VCD

Vibrational Circular Dichroism

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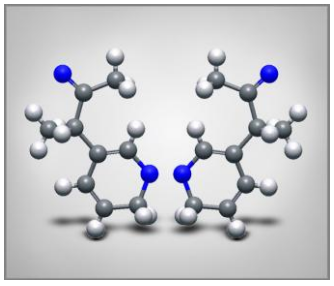
General Description of VCD

Vibrational circular dichroism (VCD) is no longer a curious novelty in the field of molecular spectroscopy. After recently celebrating twenty years of development since its early years of discovery, VCD has matured to a point where the phenomenon is well understood theoretically, can be measured and calculated routinely, and is being used to uncover exciting new information



about the structure of optically active molecules. Beyond this, VCD has been shown to be a sensitive, non-invasive diagnostic probe of chiral purity or enantiomeric separation with potential use in the synthesis and manufacture of chiral drugs and pharmaceutical products. In descriptive terms, VCD is the coupling of optical activity to infrared vibrational spectroscopy. More specifically, VCD spectra are vibrational difference spectra with respect to left and right circularly polarized radiation. The essence of VCD is to combine the stereochemical sensitivity of natural optical activity with the rich structural content of vibrational spectroscopy. The result of a VCD measurement is two vibrational spectra of a sample, the VCD and its parent infrared spectrum. These can used together to deduce information about molecular structure. The principal area of application of VCD is structure elucidation of biologically significant molecules including peptides, proteins, nucleic acids, carbohydrates, natural products and pharmaceutical molecules; also, as mentioned above, it has growing potential as a chiral diagnostic probe. VCD complements the relatively slow time scale of NMR since molecular vibrations and conformational sensitivity occur in the subpicosecond time domain. VCD is also complementary to X-ray crystallography by virtue of its applicability to molecules in gas, liquid and solution phases.

Definition of VCD

VCD is a specific way of measuring natural optical activity. The measurement of VCD involves determining the differential response of a chiral molecule to left and right circularly polarized radiation. In Fig.1 we illustrate this interaction in a general way. It can be seen that both left and right forms of circularly polarized radiation and a pair of enantiomeric molecules exhibit mirror-image relations with respect to their partners. If the optical activity for molecule (+) is defined as the intensity difference for right minus left circularly polarized radiation, namely

$$\Delta I = I_R(+) - I_L(+)$$

then it follows by mirror symmetry that the opposite optical-activity spectrum is obtained when the mirror-image molecule is used, namely molecule , so that

$$-\Delta I = I_R(-) - I_L(-)$$

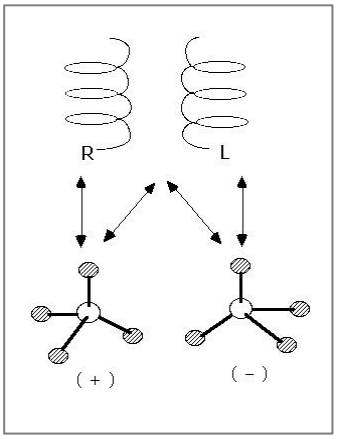


Fig. 1

Also by mirror symmetry from Fig.1, the optical activity can be measured, albeit more awkwardly, by using a fixed form (L or R) of circularly polarized radiation and changing between mirror-image pairs of molecules as

$$\Delta I = I_R(+) - I_R(-)$$

$$\Delta I = -\left[I_L(+) - I_L(-)\right]$$

where the latter relation is supported by the mirror-image equivalence of the following relations (ignoring the effect of the charge conjugation and parity violation)

$$I_R(+) = I_L(-)$$

and

$$I_R(-) = I_L(+)$$

The sensitivity of optical activity to mirror-symmetry properties of chiral molecules is the source of its remarkable ability to specify absolute stereochemical properties of chiral molecules in solution. VCD is defined simply as the difference in the absorbance of a chiral sample for left versus right circularly polarized infrared radiation,

$$\Delta A = A_L - A_R$$

If the pathlength and concentration are known, VCD can be expressed in terms of the difference in absorptivity () as

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R$$

The physical process associated with VCD can be illustrated in terms of transitions between vibrational energy levels g0 and g1, for a fundamental transition of a normal mode of vibration in the ground electronic state, as shown in Fig.2. It can be seen that VCD is associated with simple one-photon quantum transitions induced by left or right circularly polarized radiation.

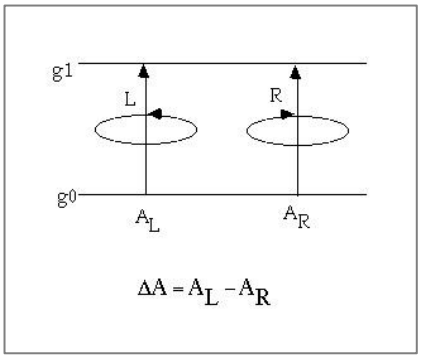


Fig. 2

Theory of VCD

In the previous section, we provided operational definitions of VCD in terms of how it is measured. Here we provide the theoretical basis for VCD at an elementary level. The sign and magnitude of VCD is conveniently expressed as the dimensionless anisotropy ratio, g, defined as the ratio of the experimental VCD band absorbance to the experimental infrared band absorbance. This same ratio can be expressed theoretically as 4 times the rotatory strength, R, divided by the dipole strength, D. The rotatory strength is the imaginary part of the scalar (dot) product of the electric dipole transition moment onto the magnetic dipole transition moment, and the dipole strength is the absolute square of the electric dipole transition moment. These relations can be expressed as

$$g = \frac{\Delta\varepsilon}{\varepsilon} = \frac{4R}{D} = \frac{4\,\mathrm{Im}\left(\vec{\mu}\cdot\vec{m}\right)}{\left|\vec{\mu}\right|^2}$$

$$g = \frac{4\,\mathrm{Im}\left(\mu_\alpha m_\alpha\right)}{\mu_\alpha^{*}\mu_\alpha}$$

where the last ratio in Eq. (7) is given in Cartesian component notation where repeated Greek subscripts are summed over the coordinate directions x, y and z. It can be seen that the dipole strength is always positive and the rotatory strength can be either positive or negative depending on the relative directions of the electric and magnetic dipole transition moments. VCD arises

from the combined effect of linear (electric-dipole) and circular (magnetic-dipole) oscillation of charges during vibrational motion, whereas ordinary infrared absorption is sensitive only to the linear oscillation of charge. MEASUREMENT OF VCD In Fig.3 we illustrate some very basic aspects of the measurement of VCD and ROA. For VCD the source is thermal, such as a SiC glower, or an electric arc as in a xenon lamp. In one instance, an infrared diode laser has been used successfully for VCD measurement, but there the application was chiral detection in high-performance liquid chromatography at a fixed frequencies, spectral measurement was not emphasized. In VCD measurement, the spectrometer, either a dispersive grating monochromator or a Fourier transform infrared (FT-IR) spectrometer, precedes the polarization-modulation stage of the instrument. The creation or selective detection of left (LCP) and right circularly polarized (RCP) radiation is carried out with the combination of a polarizer and modulating quarter-wave plate. The modulating waveplate is a photo-elastic modulator (PEM) operating between 35 and 60 kHz. After the infrared radiation passes through the sample, it is focused on a liquid-nitrogen-cooled InSb or HgCdTe (MCT) detector which is fast enough to follow the high frequency of the polarization modulation. The processing electronics employ lock-in amplifiers, and in the case of FT-VCD also necessarily involve digitization, phase correction and Fourier transformation, all prior to spectral presentation. A standard measure of performance of FT-VCD spectrometers is the mid-infrared VCD spectrum of S-(-)–pinene, as shown in Fig.4. This spectrum was obtained from a 20-minute collection of the single enantiomer on the Chiralir VCD Analyzer. The noise level was approximately 10-5 absorbance units, as shown by a separate spectral line above the VCD spectrum. The VCD spectrum was calibrated with a CdSe quarter-waveplate and a BaF2 wire-grid polarizer. No baseline corrections were applied to the VCD spectrum. The resolution was 4 cm-1 and the pathlength was 70 µm.

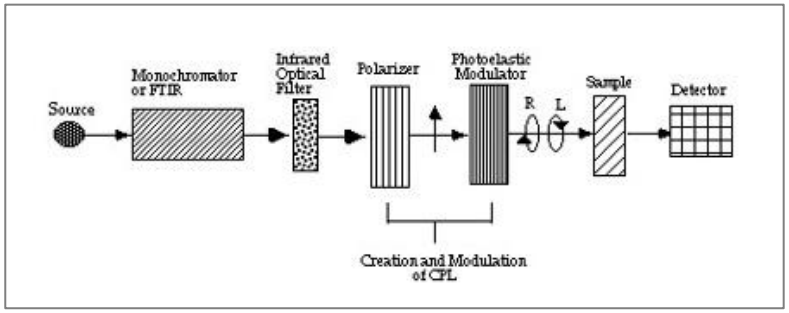


Fig. 3

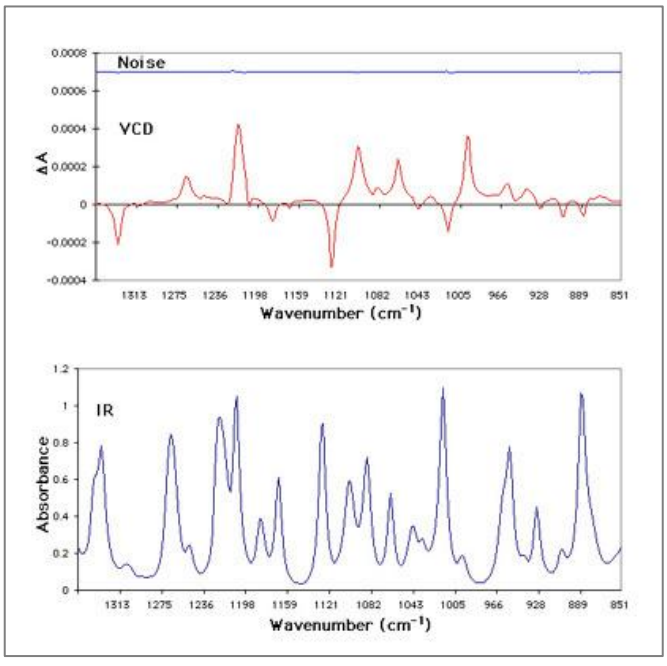


Fig. 4

Interpretation of VCD

VCD spectra can be interpreted on several levels. The simplest is the empirical level, in which VCD features are associated with a region of vibrational frequencies or normal mode of vibration in a molecule of known absolute configuration. Empirical correlations are then sought in the VCD spectra of similar molecules for similar modes or regions of the spectrum. This practice leads to the identification of marker bands that are diagnostic of particular functional groups in a given stereochemical environment. During the early days of discovery of VCD, this was virtually the only method of spectral interpretation. A more sophisticated level of empirical analysis is the statistical approach using, for example, principal components (PC) and factor analysis. In this approach, a set of spectra of samples with known characteristics is used as a training set; these spectra are then reduced to a series of orthogonal PCs of decreasing significance. An unknown spectrum can then be decomposed, or factored, into the set of PCs, and by the relative PC-weighting coefficients is correlated with spectra of known structural or conformational features. This approach takes the guess-work out of empirical correlation and provides an impartial statistical approach to the correlation of spectra among themselves and to known molecular-structure motifs. Beyond empiricism is spectral interpretation by model calculations. Here, there is an attempt to understand the VCD spectral features in terms of vibrational motion and response of electronic charge in molecules to that motion. There are two classes of models. Those that use only a molecular fragment to isolate particularly simple vibrational motions, such as the coupling, in- and out-of-phase, of similar, juxtaposed vibrational oscillators. The so-called coupled-oscillator model of VCD can be used to interpret dominant spectral features in a localized vibrational region. In principle, these models allow the prediction of the absolute stereochemistry associated with the coupled vibrational transition moments. The second class of VCD models are those based on approximate models of the electronic contribution to the VCD magnitude applied to a full normal-coordinate calculation of the vibrational modes of the molecule. These models predict the complete VCD spectrum. They have achieved only moderate success and suffer from uncertainties in the approximations associated with both electronic modeling and vibrational analysis, which is typically empirical in nature. The most powerful and successful approach to the interpretation of VCD spectra is through ab initio quantum-mechanical calculations. Aside from the approximations inherent in the quantum calculations themselves, for instance choice of basis functions, Hartree-Fock or beyond, etc., the equations governing VCD are calculated without modeling approximations. In addition, the equilibrium geometry of the molecule and the resulting vibrational force field are also obtained in the course of the ab initio calculation. For molecules with well-defined conformational structures, ab initio VCD calculations can be carried out with excellent correspondence to the experimental spectrum. In all cases, virtually all bands are predicted with the correct sign and close to the correct relative intensity. Even better results can be obtained through the use of density functional theory or when electron correlation is included. In these cases the improvements occur primarily through the force field and the description of the vibrational modes of nuclear motion. To date, this has been accomplished through the MP2 level for several molecules. Below we give two examples of the comparison of experimental VCD spectra to the results of ab initio calculations in which we seek new information about the conformation of chiral molecules in solution. In Fig.5, we illustrate the comparison of experimental to ab initio determined VCD spectra for (1S,2R)-N-methylephedrine in the OH stretching region using the locally distributed or igin gauge approximation. The experimental spectrum was obtained with a scanning dispersive VCD instrument as a 0.01 M solution in C2Cl4. The molecular orbital calculations were performed using the Gaussian 90 program package with a 6-31G* basis set. The

calculations predict two most-stable conformers, one with an OH…N intramolecular hydrogen bond and another with a free OH group, as shown in Fig.5. The VCD spectra were calculated using the sum-over-states, vibronic coupling theory (VCT) method for the two conformers, weighted as 90% for intramolecularly-hydrogen-bonded species and 10% for the free-OH species. The results show very close agreement between experiment and theory, and thus provide strong evidence that these two conformers are present in C2Cl4 solution under these conditions.

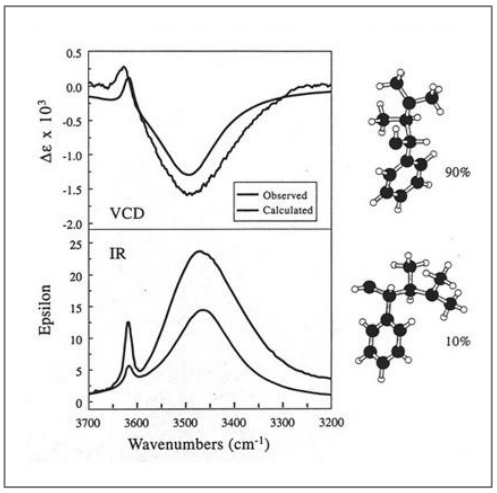


Fig. 5

Applications of VCD

In the last section we looked at how VCD spectra can be interpreted. In this section, we carry the process a step further to consider briefly the kinds of molecules for which VCD spectra have been measured. Given the instrumental and theoretical techniques that are now available for the measurement and calculation of VCD, applications in a number of areas of chemical and biological significance can now be undertaken. We refer the reader to selected recent reviews of VCD applications. Presently, there are approximately 13 laboratories world-wide in which VCD measurements are being carried out now, or have been carried out recently. While an exact count is not easy to obtain, and is constantly changing, as of last year over 450 papers had been published in the field of VCD. VCD can be applied to structural problems involving amino acids, peptides, polypeptides, proteins, carbohydrates, molecules of pharmaceutical interest, natural products, nucleic acids, as well as chiral molecules of interest to organic or inorganic chemists. Most applications of VCD to date have the goal of structure elucidation. VCD may be used as a probe of absolute configuration. The majority of applications involve the determination of the stereo-conformational features of chiral molecules. For applications to smaller molecules, ab initio calculations or some kind of model calculations can be employed to extract information from the VCD spectra. For large molecules, such as proteins, carbohydrates or nucleic acids, empirical analysis, either qualitative spectral correlation or statistical methods as discussed above, must be employed. A small but perhaps growing area of applications involves the use of VCD as a diagnostic tool to monitor optical purity or identify chiral compounds in a chromatographic column. In this setting, VCD is being applied as a spectral probe of qualitative or quantitative compound identification. In its diagnostic role, VCD is not being used to learn more about molecular structure, and the VCD spectra do not need to be interpreted to be of great value.