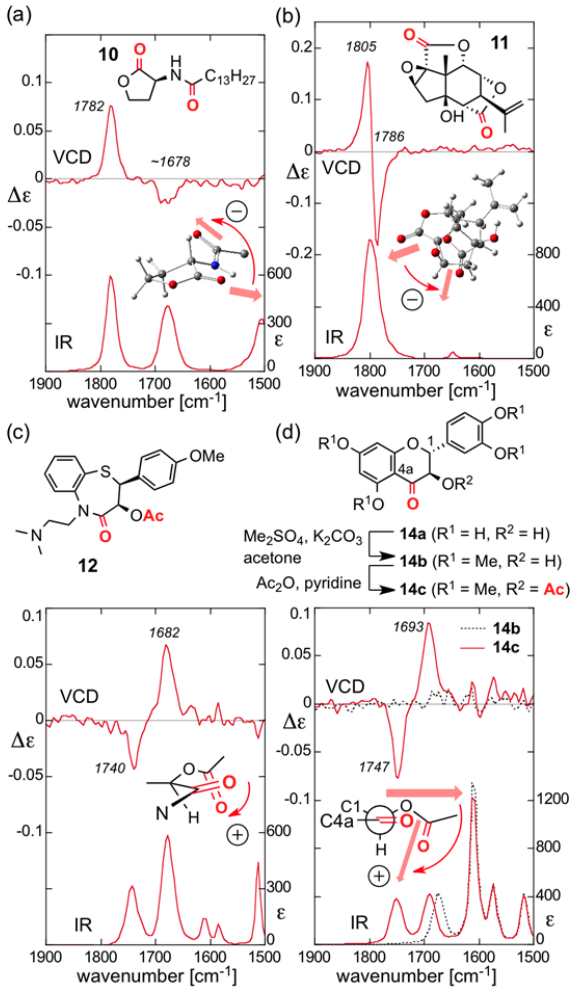

Figure 3. The VCD (top) and IR (bottom) spectra and the arrangement of two carbonyl chromophores of natural products and

drugs. The IR and VCD spectra were measured for 2 and 90 mins, respectively, in $CDCl_3$ (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,[2b,11] 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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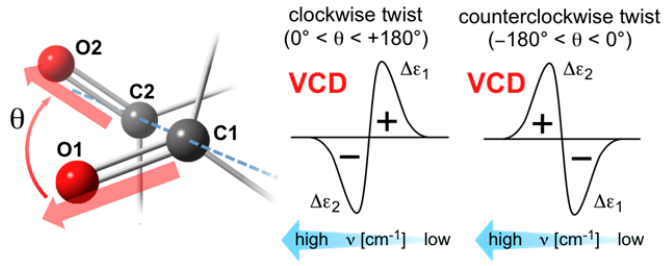
O2
C2
θ
O1
C1
clockwise twist
(0° < θ < +180°)
VCD
Δε1
+
−
Δε2
high ν [cm-1] low
counterclockwise twist
(−180° < θ < 0°)
VCD
Δε2
+
−
Δε1
high ν [cm-1] low