

# Chiroptical Spectroscopy

## Theory and Applications in Organic Chemistry

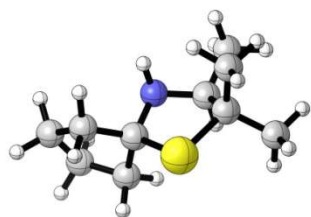
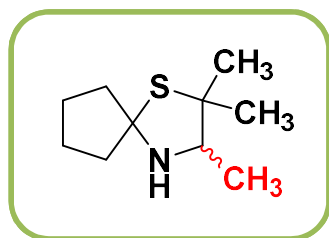
**Lecture 8:** Vibrational Optical Activity, part 2

Masters Level Class (181 041)

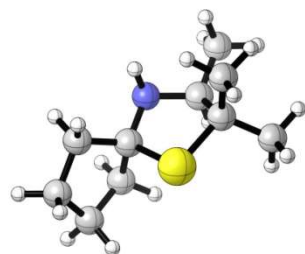
Block course, october 2020

# Absolute configurations from VCD spectroscopy

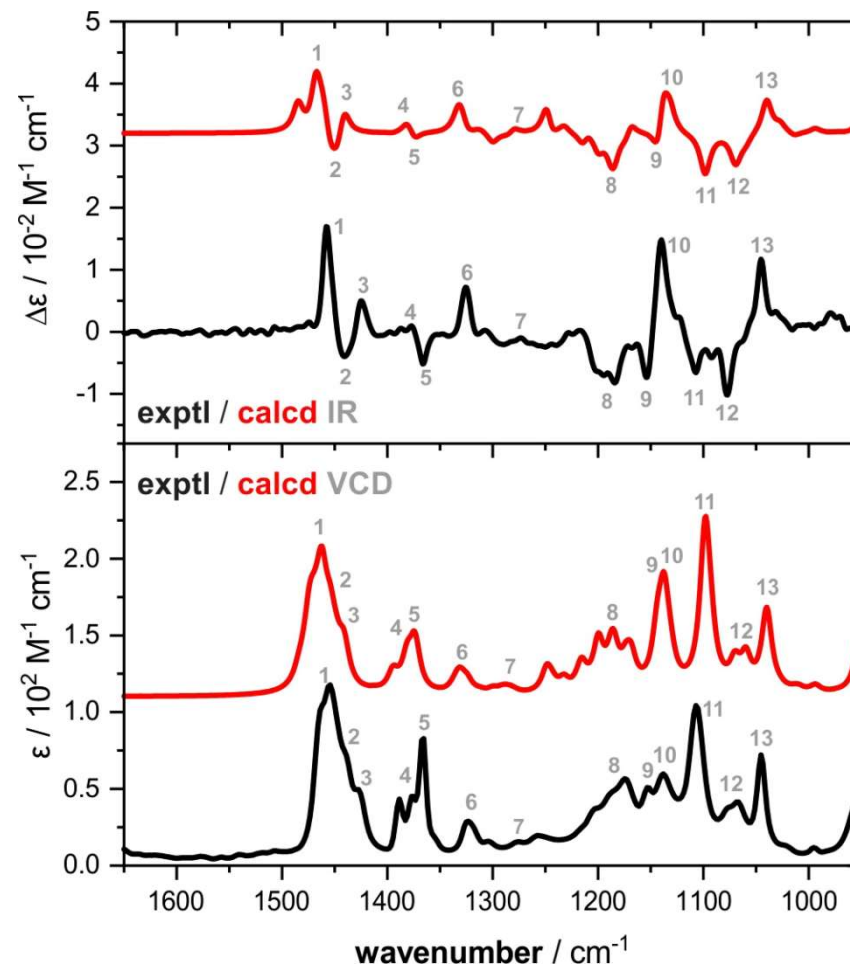
Zumbrägel, Merten, Huber, Gröger, *Nature Comm.* 2018



Lowest energy conformer  
( $\Delta G_{298K} = 0.0$  kcal/mol, 64.5 %)



2<sup>nd</sup> lowest energy conformer  
( $\Delta G_{298K} = 0.4$  kcal/mol, 34.2 %)

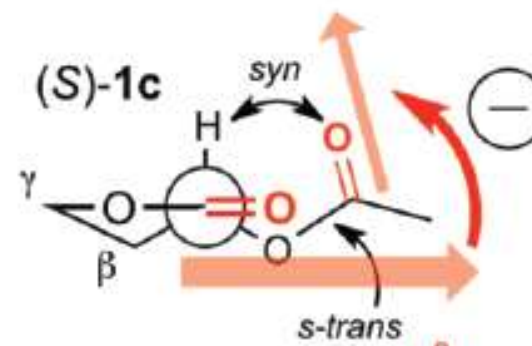
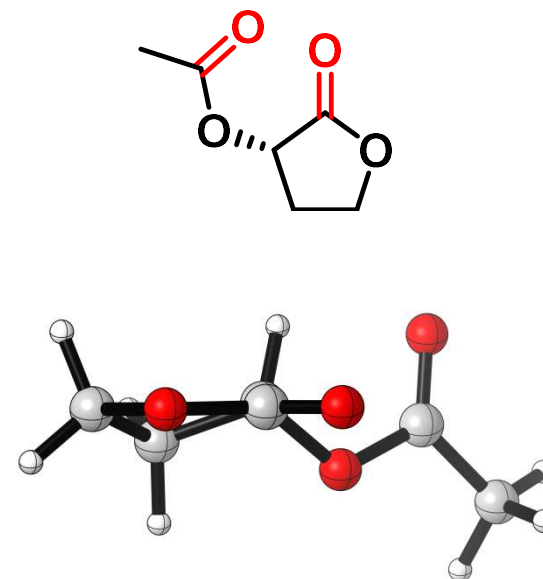
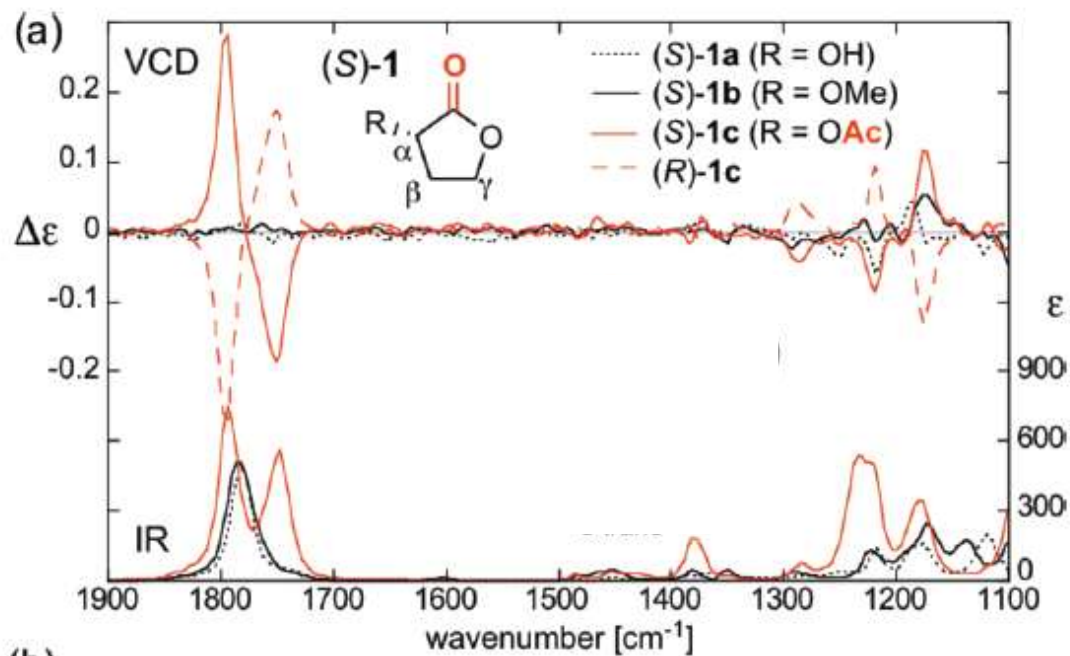


B3LYP/6-311g++(2d,p)/IEFPCM(CHCl<sub>3</sub>)

# Exciton coupling for VCD

T. Taniguchi, K. Monde, *J. Am. Chem. Soc.* **2012**, *134*, 3695-3698

**Requirement:** Two identical coupled oscillators, e.g. C=O stretching

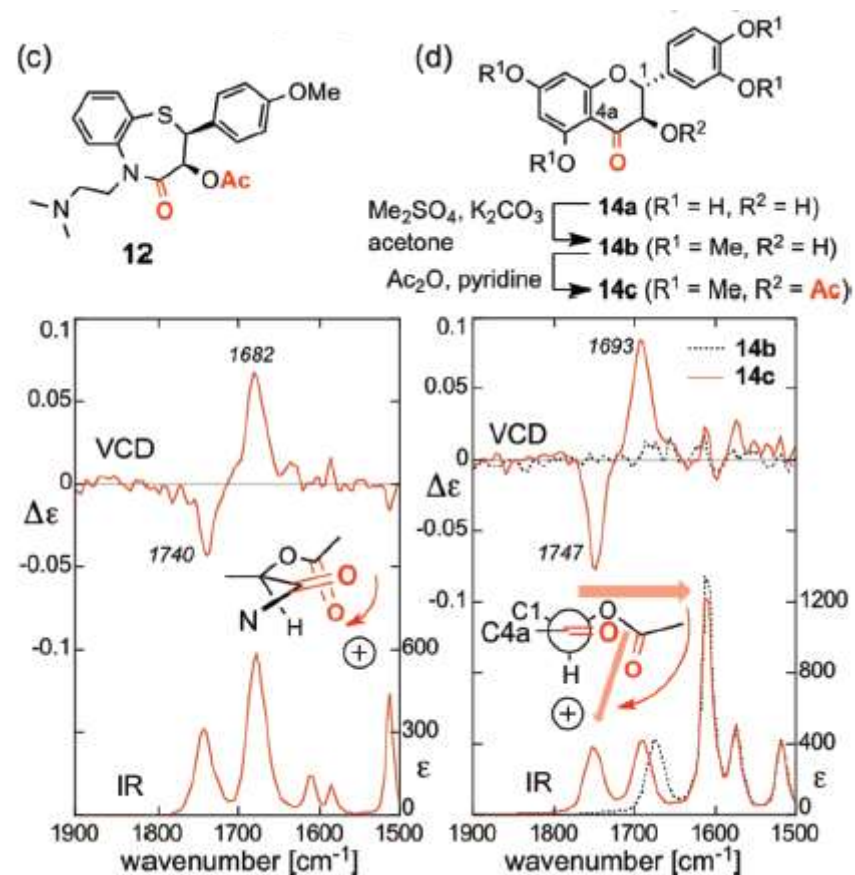
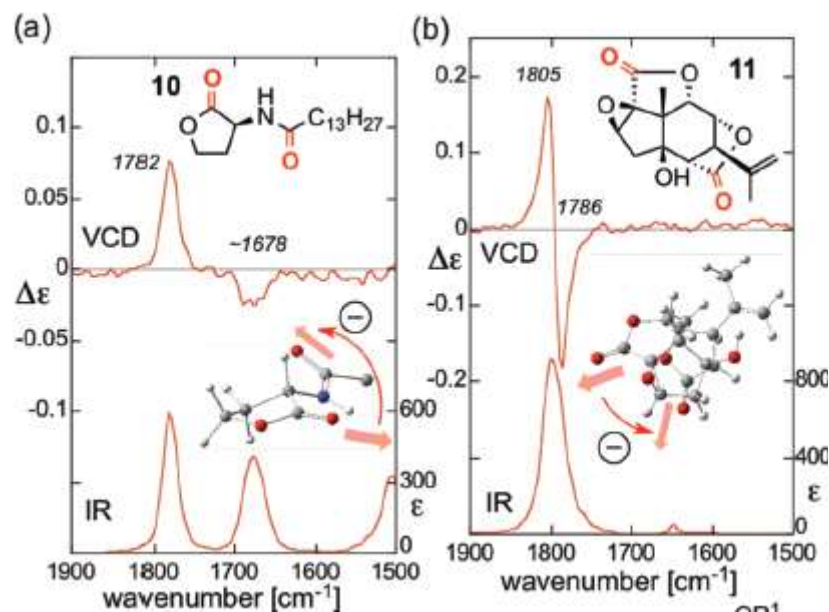


# Exciton coupling for VCD

T. Taniguchi, K. Monde, *J. Am. Chem. Soc.* 2012, 134, 3695-3698

**Pro:** Works quite well even if VCD is generally weak, as C=O is often the strongest band

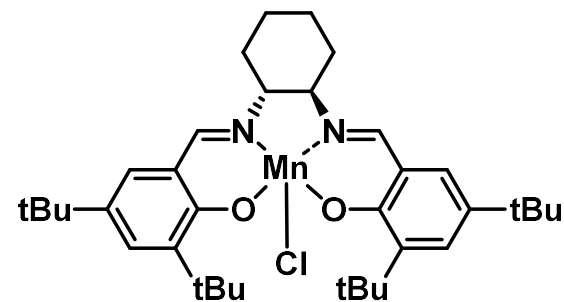
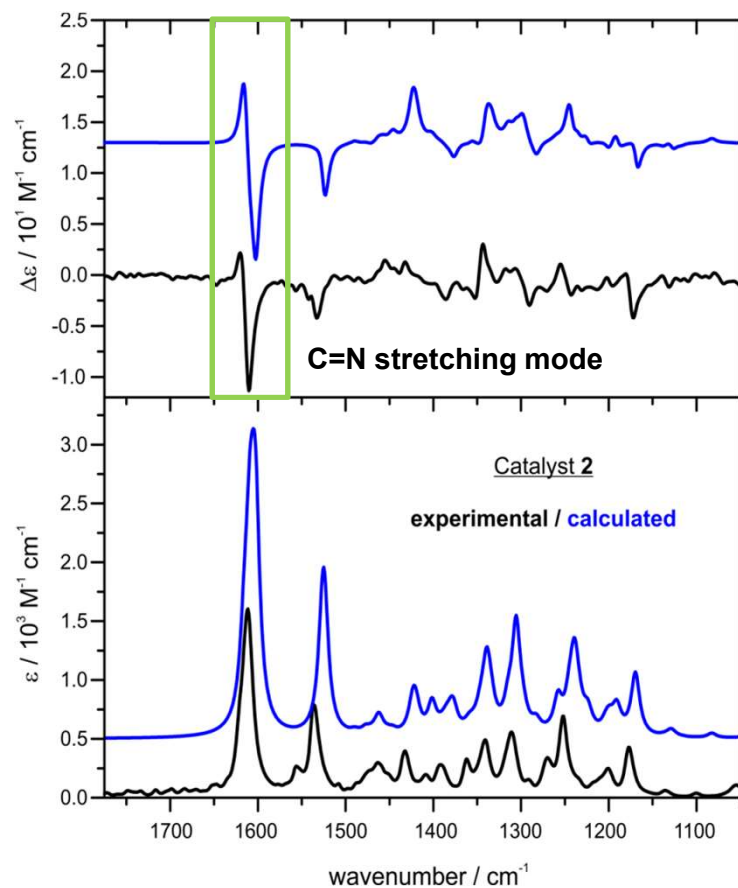
**Con:** We still need to know preferred conformation.



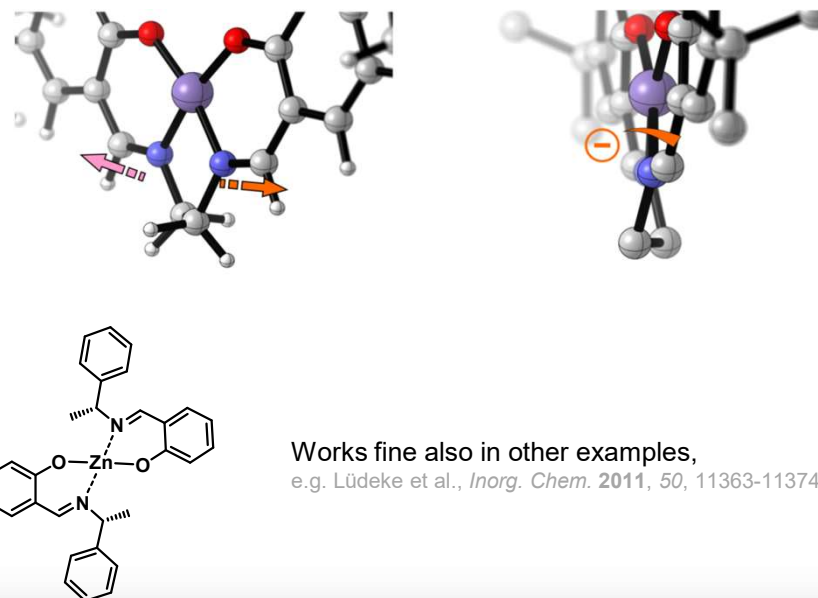
# Exciton coupling for VCD

C. Merten, C. H. Pollok, S. Liao, B. List, *Angew. Chem. Int. Ed.* 2015, 54, 8841-8845

Another well-separated coupled IR-chromophore: C=N stretching mode

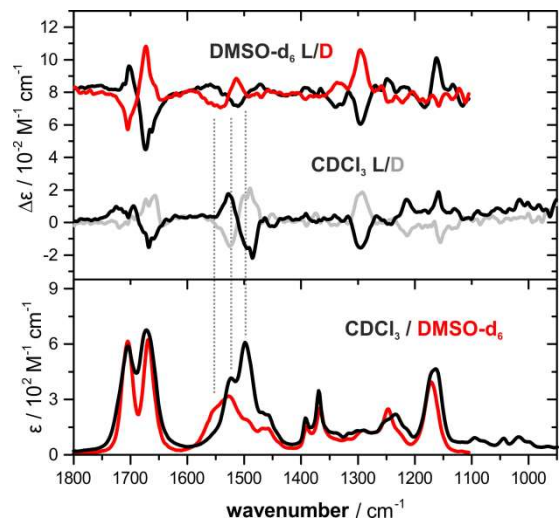


Jacobsen's catalyst



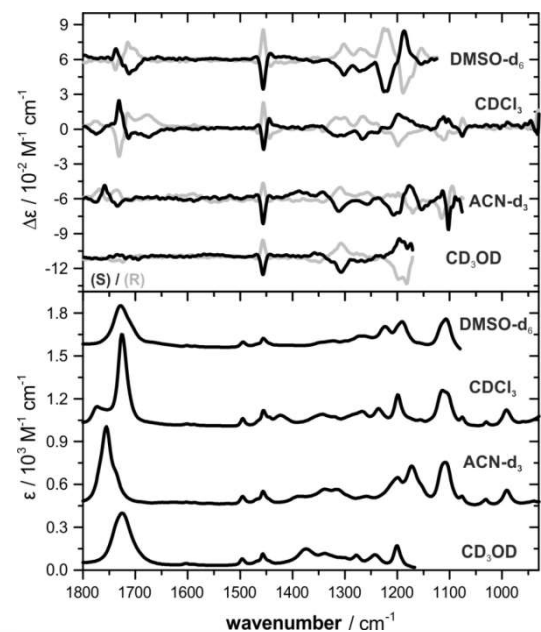
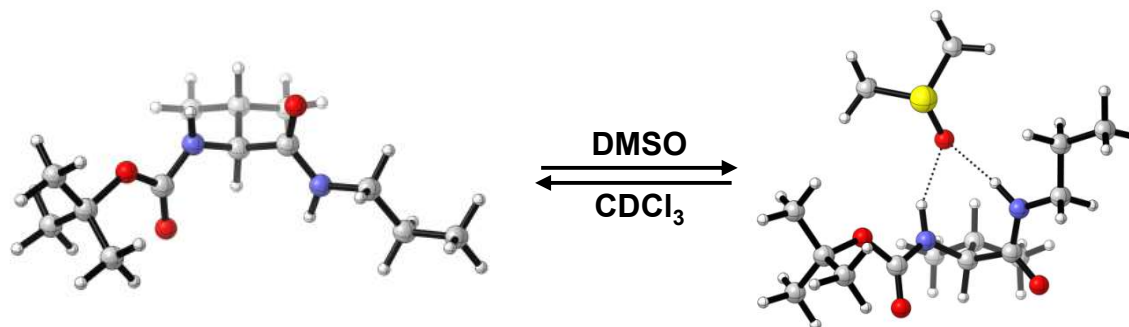
Works fine also in other examples,  
e.g. Lüdeke et al., *Inorg. Chem.* 2011, 50, 11363-11374

# Solvent effects: Monitoring conformational changes



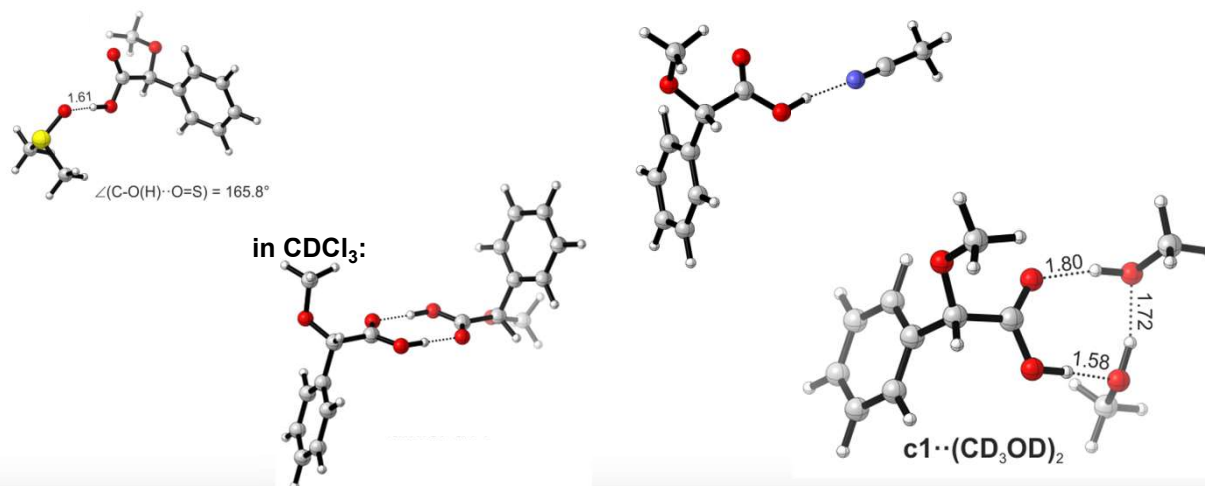
## Effect of solvation of an amide group

(K. Bünnemann, C. Merten, *J. Phys. Chem. B* **120** (2016) 9434-9442)

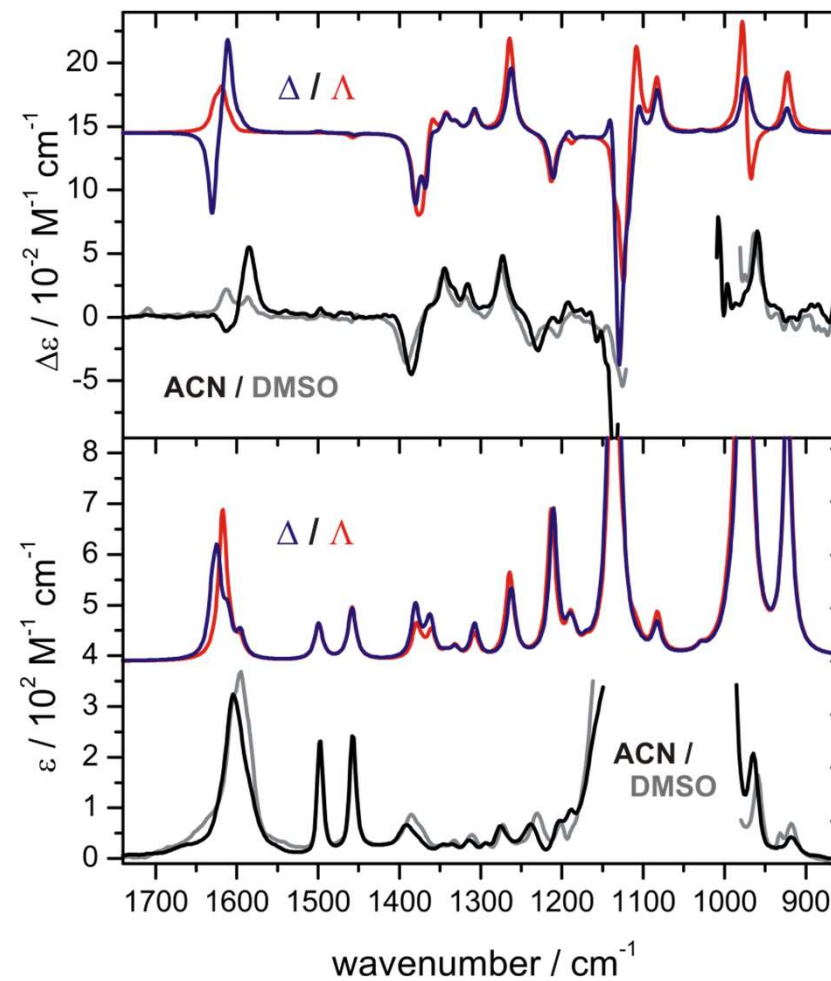
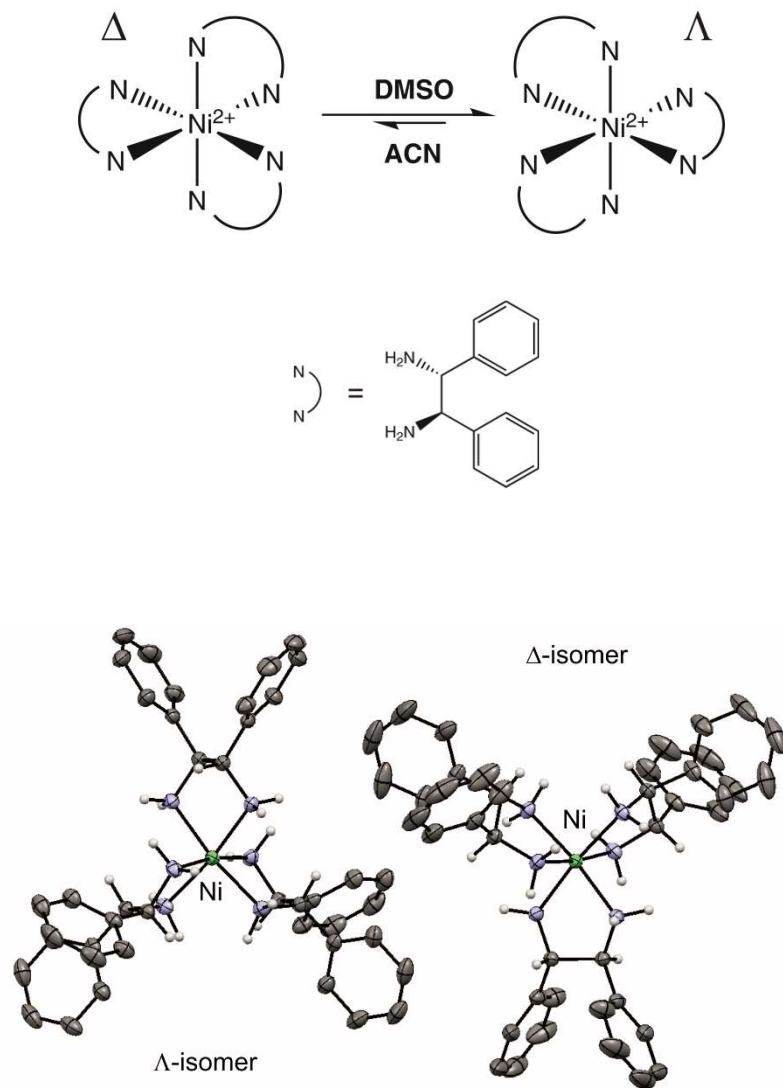


## Solvation of carboxylic acids

(K. Bünnemann, C. Merten, *Phys. Chem. Chem. Phys.* **19** (2017) 18948-18956)



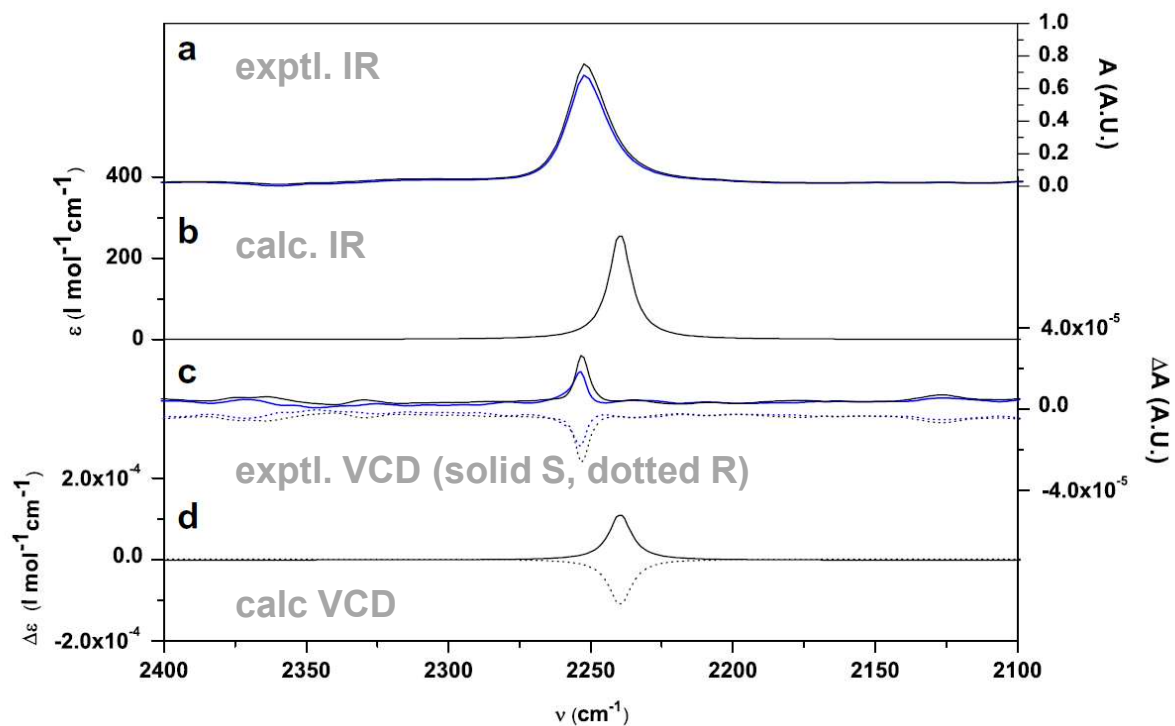
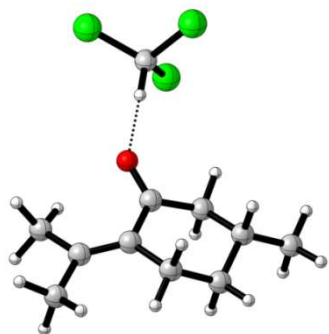
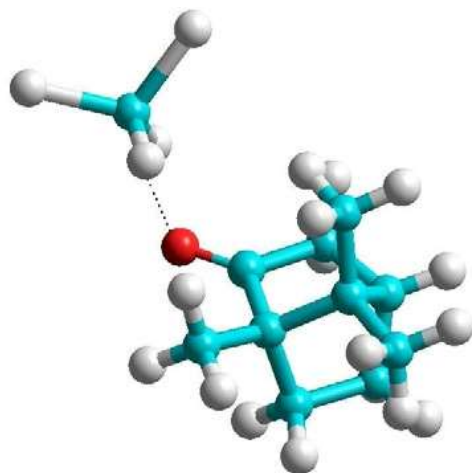
# Solvent-dependent preference of $\Delta/\Lambda$ isomers



# Inducing VCD intensity to solvents

Debie, Jaspers, Bultinck, Herrebout, van der Veken, *Chem Phys Lett.* **450** (2008) 426

camphor → chloroform C-D stretching

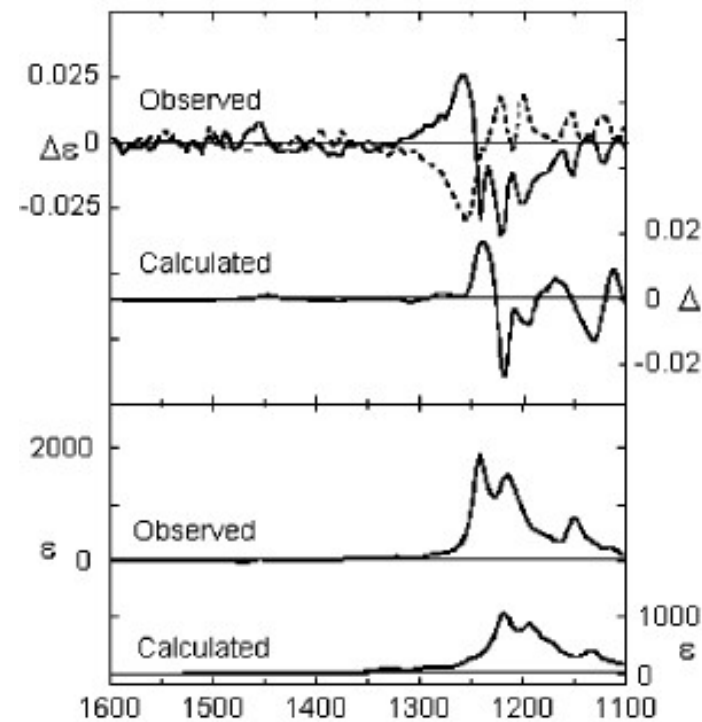
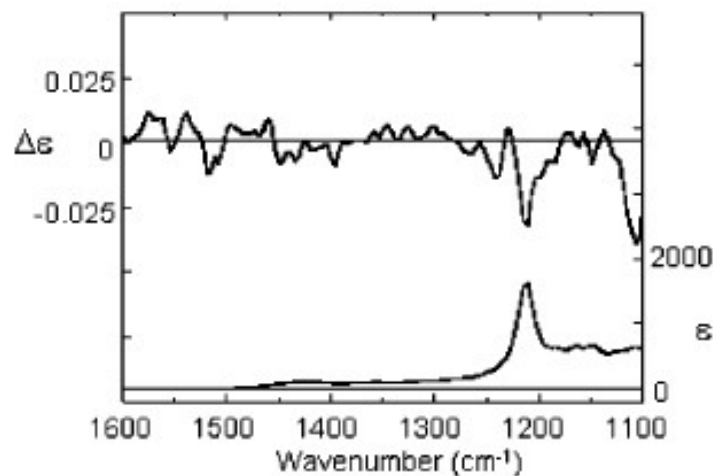
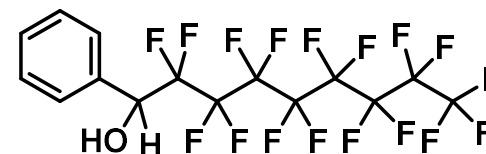
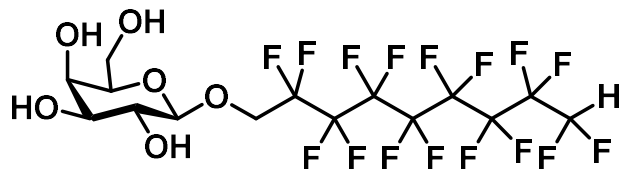


## Pulegone—CDCl<sub>3</sub>

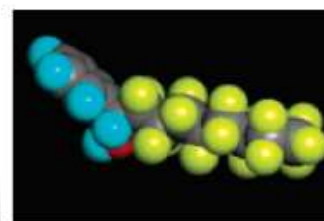
E. Debie, P. Bultinck, W. Herrebout, B. van der Veken,  
*Phys. Chem. Chem. Phys.* **10** (2008) 3498-3508

# Helical structure of perfluoro-alkyl chain

Monde et al., *J. Am. Chem. Soc.* 128 (2006) 6000-6001

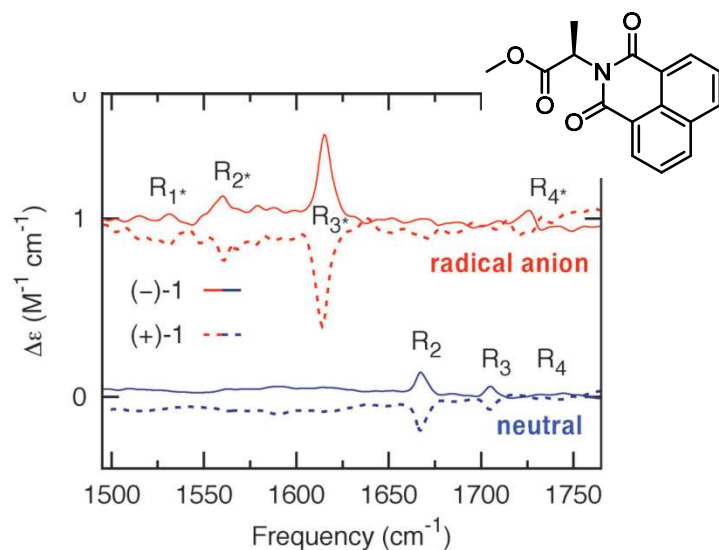


Observation of strong VCD signature of C-F stretching vibrations ( $\sim 1220$  cm<sup>-1</sup>)



**Right-handed  
(CF<sub>2</sub>) helix!**

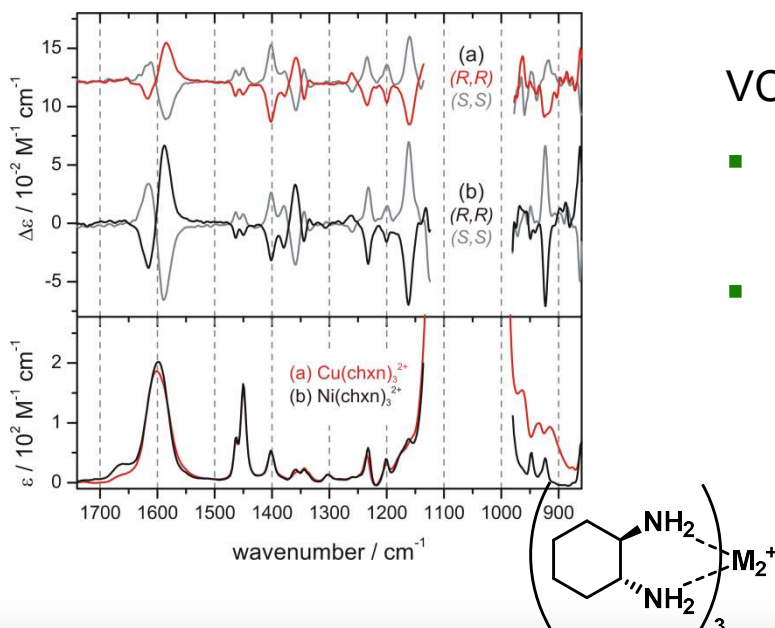
# VCD enhancement effects



$$D_{n0} = |\mu_{0n}|^2$$

$$R_{n0} = \text{Im}\{\mu_{0n} \cdot m_{n0}\}$$

There is no direct correlation between IR and VCD intensities!



VCD can be enhanced if *mdtm* is increased:

- Electrochemical reduction  
Domingos et al., *Chem Comm* 2012, **48**, 353
- Variation of metal ions in transition metal complexes: diamagnetic → paramagnetic  
Merten et al., *PCCP* 2012, **14**, 12884

# Challenges of solid state (V)CD

C. Merten, T. Kowalik, A. Hartwig, *Appl. Spectrosc.* 2008, 62, 901-906

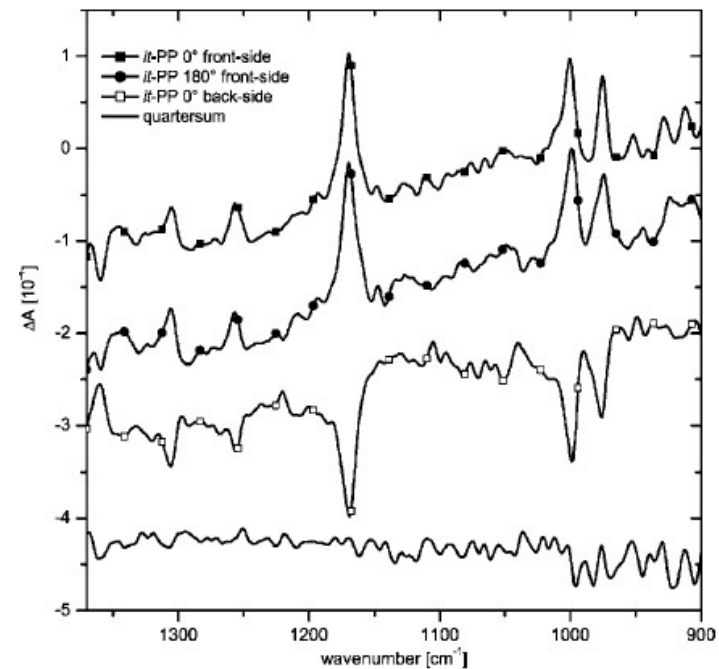
$$M_{CDSAMPLE} = 10^{-A(\tilde{\nu})} \begin{pmatrix} 1 & 0 & 0 & CD \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ CD & 0 & 0 & 1 \end{pmatrix} \quad M_{REALSAMPLE} = 10^{-A(\tilde{\nu})} \begin{pmatrix} 1 & -LD & -LD' & CD \\ -LD & 1 & CB & -LB \\ -LD' & -CB & 1 & LB' \\ CD & LB & -LB' & 1 \end{pmatrix}$$

$$S_{VCD} = CD + 0.5(LB \cdot LD' - LD \cdot LB')$$

## Problems of solid state measurements:

- Sample can exhibit LD, LB, CB due to crystalline structures
- Conformational distribution difficult to predict ... amorphous powder = solution phase ?
- KBr hydroscopic, additional scattering of pellet, reproducibility ...

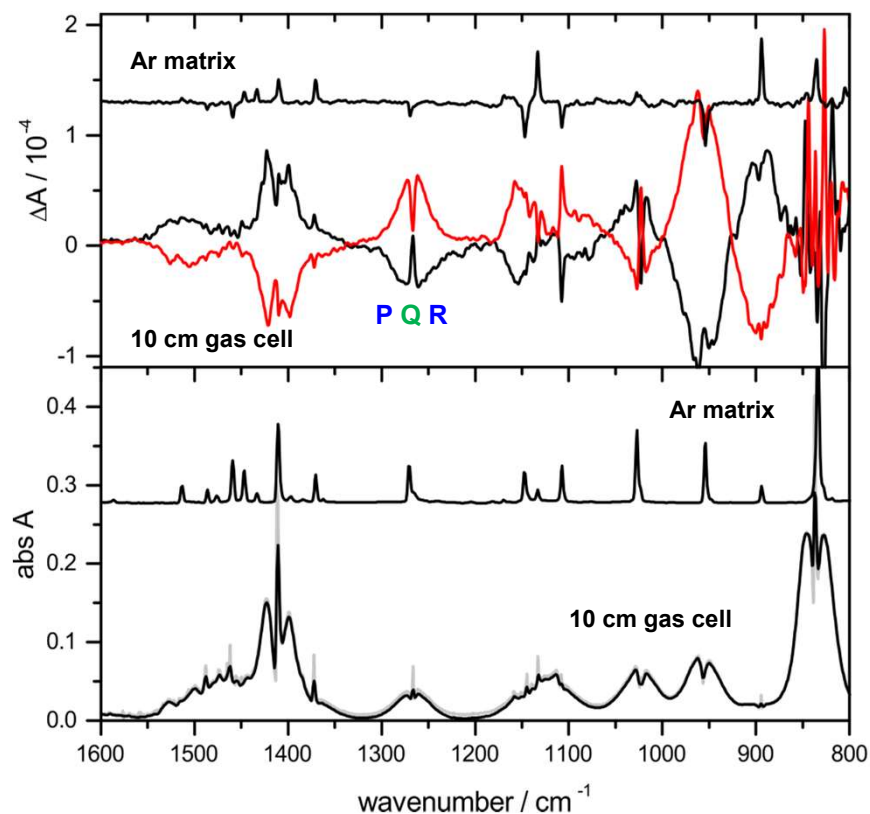
„Solution“: Rotate sample



# VCD in gas phase: The example of PO

P. L. Polavarapu, *Chem. Phys. Lett.* **1989**, *161*, 485-490  
C. Merten, J. Bloino, V. Barone, Y. Xu, *J. Phys. Chem. Lett.* **2013**, *4*, 3424-3428

**Challenges:**      Low optical density  
                         Not many samples with high vapor pressure  
                         Analysis of spectra

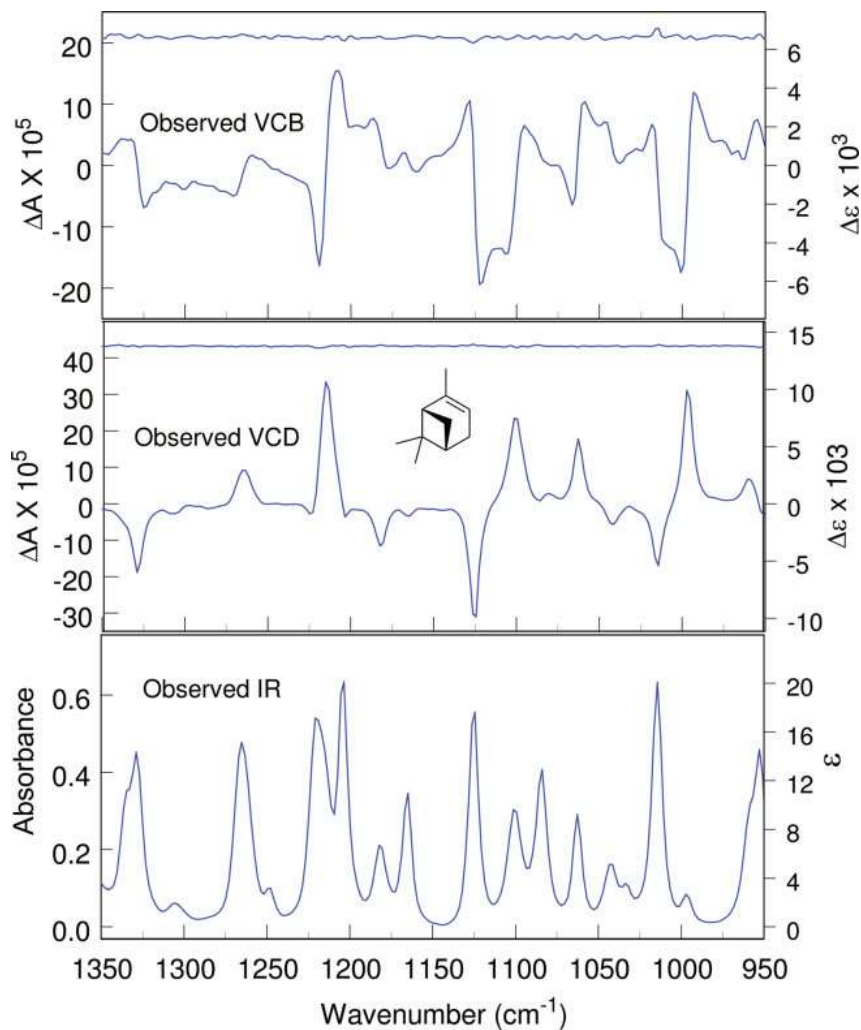


VCD bands become broad due to CD associated with P and R branches

For some bands, the Q branch can feature opposite sign to P and R, and even opposite sign to solution phase experiments!

# Vibrational ORD?

R. A. Lombardi, L. A. Nafie, *Chirality* 2009, 21 Suppl 1, E277-286

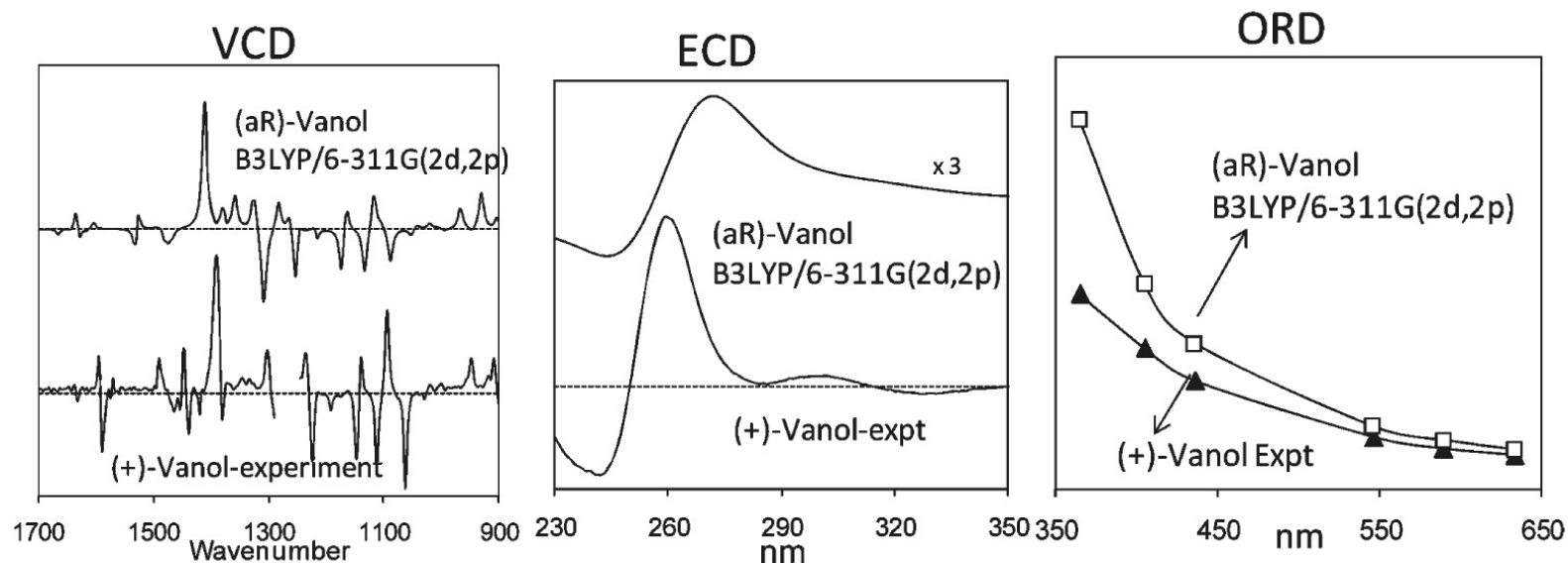


## Vibrational optical rotatory dispersion (VORD)

- can be measured using a regular VCD spectrometer (after some changes to the optical setup and signal processing)
- can be calculated based on rotational strength of VCD transition (ORD and CD are generally linked through Kramers-Kronig transformation)
- has not found important applications yet

# Summary: A comparison of the three main tools

P. L. Polavarapu et al., *J. Org. Chem.* 2009, 74, 5451-5457



**Largest** amount of sample

Solubility issues

Simulation „easy“, as only ground state is required

No special chromophores needed

**Very small** amounts of sample

Empirical rules for analysis

Simulation more elaborate as electronic excitation energies required

UV/vis active chromophores required

Often available in OChem labs

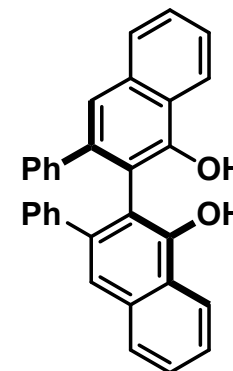
**Small** amount of sample

Qualitative AC assignments using empirical rules as in ECD

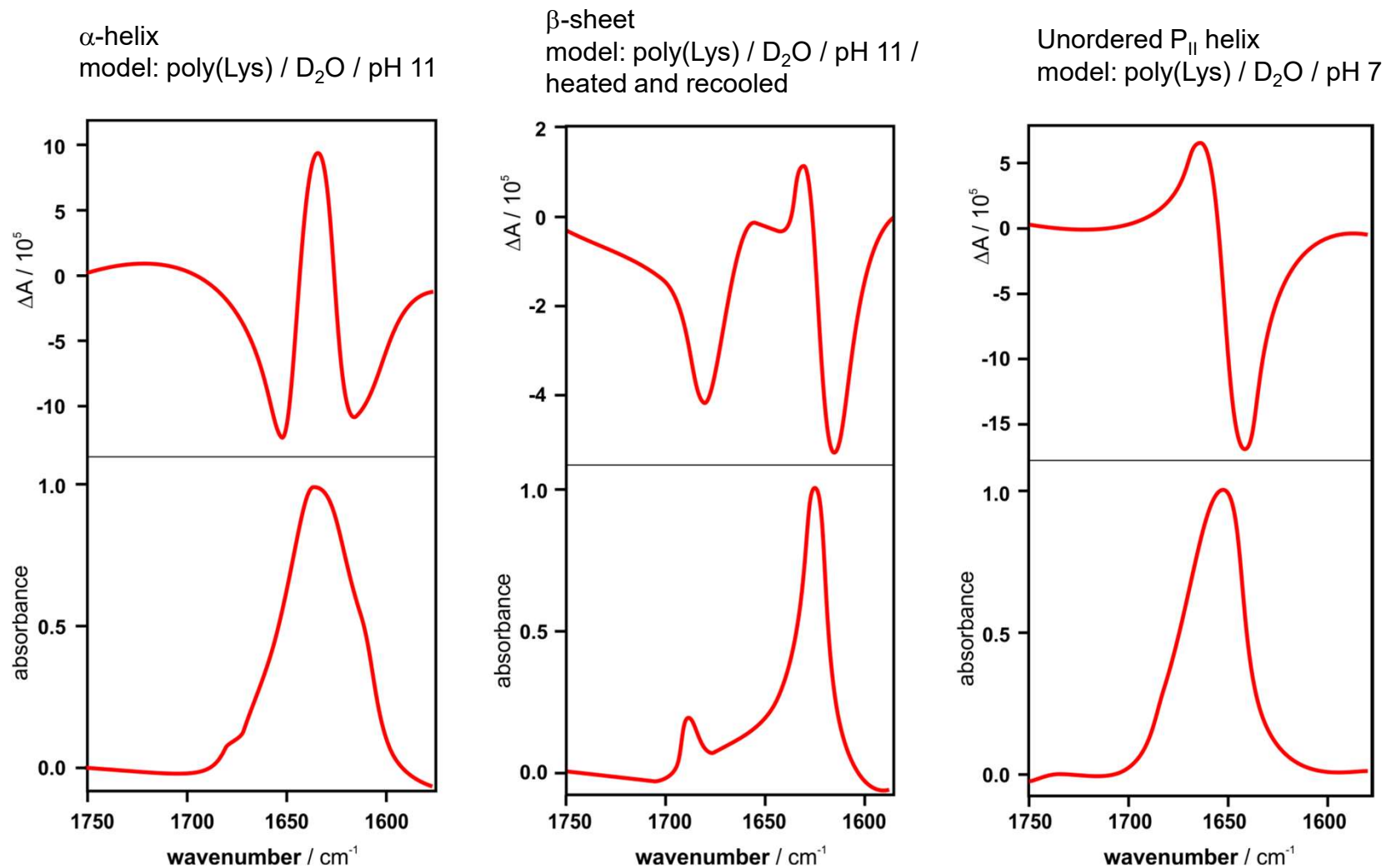
Qualitative curve can easily be calculated

No special chromophores

Often available in OChem labs



# VCD signatures of peptide secondary structures



Keiderling et al., „Conformational studies of biomolecules...“,  
in Berova et al., Comprehensive Chiroptical Spectroscopy,  
Vol 2., Wiley-VCH, 2012

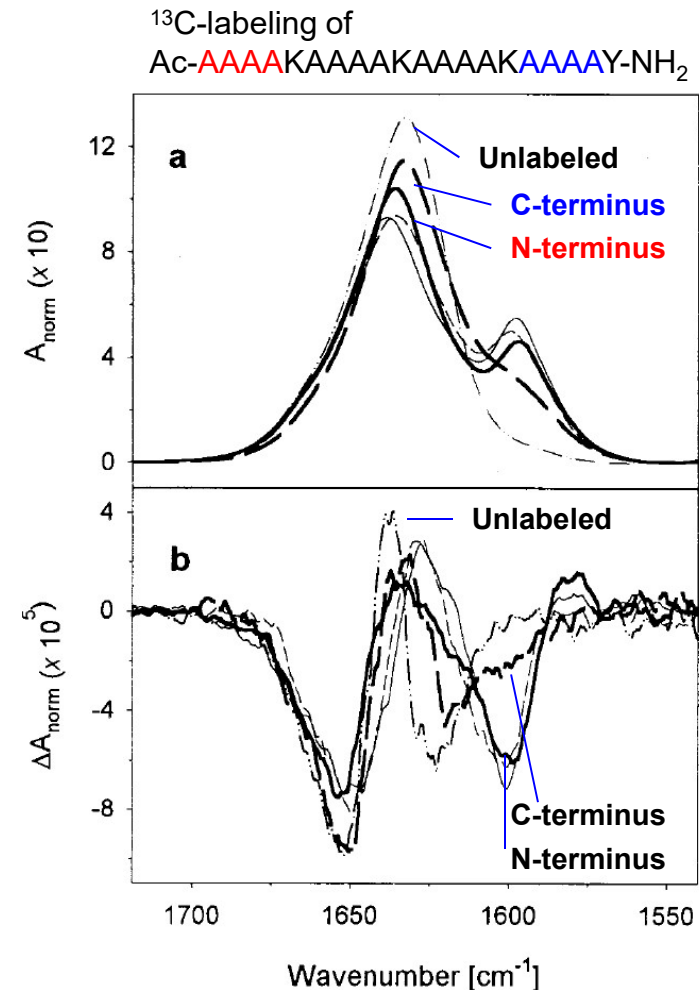
# VCD signatures of peptide secondary structures

## Advantages:

- Insensitive to side groups (especially no overlap of aromatic side groups with important chromophores)
- Local interactions such as  $\beta$ -turns
- Possibility of isotope labelling

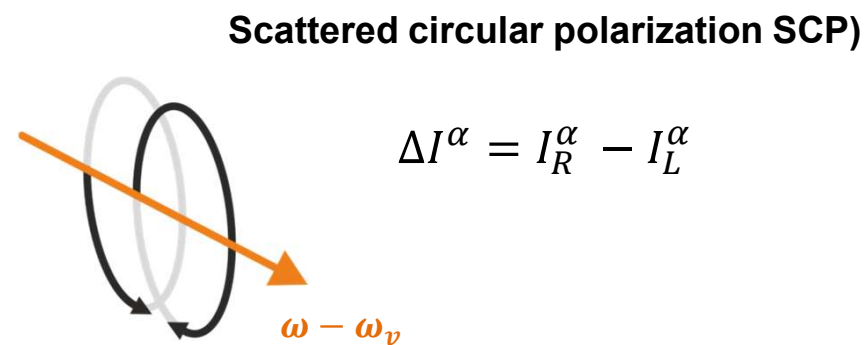
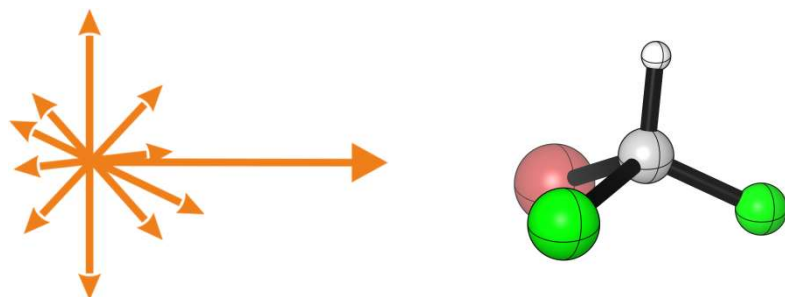
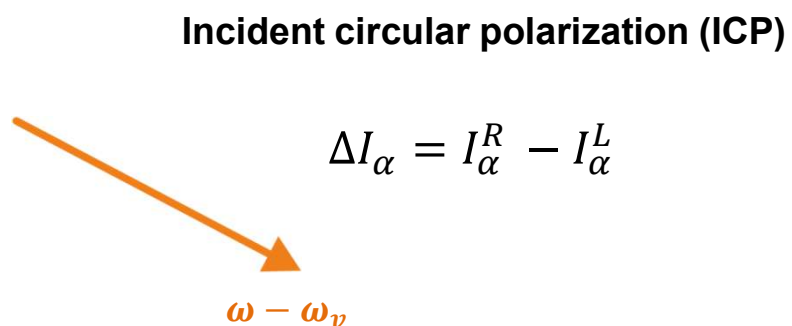
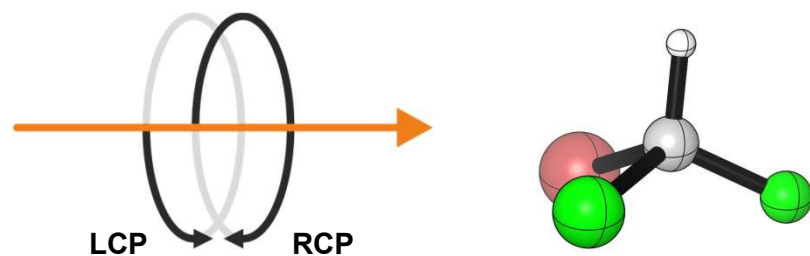
## Disadvantages:

- Water is not a good solvent for IR/VCD
- Use of  $D_2O$  might shift important bands (amide II)



# Raman Optical Activity (ROA)

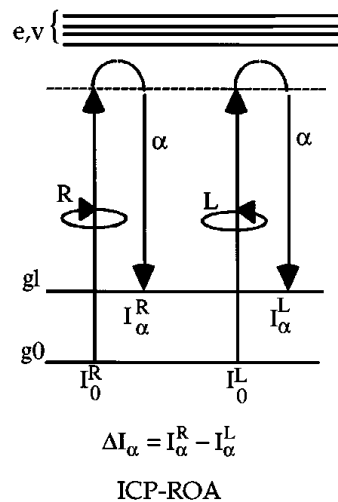
Schematic representation of the two most important ROA processes



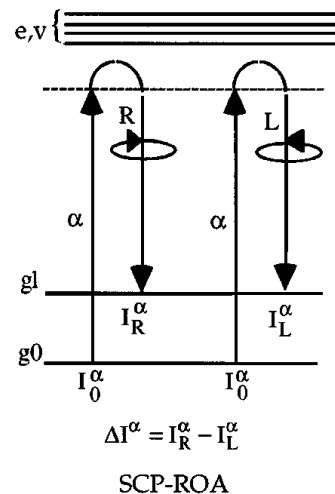
# Four forms of ROA

L. A. Nafie, *Annu. Rev. Phys. Chem.* 1997, 48, 357-386

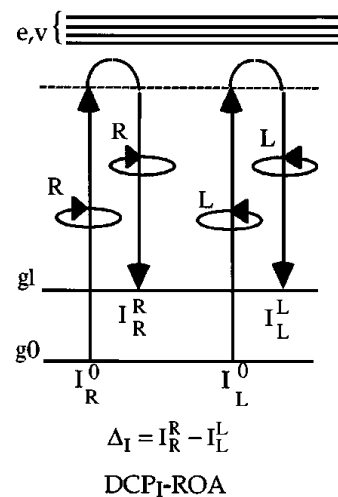
Unpolarized light in,  
Circular polarization out



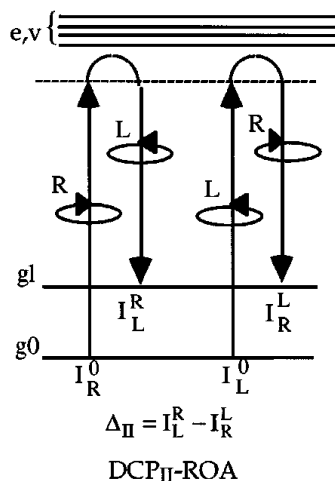
Circular polarization in,  
Unpolarized light out



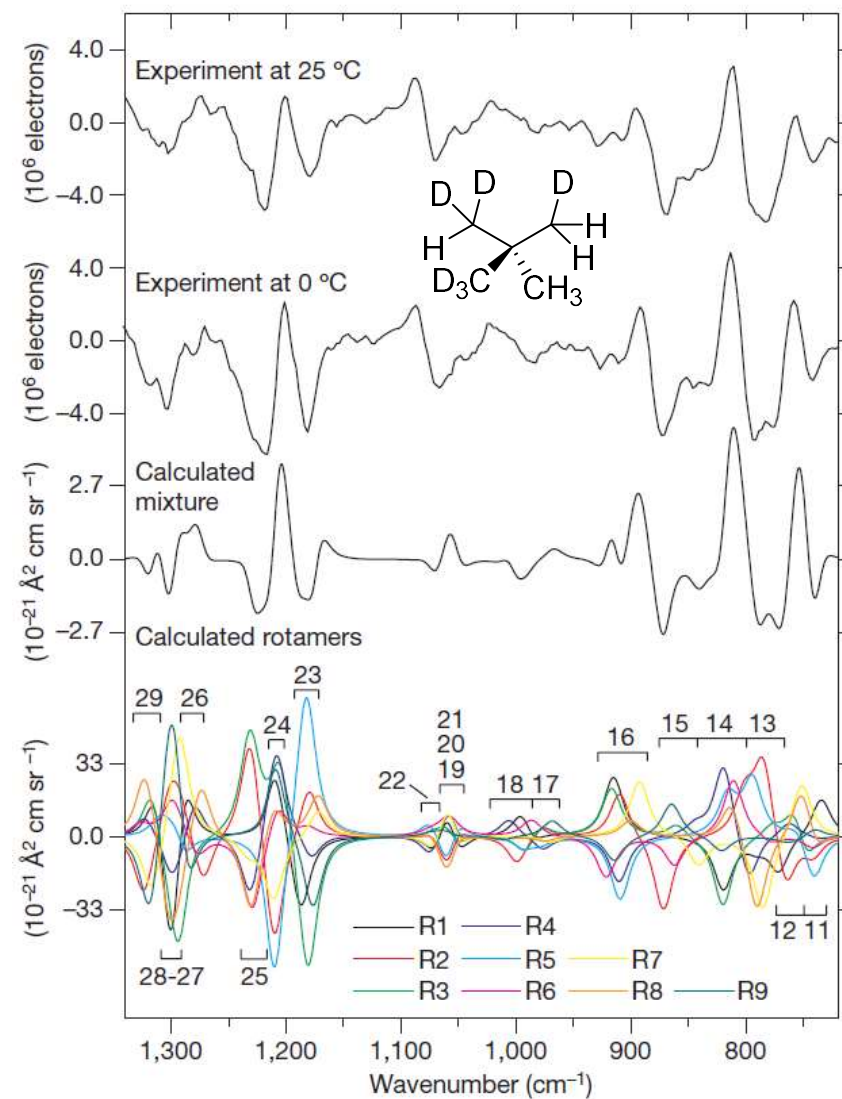
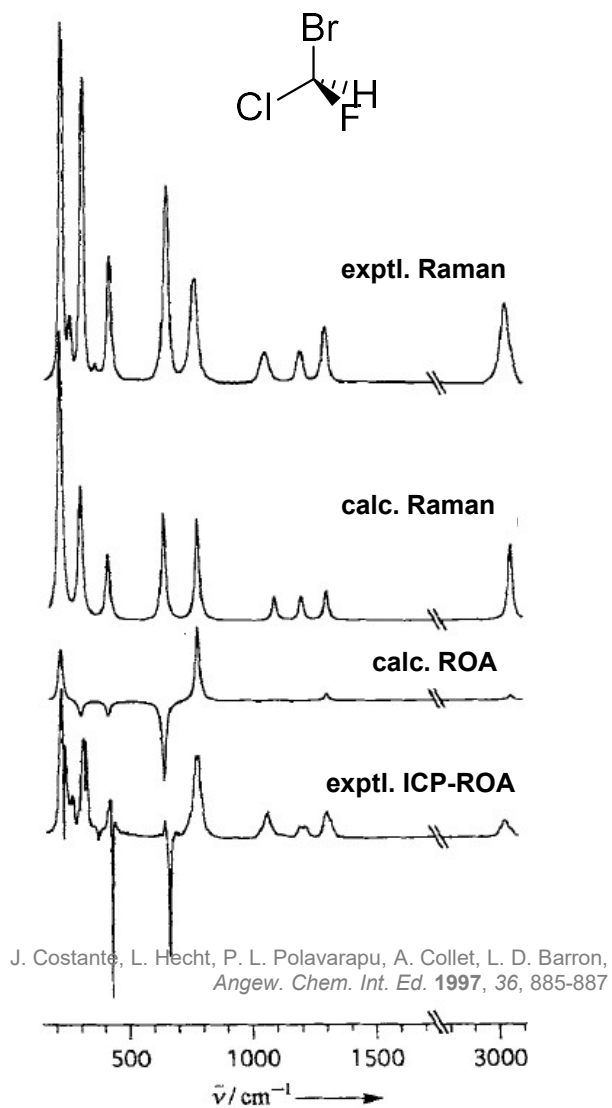
CP in, CP out  
in phase detection



CP in, CP out  
Out of phase detection



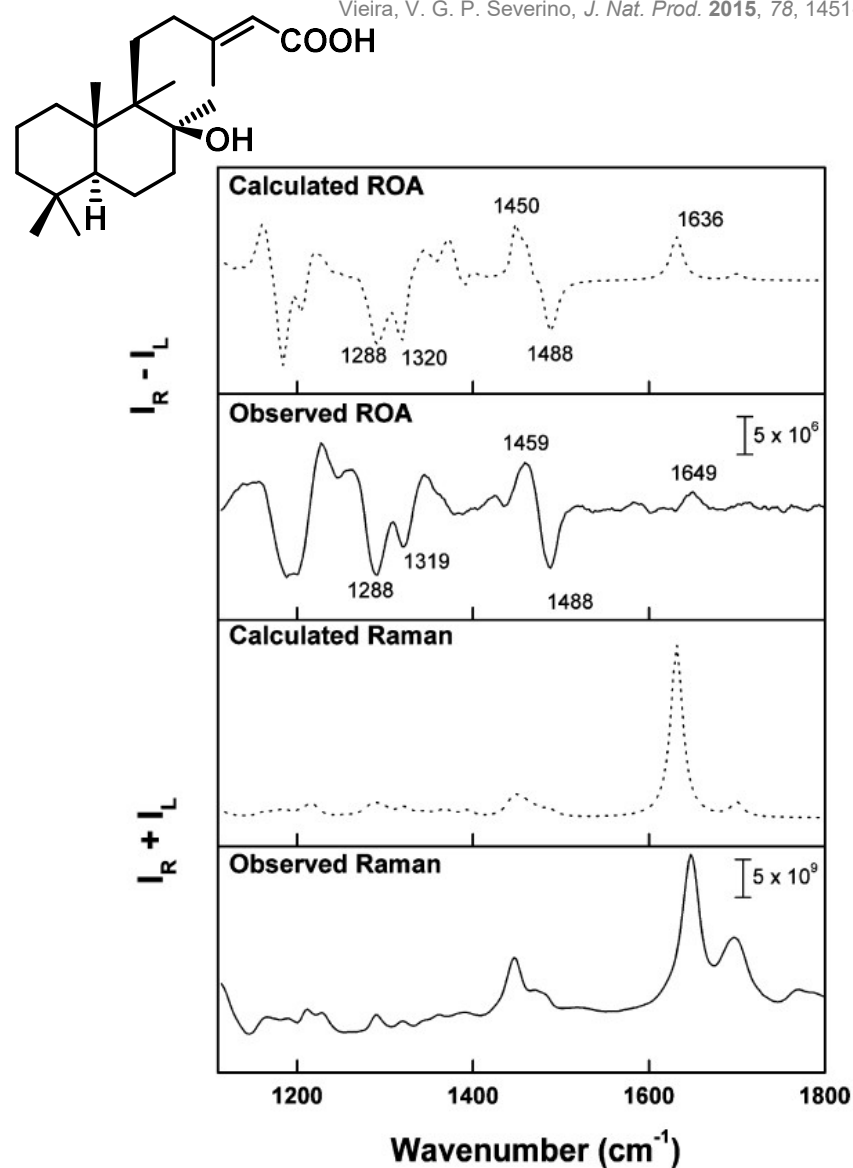
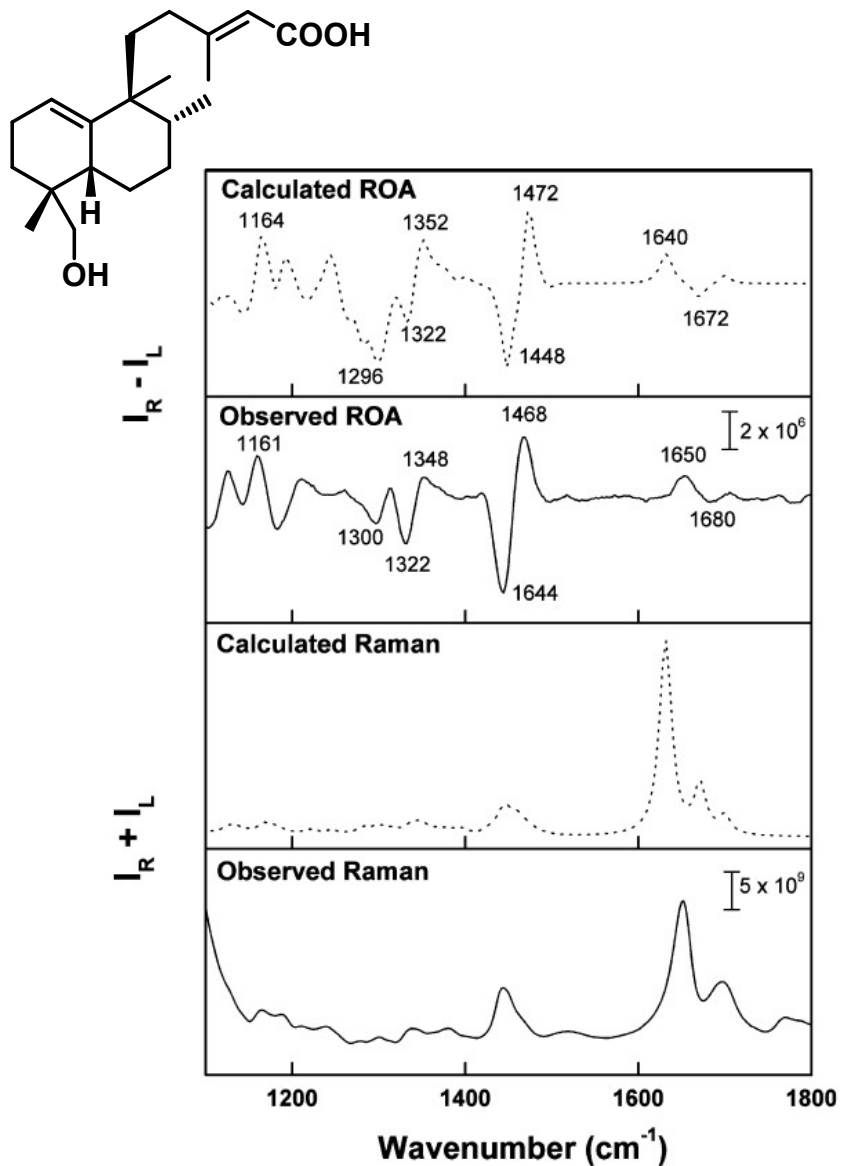
# Some ROA applications



J. Haesler, I. Schindelholz, E. Riguet, C. G. Bochet, W. Hug, *Nature* 2007, 446, 526-529.

# ROA of natural products

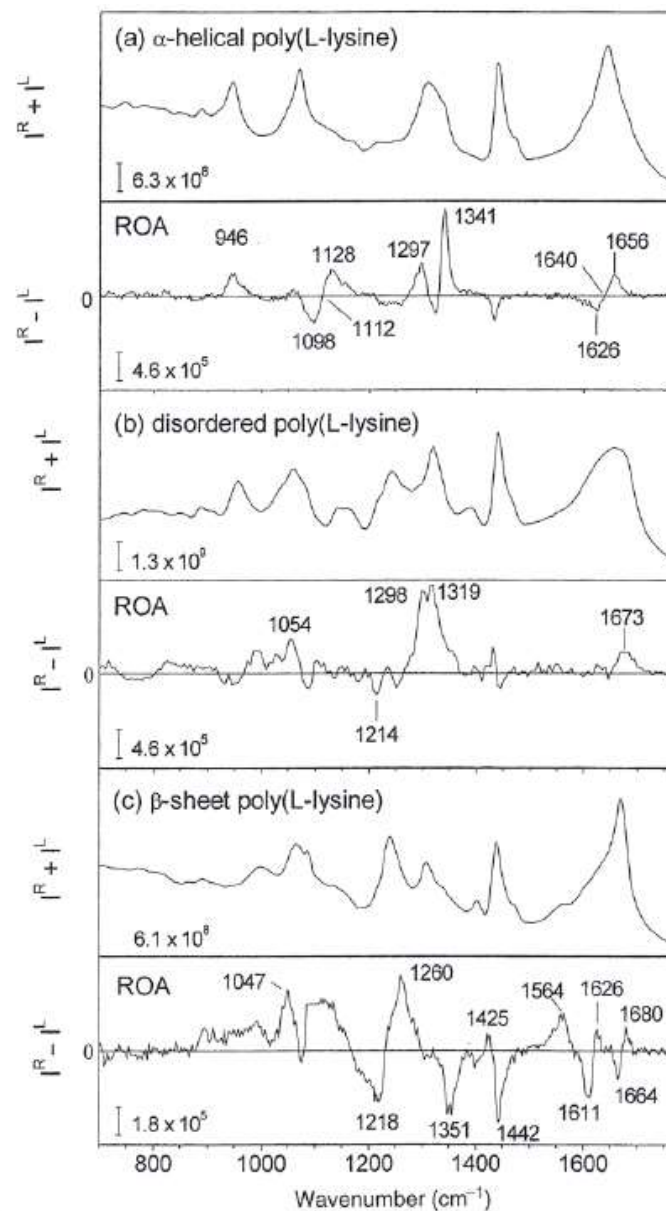
A. F. Monteiro, J. M. Batista, M. A. Machado, R. P. Severino, E. W. Blanch, V. S. Bolzani, P. C. Vieira, V. G. P. Severino, *J. Nat. Prod.* **2015**, *78*, 1451-1455



# ROA of peptides and proteins

## Advantages of ROA for proteins:

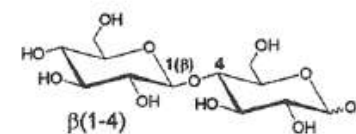
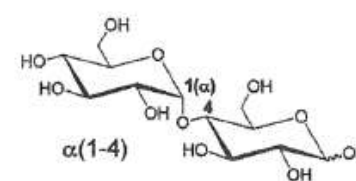
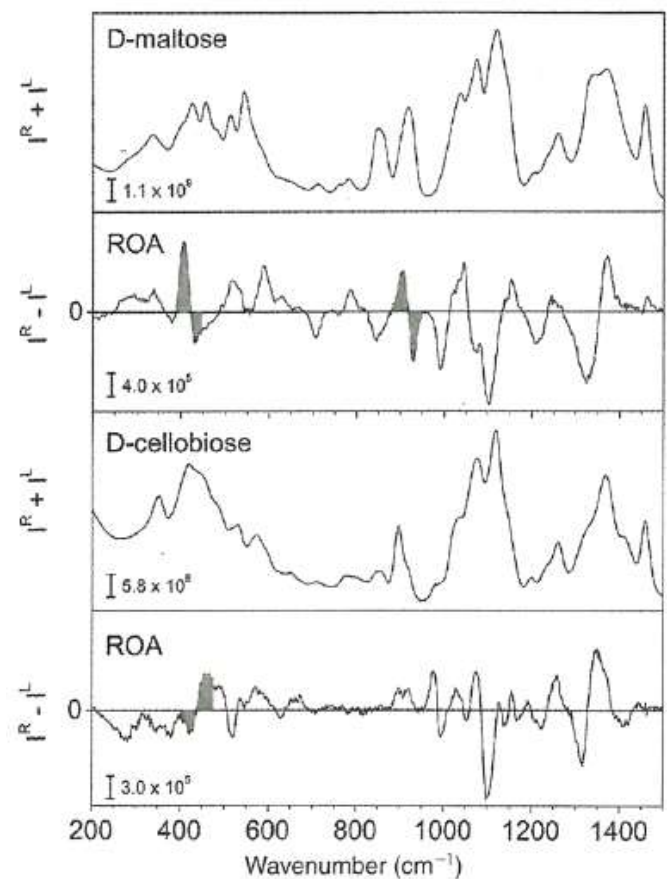
- Water does not affect the measurement
- ROA sensitive to local environment  
→ pattern of secondary structures additive!



Barron and Hecht, „Structure of biomolecules from ROA...“,  
in Berova et al., Comprehensive Chiroptical Spectroscopy,  
Vol 2., Wiley-VCH, 2012

# ROA of carbohydrates

Differentiation between  $\alpha$ - and  $\beta$ -glycosidic linkage

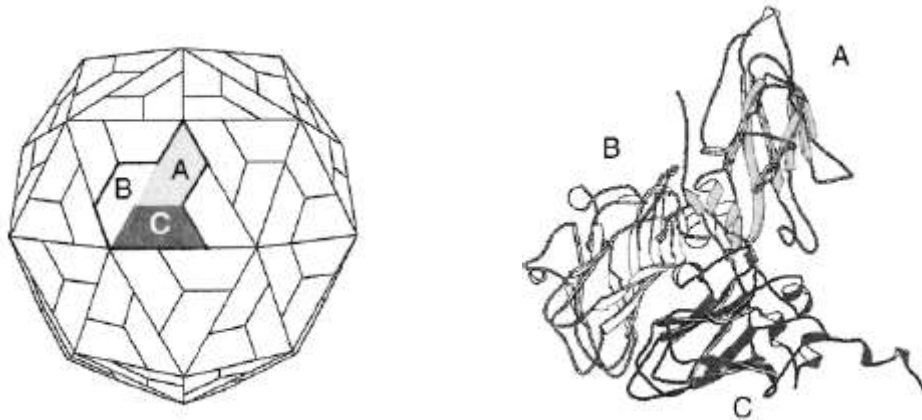


Barron and Hecht, „Structure of biomolecules from ROA...“, in Berova et al., Comprehensive Chiroptical Spectroscopy, Vol 2., Wiley-VCH, 2012

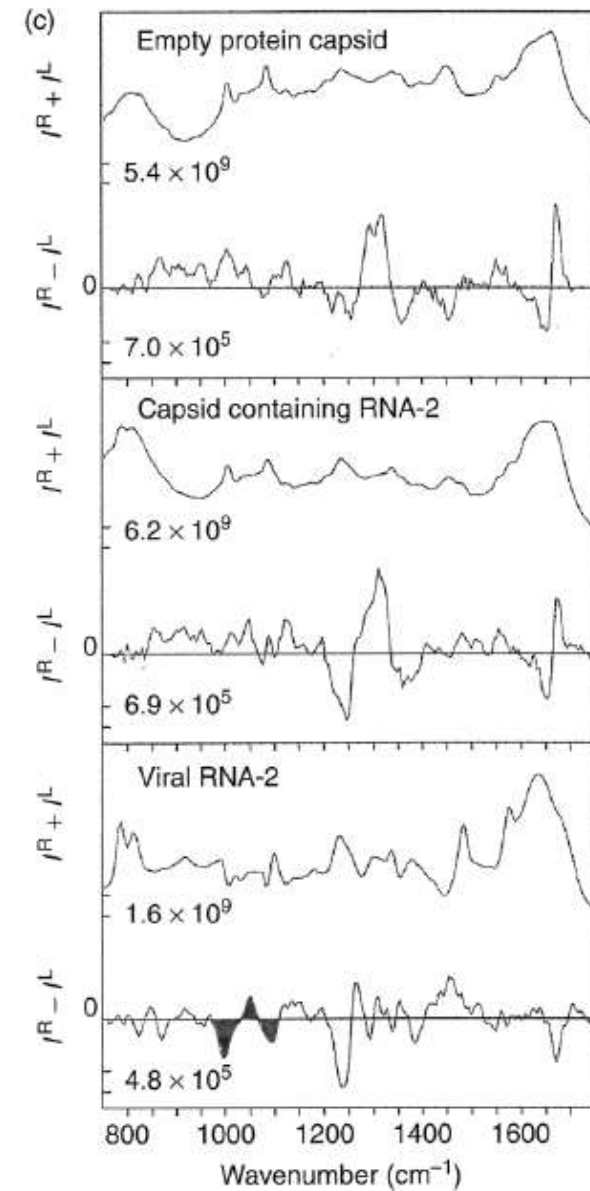
# ROA of virus RNA!

## Cowpea mosaic virus

Protein shell consists of icosahedral shell and RNA



Comparison of empty shell and full virus, i.e. calculation of the different spectrum reveals ROA spectrum of the encapsulated RNA!



*Methods* 2003, 29, 196-209  
*J. Gen. Virol.* 2002, 83, 2593-2600

# Outline of the lecture

---

	<b>Dates</b>	<b>topics</b>	
✓	Monday	Introduction	
✓		Polarization of light	
✓	Tuesday	Theoretical basis of optical activity	
✓		Optical rotation	
✓	Wednesday	Circular dichroism	
✓		Circular dichroism	
✓	Thursday	Vibrational optical activity	
✓		Vibrational optical activity	
	Oct 22?	applications	} your part
	Oct 29?	applications	

---