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ARTICLE

Vibrational circular dichroism spectroscopy in the C-D, X≡Y, and X=Y=Z stretching region

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Vibrational circular dichroism (VCD) spectroscopy is a powerful technique for structural analysis of chiral molecules, but information available from VCD spectra of large molecular systems can be limited by severe overlap of vibrational bands. While common chiral molecules do not absorb in the 1900-2400 cm^{-1} region, observation of VCD signals in this spectrally-isolated region is possible for molecules containing C-D, X≡Y, and X=Y=Z chromophores. Thus, a strategic introduction of these chromophores to a target molecule may produce VCD signals informative for molecular structures. VCD spectroscopy in the 1900-2400 cm^{-1} region is a rather unexplored research field and its basic properties remain to be investigated. This perspective article discusses insight obtained so far on the usefulness and physicochemical aspects of VCD spectroscopy in this region with briefly summarizing previous experimental VCD studies including classic examples as well as our recent results. We show that anharmonic effects such as overtones and combination bands often complicate VCD patterns. On the other hand, some molecules exhibit characteristic VCD signals that can be well interpreted by harmonic DFT spectral calculations for structural analysis. This article also discusses several examples of the use of this region for studying solute-solvent interactions and for VCD signal augmentation.

Introduction

VCD spectroscopy measures the difference of the absorptions of a chiral sample toward left- versus right-circularly polarized infrared light. The last two decades have witnessed many applications of this technique for analysis of molecular structures.[1] In particular, VCD spectroscopy with using *ab initio* spectral calculations has proven effective for elucidation of the absolute configuration of various synthetic and naturally-occurring small molecules.[2] VCD spectroscopy presents several advantages over other techniques such as X-ray crystallography and NMR spectroscopy. (1) VCD spectroscopy is highly sensitive to molecular three-dimensional structures: even subtle conformational changes may drastically alter the VCD spectrum of small molecules. (2) VCD spectra can be predicted by density functional theory (DFT) calculations with high accuracy. (3) VCD study of a solution-state sample enables the analysis of the equilibrated ensemble of fast interconverting conformers. (4) Chiral molecules usually exhibit VCD signals in the 2700-4000 cm^{-1} and below 1900 cm^{-1} regions (sometimes referred to as hydrogen-stretching and mid-IR regions, respectively) originating from fundamental vibrational modes without introduction of additional chromophores. Furthermore, the usefulness of VCD spectroscopy has been fueled by new theoretical approaches to better interpret spectra[3] and by newly established spectra-structures relationship.[4]

However, the capability of VCD spectroscopy has been restricted by the limited amount of experimentally observable signals. Because, as stated in (4), the fundamental vibrational modes of common functional groups show absorptions only in the 2700-4000 cm^{-1} and below 1900 cm^{-1} regions, severe overlap of vibrational bands may occur for the VCD spectra of bigger molecules. Thus, although the advantages (1) and (3) hold true for small molecules, spectral differences may not be significant for subtle structural changes of bigger molecules, as this point was already discussed for a Raman optical activity (ROA) study.[5]

A possible approach to increase the amount of structural information is the use of the 1900-2700 cm^{-1} region. While few chromophores exhibit their fundamental vibrational modes in the 2400-2700 cm^{-1} region, vibrational signals in the 1900-2400 cm^{-1} region can be observed in the presence of carbon-deuterium (C-D), X≡Y, and X=Y=Z chromophores (Fig. 1a). However, because such chromophores are not present in common (bio)molecules, VCD in the 1900-2400 cm^{-1} region has poorly been studied. Studies in this region have also been hampered by the limited accessible spectral range of VCD spectrometers. In fact, many of the currently used FT-VCD spectrometers are optimized only for the mid-IR region. On the other hand, this wavenumber region has extensively been studied by non-chiroptical vibrational techniques. Raman imaging technique has unveiled the biological behaviors of medicines and biomolecules labelled with cyano groups, alkynyl groups, and deuterium atoms.[6] The 1900-2400 cm^{-1} chromophores have also been used in biomolecular IR studies

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including those using femtosecond measurements.[7] VCD technique should also be benefited by the 1900-2400 cm^{-1} region such as its application to structural analysis of bigger (bio)molecules.

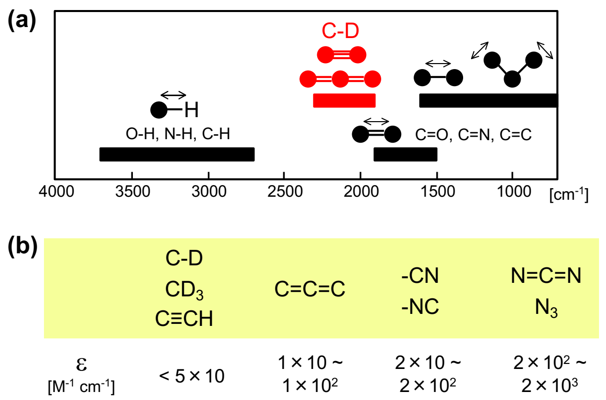


Fig. 1 (a) Carbon-deuterium (C-D), X≡Y, and X=Y=Z chromophores show vibrational signals in a region where fundamental vibrational modes of common (bio)molecules do not absorb. (b) Approximate IR intensities (in ε) of representative chromophores in the 1900-2400 cm^{-1} region.

The higher-frequency vibrational region was the only accessible region by prototypical dispersive scanning VCD spectrometers. This made stretching modes of C-H, N-H, and O-H as well as their isotopic C-D, N-D, and O-D the focus of the early VCD studies. While these studies led to the formation of several theoretical models that were useful before the establishment of DFT calculations,[1a] apparent anharmonic contributions often obscured spectral interpretations. The advent of FT-VCD spectrometers and DFT VCD calculations shifted the focus of studies to the mid-IR spectra, which display a bigger number of signals and are easier to interpret. Our group have recently revisited the 1900-2400 cm^{-1} spectral region for our interest in physical chemistry phenomena therein and its application to structural analysis. We have studied the VCD spectra of molecules containing deuterium, nitrile, isonitrile, alkyne, azido, allene, and carbodiimide functional groups. This perspective article reviews this rather unexplored area of VCD studies and discusses its usefulness for structural analysis. We also show several cases where spectral interpretation was difficult due to anharmonic contributions. Basic physicochemical aspects of VCD spectroscopy in this region are yet to be investigated, but insights obtained so far on anharmonic contributions, signal enhancement, analysis of solute-solvent interactions are also briefly summarized.

Experimental and theoretical aspects

Commercially available instruments are usually optimized for or run only for measurement below 2000 cm^{-1} in terms of optical filter, detector, and the frequency of photoelastic modulator. Moreover, vibrational signals of some of chromophores are intrinsically weak and thus are difficult to detect. Chromophores composed only of hydrogen, deuterium, and carbon atoms show especially weak IR absorptions (Fig. 1b). Consequently, VCD spectra in this region are not commonly reported even when measured molecules contain C-D, X≡Y, or X=Y=Z chromophores. For example, among 6 papers on VCD measurements on chiral allenes,[8] only 3 of them[8a, 8e, 8f] reported their C=C=C antisymmetric stretching VCD signal at around 1950 cm^{-1}. Note that low IR intensity does not necessarily lead to weak VCD signal. In fact, some of allenes produced a sufficiently strong C=C=C stretching VCD signal despite the weak IR absorptions.

Those interested in measuring VCD signals in the 1900-2400 cm^{-1} region are advised to first examine the reliability of their VCD spectrometer in this wavenumber range. This can be done by confirming the mirror-image relationship of VCD spectra measured for a pair of enantiomers. Few of commercially available compounds are suitable for this purpose and thus one may need support from synthetic chemists. For the case of our FT-VCD instrument, its optical system was optimized using synthetic D- and L-glucoses with multiple CD$_3$ groups. See the mirror-image VCD patterns of enantiomeric pairs **12α**/***ent*-12α** and **12β**/***ent*-12β**.

Vibrational spectra in this region may be associated with obvious anharmonic effects (e.g., overtone and combination bands). The degree of anharmonicity depends on the molecular structures. For example, C≡N group has been known to show a high degree of anharmonic effects compared to N$_3$ group.[9] Anharmonic effects are sometimes more pronounced in VCD spectra than in the corresponding IR spectra (see the spectra of **19**). Future systematic studies on anharmonic DFT calculations along with consideration for minimizing computational errors due to solute-solvent interactions, conformer sampling, the choice of functionals, etc. should facilitate interpretation of spectra in this region.

C-D chromophores

C-D stretching modes are the most studied vibrations by VCD spectroscopy in the 1900-2400 cm^{-1} region. One of the first molecules studied by VCD spectroscopy is a mono-deuterated neopentyl chloride reported in 1974 (**1a**).[10] The chloride **1a** was reinvestigated along with its bromide (**1b**) in 1984 (Fig. 2).[11] The C-D stretching VCD signals have also been observed for other small molecules such as cycloalkanes **2**-**4**,[12] an oxirane **5**,[13] cycloalkanones **6**-**8**,[14] a lactone **9**,[15] and phenylethanes **10**.[16] A slightly bigger molecule **11** was recently studied using a FT-VCD spectrometer and harmonic DFT calculations.[17] Isotopologues of bigger (bio)molecules have not been reported except for a small set of deuterated mono- and disaccharides (Fig. 3)[18] despite the establishment of efficient reactions to prepare various deuterated molecules.[19] VCD studies of deuterated bioactive molecules should gain more importance with the increasing trend in the development of deuterated medicines: deutetrabenazine and deucravacitinib are approved by FDA and several deuterated drug candidates are under clinical studies.[20]

As it can be approximated by Hooke's law, replacement of a carbon-hydrogen bond to a carbon-deuterium bond results in the red-shift of its stretching absorption from *ca.* 3000 cm^{-1} to *ca.* 2100 cm^{-1}. Isotopic labelling does not largely affect the electric dipole transition moment (EDTM) and magnetic dipole transition moment (MDTM) associated with a vibrational mode. Thus, in case interested C-H stretching modes are independent from other vibrational modes, one may expect to see similar sign and intensity VCD patterns with different wavenumbers for the original C-H molecule and the C-D isotopologue. Ideally, this leads to isolation of the C-D stretching VCD signals of interest in the 1900-2400 cm^{-1} region and, if the molecule is small enough, simplification of the VCD spectra in the C-H stretching region.[12a] In a more realistic scenario, C-H and C-D stretching modes are often combined with overtones and other vibrational modes and show complicated spectral patterns. Some of the reported VCD spectra in the 1900-2400 cm^{-1} region are severely perturbed by anharmonic effects as discussed in each reference.[14a, 14b, 16-17]

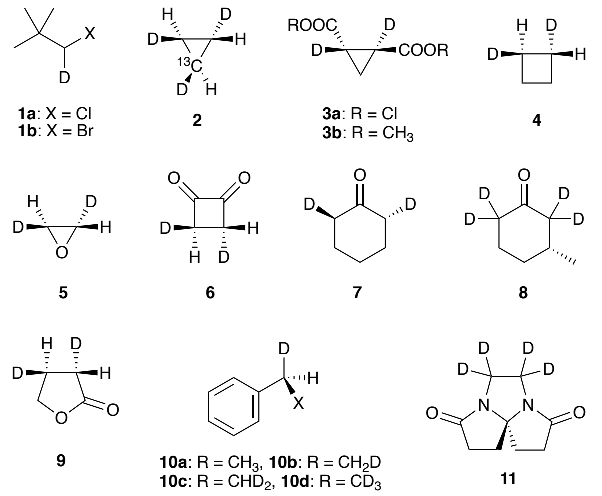


Fig. 2 Examples of deuterated chiral molecules whose experimental VCD spectra in the C-D stretching region were reported. Enantiomers of some molecules shown here were also studied.

When properly used, C-D chromophores yield VCD signals informative for molecular structures without significant anharmonic influence even for complex molecules. Our recent study explored the potential of a CD_3 group as a VCD chromophore for structural analysis. In this study, a CD_3 group was introduced at the C-1 position of various sugars with either α or β configurations.[18] Their VCD spectra were measured using DMSO-h_6 solvent. Fig. 3a-f shows the structures and experimental vibrational spectra of the C-1 epimeric pairs of selected sugars **12**-**16**. These molecules showed two major VCD bands at around 2065 cm^{-1} and 2210 cm^{-1} corresponding to symmetric and antisymmetric CD_3 stretching vibrations, respectively. Importantly, each C-1 epimeric pair exhibited almost mirror-image VCD spectra even though these are not enantiomers. The 1*S* epimers showed a positive VCD signal for symmetric CD_3 stretching and a negative one for antisymmetric CD_3 stretching whereas the 1*R* series showed VCD signals with the opposite sign. These VCD patterns are consistent for each of the tested sugars despite the differences of the configurations and substituents of other chiral centers. Even for an epimeric pair of a disaccharide with 10 chiral centers (**16α** and **16β**), their VCD signals reflected the stereochemistry solely of the C-1 position. These results suggested the usefulness of CD_3 chromophore for providing local structural information of a selected site of complex molecules as well as for establishing an empirical spectra-structures relationship in a spectrally isolated region. Furthermore, these C-D stretching VCD patterns were accurately predicted by harmonic DFT calculations (Fig. 3g). Thus, a strategic use of C-D chromophores in combination with DFT spectral calculations should lead to structural elucidation even without prior knowledge on a spectra-structures relationship.

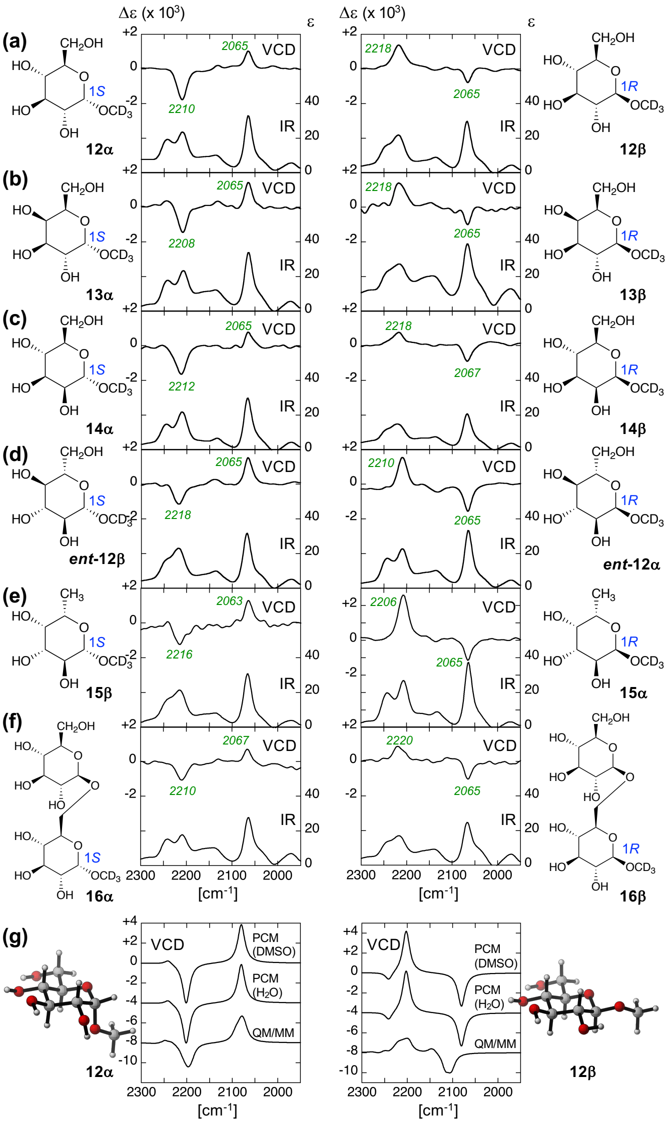


Fig. 3 VCD and IR spectra of epimeric pairs of representative sugars with a CD_3 group. Observed VCD and IR spectra of (a) methyl-d_3 α- and β-D-glucopyranosides (**12**), (b) methyl-d_3 α- and β-D-galactopyranosides (**13**), (c) methyl-d_3 α- and β-D-mannopyranosides (**14**), (d) methyl-d_3 β- and α-L-glucopyranosides (***ent*-12**), (e) methyl-d_3 β- and α-L-fucopyranosides (**15**), (f) methyl-d_3 β-D-glucopyranosyl-(1'→6)-α- and β-D-glucopyranosides (**16**). 1*S* epimers are shown in the left and 1*R* series is shown in the right. Wavenumbers at the extrema of observed VCD signals are labelled in italic. Measurement conditions: *c* 0.5-2.0 M in DMSO-h_6, *l* 50 μm. (g) Calculated VCD for **12α** and **12β** with considering solvent effects as PCM (for DMSO and for H_2O) or using QM/MM conditions for explicit *ca.* 100 water molecules. Frequency scaling factor: 0.955. Reproduced from Ref. 18 with permission from the Royal Society of Chemistry.

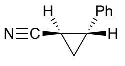
Another utility of VCD signals of C-D stretching modes is to analyze solute-solvent interactions. This could be done by observing an induced VCD signal originating from achiral solvent molecules interacting with chiral solute molecules.[21] Deuterated solvents are commonly used for VCD measurements and whereas common solute molecules do not absorb in the 1900-2400 cm^{-1} region, which makes this region suitable for detection of induced VCD signals. For example, a solution of (*S*)- or (*R*)-camphor in $CDCl_3$ was reported to show a VCD signal at around 2250 cm^{-1}. This signal was well reproduced by harmonic DFT calculations considering a 1:1 camphor-$CDCl_3$ complex with a hydrogen bond C=O••D-CCl_3.[22] An induced VCD signal was observed also for a $CDCl_3$ solution of pulegone.[23] A VCD study on a DMSO-d_6 solution of a helical poly(phenylacetylene) found that the helicity of the polymer was transferred to the solvation sphere. The induced helicity of the DMSO-d_6 solvents was detected as strong VCD signals originating from their CD_3 stretching modes.[24]

X≡Y chromophores

IR absorptions in the 1900-2400 cm^{-1} region have historically been important for characterization of triple bonds of organic molecules. Cyano and alkynyl groups have found their use as biomolecular IR and Raman probes (vibrational labelling).[6a, 6b 7a 7c] Introduction of these groups to biomolecules yields structurally linear C-C≡N and C-C≡C- moieties and thus this process does not increase the number of conformers. Furthermore, the EDTMs of the C≡N and C≡C stretching modes are assumed to exist along the C-C≡N and C-C≡C- axes. These properties make the signal interpretation of their stretching modes easier compared to rotatable chromophores. Here we discuss chromophoric properties of cyano (-CN), isocyano (-NC), and alkynyl (-C≡C-) groups for VCD studies.

Nitrile

Cyano group (-CN) is a chemically stable functional group and has been incorporated into drug molecules.[25] It exhibits a moderately strong IR absorption with its maximum at around 2250 cm^{-1}. IR studies on nitriles have indicated anharmonic effects on their vibrational signals.[9] VCD signals of C≡N stretching mode have been reported for (-)-*trans*-2-phenylcyclopropanecarbonitrile (**17**), (+)-*trans*-1,2-cyclopropanedicarbonitrile (**18**), and (*R*)-2-chloropropionitrile (**19**).[12a, 26] These simple molecules showed a monosignate C≡N stretching VCD signal without severe anharmonic perturbation. Anharmonic DFT calculations of **19** overestimated the the intensities of the IR and VCD signals of the C≡N stretching mode, whose cause is yet to be studied.[26b]



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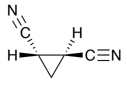

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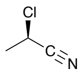

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We measured 1,1'-binaphthalene-2,2'-dicarbonitrile (**20**) to study VCD signals originating from interactions between two C≡N chromophores.[27] Chromophoric interactions of two carbonyl groups with non-coplanar orientation are known to exhibit a pair of positive and negative VCD signals in the C=O stretching region.[28] While this phenomenon has classically been known as the coupled oscillator model,[29] its usefulness for structural analysis has been demonstrated by many researchers in the last decade.[30] Axially chiral **20** was designed to have a rigid structure with the two cyano groups in a close vicinity and in an almost orthogonal orientation (the interchromophoric distance *r* as 4.3 Å and the dihedral angle θ as +97°). Harmonic DFT calculations of **20** predicted a pair of lower-frequency negative and higher-frequency positive VCD signals (Fig. 4a). Nevertheless, its experimental VCD spectrum exhibited a moderately strong but complex pattern. We ascribed the observed complex features to anharmonic effects. Unlike a simple VCD couplet observed for carbonyl groups, VCD signals originating from two interacting cyano groups are not readily used for structural analysis. To obtain more insight into the nature of its anharmonic VCD signals in the 1900-2400 cm^{-1} region, the VCD spectrum of mononitrile **21** was also measured. It showed a more than 10 times weaker VCD signal (Fig. 4b). Comparison of the VCD spectra of **20** and **21** provided an experimental proof of the enhancement of anharmonic VCD intensities by chromophoric interactions.

The anisotropy factor *g* (a value obtained by $\Delta\varepsilon/\varepsilon$) of the C≡N stretching mode of **17**-**20** is at an order of 10^{-5}, a value commonly seen for VCD signals of small molecules. Much higher VCD intensities were reported for a CN^{-} complex of myoglobin. CN^{-} ligated to heme iron of myoglobin exhibited an anisotropy factor *g* of *ca.* $+2.8 \times 10^{-3}$.[31] This point is further discussed in the section of azide.

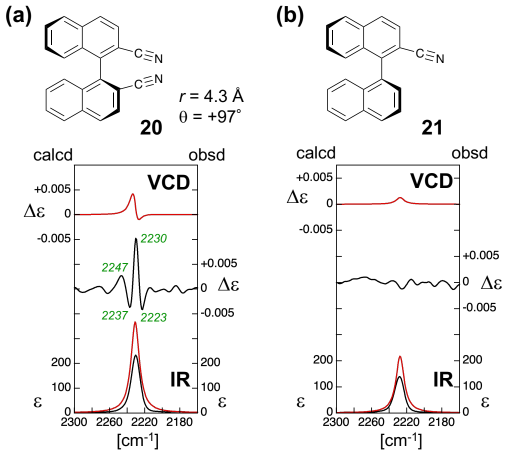


Fig. 4 VCD and IR of experimental (black) and harmonically calculated (red) spectra of (a) **20** and (b) **21**. The interchromophoric distance *r* and the dihedral angle defined by two chromophores θ are shown for **20**. Wavenumbers at the extrema of experimental VCD signals are labelled in italic. Measurement conditions: *c* 0.2 M in $CHCl_3$, *l* 50 µm (for **20**) or 100 µm (for **21**). Frequency scaling factors: 0.951 (for **20**) or 0.950 (for **21**). Reproduced from Ref. 27 with permission from the PCCP Owner Societies.

Isonitrile

VCD signals of isocyano group (-NC) had not been explored due to its chemical instability and the relative difficulties in preparation of isonitriles with a chiral scaffold. For the same reasons this functional group has rarely been used as an IR probe.[32] We nevertheless studied the VCD spectra of diisonitrile **22** to unveil the basic properties of isocyano chromophore. In a similar manner to structurally related **20**, harmonic DFT calculations of **22** predicted a simple VCD couplet for -NC stretching vibrations while its experimental spectrum presented a complex pattern (Fig. 5a).[27] In addition, its experimental IR spectrum showed a wider skirt on the higher frequency side, which is indicative of anharmonic effects. Our preliminary anharmonic DFT calculations of **22** using GVPT2 predicted a theoretical VCD spectrum that moderately reproduced the observed VCD features. Further exploration of computational conditions may enable extraction of structural information even from complex anharmonic VCD signals.

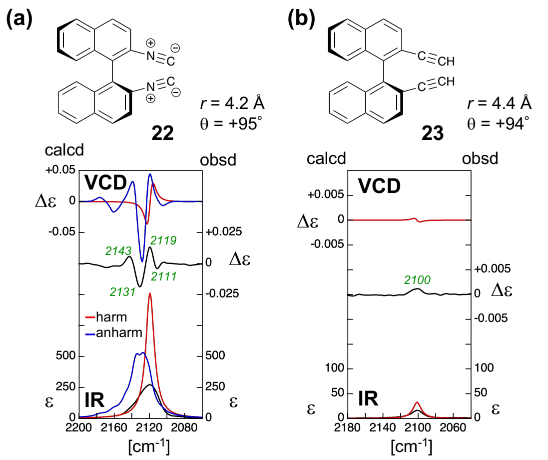
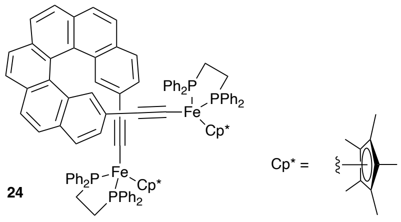


Fig. 5 VCD and IR of experimental (black) and calculated (red for harmonic DFT and blue for anharmonic DFT) spectra of (a) **22** and (b) **23**. The interchromophoric distance *r* and the dihedral angle defined by two chromophores θ are shown. Wavenumbers at the extrema of experimental VCD signals are labelled in italic. Measurement conditions: *c* 0.2 M in CHCl$_3$ (for **22**) and 0.6 M in CHCl$_3$ (for **23**); *l* 50 µm. Frequency scaling factors: 0.966 (for **22**, harmonic), 0.987 (for **22**, anharmonic) or 0.952 (for **23**). Reproduced from Ref. 27 with permission from the PCCP Owner Societies.

Alkyne

Alkyne is a chemically stable group and its C≡C stretching mode exhibits strong Raman intensity suitable for biological Raman studies.[6a] Meanwhile, due to the non-polar nature of C≡C bond, this mode results in small EDTM and thus a weak IR signal. Our work attempted to observe C≡C stretching VCD signals of **23**. We hoped that its VCD signals be augmented by interactions between two alkynyl groups; however, its experimental spectra showed a barely detectable positive VCD signal at 2100 cm^{-1} (Fig. 5b).[27]

While detection of VCD signals of C≡CH group seems difficult, the alkynyl-iron system in helicene **24** showed a strong signal at 2046 cm^{-1} (ε 8 × 10^2, $\Delta\varepsilon$ *ca.* 0.25).[33] Interestingly, oxidized species of **24** (labelled as **24**$^{\bullet\bullet 2+}$) exhibited further stronger VCD signals with a 30-times increase in its anisotropy factor *g* (from 3 × 10^{-4} for **24** to 10^{-2} for **24**$^{\bullet\bullet 2+}$). The IR spectrum of **24**$^{\bullet\bullet 2+}$ showed split signals at 2032 and 1996 cm^{-1}, which were ascribed as Fermi coupling. The origin of the signal enhancement was discussed in terms of a stronger MDTM brought by the presence of electron spin density in the C≡C-Fe moieties, whereas it should be associated also with the low-lying electronically excited states.[34]



X=Y=Z chromophores

The absorption band of the antisymmetric stretching mode of X=Y=Z appear in the 1900-2400 cm^{-1} region. As discussed so far, some chromophores such as CD$_3$ group are capable of extracting stereochemical information of target molecules. Some of X=Y=Z groups, however, are not appropriate for this purpose when the groups themselves are axially chiral. Such an axially chiral X=Y=Z system produces VCD signals even in the absence of other chiral centers. Here we discuss allene (C=C=C), carbodiimide (N=C=N), and azido (N$_3$).

Allene and carbodiimide

X=Y=Z system may become axially chiral when X and Z are connected to other atoms via single bond. While allene has been famous as a chiral species,[35] our group, for the first time, succeeded in preparing carbodiimides (N=C=N) with one-handed axial chirality and in analysing their VCD spectra.[36] Because we recently reported a short article on the use of VCD spectroscopy for studying the stereochemistry of allenes and carbodiimides,[37] this perspective article only briefly discusses allene and carbodiimide chromophores.

The antisymmetric stretching of C=C=C shows relatively weak absorption at around 1950 cm^{-1}. Somewhat similar to the stretching mode of C≡CH, the vibrational mode of non-polar C=C=C yields a small EDTM. Consequently, some chiral allenes show an undetectably weak VCD signal. This may be the reason why only 3 articles, including ours, present antisymmetric C=C=C stretching VCD signals.[8a, 8e, 8f] Keiderling and coworkers discussed the C=C=C stretching VCD signal of 7 chiral allenes, most of which are 1-haloallenes.[8a] Liu, Toste and coworkers reported the VCD spectra in the 1000-2050 cm^{-1} region for five 1-fluoroallenes.[8e] Our recent study measured the C=C=C stretching VCD signals of more than 10 chiral allenes including allenic natural products.[8f] Comparison of the VCD spectra and the structures of the allenic molecules in these 3 articles suggested that electron-withdrawing and conjugating substituents enhance the VCD intensity of the C=C=C stretching mode.

The antisymmetric stretching of carbodiimide (N=C=N) generates a much stronger IR signal appearing at around 2100 cm^{-1}. However, because axially chiral carbodiimides were not available, no VCD studies on this molecular class had been reported until 2018. Our group demonstrated that a carbodiimide with one-handed axial chirality (**25**) exhibits a strong VCD signal (Fig. 6). The negative sign of its N=C=N antisymmetric stretching VCD signal reflects the *S* axial chirality of the carbodiimide moiety, which could readily be interpreted by harmonic DFT calculations.[36]

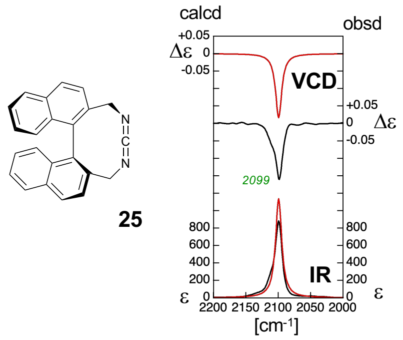


Fig. 6 VCD and IR of experimental (black) and harmonically calculated (red) spectra of **25**. Wavenumber at the extremum of the experimental VCD signal is labelled in italic. Measurement conditions: *c* 0.1 M in CDCl$_3$; *l* 50 μm. Frequency scaling factor: 0.955.

Azide

Many azido-containing biomolecular analogues are commercially available owing to the development of bioorthogonal azido-alkyne chemistry.[38] Azide is classified as a 1,3-dipole species as each nitrogen atom formally have a different charge state (-N=N^{+}=N^{-} ↔ -N^{+}-N=N^{-} ↔ other resonance structures). This dipolar charge state makes the EDTM of the antisymmetric stretching very strong even though azido group is, similar to allene, composed of the same atom. Its strong IR absorption and biocompatibility are suitable for biomolecular IR studies.[7b 9] Azido group as an IR probe is also advantageous due to the minor anharmonic contributions to the N_3 stretching absorption band.[39] The nitrogen atom connecting to a carbon atom in a C-N_3 moiety is *sp*^{2} hybridized and thus presents a bond angle of *ca.* 120°. The rotation of C-N_3 bond therefore produces different conformers, which may be considered as a drawback of azido group. When azido group is introduced to biomolecules, this conformational freedom should be considered for IR- and VCD-based structural analysis.

Our group has studied several nucleosides and their synthetic precursors containing an azido group.[40] Fig. 7 shows the VCD spectra of a pair of C-2 epimers of furanose derivatives **26a** and **26b**. The azido group of **26a** exists in the α face of the sugar ring while that of **26b** is in the β face. The difference in their orientation gave rise to the opposite signs of their N_3 stretching VCD signals at around 2100 cm^{-1}: **26a** showed a positive VCD signal whereas **26b** showed a negative one. This result is comparable to that of the CD_3 stretching VCD signals that solely reflected the stereochemistry of the chiral centre in the vicinity of CD_3 chromophore (Fig. 3).

The VCD intensity of N_3 stretching is enhanced by interactions between two azido groups. We studied the VCD spectra of diazido molecules, 2,2'-diazido-1,1'-binaphthyl (**27**) and methyl 2,3-diazido-2,3-dideoxy-4,6-*O*-benzylidene-α-D-altropyranoside (**28**).[27] Unlike the VCD signals of dicyano **20** and diisocyano **22**, these diazido molecules yielded a pair of positive and negative VCD signals (Fig. 8). The observed VCD couplets of **27** and **28** were readily reproduced by harmonic DFT calculations. Furthermore, these couplets were strong enough for the measurement at a much lower concentration (0.04 M, 50 μm) compared to concentrations for ordinary VCD measurements (for example, see the concentrations shown in the captions of Figs. 3 and 4). The results so far suggested that azido group is a promising VCD chromophore for extraction of stereochemical information of target molecule with higher sensitivity.

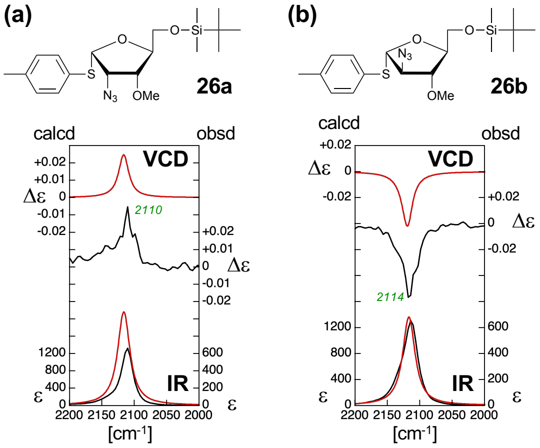


Fig. 7 VCD and IR of experimental (black) and harmonically calculated (red) spectra of (a) **26a** and (b) **26b**. Wavenumbers at the extrema of experimental VCD signals are labelled in italic. Measurement conditions: *c* 0.16 M in CDCl$_3$; *l* 100 μm. Frequency scaling factors: 0.945 (for **26a**) or 0.940 (for **26b**).

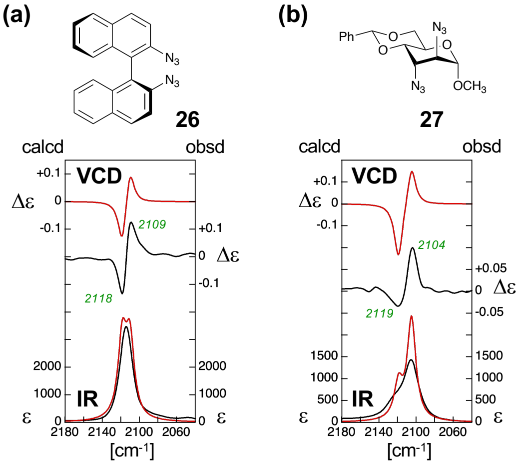


Fig. 8 VCD and IR of experimental (black) and harmonically calculated (red) spectra of (a) **27** and (b) **28**. Wavenumbers at the extrema of experimental VCD signals are labelled in italic. Measurement conditions: *c* 0.04 M in CDCl$_3$; *l* 50 μm. Frequency scaling factors: 0.930 (for **27**) or 0.927 (for **28**). Reproduced from Ref. 27 with permission from the PCCP Owner Societies.

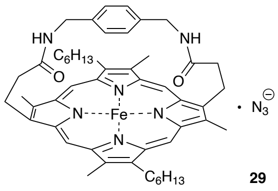


Fig. 9 Structure of an N_3^--chelated strapped porphyrin (**29**) studied in ref 43. The absolute configuration of its planar chirality and the orientation of the chelated N_3^- were not determined.

VCD signals of antisymmetric N_3 stretching have been observed also for Fe-N_3^- complexes. A pioneering VCD study on N_3^- ligated to the heme iron of hemoglobin by Marcott, Moscowitz and coworkers reported an exceptionally strong VCD signal.[41] This phenomenon was reinvestigated or reconfirmed for N_3^- complexes of hemoglobins, myoglobins, and metalloenzymes.[31, 42] For example, Teraoka, Sugeta and coworkers reported the anisotropy factor g of the N_3 stretching VCD signal of an N_3^- complex of metmyoglobin from horse skeletal muscle to be -7.8×10^{-4} (ε *ca.* 1200, $\Delta\varepsilon$ *ca.* -1, 2021 cm^{-1}).[31a] Interestingly, a CN^- complex of metmyoglobin yielded an even stronger CN stretching VCD signal but with the opposite sign (g $+2.8 \times 10^{-3}$, ε *ca.* 100, $\Delta\varepsilon$ *ca.* +0.2, 2127 cm^{-1}). The origin of the opposite VCD signs for the N_3^- and CN^- species is unclear. An enhanced VCD signal was observed for N_3^- ligated to a strapped iron porphyrin **29** even without an apo-protein (Fig. 9).[43] A crucial role of low-lying electronically excited states has been suggested as the cause of the amplified VCD signals seen for these molecular systems.[34]

Conclusions

While VCD spectroscopy is a powerful tool for structural analysis, most of its use has been limited to the hydrogen-stretching and mid-IR regions. Even when molecules with absorptions in the 1900-2400 cm^{-1} region are studied, their VCD spectra in this region have rarely been reported. This perspective article briefly summarises previous VCD studies in this spectral region and discusses the properties of 1900-2400 cm^{-1} chromophores. Some chromophores such as CD_3 and azido groups were found to yield VCD signals without obvious anharmonic contributions. Such experimental VCD signals were well interpreted by harmonic DFT calculations, which leads to structural analysis solely based on these VCD signals. Meanwhile, as encountered in many reported works, anharmonic contributions often hamper reliable spectral interpretation.

While a few physicochemical aspects of VCD spectroscopy in the 1900-2400 cm^{-1} region are described here, its basic properties largely remain to be investigated. For example, as seen for C-D and cyano chromophores, some molecules are severely affected by anharmonic contributions, while others are less perturbed. A clear relationship between molecular structures and the extent of anharmonic VCD contributions, which may be established by future systematic studies, should facilitate the application of VCD chromophores in this region. In addition, a versatile protocol for anharmonic DFT calculations is required to interpret, if observed, complex anharmonic VCD spectra. Amplification of VCD signals is also interesting as this phenomenon may be applicable for analysis of much smaller amount of samples. We hope this article be useful for performing further studies on this historically important but rather undeveloped research field to expand the capability of VCD spectroscopy as a tool to study molecular structures and physical chemistry.

Conflicts of interest

There are no conflicts to declare.

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