

# VCD

## Spectroscopy for Organic Chemists

Philip J. Stephens

Frank J. Devlin

James R. Cheeseman



CRC Press  
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**CRC Press**

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Boca Raton London New York

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CRC Press  
Taylor & Francis Group  
6000 Broken Sound Parkway NW, Suite 300  
Boca Raton, FL 33487-2742

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Printed in the United States of America on acid-free paper  
Version Date: 20120221

International Standard Book Number: 978-1-4398-2171-8 (Hardback)

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**Library of Congress Cataloging-in-Publication Data**

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Stephens, Philip J., 1940-  
VCD spectroscopy for organic chemists / Philip J. Stephens, Frank J. Devlin, James R. Cheeseman.  
p. cm.  
Includes bibliographical references and index.  
ISBN 978-1-4398-2171-8 (hardback)  
1. Vibrational spectra. 2. Vibrational circular dichroism. I. Devlin, Frank J., 1949- II. Cheeseman, James R., 1963- III. Title.

QD96.V53S74 2012  
547--dc23

2012000294

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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.

We would also like to thank our very supportive editor, Lance Wobus, the project coordinator, David Fausel, project editor, Marsha Hecht, as well as the production staff at Taylor & Francis.

Finally, we thank our wives, Anne-Marie Stephens, Ann Marie Devlin and Joanne Hiscocks, for their patience and loving support.

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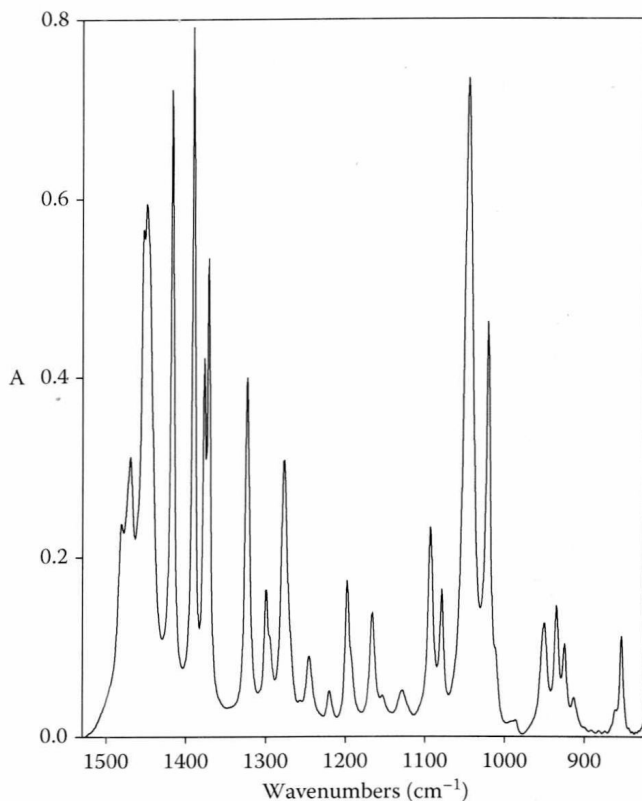
# 1 Introduction to Vibrational Circular Dichroism

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  $h\nu = hc/\lambda = hc\bar{\nu}$  ( $\nu$ ,  $\lambda$ ,  $c$ , 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 path-length 236 microns ( $\mu$ ), and over the IR frequency range, of reciprocal wavelengths (wavenumbers) 1,530–825  $\text{cm}^{-1}$ . Absorption is observed at many frequencies, demonstrating the existence of many vibrationally excited states.

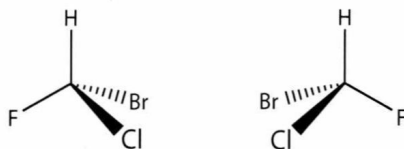
All molecules belong to one of two classes: achiral and chiral. By definition, an achiral molecule is identical to its mirror image; i.e., if the molecule is reflected in a mirror and then rotated, it can be superimposed on the original, unreflected molecule. A chiral molecule is different: the molecule 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



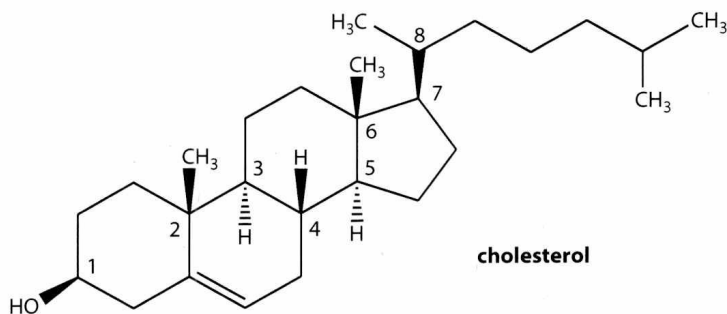
**FIGURE 1.1** The mid-IR vibrational absorption spectrum of a 0.38 M  $\text{CCl}_4$  solution of 1*R*,4*R* camphor. *A* is the absorbance (defined in Chapter 2).

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  $\text{CHFCIBr}$ . The two enantiomers are:



Any molecule of the formula  $\text{CR}_1\text{R}_2\text{R}_3\text{R}_4$  ( $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$  all being different) is also chiral. Of great biological significance is the chirality of amino acids, in which  $\text{R}_1 = \text{H}$ ,  $\text{R}_2 = \text{NH}_2$ ,  $\text{R}_3 = \text{COOH}$ , and  $\text{R}_4$  depends on the specific amino acid (e.g., in alanine,  $\text{R}_4 = \text{CH}_3$ ). 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:

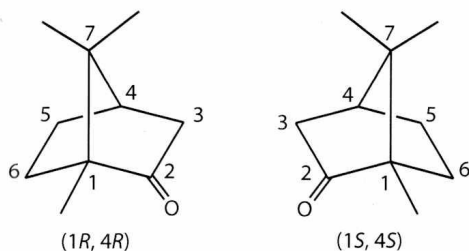


In 1956, Cahn, Ingold and Prelog introduced a notation that specifies the chiralities of stereogenic C atoms: a C atom is either *R* or *S* [1]. The overall three-dimensional (3D) structure of an enantiomer of a chiral molecule can then be defined by listing which atoms are *R* or *S*. For example, naturally 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.

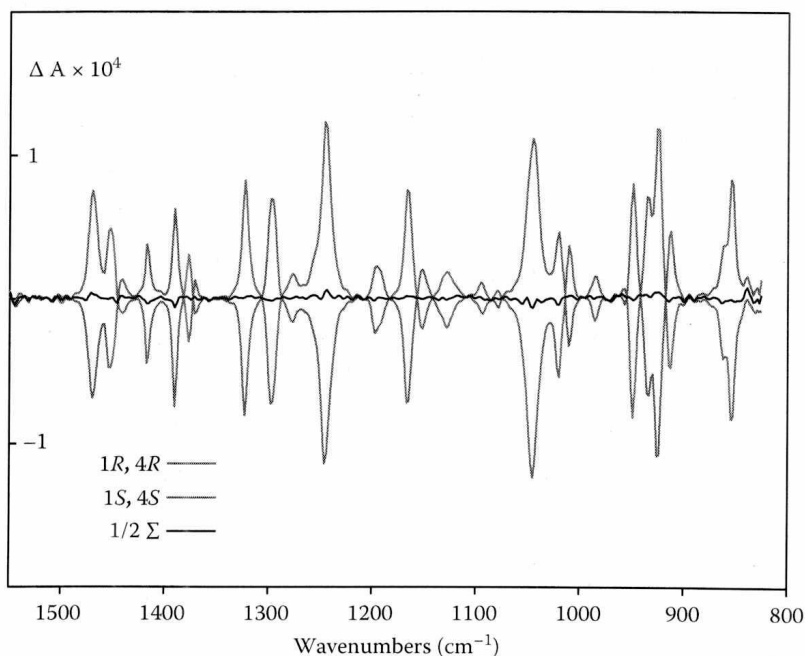
The electric and magnetic fields of a linearly polarized light wave each oscillate sinusoidally in a plane containing the propagation direction, the electric field and magnetic field planes being perpendicular to each other. Passage of a linearly polarized light wave through an optical device called 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  $\text{CCl}_4$  and a cell of pathlength 236  $\mu$ . 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  $\text{CCl}_4$  solutions of 1*R*,4*R* and 1*S*,4*S* camphor, using a cell of pathlength 236  $\mu$ .  $\Sigma$  is the sum of the spectra. The measurement of the spectra is discussed in Chapter 2.

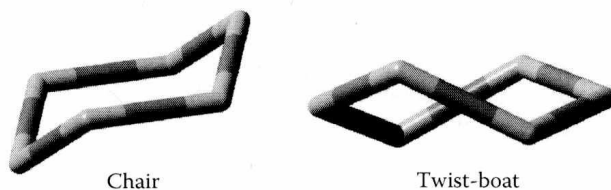
Electronic absorption and CD typically occur in the visible-ultraviolet (VIS-UV) spectral region (200–1,000 nm, 10,000–50,000  $\text{cm}^{-1}$ ), where light frequencies are much higher than in the IR spectral region.

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, Moscovitz, Klyne, and Djerassi proposed the octant rule, which predicts the sign of the ECD of the lowest energy electronic excitation of a carbonyl ( $\text{C}=\text{O}$ ) 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:



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  $\alpha$ . The OR  $\alpha$  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  $\ell$  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.  $\alpha$ -Methylbenzylamine
3. N,N- $\alpha$ -Trimethylbenzylamine
4. 3-Methyl-cyclopentanone
5. 3-Methyl-cyclohexanone
6. Menthol
7.  $\alpha$ -Pinene
8.  $\beta$ -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.  $\alpha$ -Deutero-propylbenzene
23.  $\text{Fe}(\text{C}_5\text{H}_5)_2(\text{P}(\text{C}_6\text{H}_5)_3)_2(\text{CO})(\text{Et})$

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  $>1,600\text{ cm}^{-1}$ , 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  $\sim 650\text{ cm}^{-1}$ , 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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