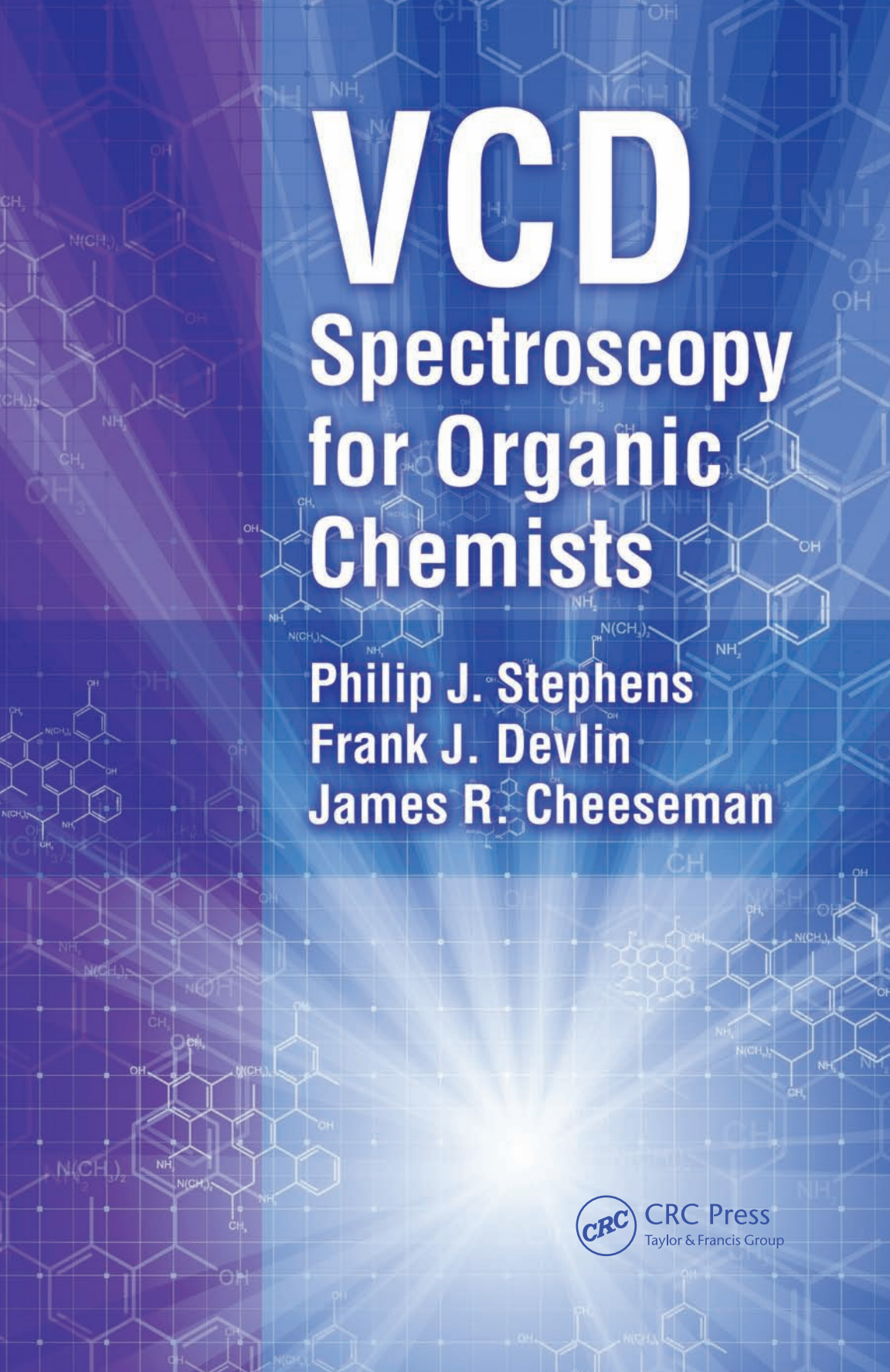
VCD
Spectroscopy for Organic Chemists
Philip J. Stephens
Frank J. Devlin
James R. Cheeseman
CRC Press
Taylor & Francis Group

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Preface

Chiral organic molecules are currently of widespread interest to organic chemists and pharmaceutical chemists. In addition to synthetic chiral molecules, naturally occurring molecules, which are invariably chiral and generally enantiomerically enriched, are of potential interest as leads for new drugs. The increasing importance of chiral molecules has stimulated the development of improved research techniques, especially chromatography, and of new asymmetric synthesis methods as well as spectroscopic methods for their structural characterization.

Circular dichroism (CD) is the differential absorption of left- and right-circularly polarized light. The vibrational circular dichroism (VCD) spectrum of a molecule, first observed in the mid 1970s, is the CD resulting from vibrational excitations of the molecule. The VCD spectra of the two enantiomers of a chiral molecule are of equal magnitude and opposite sign: mirror-image enantiomers give mirror-image VCD spectra. In principle, the absolute configuration (AC) of a chiral molecule can therefore be determined from its VCD spectrum. In practice, the determination of the AC of a chiral molecule from its experimental VCD spectrum requires a methodology that reliably predicts the VCD spectra of its enantiomers. The development of a rigorous quantum-mechanical theory of VCD and its implementation in quantum chemistry programs provides a reliable systematic technique for determining ACs from experimental VCD spectra.

Given the availability of commercial VCD instrumentation and quantum chemistry software, it became possible in the late 1990s for chemists to utilize VCD in elucidating the stereochemistries of chiral organic molecules. The purpose of this book is to increase the awareness of organic chemists of the utility of VCD spectroscopy and to provide them with sufficient knowledge to incorporate the technique into their own research.

PJS is profoundly grateful to all of his former graduate students and postdoctoral research associates. He especially thanks his former postdoctoral research associates Dr. Jack Cheng, Professor Larry Nafie (Syracuse University) and Professor Tim Keiderling (University of Illinois at Chicago) and his mentor, Professor A. David Buckingham (Cambridge University). FJD thanks his mentor Professor Hector E. Rubalcava (University College, Dublin) for teaching him the fundamentals of molecular spectroscopy. JRC thanks Dr. Michael Frisch and Dr. Gary Trucks at Gaussian, Inc. for their tremendous support over the years. We all thank the wonderful collaborators who have been involved in our research projects.

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Gaussian, Inc.

1 Introduction to Vibrational Circular Dichroism

Molecules are not totally rigid. Even at absolute zero (0 K), the lengths of bonds between atoms oscillate, the angles between adjacent bonds oscillate, and the dihedral angles between bonds separated by a bond oscillate. These motions are termed molecular vibrations. According to quantum mechanics, the energies of the vibrational states of molecules are quantized, the lowest energy state being termed the ground vibrational state.

When a molecule is exposed to electromagnetic radiation (light), the interaction between the radiation and the molecule can cause light photons to be absorbed by the molecule, and the molecule to be excited from the ground vibrational state, g, to higher energy vibrational states, e. The excitation $g \rightarrow e$, of energy $\Delta E = E_e - E_g$, is caused by photons of energy $h\nu = \Delta E$, where $h\nu = hc/\lambda = hc\bar{\nu}$ (ν, λ, c, and $\bar{\nu}$ are the light frequency, wavelength, velocity, and reciprocal wavelength, respectively, and h is Planck's constant).

The absorption of light, resulting from vibrational excitations of a molecule, as a function of the light frequency, is termed the vibrational absorption spectrum of the molecule. The vibrational absorption spectrum of a molecule is measured using an infrared (IR) absorption spectrometer, in which IR light is passed through a sample containing the molecule. The sample can be a pure solid, liquid, or gas, or a solid, liquid, or gaseous solution of the molecule in a solvent. When the molecules in the sample are selectively oriented, as in a crystalline solid sample, the absorption spectrum is dependent on the linear polarization of the light. When the molecules are randomly oriented, as is the case in pure liquid and gaseous samples, and in liquid and gaseous solutions, the absorption spectrum is linear polarization independent. Most commonly, vibrational absorption spectra are measured using unpolarized IR light and samples in which the molecules are randomly oriented. An example of a molecular vibrational absorption spectrum is shown in Figure 1.1. The molecule is camphor; the spectrum was measured using unpolarized IR light, in a cell of pathlength 236 microns (μ), and over the IR frequency range, of reciprocal wavelengths (wavenumbers) 1,530–825 cm^{-1}. Absorption is observed at many frequencies, demonstrating the existence of many vibrationally excited states.

All molecules belong to one of two classes: achiral and chiral. By definition, an achiral molecule is identical to its mirror image; i.e., if the molecule is reflected in a mirror and then rotated, it can be superimposed on the original, unreflected molecule. A chiral molecule is different: the molecule and its mirror image are not superimposable, and therefore constitute different molecules. The two forms of the molecule are termed enantiomers. Since human left and right hands are mirror

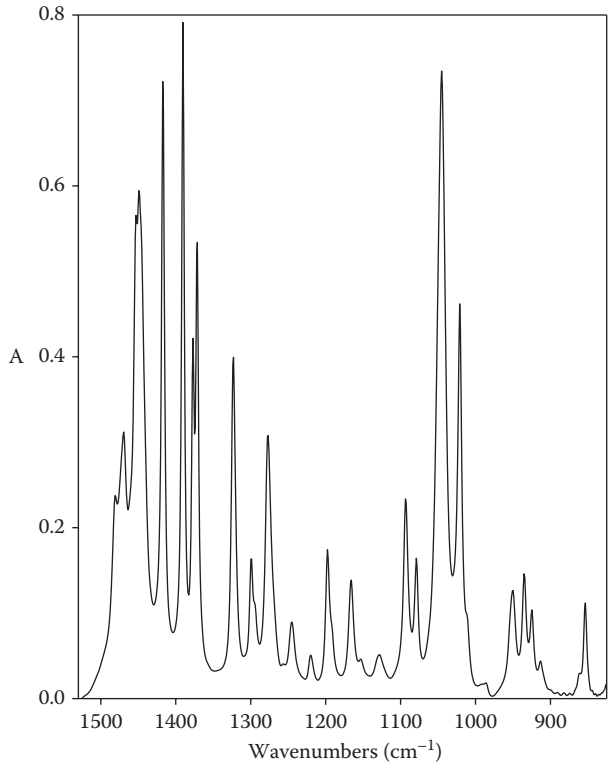
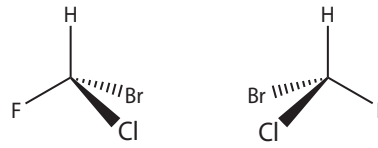


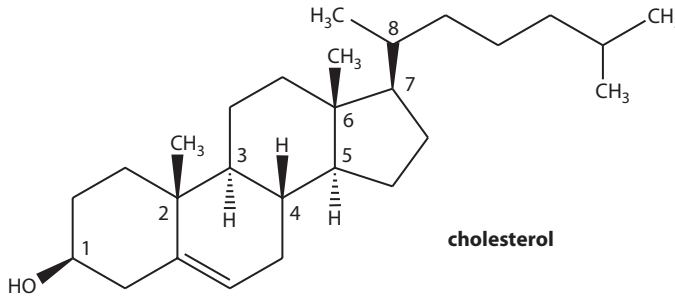
FIGURE 1.1 The mid-IR vibrational absorption spectrum of a 0.38 M CCl_4 solution of 1*R*,4*R* camphor. A is the absorbance (defined in Chapter 2).

images, and not superimposable, the two mirror image forms of a chiral molecule are sometimes also referred to as left-handed and right-handed.

A simple example of a chiral molecule is CHFClBr. The two enantiomers are:



Any molecule of the formula $CR_1R_2R_3R_4$ (R_1, R_2, R_3, and R_4 all being different) is also chiral. Of great biological significance is the chirality of amino acids, in which R_1 = H, R_2 = NH_2, R_3 = COOH, and R_4 depends on the specific amino acid (e.g., in alanine, R_4 = CH_3). A C atom bonded to four different groups is termed a stereogenic C atom. Many chiral organic molecules contain multiple stereogenic C atoms. For example, in the steroid natural product cholesterol, C atoms 1, 2, 3, 4, 5, 6, 7, and 8 are stereogenic:



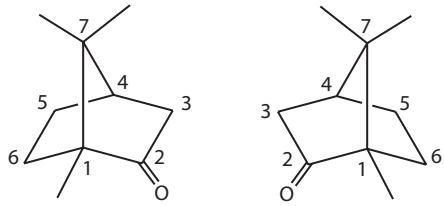
cholesterol

In 1956, Cahn, Ingold and Prelog introduced a notation that specifies the chiralities of stereogenic C atoms: a C atom is either *R* or *S* [1]. The overall three-dimensional (3D) structure of an enantiomer of a chiral molecule can then be defined by listing which atoms are *R* or *S*. For example, naturally occurring cholesterol is 1*S*,2*R*,3*S*,4*S*,5*S*,6*R*,7*R*,8*R* [2]. This label is termed the absolute configuration (AC).

Although the 3D geometries of the two enantiomers of a chiral molecule are not identical, they do possess considerable similarity. In particular, all bond lengths, bond angles, and nonbonded interatomic distances are unchanged on reflection in a mirror. As a result, the vibrational excitation energies of the two enantiomers and the vibrational absorption spectra, measured using samples of randomly oriented molecules and unpolarized IR light, are identical.

The electric and magnetic fields of a linearly polarized light wave each oscillate sinusoidally in a plane containing the propagation direction, the electric field and magnetic field planes being perpendicular to each other. Passage of a linearly polarized light wave through an optical device called a quarter-wave plate [3] converts the light wave into a circularly polarized (CP) light wave. Two forms of CP light can be generated, termed right circularly polarized (RCP) and left circularly polarized (LCP). In both RCP and LCP light, the electric and magnetic fields rotate helically about the propagation direction of the wave. In RCP light the helix is right-handed and in LCP light the helix is left-handed. Thus, RCP and LCP light waves of the same frequency are mirror images.

The vibrational absorption spectrum of a molecule can also be measured using CP light. If the molecule is achiral and randomly oriented, the spectra obtained using RCP and LCP light are identical. However, if the molecule is chiral, this is not the case. The difference in absorption of RCP and LCP light is termed circular dichroism (CD). Conventionally, CD is defined as the absorbance (defined in Chapter 2) of LCP light (A_L) minus the absorbance of RCP light (A_R): $CD = \Delta A = A_L - A_R$. CD is therefore positive if $A_L > A_R$ and negative if $A_L < A_R$. For the two enantiomers of the chiral molecule, the CD at every light frequency is of equal magnitude, but is opposite in sign; their CD spectra are thus mirror images. The vibrational circular dichroism (VCD) spectrum of a molecule is the CD resulting from vibrational excitations of the molecule. Examples of the VCD spectra of the enantiomers of a chiral molecule are shown in Figure 1.2. The chiral molecule is camphor. The two enantiomers are:



The VCD spectra of the two enantiomers were measured using 0.38 M solutions of camphor in the achiral solvent CCl_4 and a cell of pathlength 236 μ. The mirror image property of the VCD spectra of the two enantiomers is qualitatively obvious. Quantitatively, it is proven by addition of the two VCD spectra; as shown in Figure 1.2, the sum of the two VCD spectra is very close to zero at all frequencies.

The phenomenon of circular dichroism was first discovered by the French scientist Aimé Cotton in 1896 [4] and subsequently became known as the Cotton effect. The CD measured by Cotton was in the near-ultraviolet (UV) spectral region and originated in electronic excitations of molecules. As with the vibrational states of molecules, the electronic states of molecules are quantized. Light photons of the same energy as the energy of excitation from the lowest energy (ground) electronic state to a higher energy (excited) electronic state are absorbed by the molecule.

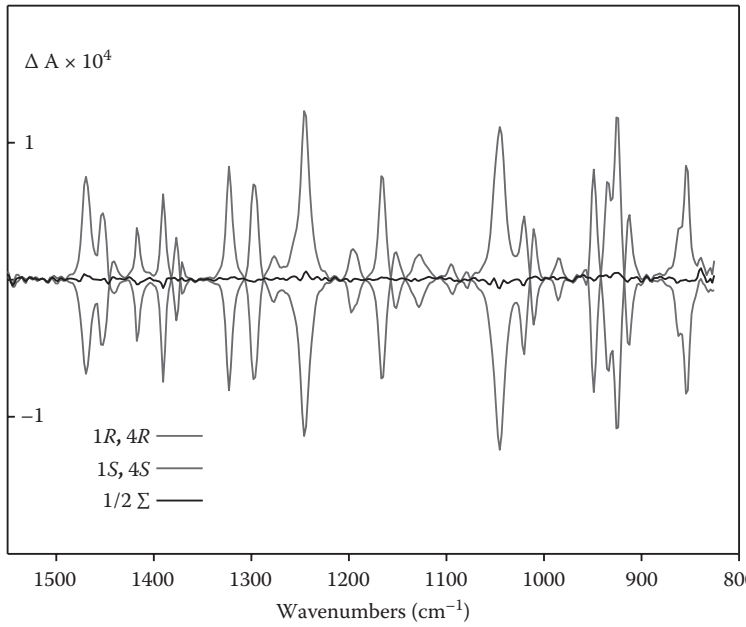


FIGURE 1.2 (SEE COLOR INSERT.) The mid-IR VCD spectra of 0.38 M CCl_4 solutions of 1*R*,4*R* and 1*S*,4*S* camphor, using a cell of pathlength 236 μ. Σ is the sum of the spectra. The measurement of the spectra is discussed in Chapter 2.

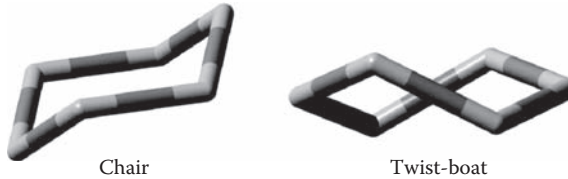
Electronic absorption and CD typically occur in the visible-ultraviolet (VIS-UV) spectral region (200–1,000 nm, 10,000–50,000 cm^{-1}), where light frequencies are much higher than in the IR spectral region.

Electronic CD (ECD) spectra of chiral molecules were not widely studied until after the Second World War, when new instrumentation for VIS-UV CD measurement was developed, using modulation techniques and electro-optic modulators named Pockels cells, permitting ECD spectra to be more efficiently measured [5]. This led rapidly to a much higher level of interest in the application of ECD spectra to the elucidation of the stereochemistries of organic molecules. An important development, which facilitated such applications, occurred in 1961 when Moffitt, Woodward, Moscowitz, Klyne, and Djerassi proposed the octant rule, which predicts the sign of the ECD of the lowest energy electronic excitation of a carbonyl (C=O) group in a chiral molecule [6]. The octant rule enabled the ACs of chiral molecules containing carbonyl groups to be determined. In addition, it led to the development of similar rules for the electronic excitations of other functional groups, which further widened the application of ECD spectra to the determination of ACs [7,8].

The reason for the interest in the determination of the ACs of chiral molecules using ECD spectroscopy was that it provided a less laborious procedure than other available methods. Two approaches were predominant in determining ACs prior to the introduction of the ECD approach: (1) x-ray crystallography and (2) chemical synthesis. X-ray crystallography was used in two ways. One procedure was developed by Bijvoet et al. [9] and used the anomalous x-ray scattering dispersion of a high atomic number atom (a "heavy atom") in the molecule. For example, the AC of camphor was determined by replacing one of its H atoms by a Br atom and determining the AC of the resulting 3-Br-camphor [10]. Since the bromination of camphor does not change its AC, the AC of the 3-Br-camphor is identical to that of camphor. A second x-ray crystallography procedure used a derivatization reaction of the chiral molecule with a second chiral molecule, of known AC. Determination of the relative stereochemistry of the product molecule via x-ray crystallography then determines the AC of the underivatized chiral molecule. Since x-ray crystallography is widely used, and the most definitive method for determining the geometry of a molecule, these two procedures are highly reliable ways to determine the ACs of chiral molecules. However, there are disadvantages: (1) in the first procedure, if the molecule does not possess a heavy atom, a chemical reaction must be carried out; (2) in the second procedure, a chemical reaction must always be carried out; and (3) in both procedures, single crystals of sufficient size to permit x-ray crystallography must be obtainable. Since, sometimes, neither the reactions chosen nor the crystallization of the products are practical, x-ray crystallography is not always easily used in determining ACs. The principal alternative approach to x-ray crystallography was to synthesize the chiral molecule of interest from a precursor chiral molecule of known AC, using reactions whose mechanisms are understood and whose impacts on the molecular stereochemistry are predictable. This procedure is useful if such a synthetic procedure is practical, which is often, but not always, the case.

An additional application of ECD spectroscopy was also of interest to organic chemists after the development of ECD instrumentation: the conformational analysis of conformationally flexible chiral molecules. In the 1950s, it became clear,

especially due to the work of Barton [11], that some organic molecules can have more than one structure: the multiple structures are termed conformations, and such molecules are termed conformationally flexible. An early example of a conformationally flexible molecule was cyclohexane, whose C6 ring can have two structures, termed chair and twist-boat conformations, discussed in Chapter 5:



Chair Twist-boat

When the energy barriers between the conformations of a conformationally flexible molecule are not very high, the conformations can interconvert rapidly at room temperature, and therefore exist in equilibrium. The percentage populations of the conformations are determined by their relative free energies and the temperature, according to Boltzmann statistics [12]. Since the ECD of a molecule is sensitive to its geometry, different conformations of a given enantiomer of a chiral molecule exhibit different ECD spectra. Consequently, ECD spectroscopy provides a technique for elucidating the conformations populated in a chiral molecule [13].

In addition to CD, chiral molecules exhibit other properties, which are different for the two enantiomers. The earliest such property to be discovered was optical rotation (OR) [14]. When linearly polarized light is passed through a sample containing randomly oriented chiral molecules, the plane of the polarization is rotated by an angle α. The OR α is equal in magnitude, but opposite in sign, for the two enantiomers. Historically, OR was most often measured using light emitted by a sodium lamp at a wavelength referred to as the sodium D line (589 nm), and converted to the specific rotation, $[\alpha]_D$, defined by $[\alpha]_D = \alpha/\ell c$, where ℓ is the cell pathlength in dm and c is the concentration of the chiral molecule in the sample in g/100 ml. The two enantiomers with positive and negative $[\alpha]_D$ values were then termed (+) and (–), respectively. The AC of a chiral molecule is determined for either the (+) or the (–) enantiomer. In reporting the conclusion, both the AC and OR sign are listed. Thus, for example, the AC of (+)-camphor is (1*R*,4*R*)-(+) and the AC of (–)-camphor is (1*S*,4*S*)-(–).

Following the development of efficient instrumentation for the measurement of VIS-UV ECD spectra and the widespread application of ECD spectra to the elucidation of the ACs and/or conformational structures of chiral organic molecules, the obvious questions arose: Can CD due to vibrational excitations, vibrational circular dichroism (VCD), be measured in the IR spectral region, and if so, can VCD also be used to determine the ACs and/or conformational structures of chiral organic molecules? As a result, in the early 1970s, instruments capable of measuring CD in the IR spectral region were designed and built in two laboratories: the Stephens laboratory at the University of Southern California (USC) [15] and the Holzwarth laboratory at the University of Chicago (UC) [16]. In the 1970s experimental VCD spectra of chiral organic and organometallic molecules were measured and published: one molecule, 2,2,2-trifluoro-1-phenylethanol, at UC [17] and the 23 molecules listed in Table 1.1

TABLE 1.1
Chiral Molecules Whose VCD was Measured at USC in the 1970s

1. 2,2,2-Trifluoro-1-phenylethanol
2. α-Methylbenzylamine
3. N,N-α-Trimethylbenzylamine
4. 3-Methyl-cyclopentanone
5. 3-Methyl-cyclohexanone
6. Menthol
7. α-Pinene
8. β-Pinene
9. Camphor
10. 3-Br-camphor
11. Borneol
12. Tris (3-trifluoromethylhydroxymethylene-d-camphorato) praseodymium
13. Tris (3-trifluoromethylhydroxymethylene-d-camphorato) europium
14. Poly-1-methyl-propyl-vinyl-ether
15. Poly-4-methyl-1-hexene
16. Dimethyl tartrate
17. Alanine
18. Camphoric anhydride
19. 1,6-Spiro [4.4] nonadiene
20. Exo-3-deutero-isoborneol
21. Exo-3-deutero-camphor
22. α-Deutero-propylbenzene
23. $Fe(C_5H_5)$ $(P(C_6H_5)_3)$ (CO) (Et)

at USC [18]. This work proved that VCD spectra could indeed become a practical technique for determining the stereochemistries of chiral organic molecules. In order to realize this promise, two developments remained to be accomplished. First, the frequency range of the existing VCD instrumentation, which was limited to frequencies of >1,600 cm^{-1}, had to be extended, to permit a wider fraction of the IR spectral region to be accessed, and the sensitivity (i.e., the signal-to-noise ratio) of the existing VCD instrumentation had to be increased, to permit VCD to be measured reliably for a larger number of molecules. Second, a methodology by which molecular stereochemistries could be reliably deduced from experimental VCD spectra had to be developed; otherwise, the spectra would be of no practical value. By the mid-1980s the frequency range of the USC VCD instrument had been greatly expanded by Devlin and Stephens [19], the lower frequency limit having been extended to ~650 cm^{-1}, and the sensitivity substantially increased. At the same time, a rigorous quantum mechanical theory of VCD had been developed by Stephens [20], which was implemented for a number of chiral molecules using the *ab initio* Hartree-Fock (HF) molecular orbital theory [21]. Comparison of *ab initio* HF calculations of VCD spectra using the Stephens theory to experimental VCD spectra led to great optimism that VCD spectroscopy could soon become a widely used technique. Two further developments added to this optimism. First, the explosion in the late 1980s of *ab initio*

density functional theory (DFT) and the documentation of its much greater accuracy than HF theory in predicting molecular properties made it desirable to implement the Stephens theory of VCD using DFT. This was carried out in the 1990s by Cheeseman and Frisch at GAUSSIAN, Inc. [22], using the GAUSSIAN program, which was originally developed in John Pople's laboratory and subsequently has become a widely distributed program, frequently used by both quantum chemists and organic chemists for predicting molecular properties. Comparison of the VCD spectra of chiral organic molecules, calculated using DFT in the Gaussian programs G92, G98, G03, and G09 [23], to experimental VCD spectra proved the superior accuracy of DFT VCD spectra [24]. Second, the extension of the methodology used by Stephens and Holzwarth for measuring VCD using dispersive IR spectrometers to Fourier transform IR (FTIR) spectrometers demonstrated that VCD spectra could also be obtained using FT instrumentation [25]. Following the DFT implementation of the Stephens theory of VCD, several companies manufacturing and marketing FTIR spectrometers realized that a market for commercial FT VCD instrumentation could exist, and began the manufacturing and marketing of VCD instruments. As a result, potential users of VCD spectroscopy no longer had to build their own instrumentation.

Given the availability of commercial software, permitting the prediction of VCD spectra using DFT, and of commercial VCD instrumentation, it became possible in the late 1990s for chemists to utilize VCD in elucidating the stereochemistries of chiral organic molecules. As a result, the number of publications per year reporting VCD studies of chiral organic molecules substantially increased. Despite this boom, many organic chemists remain unfamiliar with VCD spectroscopy. The purpose of this book is to increase the awareness of organic chemists of the utility of VCD spectroscopy. To achieve this purpose, we discuss in detail the experimental measurement of VCD spectra and their analysis using the Stephens theory of VCD, implemented using *ab initio* DFT. In Chapter 2, we discuss the experimental measurement of vibrational absorption and VCD spectra. In Chapter 3, we discuss the fundamental quantum mechanical theory of the vibrational states of molecules and of their vibrational absorption and VCD spectra. In Chapter 4, we discuss the application of the *ab initio* HF and DFT methods of quantum chemistry to the prediction of the molecular structures and vibrational states of organic molecules. In Chapter 5, we discuss the conformational analysis of conformationally flexible molecules. In Chapter 6, we discuss the analysis of the vibrational absorption and VCD spectra of a number of conformationally rigid chiral organic molecules, in order to define the optimum basis sets and DFT functionals for calculations of vibrational absorption and VCD spectra, and to define the methodology by which ACs are deduced from VCD spectra. Finally, in Chapter 7, we present studies of a set of chiral organic molecules that further document the power of VCD spectroscopy and make clear how wide is the applicability of this technique.

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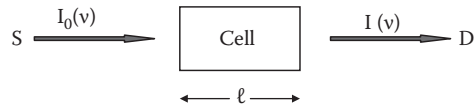
2 The Experimental Measurement of Vibrational Absorption and Vibrational Circular Dichroism Spectra

In this chapter we discuss the measurement of the vibrational absorption spectrum and the vibrational circular dichroism (VCD) spectrum of a solution of a chiral solute in an achiral solvent.

VIBRATIONAL ABSORPTION MEASUREMENT

The vibrational absorption spectrum of a solution is measured as follows. A cell of pathlength ℓ (cm) is filled with the solution and placed in an IR absorption spectrometer between the IR light source, S, and the IR detector, D:



The absorption of the solution causes the intensity of the light of frequency ν entering the cell, $I_0(\nu)$, to be reduced to $I(\nu)$. The transmittance T and the absorbance A of the solution at frequency ν are defined by:

$$T(\nu) = \frac{I(\nu)}{I_0(\nu)} \qquad A(\nu) = -\log_{10} T(\nu)$$

If $T = 10^{-1}$, i.e., 90% of the light is absorbed, A = 1. The intensities I and I_0 are measured by the detector with the cell inside and outside the spectrometer, respectively. The IR absorption spectrometer measures T and A over a range of frequencies, generating the vibrational absorption spectrum of the solution, now termed the IR absorption spectrum.

The IR absorbance of the solution is the sum of the absorbances of the solute molecules and solvent molecules:

$$A(\text{solution}) = A(\text{solute}) + A(\text{solvent})$$

In order to determine the IR absorbance of the solute, the solvent absorbance must be subtracted. To do this, the solution is replaced in the cell by the pure solvent, the IR absorption spectrum of the solvent measured and subtracted from the solution spectrum, to give the absorbance spectrum of the solute.

For a dilute solution, the absorbance of the solute obeys Beer's law:

$$A(\text{solute}) = \varepsilon\, c\, \ell$$

where c is the concentration in moles/L of the solution and ε is the molar extinction coefficient. Determination of the frequency-dependent molar extinction coefficient spectrum of the solute is the ultimate goal in measuring the IR absorption of the solution.

Historically, commercial IR absorption spectrometers were dispersive spectrometers, in which the light from the light source was passed through a monochromator to make the light passing through the solution and measured by the detector monochromatic (i.e., of single frequency) [1]. Subsequently, Fourier transform IR (FTIR) spectrometers, in which an interferometer replaces the monochromator of a dispersive spectrometer, have become the dominant instrumentation for the measurement of IR absorption spectra [2]. Currently, many FTIR spectrometers are commercially available. Throughout the book, the IR vibrational absorption spectra presented have been measured using a Thermo Nicolet Nexus 670 FTIR spectrometer in the Stephens laboratories at USC. This spectrometer uses a silicon carbide globar light source (Ever-Glo), a CsI beamsplitter, and a deuterated triglycine sulfate (DTGS) room temperature pyroelectric bolometer detector with a CsI window, and measures spectra over the frequency range 200–6,400 cm^{-1}.

In measuring the vibrational absorption spectrum of an organic solute, the choices of cell and solvent are important. The IR absorption of both the cell windows and the solvent needs to be as small as possible to optimize the signal-to-noise ratio (S:N) of the solute absorption spectrum. Cells with windows of highly IR-transparent solids, such as crystalline KBr, are widely available. The greater problem is that organic solvents always exhibit IR absorption. For a given solute molecule, it is important to examine the IR absorption of the solvents, in which it is soluble and chemically stable, and select the solvent with the minimum absorption. The IR spectra of the organic solvents, $CHCl_3$, CCl_4, CS_2, C_6H_6, CH_3CN, and C_6H_{12}, over the frequency range 800–2,000 cm^{-1}, are shown in Figure 2.1.

If a solvent contains H atoms, the possibility exists to measure the solute IR spectrum in the deuterated solvent as well, since the substitution of H atoms by D atoms substantially shifts the vibrational frequencies of the solvent molecule. For example, the IR absorption spectra of $CHCl_3$ and $CDCl_3$ over the range 800–2,000 cm^{-1}, shown in Figure 2.2, are substantially different, so the use of both $CHCl_3$ and $CDCl_3$ solutions permits the IR absorption of a solute to be measured reliably over most of the frequency range 800–2,000 cm^{-1}.

A further issue of importance in selecting the solvent to be used is the magnitude of the solute-solvent interaction. In using the IR absorption of the solute molecule to analyze its structure, it is important that the solute be as little perturbed by the solvent as possible, so solute-solvent intermolecular interactions should be minimized as much as possible. For example, solute-solvent intermolecular hydrogen

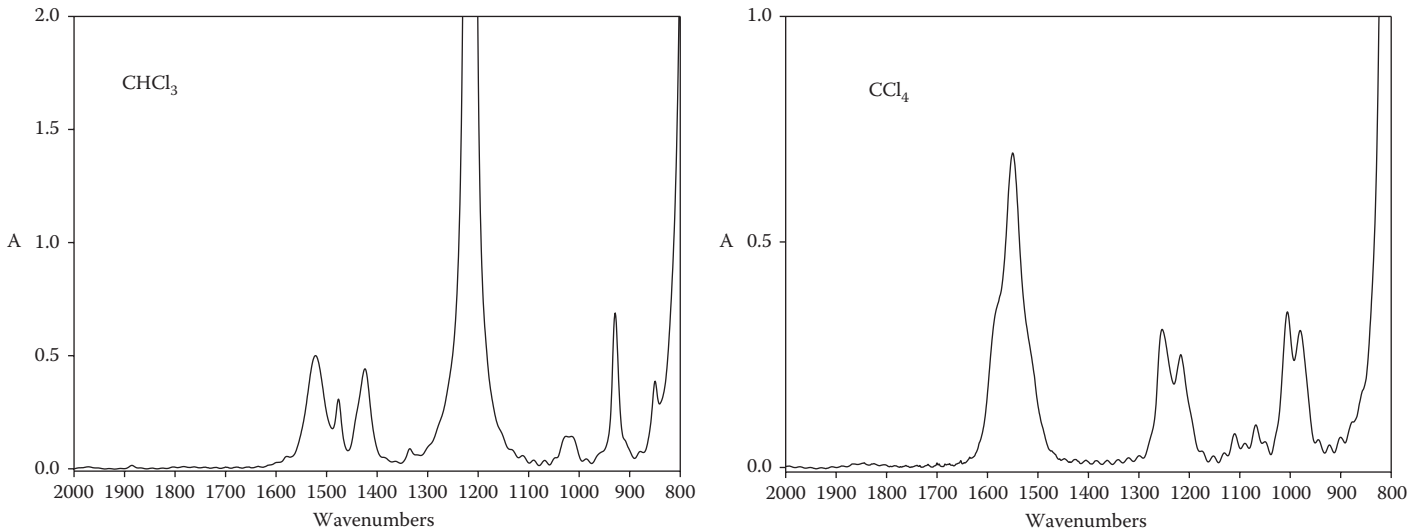


FIGURE 2.1 The IR absorption spectra of six organic solvents; pathlength 236 μ.

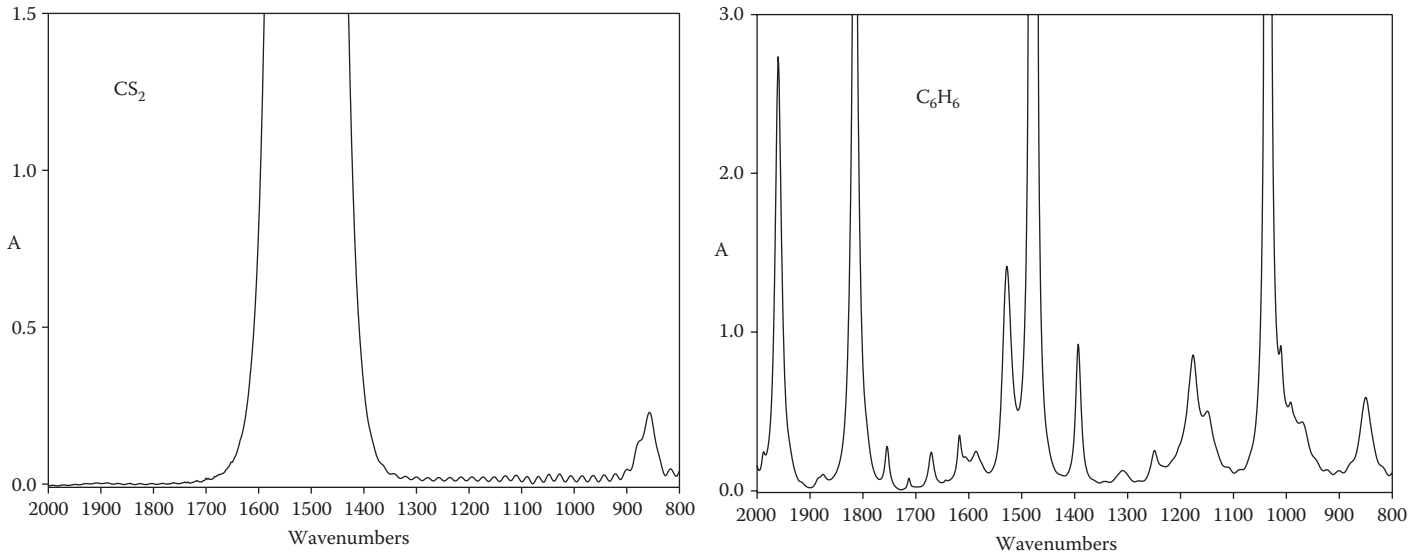


FIGURE 2.1 (CONTINUED)

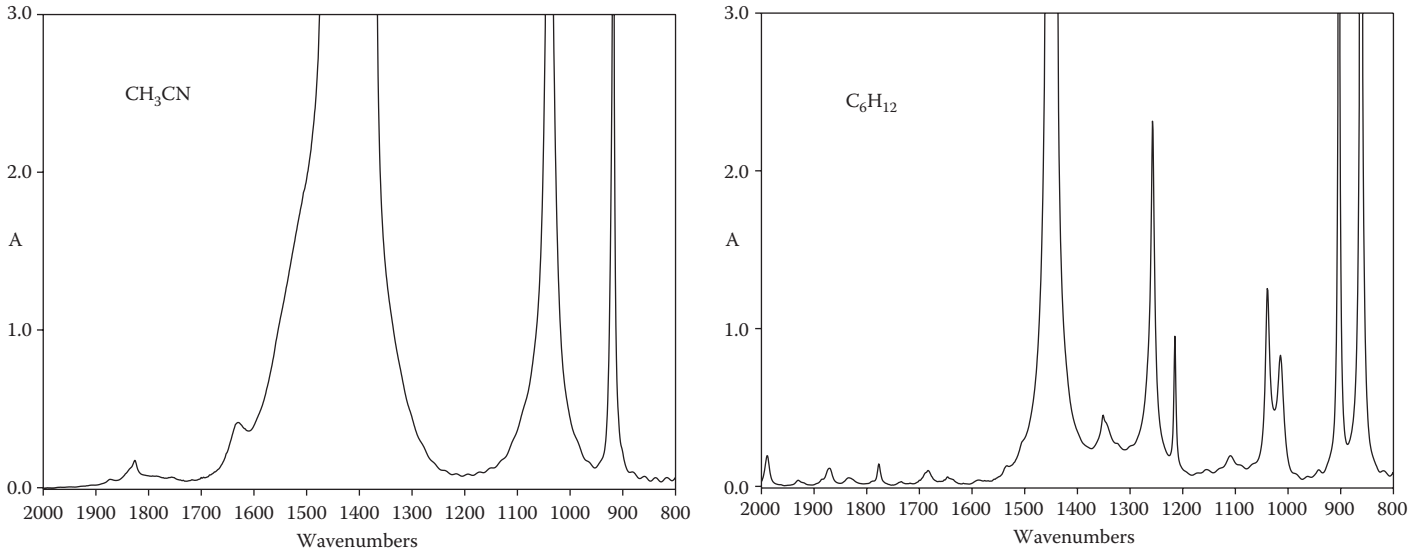


FIGURE 2.1 (CONTINUED)

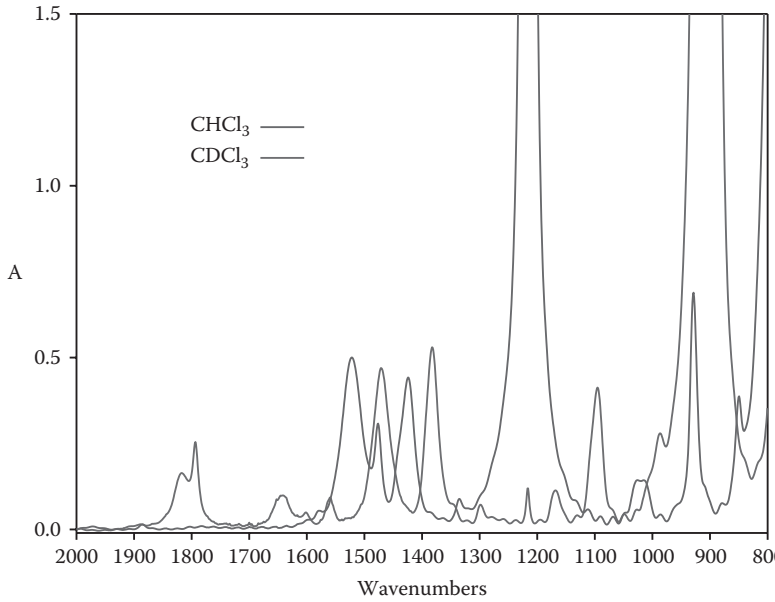


FIGURE 2.2 (SEE COLOR INSERT.) The IR absorption spectra of $CHCl_3$ and $CDCl_3$; pathlength 236 μ.

bonding should be avoided. For this reason, nonpolar solvents such as CS_2 and CCl_4 are ideal.

Given the choice of solvent, it remains to choose the solution concentration, c, and the cell pathlength, ℓ. The concentration must be sufficiently low that Beer's law is obeyed. The pathlength must be sufficiently low that the absorption of the solvent is small. Beer's law is obeyed only when solute-solute intermolecular interactions are zero. For solute molecules that do not have a significant tendency to aggregate, it is generally the case that Beer's law is obeyed up to concentrations of ~1 M. For example, the concentration dependences of the IR absorption spectra of camphor and of α-pinene in CCl_4 solutions are shown in Figure 2.3 for the concentration ranges 0.981–0.033 and 2.965–0.099 M. For both molecules the molar extinction coefficient spectra are concentration independent over the concentration ranges studied. In the case of α-pinene, Beer's law is obeyed up to 3 M.

In contrast, alcohols and carboxylic acids are well known to aggregate at concentrations much lower than 1 M, due to intermolecular hydrogen bonding. For example the concentration dependences of the IR absorption of the alcohol *endo*-borneol in CCl_4 solution [3a] and the acid benzoic acid in $CHCl_3$ solution [3b] are shown in Figures 2.4 and 2.5 for the concentration ranges 0.306–0.008 M and 0.4–0.005 M, respectively. In both cases the O–H stretching IR spectra are very concentration dependent, demonstrating that Beer's law is not obeyed over these concentration ranges, due to intermolecular hydrogen bonding. In the case of benzoic acid, the C=O stretching IR spectrum at ~1,700 cm^{-1} is also very concentration dependent, since the C=O group participates in intermolecular hydrogen bonding. For alcohols and carboxylic acids, very low concentrations must be used in measuring their IR absorption spectra.

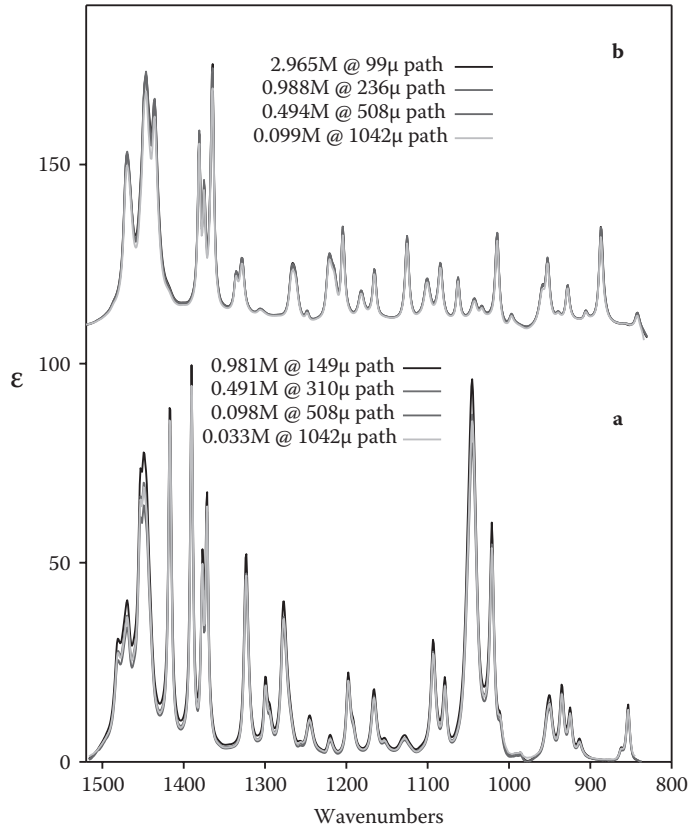


FIGURE 2.3 The concentration dependences of the IR absorption spectra of (1*R*,4*R*)-(+) camphor (a) and (1*R*,5*R*)-(+) α-pinene (b) in CCl_4 solutions.

Given the choice of solvent, solution concentration, and cell pathlength, there remain instrumental parameters that affect the solute IR absorption spectrum. These include the spectrometer resolution and the scan time. The resolution determines the degree to which bands close in frequency are resolved in the absorption spectrum. For solutions in which solute-solute intermolecular interactions are minimal, and the widths of vibrational absorption bands are consequently also minimal, 1 cm^{-1} resolution is generally sufficient to ensure a fully resolved absorption spectrum. The scan time determines the signal-to-noise ratio of the spectrum. By increasing the scan time, the noise level is decreased and the S:N ratio is increased. A typical solute IR absorption spectrum is the average of 32 scans and requires a collection time of about 1 min. However, if the sample solution is very dilute or if the solute has a particularly small molar extinction coefficient, then longer collection times are required in order to obtain a spectrum with an acceptable S:N ratio.

We have assumed so far that the solute is 100% pure. Since the IR absorption spectrum of a molecule is a sensitive function of both its formula and its geometrical structure, it follows that the presence of an impurity in the solute sample can be

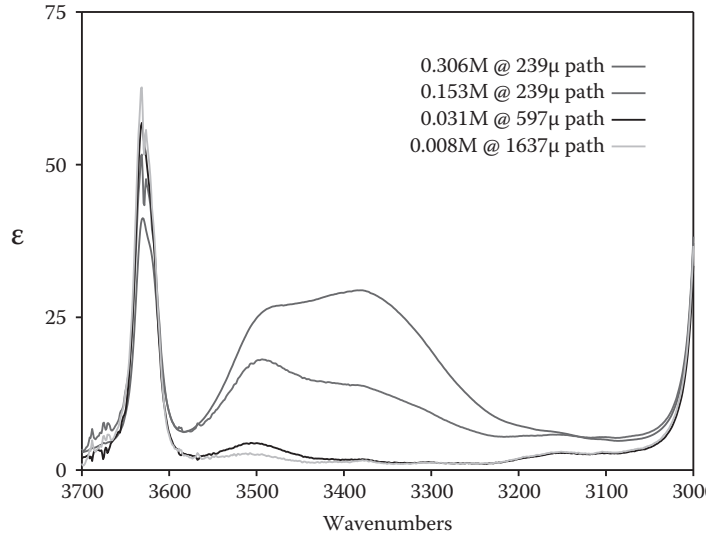


FIGURE 2.4 (SEE COLOR INSERT.) The concentration dependence of the IR absorption in the O–H stretching region of *endo*-borneol in CCl_4 solution.

expected to give rise to additional bands in the absorption spectrum. As a result, the IR absorption spectrum is sensitive to the presence of impurities. Ideally, the solute is purified to 100% before its IR absorption spectrum is measured. However, this is not always the case. When only a single sample is available, there is no easy way to identify which bands in the absorption spectrum might be due to impurities. However, in the case of chiral solutes, one often has available samples of both enantiomers and the racemate. In such cases, it often occurs that their chemical purities vary, and as a result, their IR absorption spectra are not exactly identical. Absorption bands that are of different intensity in different samples can be assigned to impurities, and the sample for which these bands are the least intense is that of highest purity. For example, the IR absorption spectra of both enantiomers and the racemate of an oxadiazol-3-one derivative in $CDCl_3$ solution are shown in Figure 2.6. Both enantiomers show additional bands in their absorption spectra when compared to the racemate spectrum. Since the racemate has the least number of bands, it is therefore the compound of highest purity.

VCD MEASUREMENT

The vibrational circular dichroism (VCD) of a solution is

$$\Delta A = A_L - A_R$$

where A_L and A_R are the absorbances of left circularly polarized (LCP) and right circularly polarized (RCP) light. ΔA is termed the differential absorbance. When Beer's law is obeyed,

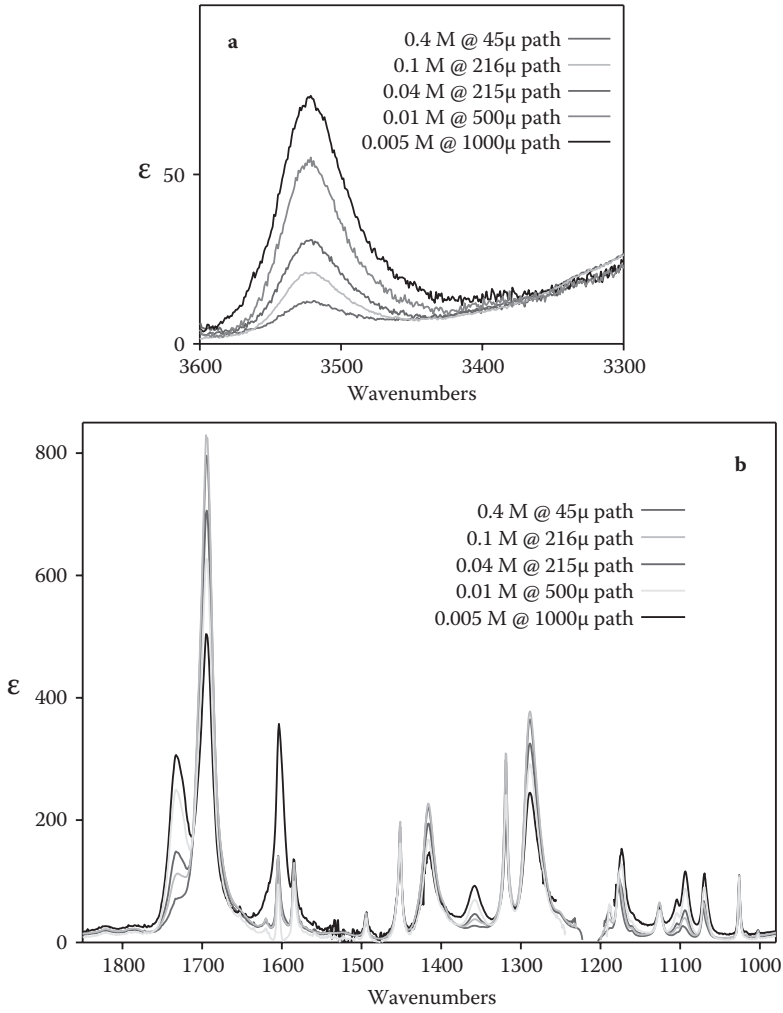


FIGURE 2.5 (SEE COLOR INSERT.) The concentration dependence of the IR absorption spectrum of benzoic acid in $CHCl_3$ solution, in the O–H stretching region (a) and in the mid-IR (b).

$$\Delta A = (\Delta\varepsilon)\, c\ell$$

where $\Delta\varepsilon$ is the differential molar extinction coefficient,

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

The ratio of $\Delta\varepsilon$ to ε, $\Delta\varepsilon/\varepsilon$, is termed the anisotropy ratio. VCD anisotropy ratios are typically $<10^{-4}$.

All measurements of VCD have been made using a technique termed modulation spectroscopy. This technique was developed after World War II and applied to the measurement of ECD in the visible ultraviolet spectral region [4]. In a CD

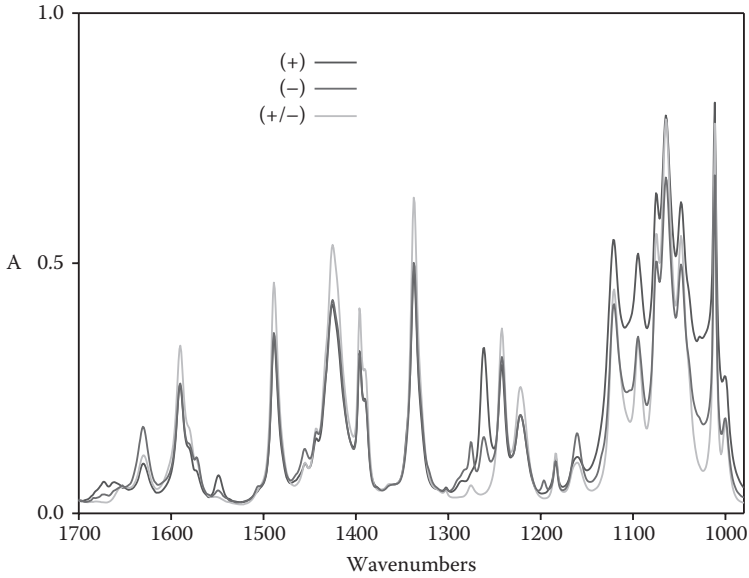
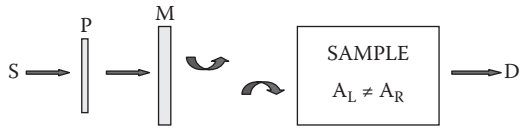


FIGURE 2.6 (SEE COLOR INSERT.) The IR absorption spectra of 0.04 M $CDCl_3$ solutions of (+), (–), and (±) (8-(4-bromophenyl)-8-ethoxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]-oxadiazol-3-one; pathlength 597 μ.

instrument using modulation spectroscopy, the light from the source, S, is linearly polarized, using a linear polarizer, P, and then passed through a phase modulator, M, which generates light oscillating between right and left circular polarizations at a frequency ν_M. The RCP and LCP light waves have the same intensities, $I_0(\nu)$. Passage of this light through a cell containing a solution of a chiral molecule with CD at the light frequency causes the intensities of the RCP and LCP light waves to be differently reduced, due to the difference in the absorbances, A_R and A_L. As a result, the intensity of light at the detector, D, oscillates between unequal intensities I_R and I_L at the frequency ν_M. The magnitude of the oscillation is proportional to the CD, ΔA.



The earliest CD instruments based on modulation spectroscopy used electro-optic modulators, in which an electric voltage, oscillating at frequency ν_M, is applied to a crystal of potassium di-deuteriumphosphate (KD_2PO_4); these modulators were also termed Pockels cells. Subsequently, in the 1960s, a new type of phase modulator, termed photoelastic modulator (PEM), was invented, in which oscillating stress is applied to a solid optical element [5]. The earliest PEMs used such solid optical elements as fused quartz and crystalline CaF_2, which are transparent in the visible ultraviolet spectral region, and therefore can be used to measure ECD spectra.

To measure CD in the IR spectral region, a modulator transparent in the IR is required. The instruments that yielded the first measurements of VCD both used PEMs; the UC instrument used a Ge PEM [6] and the USC instrument used a ZnSe PEM constructed at USC [7]; both were new PEMs. Subsequently, ZnSe PEMs were commercialized by Hinds International [8], and thereafter almost all VCD instruments constructed have used commercial ZnSe PEMs. ZnSe is IR transparent down to ~650 cm^{-1}. The VCD of vibrational transitions at frequencies <650 cm^{-1} cannot be measured using a ZnSe PEM.

For a PEM to turn linearly polarized light of frequency ν into light oscillating between right and left circular polarizations, a specific magnitude of stress must be applied to the optical element. This magnitude is a function of ν. To measure VCD over a range of frequencies, the PEM stress magnitude has to be tuned. In order for a given solid to be usable as the optical element of a PEM, the stress magnitudes required to create oscillating circularly polarized light must be below the level of stress that causes the solid to fracture.

The magnitude of the oscillation of the light intensity at the detector, of frequency ν_M, is measured by the detector electronics, using a lock-in amplifier tuned to ν_M. In order to obtain the magnitude of the CD, ΔA, responsible for the oscillation, calibration is required. The calibration method used in the earliest VCD measurements at USC involved the substitution of the sample and cell by a linear polarizer and a crystalline window possessing linear birefringence, which together cause the intensity at the detector to oscillate at frequency ν_M with a predictable magnitude [9]. Comparison of the magnitudes of the oscillation of the light intensity due to the CD of the sample and the polarizer/birefringent window device permits the magnitude of the CD, ΔA, to be determined. This calibration method remains the standard used in VCD instruments.

The earliest VCD instruments were dispersive. Eventually, the modulation spectroscopic techniques used by these instruments were extended to Fourier transform IR (FTIR) instruments [10]. Currently, FTVCD instruments are commercially available [11]. Throughout the book, VCD spectra presented have been measured using a Bomem/BioTools FTVCD spectrometer in the Stephens laboratories at USC.

The accurate measurement of VCD requires that the optical elements of the instrument perform perfectly. In addition to the linear polarizer and the PEM performing perfectly, the windows of the cell and detector must be without linear birefringence and the detector must be insensitive to the polarization of the light. The use of a mirror to focus the light beam on the detector can cause distortion of the polarization; a lens without linear birefringence should be used instead. If these requirements are not satisfied, VCD spectra exhibit errors termed artefacts. To determine whether artefacts are present or not, the VCD spectra of the solvent and of the racemate of the chiral molecule of interest should be measured. In both cases, the VCD should be zero at all frequencies. In practice, when artefacts do occur, they are generally of larger magnitude at frequencies corresponding to strong absorption of the solvent or the racemate. For this reason, choosing the solvent to have minimal absorption over the frequency range being studied is important. In addition, the absorbance of the racemate should be limited to <1.0. When artefacts do occur, and are caused by the absorbance of the solution, the VCD spectra of the (+) and (–) enantiomers and the racemate of the chiral molecule should be measured using identical concentrations and cell pathlengths, so that their absorbances are identical. The VCD spectrum of the racemate is then used as the baseline for the spectra of the enantiomers, to cancel their artefact contributions.

When the (+) and (–) enantiomers have identical ee's the resulting racemate-subtracted VCD spectra, $\Delta\varepsilon(+)$ and $\Delta\varepsilon(-)$, should then be mirror images if their artefacts have been successfully removed by subtraction of the racemate VCD. To determine whether or not this is the case, the half-difference and half-sum spectra are plotted:

$$½\,\Delta = [\Delta\varepsilon(+) - \Delta\varepsilon(-)] \times 0.5$$

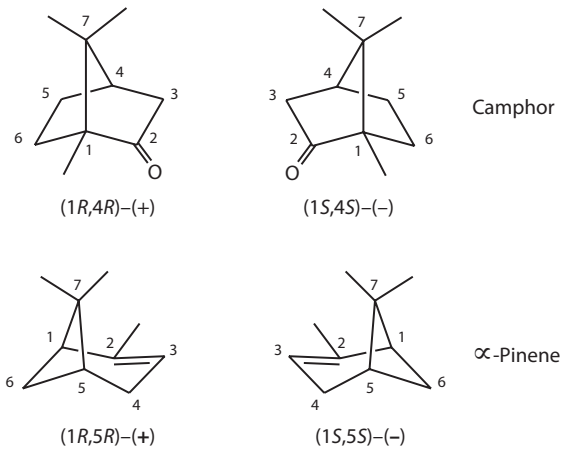
$$½\,\Sigma = [\Delta\varepsilon(+) + \Delta\varepsilon(-)] \times 0.5$$

In the absence of artefacts the half-sum spectrum is zero at all frequencies; if this is the case, the half-difference spectrum is the VCD spectrum of the (+) enantiomer.

Unfortunately, in some cases, for example, natural products, only a single enantiomer is available. In this case, the half-sum spectrum is not measurable and the magnitude of the artefact contributions cannot be determined. In such cases, the VCD spectrum of the solvent has to be used as the baseline for the VCD spectrum of the solution. The magnitudes of artefacts to be expected in the solvent-baseline-subtracted VCD spectrum of the solution can be estimated by measurement of the difference between the solvent-baseline-subtracted spectrum of another chiral molecule in the same solvent and its racemate-subtracted VCD spectrum. In 1975, Dr. Cheng at USC developed an instrumental technique for reducing artefact contributions to VCD spectra [12], in which a second PEM was inserted prior to the detector. This technique has been incorporated in the Bomem FTVCD instrument at USC. All of the VCD spectra in the book, including the spectra of camphor and α-pinene in the next sections of this chapter, have been measured using the Cheng artefact reduction technique.

IR ABSORPTION AND VCD SPECTRA OF SPECIFIC MOLECULES

The performance of a VCD instrument is optimally evaluated using measurements of the VCD spectra of conformationally rigid chiral molecules, whose enantiomers are both available, and both optically pure and chemically pure, and whose racemates are also available and chemically pure. Here, we present measurements of the VCD spectra of the two chiral molecules, camphor and α-pinene:



whose optically and chemically pure enantiomers and chemically pure racemates are commercially available. As discussed in Chapter 5, both molecules are conformationally rigid. The IR absorption spectra of camphor and α-pinene are simultaneously measured.

VCD spectra of camphor and α-pinene were first measured at USC in the 1970s [13]. Subsequently, these molecules were frequently used to test the performance of VCD instruments and the reliability of VCD theories [14].

CAMPHOR

The IR and VCD spectra of camphor were measured using samples of (1*R*,4*R*)-(+), (1*S*,4*S*)-(–), and (±) camphor obtained from Aldrich [15]. According to Aldrich, the purities of the (+), (–), and (±) samples were 98, 99, and 96% respectively. In order to assess the optical purities of the (+) and (–) samples, their $[\alpha]_D$ values were measured in ethanol solutions. According to Ramachandran et al. [16], for 100% ee (+) camphor $[\alpha]_D$ = + 43.6 (c5, EtOH). The Aldrich (+) and (–) samples at c5 concentration in EtOH had $[\alpha]_D$ values of +44.0 and –43.5, respectively, and therefore are both optically pure (ee 100%). The solvent used in measuring the IR and VCD spectra of camphor was CCl_4, to minimize the solvent IR absorption and the solute-solvent intermolecular interaction. Solutions of concentrations 0.38 M were used and Harrick cells [17] with KBr windows and pathlengths 236 and 546 μ.

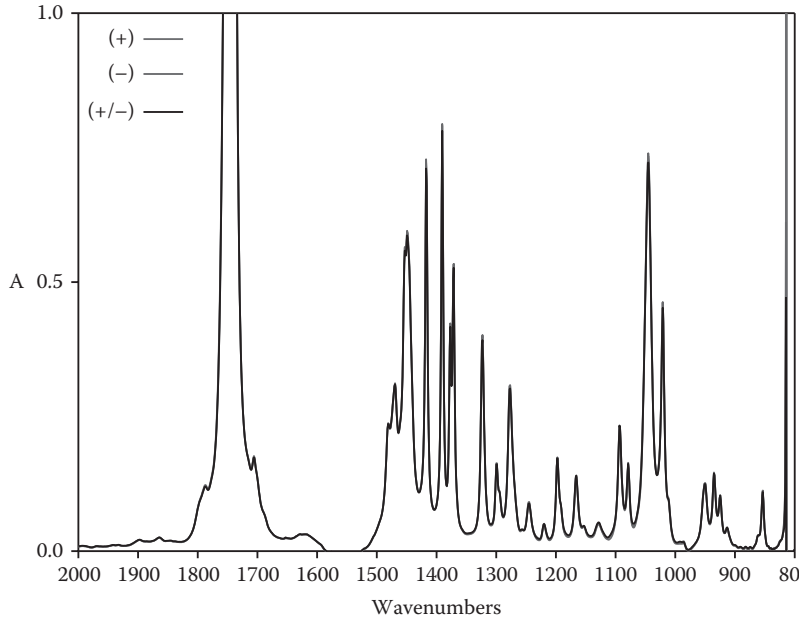


FIGURE 2.7 The IR absorption spectra of 0.38 M CCl_4 solutions of (+), (–), and (±) camphor; pathlength 236 μ.

The IR spectra obtained using the 236 and 546 μ cells are shown in Figures 2.7 and 2.8, respectively, over the frequency range 800–2,000 cm^{-1}. The excellent superposition of the spectra of the (+), (–), and (±) solutions confirms that their purities are identical, as specified by Aldrich. At the pathlength 236 μ, the absorbances of all bands are <1.0, except for the C=O stretching band at 1,745 cm^{-1}, whose absorbance is >>1.0. At the pathlength 546 μ, the absorbances of several bands in the range 1,000–1,500 cm^{-1} are >1.0. The IR spectra in Figures 2.7 and 2.8 are obtained using the IR spectra of neat CCl_4 as the baselines. The IR spectra of neat CCl_4 at 236 and 546 μ pathlengths are shown in Figure 2.9. The strongest absorption of CCl_4 is at the frequencies 790 cm^{-1} and 1,550 cm^{-1}. The impact of the absorption of CCl_4 on the IR spectra of camphor at these frequencies can be seen in Figures 2.7 and 2.8. In the region 800–825 cm^{-1}, the spectra are very noisy. At frequencies close to 1,550 cm^{-1}, the absorbances are negative.

The VCD spectra of the CCl_4 solutions of the (+), (–), and (±) samples, using the 236 and 546 μ cells, are shown in Figures 2.10 and 2.11, over the range 800–1,550 cm^{-1}. The VCD spectra of the (±) solution are compared to the VCD spectra of neat CCl_4 in Figure 2.12. At each pathlength the spectra of the (±) solution and neat CCl_4 differ. The largest difference is at the 546 μ pathlength at 1,045 cm^{-1}, coincident with the IR band at 1,045 cm^{-1}, whose absorbance is 1.6. The difference at this frequency at the 236 μ pathlength is smaller, demonstrating that the VCD artefact is absorbance dependent. To reduce the artefacts in the VCD spectra of the (+) and (–) solutions, the (±) VCD spectrum is subtracted, leading to the (±)-baseline-corrected VCD spectra

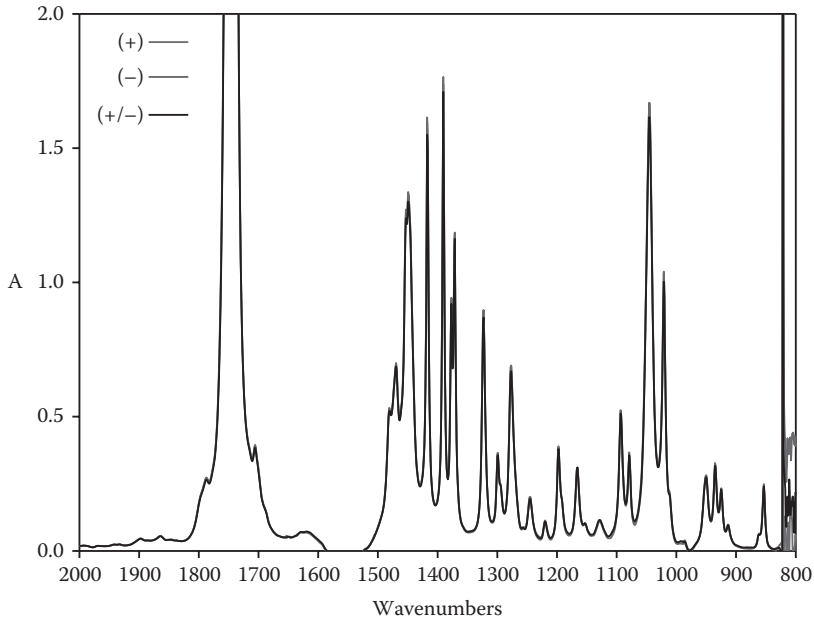


FIGURE 2.8 The IR absorption spectra of 0.38 M CCl_4 solutions of (+), (–), and (±) camphor; pathlength 546 μ.

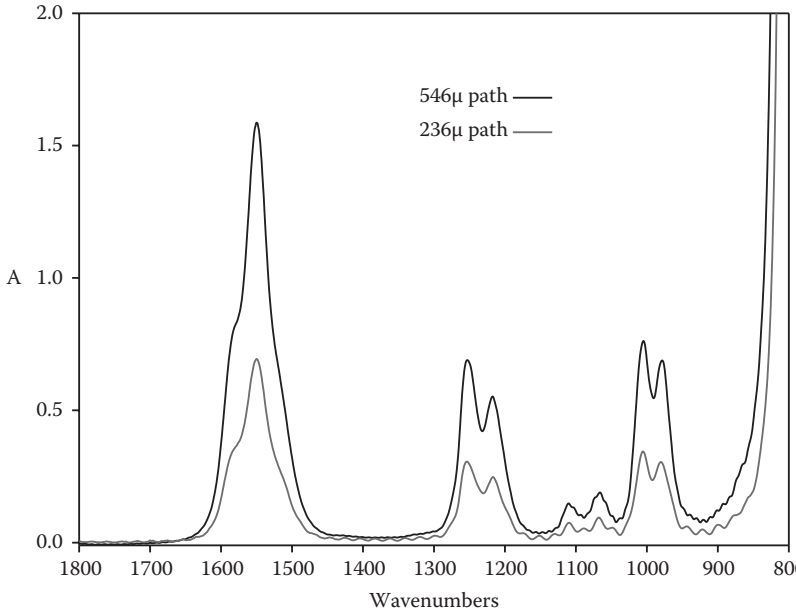


FIGURE 2.9 The IR absorption spectra of neat CCl_4; pathlengths 236 and 546 μ.

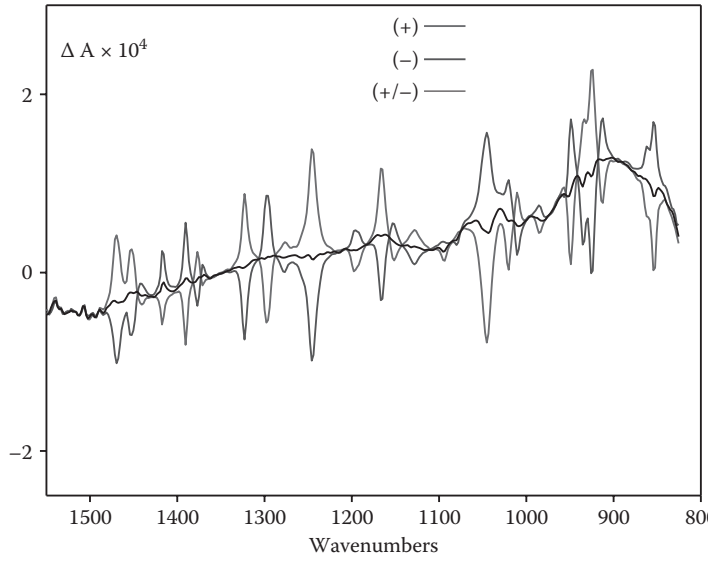


FIGURE 2.10 (SEE COLOR INSERT.) The VCD spectra of 0.38 M CCl_4 solutions of (+), (–), and (±) camphor; pathlength 236 μ.