Look at molecules with a new twist of light

CHIRAL*IR*-2X™

VCD Spectrometer

BioTools Characterization Experts: Chirality & Biologics

Vibrational Circular Dichroism

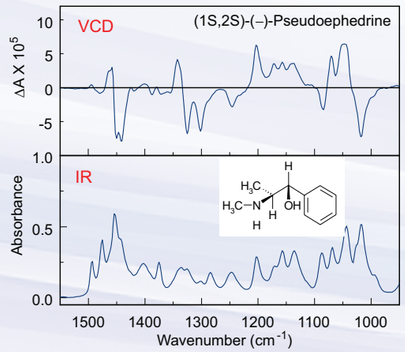
VIBRATIONAL CIRCULAR DICHROISM (VCD) WAS FIRST MEASURED IN 1973

In 1997, BioTools commercialized the technology by introducing the ChiralIR™. We are proud to be the first company to present a stand-alone dedicated VCD spectrometer and its powerful applications in the fields of chemistry and biology.

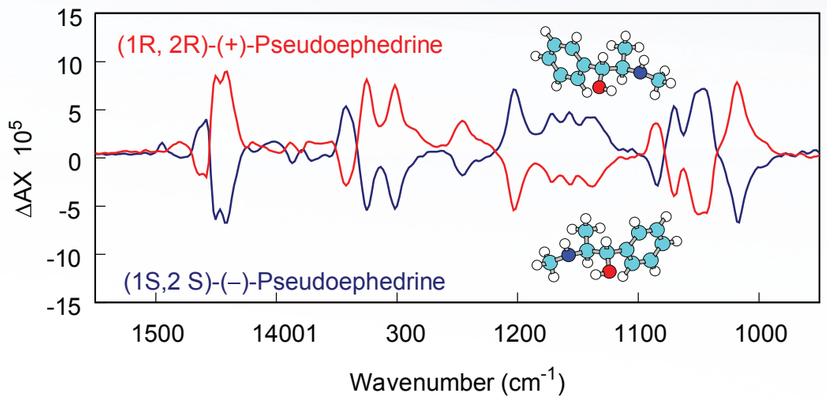
VCD is defined as the difference in the absorbance (A) of left minus right circularly polarized infrared radiation, $A=A_L-A_R$. VCD extends the functionality of electronic Circular Dichroism (CD) into the infrared spectral region where vibrational tranisitions in molecules are observed.

VCD combines the structural specificity of FT-IR spectroscopy with the stereo-sensitivity of circular dichroism. This gives access to multiple, well-defined bands that provide molecular quantitative information. Measurements can be done in solids and solutions.

ONE MEASUREMENT GIVES TWO SPECTRA:
FT-IR AND VCD



ENANTIOMERIC PAIRS OF CHIRAL MOLECULES



Chiral *IR -2X*™ VCD Spectrometer

Unique Advantages of the CHIRAL*IR-2X*™ VCD Spectrometer

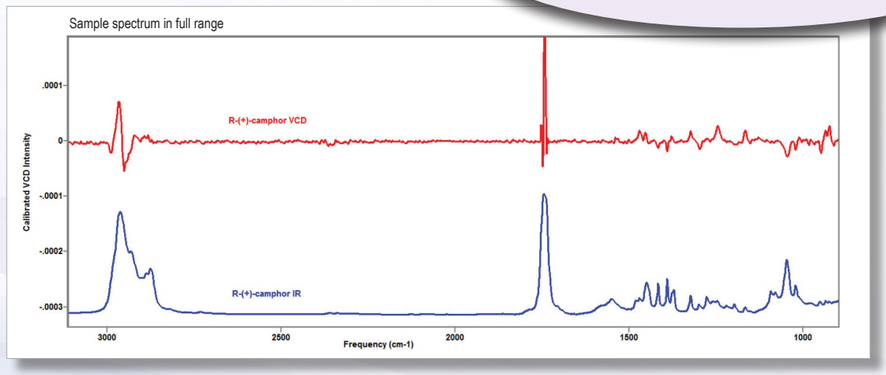
Dual Source increases signal-to-noise ratio (S/N) of approximately 3.6 times over any single-source system

Exclusive stage for elimination of cell artifacts with *Sync*RoCell™

30-48 hour hold detector time

Simultaneous collection of IR & VCD spectra (AC & DC)

Complete spectral range of measurement 4000-850 cm^{-1} (no change of filters required)



- Upgrade availability to patented Dual*PEM*™ technology which allows artifact-free measurement of solids
- Factory aligned baseline resulting in immediate and routine operation
- Digital signal processing — no lock-in or electronic filter needed
- Permanently aligned - Lifetime warranty on scan mechanism
- Training and support by the experts with unprecedented knowledge in design and applications of VCD

Standard IR Cell

- Micro measurements with new *VCDμ*Sampl*IR*™
- Chiral*IR-2X*™ comes with standard IR cells (optional *Bio*Cell™ and TempCon available)
- Chiral*IR-2X*™ is also available in the Near-IR region.
  The instrument can also be configured for coverage from 2000 to 4000 cm^{-1} or from 4000 to 10000 cm^{-1}

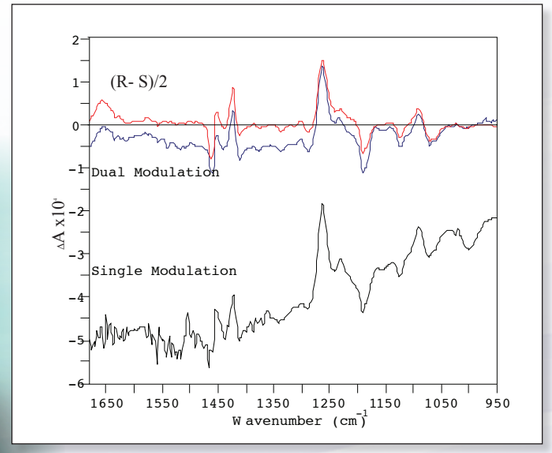
BioTools

Dual*PEM*™ Accessory (internal)

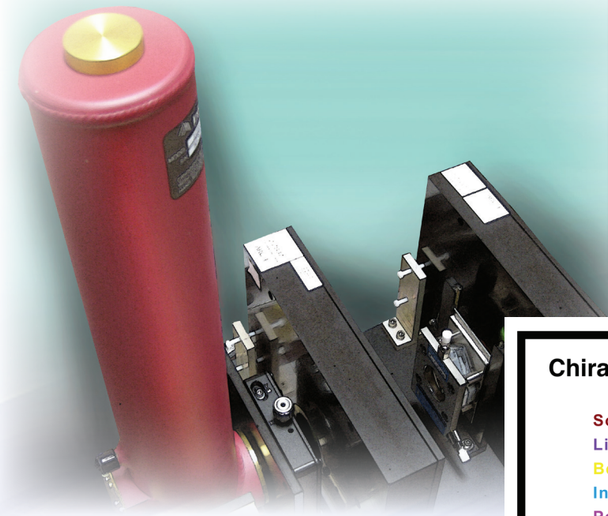
Dual*PEM*™ provides significant improvement in baseline position and stability over single PEM systems.

The second PEM subtracts birefringence from optics in real-time thus providing a significant reduction in artifacts, improved stability and is a requirement for measuring VCD of solid samples.

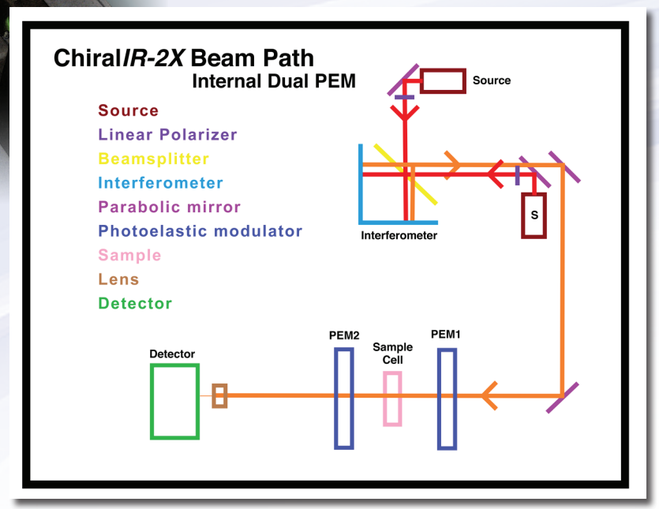
- Now available as an internal or external accessory
- Dual*PEM*™ is a patented technology of BioTools



Dual*PEM*™ inside the CHIRAL*IR-2X*™ VCD Spectrometer



Look at molecules with a new twist of light



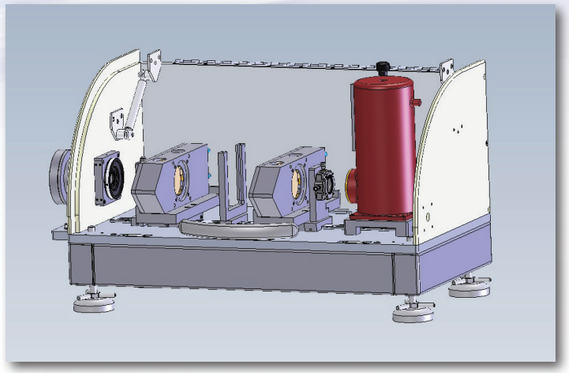
MANTIS™ Dual*PEM*™ Accessory (external)

MANTIS™ — External Dual*PEM*™ Option

Chiral*IR-2X*™ Instrument

MANTIS™ Dual*PEM*™ Accessory

(connects seamlessly to side of **Chiral*IR-2X*™**)



MANTIS™ Dual*PEM*™

External Dual*PEM*™ Applications

- Reaction Monitoring
- Micro Measurements – VCDμSamplIR™
  Sampling of solid samples at 1mm² spatial resolution
- Magnetic VCD (MVCD)
- Matrix Isolation
- Gas Sampling

...any other accessory that needs more space than a standard sample or compartment

To upgrade your existing FT-IR Spectrometer to VCD capability, please contact us

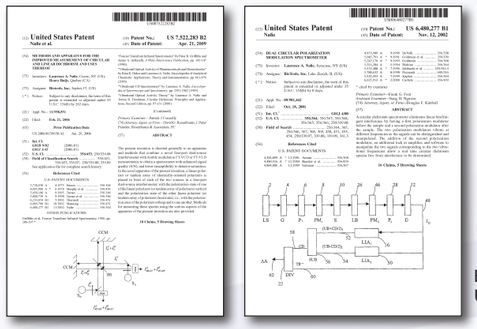
BioTools

Award Winning Patented Technology

Chiral*IR-2X*™ Technology

- Thousands of molecules measured using the Chiral*IR* platform
- Hundreds of patents on new compounds
- Hundreds of customer scientific papers using the Chiral*IR* series
- Used for submissions to regulatory agencies
- Articles in U.S. Pharmacopoeia

Award Winning Features & Technology



BioTools
U.S. Patents

WE PROUDLY SERVE HUNDREDS OF COMPANIES, UNIVERSITIES AND GOVERNMENT AGENCIES

AMGEN • Astellas • Astra-Zeneca • GlaxoSmithKline • Bristol-Myers Squibb
Eli Lilly • Janssen • Lupin • Merck • Pfizer • Takeda • *and others...*

WHAT OUR CUSTOMERS ARE SAYING

"Over the last several years, the Vibrational Circular Dichroism (VCD) technique has dramatically revitalized the utility and visibility of vibrational spectroscopy within pharmaceutical drug discovery. The ability of VCD to deliver absolute chiral assignments without the need for standards or crystallizations, renders the technology a vital complement to traditional pharmaceutical analytical technologies. "

Dr. Don Pivonka, AstraZeneca

"As a long-standing analytical chemist in pharmaceutical research with a focus on vibrational spectroscopy, I recognized the potential impact VCD could have on many aspects of big pharma. With the ChiralIR I have successfully assigned the configurations of more than 600 exploratory drug molecules, providing an international service to research facilities in Europe and the United States.I consider this instrument to be world-class and a bargain for the price given its state-of-the art technology and incredible level of reliability. "

Dr. Douglas James Minick, Senior Research Investigator, GlaxoSmithKline

VCD Accessories

*Sync*RoCell™

Rotating stage for elimination of cell artifacts

TempCon™

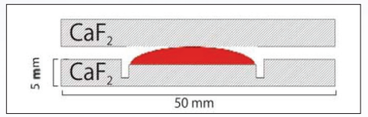
Peltier based temperature controller

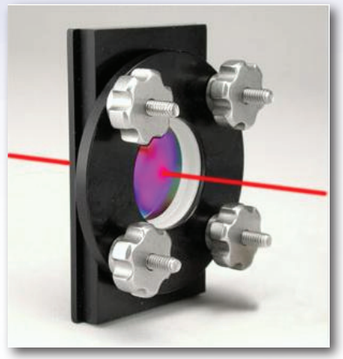
TempCon™ temperature controller unit is designed for use in FT-IR spectrometers with two types of windows: large circular BioCell™ windows and rectangular windows. The controller can be controlled either manually or through computer input.

The Ramp-Soak Control Interface allows for temperature studies that can be aligned with FT-IR scanning software and can be used in applications such as effect of temperature on protein conformation.

BioCell™

The CaF_2 cell for IR/UV-CD spectroscopy is created between a perfectly flat, optically clear plate and another plate, the center of which is deepened to form a recessed parallel surface surrounded by a groove. The cells are very easily assembled and disassembled, filled with solution, and washed between measurements.





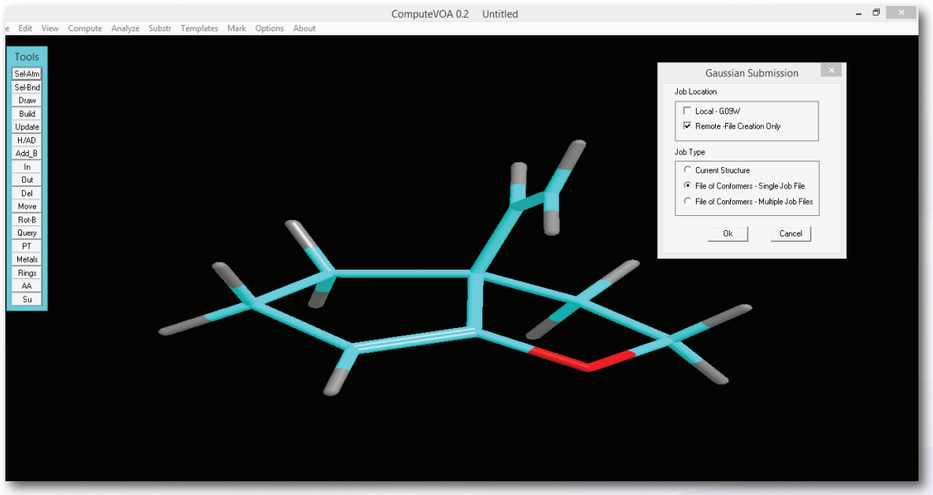
Wide range of available path lengths: ~5-10, ~20, ~40, ~80 and ~120 mm

5 mm thickness x 50 mm diameter standard size. Cells with 4 mm x 40 mm dimensions and other custom sizes are also available

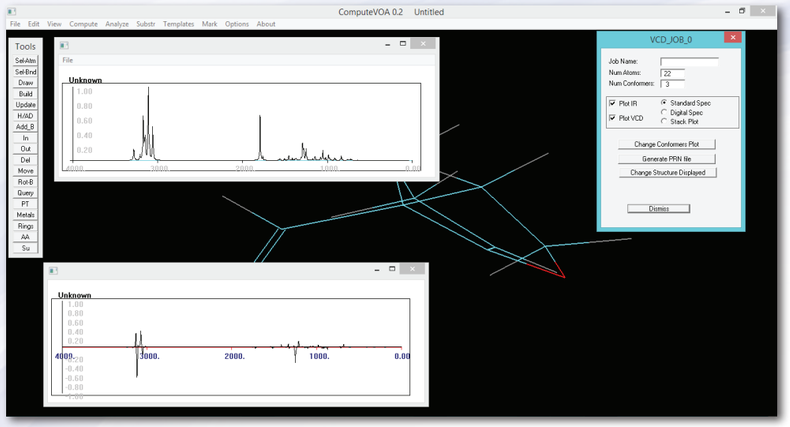
BioTools

Compute*VOA*™ Software

An all inclusive package for calculation of VCD spectra. Combines: structure building, extensive conformational search, easy integration with Gaussian09 and plotting of calculated spectra.

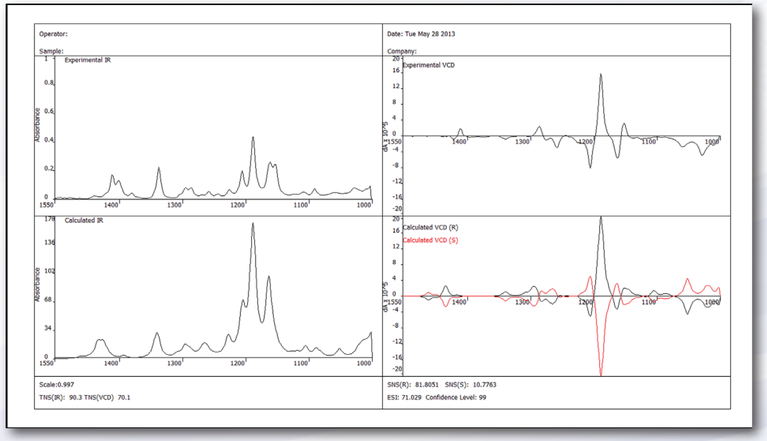


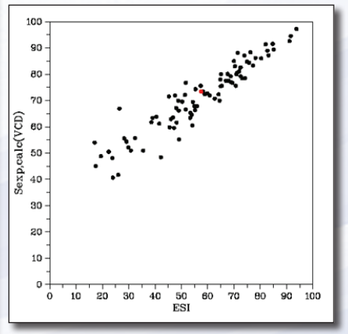
Compute*VOA* orchestrates a complex molecular dance. Data enters the stream through a molecule builder/ structure importer then moves into a robust molecular mechanics conformational search algorithm. The results then pass through a transparent handshake to Gaussian 09 (Gaussian, Inc. Pittsburgh,PA) where quantum mechanics determines the molecule's structure and properties. It then returns seamlessly to ComputeVOA for a Boltzmann-averaging of conformers and plotting of the IR and VCD spectra. The final output: The specific stereo isomers' 3D structure and accompanying InfraRed and Vibrational Circular Dichroism spectra.



Compare*VOA*™ Software

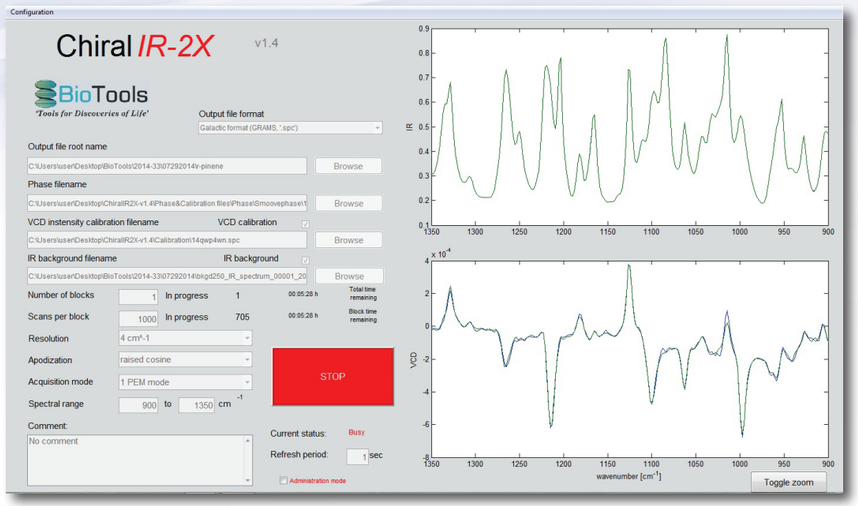
Confidence level algorithm for comparing VCD (and ROA) experimental and theoretical spectra; the output generates two plots: IR and VCD comparisons of measured and calculated spectra, and statistical plot against a database of prior comparisons.





Chiral*IR-2X*™ Software

Included with the CHIRAL*IR*-2X™. Easy to use, no learning curve.



Chiral Drugs

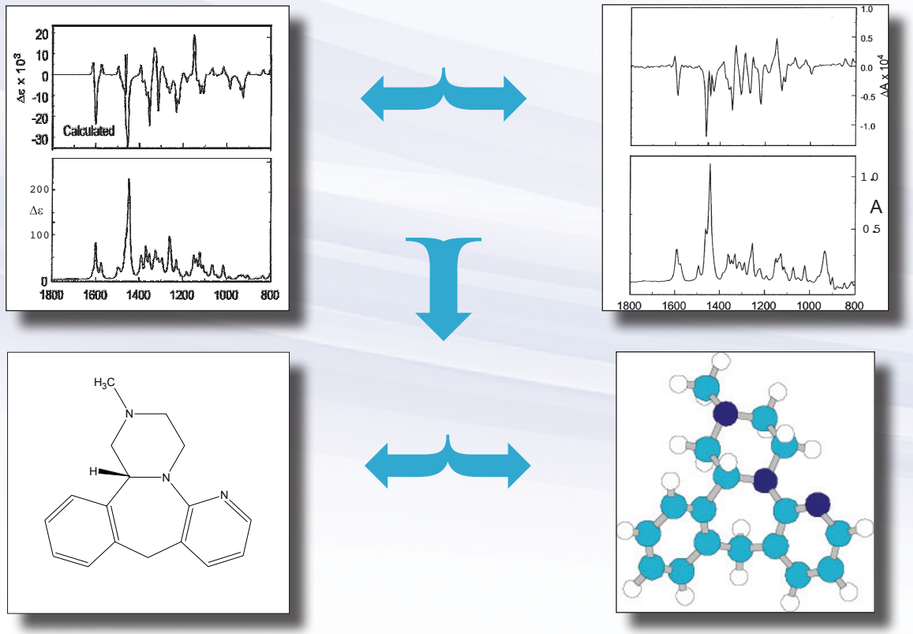
Since commercial introduction of VCD by BioTools thousands of compounds have been determined using this technology. It has become the-must-have-tool in the pharmaceutical and other industries.

ABSOLUTE CONFIGURATION DETERMINATIONS

Step 1: Choose Configuration
e.g. (R) - Mirtazapine Configuration

Step 2: Calculate IR (bottom) and VCD (top) spectra of (R) - Mirtazapine

Step 3: measure IR (bottom) and VCD (top) spectra of available enantiomer, e.g. (-) -Mirtazapine



Comparison of observed VCD spectra (right) with calculated VCD spectra (left) unambiguously determines absolute configuration (-)-(R)-Mirtazapine and conformation in solution as shown above.

Chiral Drugs Quality Control

VCD can be used as a chiral measure for characterization of raw materials for process analytical technology (PAT) during development, synthesis, formulation, and final production of drug substances and drug products. VCD also can be used to test the interaction between formulated chiral drug substances and excipients.

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Vibrational Circular Dichroism as a New Technology for Determining the Absolute Configuration, Conformation, and Enantiomeric Purity of Chiral Pharmaceutical Ingredients

Laurence A Nafie (Syracuse University); Oliver McConnell (John I Hass, Inc.); Doug Minick (GlaxoSmithKline); Edwin Kellenbach (Merck & Co., Inc.); Yanan He, Bo Wang, Rina K Dukor (BioTools, Inc.); Michael D. Bartberger (Amgen, Inc.)

“The absolute configuration of chiral compounds is critical in understanding structure-activity relationships, and in developing appropriate chiral separation, resolutions, or synthesis.”

“Vibrational Circular Dichroism (VCD) data are now being used to support New Drug Applications and patents.”

“The bottom line with VCD or any new analytical method is if the data are convincing to the scientists developing the drug, then that data should be convincing to the scientists here at the FDA.”
Stephen P. Miller, Office of New Drug Chemistry,FDA’s Center for Drug Evaluations & Research

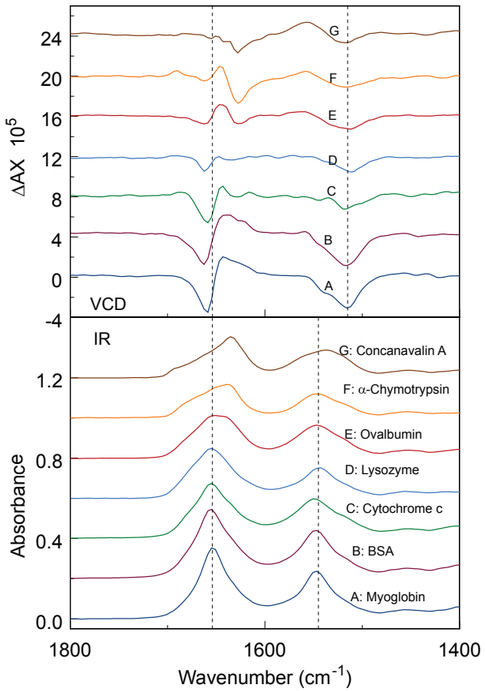
Chemical & Engineering News - 7/18/05

VCD Application Examples

Proteins - Peptides - Carbohydrates - Nucleic Acids

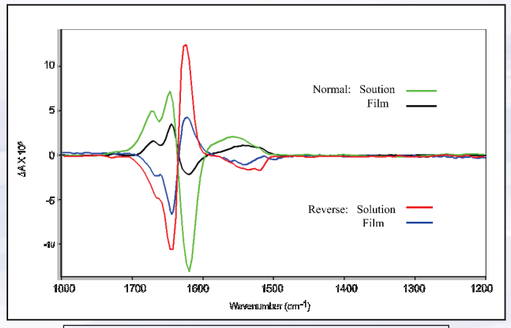
PROTEIN / PEPTIDE STRUCTURAL STUDIES

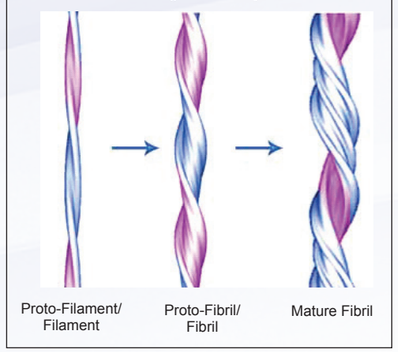
a) Secondary Structure



b) Characterization of Fibrils

VCD SHOWS A HIGH SENSITIVITY TO STRUCTURE OF FIBRILS





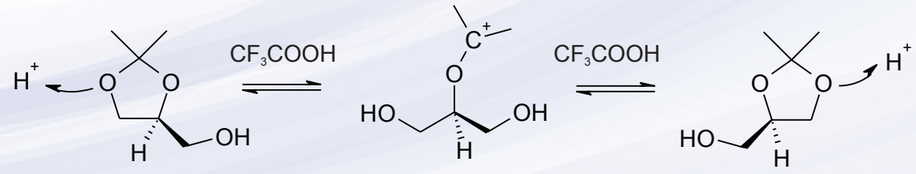
VCD provides an enhanced sensitivity to secondary structure of proteins and peptides. The changes in VCD spectra are observed in both the Amide I and II regions. The VCD sign of Amide I band changes for proteins with the two most common motifs - α-helical protein myoglobin (lower spectra) and a primarily β-sheet containing proteins concanavalin A and chymotrypsin (upper spectra).

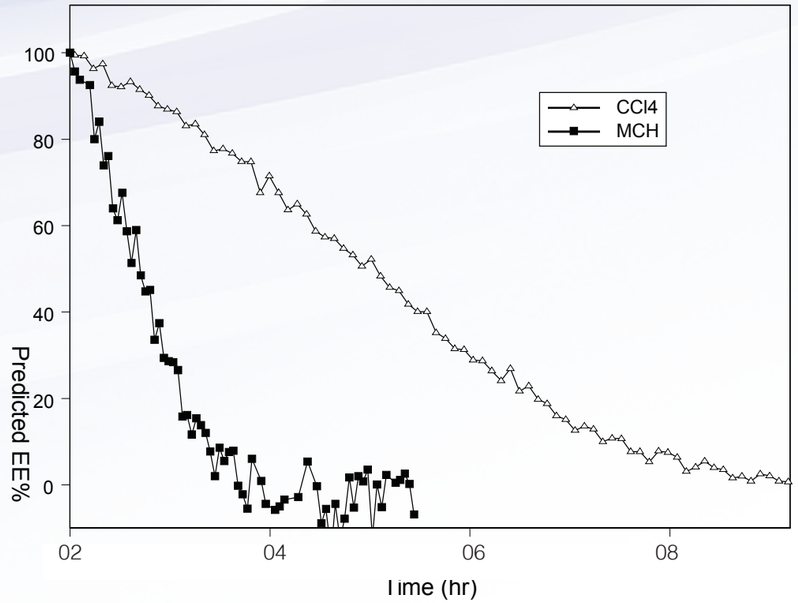
FEATURES:

- The largest FT-VCD protein database available
- Dedicated software for protein data analysis

Reaction Monitoring

ASYMMETRIC REACTION MONITORING





During the course of a chemical stereospecific reaction, the combination of *IR*, for detection of changes in mole fraction composition, and *VCD*, for combined mole fraction composition and enantiomeric excess (%EE), enables one to follow %EE of each chiral species as a function of time. The figure above shows epimerization versus time of DDM with trifluoroacetic acid in two different solvents.

Customer Support

CHIRAL*IR-2X*™ Installation

- Installation and training on measurement and interpretation of VCD spectroscopy of small molecules by experienced scientists
- Qualification provided (IQ/OQ/PQ)
- BioTools' combined service and application knowledge

Technical Support and Maintenance

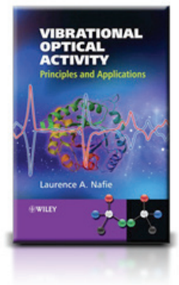
BioTools provides users of CHIRAL*IR-2X*™ with complete maintenance and technical support. Each instrument sold comes with a full one year warranty. Additional maintenance contracts can be purchased.

E-mail based help desk is open 365/24/7 at info@btools.com

Consulting

BioTools offers consulting services that bring our expertise on spectroscopy of chiral molecules to bear on your applications and needs. Costs depend on the extent of the study and degree of urgency.

Vibrational Optical Activity: Principles and Applications



by Laurence A. Nafie

This unique book stands as the only comprehensive introduction to vibrational optical activity (VOA) and is the first single book that serves as a complete reference for this relatively new, but increasingly important area of molecular spectroscopy.

"Vibrational Optical Activity: Principles and Applications" will take the reader from the basic theory through the practical and instrumental approaches, providing a unified, comprehensive description to the field of VOA that gives both introductory and in-depth coverage to VCD and ROA. Applications include the analysis of all classes of chiral molecules, including organic and inorganic molecules, metal complexes, pharmaceutical and natural product molecules, and the full range of biological molecules such as amino acids, peptides, sugars, proteins, protein fibrils, carbohydrates, nucleic acids, viruses and bacteria.

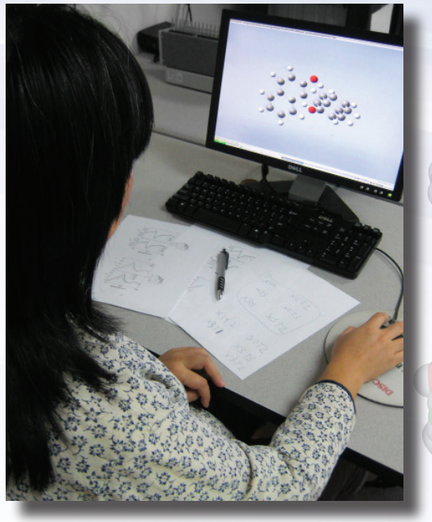
Written in a thorough and progressive style, it will appeal to advanced undergraduates, graduates and research groups in academia as well as researchers and technicians in the pharmaceutical and biotechnology industries.

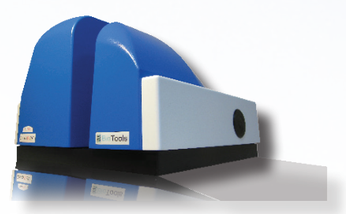
Signed Copies Available

Lab Services

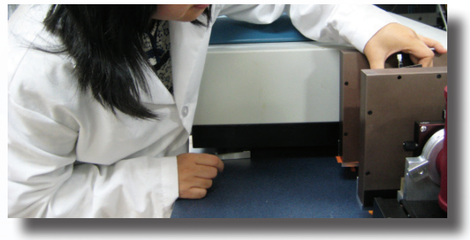
CHIRAL MOLECULES

- Absolute Configuration
- VCD Measurements
- *ab initio* calculations (VCD, ECD, ROA)
- VCD Consulting & Training
- Chiral Methods Development
- % Enantiomeric Excess
- Small Scale (~1g) Purifications





ChiralIR-2X™



PROTEINS / PEPTIDES

- Secondary Structure
- Formulation of Biologics
- Effect of Environmental Changes - temperature, pH, storage
- Structural comparison of production lots
- Comparability

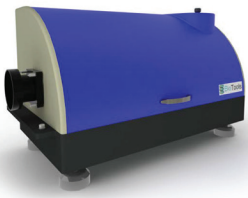
BioTools

Characterization Experts: Chirality & Biologics

Prota-*3S*™ FT-IR

Chiral*RAMAN*-2X™ (ROA, Now with AFM / TERS)

µBio*RAMAN*™



Mantis™ (Dual*PEM* VCD accessory)

ComputeVOA™

CompareVOA™

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