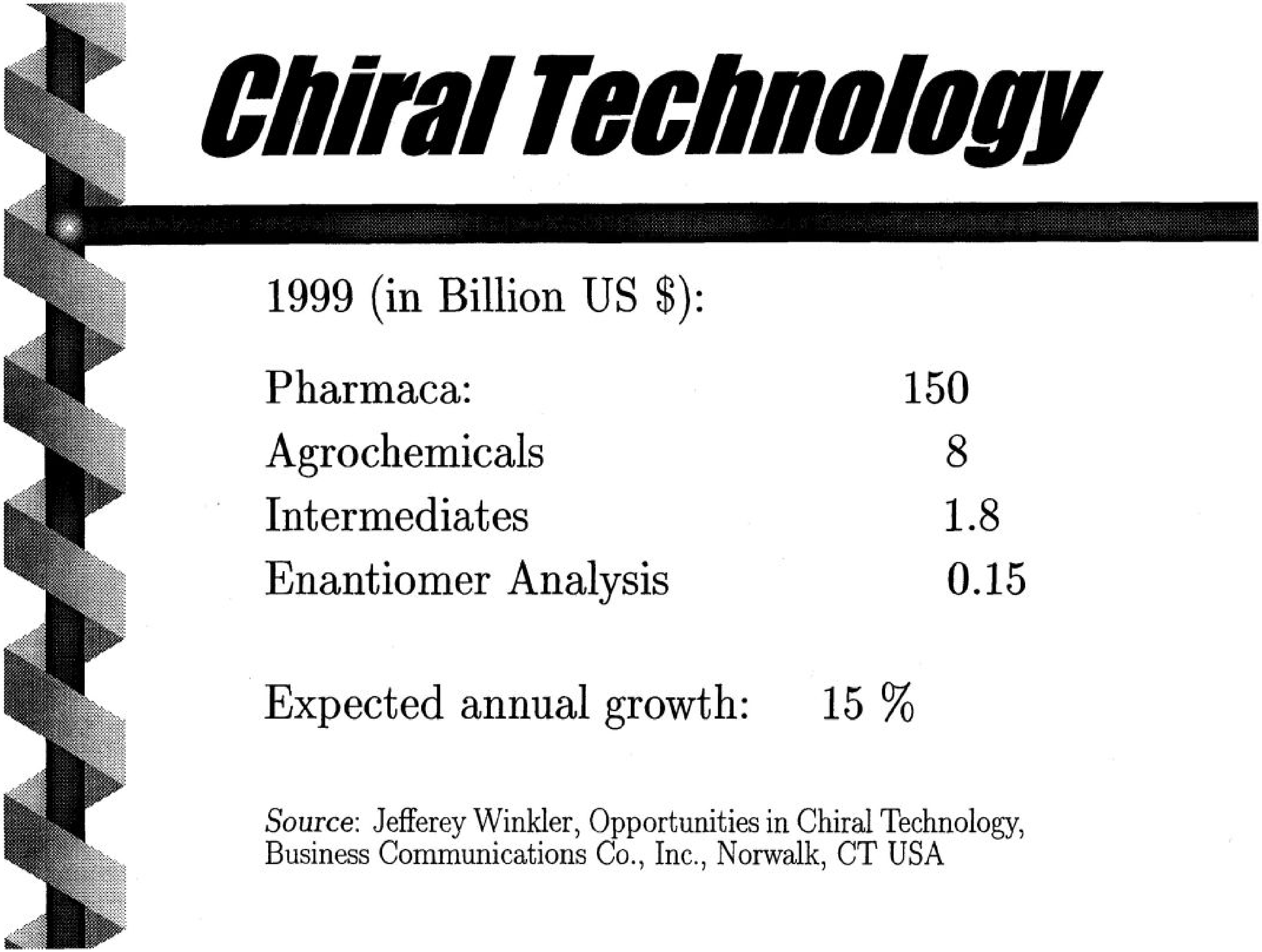
Chirality

Importance of chirality



Chiral Technology

1999 (in Billion US $):

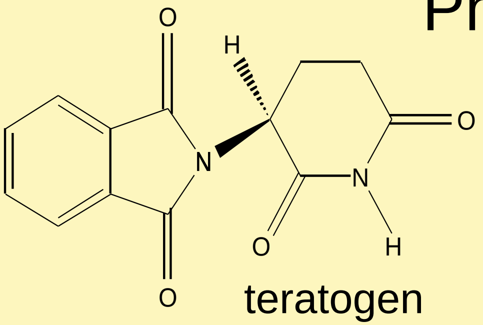
Pharmaca:	150
Agrochemicals	8
Intermediates	1.8
Enantiomer Analysis	0.15

Expected annual growth: 15 %

Source: Jefferey Winkler, Opportunities in Chiral Technology, Business Communications Co., Inc., Norwalk, CT USA

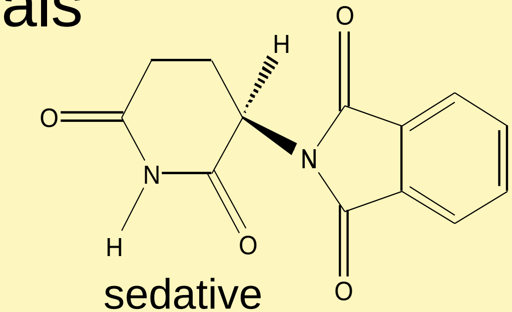
Importance of chirality

Pharmaceuticals



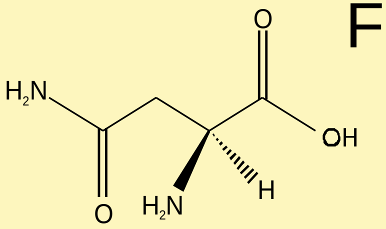
teratogen

Thalidomide



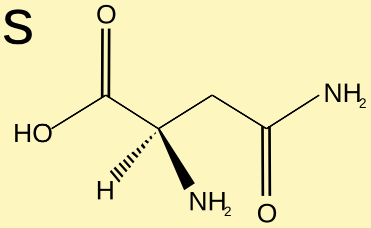
sedative

Flavors & Fragrances



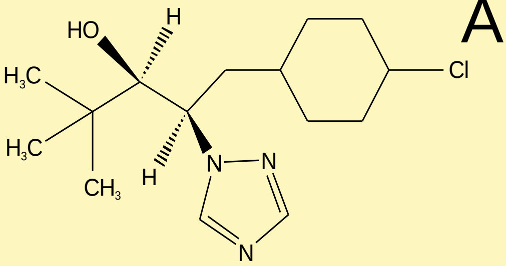
bitter

Asparagine



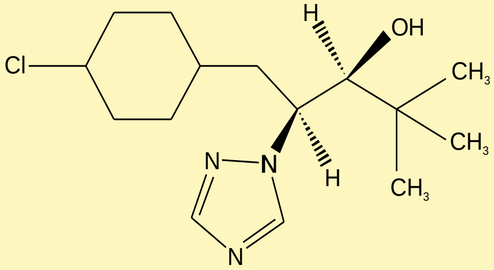
sweet

Agrochemicals



fungicide

Paclobutrazol



Plant growth regulator

Determination of absolute configuration (legislation)

Chiroptical Methods

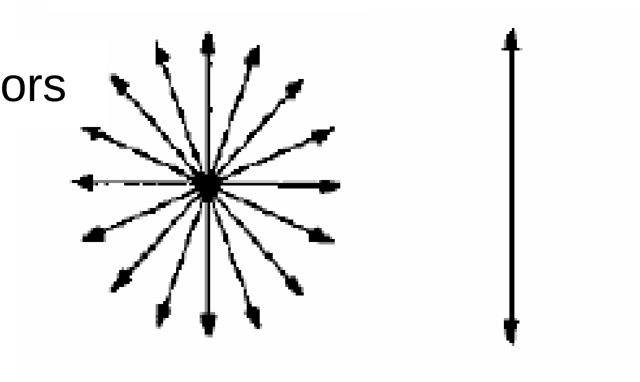
- Chiral molecules interact differently with left- and right-circular polarized light!

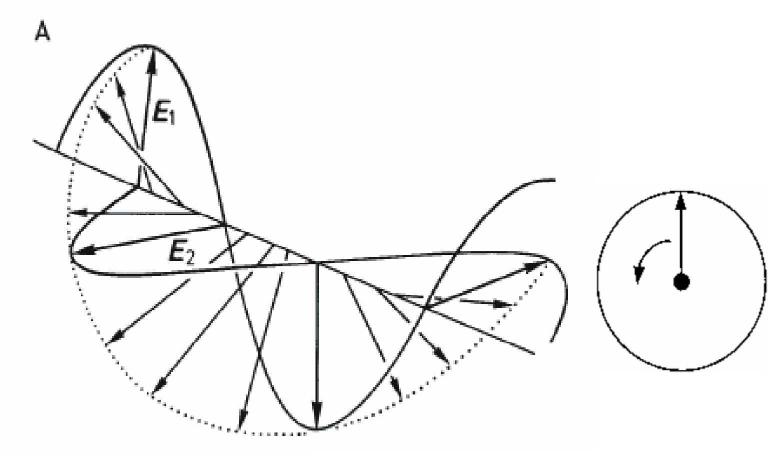
circular polarized
superposition of linear polarized
plane waves (phase shift!)

isotropic

linear polarized

E-field vectors





L: left, R: right

Refractive index $\eta = c_0 / c$ $c =$ Speed of light in medium

Absorption $A = \varepsilon \cdot c \cdot d$ $\varepsilon =$ Extinction coefficient

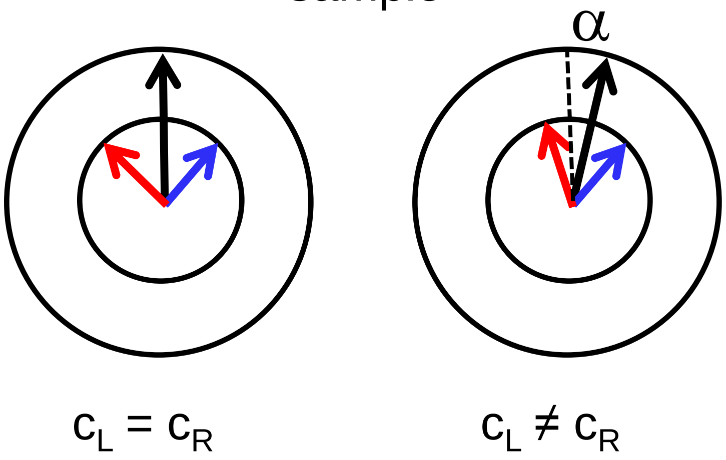
$c_L \neq c_R$
$\eta_L \neq \eta_R$

$\varepsilon_L \neq \varepsilon_R$

Linear polarized light - Circular polarized light

Linear polarized light can be viewed as a superposition of left- and right-circular polarized light

Polarization state after transmission of linear polarized light through a non-absorbing sample

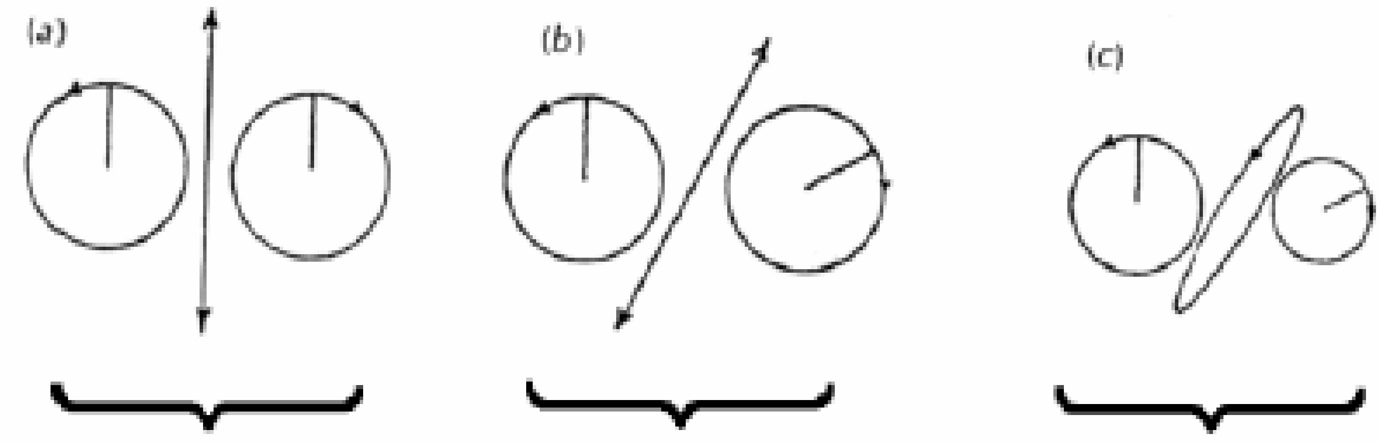


Plane of linearly polarized light is turned by angle α

Circular dichroism (CD)

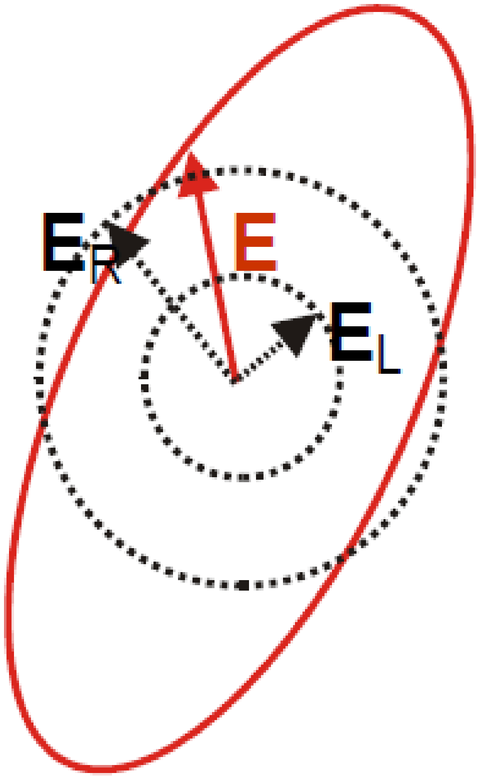
Differential absorption of left- and right-circularly polarized light leads to elliptically polarized light.

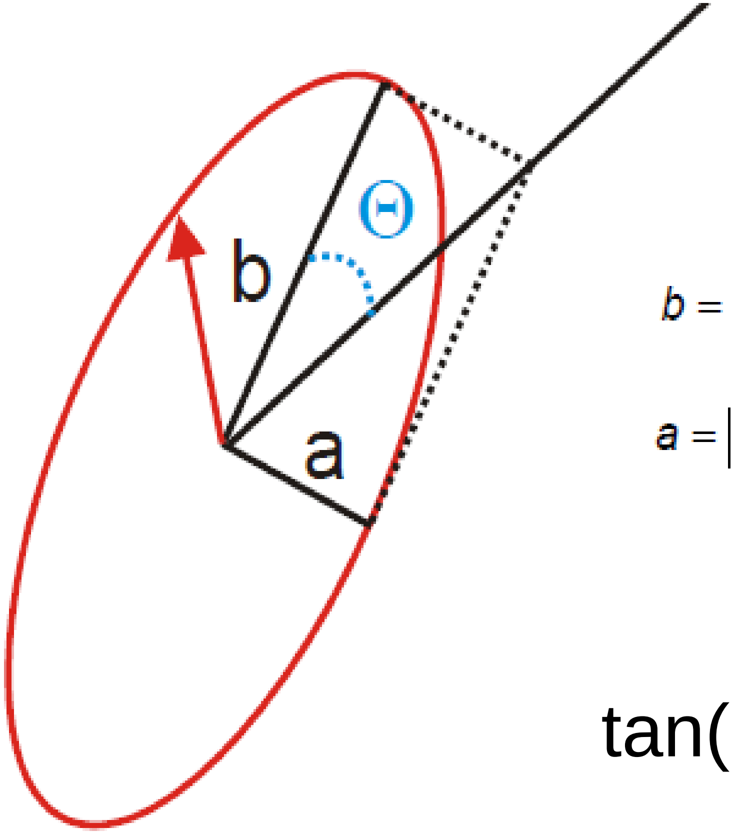
Polarization state of an incident linear polarized plane wave after the sample



•equal velocity of light •equal absorption	•unequal velocity of light •equal absorption	•unequal velocity of light •unequal absorption
optically inactive	Optical rotation, ORD	CD

Ellipticity





$$b = |\mathbf{E}_R| + |\mathbf{E}_L|$$

$$a = |\mathbf{E}_R| - |\mathbf{E}_L|$$

$$\tan(\theta) = a/b$$

Θ: Ellipticity

CD / VCD: Physical basis

Remember: Absorption

Electric transition dipole moment

$$\mu_{21}^{\mathrm{el}} = \langle \Psi_2 \,|\, \mu_{\mathrm{el}} \,|\, \Psi_1 \rangle$$

Oscillator strength

$$D_{21} = \mu_{12}^{\mathrm{el}} \cdot \mu_{21}^{\mathrm{el}} \sim \int_{\mathrm{band}} \frac{\varepsilon(\nu)}{\nu} \mathrm{d}\nu$$

← Molar absorption coefficient

CD / VCD: Physical basis

CD / VCD

Magnetic transition dipole moment

$$\mu_{21}^{m} = \langle \Psi_2 | \mu_m | \Psi_1 \rangle$$

Rotational strength

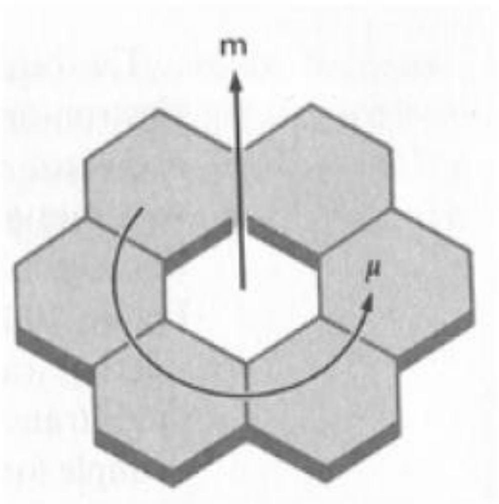
$$R_{21} = \mathrm{Im}\left(\mu_{21}^{el} \cdot \mu_{21}^{m}\right) \sim \int_{band} \frac{\Theta(\nu)}{\nu} d\nu$$

← Ellipticity

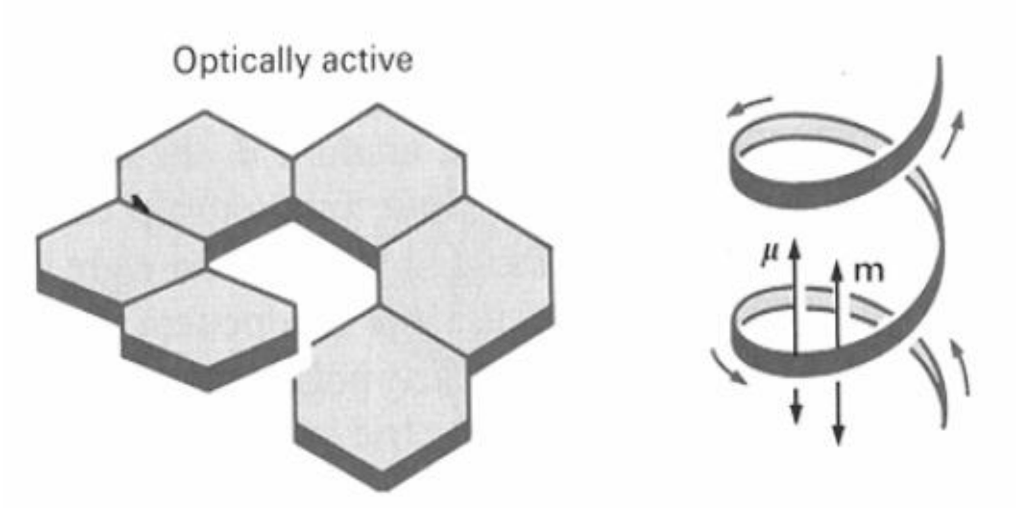
There must be a parallel component between μ^{el} and μ^{m}!

CD / VCD: Physical basis

Examples CD (electronic transitions)



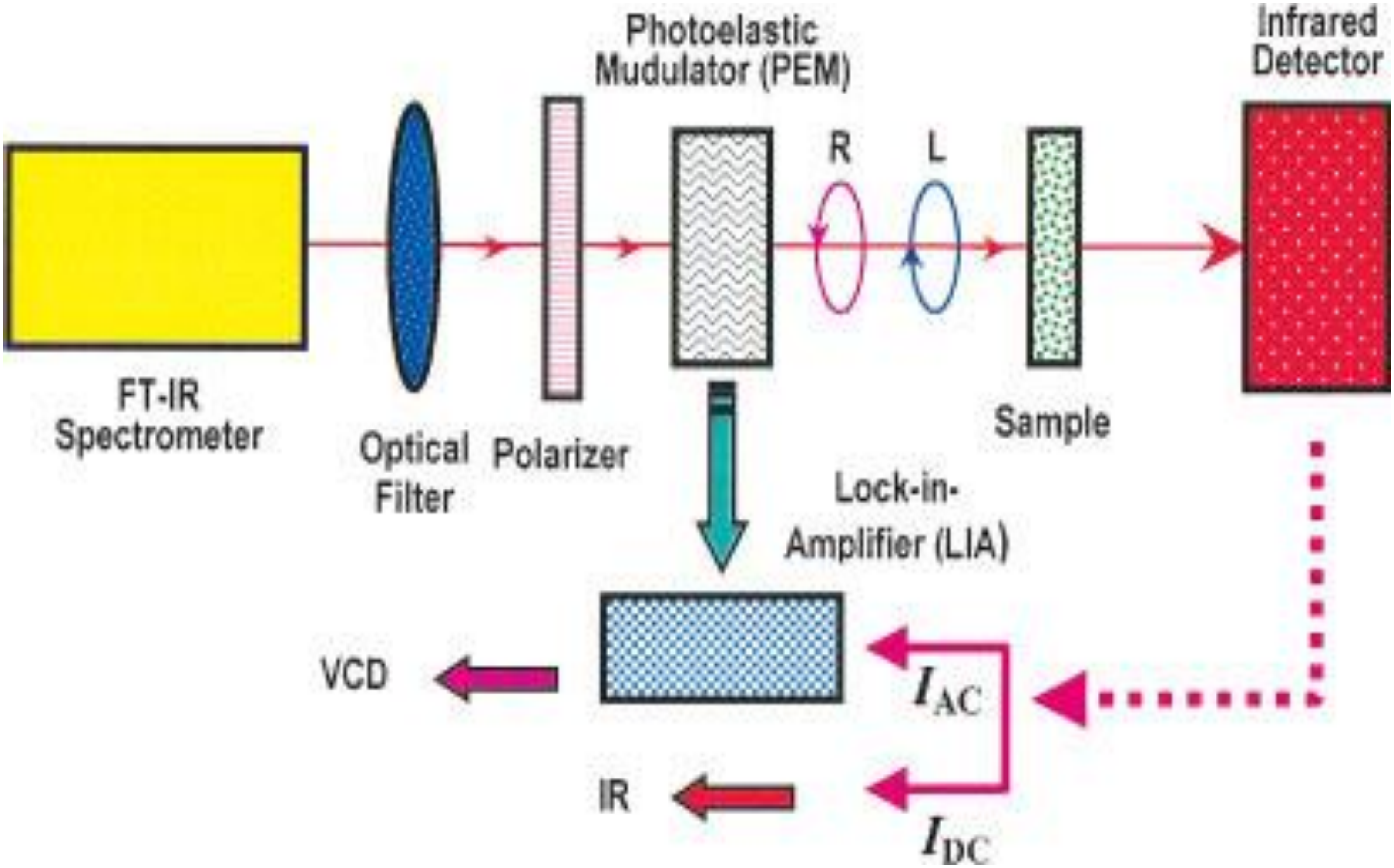
Coronene
Optically inactive



Helicenes
Optically active

There must be a parallel component between μ^{el} and μ^{m}!

Experimental set-up for VCD measurements



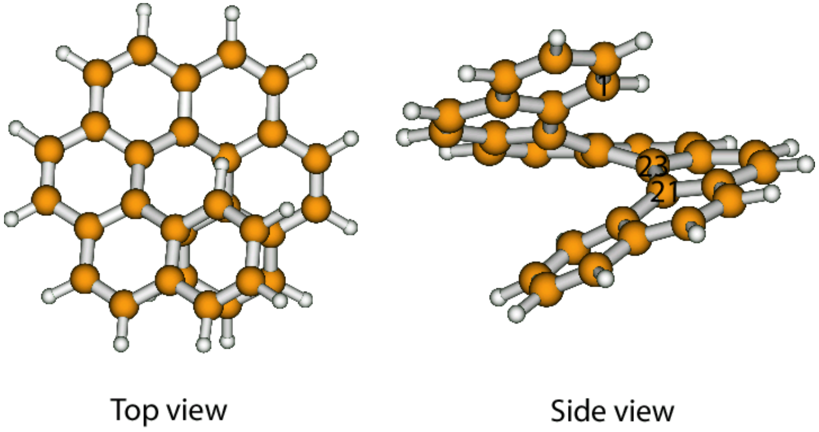
Vibrational circular dichroism (VCD)

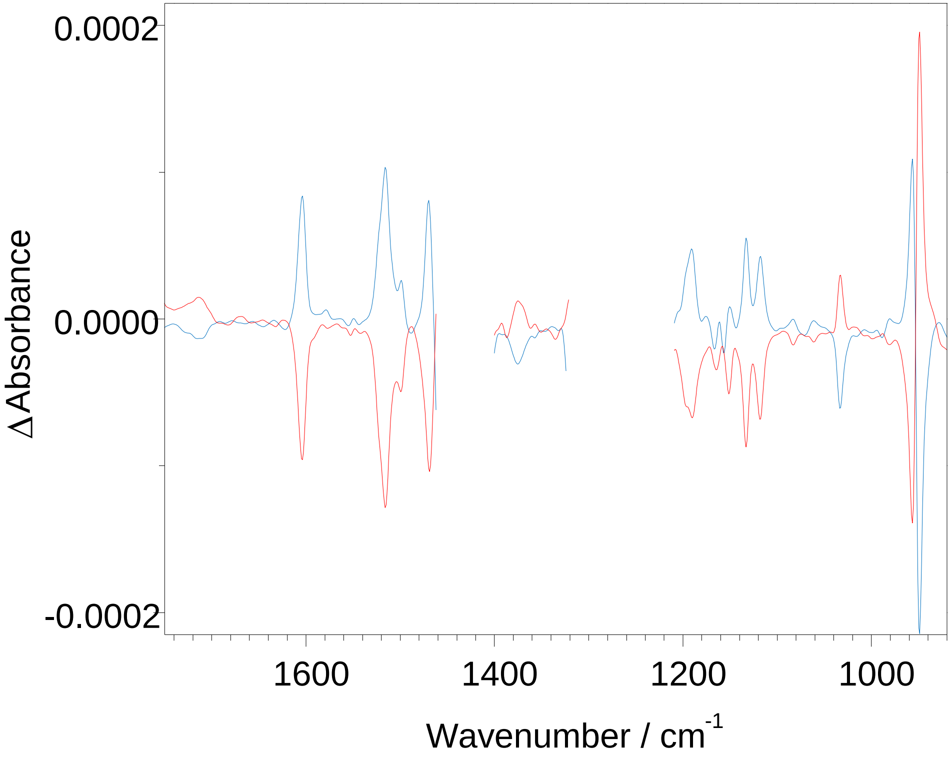
- Analogous to CD but in the infrared
- CD: electronic transitions
- VCD: vibrational transitions

VCD spectra of both enantiomers

Heptahelicene

rigid



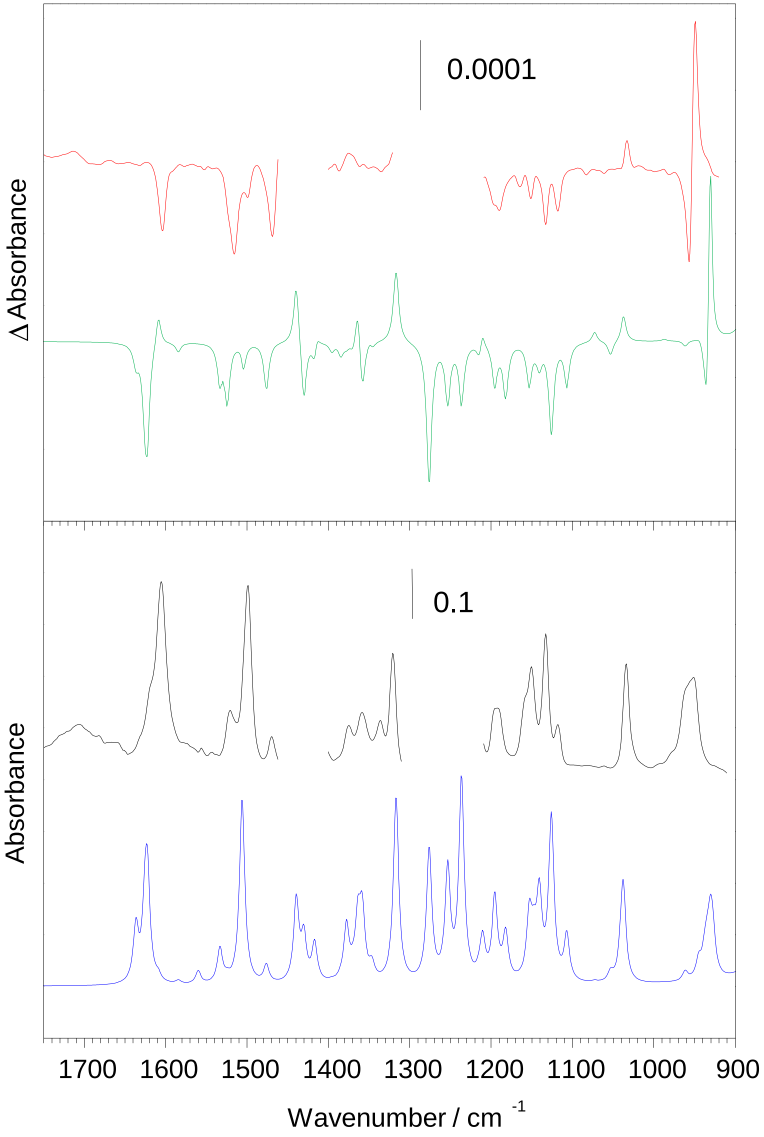


T. Bürgi et al. New J. Chem., 2004, 28, pp 332–334

Heptahelicene

VCD spectra

IR Spectra



Experiment

Theory

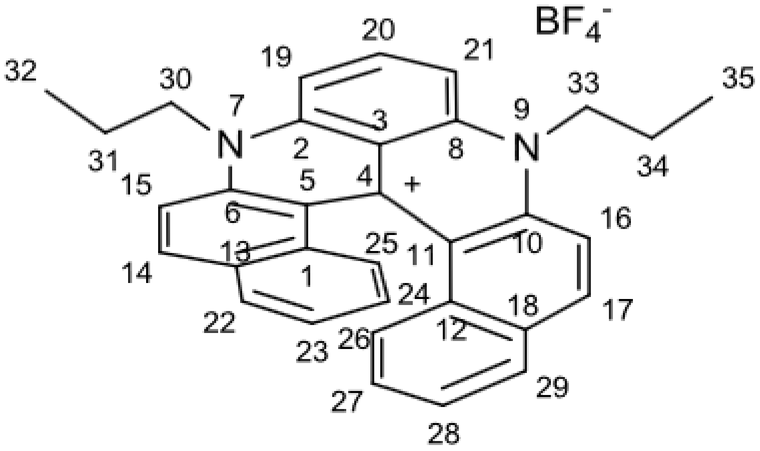
Experiment

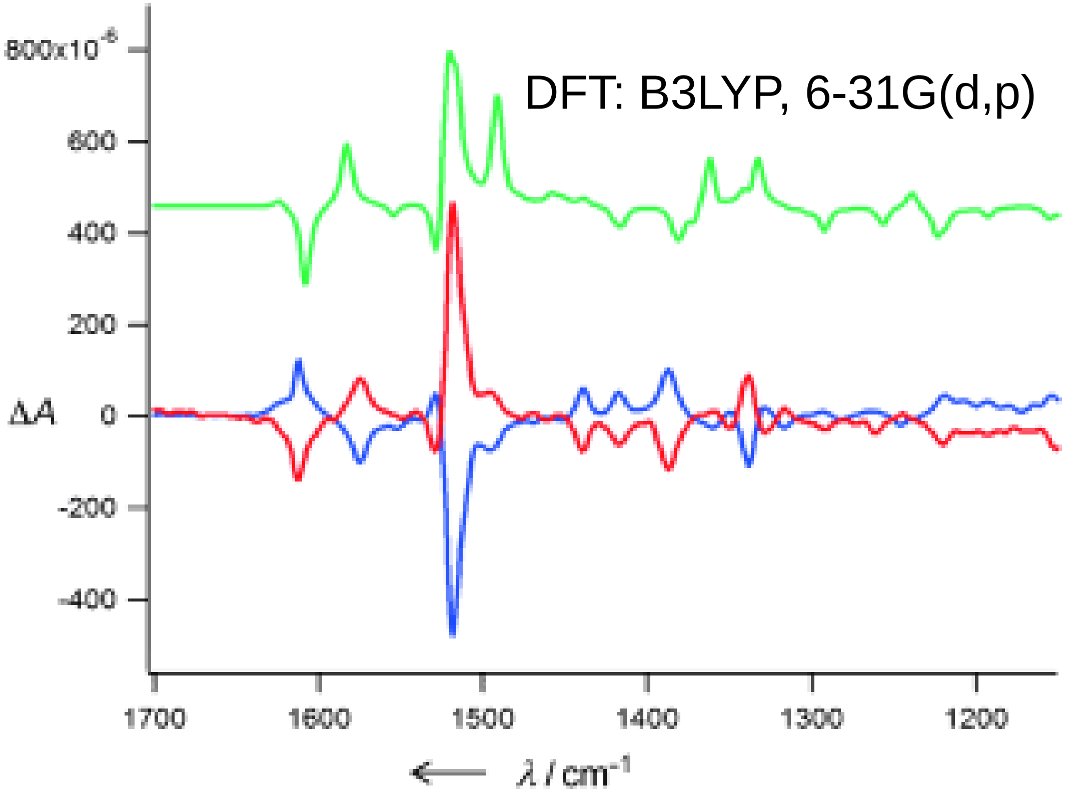
Theory

DFT: B3LYP, 6-31G(d,p)

Cationic [6] helicene

Determination of absolute configuration



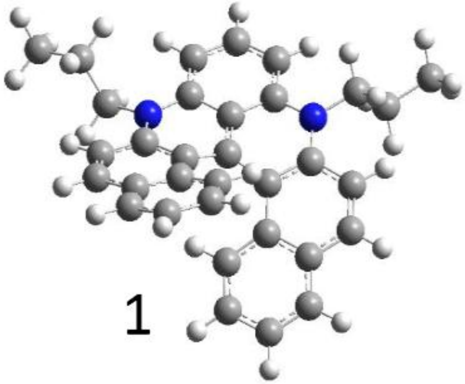


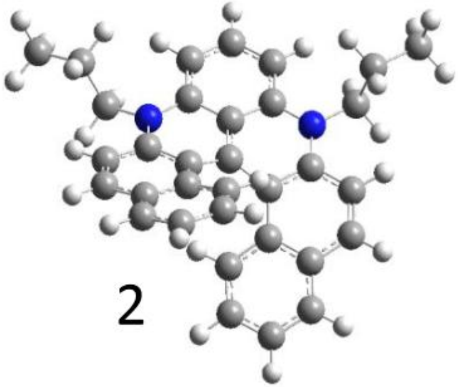
DFT: B3LYP, 6-31G(d,p)

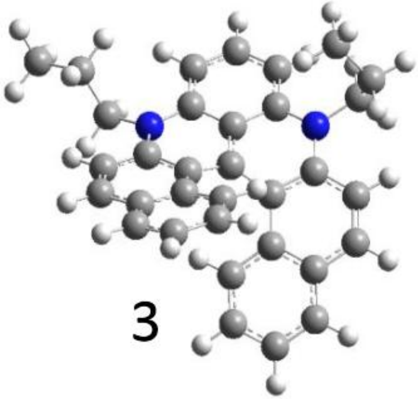
J. Lacour et al. Angewandte Chemie International Edition 52, 1796 (2013)

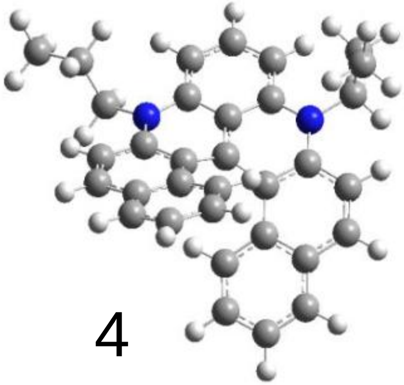
Cationic [6] helicene

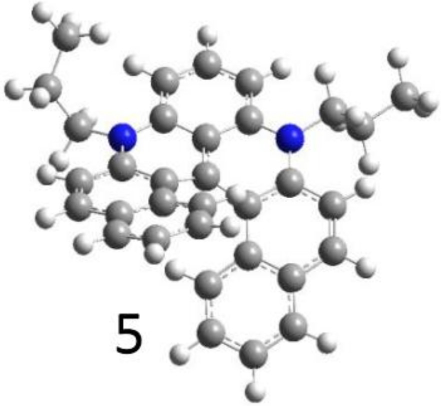
Several conformers


1


2


3


4

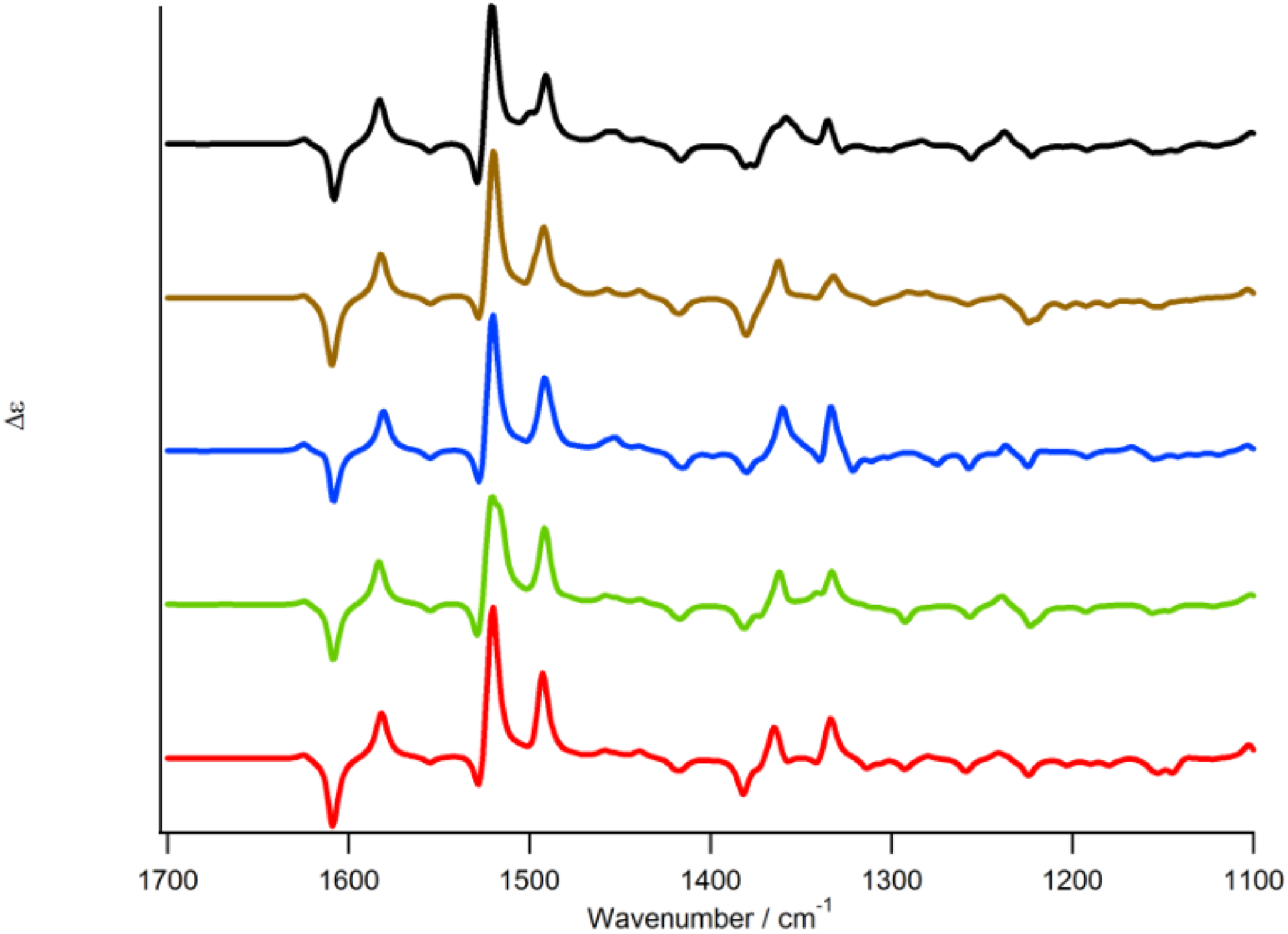

5

DFT: B3LYP, 6-31G(d,p)

J. Lacour et al. Angewandte Chemie International Edition 52, 1796 (2013)

Cationic [6] helicene

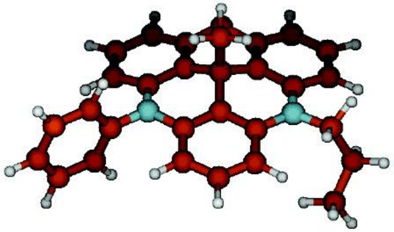
Calculated VCD spectra for several conformers



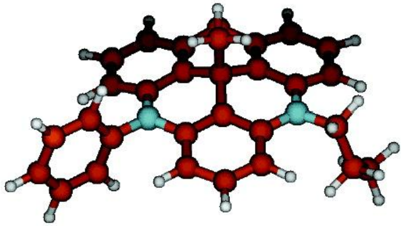
J. Lacour et al. Angewandte Chemie International Edition 52, 1796 (2013)

Diazaoxatricornan Derivative

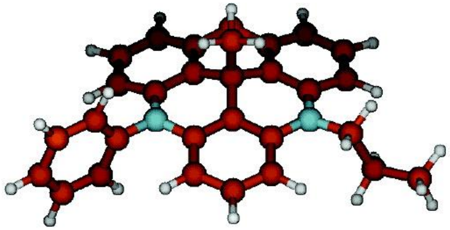
Calculated conformers



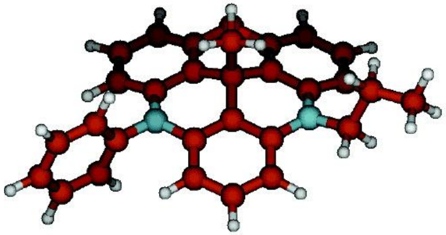
1, 2.91 kcal/mol



2, 2.86 kcal/mol

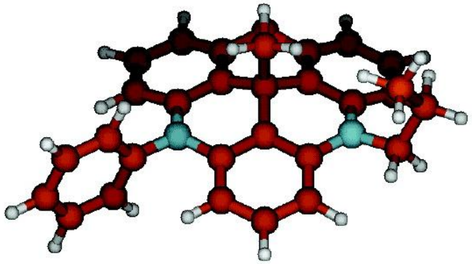


3, 0.0 kcal/mol



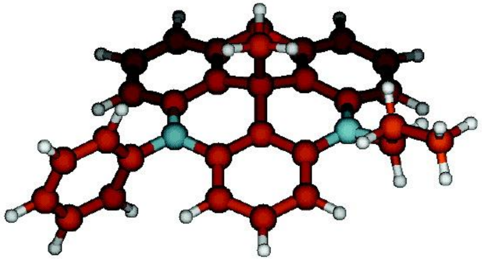
4, 1.70 kcal/mol

5, not stable

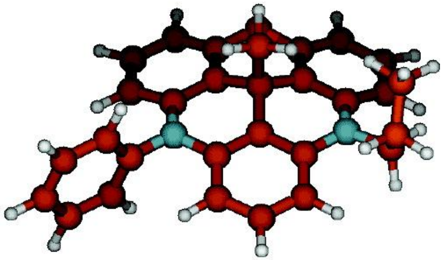


6, 2.30 kcal/mol

7, not stable



8, 1.66 kcal/mol



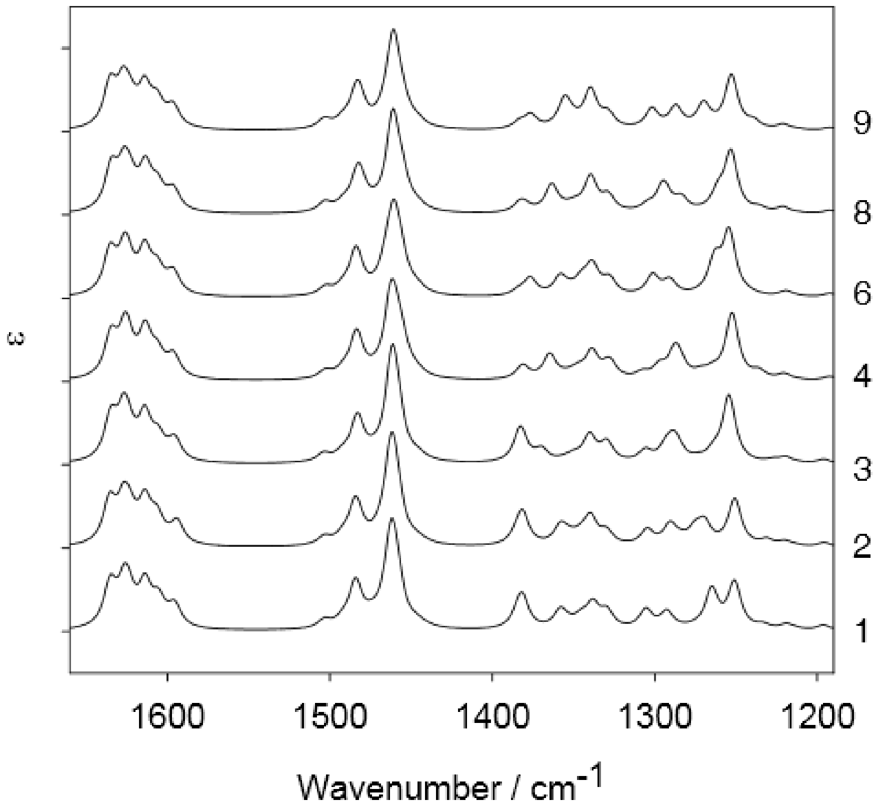
9, 2.20 kcal/mol

DFT: P3PW91, 6-31G(d,p)

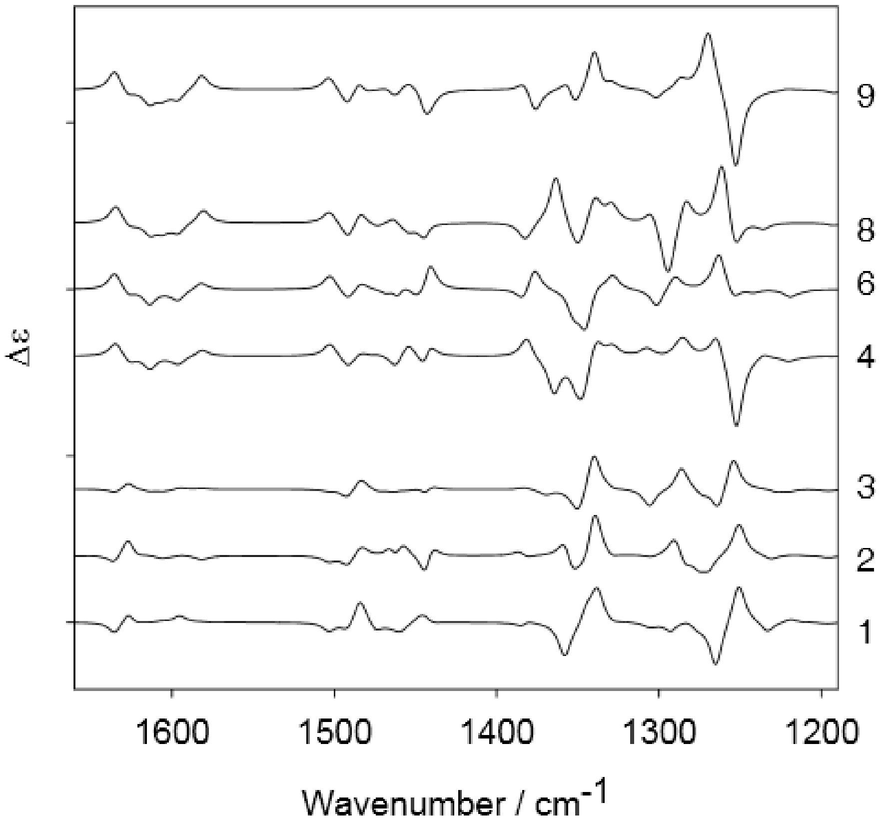
J. Lacour et al. *J. Am. Chem. Soc.*, 2008, 130 (20), pp 6507–6514

Diazaoxatricornan Derivative

Calculated IR and VCD spectra for several conformers



IR



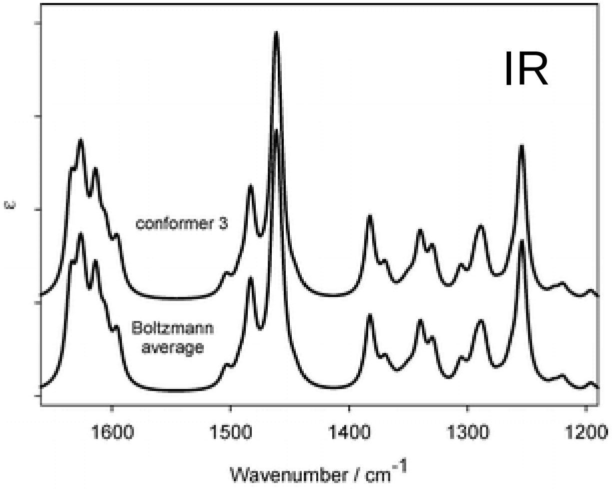
VCD

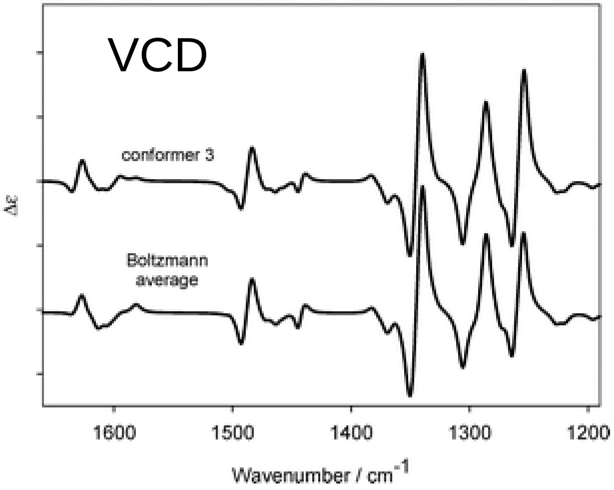
DFT: P3PW91, 6-31G(d,p)

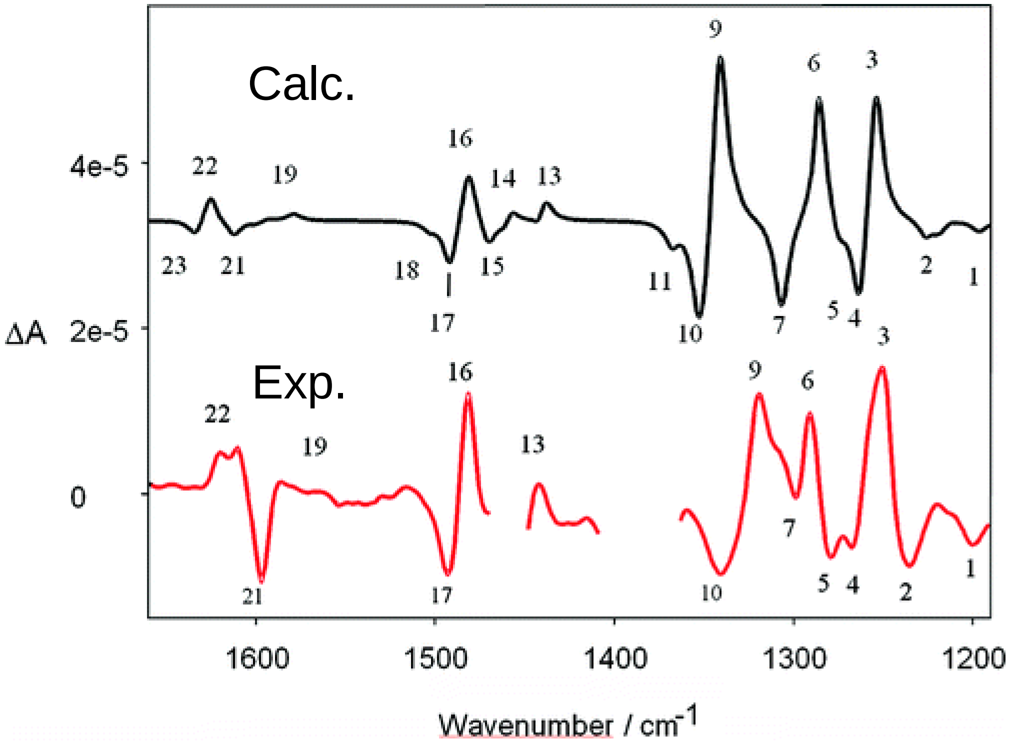
J. Lacour et al. *J. Am. Chem. Soc.*, 2008, 130 (20), pp 6507–6514

Diazaoxatricornan Derivative

Comparison experiment - theory





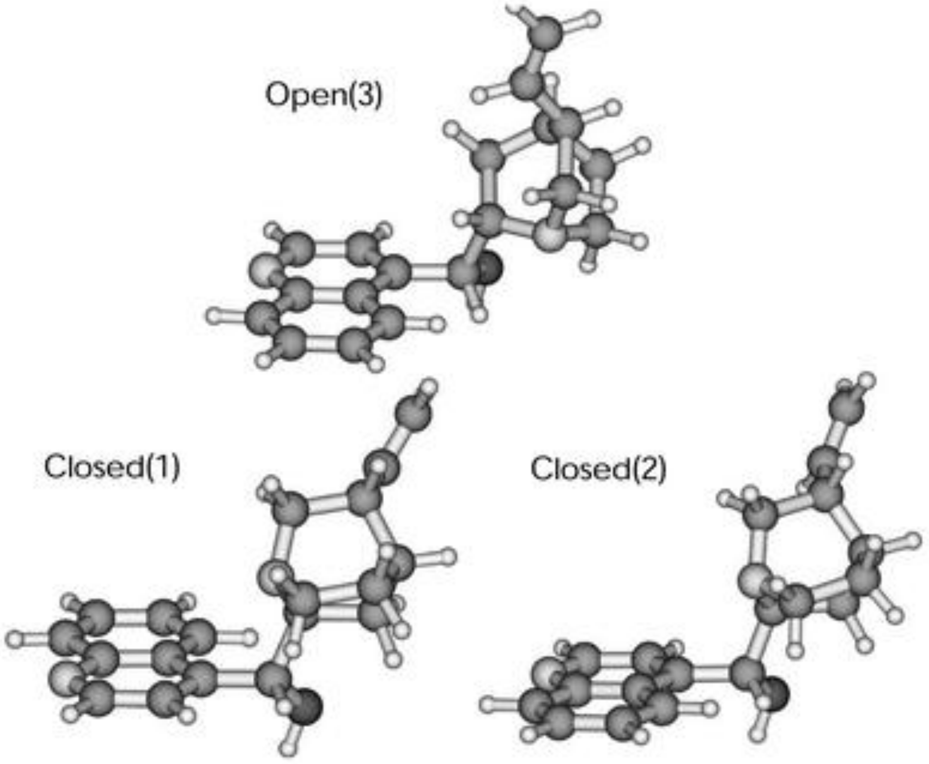


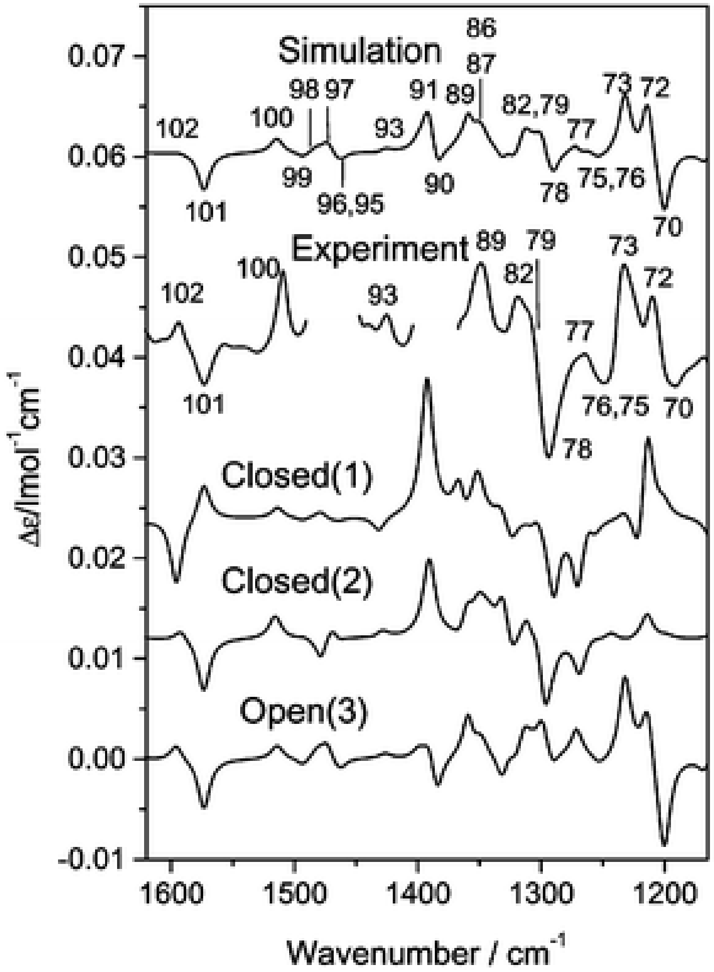
DFT: P3PW91, 6-31G(d,p)

J. Lacour et al. *J. Am. Chem. Soc.*, 2008, 130 (20), pp 6507–6514

Cinchonidine

Comparison experiment - theory





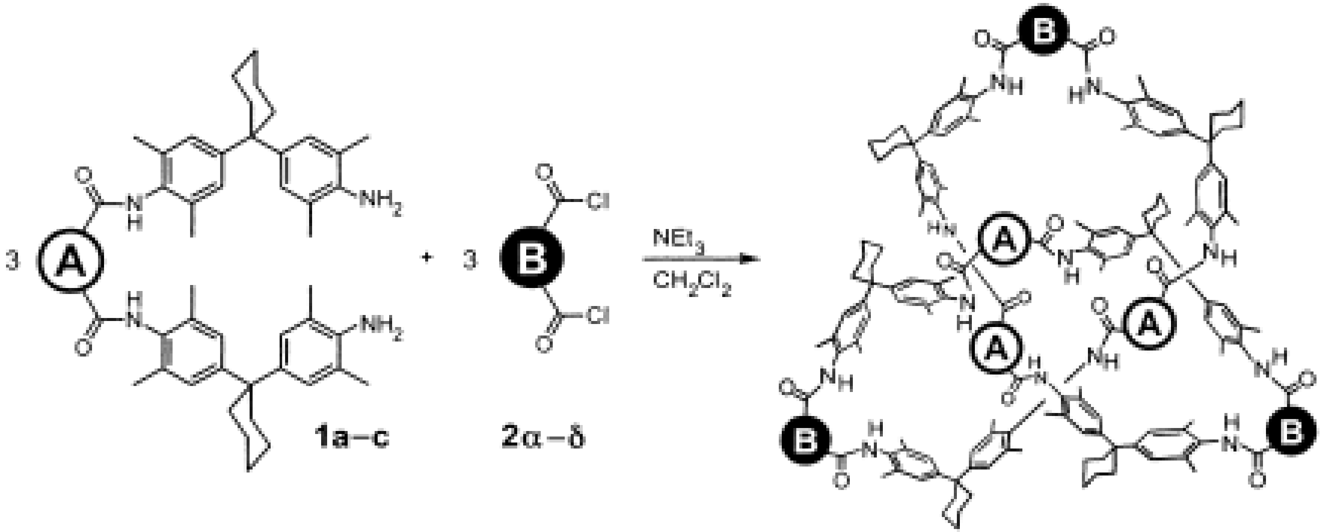
DFT: B3LYP, 6-31G(d)

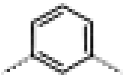
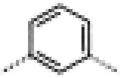
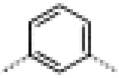
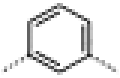
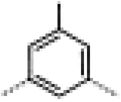
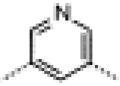
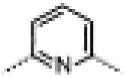
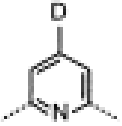
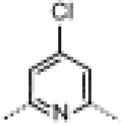
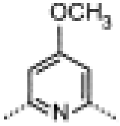
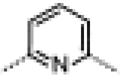
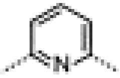
Simulation (VCD) : 70% Open(3) + 15% Closed(1) + 15% Closed(2)

T. Bürgi et al. *J. Chem. Soc.*, Perkin Trans. 2, 2002, 1596–1601

Molecular knots

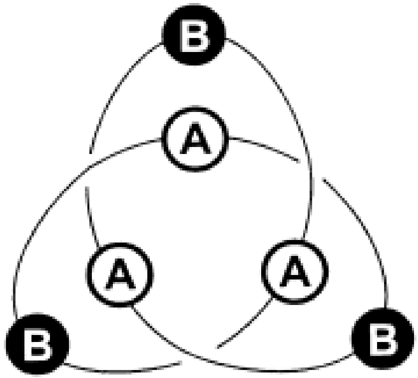
A challenge...

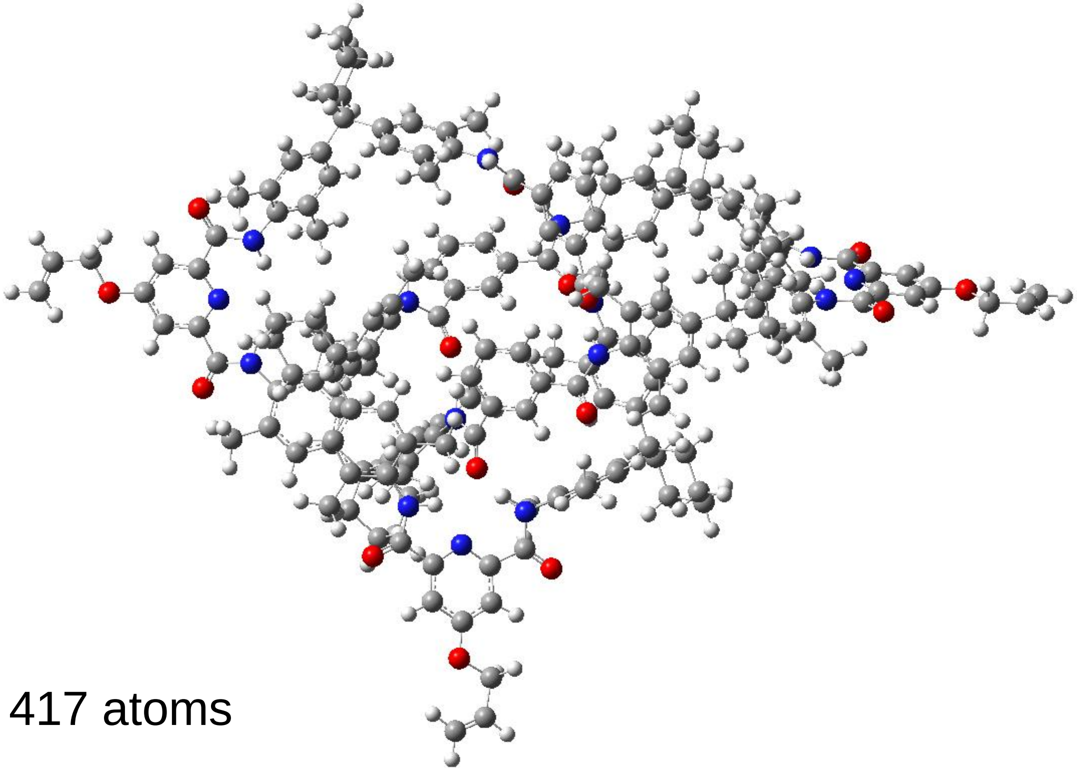


3	aα	aβ	aγ	aδ	bα	cα
A	 a	 a	 a	 a	 b	 c
B	 α	 β	 γ	 δ	 α	 α
Ausb. [%]	20	4	9	10	1	2

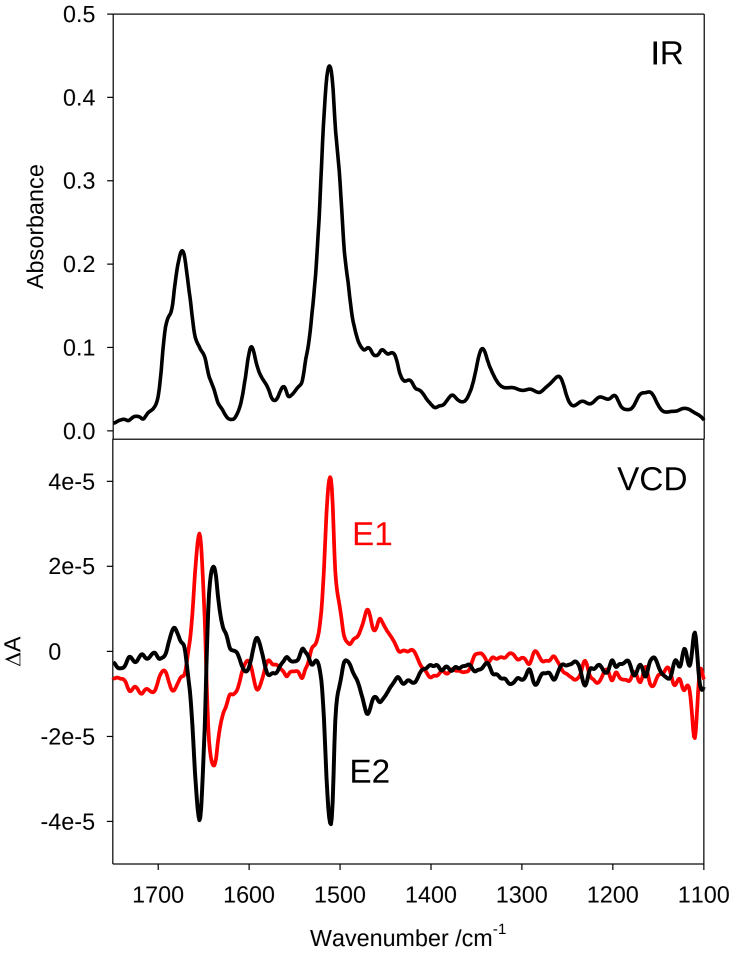
F. Vögtle et al. Angewandte Chemie 113, 2534-2537, 2001

Molecular knots





417 atoms

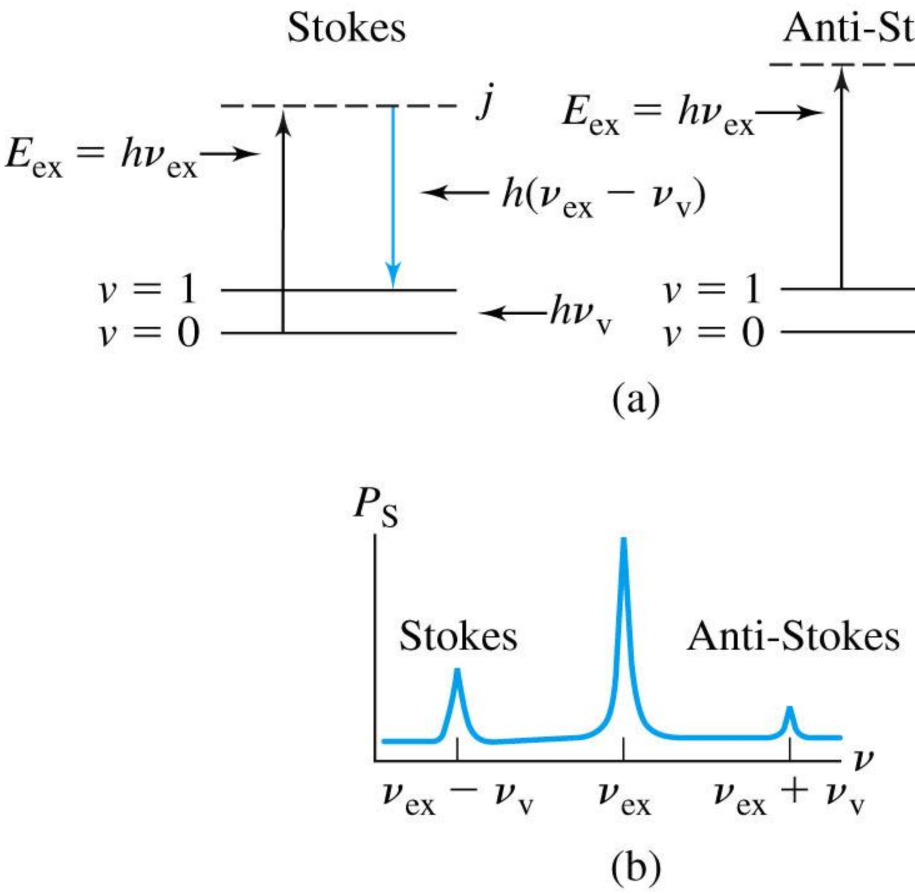


F. Vögtle

Summary VCD

- Powerful tool to determine the absolute configuration of molecules
- Sensitive to structure (conformation)
- Information only through comparison with theory
- Challenges:
    - size of system
    - flexible molecules (conformers)
    - solvent effects

Raman spectroscopy



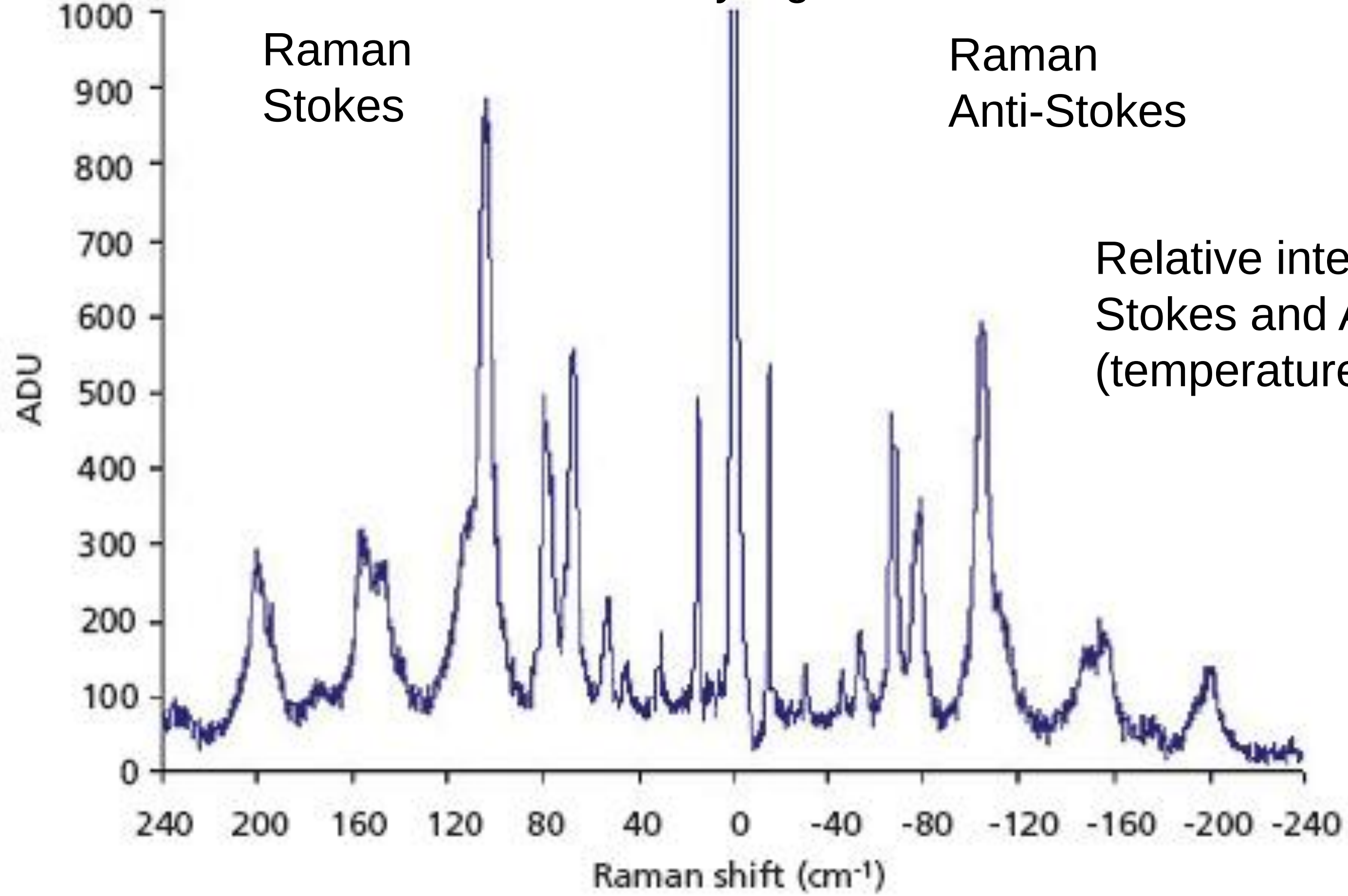
α

$$\left(\frac{\partial a}{\partial Q}\right) \neq 0$$

Efficiency: Typically only one Raman photon per 10^6 -10^7 primary photons!

Intensity: $I_s \propto v_p^{\;4}$

Raman spectrum of L-cystine



Rayleigh

Raman
Stokes

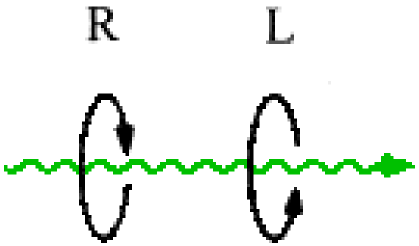
Raman
Anti-Stokes

Relative intensity of
Stokes and Anti-Stokes!
(temperature!)

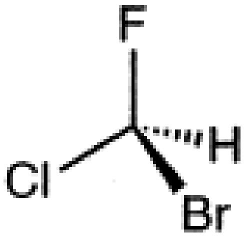
Raman spectrum of L-cystine

Raman Optical Activity (ROA)

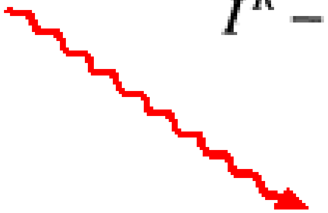
ROA is a tiny difference in the intensity of Raman scattering from chiral molecules in right (R)- and left (L)-circularly polarized incident light (ICP):



incident beam with
angular frequency ω

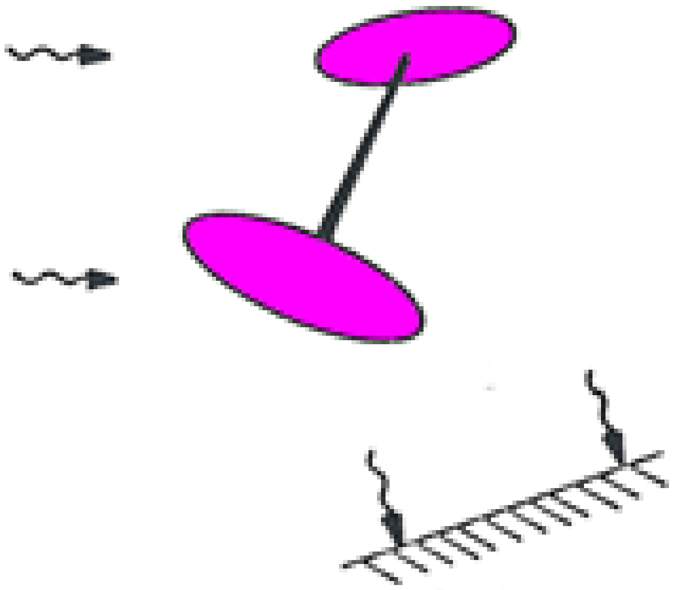


$$I^R - I^L \neq 0$$



Raman component of scattered beam
with angular frequency $\omega - \omega_v$

Two-Group Model of ROA



ROA is generated by interference between light waves scattered independently from two achiral anisotropic groups held in a twisted chiral arrangement. L. D. Barron and A. D. Buckingham, *J. Am. Chem. Soc.* **96**, 4769 (1974).

Basic theory for ROA

ROA originates in interference between light waves scattered via the polarizability and optical activity tensors of the molecule. These are introduced through the oscillating electric dipole moment μ, magnetic dipole moment **m** and electric quadrupole moment Θ induced by the incident light wave:

$$\mu_\alpha = \alpha_{\alpha\beta} E_\beta + \tfrac{1}{\omega} G'_{\alpha\beta} \dot{B}_\beta + \tfrac{1}{3} A_{\alpha\beta\gamma} \nabla_\beta E_\gamma + \ldots, \qquad m_\alpha = \ldots, \qquad \Theta_{\alpha\beta\gamma} = \ldots$$

$$\alpha_{\alpha\beta} = \frac{2}{\hbar} \sum_{j \neq n} \frac{\omega_{jn}}{(\omega_{jn}^2 - \omega^2)} \mathrm{Re}\left(\langle n|\mu_\alpha|j\rangle\langle j|\mu_\beta|n\rangle\right)$$

(μ.μ) polarizability

$$G'_{\alpha\beta} = -\frac{2}{\hbar} \sum_{j \neq n} \frac{\omega}{(\omega_{jn}^2 - \omega^2)} \mathrm{Im}\left(\langle n|\mu_\alpha|j\rangle\langle j|m_\beta|n\rangle\right)$$

(μ.**m**) optical activity

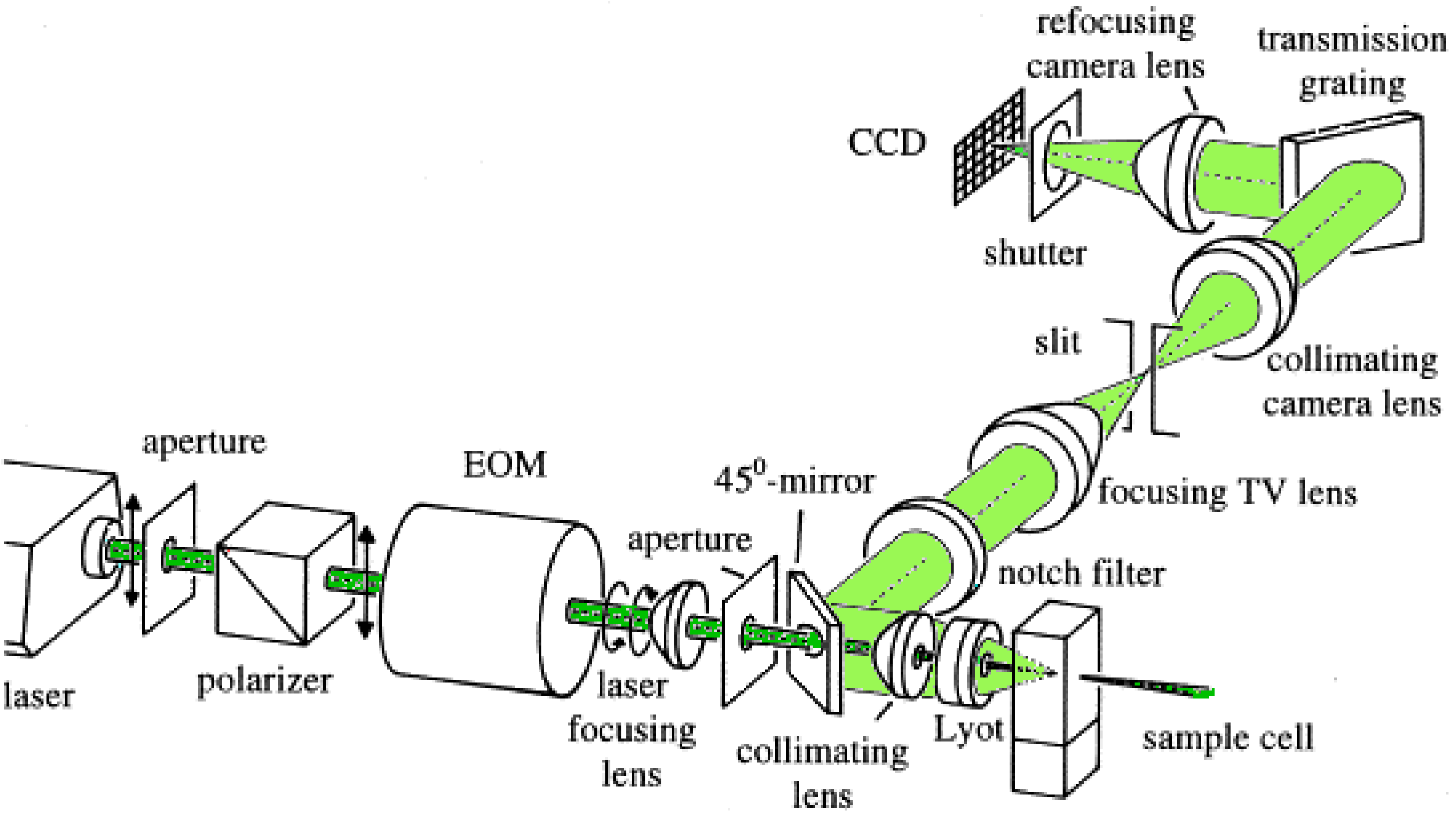
$$A_{\alpha\beta\gamma} = \frac{2}{\hbar} \sum_{j \neq n} \frac{\omega_{jn}}{(\omega_{jn}^2 - \omega^2)} \mathrm{Re}\left(\langle n|\mu_\alpha|j\rangle\langle j|\Theta_{\beta\gamma}|n\rangle\right)$$

(μ.Θ) optical activity

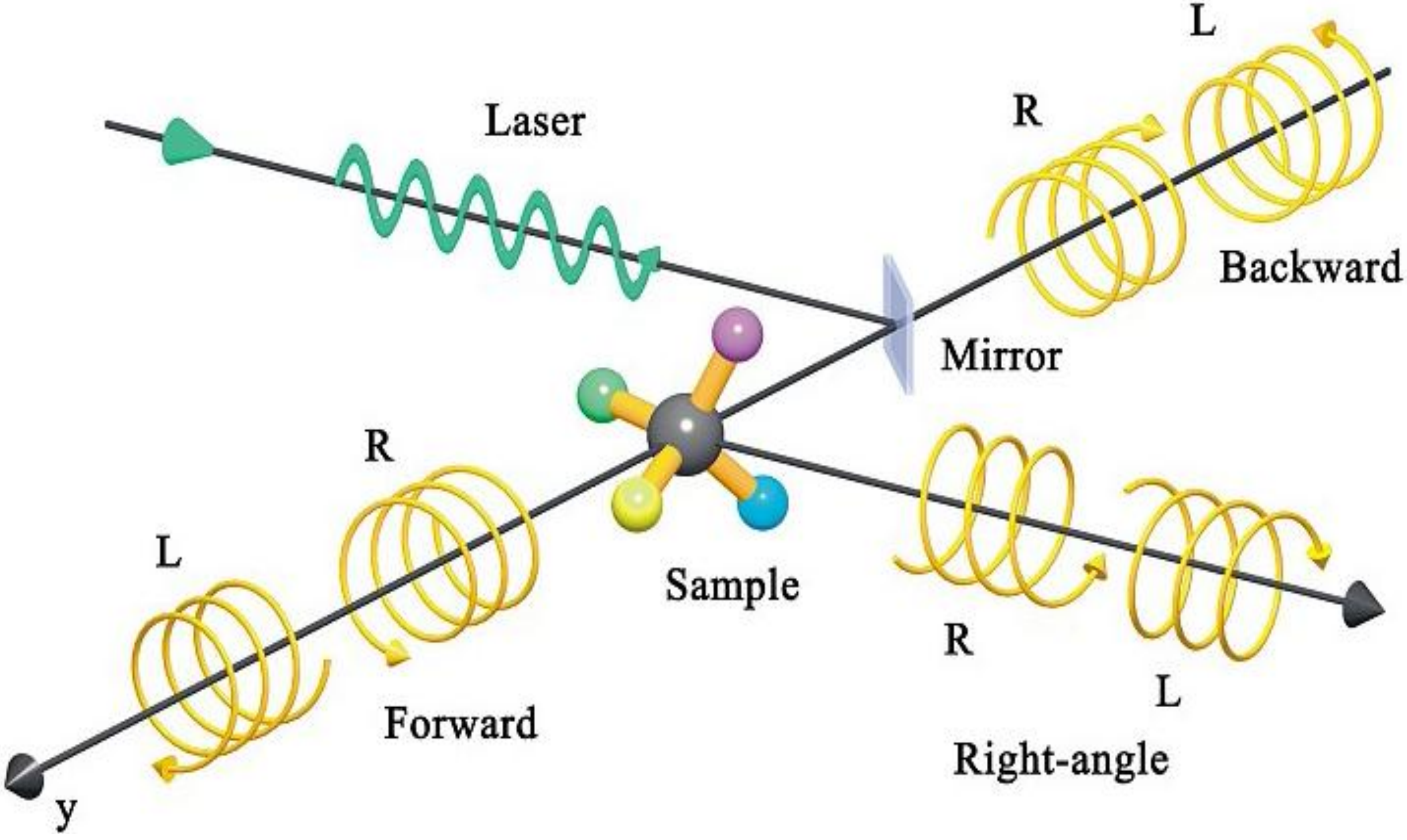
$$\Delta = \frac{I^R - I^L}{I^R + I^L} \approx \frac{\alpha G' + \alpha A}{\alpha^2} \cong 10^{-3} \qquad \Delta(180^\circ) = \frac{8(3\alpha_{\alpha\beta} G'^*_{\alpha\beta} - \alpha_{\alpha\alpha} G'^*_{\beta\beta} + \frac{1}{3}\omega \alpha_{\alpha\beta} \varepsilon_{\alpha\gamma\delta} A^*_{\gamma\delta\beta})}{c(7\alpha_{\lambda\mu}\alpha^*_{\lambda\mu} + \alpha_{\lambda\lambda}\alpha^*_{\mu\mu})}$$

L. D. Barron and A. D. Buckingham, *Mol. Phys.* **20**, 1111 (1971)

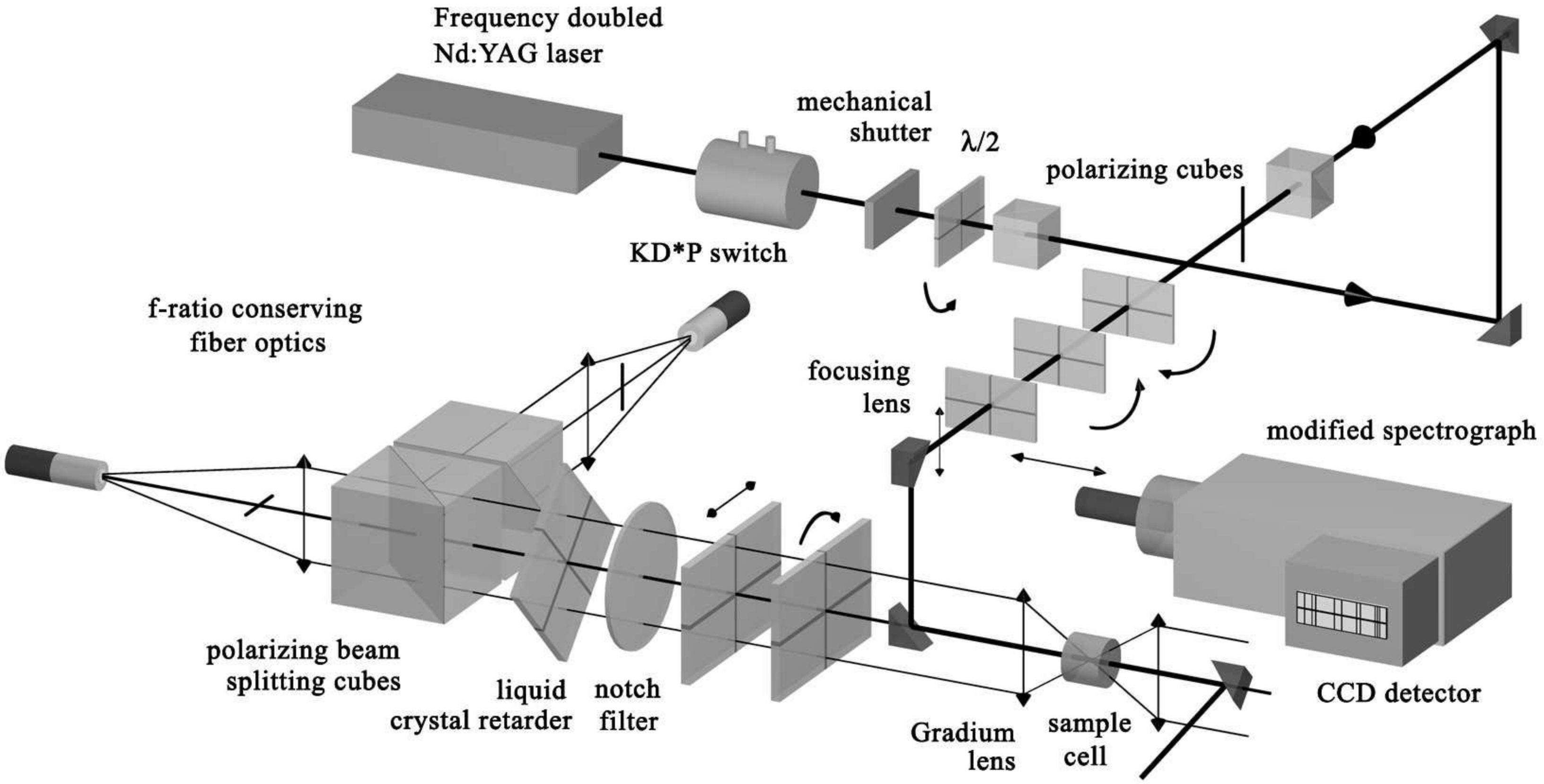
ROA spectrometer (Glasgow, Barron) ICP ROA



Different geometries for scattered circular polarization (SCP) ROA

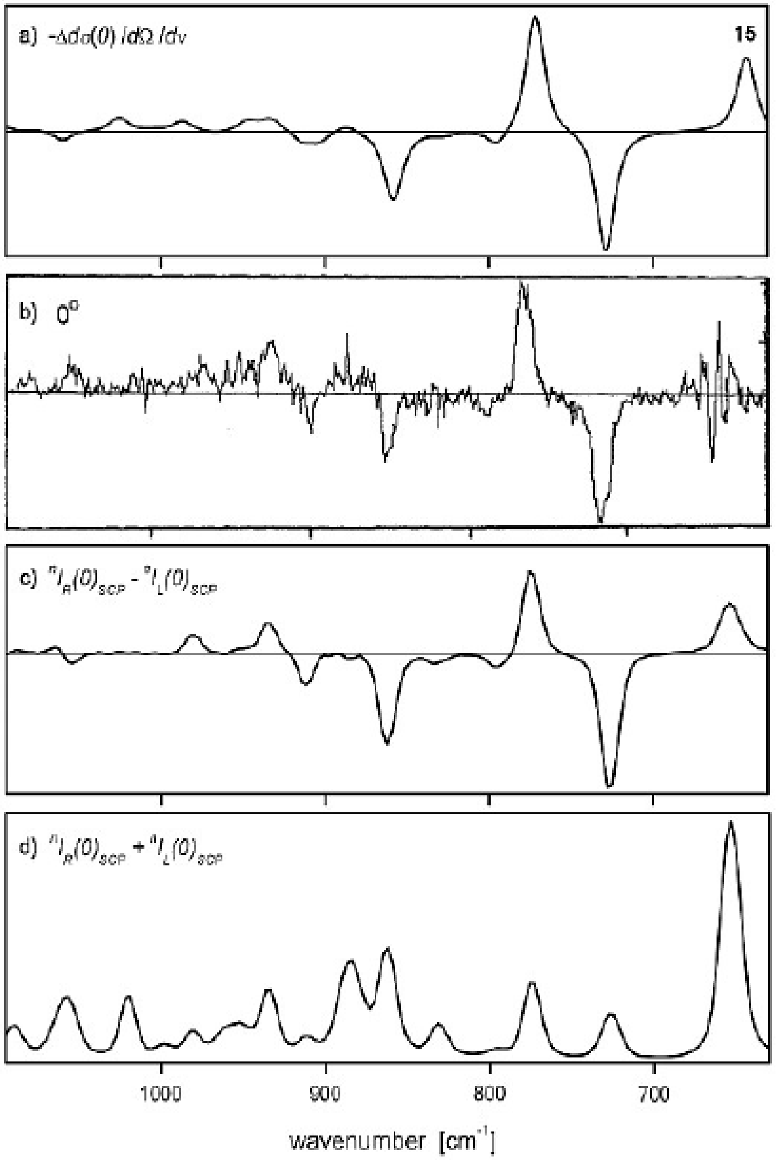


ROA spectrometer (Prof. W. Hug)
SCP ROA



Now in Geneva

Raman and ROA spectra of (-)-β-pinene



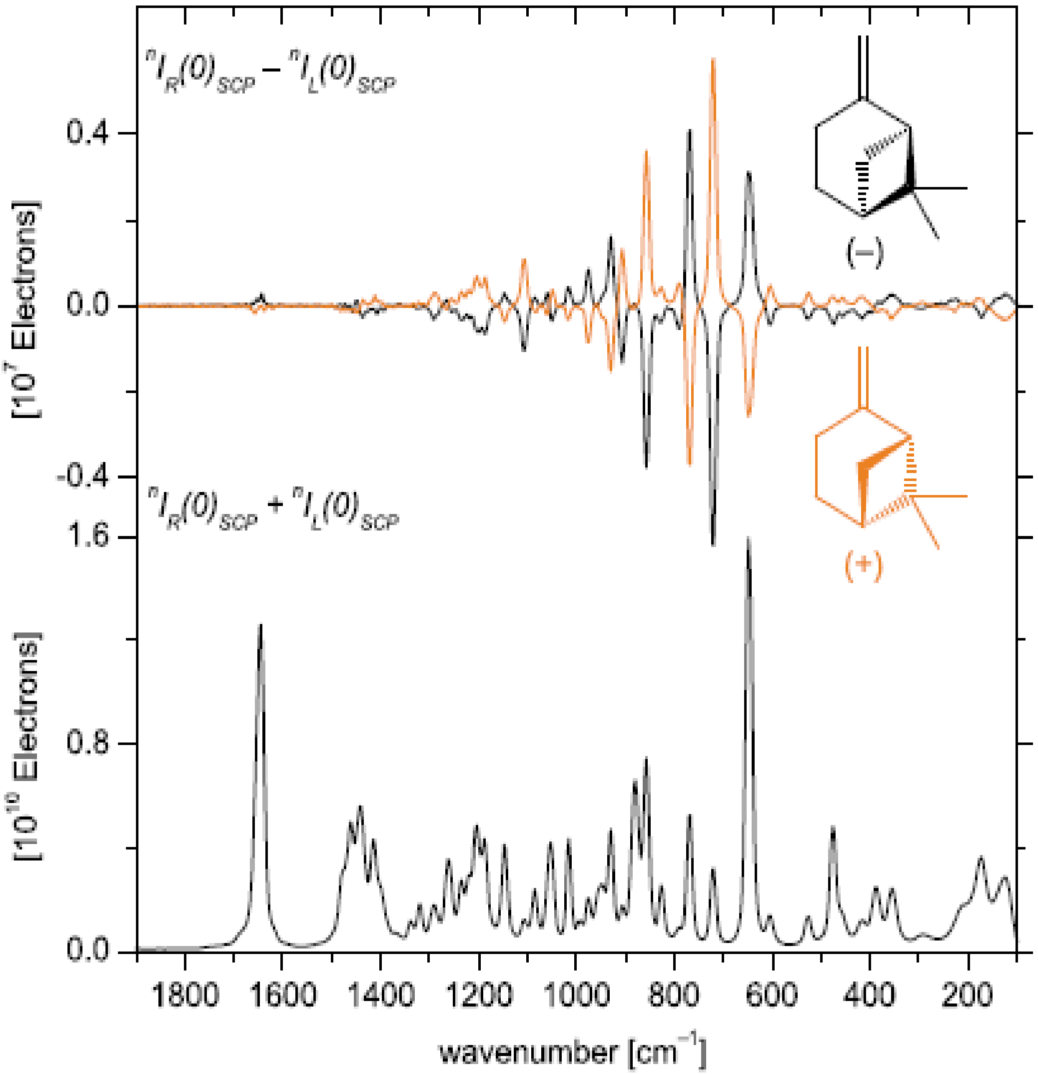
Calculated

Measured ROA 1990
(Barron, Glasgow)

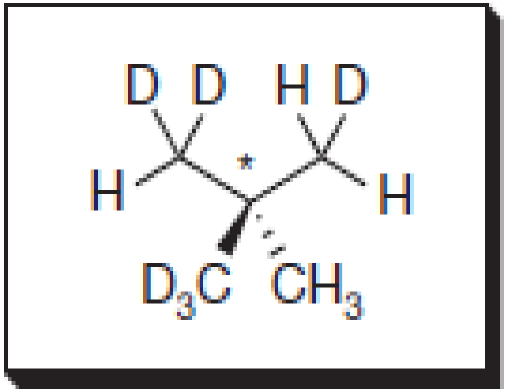
Measured ROA 2007
(Hug, Fribourg,
20 min, 8,5 μl sample)

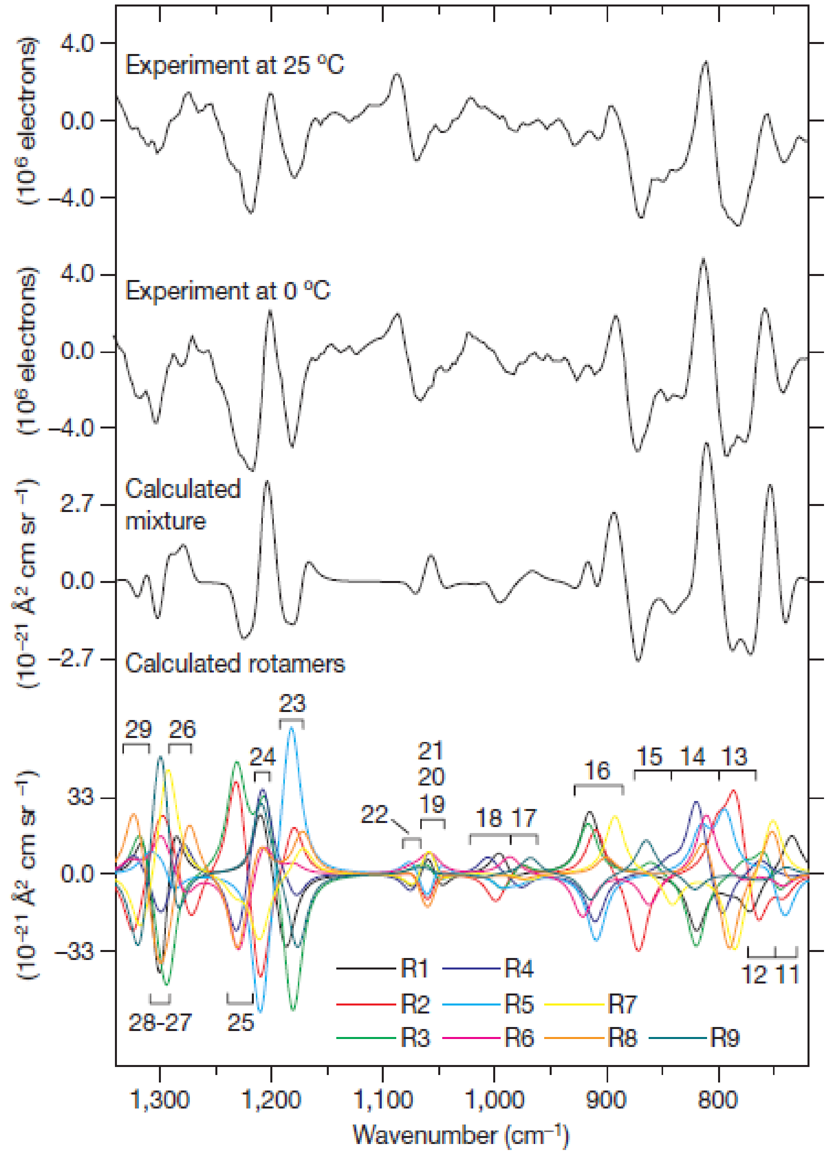
Measured Raman

ROA of β-pinene



ROA of chirally deuterated neopentane





W..Hug et al., Nature 446, 05653, 2007