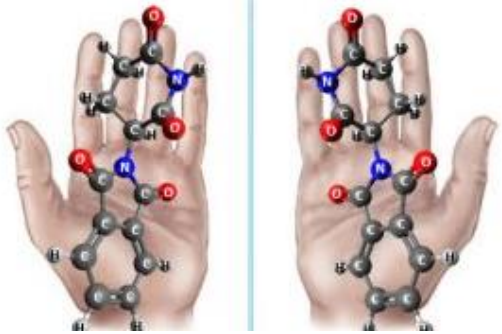
Determination of Enantiomeric Excess

Chiral Molecules in Bio-Ecosphere

Flavour and Fragrance
>20 B$/year; >1400 enantiomers



Pharmaceuticals
>850 B$/year; ~50% chiral drugs

Agrochemicals
>200 B$/year; ~30% chiral pesticides

Determination of Enantiomeric Excess

Classic	Chiral
UV-Vis	Optical rotatory dispersion (ORD)
UV-Vis	Electronic Circular Dichroism (CD)
IR	Vibrational Circular Dichroism (VCD)
Raman	Raman Optical Activity (ROA)
Near-infrared spectroscopy (NIR)	Near IR Circular Dichroism (NIR-VCD)
Luminescence (Fluorescence)	Circularly Polarized Luminescence (CPL)
Microwave	Chiral Rotational Spectroscopy (CRS)
GC HPLC	Chiral-GC Chiral-HPLC
X-Ray crystallography	Bjovet Pairs
Mass Spectrometry	Chiral Ion Mobility Coulomb Explosion MS + Optical Methods
NMR	Chiral Solvating Agents Chiral Shift Reagents

ORD + CD

Polarimetry, optical rotation, circular birefringence:

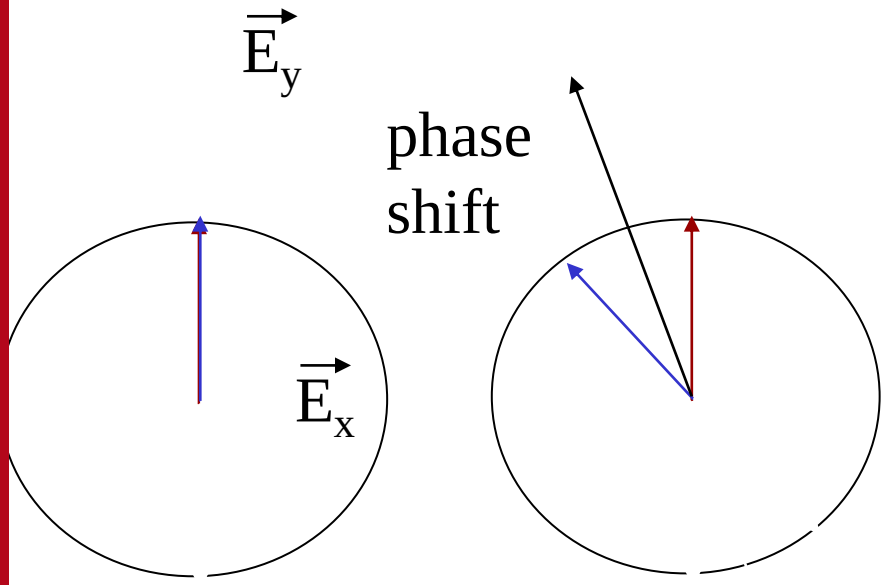
Turning of the plane of linearly polarized light. Optically active molecules exhibit different refractive indices for right n_R and left n_L polarized light nR ≠ nL

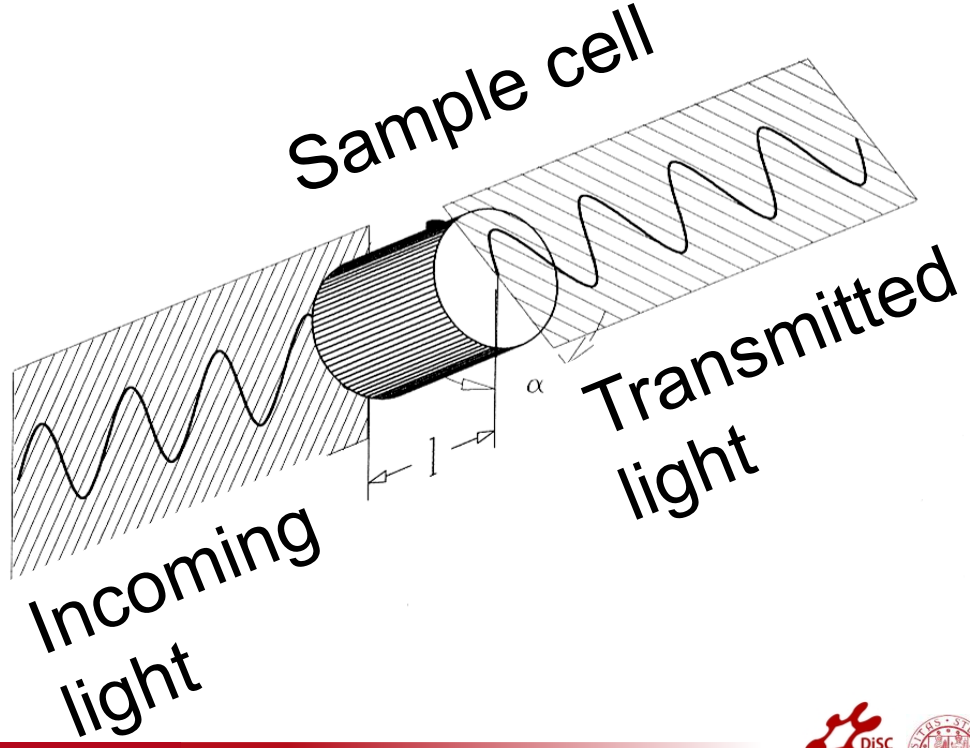
Optical rotatory dispersion (ORD):
Wavelength dependency of rotation. Allows determination of absolute configuration of chiral molecules

Circular dichroism:
Linearly polarized light is transformed into elliptically polarized light upon traveling through matter. Different absorption coefficients for left and right circular polarized light ($\varepsilon_R \neq \varepsilon_L$).

Polarimetry,

Linearly polarized light. Different refractive index for its left and right circular constituents. Relative phase shift between left and right. Vector addition yields again linear polarized light with rotated polarization plane.





Polarimetry

The measured angle-of-rotation results in:

$$\alpha_{obs} = [\alpha]^T_\lambda \cdot l \cdot c$$

α in angular degree, length in decimeter(!) and c in g ml^{-1}.

Specific rotation is a substance specific constant (dependent on temperature and wavelength) and is a measure for the optical activity of this particular substance.

Molar rotation is defined as follows:

$$[\Phi]^T_\lambda = \frac{[\alpha]^T_\lambda M}{100} = \frac{\alpha_{obs} \cdot M}{100\, l \cdot c}$$

Tabelle 8.1. Einige spezifische Drehwinkel optisch aktiver Komponenten bei 20 °C; der Index *D* bezieht sich hierbei auf die Na-D-Linie bei 589 nm (vgl. Abb. 2.13).

Verbindung	Lösungsmittel	$[\alpha]^{20}_D$
D-Milchsäure	Wasser	–2,3
L-Milchsäure	Wasser	+2,3
Hexose ($C_7H_{14}O_4$)	Wasser	–11
D-Glucose ($C_6H_{13}NO_5$)	Wasser	+19
L-Mannose ($C_7H_{14}O_5$)	Wasser	+30
D-Ribose ($C_5H_{11}NO_4$)	Hydrochlorid	–24,6
Hexose (Aminozucker, $C_8H_{17}NO_3$)	Hydrochlorid	+49,5
L-Alanin	Wasser	+2,7
Rohrzucker	Wasser	+66,4
Cholesterin	Ether	–31,5

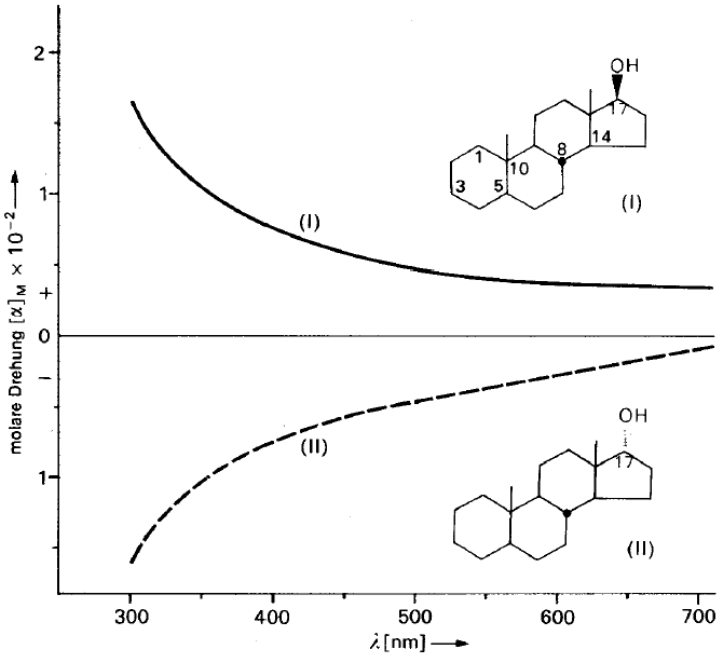
Optical rotatory dispersion(ORD)

ORD measures molar rotation [Φ] as function of the wavelength!

If the substance to be investigated has no electronic absorption within the investigated spectral region the following ORD spectra are obtained

Reason: refractive indices for left and right polarized light change differently with wavelength (rotatory dispersion is proportional to refractive index difference).

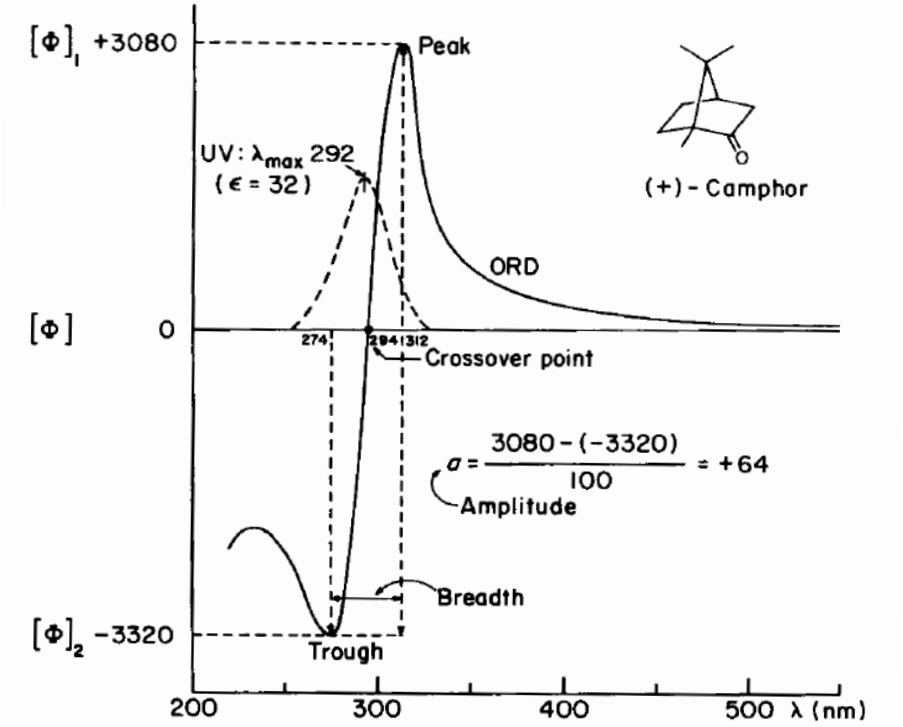
ORD-spectra of 17ß- and 17α-hydroxy-5α-androstan

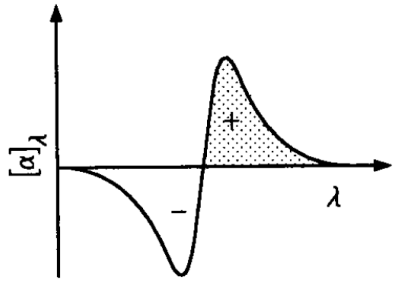


Optical rotatory dispersion(ORD)

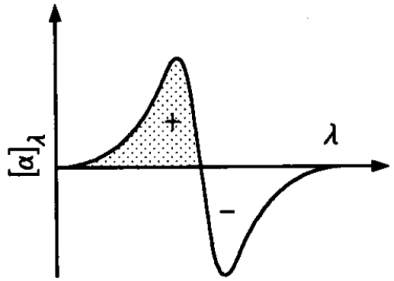
Refractive indices for left and right polarized light exhibit anomalous dispersion in the range of an absorption band

Cotton effect





PositivE

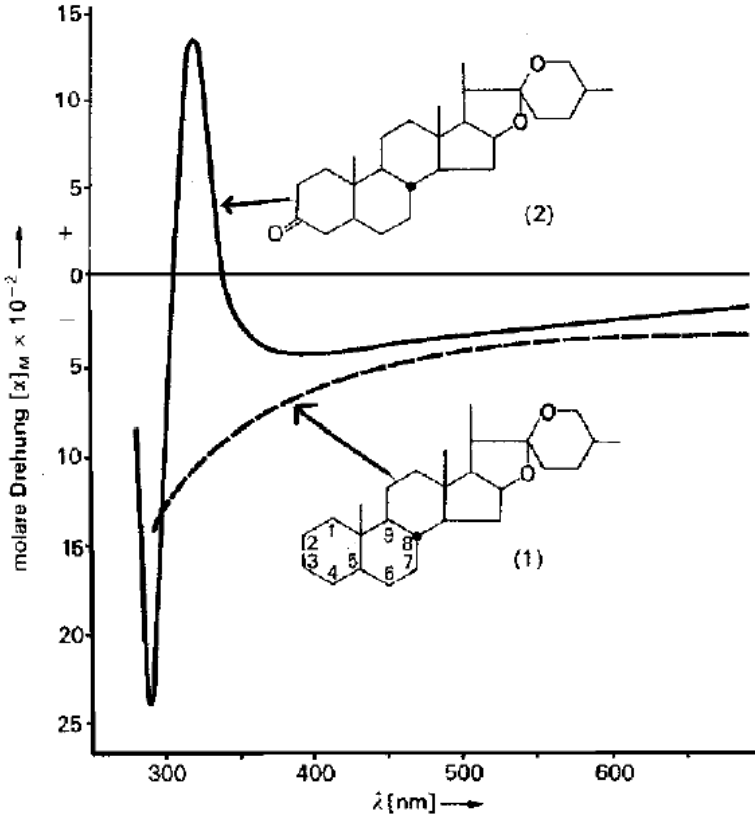


negativE Cotton effect

Optical rotatory dispersion(ORD)

Quantitative theoretical correlations between molecular structure and ORD (Cotton effect) are difficult to derive; Empirical investigation are important.

ORD has been successfully applied for constitution elucidation e.g. to position carbonyl groups in complex optically active molecules. By comparing ORD curves for structurally isomeric ketons (reference material needed!) the keto group can be localized.



ORD curve of molecule (2) is a superposition of a negative curve i.e. molecular skeleton without a chromophore (background curve) a… positive

Circular Dichroism (CD)

Enantiomeric molecules exhibit besides different refractive indices for left and right circular polarized light also different absorption coefficients:

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R \longrightarrow$$ Circular Dichroism

It follows: $$\Delta A(\lambda) = \Delta\varepsilon(\lambda) \cdot l \cdot c = A_L(\lambda) - A_R(\lambda)$$

Left and right circular components
ORD:different retardation
CD: also different absorption

Transmitted light is elliptically polarized.

Circular Dichroism (CD)

Signal heights are displayed either as absorption difference $\Delta\varepsilon$ or as ellipticity $[\theta]$. Molar ellipticity and circular dichroism can be interconverted:

$$[\theta] = 3300\Delta\epsilon \qquad [\theta] = [\text{grad cm}^2\ \text{dmol}^{-1}]$$

Correlation between ORD and CD:
ORD is based on the different refractive indices of left and right circular polarized light ($n_R \neq n_L$)
CD results from the different absorption behavior for left and right circular polarized light ($\varepsilon_R \neq \varepsilon_L$)
Connection of both phenomena via Kronig-Kramer relationship.

Circular Dichroism (CD)

For an electronic transition to be CD active the following must be true: $\mu_e \cdot \mu_m \neq 0$

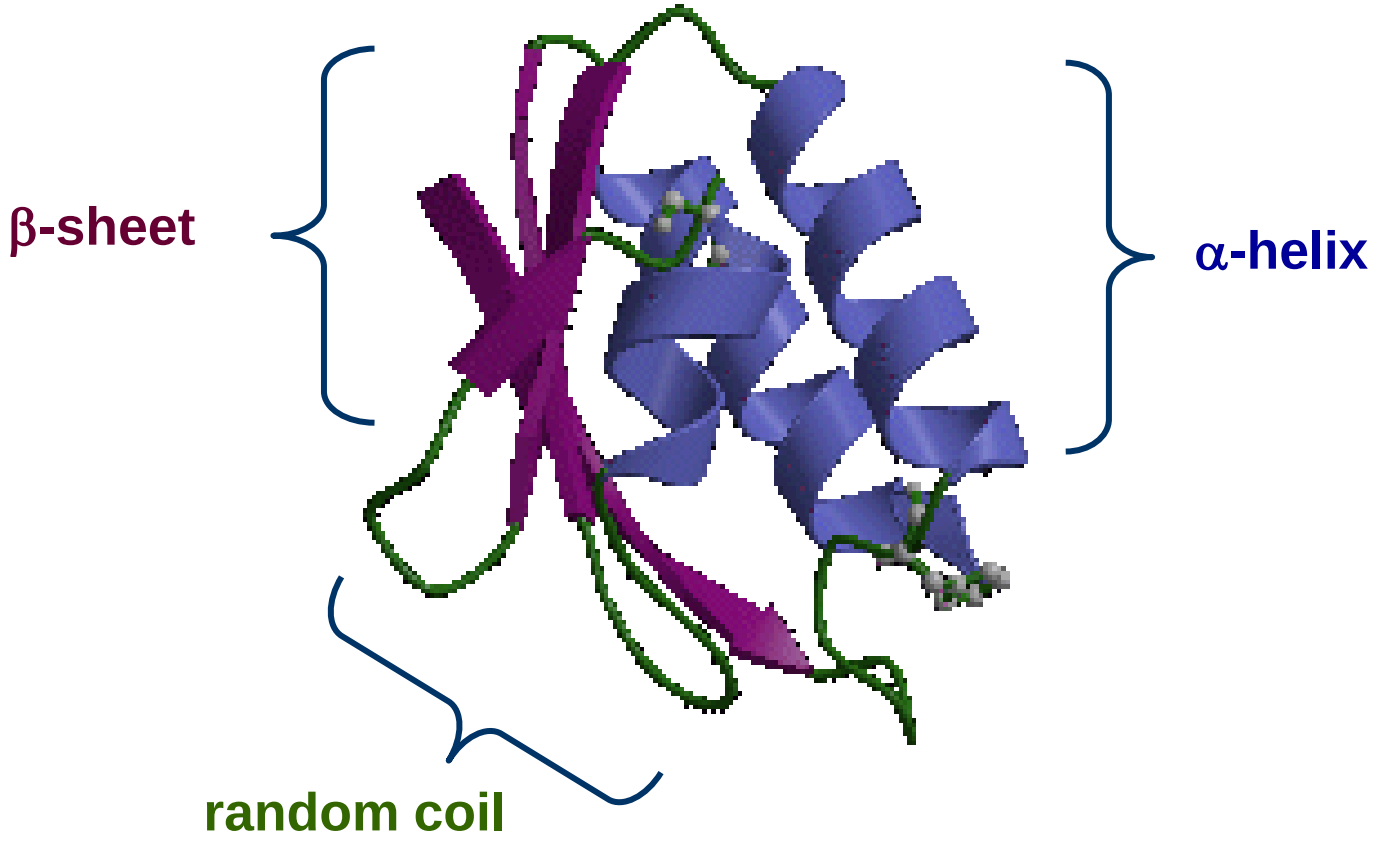
μ_e is the electronic transition dipole moment (linear displacement of electrons upon transition into an excited state) μ_m is the magnetic transition moment (radial displacement of electrons upon excited state transition)

Scalar product is characterized by a helical electron displacement. Depending on the chirality of the helix preferably more right or left circular polarized light will be absorbed, respectively.

Electronic transition Magnetic transition Optical activity

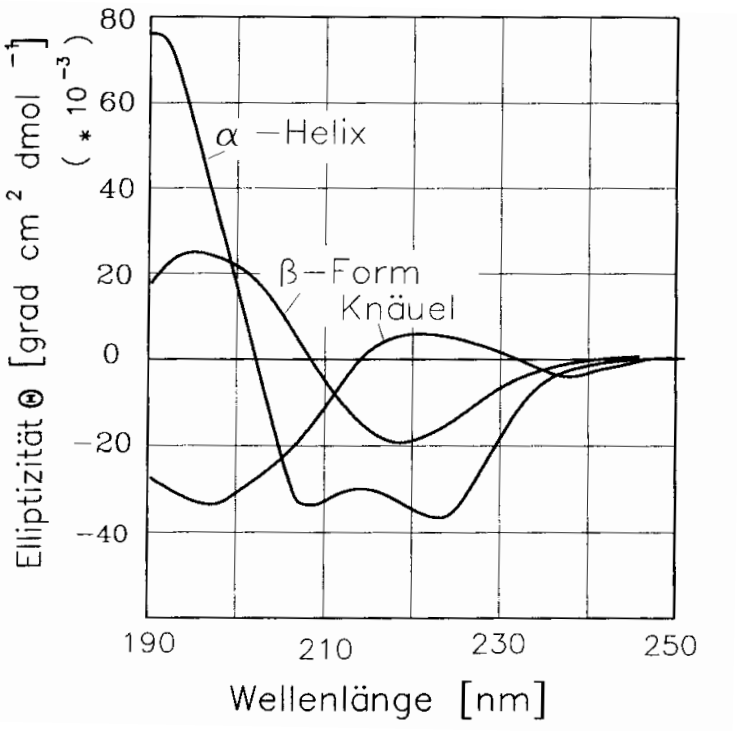
Circular Dichroism (CD)

Application

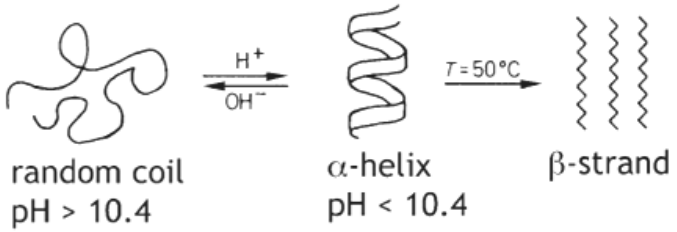


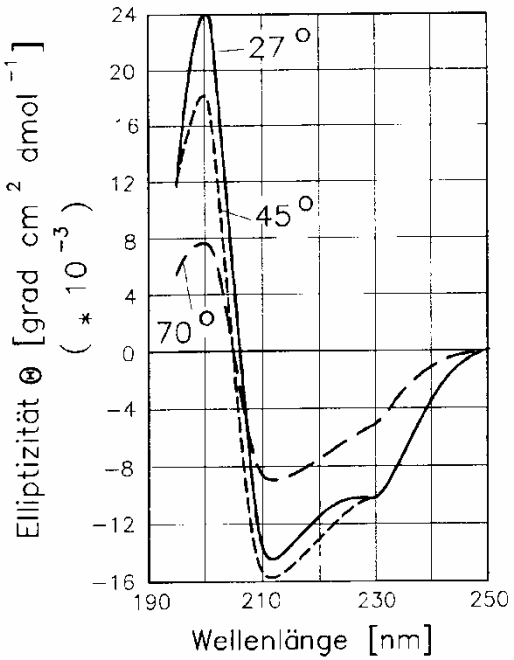
Circular Dichroism (CD)

Application



Typical reference CD spectra:
Poly-L-Lysine in different conformations:
α-Helix, β-sheet and random coil.

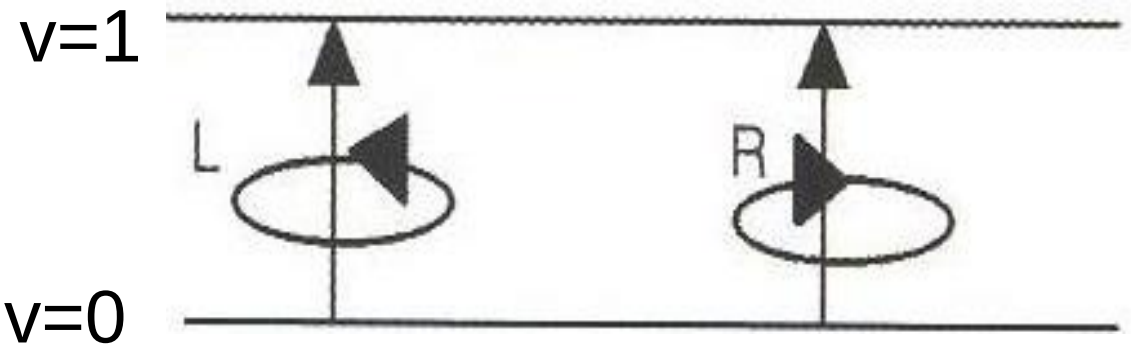




Temperature dependent CD spectra of insuline: For increasing temperature the molecule changes form α-helix into the denaturated random coil form with ß-sheet contributions.

Vibrational-Circular-Dichroism (VCD)

Vibrational transitions in the IR and NIR



VCD monitors difference in absorption between left and right circular polarized light

$$\begin{aligned} \Delta A(\tilde{\nu}) &= A_L(\tilde{\nu}) - A_R(\tilde{\nu}) \\ \Delta\epsilon(\tilde{\nu}) &= \frac{\Delta A(\tilde{\nu})}{l \cdot c} \\ &= \varepsilon_L(\tilde{\nu}) - \varepsilon_R(\tilde{\nu}) \end{aligned}$$

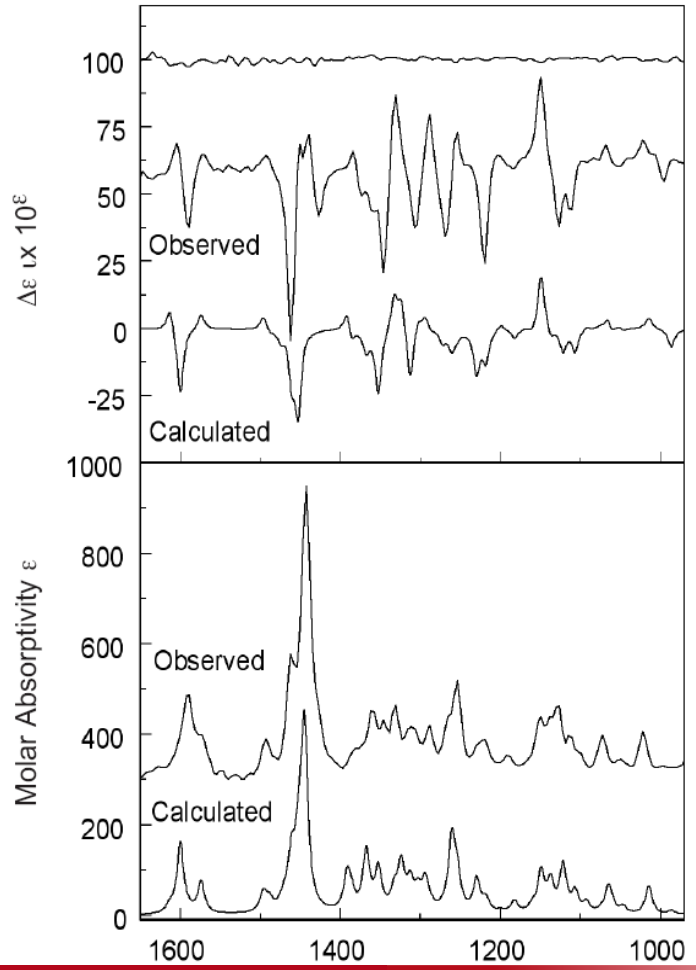
Vibrational-Circular-Dichroism (VCD)

Determination of the absolute configuration

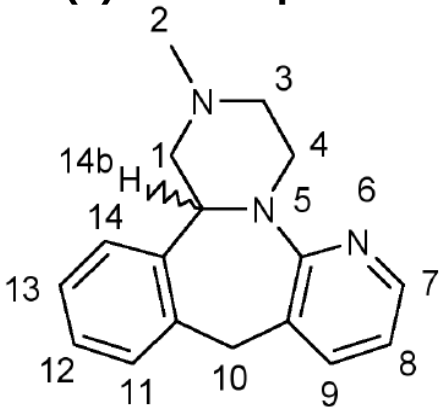
Advantages VCD vs. CD

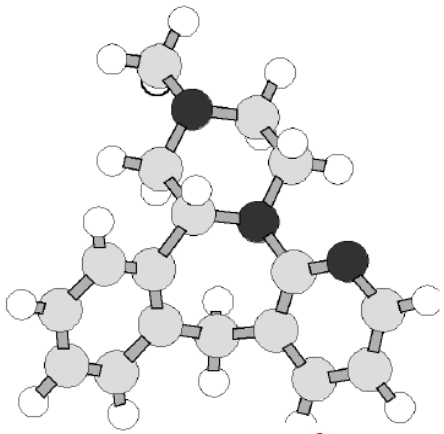
Electronic chromophore is not necessary

VCD exhibits more characterisitic bands



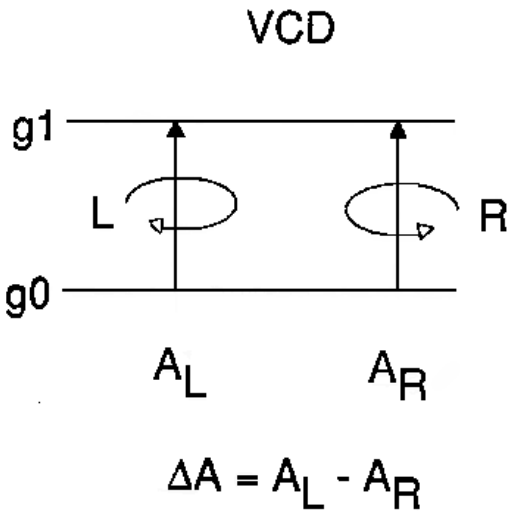
(–)-Mirtazapine



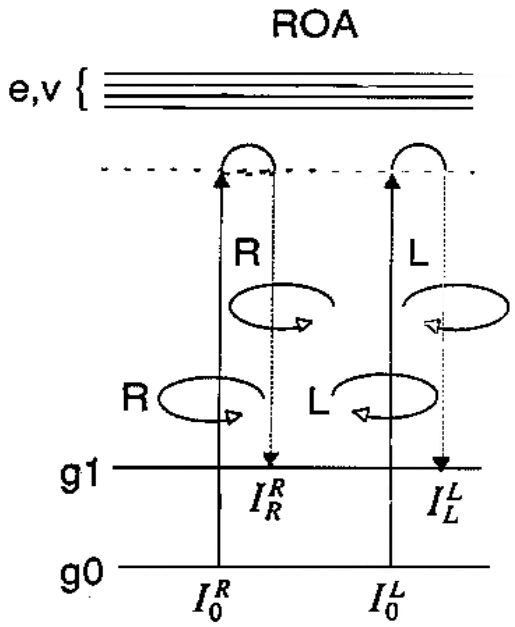


Vibrational Optical Activity

VIBRATIONAL CIRCULAR DICHROISM
Differential Absorption of Left and Right

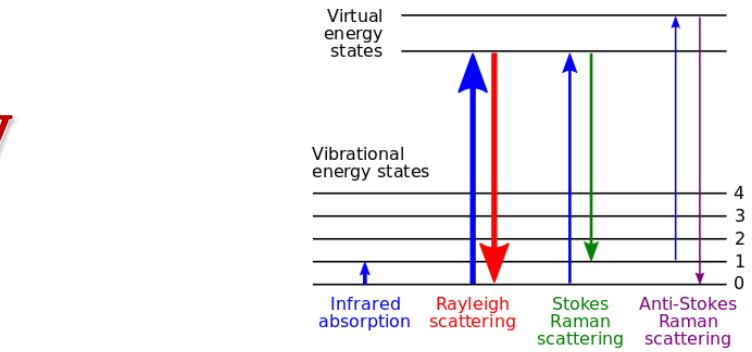


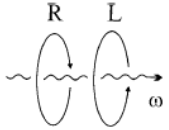
RAMAN OPTICAL ACTIVITY
Differential Raman Scattering of
Left Circularly Polarized Infrared Radiation

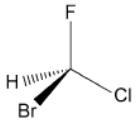


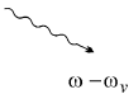
DCP$_I$-ROA: $\Delta I_I = I_R^R - I_L^L$

Raman Optical Activity
ROA

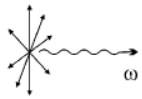


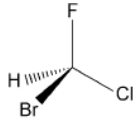




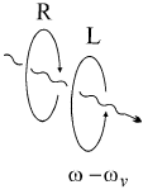


Induced Circular Polarisation

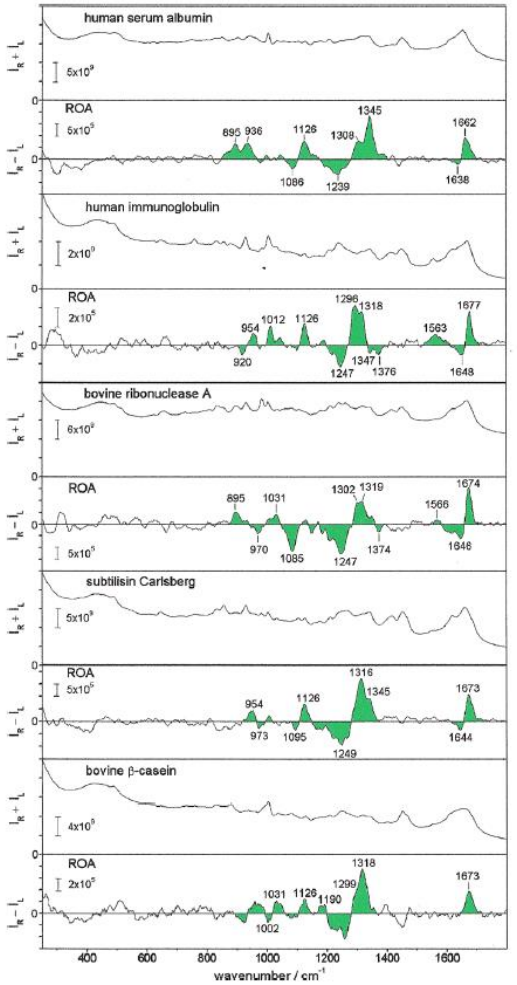




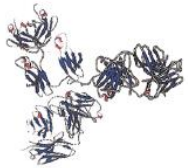
(b) SCP ROA



Scattered Circular Polarisation

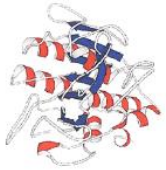


all α



all β

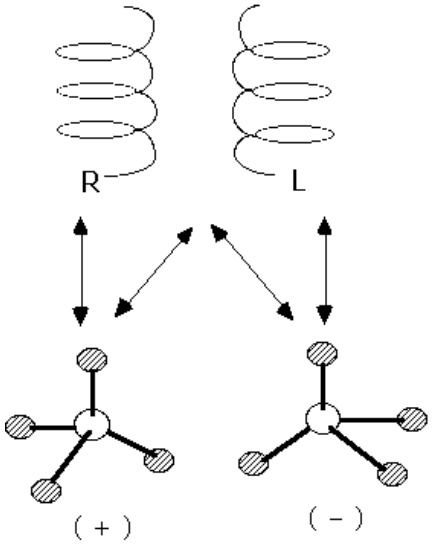
$\alpha + \beta$

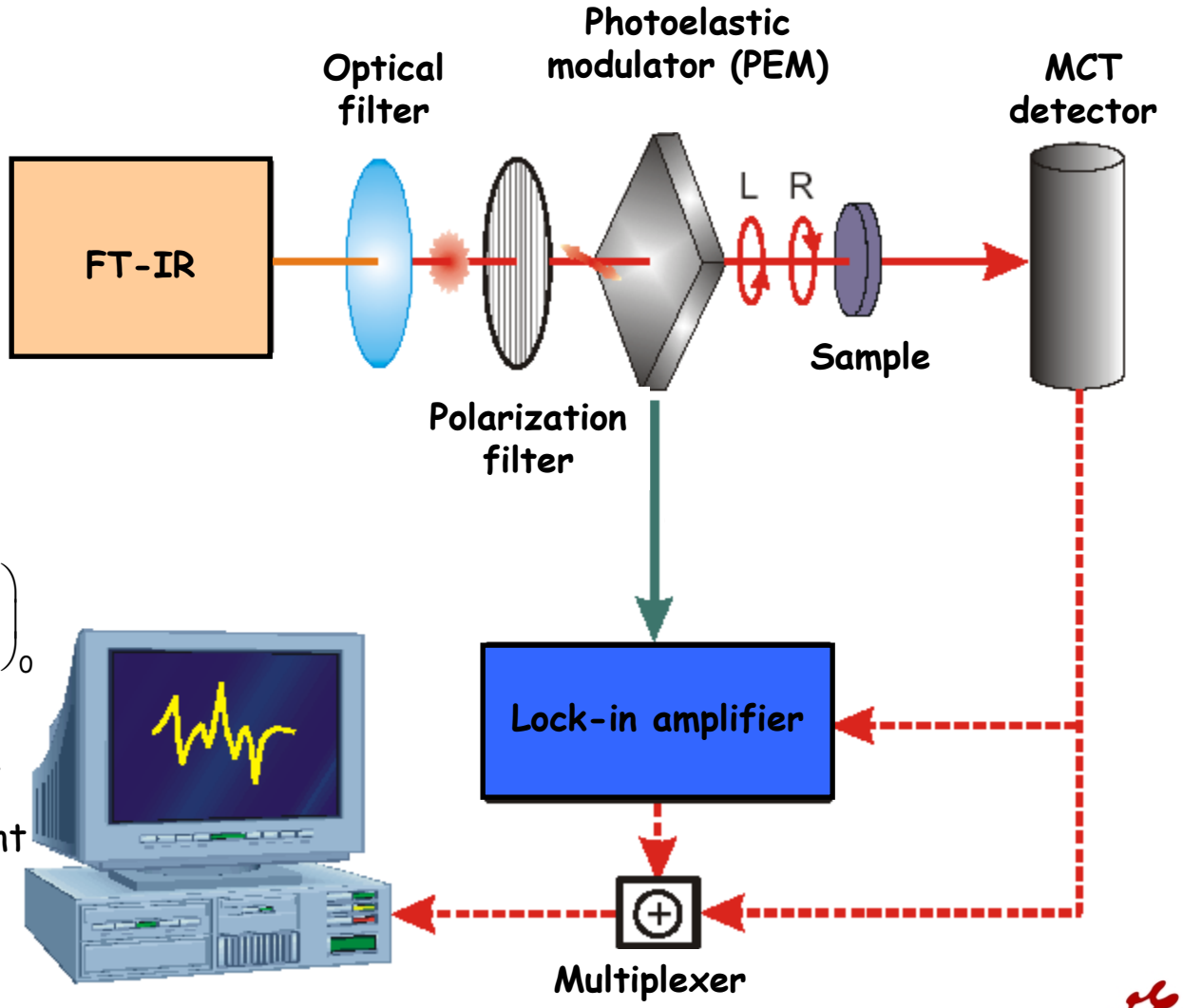


α / β

natively unfolded

Vibrational Optical Activity





$$\Delta\varepsilon_{01}^{a} \sim R_{01}^{a} = \frac{\hbar}{2}\left(\frac{\partial\vec{\mu}}{\partial Q_a}\right)_0 \cdot \left(\frac{\partial\vec{m}}{\partial P_a}\right)_0$$

R : rotatory strength

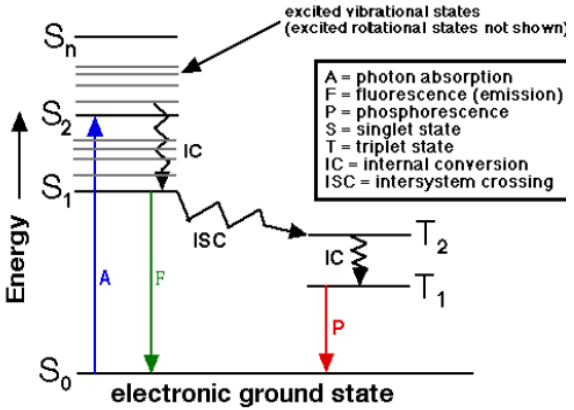
$\vec{\mu}$: electric dipole moment

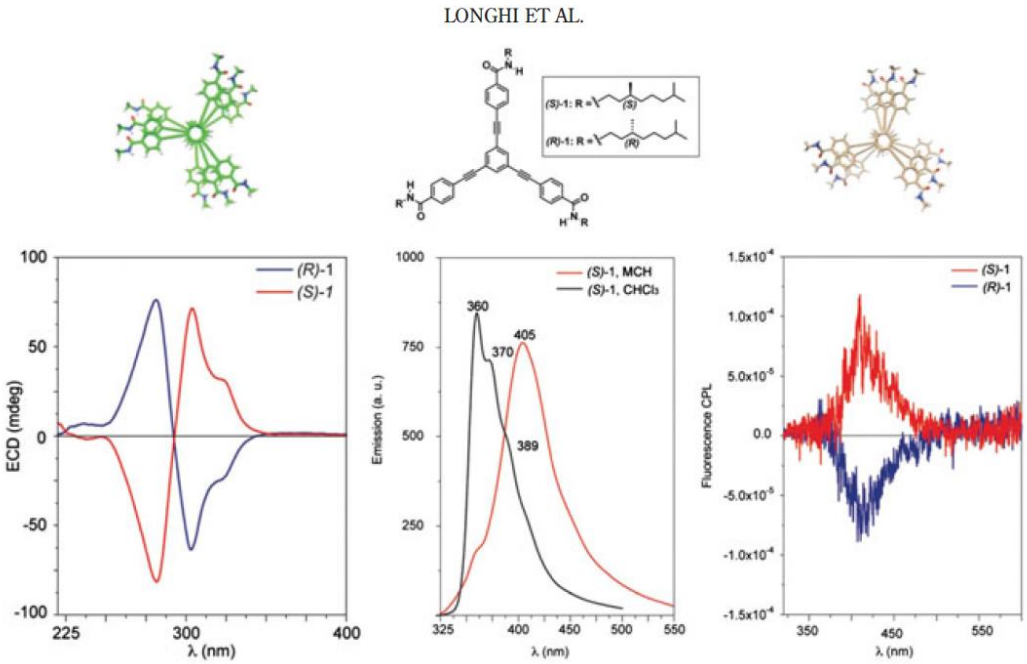
$\vec{m}$: magnetic dipole moment

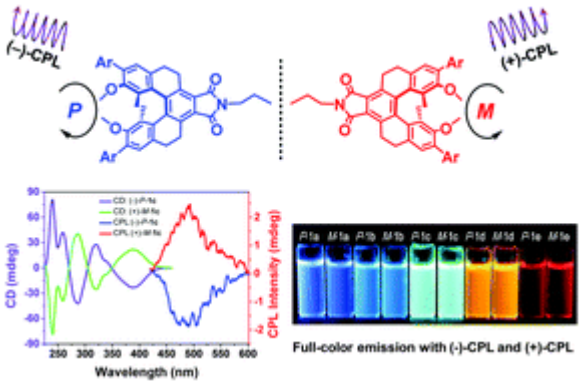
Q : displ. in normal coord.

P: conjugate momentum

Circular Polarised Luminescence CPL

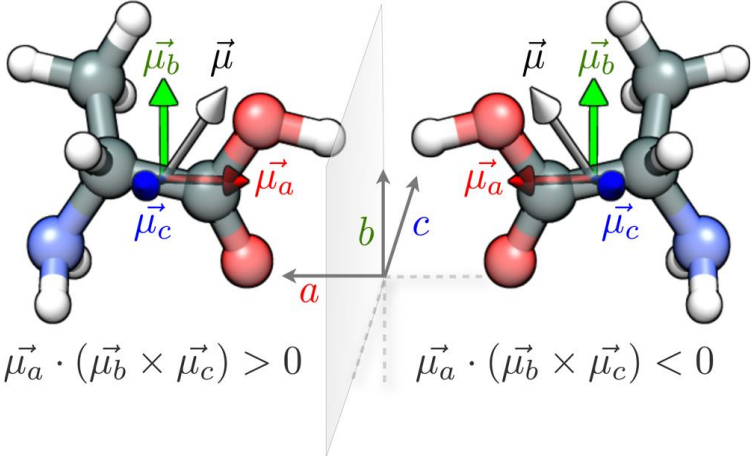


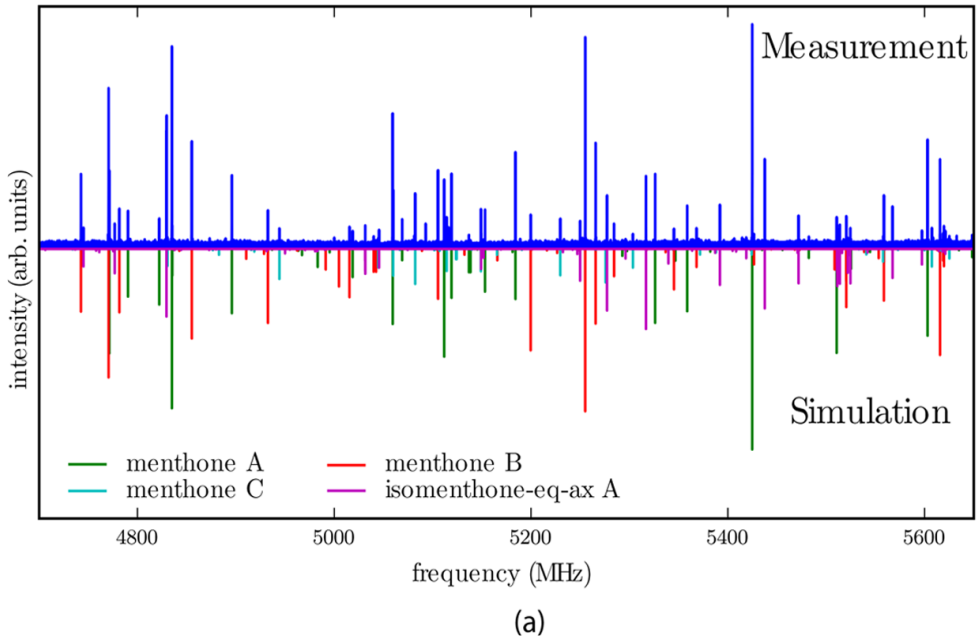


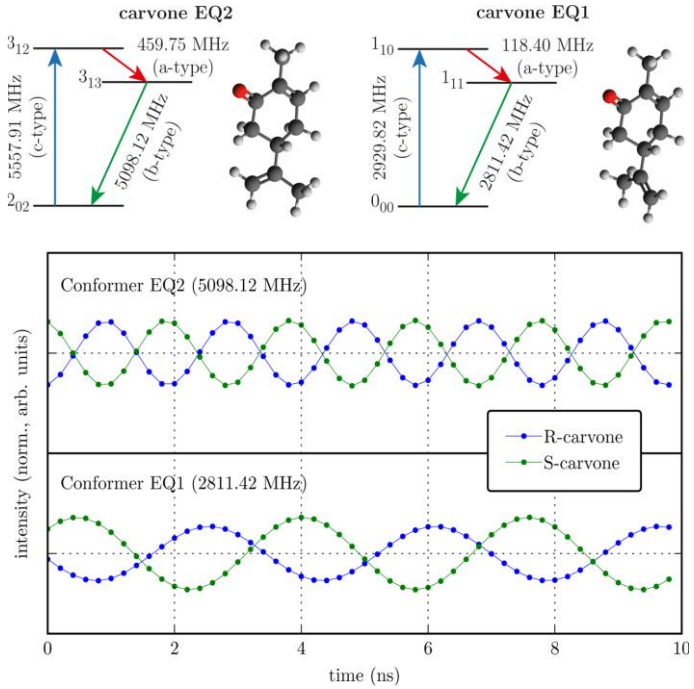


G. Longhi, E. Castiglioni, J. Koshoubu, G. Mazzeo, S. Abbate *Chirality* **2016**, 696-707

Chiral Rotational Spectroscopy CRS

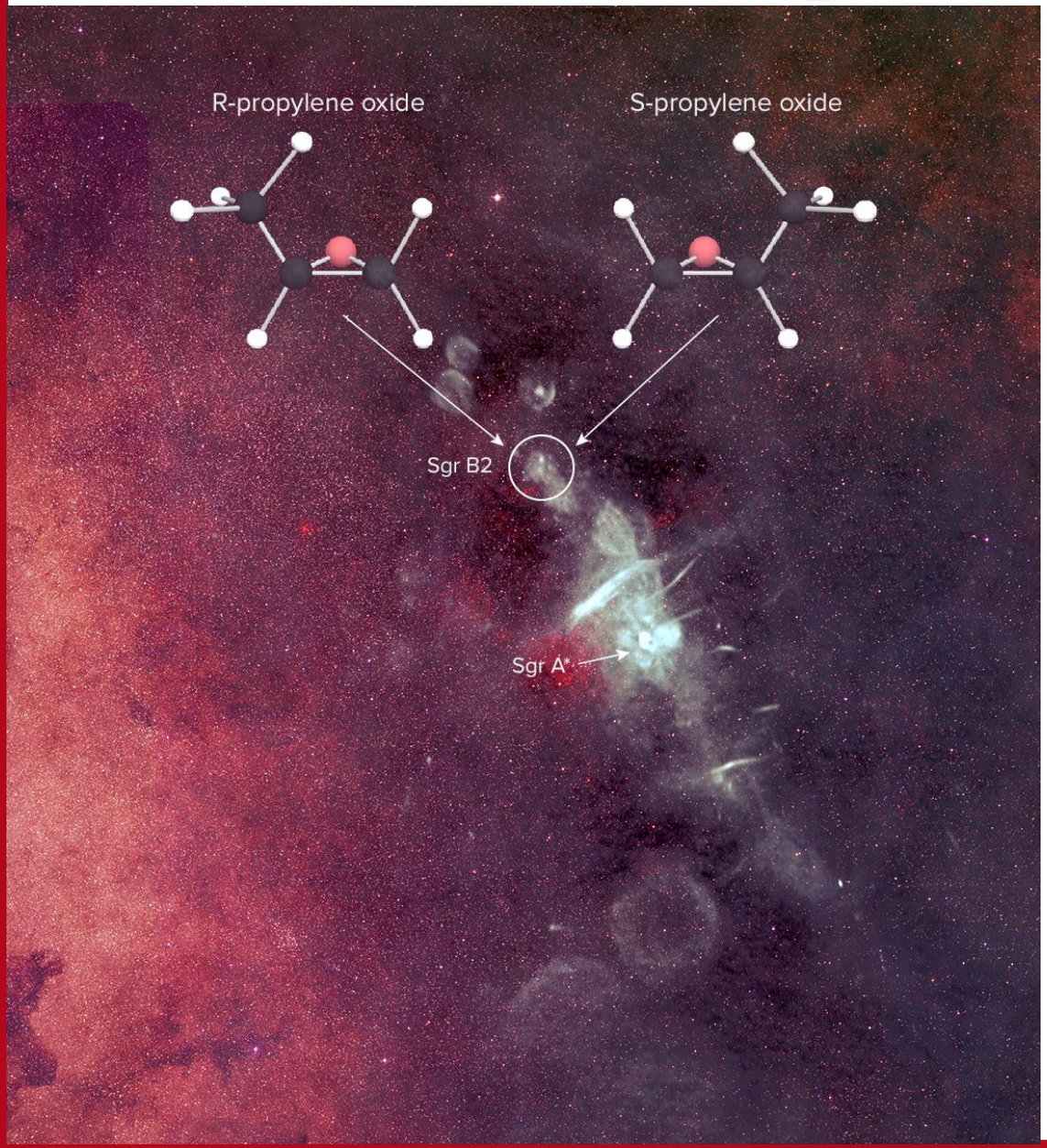


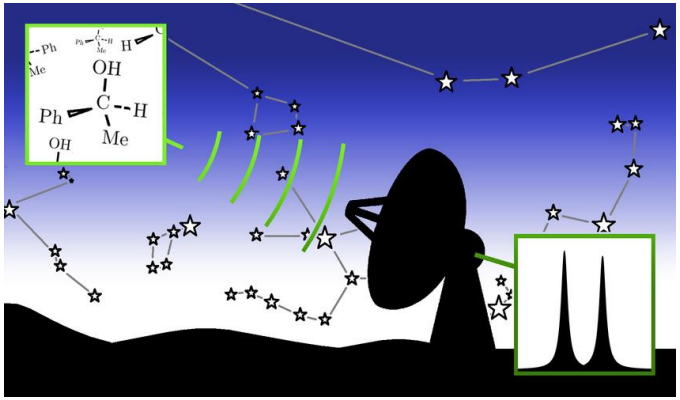


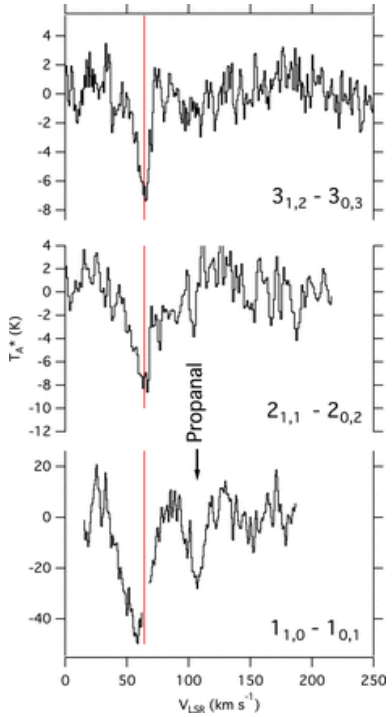


M. Schnell et al. *J. Phys. Chem. Lett.* **2016**, *7*, 341−350

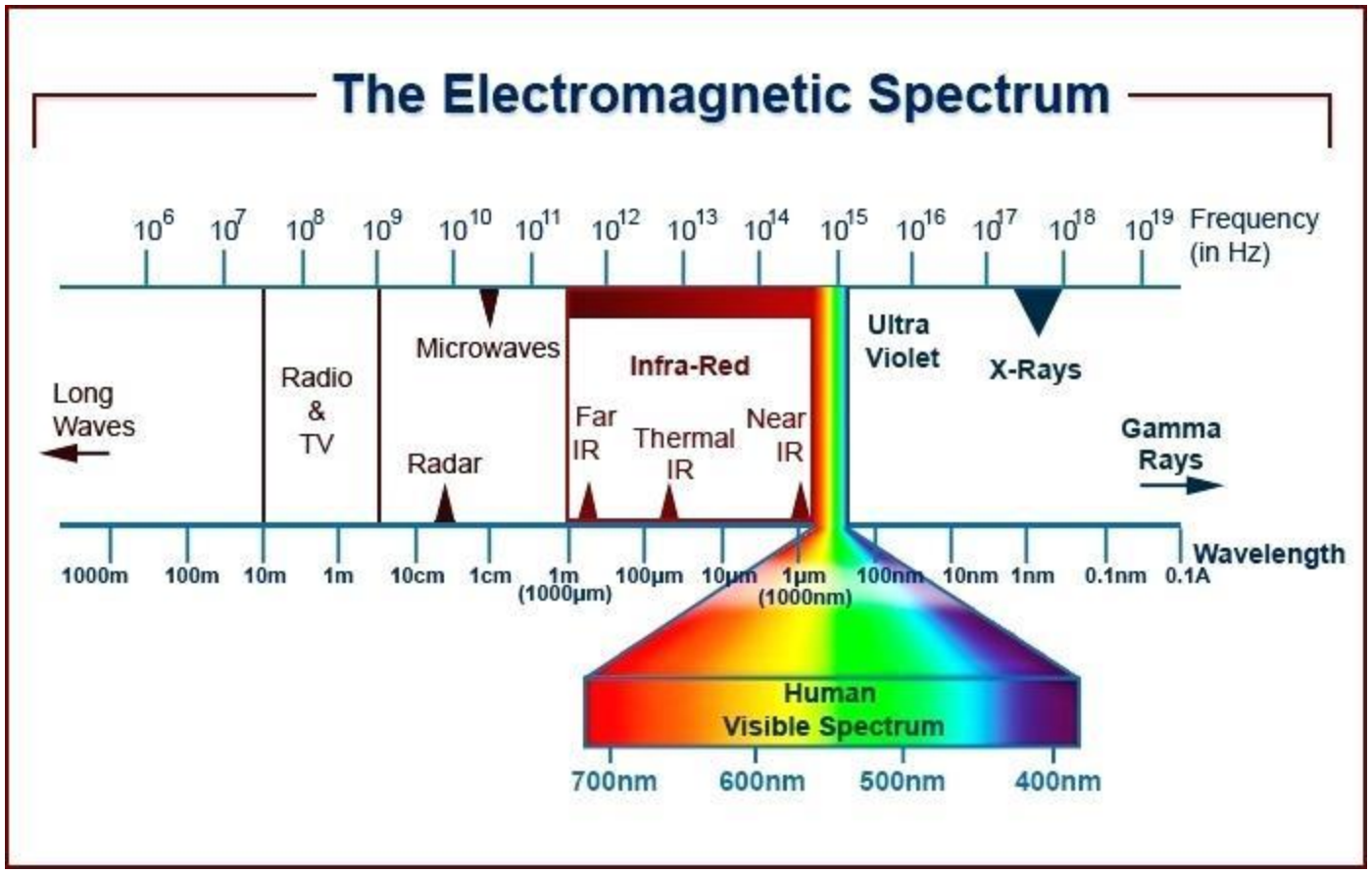
Chiral Rotational Spectroscopy







McGuire. B.A. *Science* **2016**, *352*, 1449-1452


The Electromagnetic Spectrum
10^6 10^7 10^8 10^9 10^{10} 10^{11} 10^{12} 10^{13} 10^{14} 10^{15} 10^{16} 10^{17} 10^{18} 10^{19} Frequency (in Hz)
Long Waves
Radio & TV
Microwaves
Radar
Infra-Red
Far IR
Thermal IR
Near IR
Ultra Violet
X-Rays
Gamma Rays
1000m 100m 10m 1m 10cm 1cm 1m (1000μm) 100μm 10μm 1μm (1000nm) 100nm 10nm 1nm 0.1nm 0.1A
Wavelength
Human Visible Spectrum
700nm 600nm 500nm 400nm