Chiroptical Spectroscopy

Theory and Applications in Organic Chemistry

Lecture 6: Circular dichroism (exciton coupling)

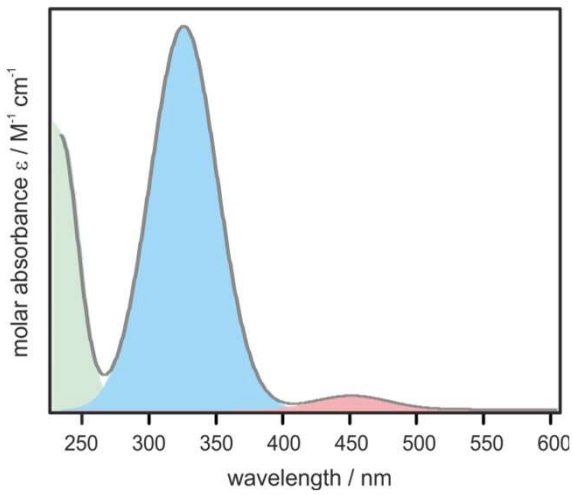
Masters Level Class (181 041)

Block course, october 2020

Exciton coupling

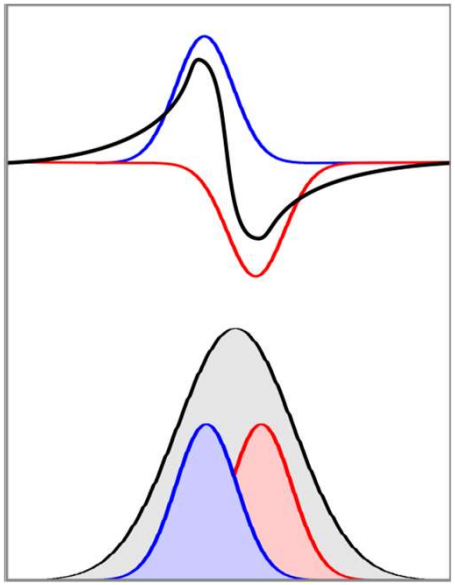
Trivial case:

- One or more separated chromophores, i.e. a carbonyl and a remote C=C group
- Spectrum is superposition of individual contributions

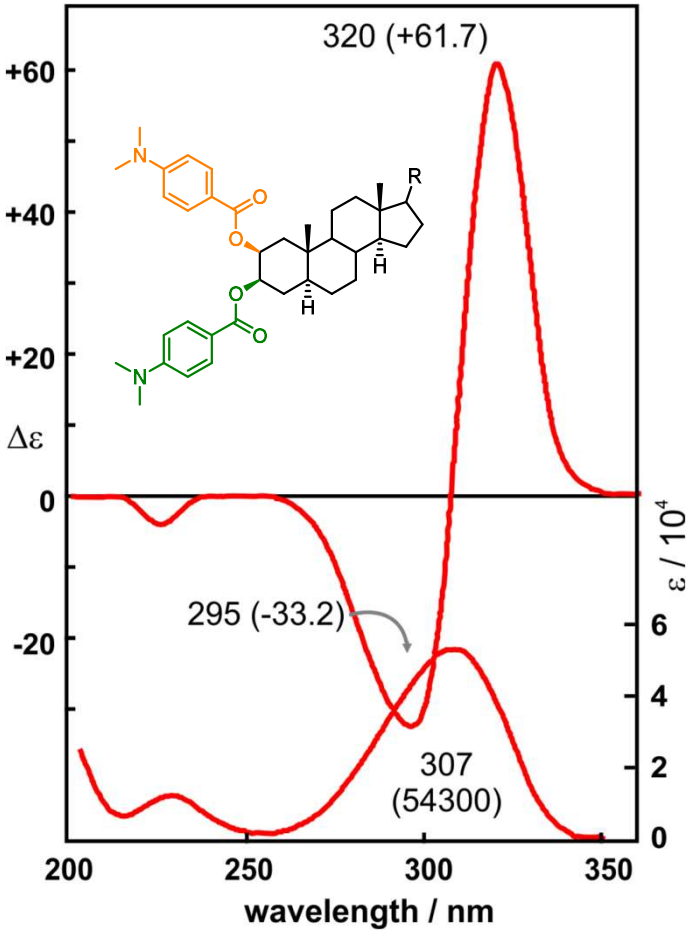


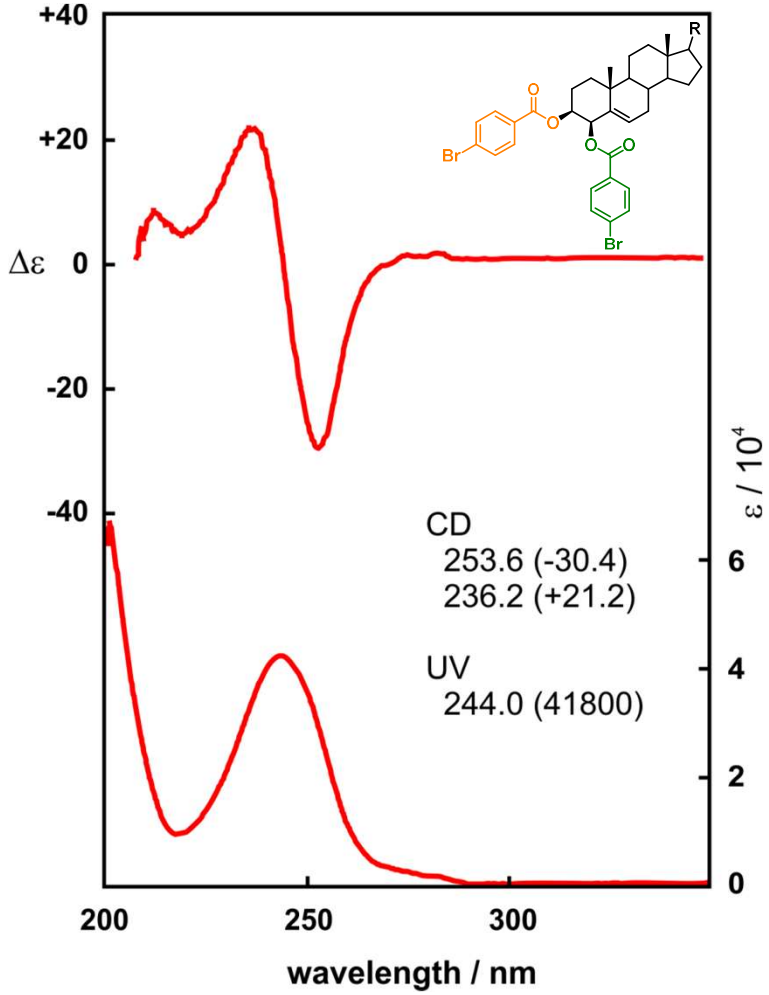
Exciton coupling:

- Simultaneous excitation of two identical chormophores (not conjugated, but spatially close)
- UV band composed of two strong transitions
- CD band shows strong Cotton effect (+/- or –/+ pattern)



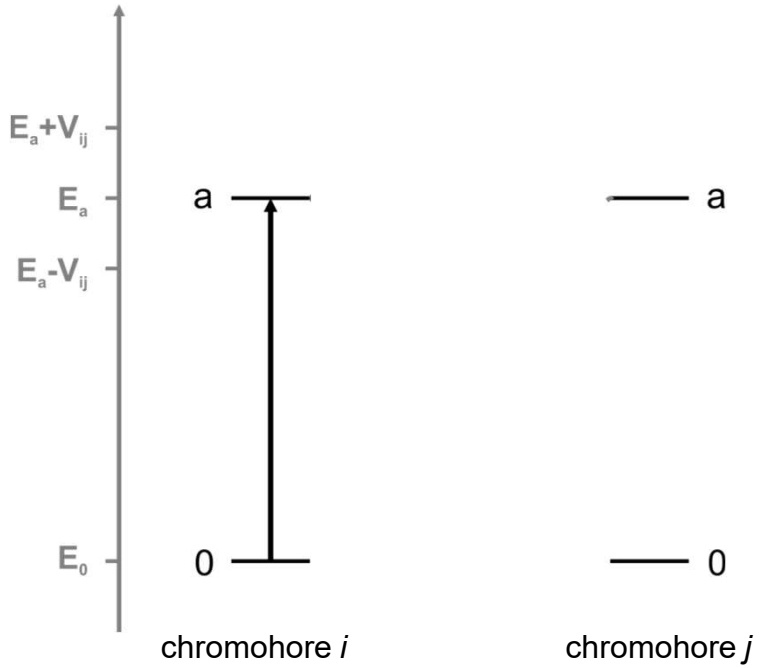
Exciton coupling: Benzoates





Harada et al. *„Electronic CD exciton chirality…“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

Exciton coupling: Not just an empirical rule



α-state

energy $E^\alpha = E_a - V_{ij}$

dipole strength $D^\alpha = 1/2\left(\mu_{i0a} - \mu_{j0a}\right)^2$

rotational strength $R^\alpha = +\frac{1}{2}\pi\sigma_0 \cdot \overrightarrow{r_{ij}}\left(\mu_{i0a} \times \mu_{j0a}\right)$

β-state

energy $E^\alpha = E_a + V_{ij}$

dipole strength $D^\alpha = 1/2\left(\mu_{i0a} + \mu_{j0a}\right)^2$

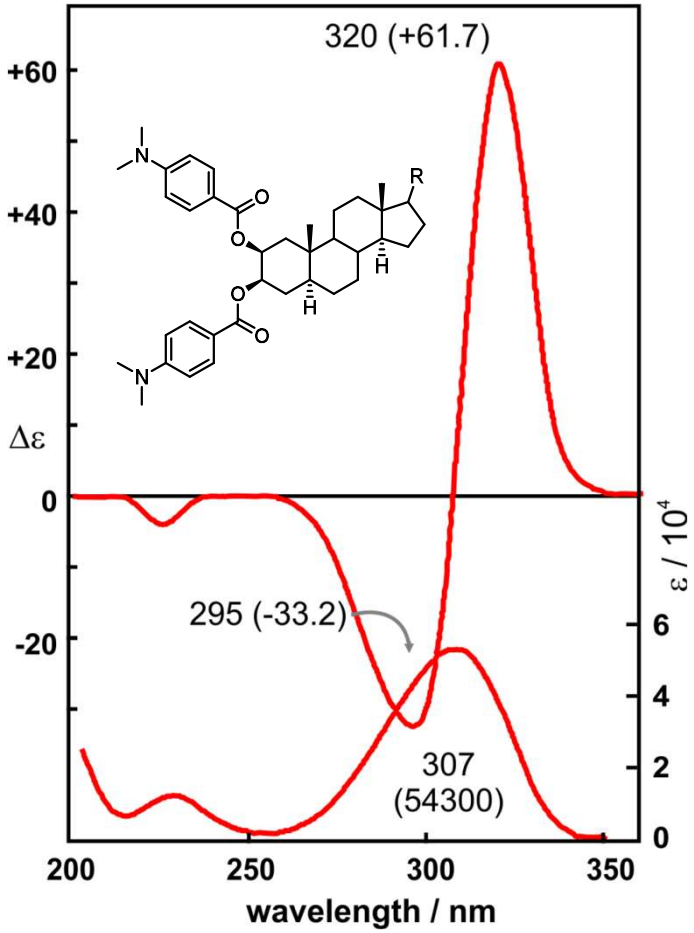
rotational strength $R^\alpha = -\frac{1}{2}\pi\sigma_0 \cdot \overrightarrow{r_{ij}}\left(\mu_{i0a} \times \mu_{j0a}\right)$

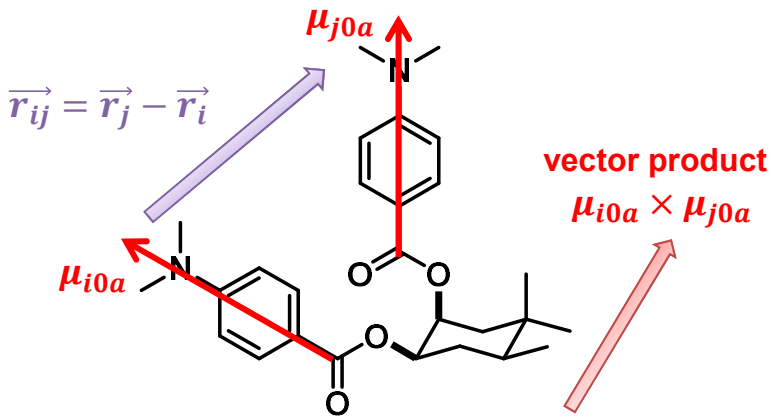
If $V_{ij} > 0$, α-state lower in energy than β-state,
i.e. longer wavelength side features positive sign.

The outcome of the theoretical consideration for **π-π* transitions**:

- Mixing of chromophores *i* and *j* leads to splitting of bands by V_{ij}.
- Rotational strength of α-state is of opposite sign than β-state!
- Rotational strength (approxmiately) depends on distance of edtm (as intra-chromphore magnetic contribution are negligible).

Exciton coupling: Benzoates





$$R^{\alpha} \propto \overrightarrow{r_{ij}}\left(\mu_{i0a} \times \mu_{j0a}\right) \Rightarrow R^{\alpha} > 0$$

$$R^{\beta} \propto -\overrightarrow{r_{ij}}\left(\mu_{i0a} \times \mu_{j0a}\right) \Rightarrow R^{\beta} < 0$$

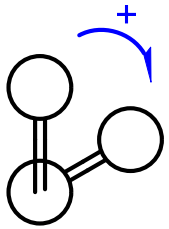
Only mutual spatial orientation of the two dipole moments matter and determine the sign!

Try reversing the directions of μ_{0a} and see yourself!

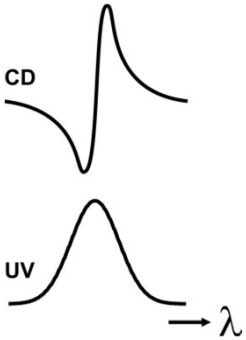
Harada et al. *„Electronic CD exciton chirality…“*, in Berova et al., Comprehensive Chiroptical Spectroscopy, Vol 2., Wiley-VCH, 2012

Exciton coupling: Qualitative definition

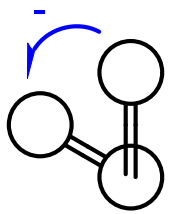
If two EDTM constitute a clockwise screw sence, CD shows positive first at longer wave length and negative second Cotton effect at shorter wavelength, and vice versa.



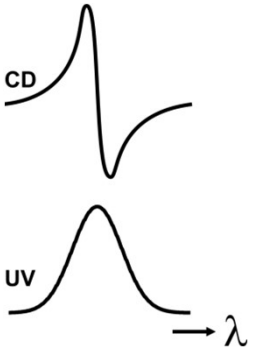
Positive exciton chirality



$$\overrightarrow{r_{ij}} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij} > 0$$

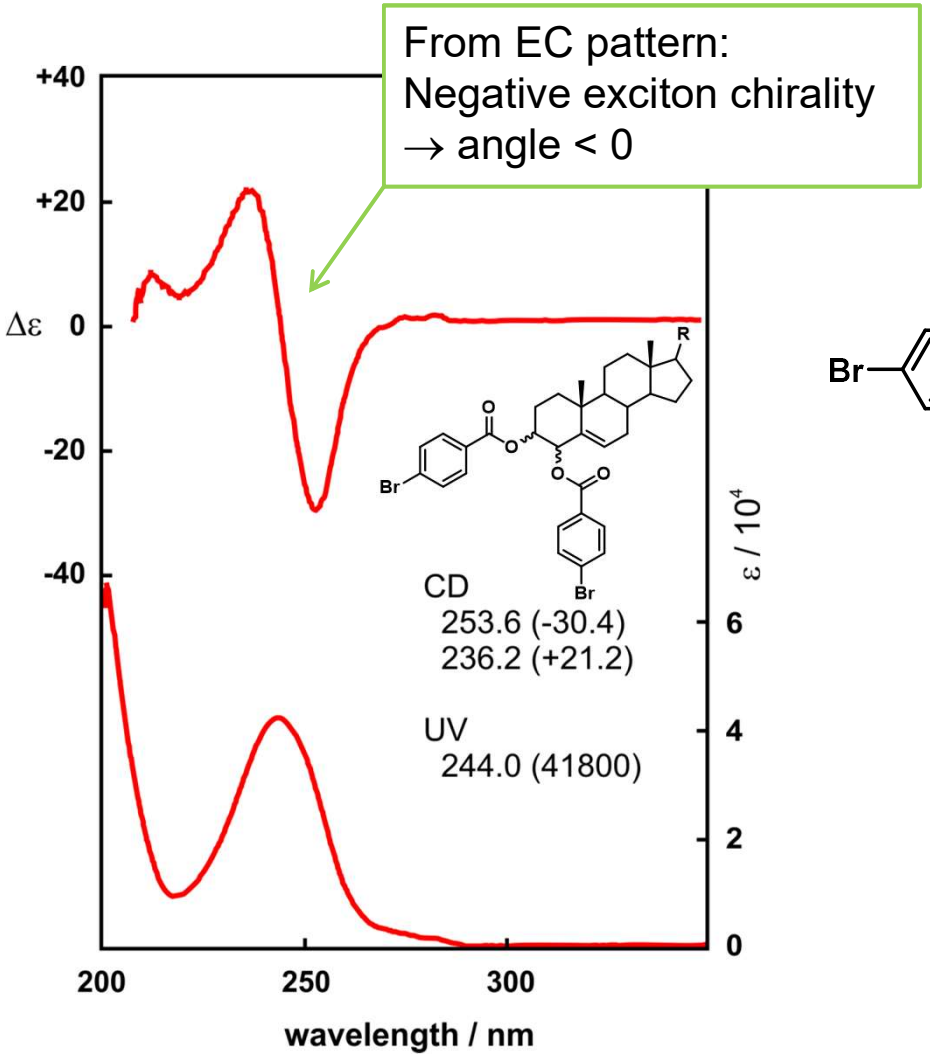


Negative exciton chirality

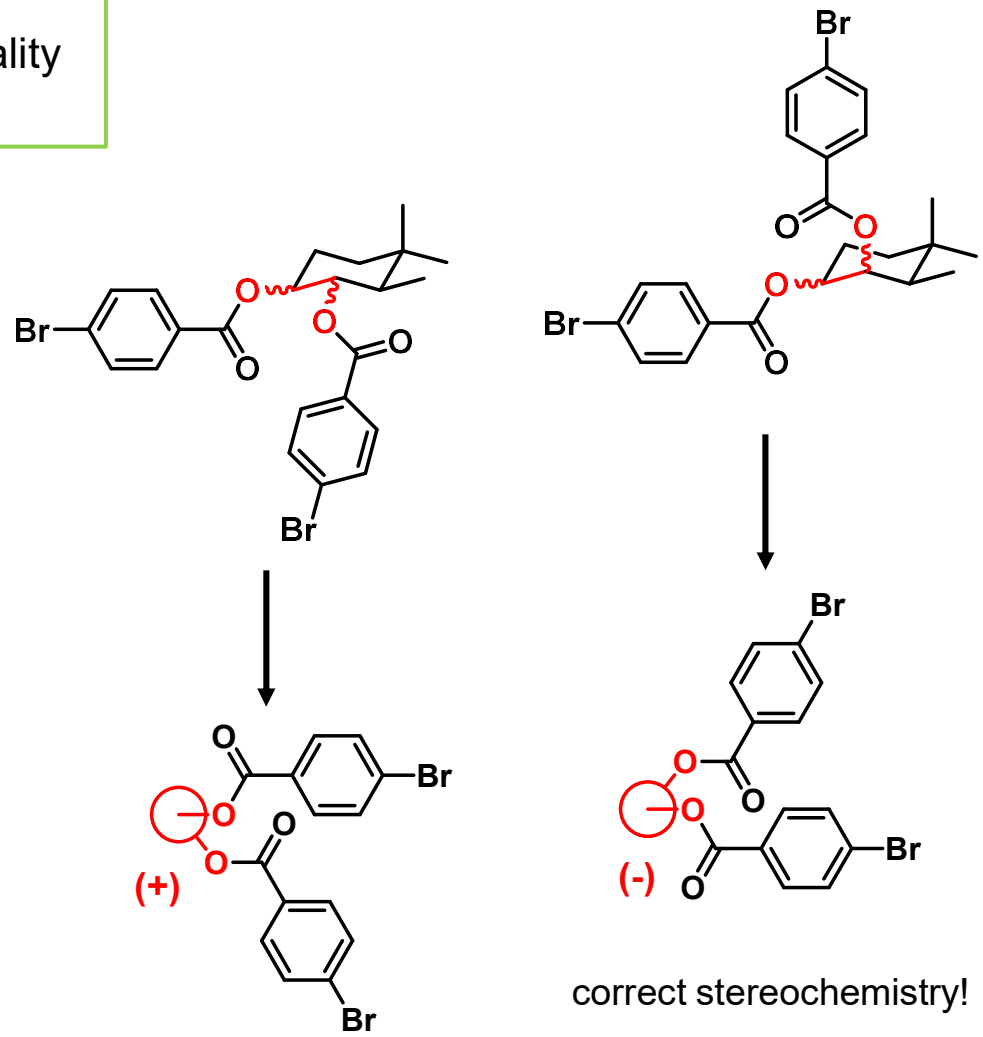


$$\overrightarrow{r_{ij}} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij} < 0$$

Exciton coupling



Harada et al. *„Electronic CD exciton chirality…“*, in Berova et al., Comprehensive Chiroptical Spectroscopy, Vol 2., Wiley-VCH, 2012

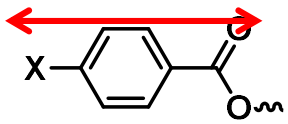


correct stereochemistry!

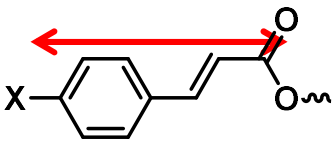
Advantage of benzoates: edtm almost parallel to C-O of alcohol
→ Benzoate EC directly reflects angle of diols!

Useful chromophores for EC

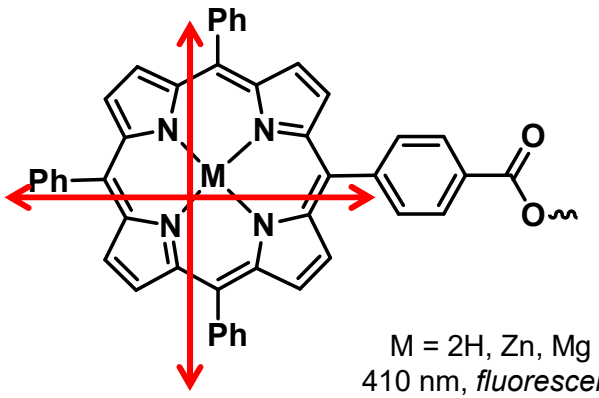
Chromophores for OH groups:



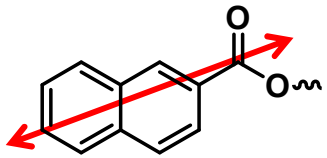
X = H, Br, OMe, NMe_2
230-310 nm



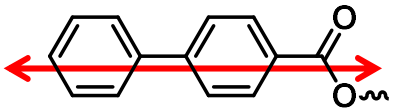
X = OMe, NMe_2
300-360 nm



M = 2H, Zn, Mg
410 nm, *fluorescent*



235 nm, *fluorescent*



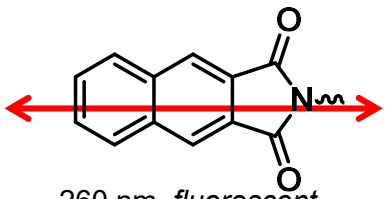
270 nm, *fluorescent*

Only para-substituted phenyl has edtm parallel to C-CO_2R axis, ortho and meta not!

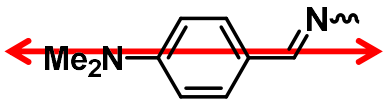
TPP-COOH shows very strong band at 410 nm, so that even microanalysis is possible!

Useful chromophores for EC

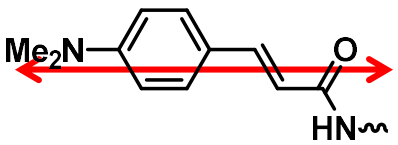
For NH_2 groups:



260 nm, *fluorescent*

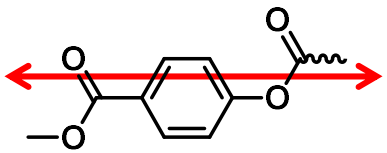


305 nm

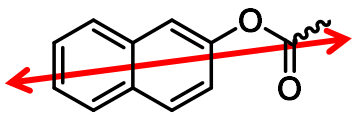


350 nm

For –COOH groups

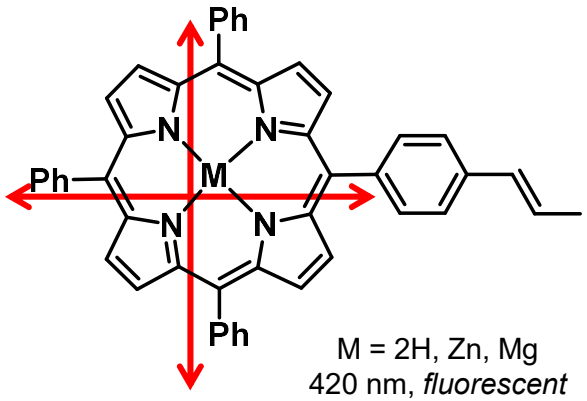


230 nm, *fluorescent*

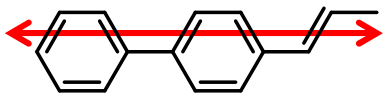


260 nm

For –C=C – groups

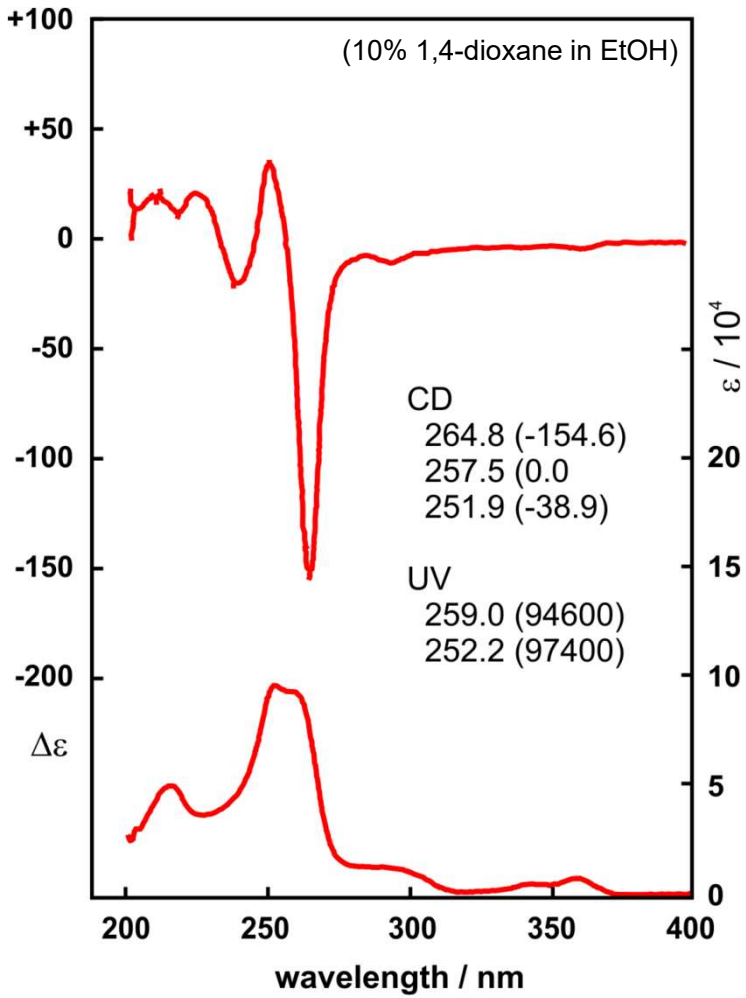


M = 2H, Zn, Mg
420 nm, *fluorescent*



280 nm, *fluorescent*

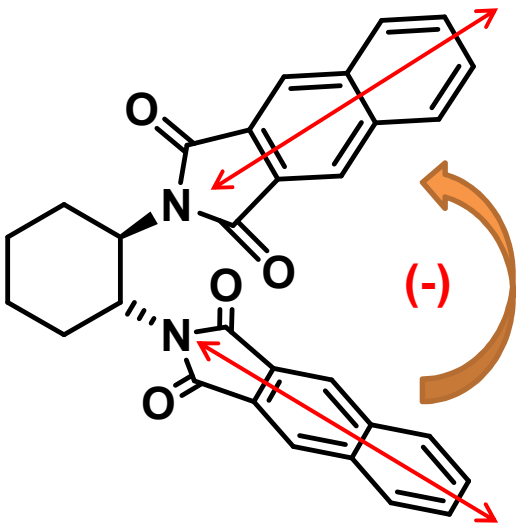
Exciton coupling: Amines



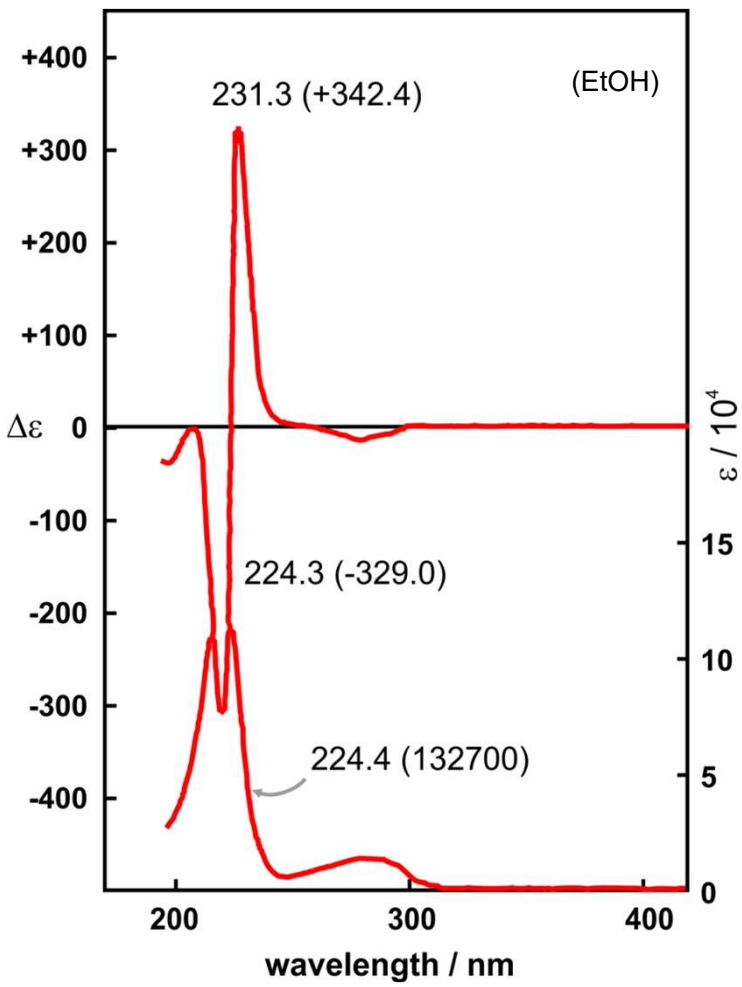
Harada et al. *„Electronic CD exciton chirality…“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

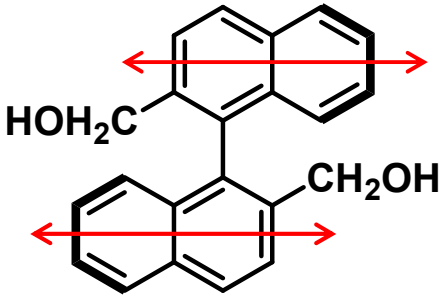
Intramolecular charge-transfer band of benzamides:

polarized along long axis of chormophore



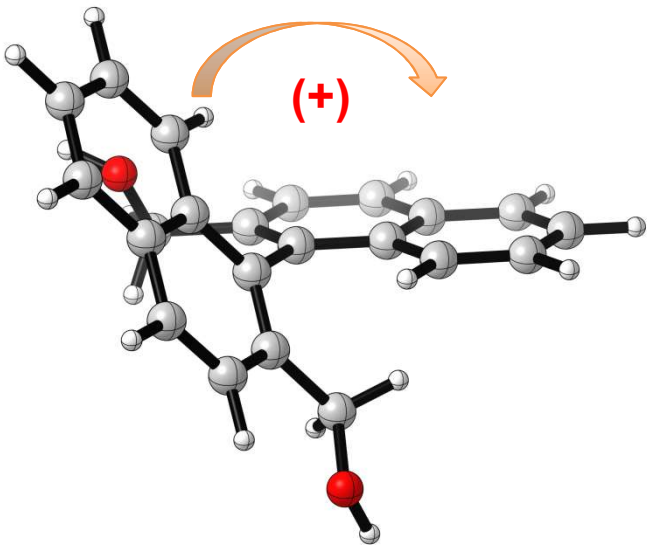
Exciton coupling: Binaphthyl systems





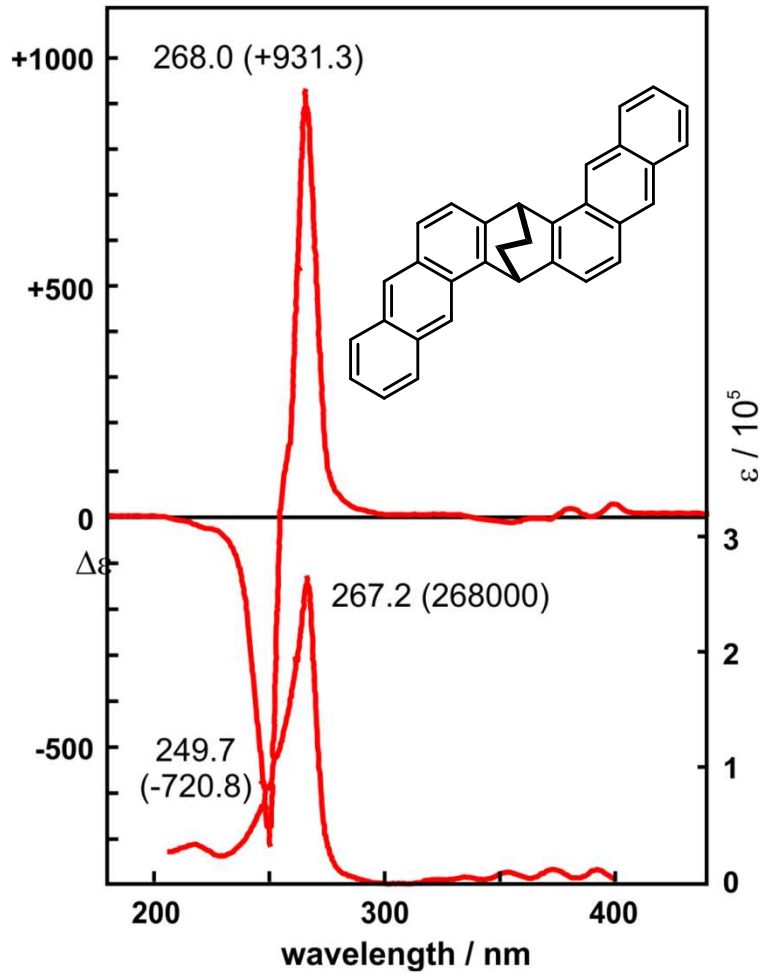
positive exciton chirality

→ **positive angle** between naphthyl planes

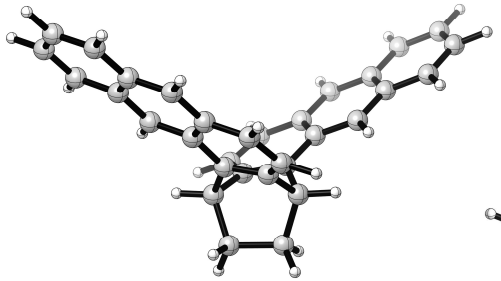


Harada et al. *„Electronic CD exciton chirality…“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

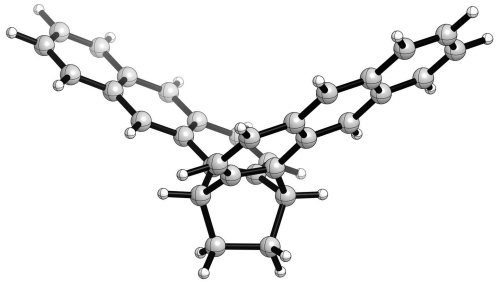
Exciton coupling

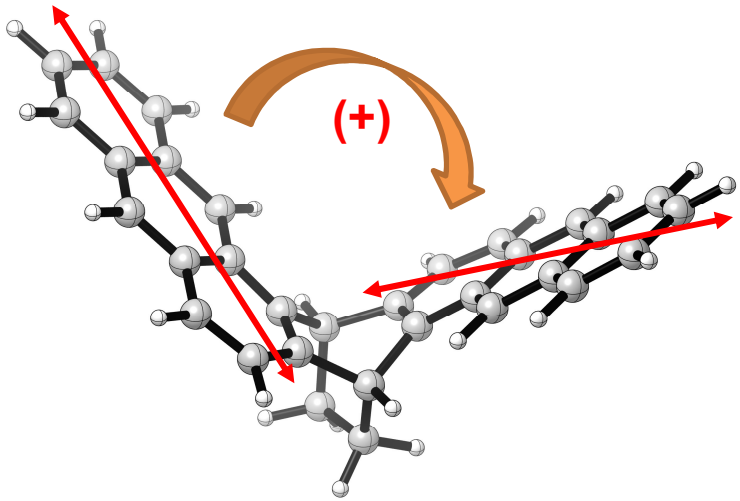


Stereoisomer A



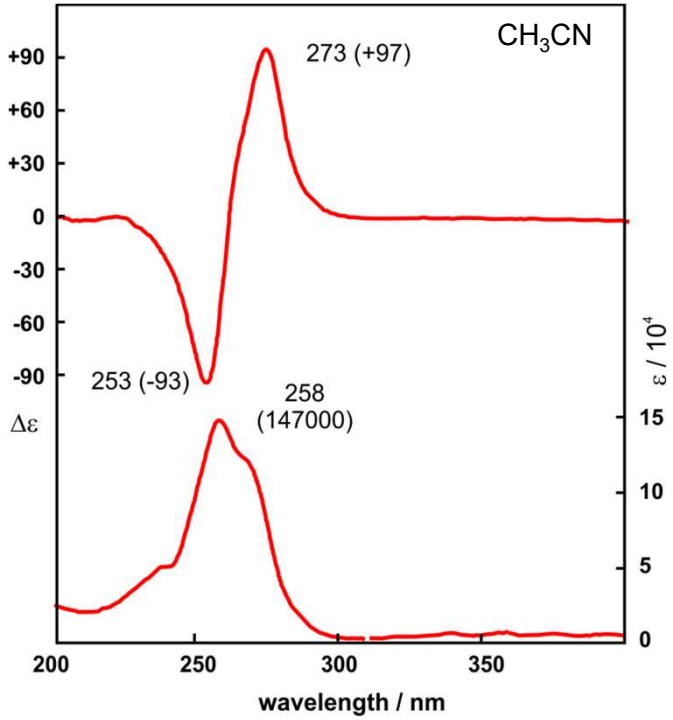
or stereoisomer B?

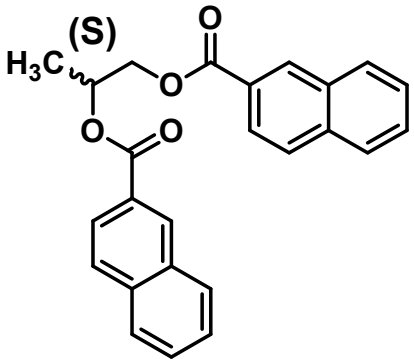


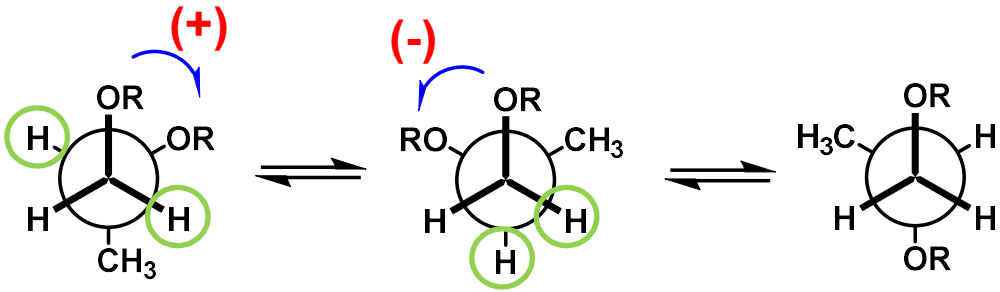


Harada et al. *„Electronic CD exciton chirality…“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

Exercise on exciton coupling: Determination of AC of diols



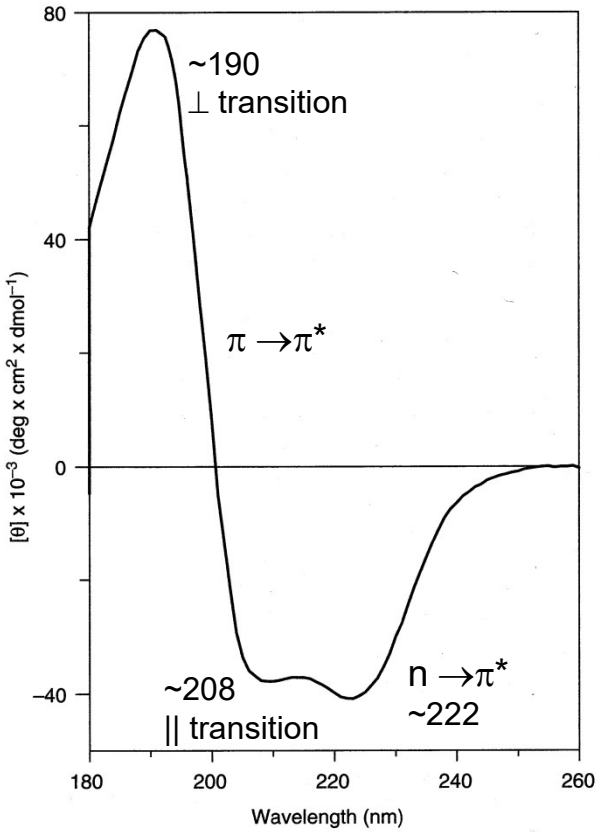




Additional measurement of ^{1}H-coupling constants necessary to confirm the preferred conformation before AC assignment.

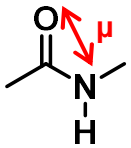
Harada et al. *„Electronic CD exciton chirality…“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

Peptide secondary structures: Applications in biophysical chemistry

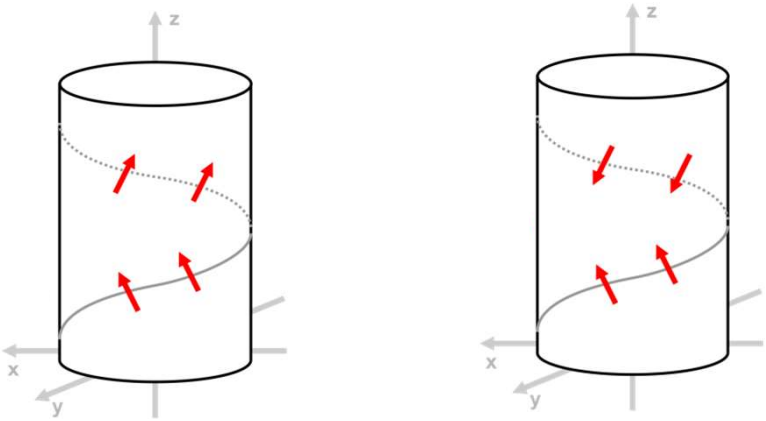


CD spectrum of poly(L-Glu) at pH 4.3:

Characteristic CD pattern of α-helical structure



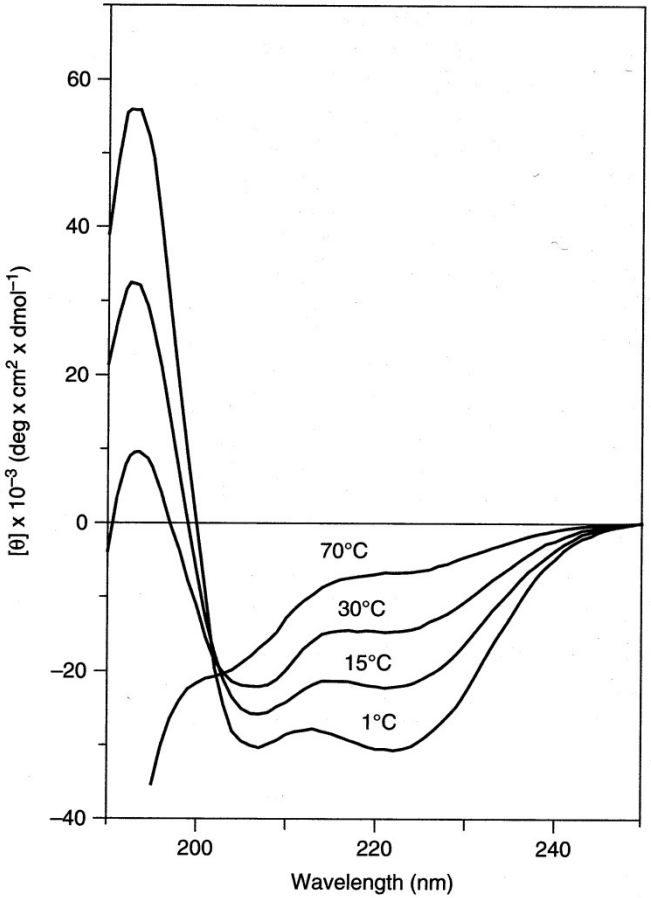
μ_e of K-band



G. Snatzke, *Angew. Chem. Int. Ed.* **7** (1968) 14-25

Toniiolo et al. *„Electronic CD of peptides“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

Peptide secondary structures: Applications in biophysical chemistry



Toniiolo et al. *„Electronic CD of peptides“*,
in Berova et al., Comprehensive Chiroptical Spectroscopy,
Vol 2., Wiley-VCH, 2012

Main applications in biophysical chemistry:

1) Monitoring structural changes

Example of N$^{\alpha}$-acetylated 17mer consisting of L-Ala, L-Glu and L-Lys (pH 7)

Thermal degradation
from α-helical to unordered structure

2) Drug binding studies

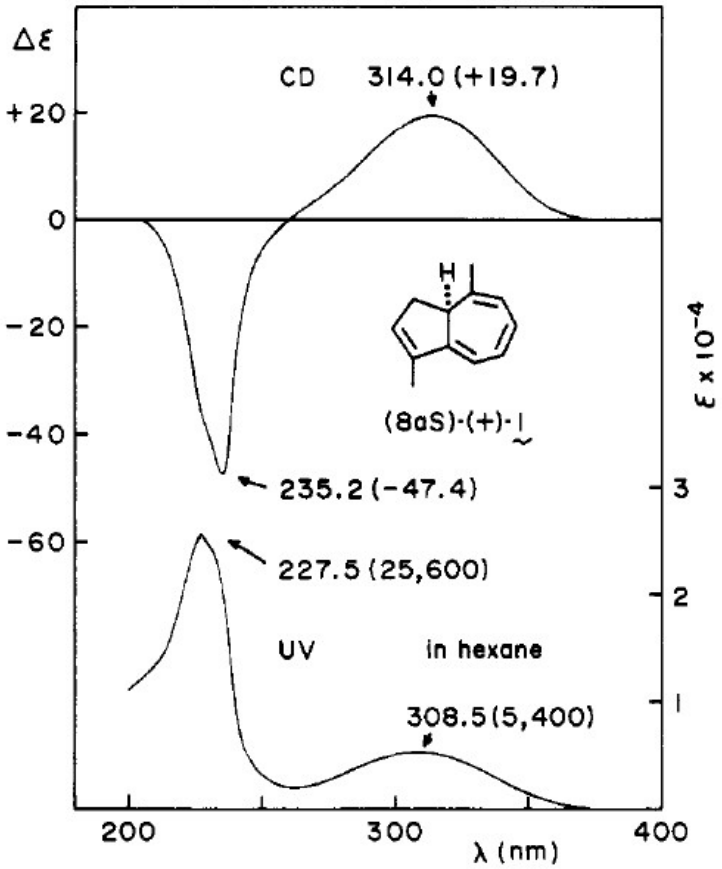
Databases and component analysis software are available to quantify the %-contributions of individual secondary structures from their characteristic model spectra!

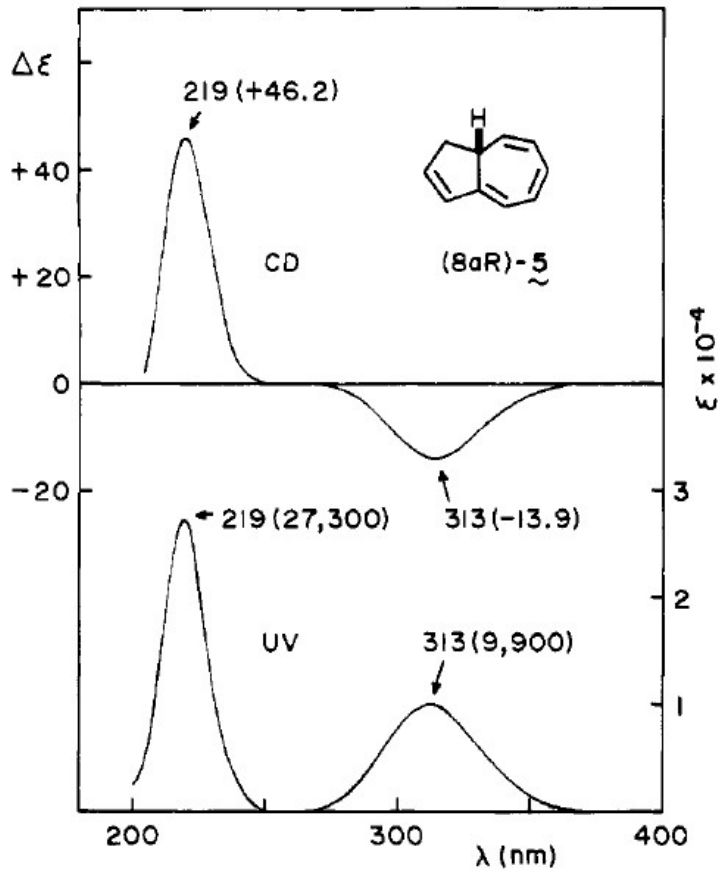
From MO models to calculations

Harada et al, *J. Am. Chem. Soc.* **1985,** *107,* 423-428

CD response mainly arising from strongly twisted tetraene system

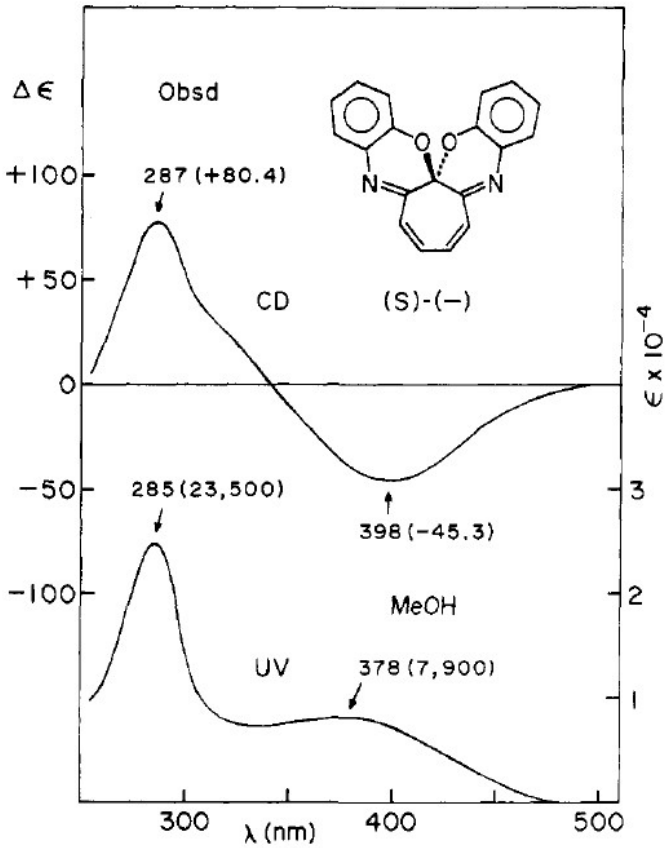
- CD can be calculated in π-approximation: SCF-CI-DV MO method

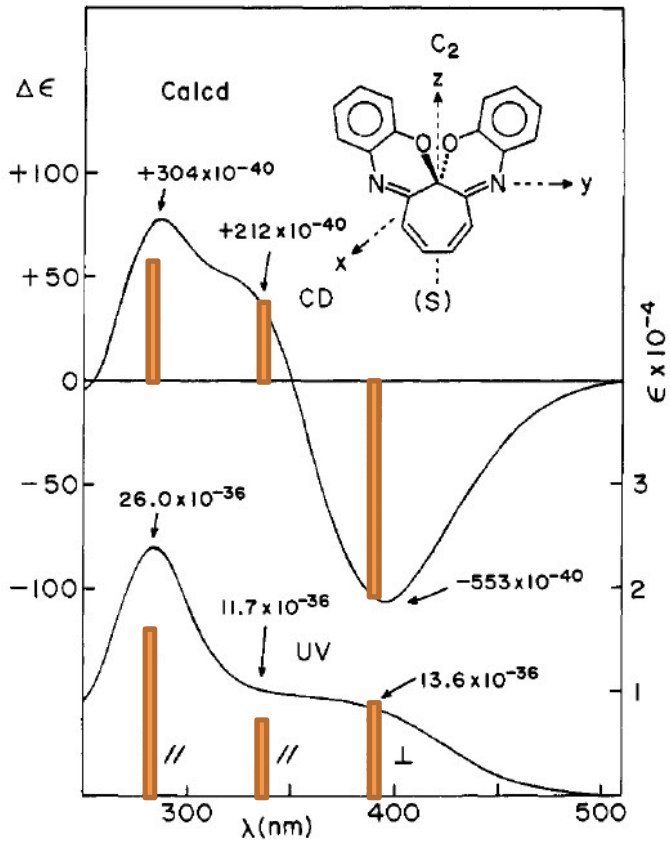




From MO models to calculations

Harada et al, *J. Am. Chem. Soc.* **1987,** *109,* 1661-1665





Calculation predicts rotational strength and dipole strength ($D_i = \frac{3h^{\ 2}}{8\pi^2\tilde{\nu}m_e c} \cdot f_i$) in cgs units

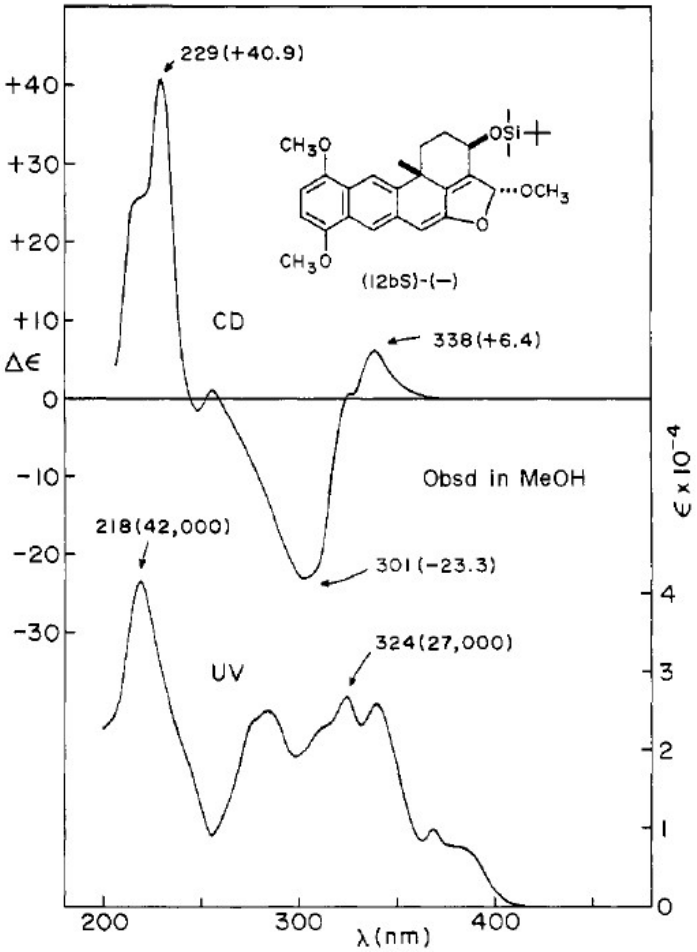
- Calc. yields stick spectra which need to be broadened by assigning Gaussian band shape

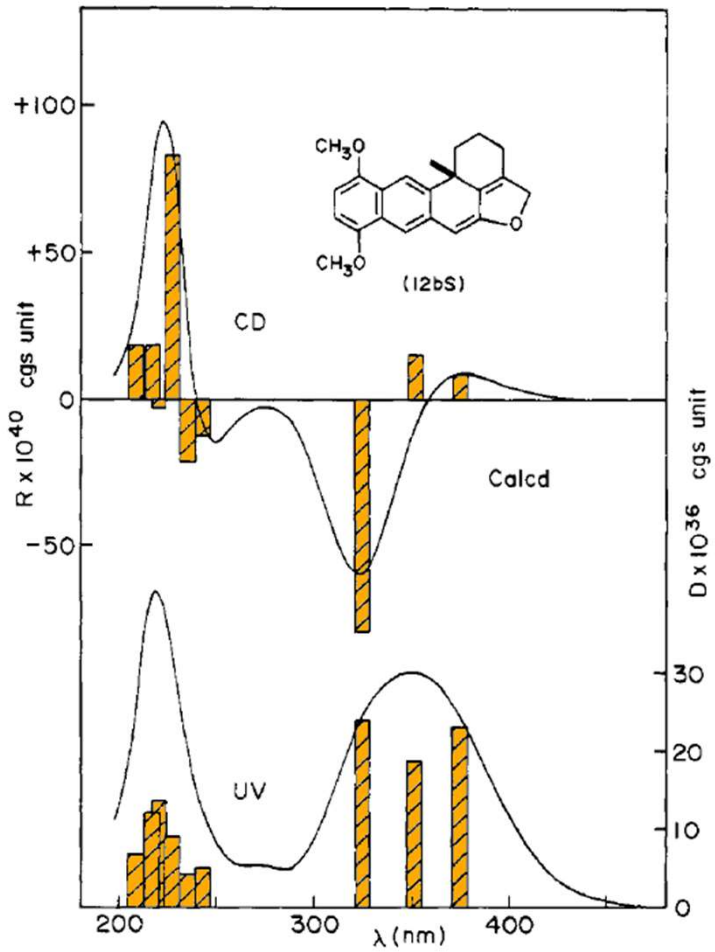
From MO models to calculations

Harada et al, *J. Am. Chem. Soc.* **1989,** *111,* 5668-5674

Even in presence of several functional groups,

the π-system can be shown to dominate the CD spectrum

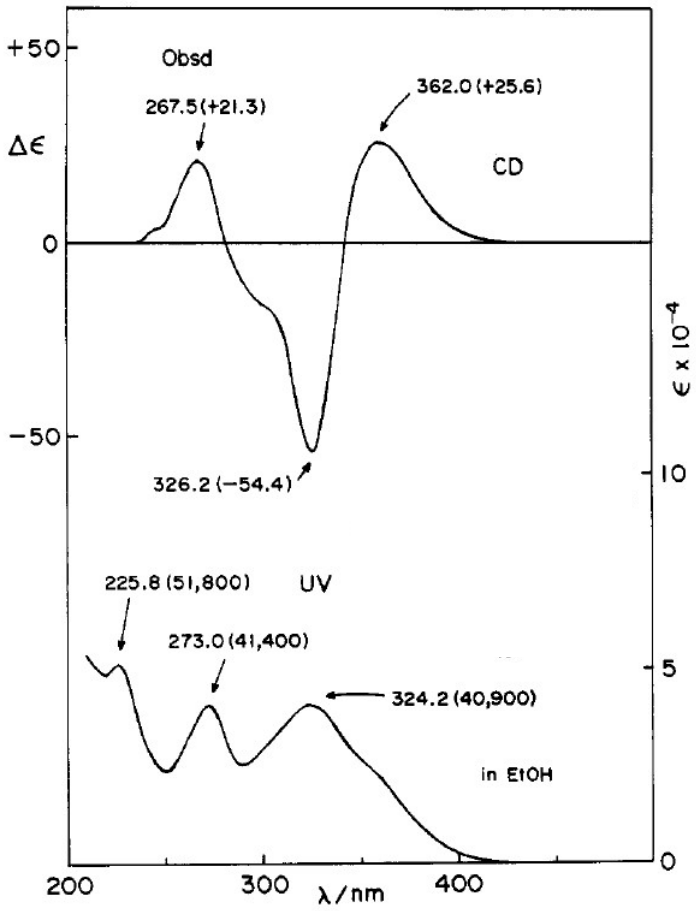




Reassignments of AC based on calculations

Harada et al, *J. Am. Chem. Soc.* **1992,** *114,* 7687-7692

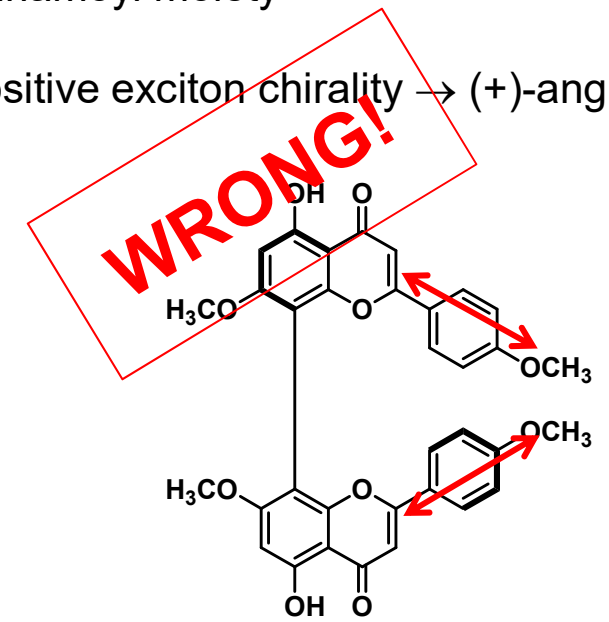
Assignment of AC based on exciton coupling: (aS)



Assumption for exciton coupling analysis:

UV transition at 324 nm arises from p-methoxy cinnamoyl moiety

Positive exciton chirality → (+)-angle



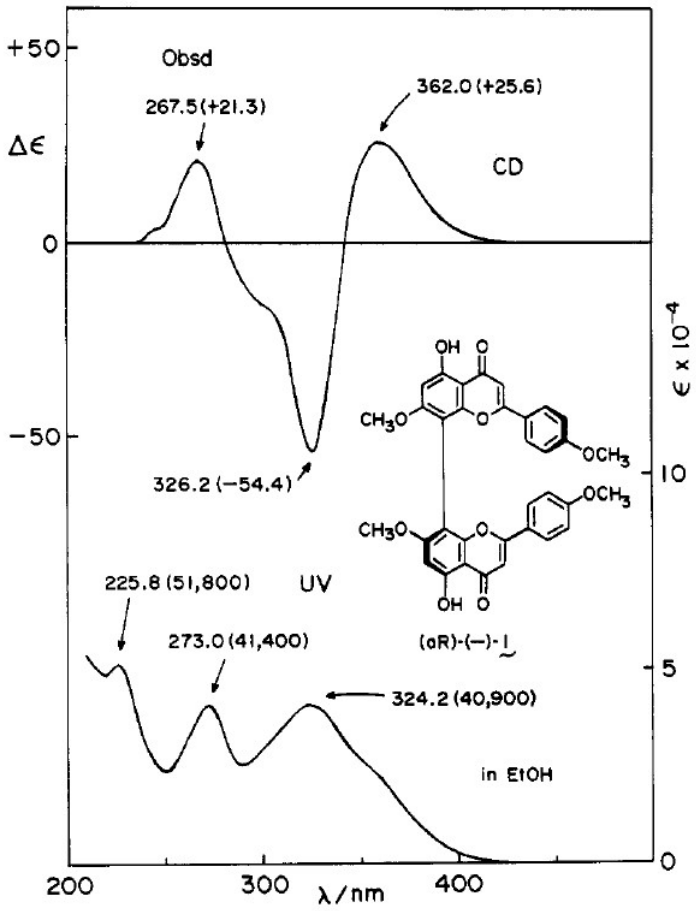
- Orientation of edtm difficult to determine
- π-system actually extended over entire fragment

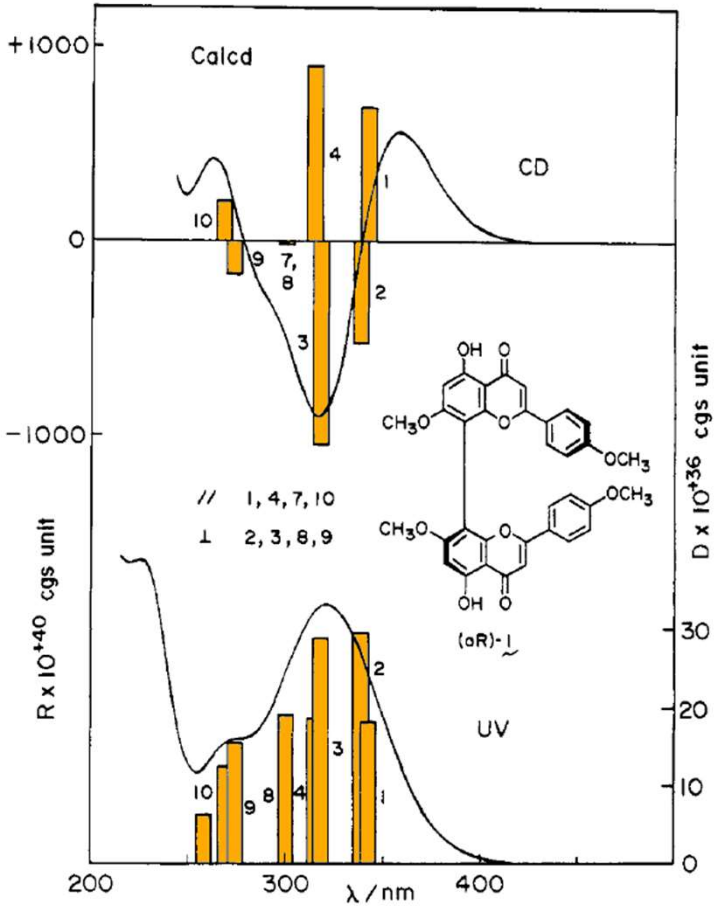
Reassignments of AC based on calculations

Harada et al, *J. Am. Chem. Soc.* **1992,** *114,* 7687-7692

Assignment of AC based on exciton coupling: (aS)

based on calculations: (aR)!

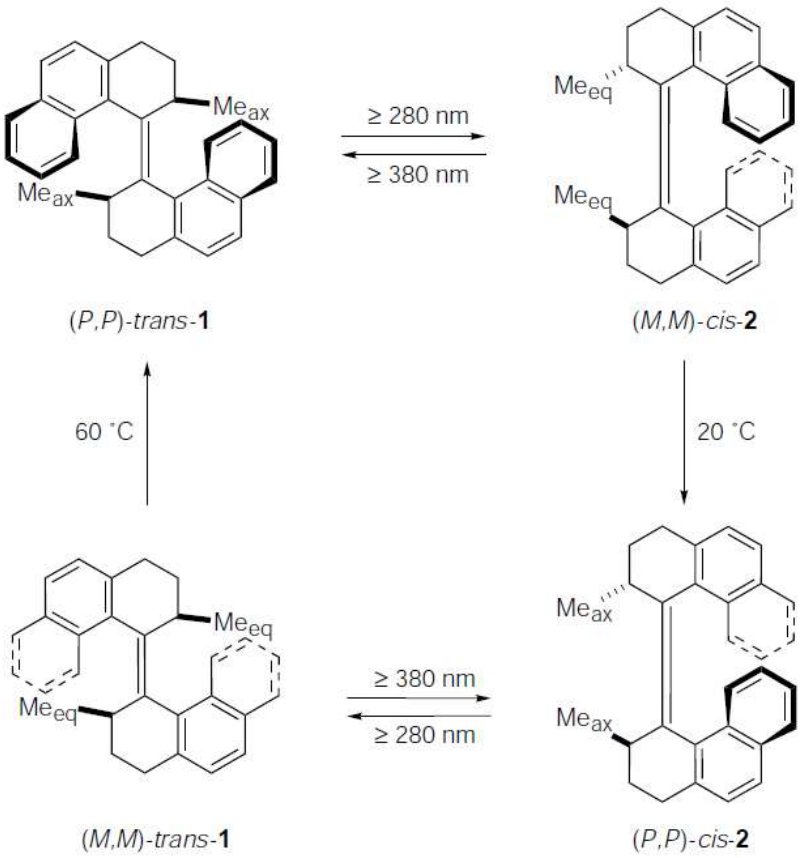


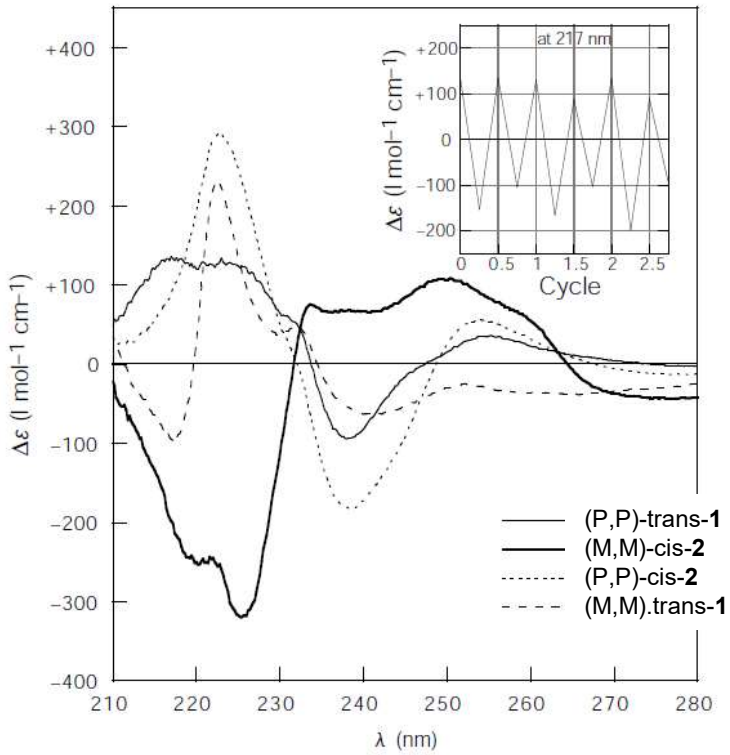


Supramolecular chemistry: Characterization of a molecular motor

Koumura et al. *Nature* **401** (1999) 152-155

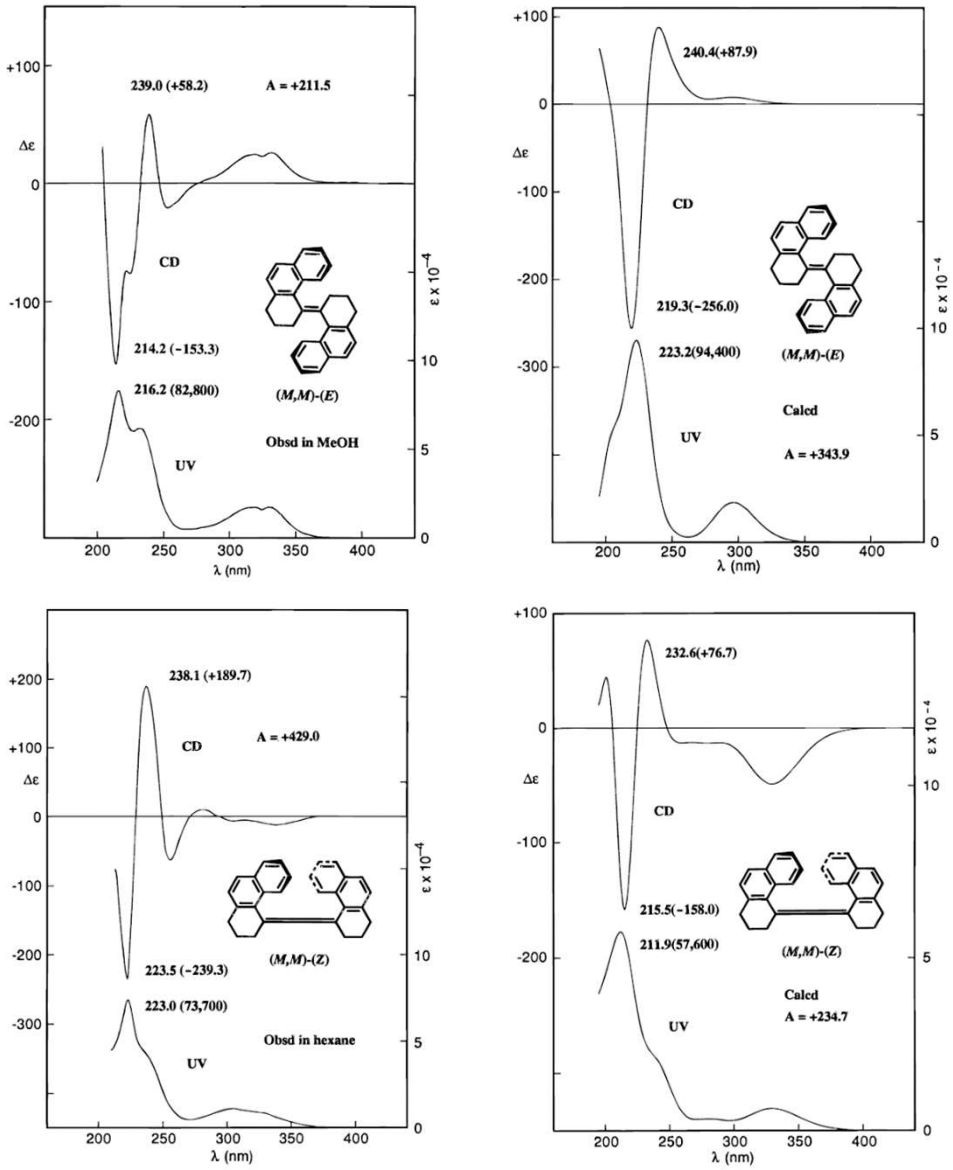
Unidirectional molecular motors designed by Feringa and co-workers show distinct CD spectra for each switching state





Supramolecular chemistry: Characterization of a molecular motor

Harada et al. *J. Am. Chem. Soc.* **1997**, *119*, 7241-7248



Configurations could be assigned to switching states by comparison with calculated CD spectra

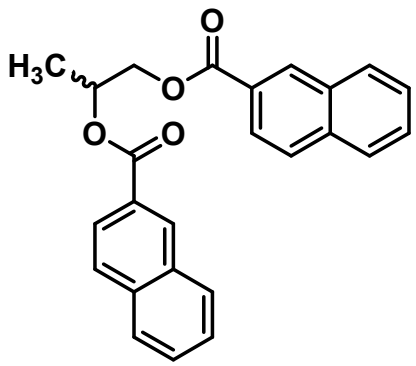
Computing chiroptical spectra

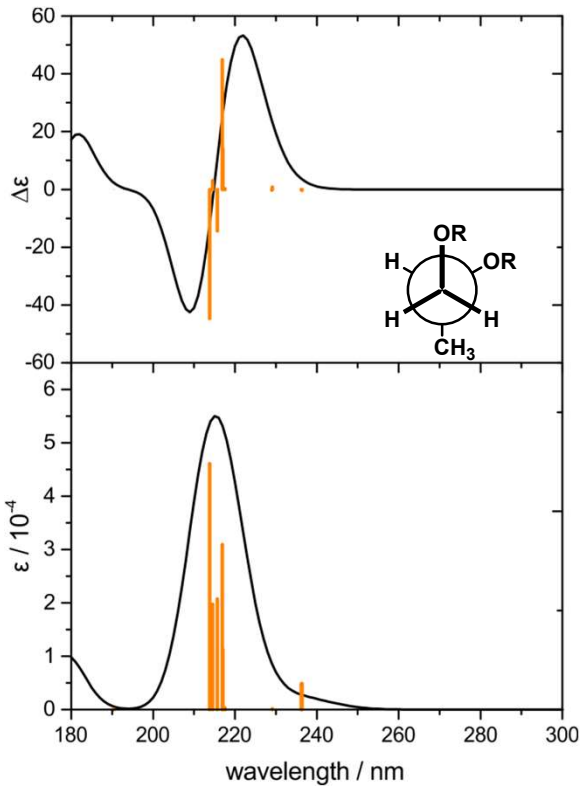
Today‘s standard: **Time-dependent DFT**

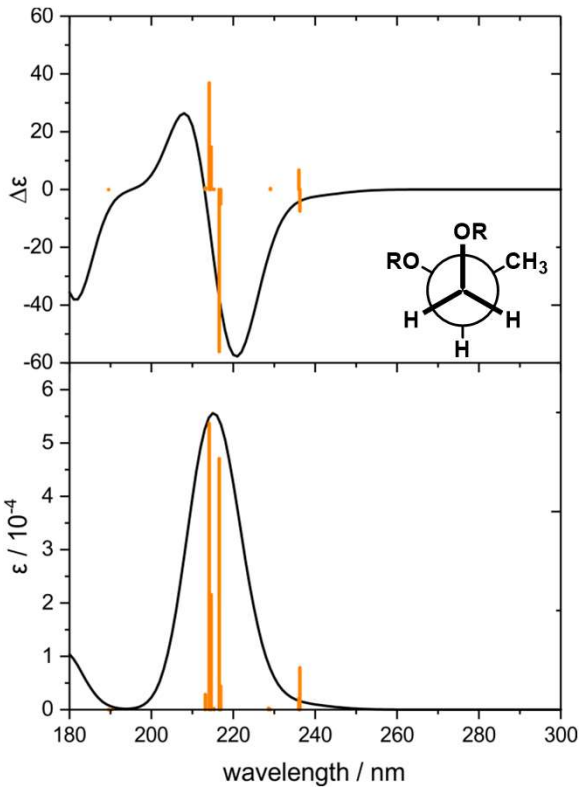
… implemented in all major software packages

… computes vertical excitations

… difference to previous examples: not just π-electrons!

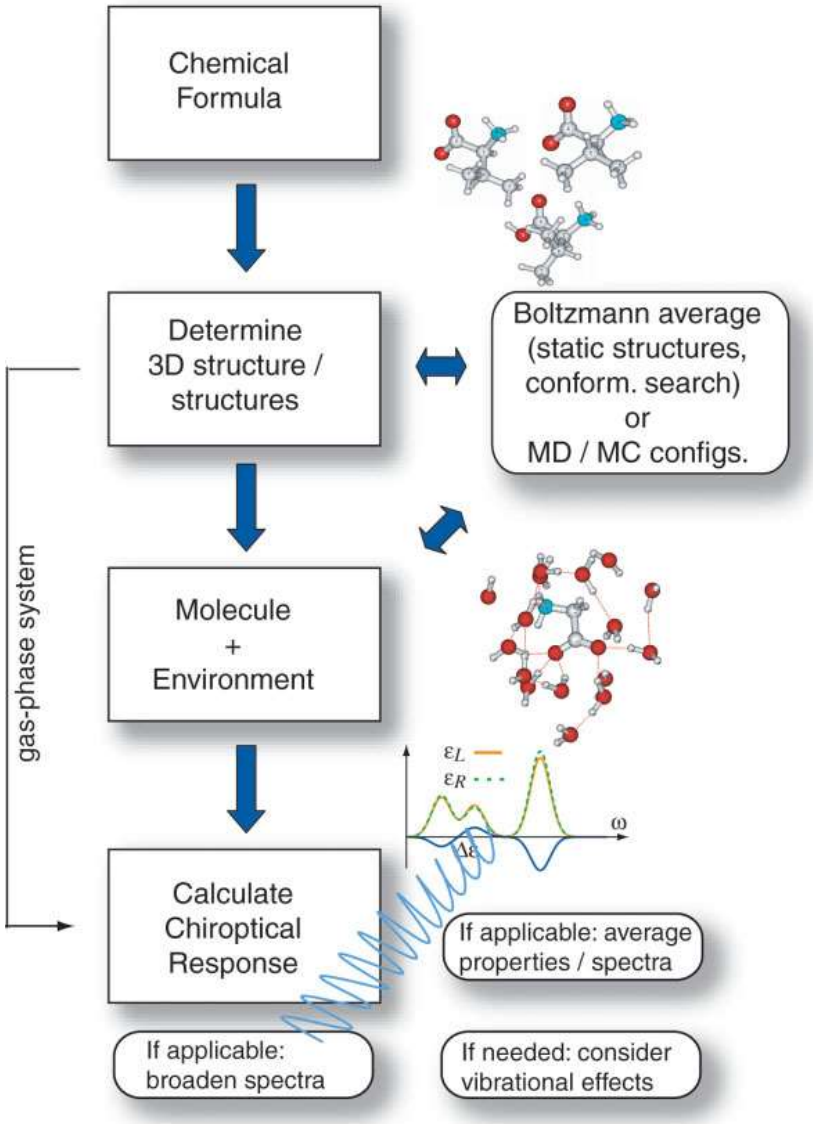






Computing chiroptical spectra

J. Autschbach, *Chirality* **21** (2009) E116-E152
G. Pescitelli, T. Bruhn, *Chirality* **28** (2016) 466–474



If the molecules can adopt many different conformations, their individual spectra need to be averaged using Boltzmann statistics:

$$p = \frac{e^{-kT\Delta E_n}}{\sum_n e^{-kT\Delta E_n}}$$

Important:

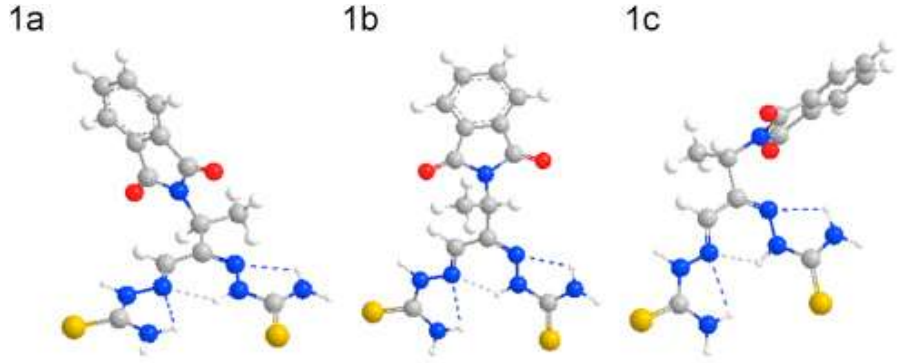
Getting good single conformer energies ΔE!

Note:

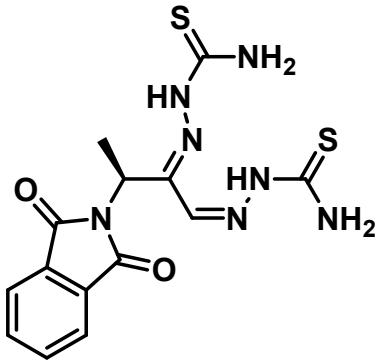
Computed excitation energies often too high, therefore energy axis often empirically scaled to allow better comparison!

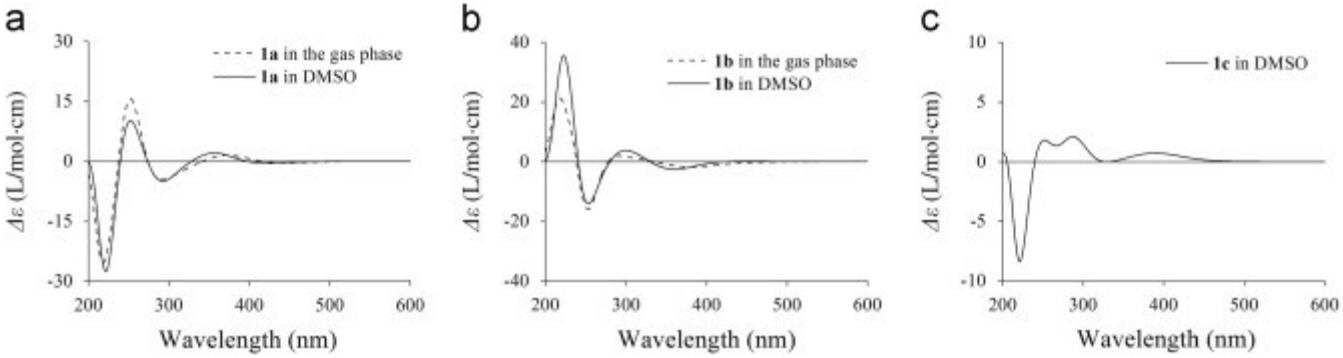
An everyday example

Li et al., *Acta Pharmaceutica Sinica B*, **4** (2014) 167-171

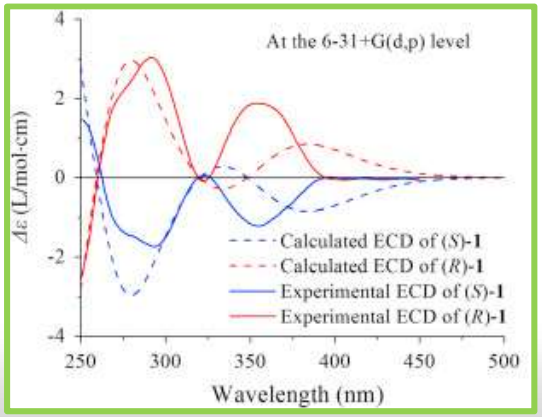


63.0% 15.6% 10.6%

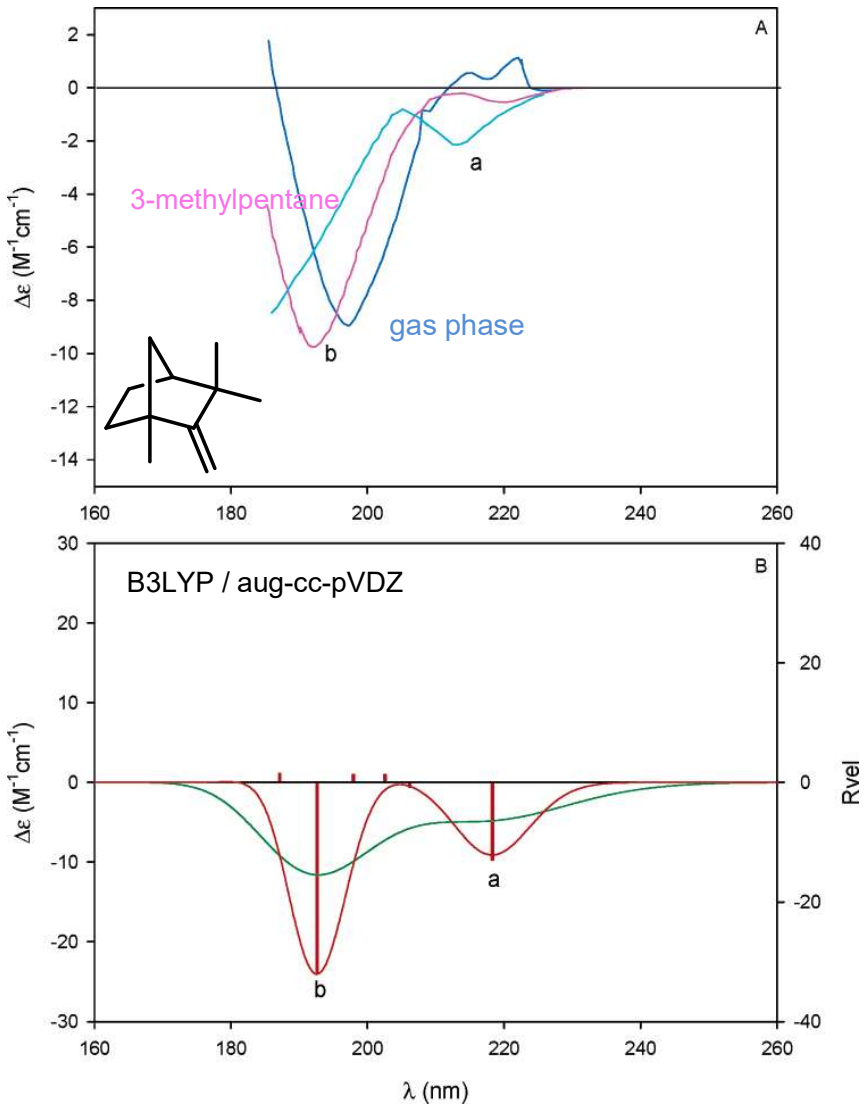




Boltzmann averaging



Influences on the quality of agreement



Theoretical level of calculation

Solvent effects:

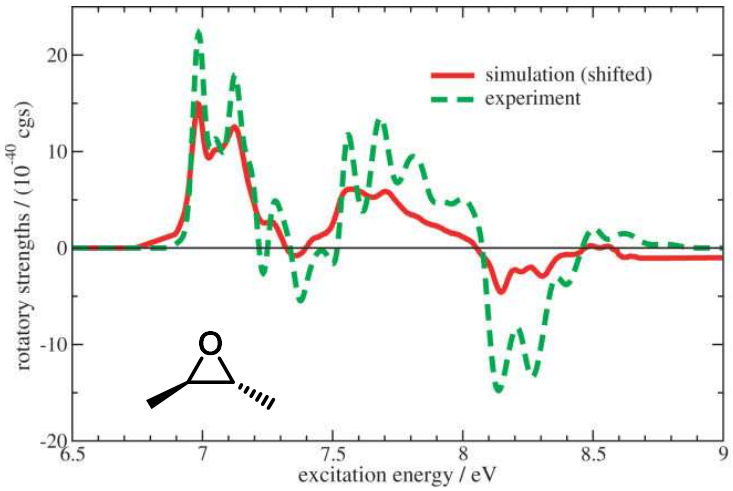
- Shifting of excitation energies (polar vs. non-polar)
- Explicit solvation (affects conformations or excitation energies)

Vibronic fine structure of bands

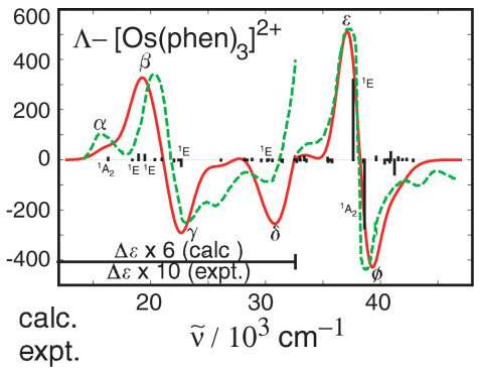
Line width used in Gaussian broadening of bands (user-dependent)

Not so every day: More challenging tasks

J. Autschbach, *Chirality* **21** (2009) E116-E152



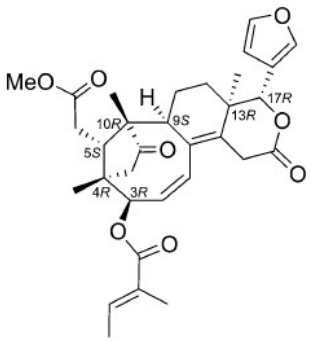
For small molecules, it is even feasible to calculated the vibrational fine structure together with the CD signature



Transition metal complexes still challenging, but quite acceptable results can be obtained.

Discussion: How reliable are AC assignments?

Nugroho et al, *J Nat Med* **68** (2014) 1–10



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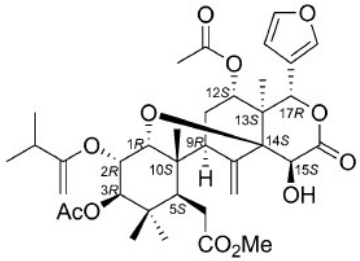

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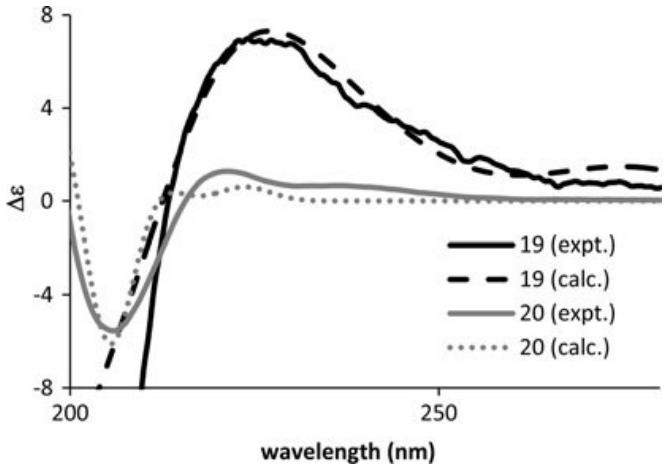

Are these reliable assignments?

Which information do you need to be sure this assignment is correct?

Which additional information might be required?

Outline of the lecture

	Dates	topics	
✓	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	your part