Chirality in Molecular Vibrations: VCD and ROA

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Parma
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Outline

- Definitions of VOA
- Measurement of VCD and ROA
- Levels of Resonance Raman Scattering
- Resonance ROA
- Velocity Formulation of VCD
- Vibrational Current Density
- Determination of Absolute Configuration
- Enhanced VCD – Amyloid Fibrils and Low-Lying Electronic States
- Conclusions

Definitions of VOA

Classical Forms of Optical Activity

Optical Rotation (Optical Rotatory Dispersion, ORD, CB)

$$\alpha = \frac{\pi}{\lambda}(n_L - n_R)$$

Ellipticity (Circular Dichroism, CD)

$$\psi = \frac{\pi}{\lambda}(k_L - k_R)$$

Complex Refractive Index

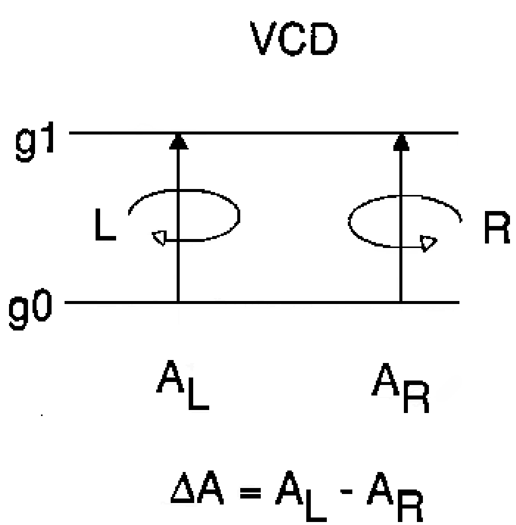
$$\tilde{n} = n + ik = n' + in''$$

VIBRATIONAL OPTICAL ACTIVITY

Differential Interaction of a Chiral Molecule with Left and Right Circularly Polarized Radiation During Vibrational Excitation

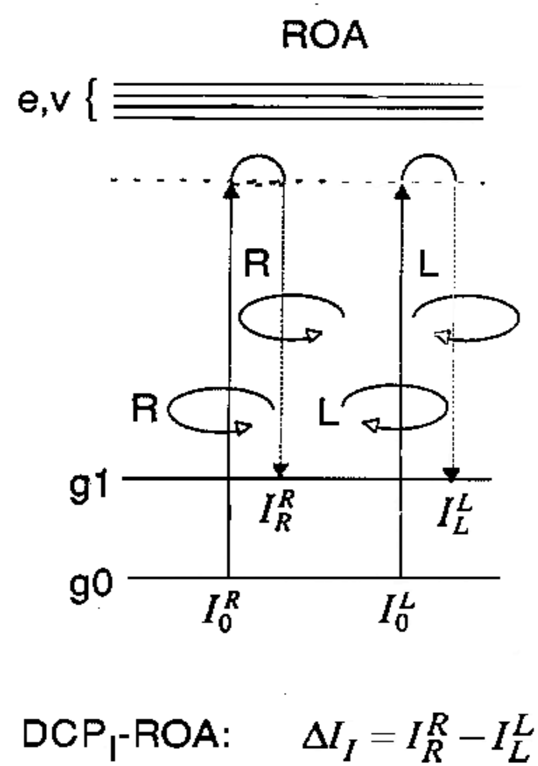
VIBRATIONAL CIRCULAR DICHROISM

Differential Absorption of Left and Right Circularly Polarized Infrared Radiation



RAMAN OPTICAL ACTIVITY

Differential Raman Scattering of Left and Right Incident and/or Scattered Radiation



Forms of Circular Polarization
Vibrational Optical Activity

VCD

$$\Delta A(\bar{\nu}) = A_L(\bar{\nu}) - A_R(\bar{\nu})$$

ICP-ROA

$$\Delta I_\alpha(\bar{\nu}) = I_\alpha^R(\bar{\nu}) - I_\alpha^L(\bar{\nu})$$

(Incident CP)

SCP-ROA

$$\Delta I^\alpha(\bar{\nu}) = I_R^\alpha(\bar{\nu}) - I_L^\alpha(\bar{\nu})$$

(Scattered CP)

DCP_I-ROA

$$\Delta I_I(\bar{\nu}) = I_R^R(\bar{\nu}) - I_L^L(\bar{\nu})$$

(In-Phase Dual CP)

DCP_{II}-ROA

$$\Delta I_{II}(\bar{\nu}) = I_L^R(\bar{\nu}) - I_R^L(\bar{\nu})$$

(Out-of-Phase DCP)

VCD & ROA Short History

- VCD
- Discovered in 1974 by Holzwarth
- Confirmed by Nafie, Cheng, Keiderling & Stephens in 1975, 1976
- FT-VCD discovered by Nafie in 1978
- Commercialized by BioTools and ABB Bomem in 1997
- 2nd generation spectrometers w/time sampling - 2010

ROA

- Discovered in 1973 by Barron & Buckingham, ICP-ROA
- Confirmed by Hug in 1975
- SCP/DCP-ROA discovered by Nafie 1987
- New ROA Design, Hug 1999
- Commercialized by BioTools in 2003
- 2nd generation spectrometer w/ microscope - 2009/10

Classes of Molecules and Techniques VCD & ROA

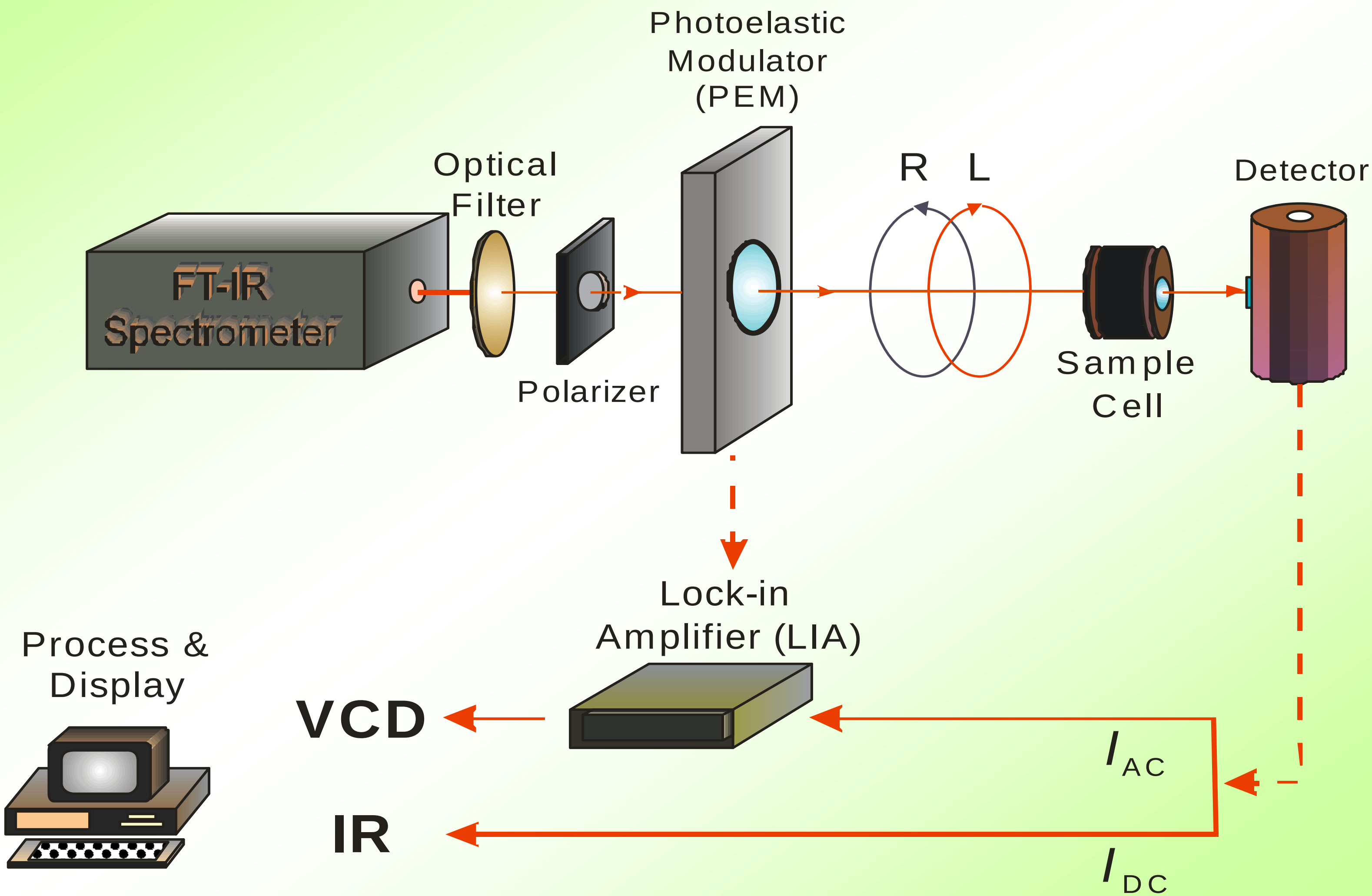
- VCD
- Small Organic Molecules, Pharmaceuticals and Natural Products
- Proteins, Peptides, Amino Acids, Sugars,Nucleic Acids, DNA, RNA Glycoproteins
- Transition Metal Complexes with Enhance VCD for Low-Lying States
- Chiral Polymers
- Supramolecular Structures including Protein Fibrils
- Solutions, Films, Solid Microcrystals, Spray-Dried Films
- Accurate Quantum Calculations

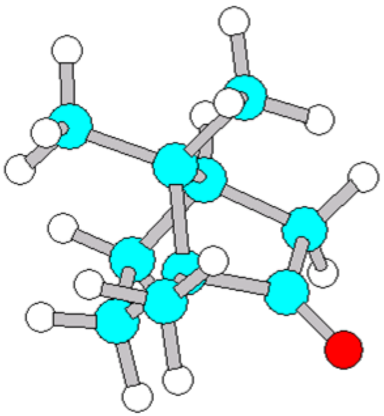
ROA

- Proteins, Peptides, Amino Acids, Sugars, Nucleic Acids, DNA, RNA, Glycoproteins
- Small Organic Molecules, mostly neat liquids
- Viruses
- Surface-Enhanced ROA (SEROA) of Adsorbed Molecules on Metal Surfaces
- Resonance ROA (RROA)
- Accurate Quantum Calculations

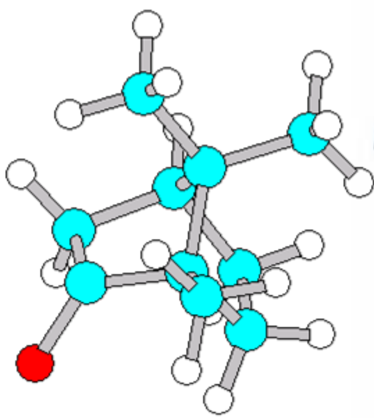
FT-VCD Measurements

FT-VCD Instrumental Layout

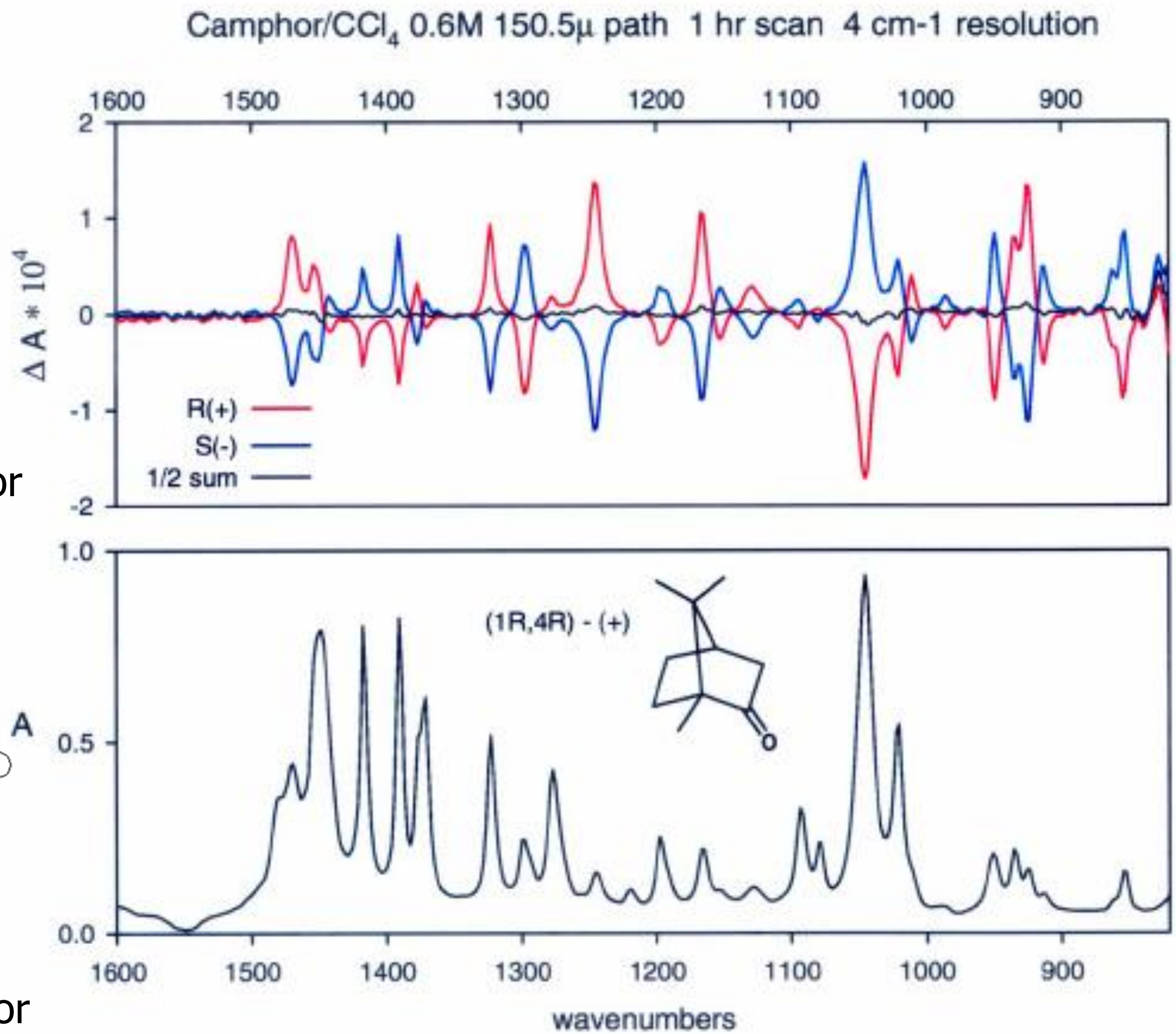




(1*R*,4*R*)-(+)-camphor



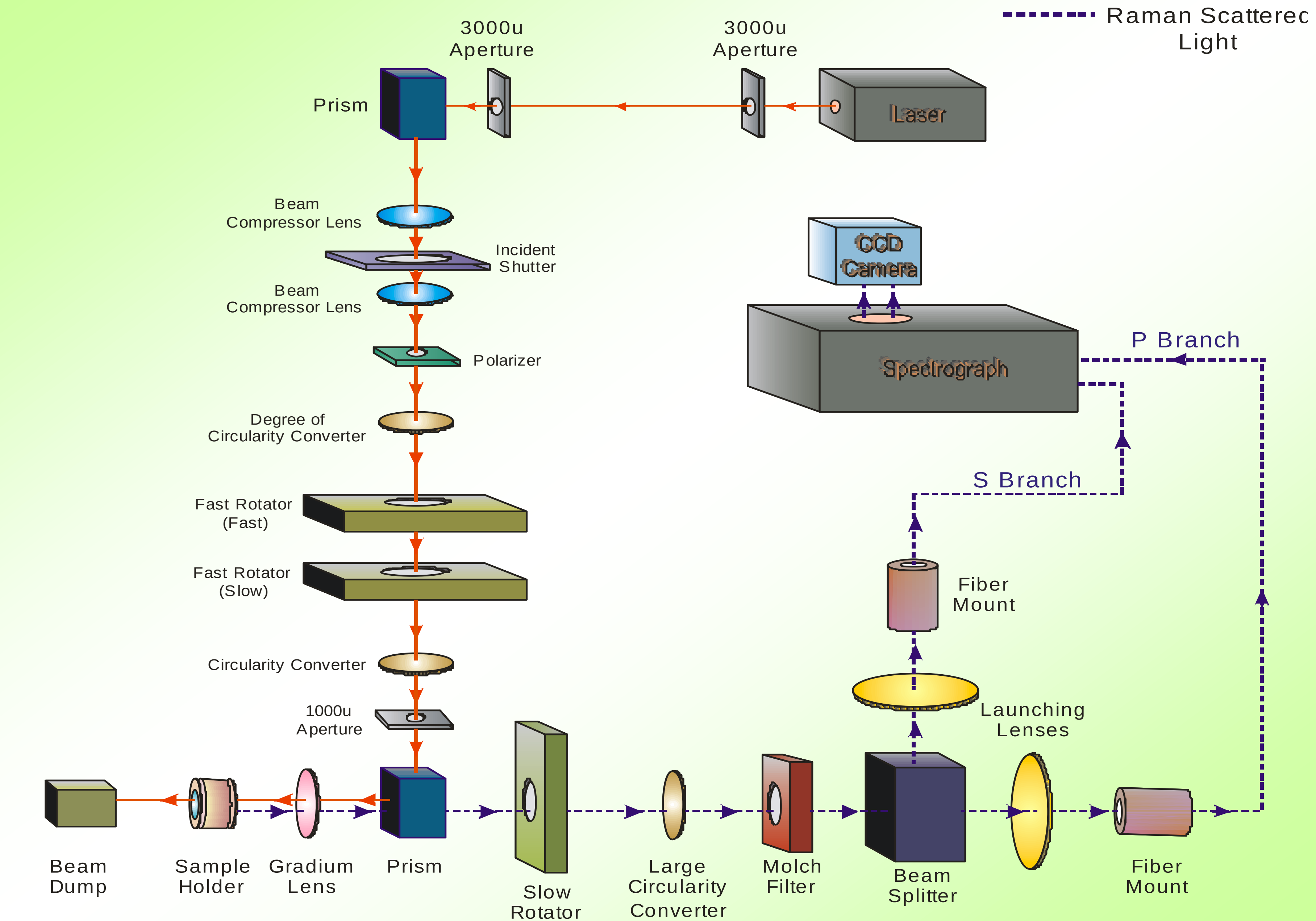
(1*S*,4*S*)-(-)-camphor

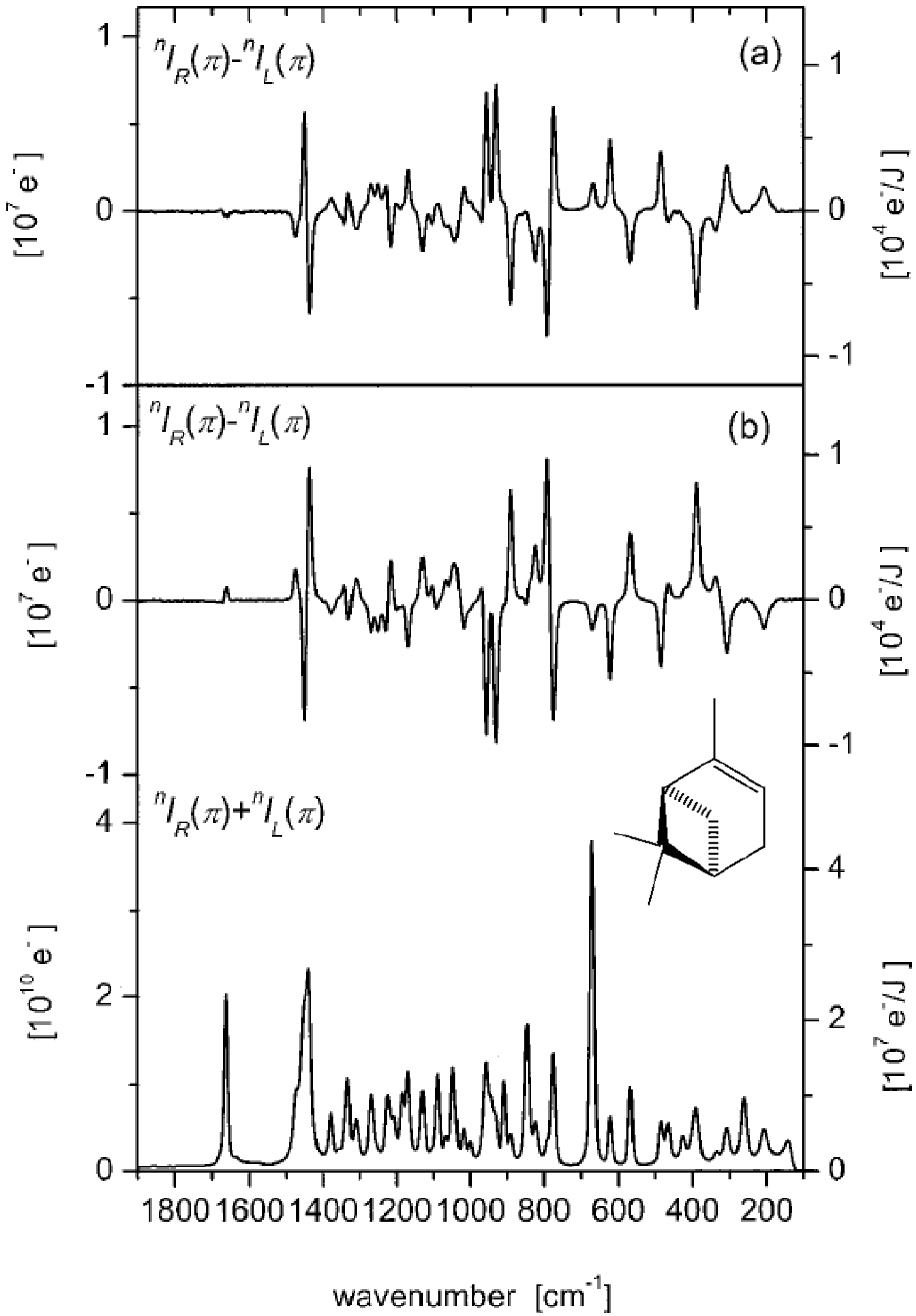


Enantiomers: IR spectra are identical, VCD spectra are opposite in sign

CCD-ROA Measurements

Path of Laser Activity in Chiral *RAMAN*





Measured SCP-ROA Spectra

(a) ROA of S-(-)-α-pinene

(b) ROA of R-(+)-α-pinene

(c) Raman spectrum of α-pinene

Research Article

Journal of RAMAN SPECTROSCOPY

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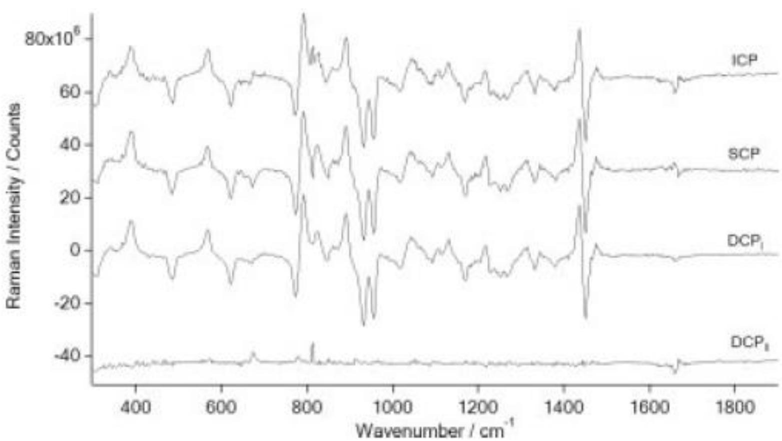
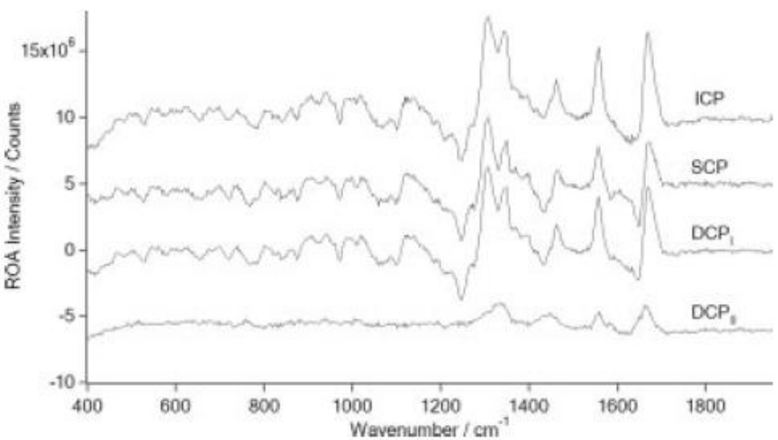
(wileyonlinelibrary.com) DOI 10.1002/jrs.3000

Simultaneous acquisition of all four forms of circular polarization Raman optical activity: results for α-pinene and lysozyme

Honggang Li[a]* and Laurence A. Nafie[a,b]





Degrees of RR and RROA

Degrees of RR and RROA

GU – General Unrestricted Theory

FFR – Far-From-Resonance Theory

NR – Near-Resonance Theory

SES – Single-Electronic-State Theory

MES – Multiple-Electronic-State Theory

General Unrestricted Theory

(GU Level)

Exact Excited-State Vibronic Detail

- Raman tensor is not symmetric
- Raman tensor is time-reversal invariant
- 3 Raman Invariants, 10 ROA Invariants
- ICP-ROA does not equal SCP-ROA
- DCP_{II}-ROA is non-zero
- Software routines not available

Far-From-Resonance (FFR) Theory

No Excited State Vibronic Detail

- Raman tensor is symmetric
- Raman tensor is not time-reversal invariant
- Incident and scattered radiation have the same degree of pre-resonance
- 2 Raman Invariants, 3 ROA Invariants
- ICP-ROA, SCP-ROA and DCP_I-ROA equal
- DCP_{II}-ROA is equal to zero
- Software routines available commercially from Gaussian, Inc.

Near-Resonance (NR) Theory
(GU Invariant Level)

Simple Excited State Vibronic Detail

- Raman Tensor is not symmetric
- Raman tensor is time-reversal invariant
- Incident and scattered radiation have different degrees of pre-resonance
- 3 Raman Invariants, 10 ROA Invariants
- ICP-ROA, SCP-ROA, and DCP_{II}-ROA differ from each other
- DCP_{II}-ROA is non-zero
- Software routines not available

Near Resonance (NR) Theory of Vibrational Raman and ROA

Theor Chem Account (2008) 119:39–55
DOI 10.1007/s00214-007-0267-9

REGULAR ARTICLE

Theory of Raman scattering and Raman optical activity: near resonance theory and levels of approximation

Laurence A. Nafie

Comparison of FFR Theory to NR Theory

FFR Theory (Symmetric Raman Tensor)

$$\left(\alpha_{\alpha\beta}\right)^{a}_{g1,g0} = \frac{2}{\hbar}\sum_{e}\omega^{0}_{eg}\,\mathrm{Re}\left[\frac{[(\hat{\mu}_{\alpha})^{0}_{ge}(\hat{\mu}_{\beta})^{Q_a}_{eg}]}{(\omega^{0}_{eg})^{2}-\omega_{0}^{2}}+\frac{[(\hat{\mu}_{\alpha})^{Q_a}_{ge}(\hat{\mu}_{\beta})^{0}_{eg}]}{(\omega^{0}_{eg})^{2}-\omega_{0}^{2}}\right](Q_a)_{10}$$

NR Theory (Restores Asymmetry to Raman Tensor)

$$\left(\alpha_{\alpha\beta}\right)^{a}_{g1,g0} = \frac{2}{\hbar}\sum_{e}\omega^{0}_{eg}\,\mathrm{Re}\left[\frac{[(\hat{\mu}_{\alpha})^{0}_{ge}(\hat{\mu}_{\beta})^{Q_a}_{eg}]}{(\omega^{0}_{eg})^{2}-\omega_{R}^{2}}+\frac{[(\hat{\mu}_{\alpha})^{Q_a}_{ge}(\hat{\mu}_{\beta})^{0}_{eg}]}{(\omega^{0}_{eg})^{2}-\omega_{0}^{2}}\right](Q_a)_{10}$$

$$\omega_R = \omega_0 - \omega_a = \omega_0(1-\omega_a/\omega_0)$$

GU/NR Theory -3 Raman 10 ROA invariants,
FFR Theory -2 Raman and 3 ROA Invariants

SES Theory of natural vibrational RROA

ELSEVIER

Chemical Physics 205 (1996) 309–322

Chemical Physics

Theory of resonance Raman optical activity: the single electronic state limit

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Department of Chemistry, Syracuse University, Syracuse, NY 13244-4100, USA

Received 27 June 1995

Ratio of RROA to RR in Backscattering DCP_I equals

$$\frac{I_R^R(180^\circ) - I_L^L(180^\circ)}{I_R^R(180^\circ) + I_L^L(180^\circ)} =$$

$$= -\left(\frac{4}{c}\right)\frac{\mathrm{Im}\left[(\vec{\mu}_{ge}^{0} \cdot (\vec{m})_{eg}^{0}\right]}{\left|(\vec{\mu})_{eg}\right|^2} = -g_{ge}$$

The Negative of the Ratio of CD to Absorbance of Resonant Electronic State

First observation of natural RROA
Confirmation of SES-RROA Theory

ELSEVIER

1 May 1998

Chemical Physics Letters 287 (1998) 359–364

CHEMICAL
PHYSICS
LETTERS

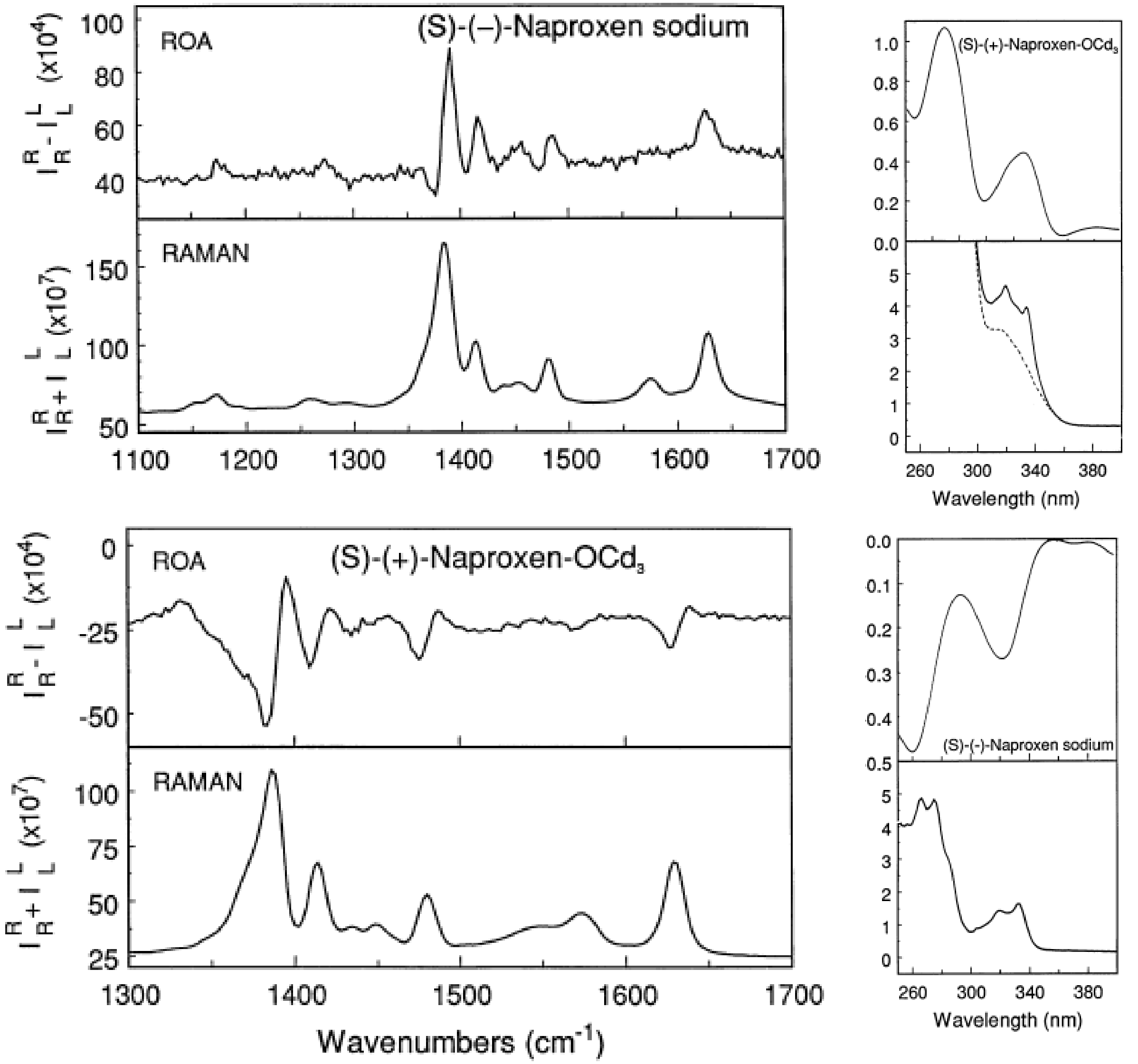
Experimental observation of resonance Raman optical activity

Mária Vargek, Teresa B. Freedman, Eunah Lee, Laurence A. Nafie

Department of Chemistry, Syracuse University, Syracuse, NY 13244-1400, USA

Received 24 October 1997; in final form 31 December 1997

First observation of natural RROA
Confirmation of SES-RROA Theory



THE JOURNAL OF CHEMICAL PHYSICS **127**, 134101 (2007)

Resonance vibrational Raman optical activity: A time-dependent density functional theory approach

L. Jensen[a)]
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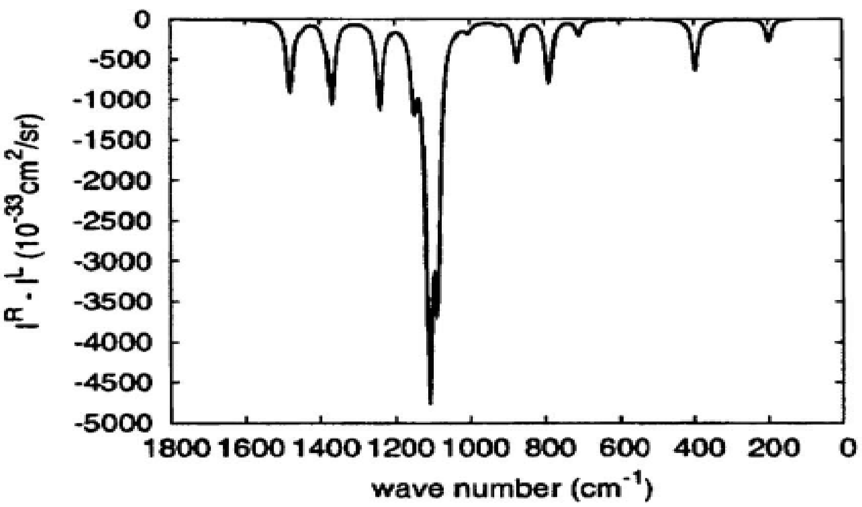
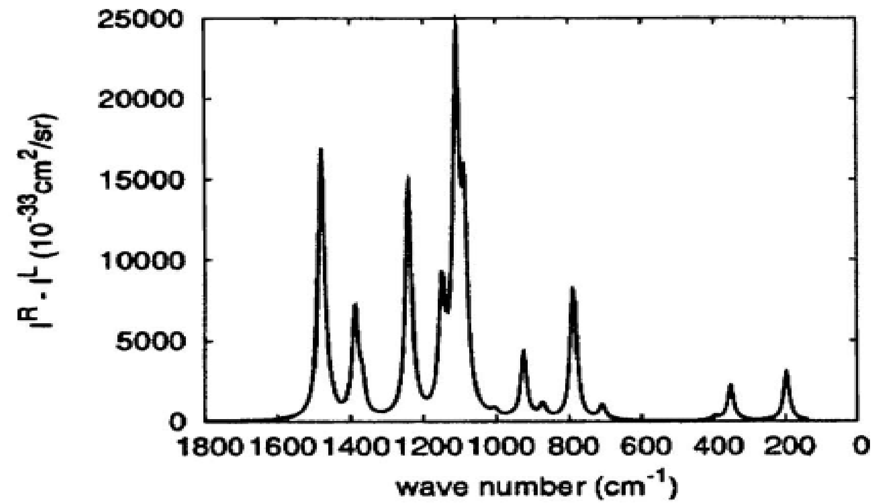
(Received 16 May 2007; accepted 11 July 2007; published online 2 October 2007)

Calculated ROA show monosignate spectra with the same form as the RR spectrum and with the same ratio as the electronic CD to the absorption spectrum, with the opposite sign, of the resonant electronic state

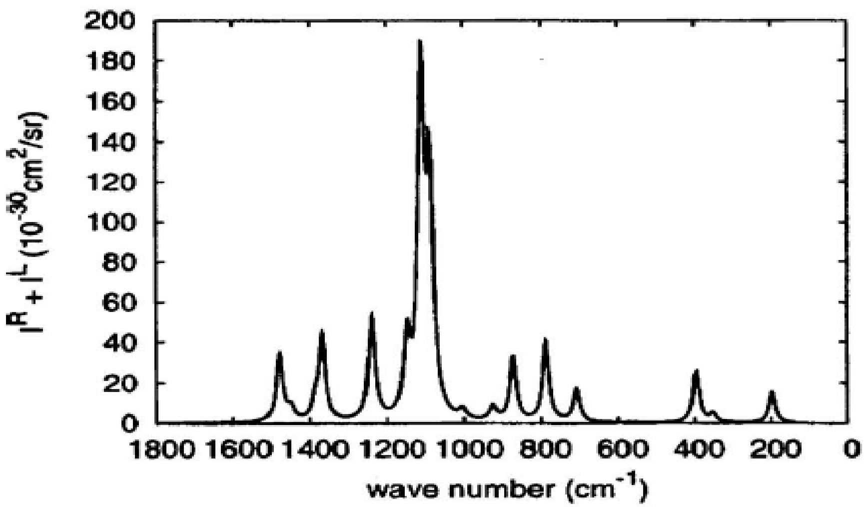
RR and ROA of Methyloxirane at 202 and 185 nm Excitation



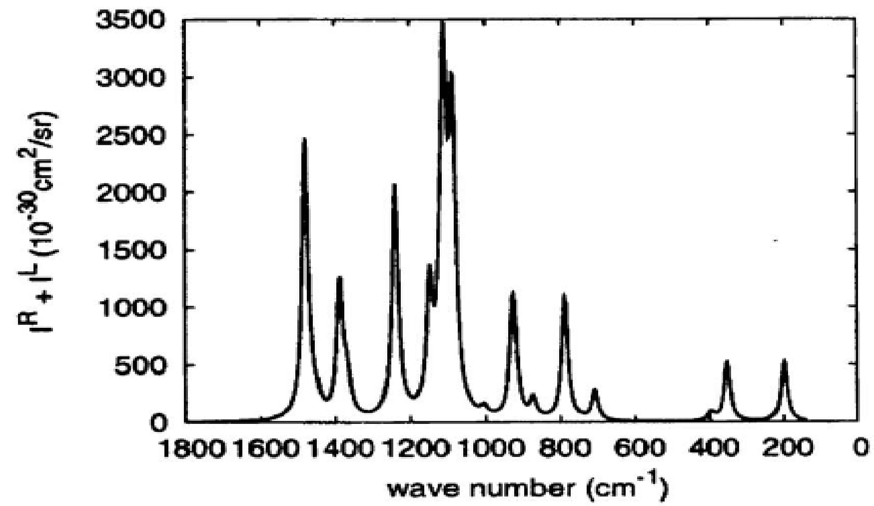
(a) RVROA @ 202 nm



(b) RVROA @ 185 nm



(c) RRS @ 202 nm



(d) RRS @ 185 nm

Theoretical Background of VCD

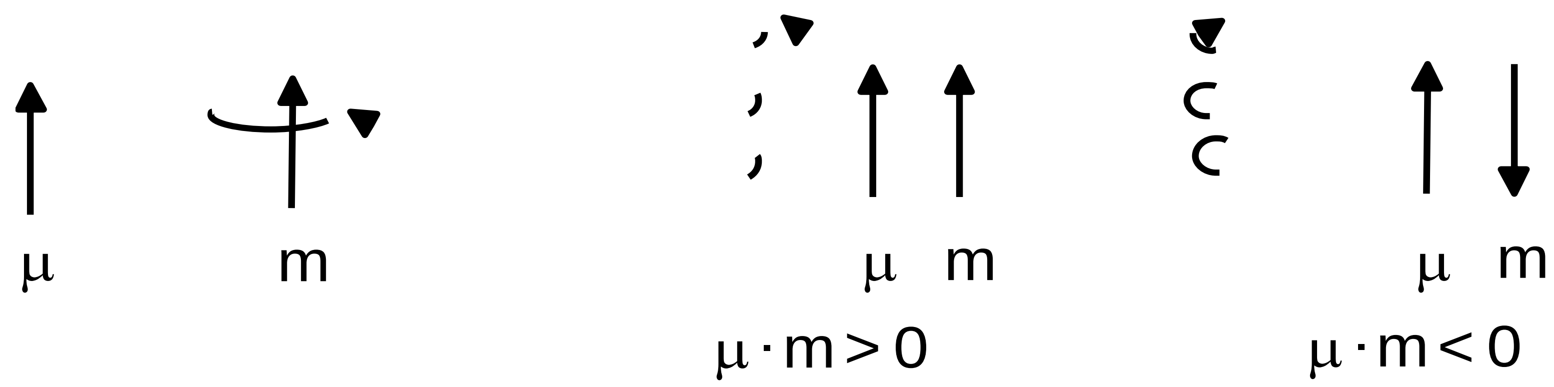
Dipole and Rotational Strength for Vibrational Transition of *gv* to *gv′*

IR

$$D^{a}_{r,g\upsilon',g\upsilon'} = \left| \left(\frac{\partial \langle \boldsymbol{\mu} \rangle}{\partial Q_a} \right)_{Q_a=0} \left\langle \phi^{a}_{g\upsilon'} \middle| Q_a \middle| \phi^{a}_{g\upsilon} \right\rangle \right|^2$$

VCD

$$R^{a}_{r,g\upsilon',g\upsilon'} = \mathrm{Im}\left[\left(\frac{\partial \langle \boldsymbol{\mu} \rangle}{\partial Q_a} \right)_{Q_a=0} \cdot \left(\frac{\partial \langle \boldsymbol{m} \rangle}{\partial P_a} \right)_{P_a=0} \left\langle \phi^{a}_{g\upsilon} \middle| Q_a \middle| \phi^{a}_{g\upsilon'} \right\rangle \left\langle \phi^{a}_{g\upsilon'} \middle| P_a \middle| \phi^{a}_{g\upsilon'} \right\rangle \right]$$



Vibrational Current Density

$$\rho_g^{CA}(\boldsymbol{r},\boldsymbol{R},0) = \rho_g^{A}(\boldsymbol{r},\boldsymbol{R}) = \psi_g^{A}(\boldsymbol{r})\psi_g^{A}(\boldsymbol{r}) \cong \rho_g^{0}(\boldsymbol{r}) + \sum_J \left(\frac{\partial \rho_g^{A}(\boldsymbol{r})}{\partial \boldsymbol{R}_J} \right)_{R=0} \cdot \boldsymbol{R}_J$$

$$\boldsymbol{j}_g^{CA}\left(\boldsymbol{r},\boldsymbol{R},\dot{\boldsymbol{R}}\right) = \frac{\hbar}{2mi}\left[\tilde{\psi}_g^{CA*}(\boldsymbol{r})\nabla\tilde{\psi}_g^{CA}(\boldsymbol{r}) - \tilde{\psi}_g^{CA}(\boldsymbol{r})\nabla\tilde{\psi}_g^{CA*}(\boldsymbol{r})\right] \cong \sum_J \left(\frac{\partial \boldsymbol{j}_g^{CA}(\boldsymbol{r})}{\partial \dot{\boldsymbol{R}}_J} \right)_{\substack{R=0 \\ \dot{R}=0}} \cdot \dot{\boldsymbol{R}}_J$$

Continuity Equation - Conservation of Charge Density

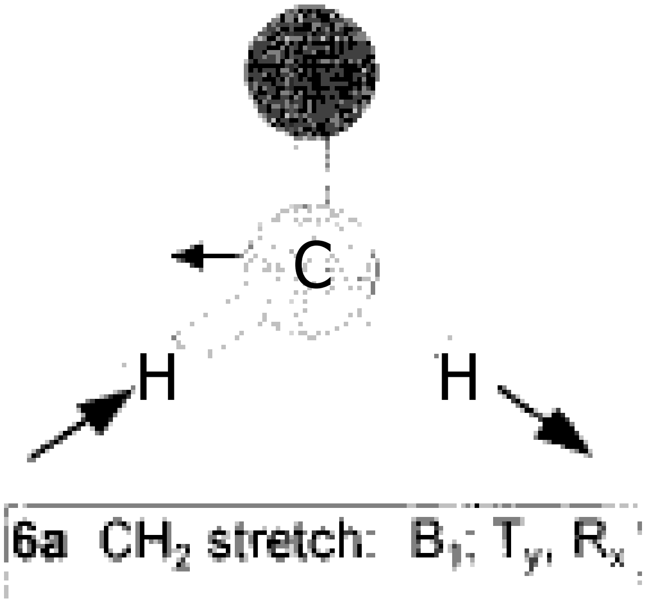
$$-\nabla \cdot \boldsymbol{j}_g^{CA}\left(\boldsymbol{r},0,\dot{\boldsymbol{R}}\right) = \frac{\partial \rho_g^{CA}(\boldsymbol{r},\boldsymbol{R},0)}{\partial t}$$

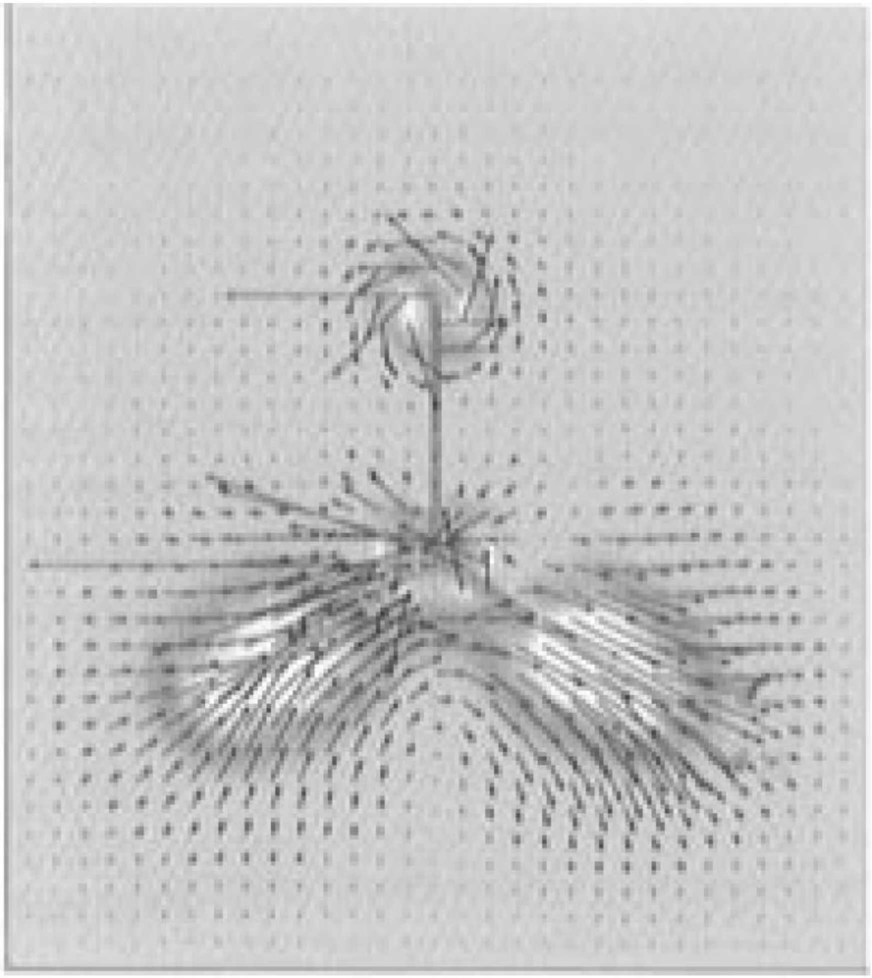
$$-\nabla \cdot \left(\frac{\partial \boldsymbol{j}_g^{CA}(\boldsymbol{r})}{\partial \dot{\boldsymbol{R}}_J} \right)_{\substack{\dot{R}=0 \\ R=0}} = \left(\frac{\partial \rho_g^{A}(\boldsymbol{r})}{\partial \boldsymbol{R}_J} \right)_{R=0}$$

Beyond BO BO

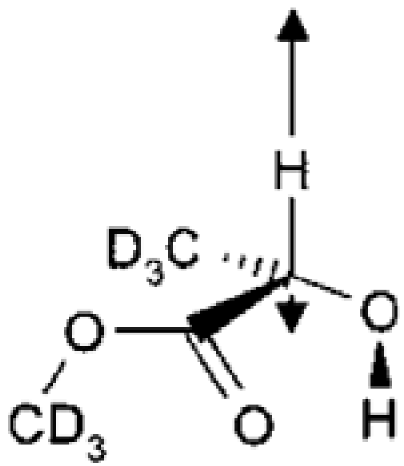
Vibrational Current Density

Anti-symmetric CH Stretch in Formaldehyde

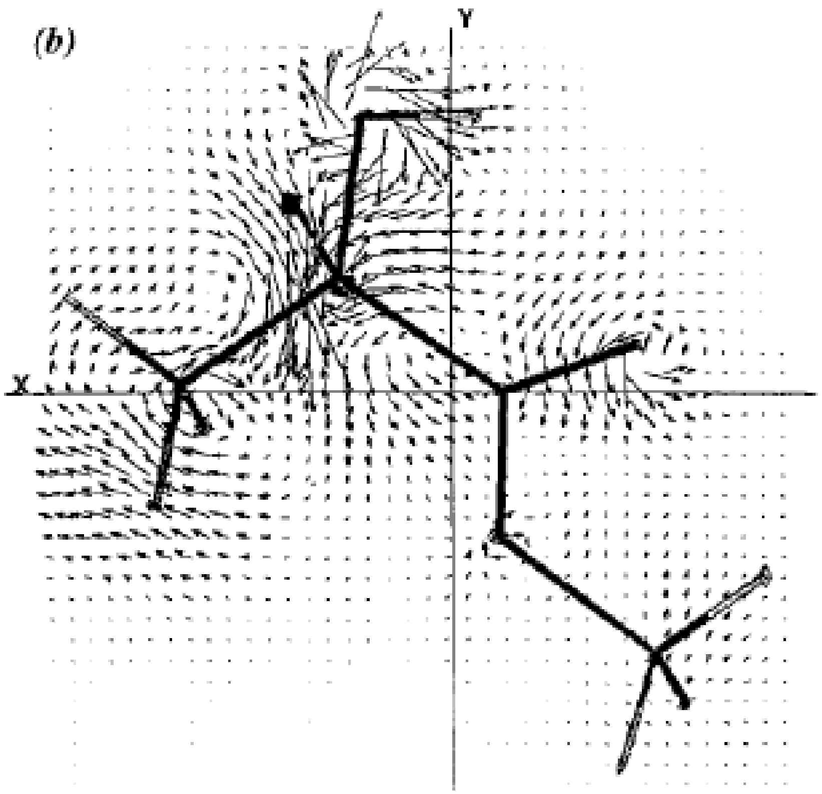




Vibrational Current Density



(S)-Methyl-d_3 Lactate-Cd_3
Methine Stretch



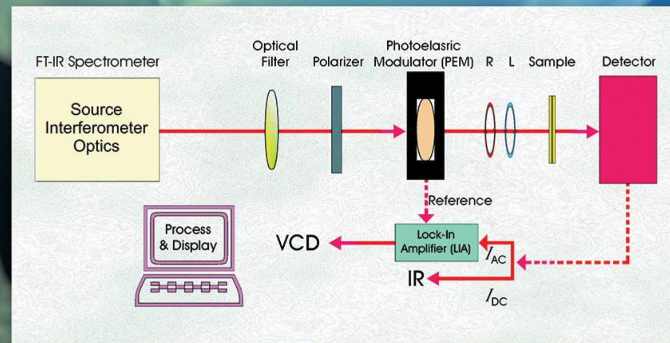
View along electric dipole transition moment of CH stretch

Determination of Absolute Configuration using VOA

applied spectroscopy

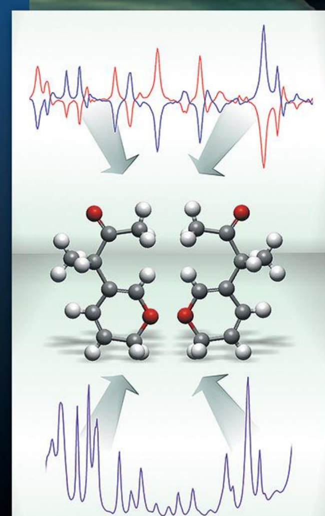
65/7
JULY 2011
ISSN: 0003-7028

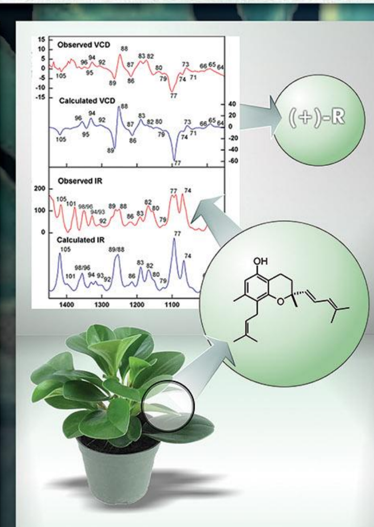
An International Journal of Spectroscopy



FOCAL POINT:
Determination of Absolute Configuration of Chiral Molecules Using Vibrational Optical Activity: A Review

Report on the First UK Meeting of the SAS



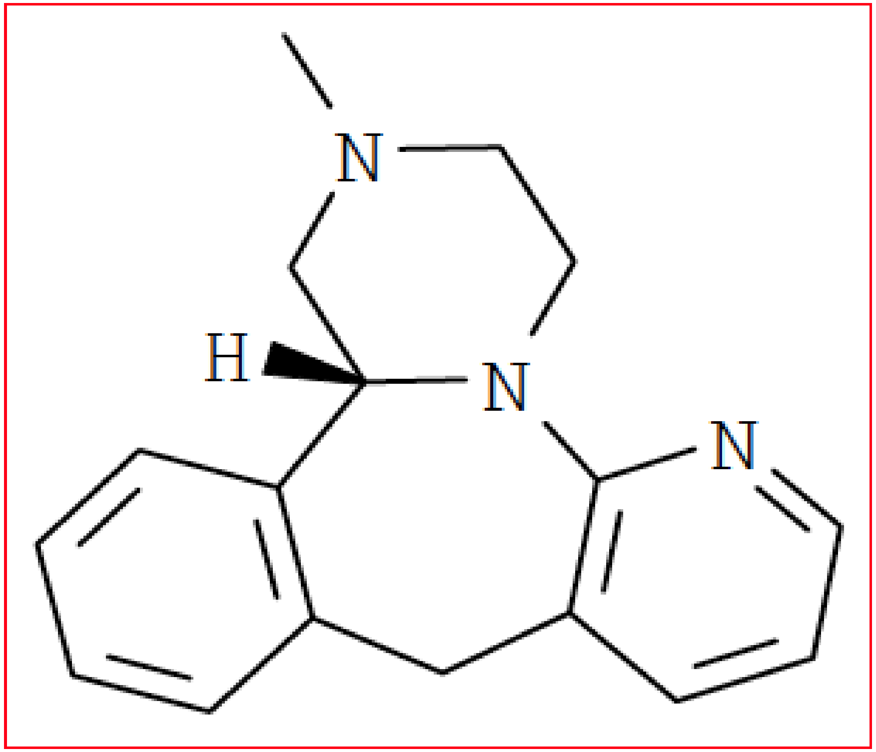


ABSOLUTE CONFIGURATION BY VOA

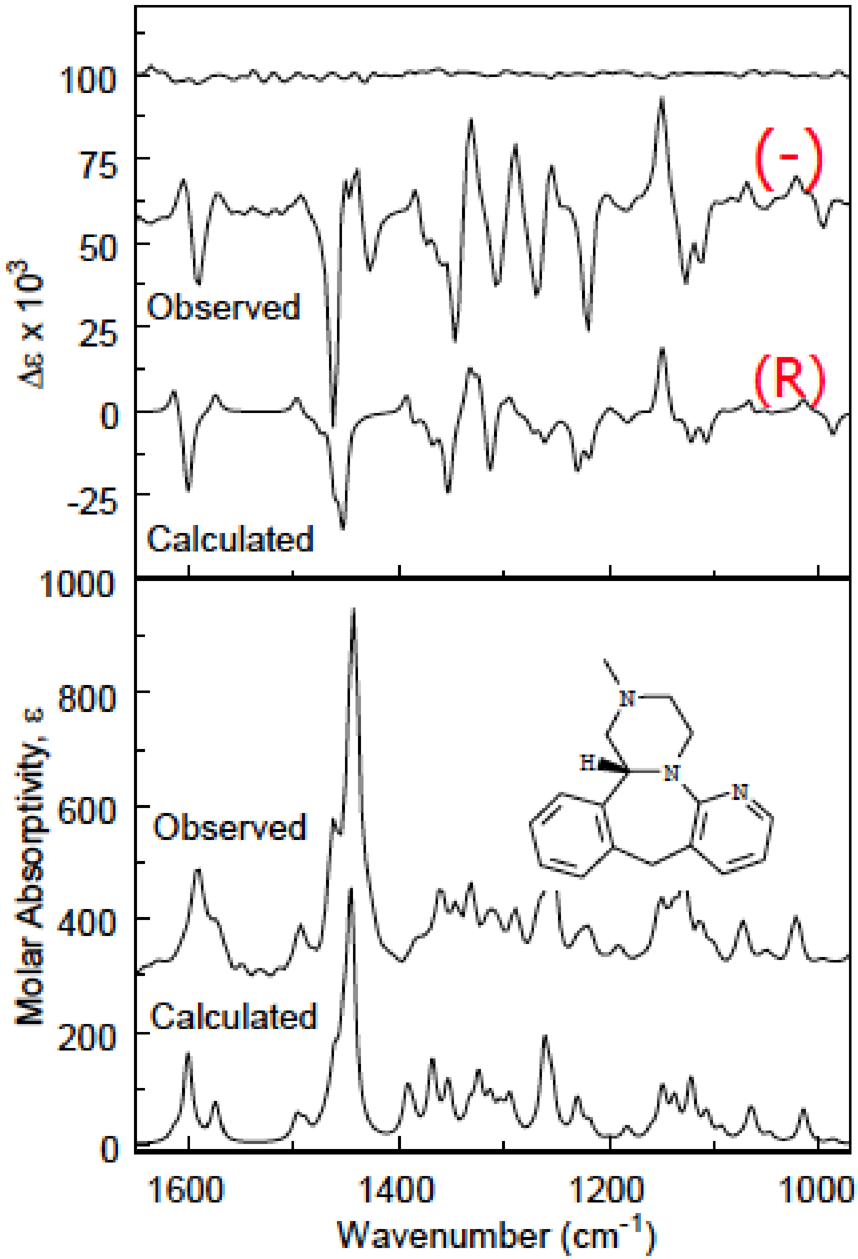
Official Publication of the Society for Applied Spectroscopy

Absolute configuration of a Mirtazapine enantiomer

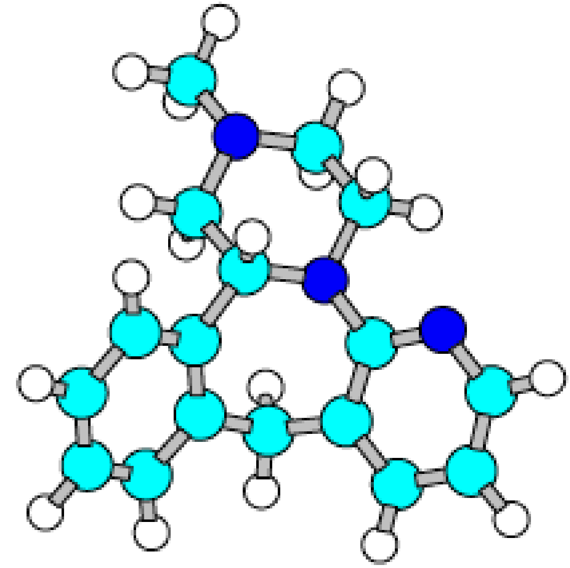
- Mirtazapine the active ingredient of an antidepressant drug
- 20 heavy atoms
- 1 chiral center



Drs. Edwin Kellenbach, Organon Laboratories, Riom, France & Petr van Hoof, Organon NV



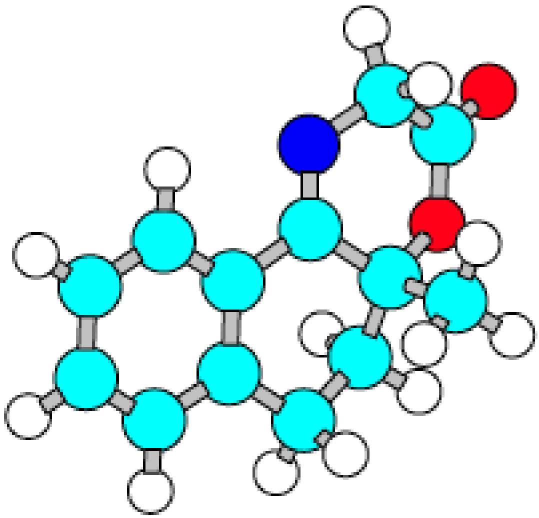
Helv. Chim. Acta, 85, 1160 (2002)

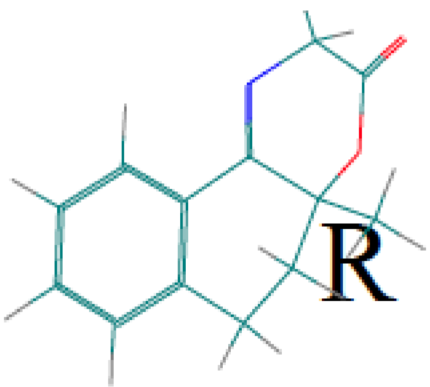


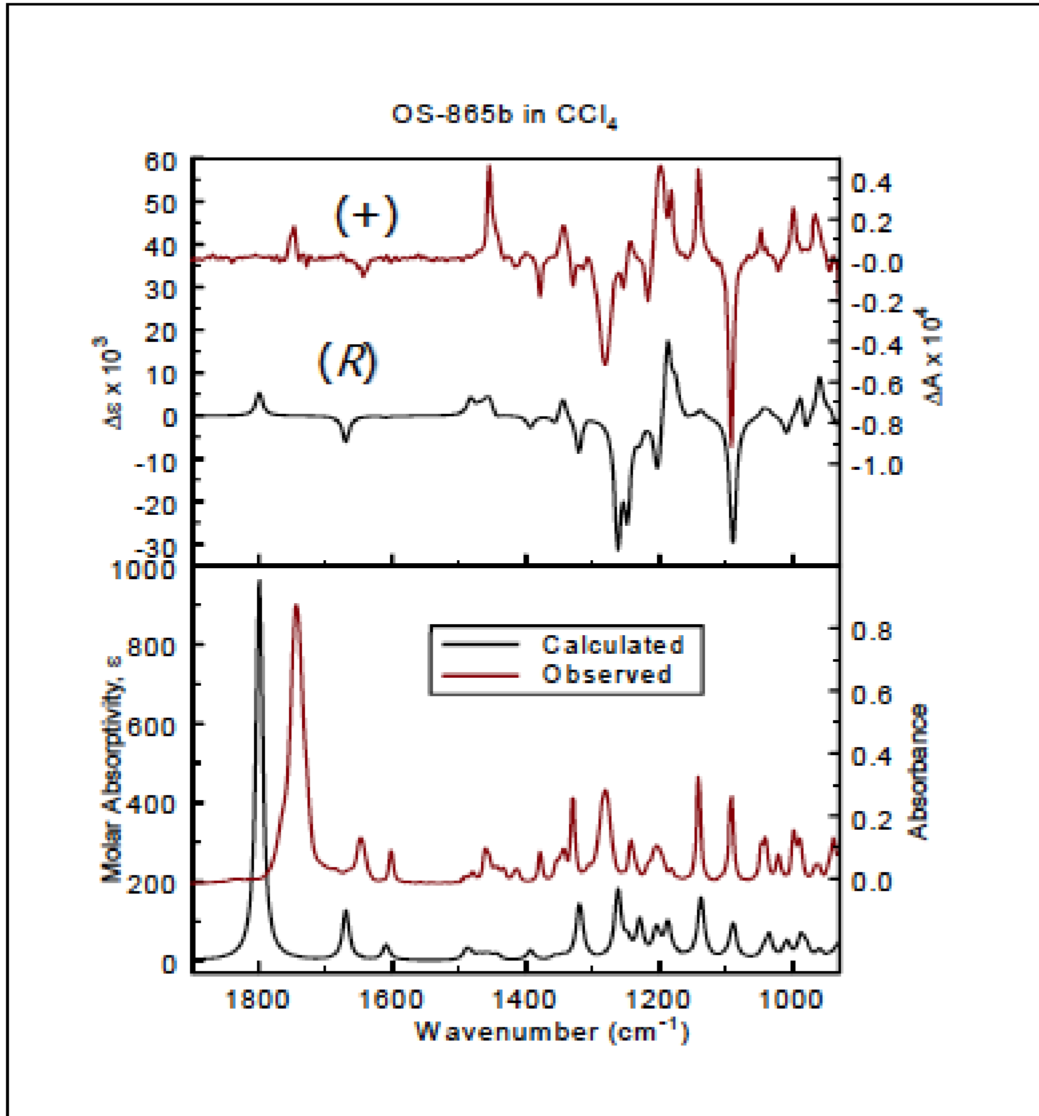
Vibrational circular dichroism (VCD) is used to identify ***unambiguously*** the absolute configuration of Mirtazapine as ***(-)-R*** and solution conformation as shown above

AC Determination of Small Organic Molecules

New Iminolactone: 16 heavy atoms, 1 chiral center



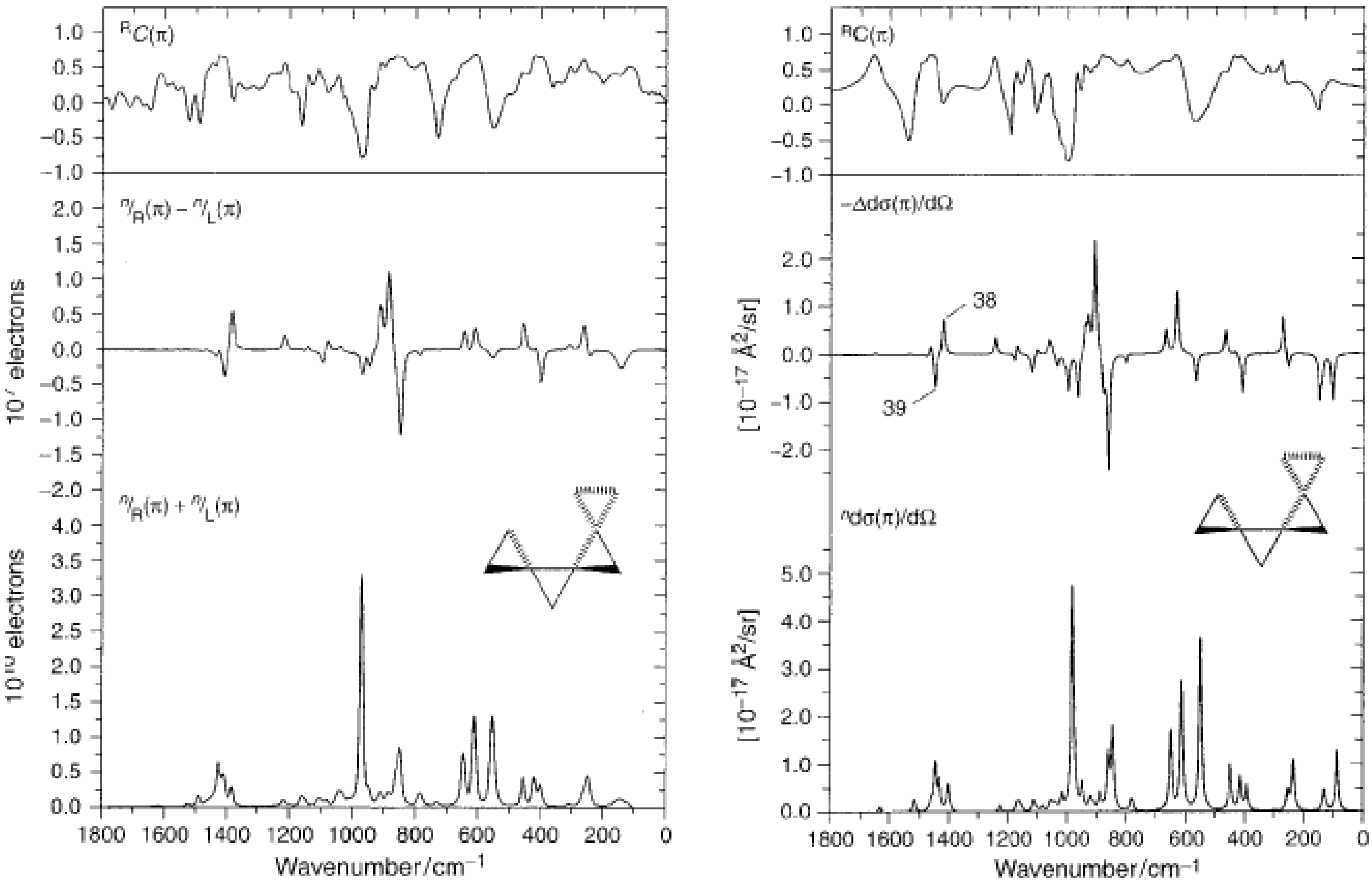




Professor Arlette Solladie-Cavallo, University of Strasbourg

Tetrahedron Asymmetry, 12, 2703, 2001

Comparison of Measured and Calculated SCP-ROA



W. Hug et al. *Helv. Chim. Acta*, 84, 1, 2001

Paper describing application of VCD to the Determination of Absolute Configuration of Chiral Pharmaceutical Molecules

Bioorganic & Medicinal Chemistry Letters 23 (2013) 4019–4025

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

BMCL Digest

A rapid alternative to X-ray crystallography for chiral determination: Case studies of vibrational circular dichroism (VCD) to advance drug discovery projects

Steven S. Wesolowski [*,†], Don E. Pivonka [‡]

AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, USA

VOA in
Pharma and Biopharma

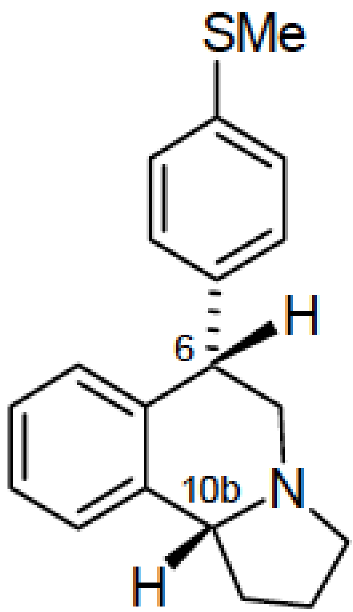

CHEMICAL & ENGINEERING NEWS
C&EN
OCTOBER 9, 1995
CHEMICAL, BIOLOGICAL WORK INSPIRED BY PASTEUR IS FOCUS OF MEETING PAGE 33
Chiral Drugs
Market growth in single-isomer forms spurs research advances
Page 44
CTOBER 20, 1997
CHEMICAL
& ENGINEERING NEWS
CHIRAL DRUGS
Robust Market Starts To Mature
Page 38
EPTEMBER 21, 1998
75 YEARS OF GREAT CHEMISTRY
CHEMICAL
& ENGINEERING NEWS
Tensions Surface In Industry-Academe Research Agreements
Page 21
CHIRAL DRUGS
Product Development Pays Off In Sales
Page 83

VCD / ROA in Pharma

- Amgen, Astra-Zeneca, BMS, GSK, Eli Lilly, Wyeth/Pfizer, J&J, Roche, Novartis, Boehringer-Ingelheim, Organon (Akzo Nobel, now Merck), Merck, Pfizer, Abbott/AbbVie, Cell Therapeutics, Solvay, Neurocrine, Sanofi-Aventis, Sepracor / Sunovion, Gilead, and many more use VCD for AC by outsourcing measurements and calculations.
- VCD is now used as a routine **tool** for AC and not just a research technique. Hundreds of AC determinations carried out in Pharma each year. Over 100 US Patents cite VCD for AC determination of new drugs
- VCD is 'accepted' by regulatory agencies as proof of Absolute Configuration.
- VCD is in the initial stages of becoming a standard method for AC determination in the US Pharmacopeia (Stimuli article published in July)

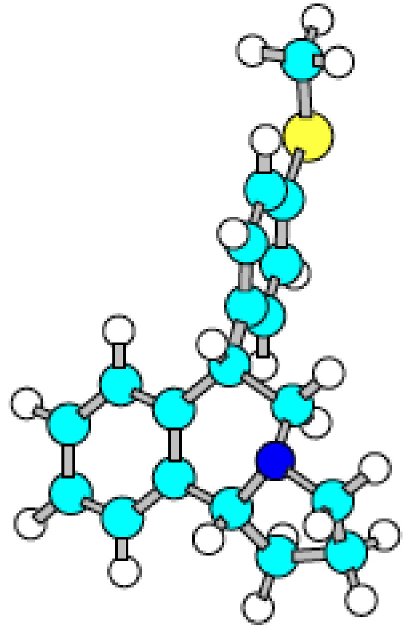
AC Determination of Pharmaceutical Molecules

McN 5652-X Inhibitor of Seratonin Reuptake



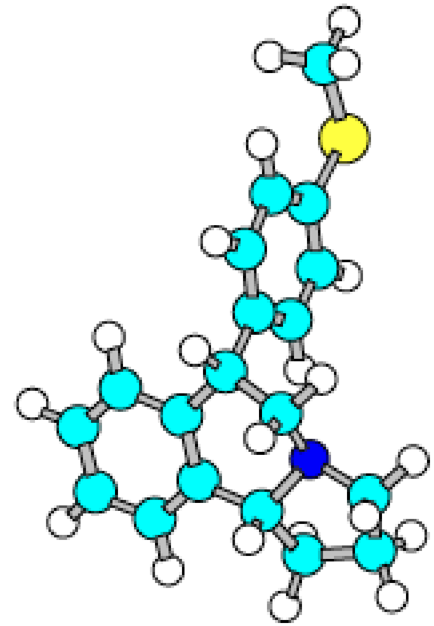
(+)-**1** (McN-5652-X)

trans-(6*S*,10b*R*)



Conformer SRa

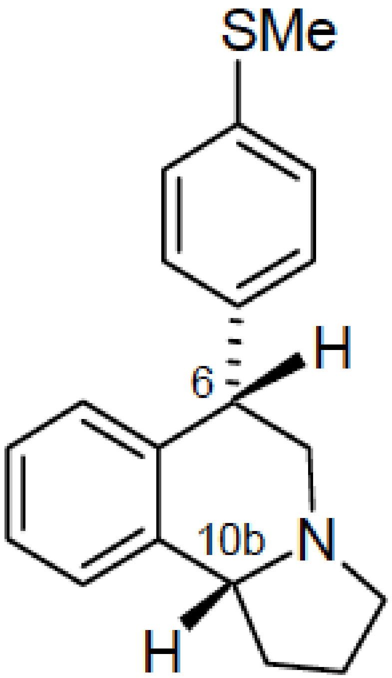
+1.63 kcal/mol



Conformer SRb

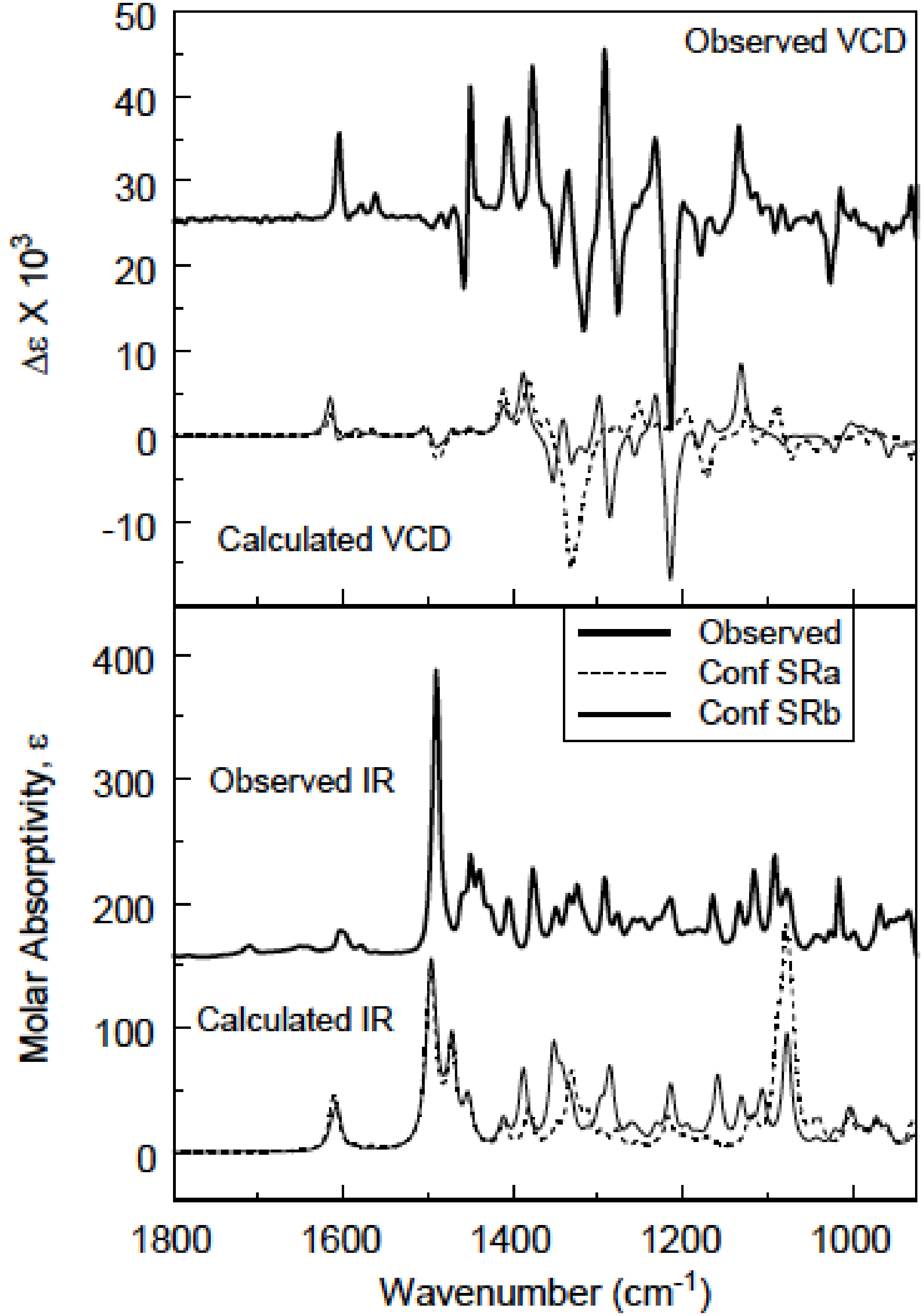
0.0 kcal/mol

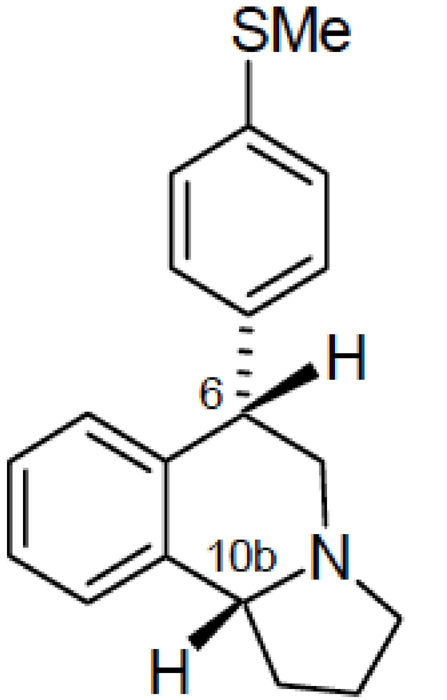
Bruce E. Maryanoff, David F. McComsey, Rina K. Dukor, Laurence A. Nafie, Teresa B. Freedman, Xiaolin Cao, and Victor W. Day, *Biorg. Med. Chem.*, **11**, 2463-2470, (2003).



(+)-**1** (McN-5652-X)

trans-(6*S*,10b*R*)

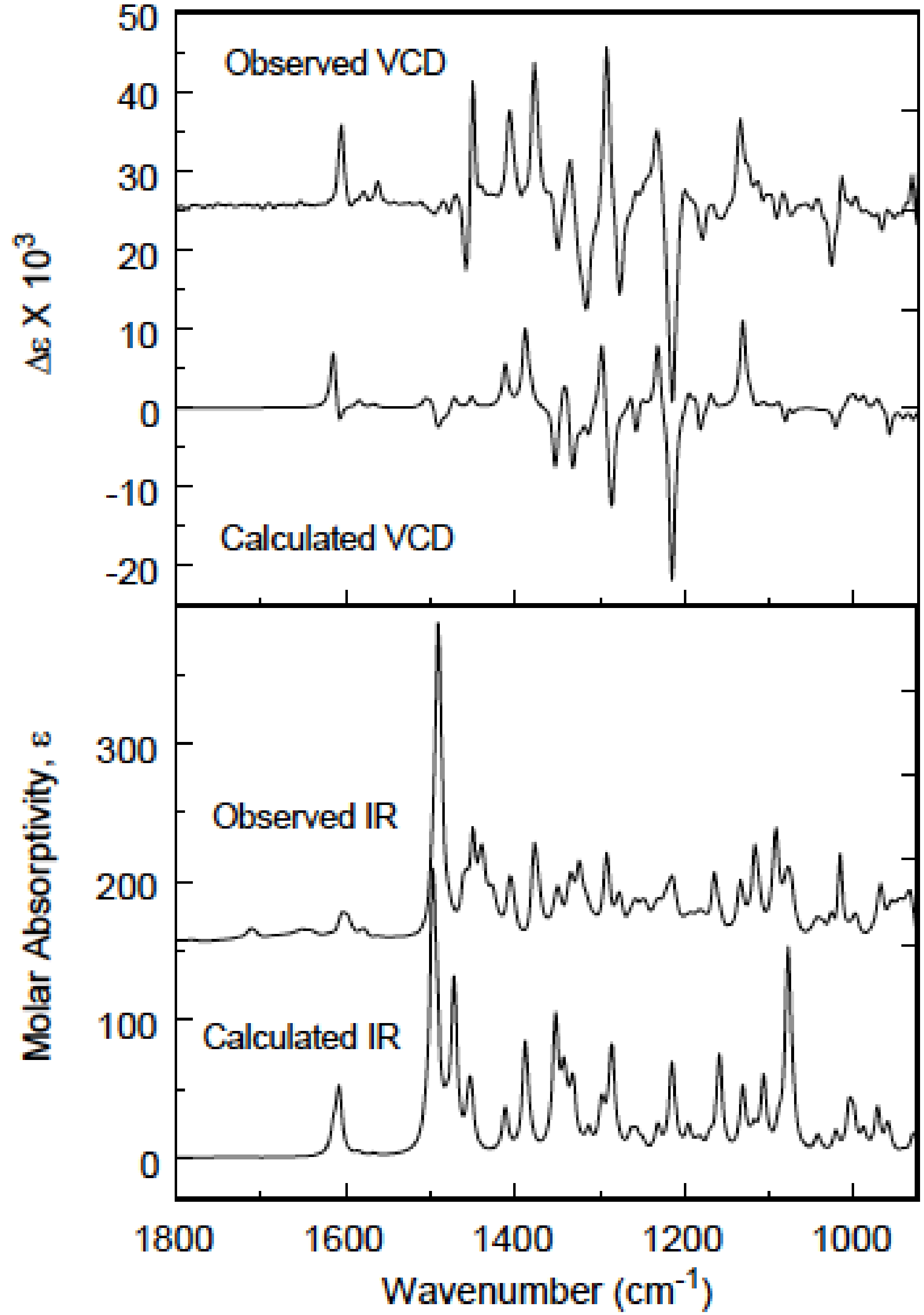




(+)-**1** (McN-5652-X)

trans-(6*S*,10b*R*)

Composite VCD
85% SRb
15% SRa



NPC Natural Product Communications

2008
Vol. 3
No. 3
451 - 466

Vibrational Circular Dichroism: A New Tool for the Solution-State Determination of the Structure and Absolute Configuration of Chiral Natural Product Molecules

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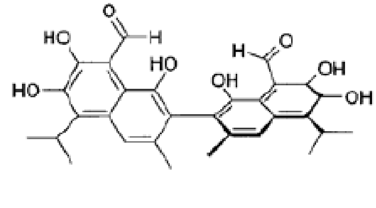
Received: October 30th, 2007; Accepted: January 25th, 2008

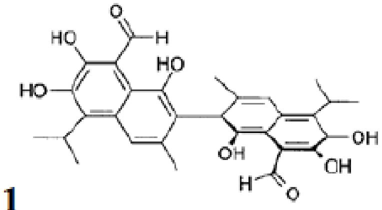
This paper is dedicated to Professor Pedro Joseph-Nathan for his 65th birthday.

L.A. Nafie, *Nat. Prod. Comm.* **3**, 451-466 (2008)

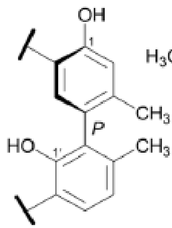


(*aR*)-Gossypol (*M*)

1



(*aS*)-Gossypol (*P*)



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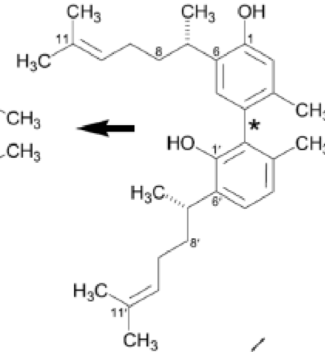

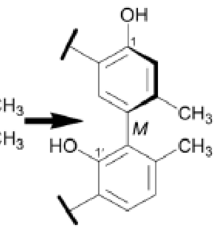

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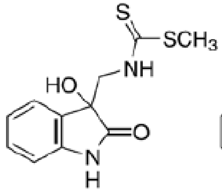
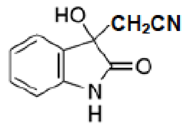
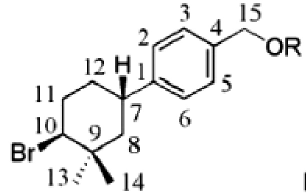
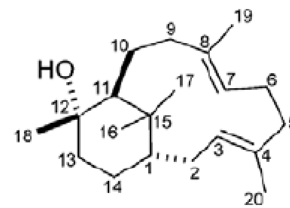
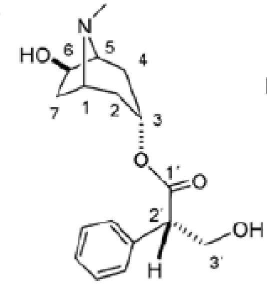
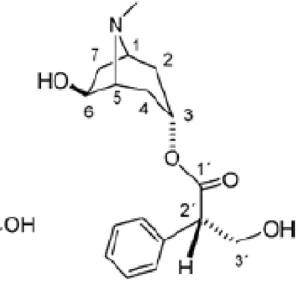


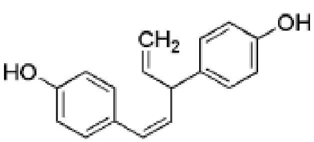


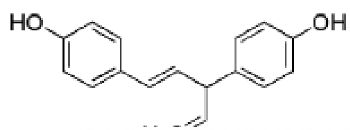


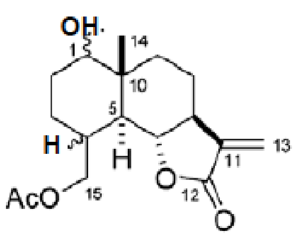


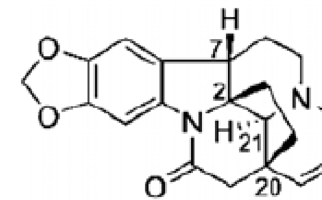


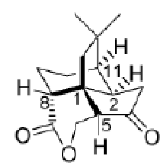


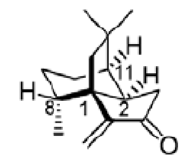


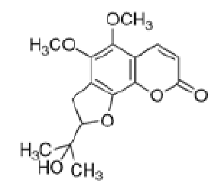


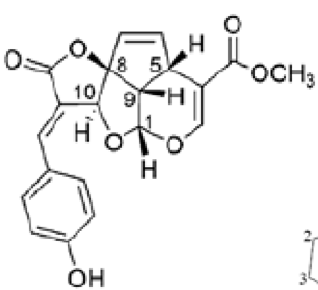


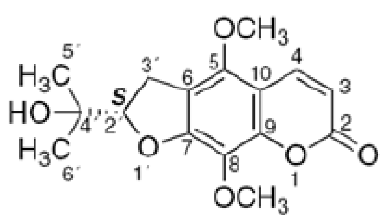


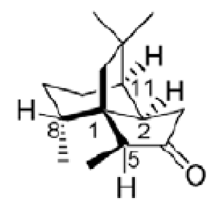


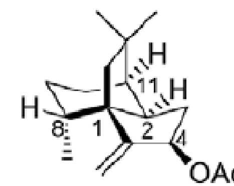


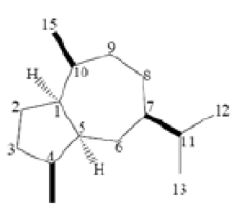


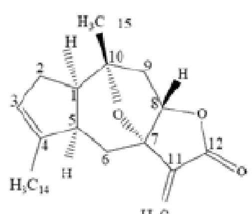


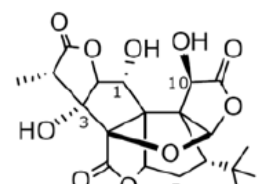


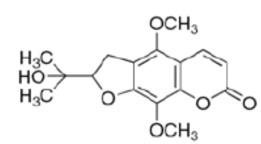


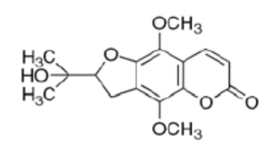








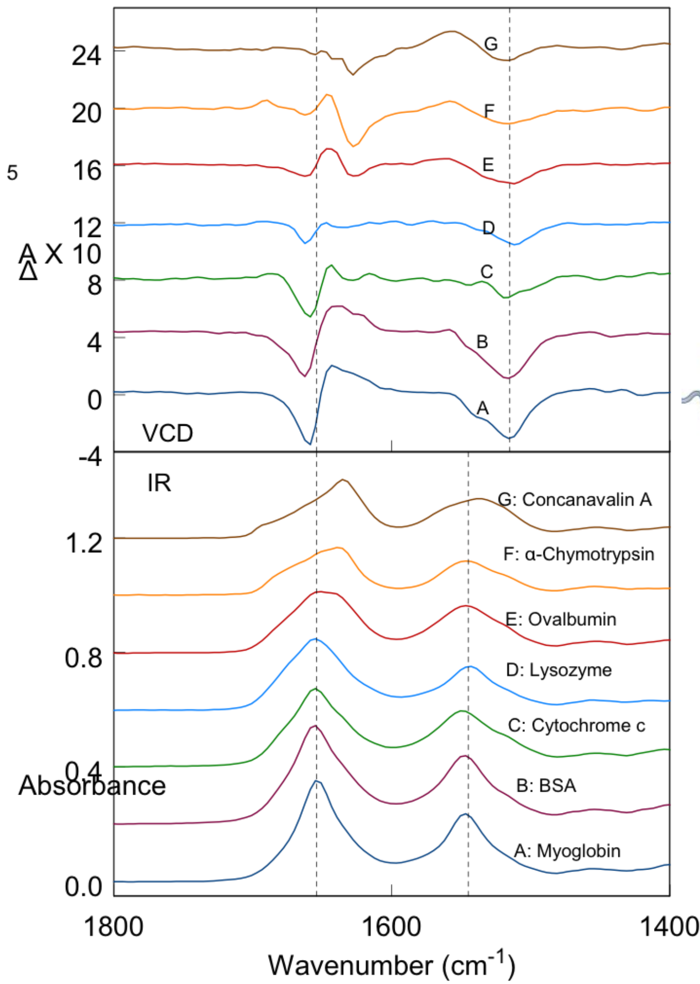


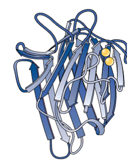


VOA Analysis of Proteins for Biopharma Applications

Near-Infrared and Mid-Infrared Fourier Transform Vibrational Circular Dichroism of Proteins in Aqueous Solution

SHENGLI MA,* TERESA B. FREEDMAN, RINA K. DUKOR, and LAURENCE A. NAFIE†
Department of Chemistry, Syracuse University, Syracuse, New York 13244 (S.M., T.B.F., L.A.N.); and BioTools Inc, 17546 Bee Line Hwy, Jupiter, Florida 33458 (R.K.D., L.A.N.)



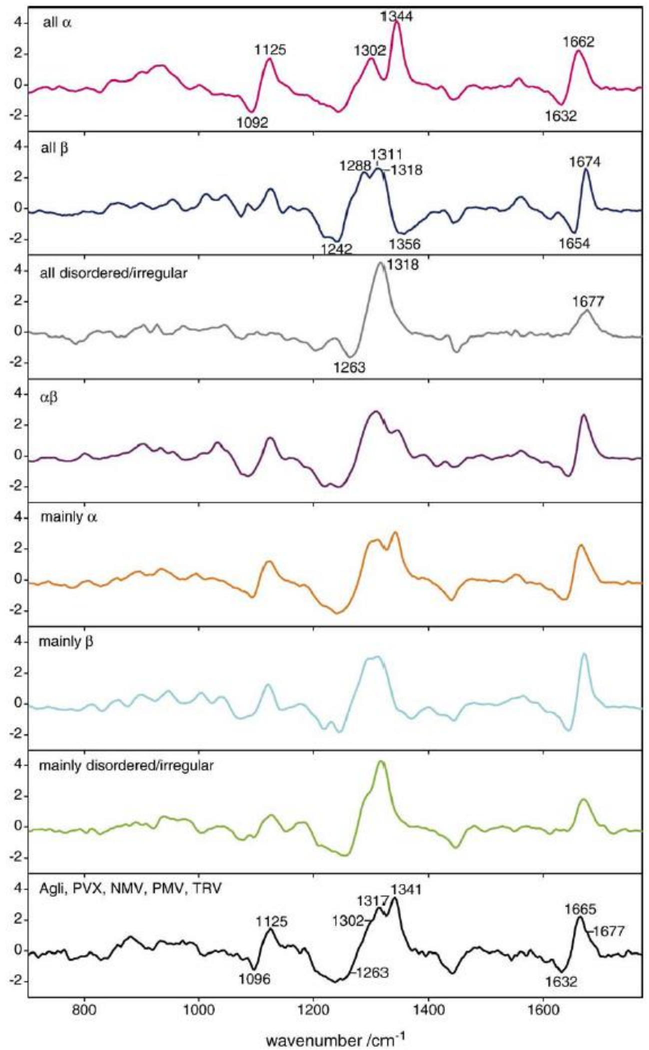


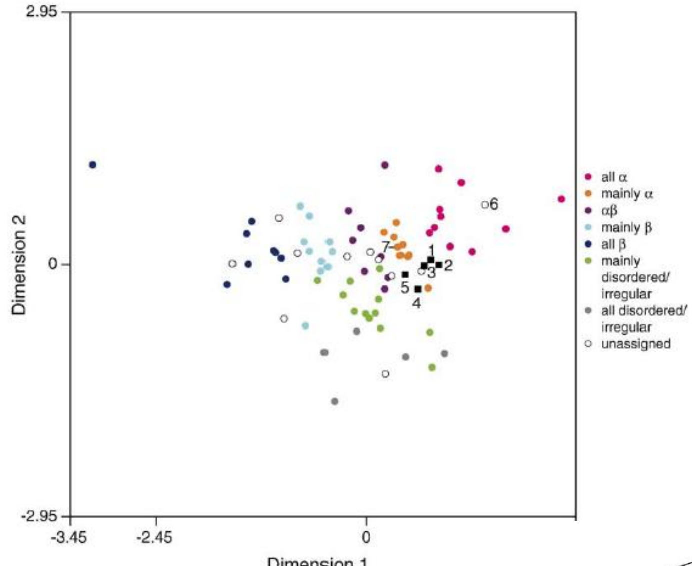
Beta sheet

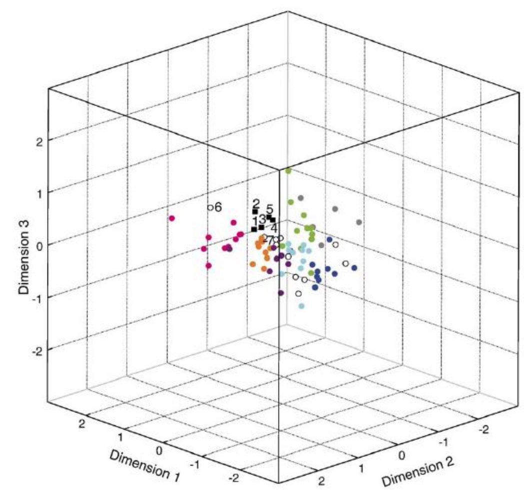
Alpha helical

VCD and IR protein spectra

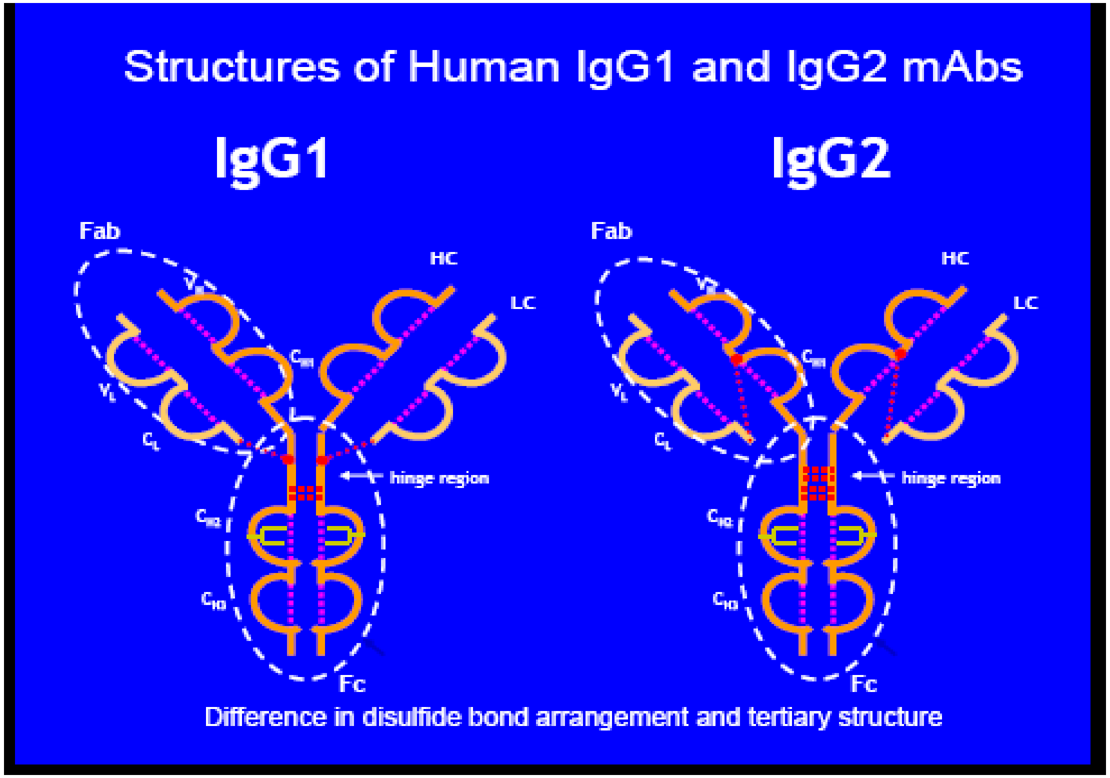
Nonlinear mapping algorithm for classification 80 protein ROA spectra
Barron et al. *J Mol Bio* **363** 19-26 (2006)







Aggregation of Human IgG1

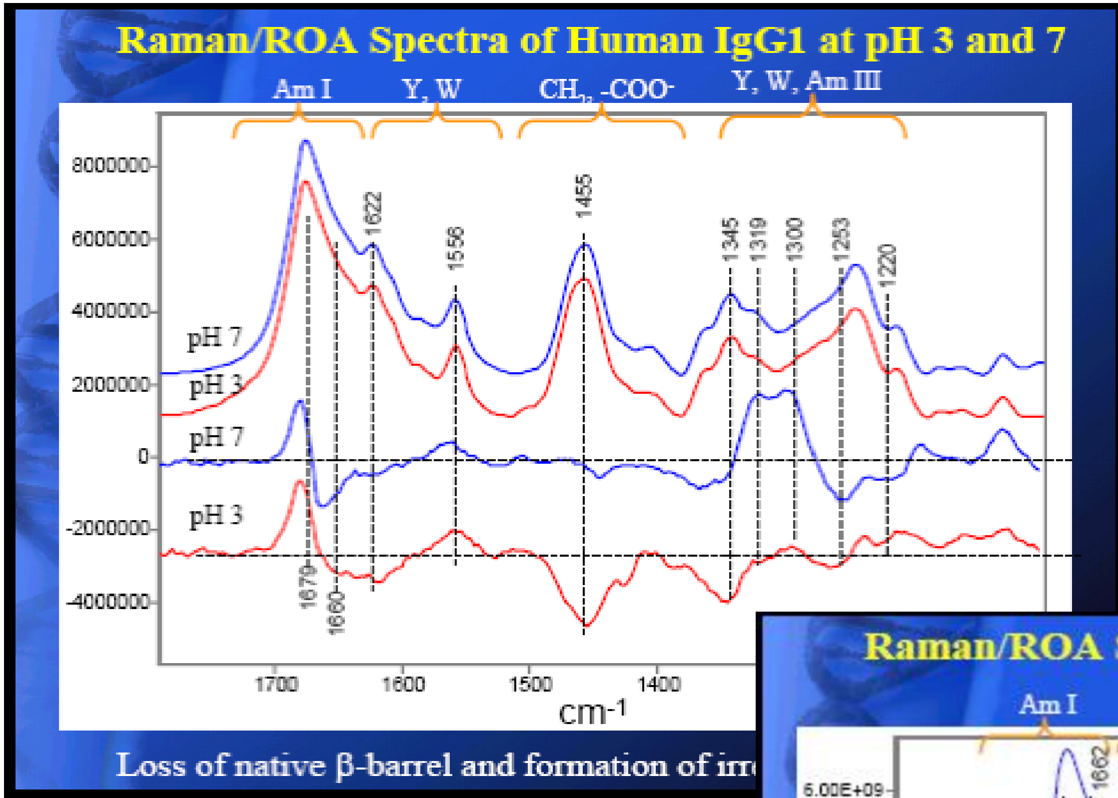


CAUSES OF SOLUBLE & INSOLUBLE AGGREGATES:

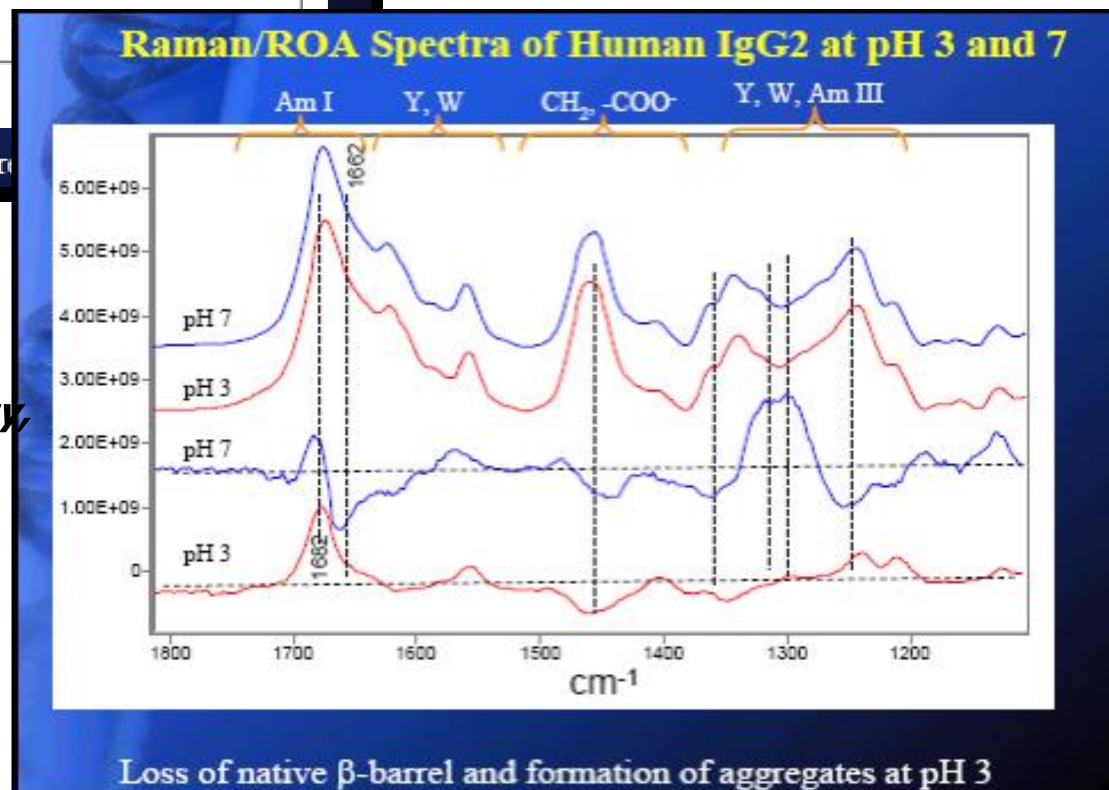
- temperature
- shear force
- freeze-thawing
- pH
- high concentration

-- long term storage

Work and slides courtesy of Dr. Tiansheng Li – Amgen, Inc.



Higher-Order Pre-Aggregation seen by ROA but not by Raman



Cynthia Li and Tiansheng Li
Current Pharmaceutical Biotechnology, 2009, 10, 391-399

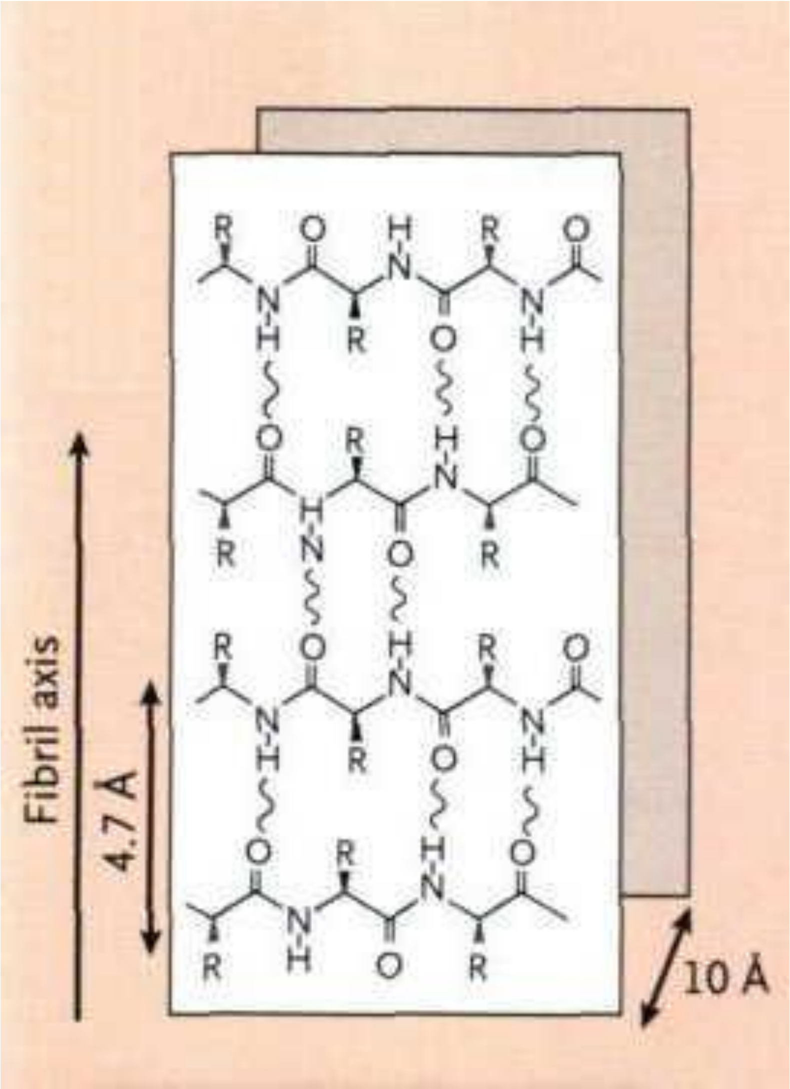
Enhanced VCD Intensity

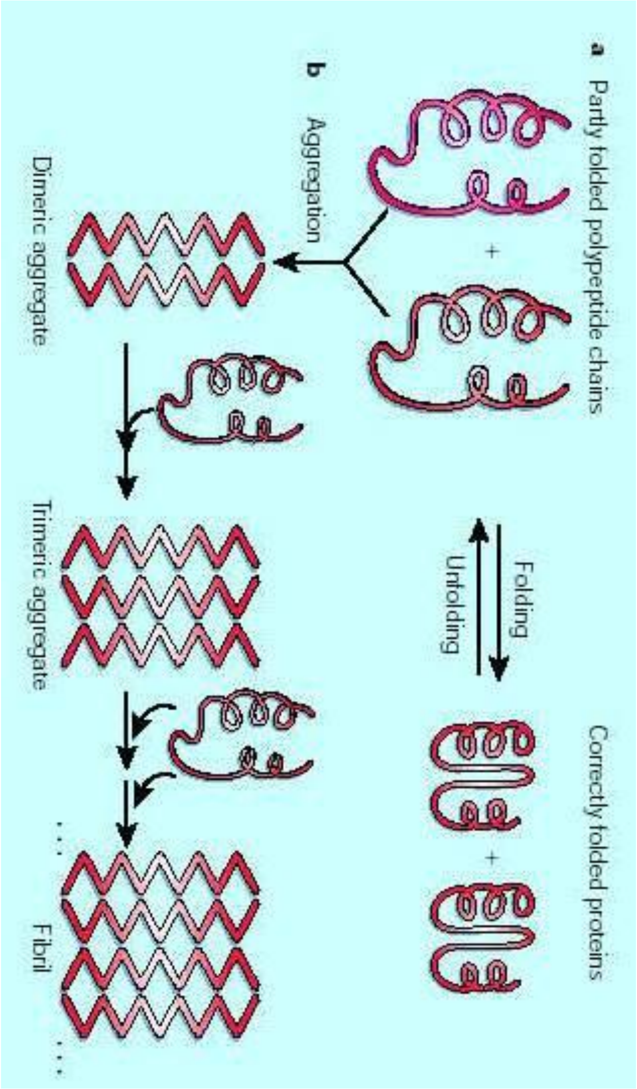
Examples of Enhanced VCD Intensity

- Protein Fibrillation and Development
- Molecules with Low-Lying Electronic States
- Negative Index Materials and Helicene and Cyclocene Molecules
- Spray-Dried Films of Amino Acids and Peptides
- Heme Protein Ligands

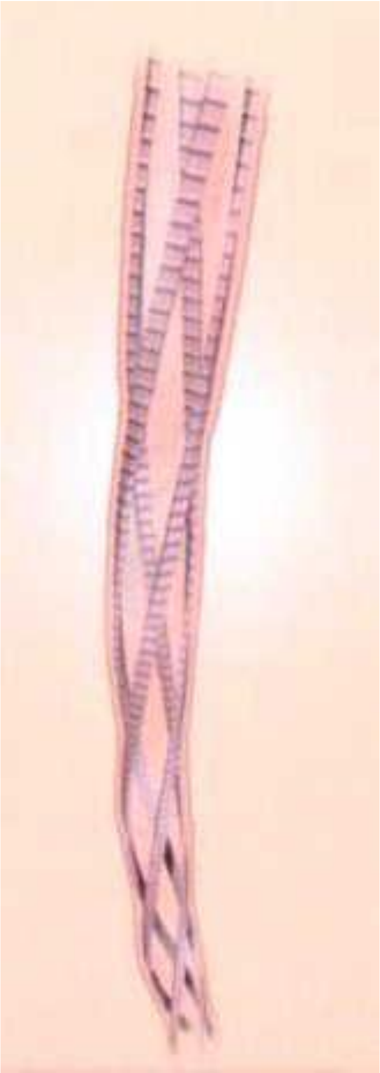
Enhanced VCD Intensity in Protein Fibrils

Initial Stages of Fibril Formation





More Advanced Fibril Formation and Development



JACS COMMUNICATIONS

Published on Web 09/26/2007

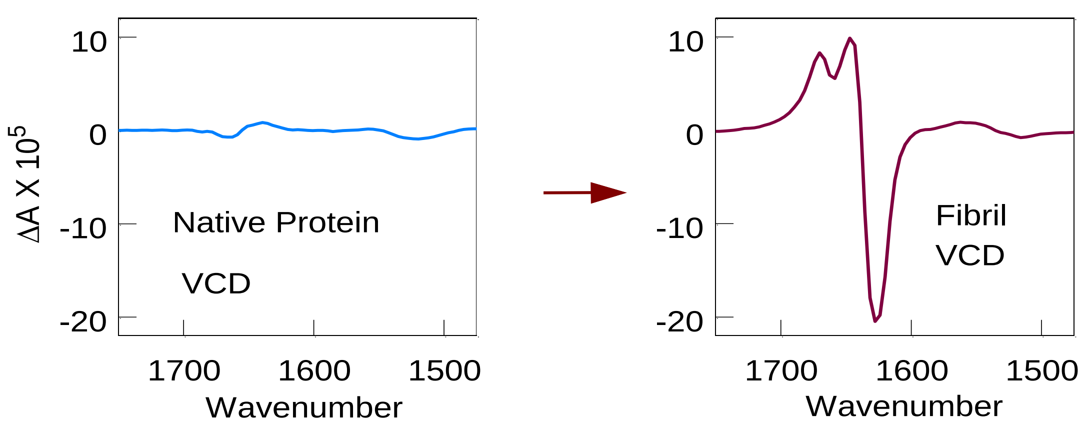
Vibrational Circular Dichroism Shows Unusual Sensitivity to Protein Fibril Formation and Development in Solution

Shengli Ma,† Xiaolin Cao,†,¶ Mimi Mak,† Adeola Sadik,† Christoph Walkner,† Teresa B. Freedman,† Igor K. Lednev,‡ Rina K. Dukor,§ and Laurence A. Nafie*,†,§

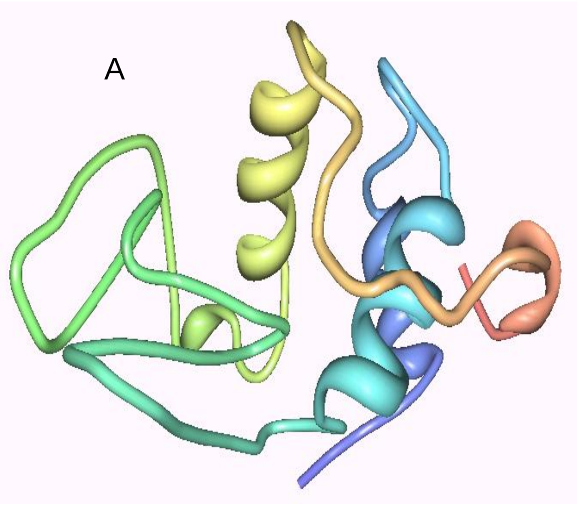
Department of Chemistry, Syracuse University, Syracuse, New York 13244, Department of Chemistry, University at Albany, SUNY, Albany, New York 12222, and BioTools, Inc., 17546 Bee Line Highway, Jupiter, Florida 33458

Received June 8, 2007; E-mail: lnafie@syr.edu

J. Am. Chem. Soc. **129**, 12364-12365 (2007)

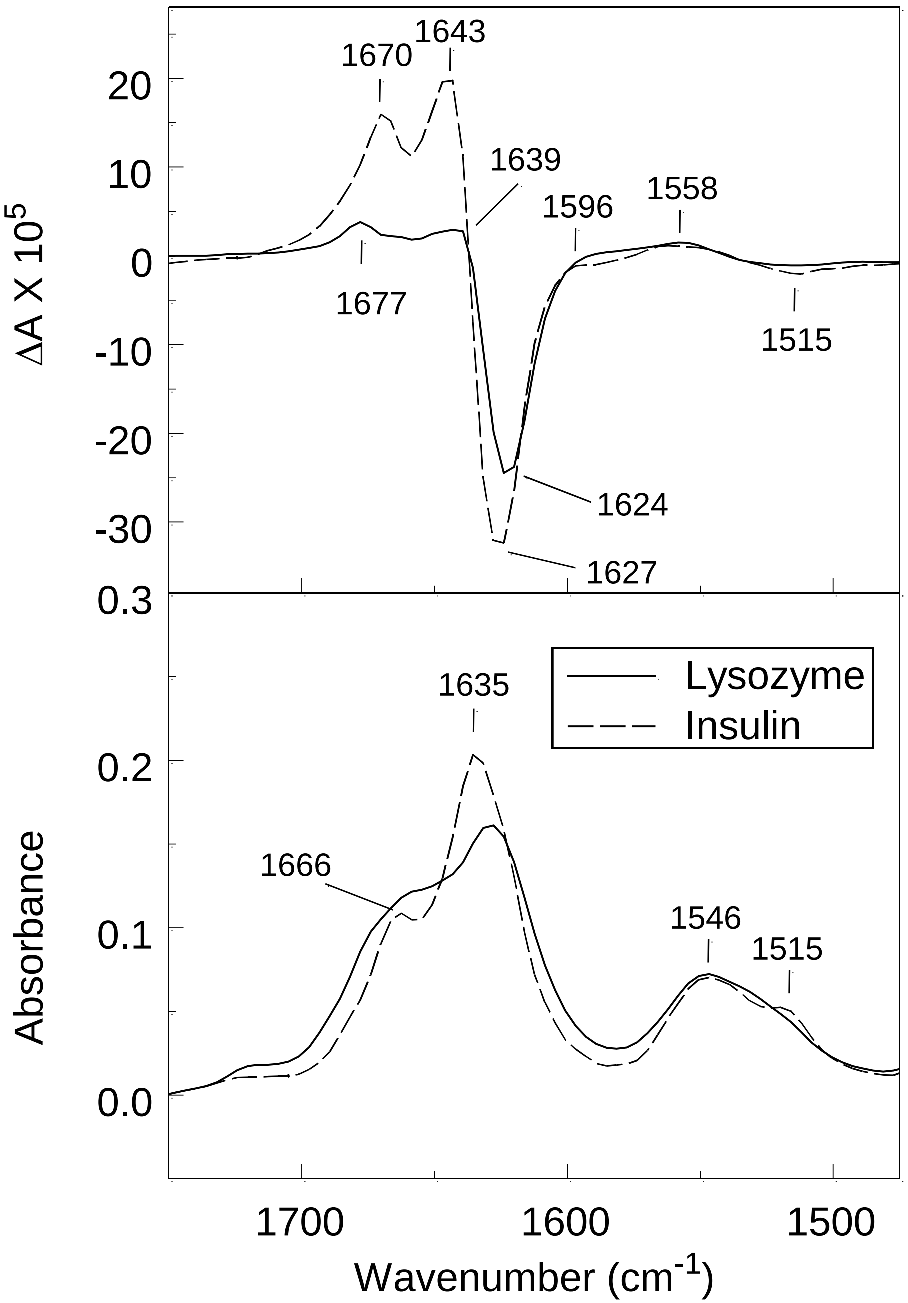


VCD of Fibrils of Lysozyme and Insulin



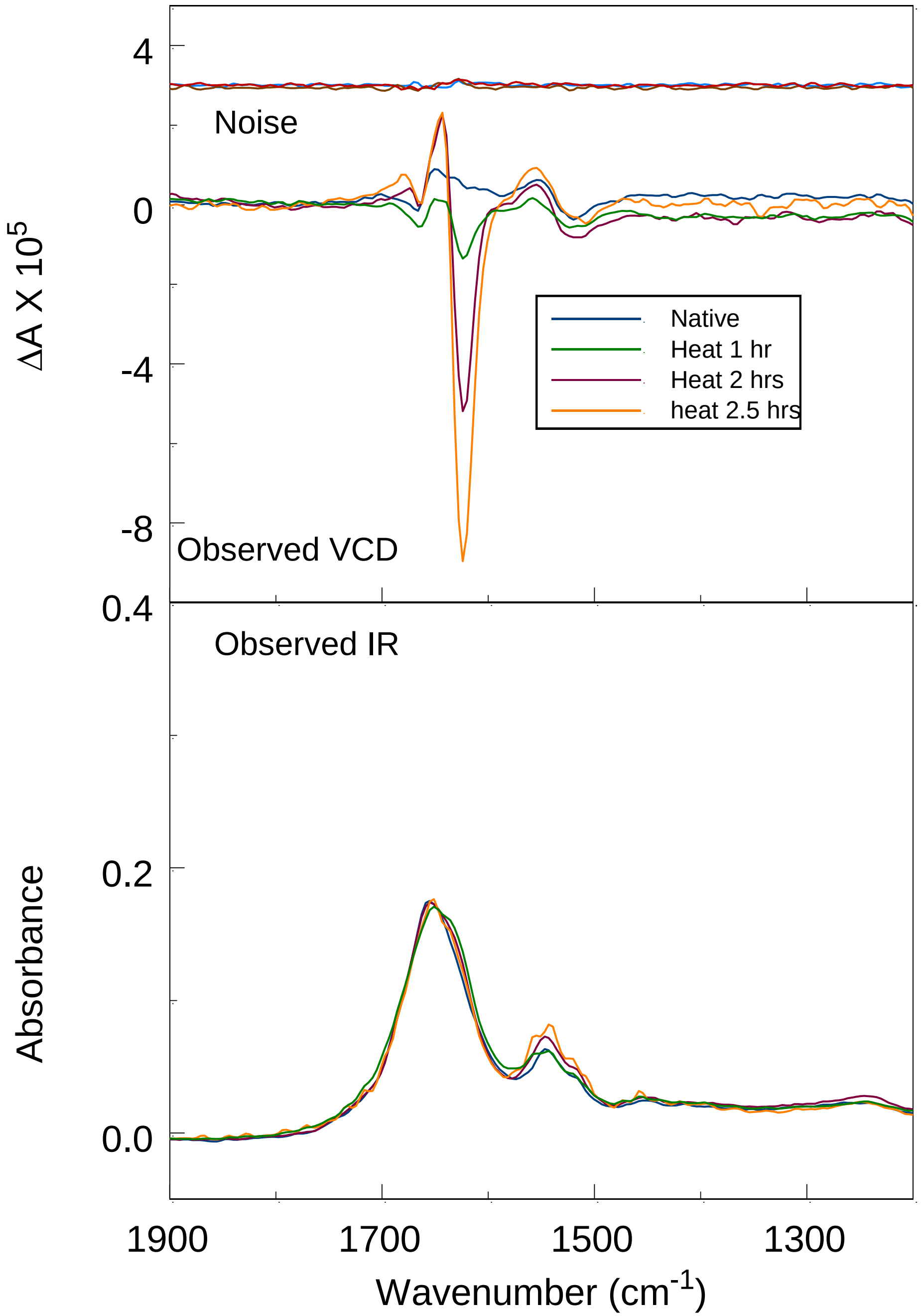
Lysozyme

Insulin



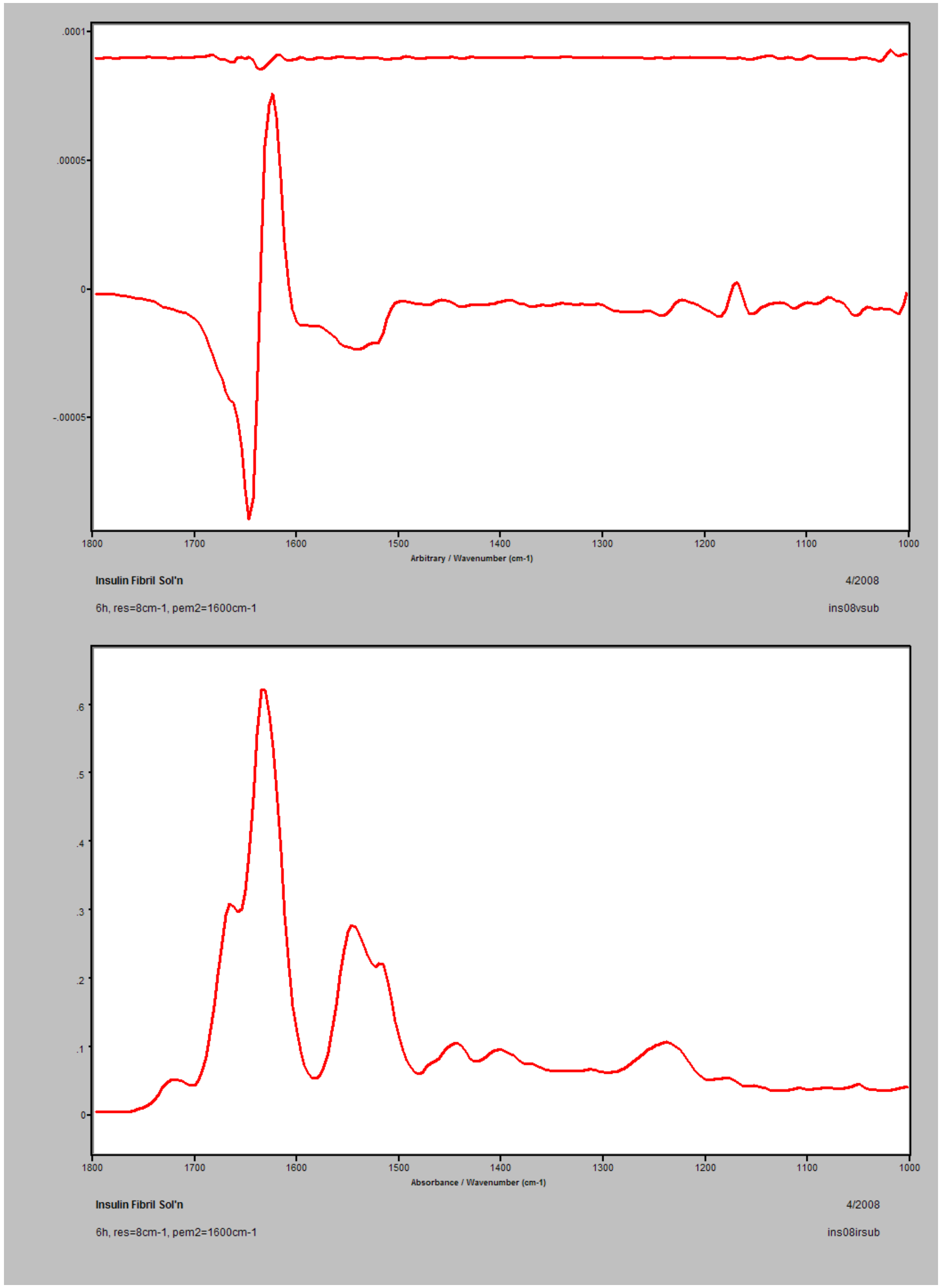
Normal VCD and IR for Lysozyme and Insulin

g ~ 10^{-2} to 10^{-3}



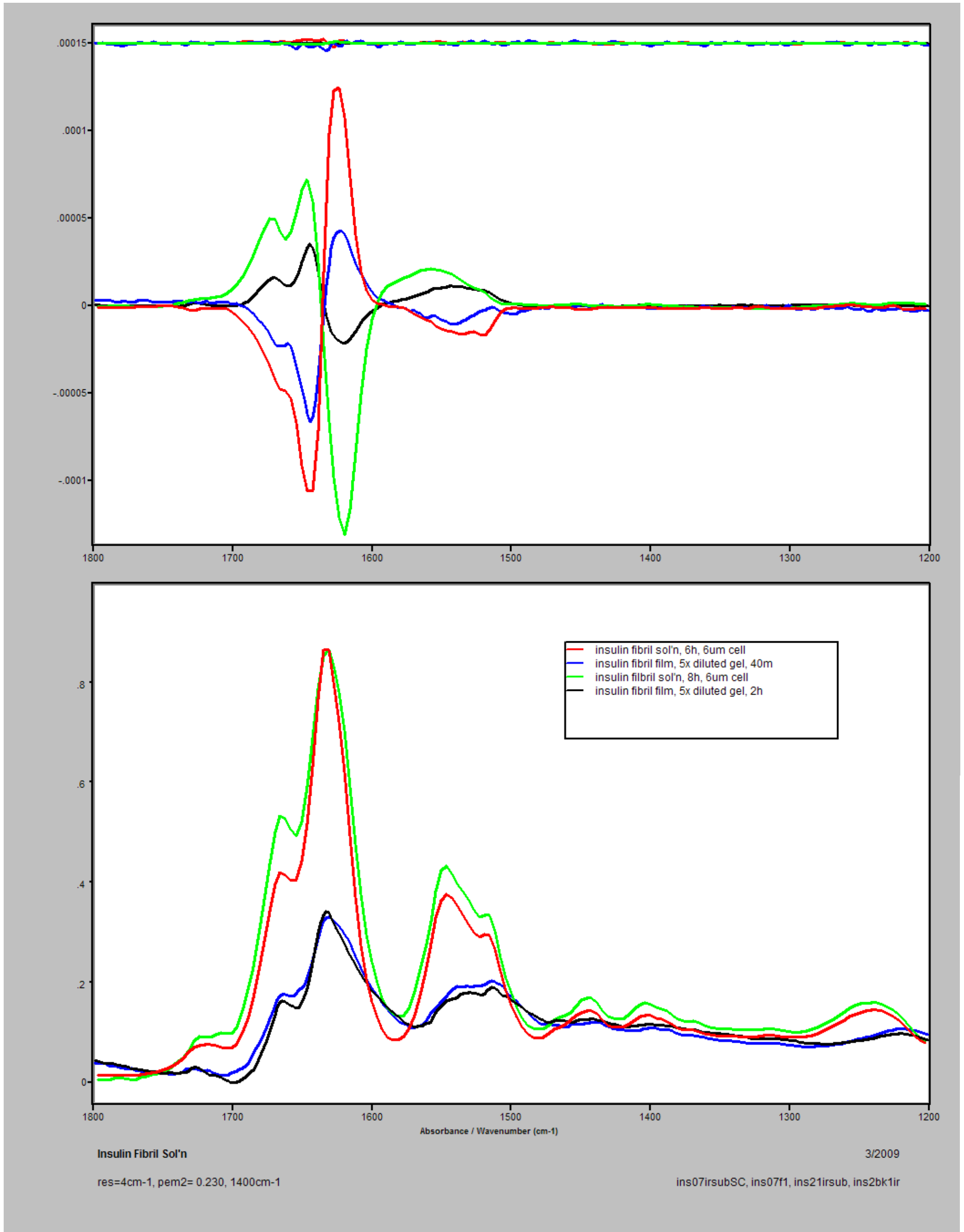
Insulin Fibril Formation and Growth at pH 2 with heating at 60°C

Reversed Supramolecular Chirality in Insulin Fibrils

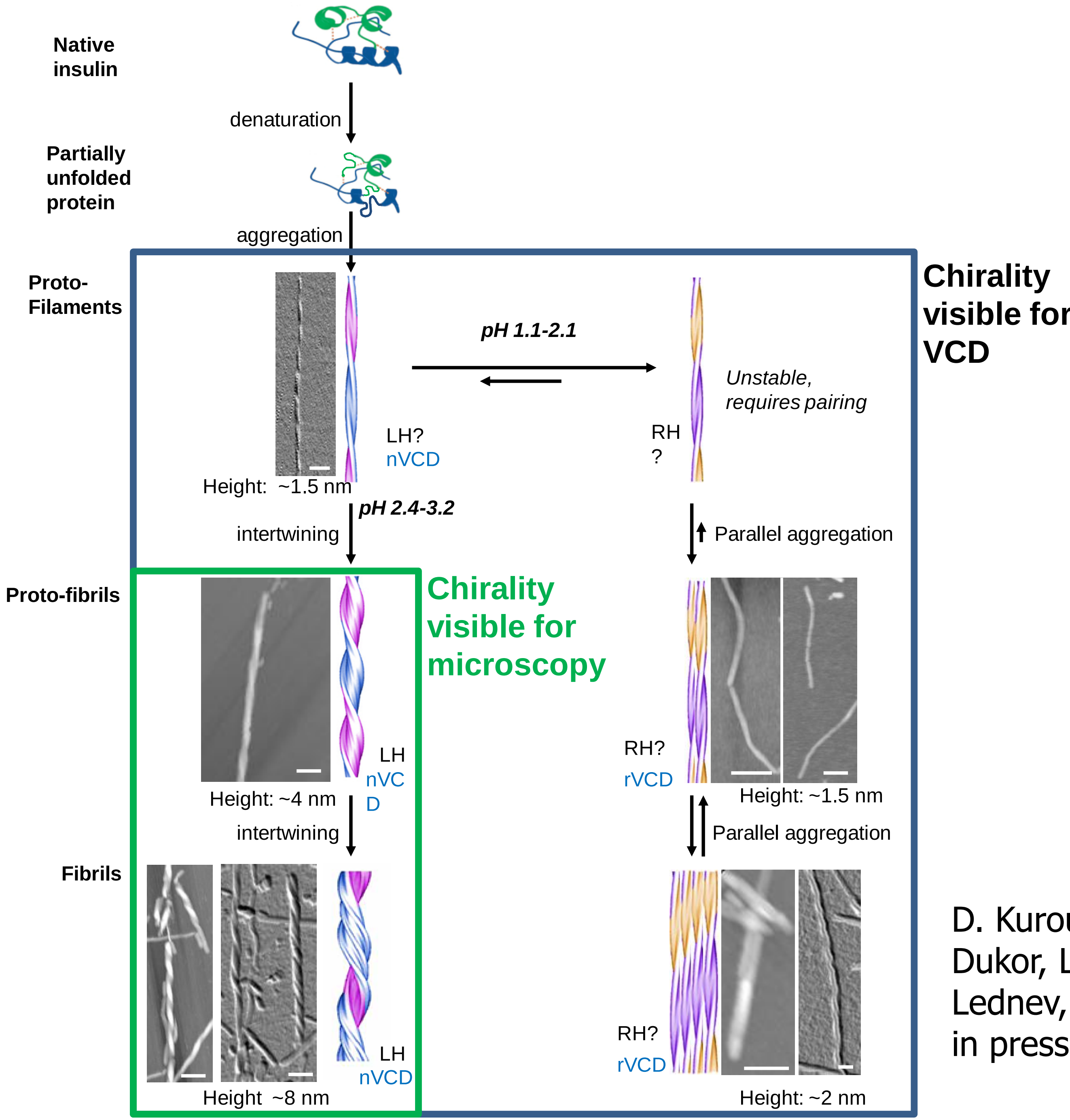


Reversed Large VCD of Insulin Protein Fibrils

Implications of Reversed Supramolecular Chirality



Comparison of Insulin Fibrils in the Solution and Film State for Normal and Reversed Supramolecular Chirality



D. Kurouski, X. Lu, R. K. Dukor, L. A. Nafie and I. K. Lednev, ***Biophys. J.***, *2012*, in press

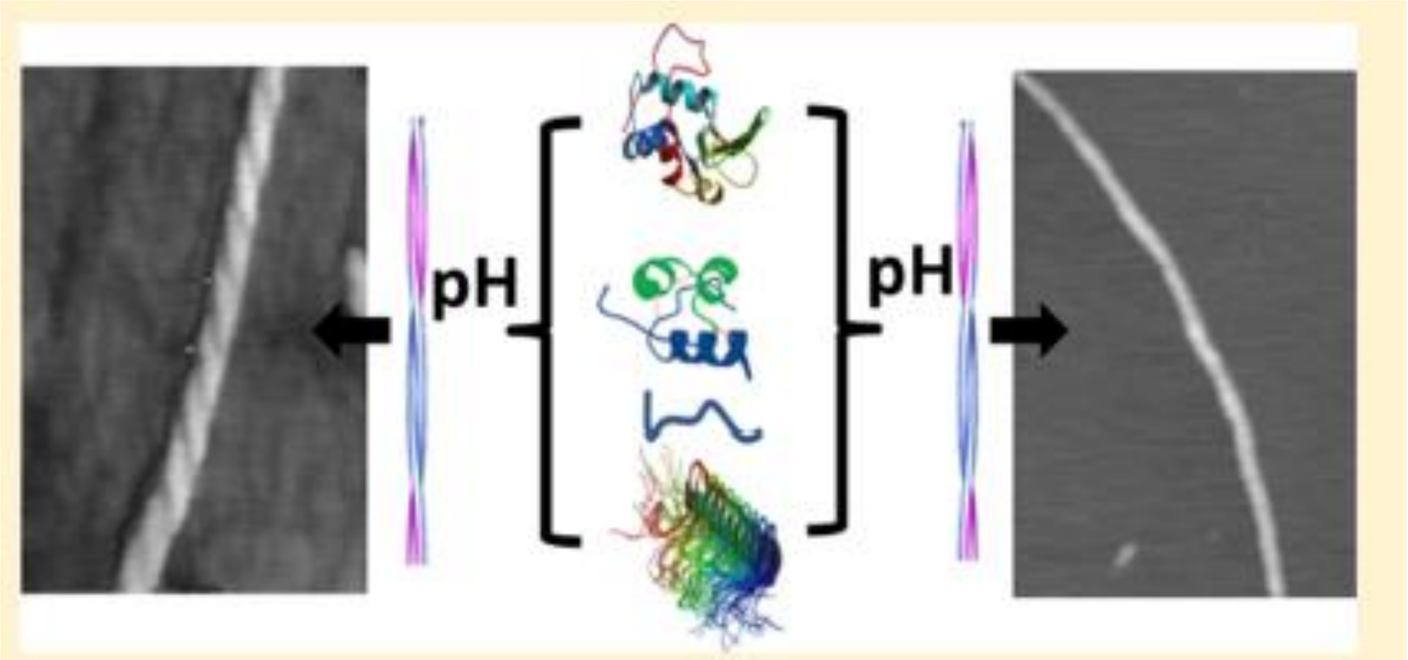
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

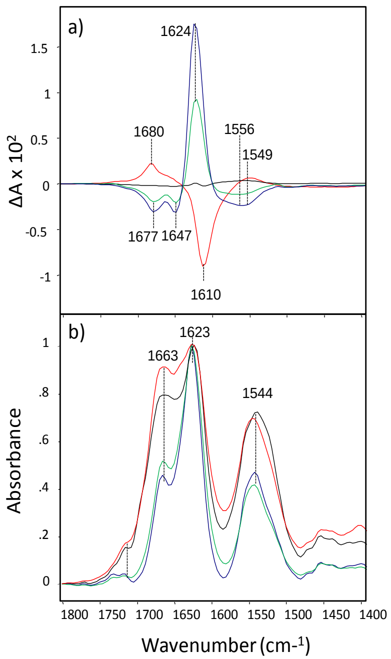
Is Supramolecular Filament Chirality the Underlying Cause of Major Morphology Differences in Amyloid Fibrils?

Dmitry Kurouski,[†] Xuefang Lu,[‡] Ludmila Popova,[†] William Wan,[§] Maruda Shanmugasundaram,[†] Gerald Stubbs,[§] Rina K. Dukor,[‡] Igor K. Lednev,[†] and Laurence A. Nafie*[,∥,‡]

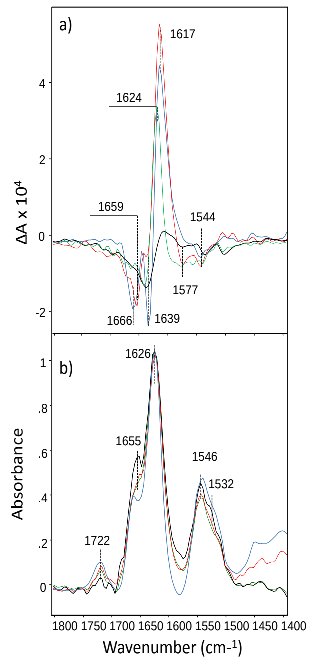


dx.doi.org/10.1021/ja407583r | J. Am. Chem. Soc. 2014, 136, 2302−2312

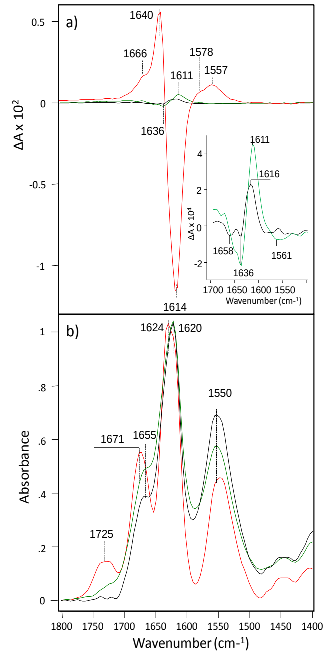
VCD versus pH for 4 additional proteins/peptides



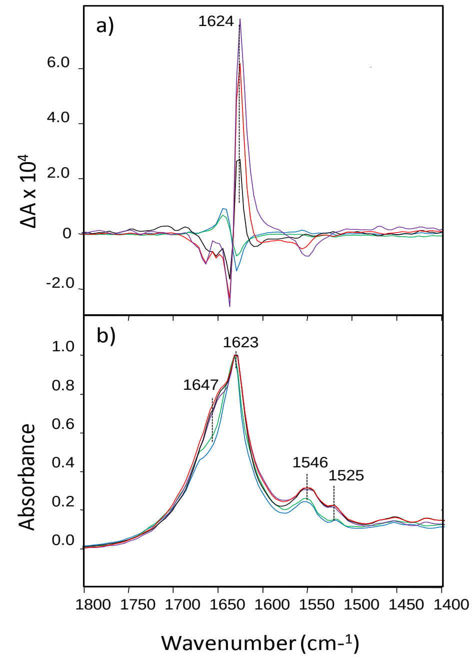
VCD (a) and IR (b) spectra of lysozyme fibrils grown at pH 1.0 (blue), 1.5 (green), 2.3 (black) and 2.7 (red) for 3 days at 65 ^{0}C.



VCD (a) and IR (b) spectra of apo-alpha lactalbumin fibrils grown at pH 1.5 (blue), 2.5 (red), 3.0 (green) and 4.0 (black) for 3 days at 37 ^{0}C.



VCD (a) and IR (b) spectra of HET-s mouse prion protein fibrils grown at pH 2.0 (red), 3.3 (green), 3.9 (black) room temperature, 2 months



VCD (a) and IR (b) spectra of TRR $_{105-115}$ fragment of transthyretin fibrils grown at pH 1.0 (blue), 1.5 (green), 2.0 (black), 2.5 (red) and 3.0 (violet) for 2 days at 37 ^{0}C.

For insulin, lysozyme, apo-alpha-lactalbumin, HET-s mouse prion protein and the TTR$_{105-115}$ peptide fragment maintain correlation of **normal VCD to left-twisted fibril** morphology and **reversed VCD to flat tape-like fibrils**

THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

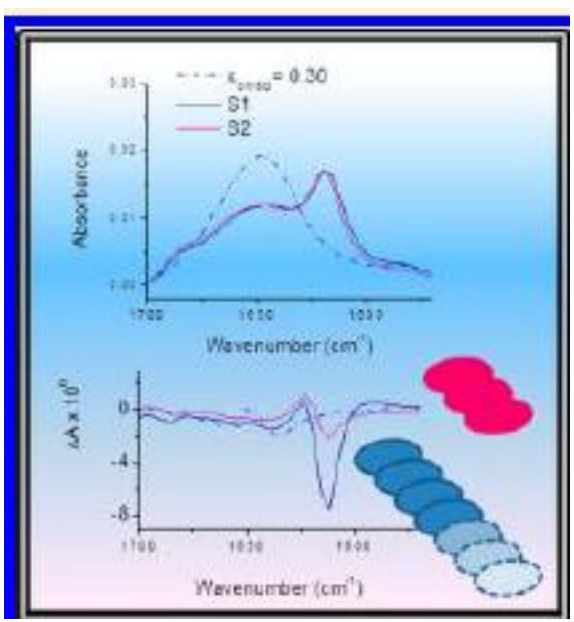
Vibrational Circular Dichroism Spectra of Lysozyme Solutions: Solvent Effects on Thermal Denaturation Processes

Alessandra Giugliarelli,[†] Paola Sassi,*[,†] Marco Paolantoni,[†] Assunta Morresi,[†] Rina Dukor,[‡] and Laurence Nafie[§]

[†]Dipartimento di Chimica, Università di Perugia, Via Elce di sotto 8, 06123 Perugia, Italy

[‡]BioTools, Inc., 17546 Bee Line Highway, Jupiter, Florida, 33458, United States

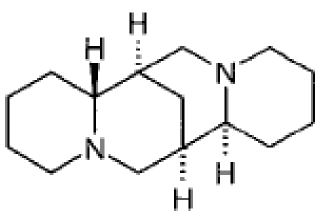
[§]Department of Chemistry, Syracuse University, Syracuse, New York, 13244, United States



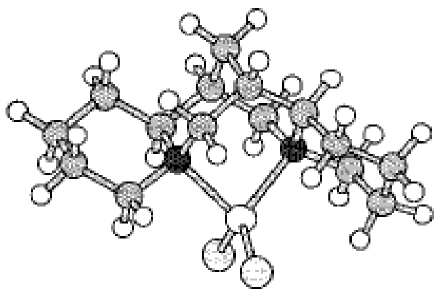
J. Phys. Chem. B 2013, 117, 2645−2652

Enhanced VCD Intensity in Molecules with Low-Lying Electronic States

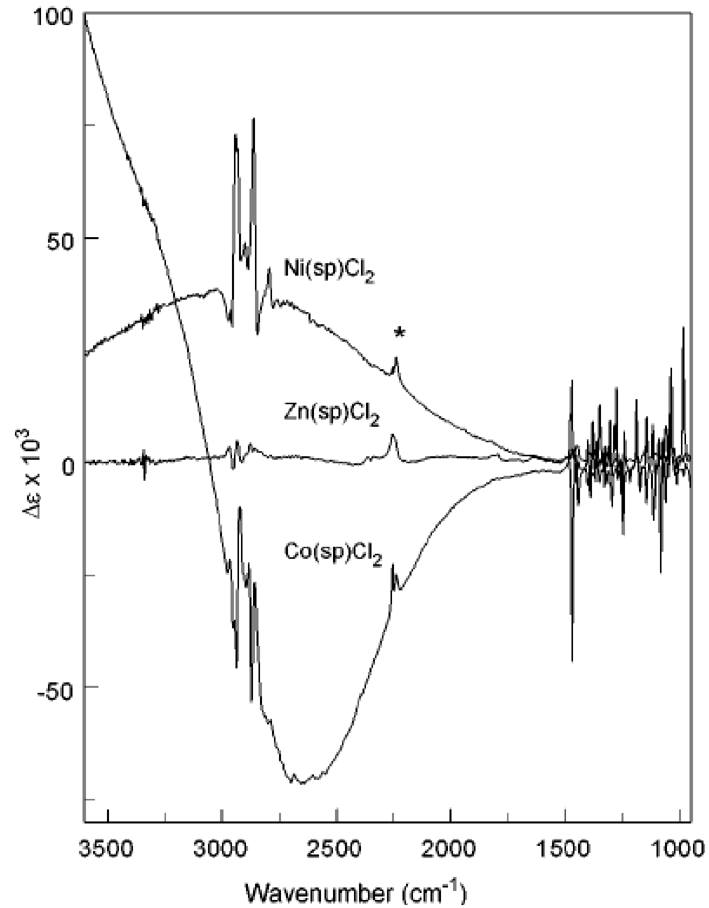
Sparteine Transition Metal Complexes



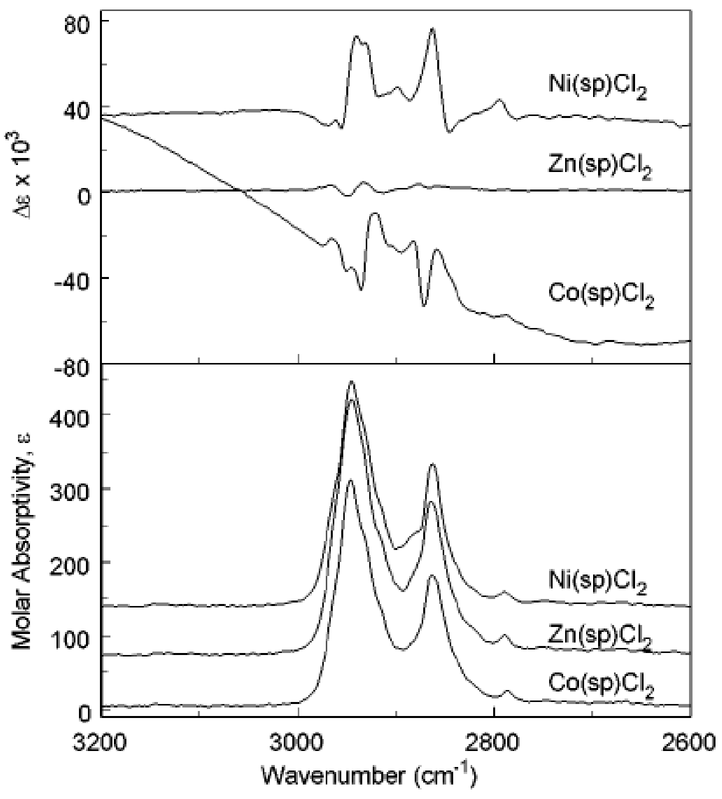
6R,7S,9S,11S-(-)-Sparteine

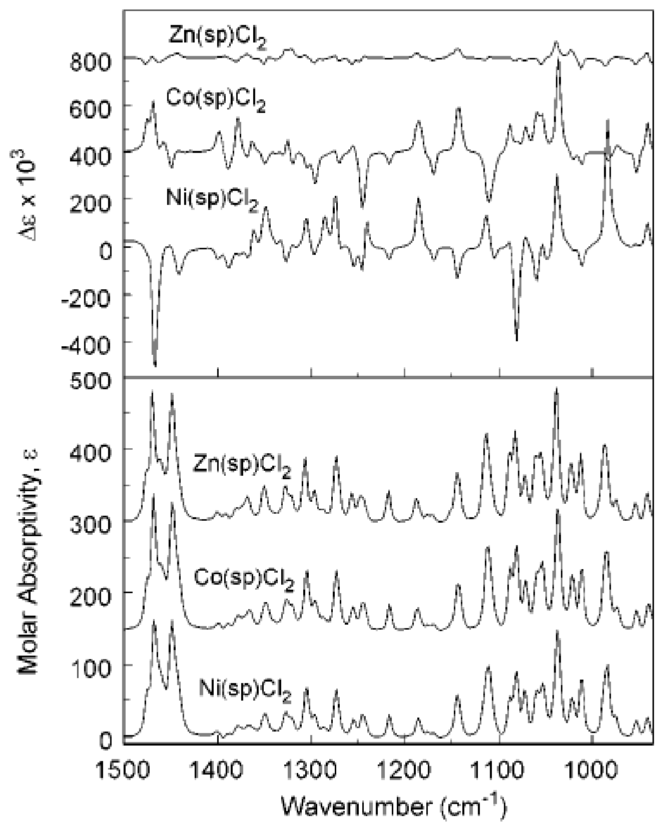


Optimized geometry of $Zn(sp)Cl_2$

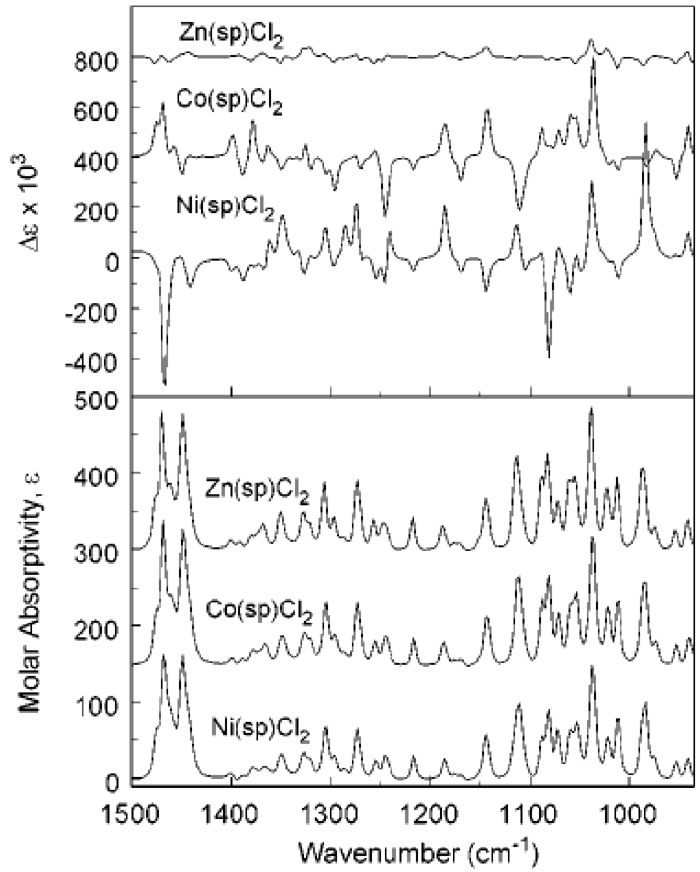


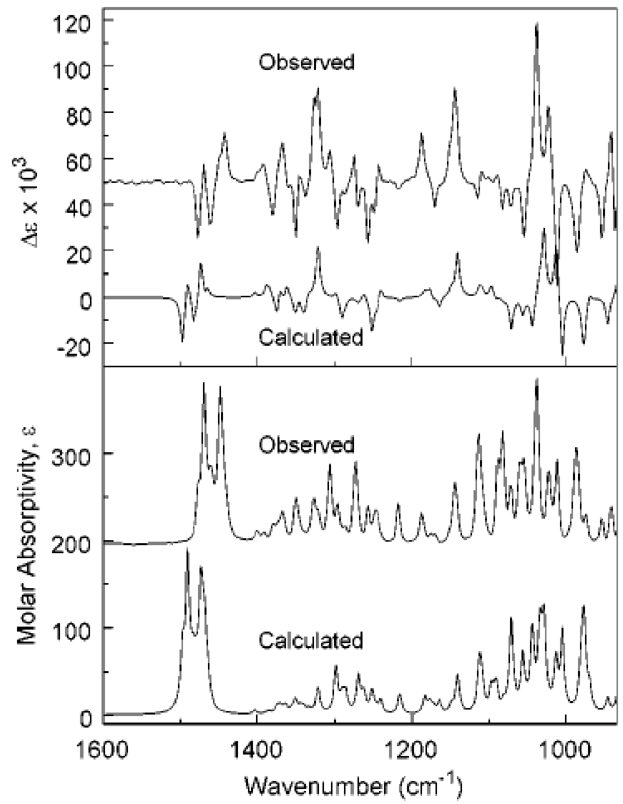
Sparteine Transition Metal Complexes





Sparteine Transition Metal Complexes





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Amplified Vibrational Circular Dichroism as a Probe of Local Biomolecular Structure

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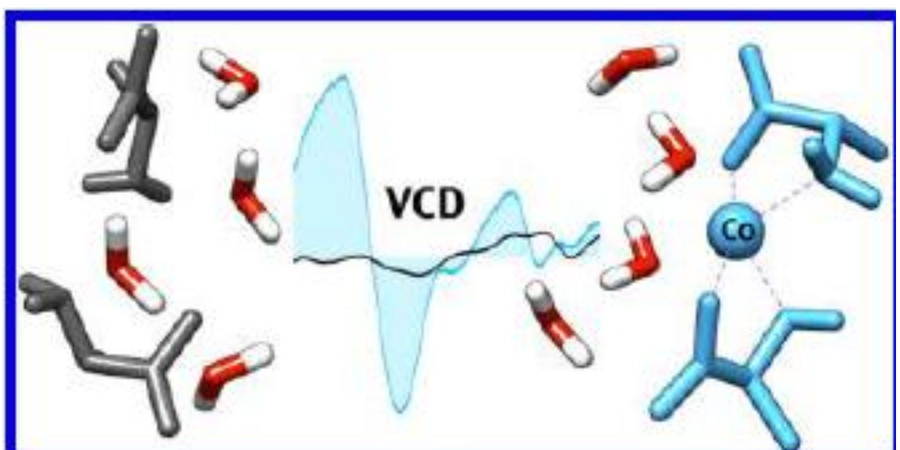

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Conclusions

- VCD and ROA are a sensitive spectroscopic probes of absolute molecular stereochemistry of all classes of chiral molecules and biomolecules
- Velocity formulation of VCD allows visualization of vibrational current density
- Enhanced VCD can be seen in
  - Protein fibril formation and development
  - Molecules with low-lying excited electronic states
  - Extended chiral cyclic π-electron systems including chiral conducting polymers

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