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Innovation Pipeline

INNOMOL
Molecular Interactions Workshop

Exciton-coupled CD spectroscopy in the study of supramolecular systems: functional polymers, organogels, retinylidene proteins

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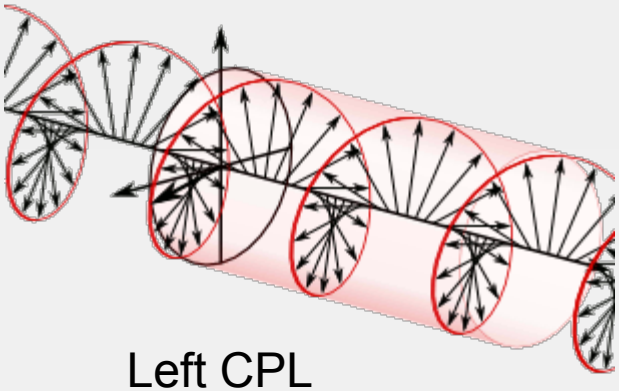
Synopsis

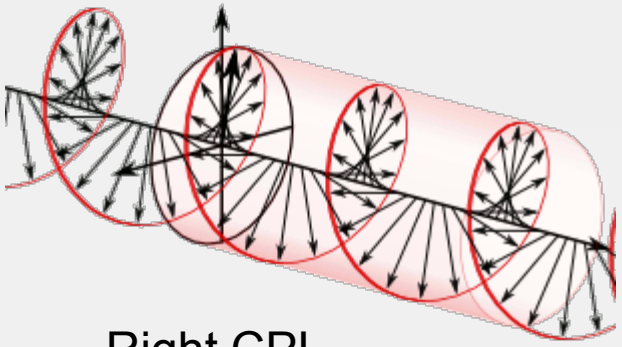
1. Electronic Circular Dichroism (CD)
   a. Instrumentation & basics
   b. Exciton coupling and exciton chirality
   c. Exciton-coupled CD calculations
2. Chiral supramolecular systems
   a. Induced circular dichroism (ICD)
   b. CD and supramolecular helicity
3. Chiral functional materials
   a. Conjugated polymers
   b. Organogels
4. Proteins
   a. CD of peptides and proteins
   b. Retinylidene proteins

Chiroptical vs. non-chiral spectroscopies

- UV-vis absorption spectroscopy:
  absorption of isotropic (unpolarized) light
- Electronic circular dichroism:
  differential absorption of left vs. right
  circularly polarized light in the UV-vis range
- Both allied with low-lying electronic transitions



Left CPL

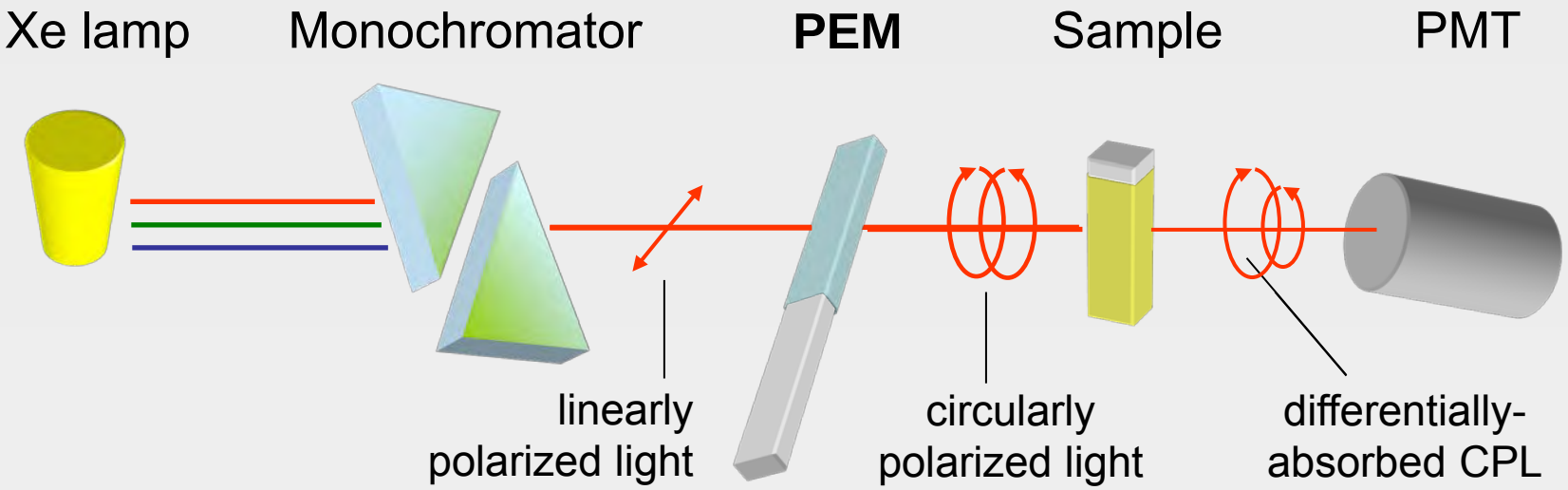


Right CPL

Chiroptical vs. non-chiral spectroscopies

- Electronic circular dichroism (ECD or CD)
  - UV-vis absorption spectroscopy
- Optical rotatory dispersion (ORD)
  - Refractive index dispersion
- Vibrational circular dichroism (VCD)
  - IR spectroscopy
- Raman optical activity (ROA)
  - Raman spectroscopy
- Circularly polarized luminescence (CPL)
  - Fluorescence (emission spectrum)

ECD: instrumentation and basics

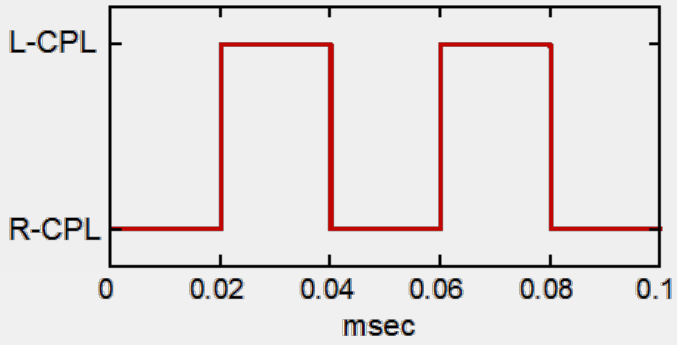


$$\mathrm{Abs} = \frac{1}{2}(A^l + A^r)$$

$$\mathrm{CD} = A^l - A^r$$

$$\Delta\varepsilon = \varepsilon^l - \varepsilon^r = \frac{A^l - A^r}{33000 \cdot c \cdot b}$$

($\Delta\varepsilon$ in $M^{-1}\,cm^{-1}$, c in M, b in cm)



ECD: instrumentation and basics

Measurement conditions:

- Near UV-transparent solvent
  (water, CH_3OH, CH_3CN, dioxane, hexane)
- Sample absorbance < 1 (ideally ≈0.8)
- Commonly observed range 185-700 nm
- State of the matter: mainly solutions, but also solid state
  (thin films, powders, microcrystals)
- Optionals: variable-temperature module, stopped-flow etc.

Non-negligible ECD spectrum requires:

- Chirality: structure devoid of symmetry elements (planes, centers)
- Resonance: presence of one or more light-absorbing units
  (chromophores)

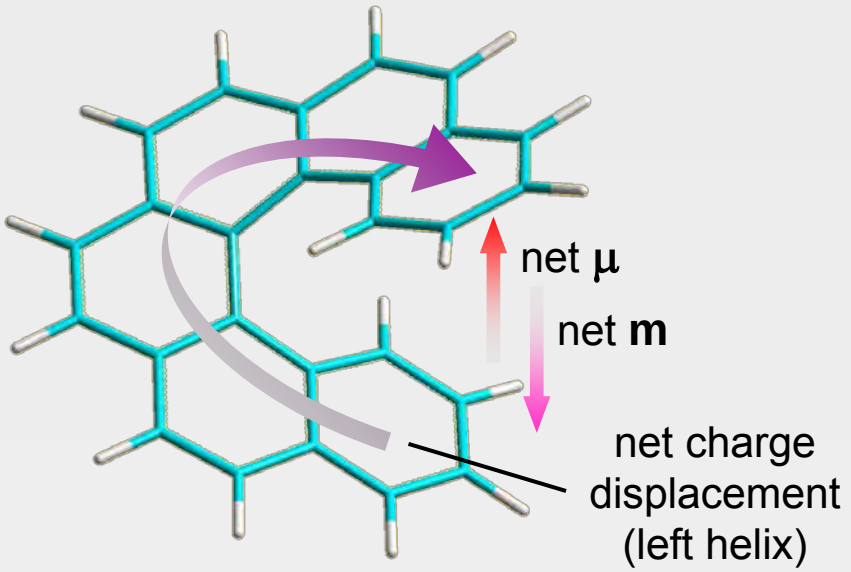
ECD: instrumentation and basics

Rosenfeld's equation:

$$R_{0i} = \boldsymbol{\mu}_{0i} \cdot \mathbf{m}_{i0}$$

electric transition dipole

magnetic transition dipole



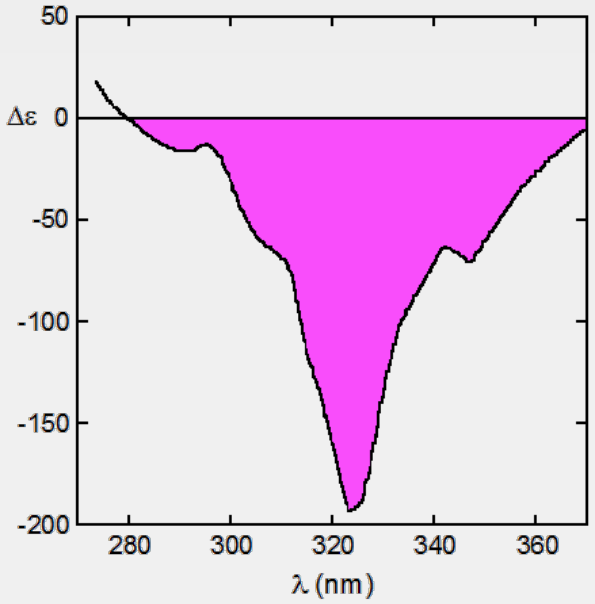
CD band integral:

$$R_i = C\int_{\nu} \frac{\Delta\varepsilon_i(\nu)}{\nu} d\nu$$

$$\Delta\varepsilon(\nu) = \frac{1}{\sqrt{\pi}C} \sum_i \Gamma_i \, \nu_i \, R_i$$

R_i rotational strength ν_i transition frequency

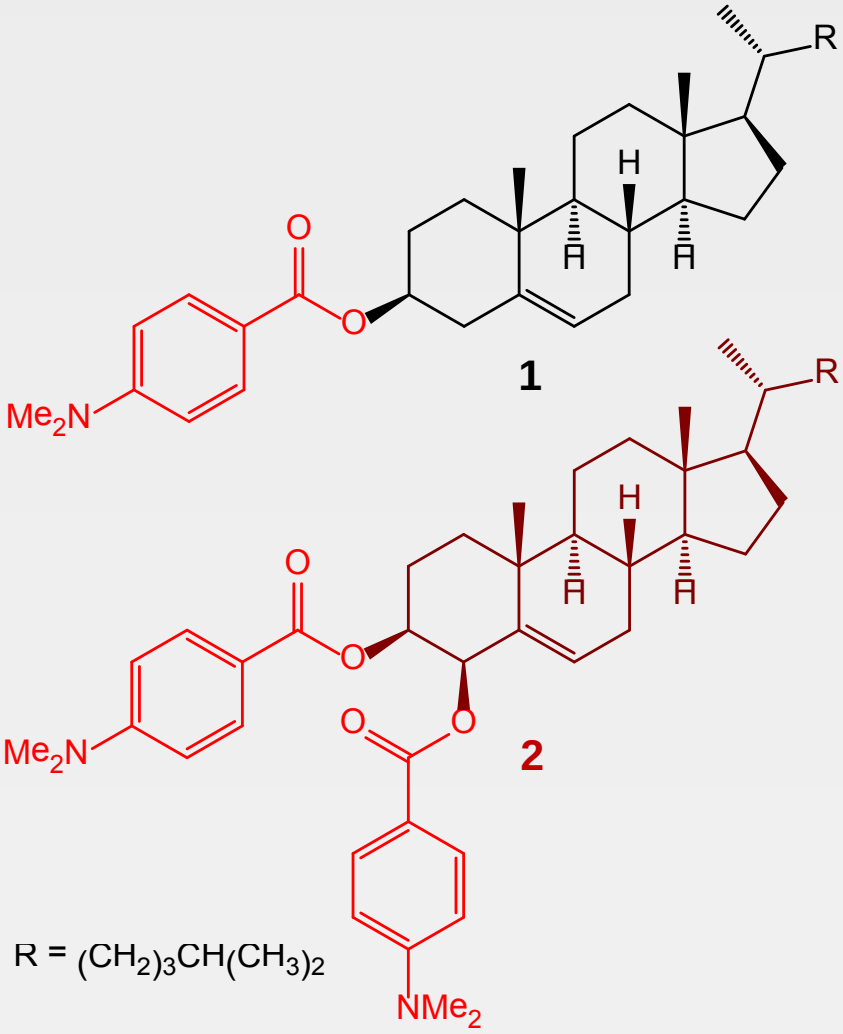
C constant & units Γ_i band-shape function

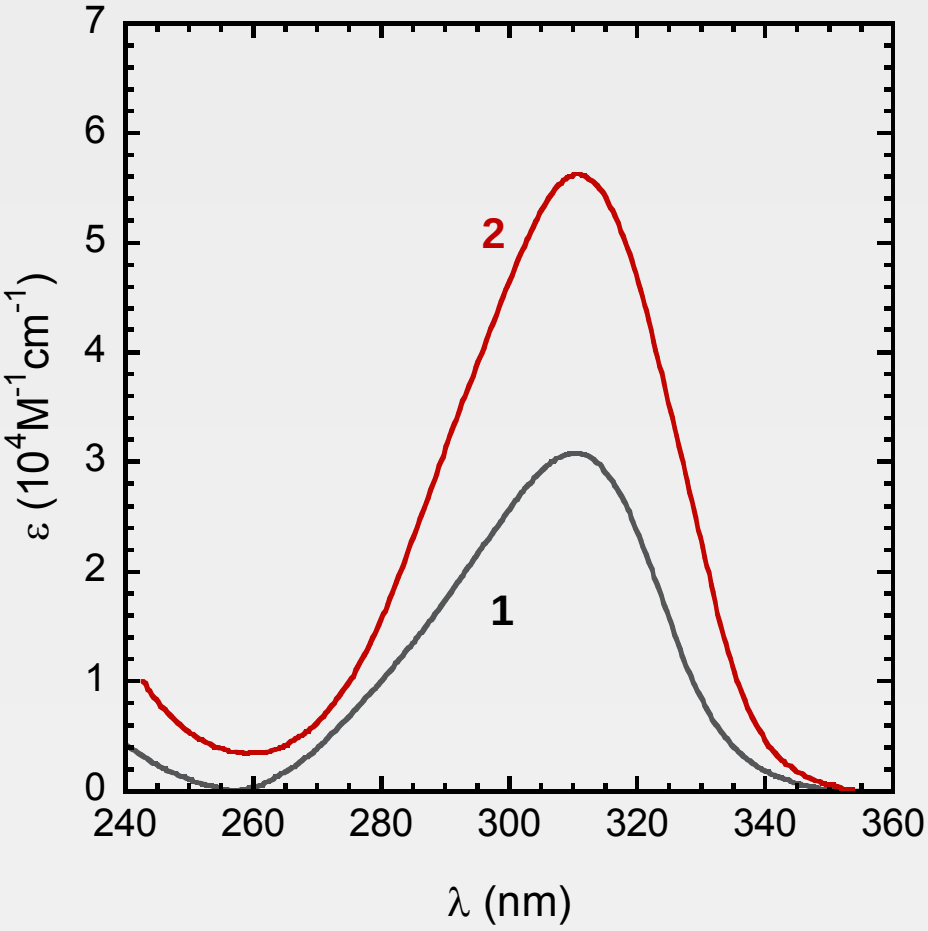


Chem Soc Rev 2007, 914

Exciton-coupled CD spectra: dibenzoates

Bis-(p-DMA benzoates) of steroidal diols





Harada&Nakanishi, Circular Dichroic Spectroscopy, 1983

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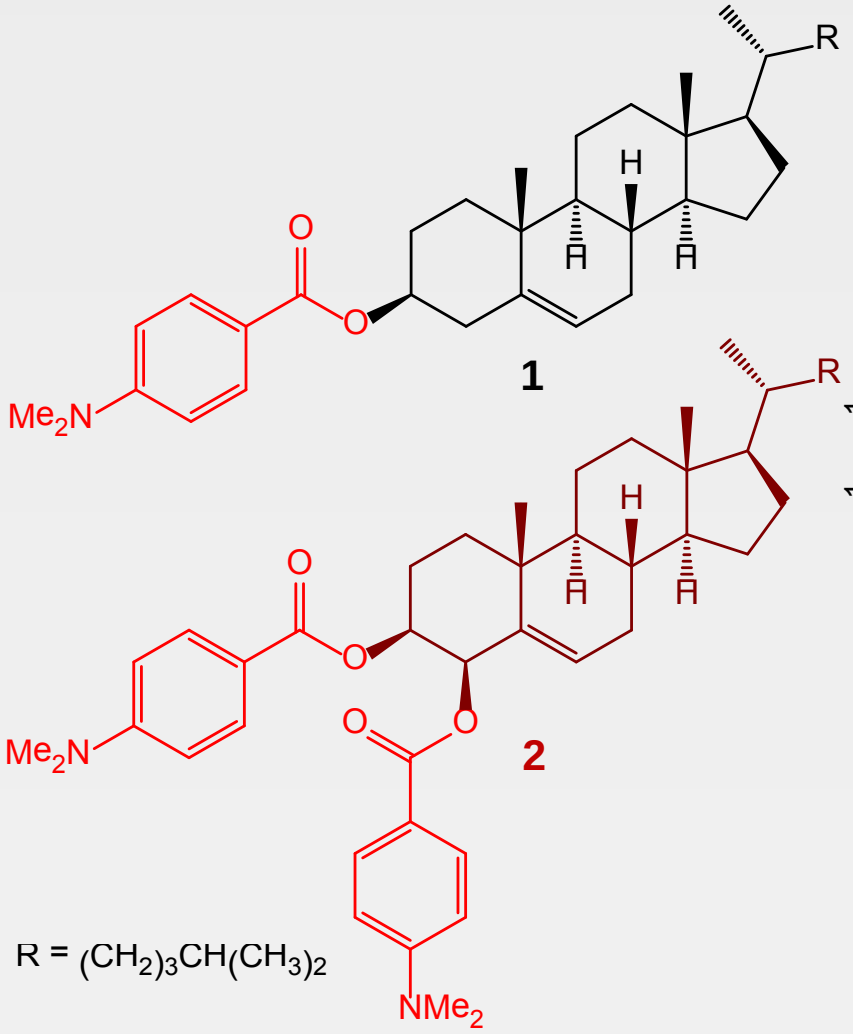
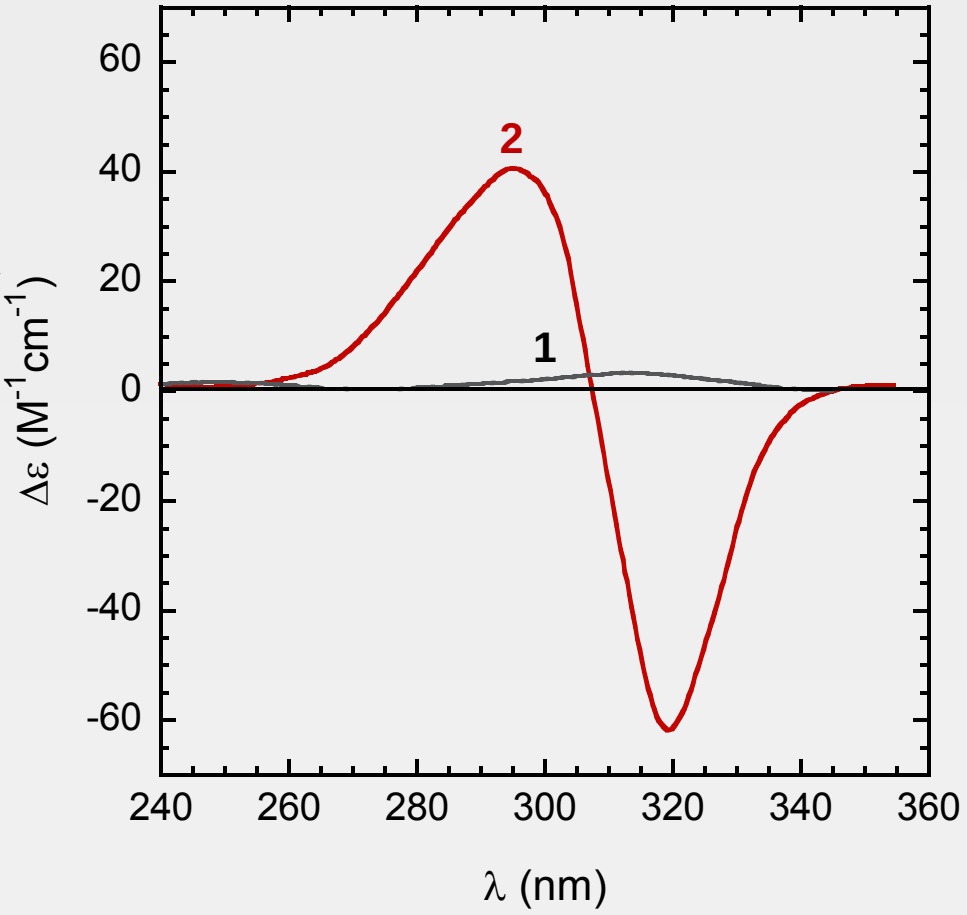
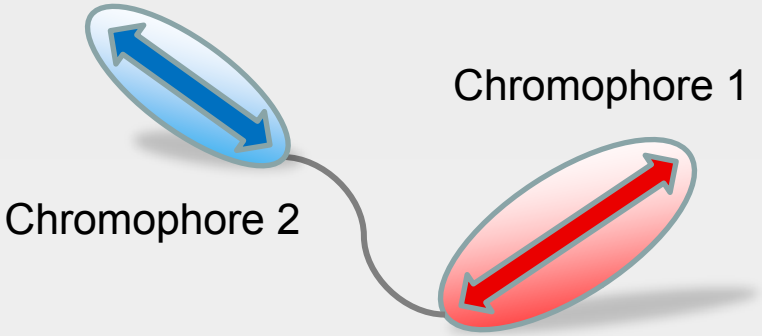


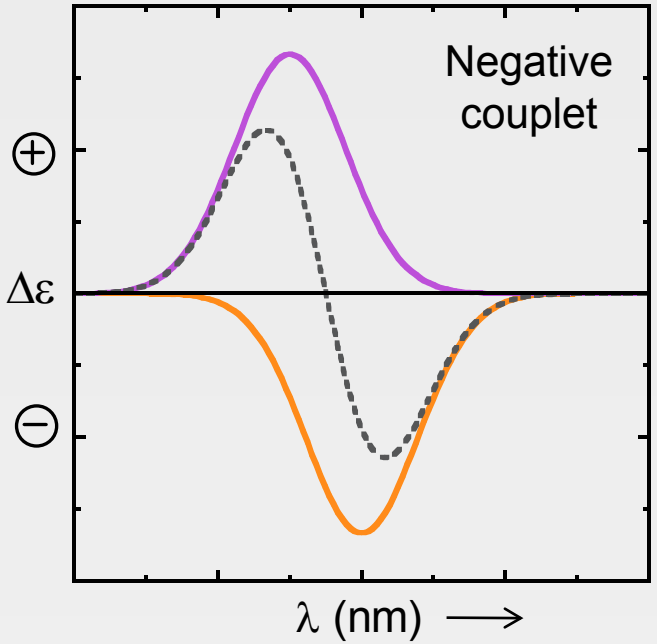


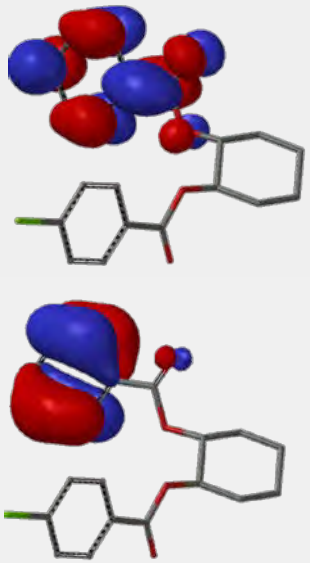
Harada&Nakanishi, Circular Dichroic Spectroscopy, 1983

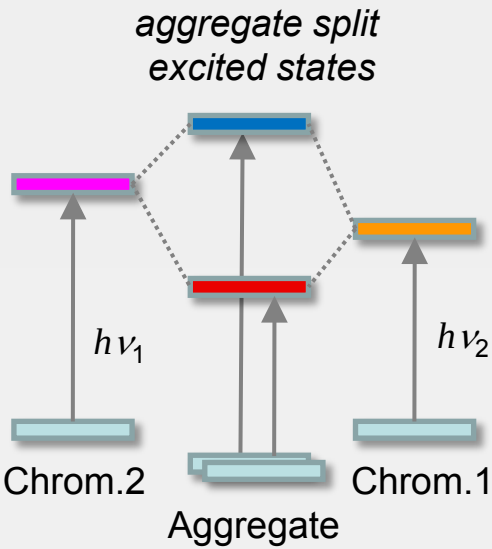
Exciton coupling and exciton chirality

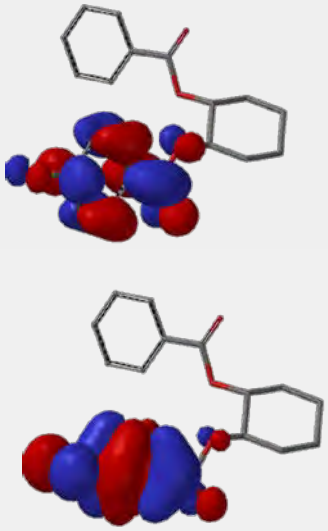
- Electronically isolated chromophores (no conjugation, resonance, charge-transfer)
- Skewed moments (not coplanar or collinear)

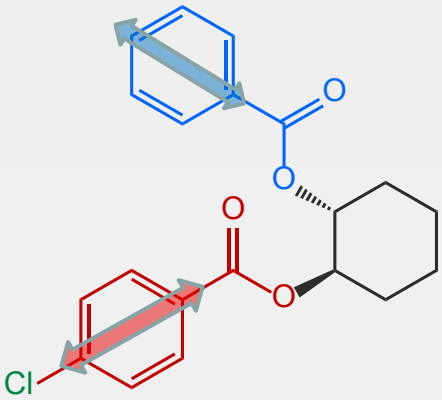




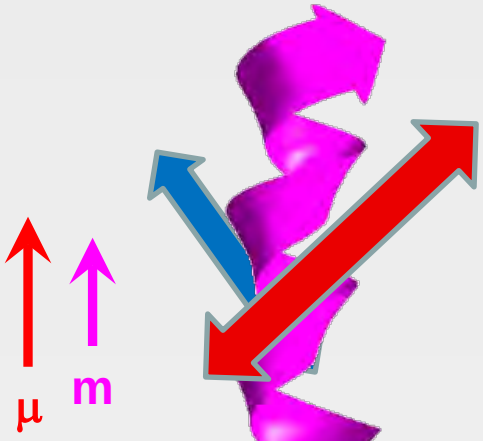




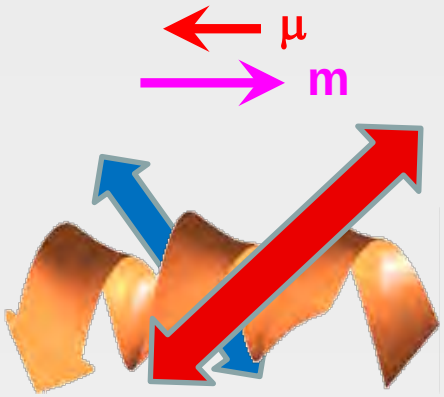




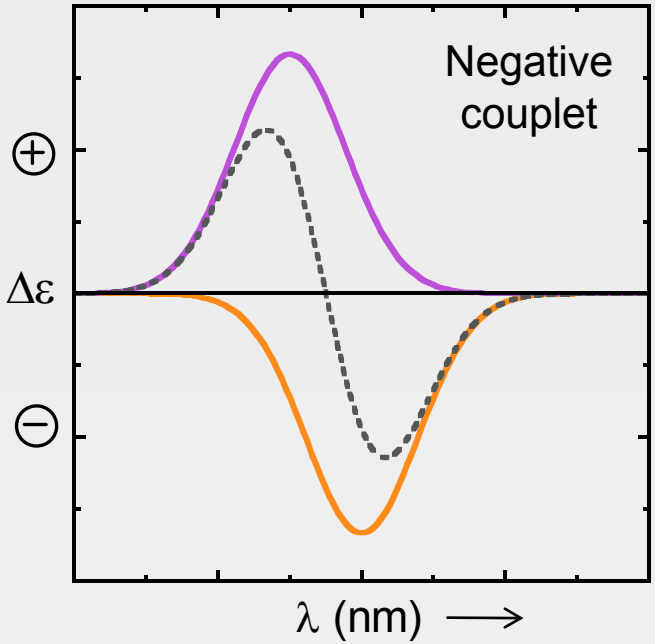
Exciton coupling and exciton chirality

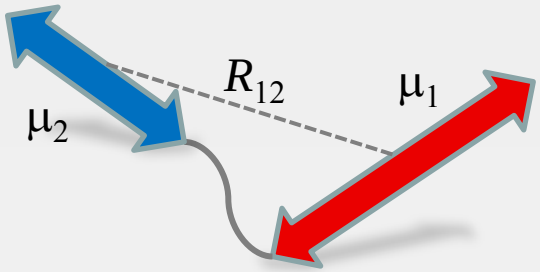


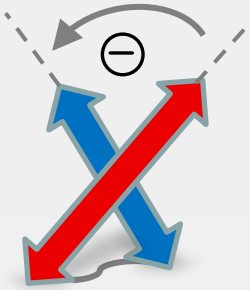
In-phase
(high energy)



Anti-phase
(low energy)







Negative chirality

$$R_{1,2} = \pm \frac{2\pi\nu_1\nu_2}{\nu_2^2 - \nu_1^2} V_{12} \mathbf{R}\boldsymbol{\mu}_2 \cdot \boldsymbol{\mu}\times \quad 2$$

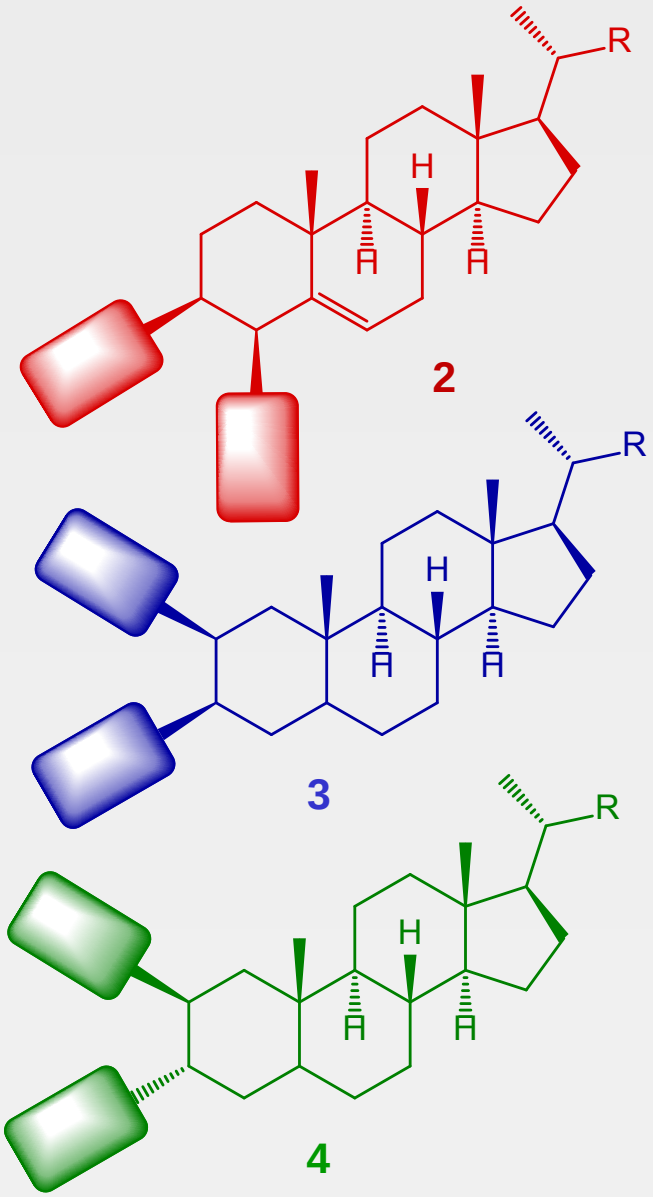
$$V_{12} = \frac{\mu_1\mu_2}{R_{12}^3}\left[\mathbf{e}_1 \cdot \mathbf{e}_2 - 3(\mathbf{e}_1 \cdot \mathbf{e}_{12})(\mathbf{e}_2 \cdot \mathbf{e}_{12})\right]$$

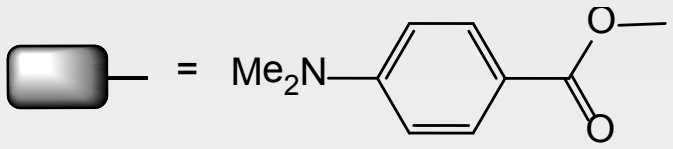
$\boldsymbol{\mu}_i$ transition moment V_{12} dipolar coupling
$\mathbf{R}_{12}$ distance vector $\mathbf{e}_i$ and $\mathbf{e}_{12}$ unit vectors

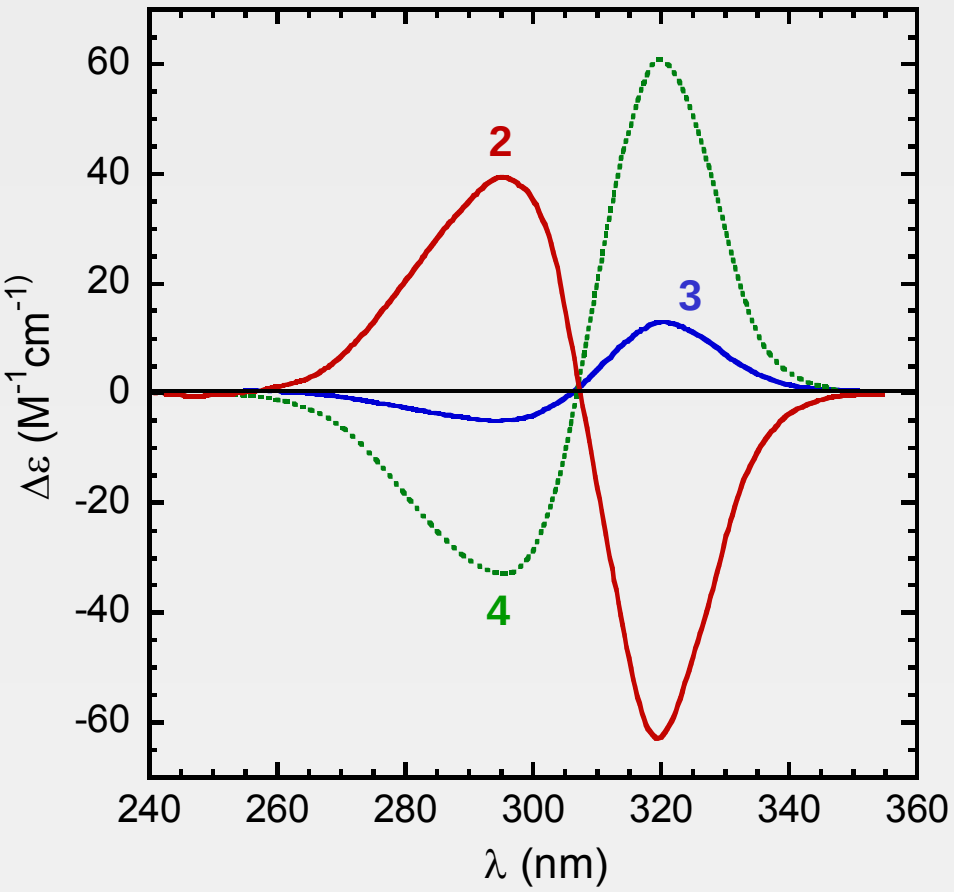
Exciton chirality rule: ⊖ chirality ⟺ ⊖ couplet

Harada&Nakanishi, Circular Dichroic Spectroscopy, 1983

Exciton-coupled CD spectra: dibenzoates







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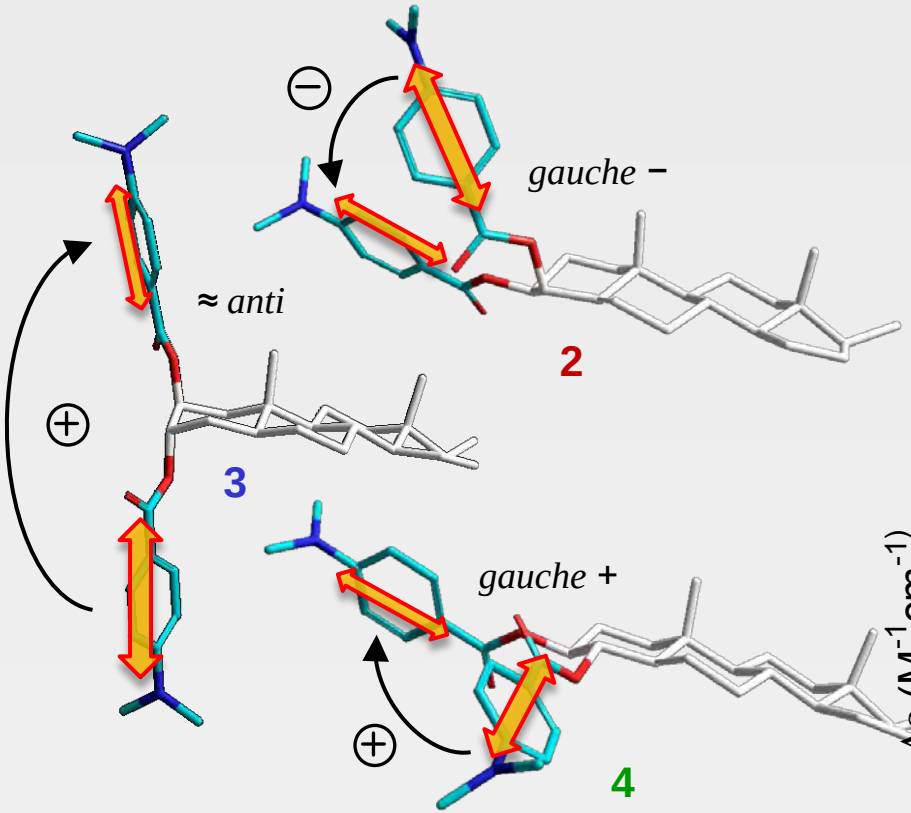
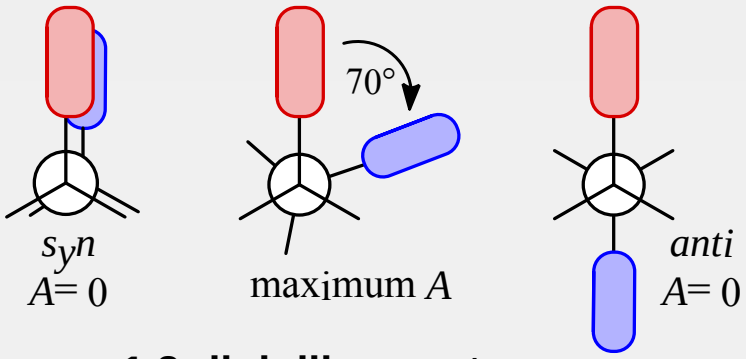
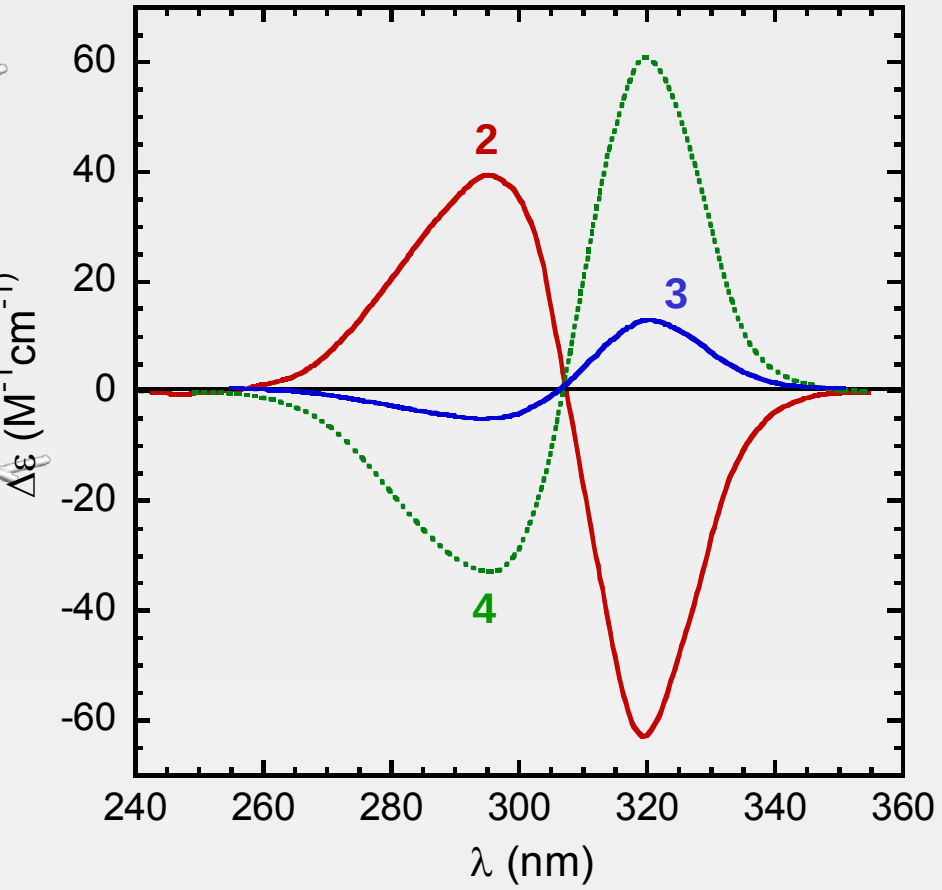






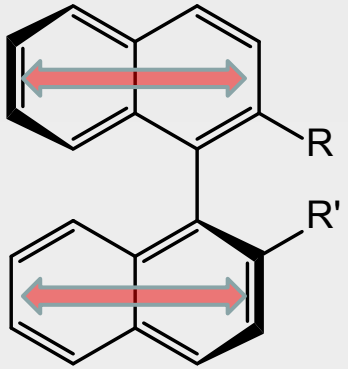
1,2-diol dibenzoates

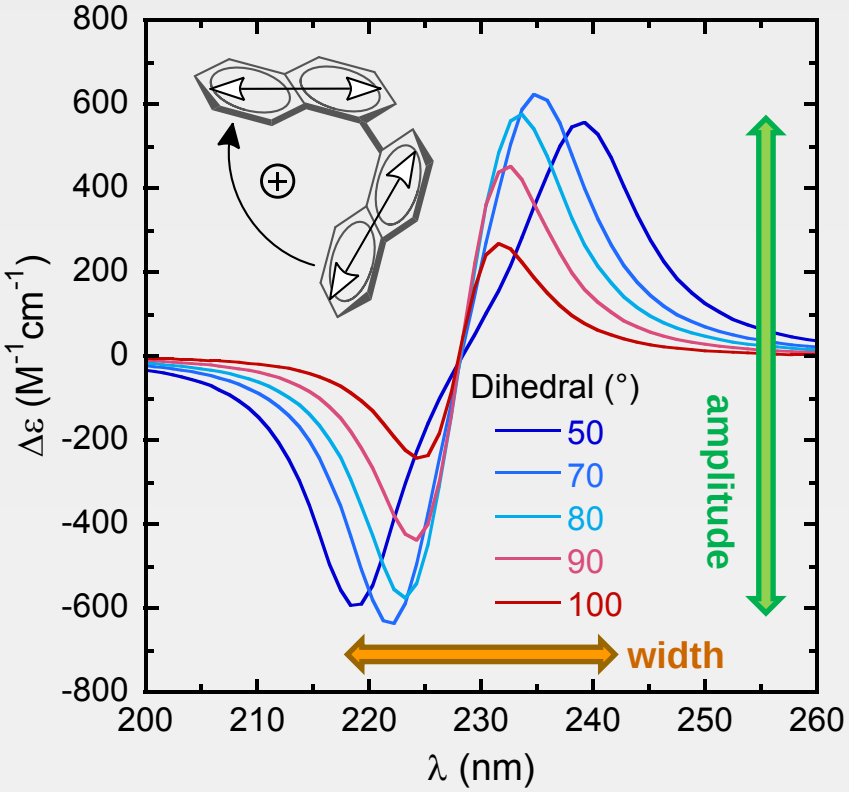
Harada&Nakanishi, Circular Dichroic Spectroscopy, 1983

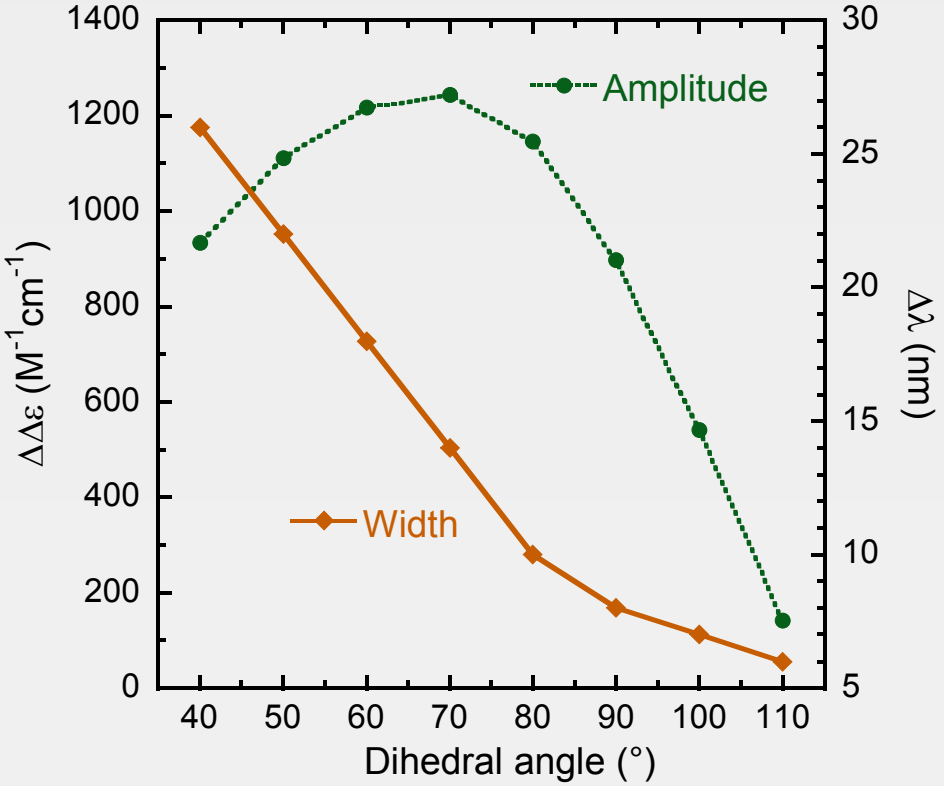
Exciton-coupled CD spectra: biaryls

1,1'-Binaphthyls

- Interplay between configuration and conformation
- CD sign determined by axial chirality configuration
- CD shape and amplitude related to dihedral angle value (conformation)







JACS 1999, 7998

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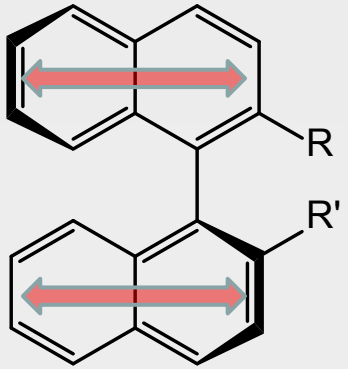
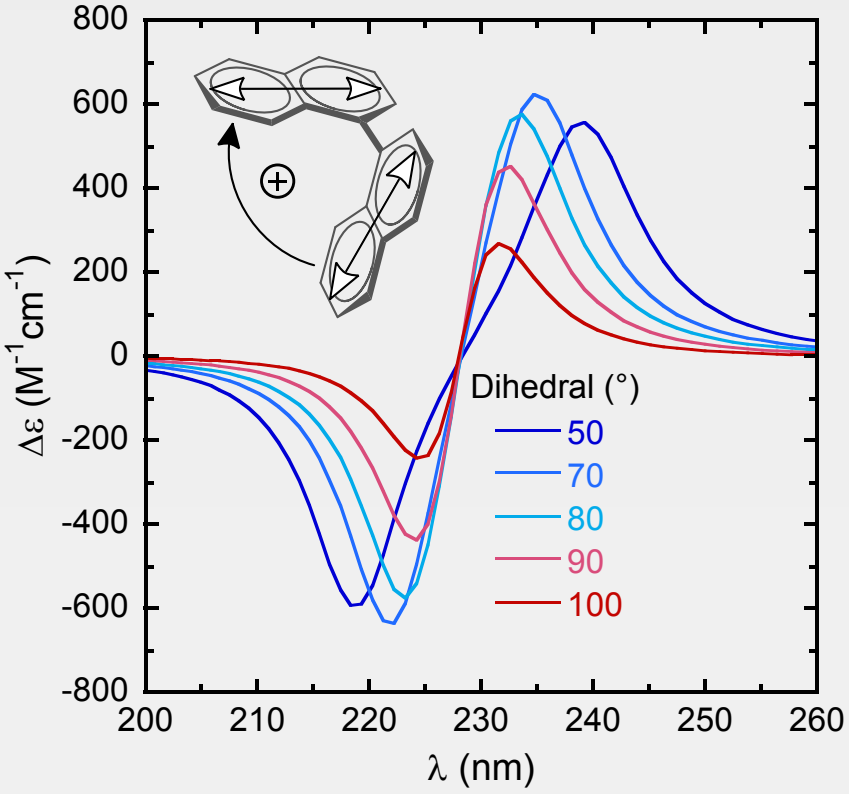
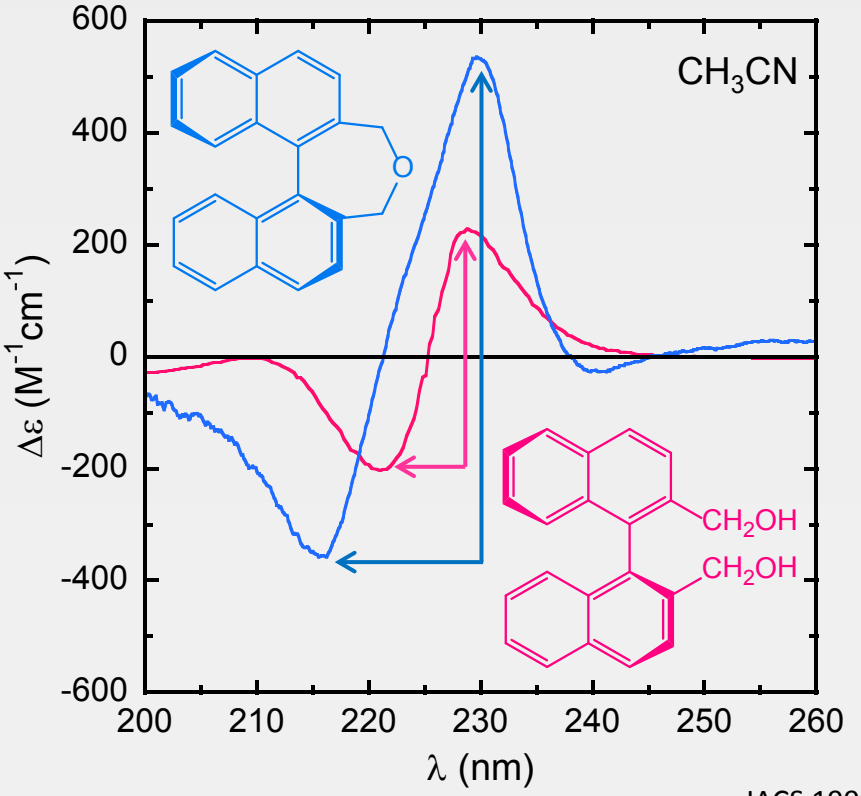


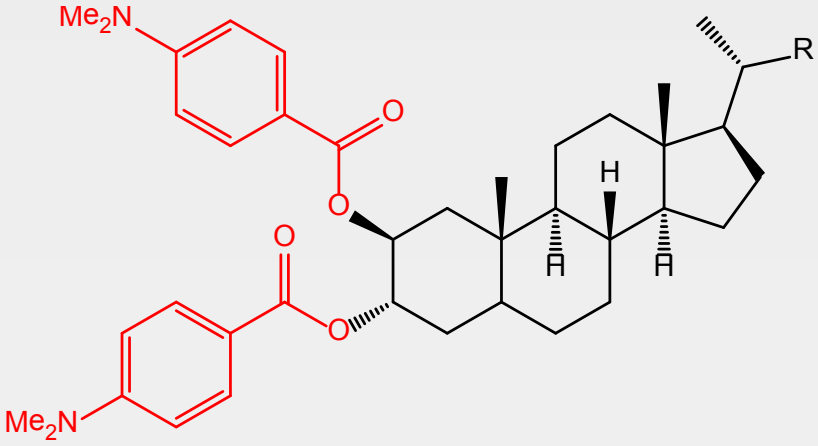


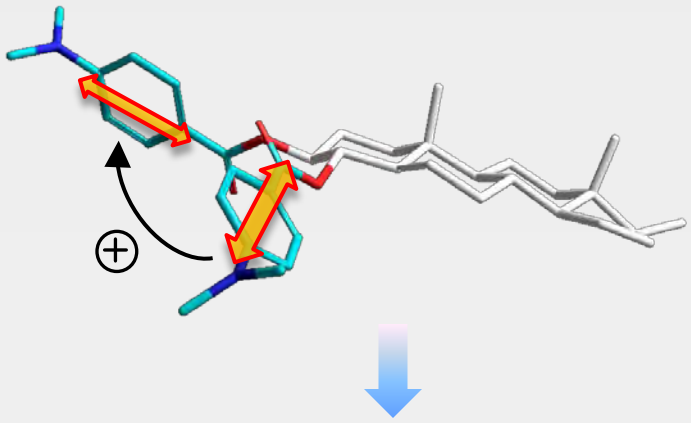


JACS 1999, 7998

Exciton-coupled CD evaluation

- "Visual" estimation: exciton chirality rule
- Semi-classical calculation approaches: matrix-method, DeVoe
- Quantum-mechanics fragmentation methods
- Full quantum-mechanics calculations



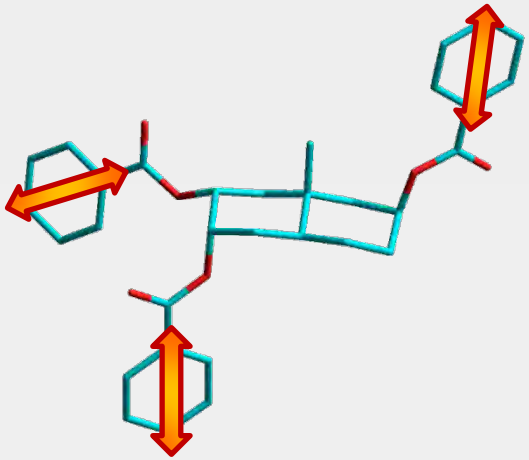


Positive CD couplet expected

- Immediate response
- Feasible for well-known chromophores
- Provides only the couplet sign
- Very prone to errors

Exciton-coupled CD evaluation

- "Visual" estimation: exciton chirality rule
- Semi-classical calculation approaches: matrix-method, DeVoe
  - Transition dipoles as oscillating dipoles
  - Dipole interaction by classical physics
- Quantum-mechanics fragmentation methods
- Full quantum-mechanics calculations



$$\mathbb{H} = \begin{bmatrix} E_1 & V_{12} & V_{13} \\ V_{12} & E_2 & V_{23} \\ V_{13} & V_{23} & E_3 \end{bmatrix}$$

interaction potential between transition dipoles

isolated transitions frequencies (site energies)

Eigenvalues:
aggregate energies

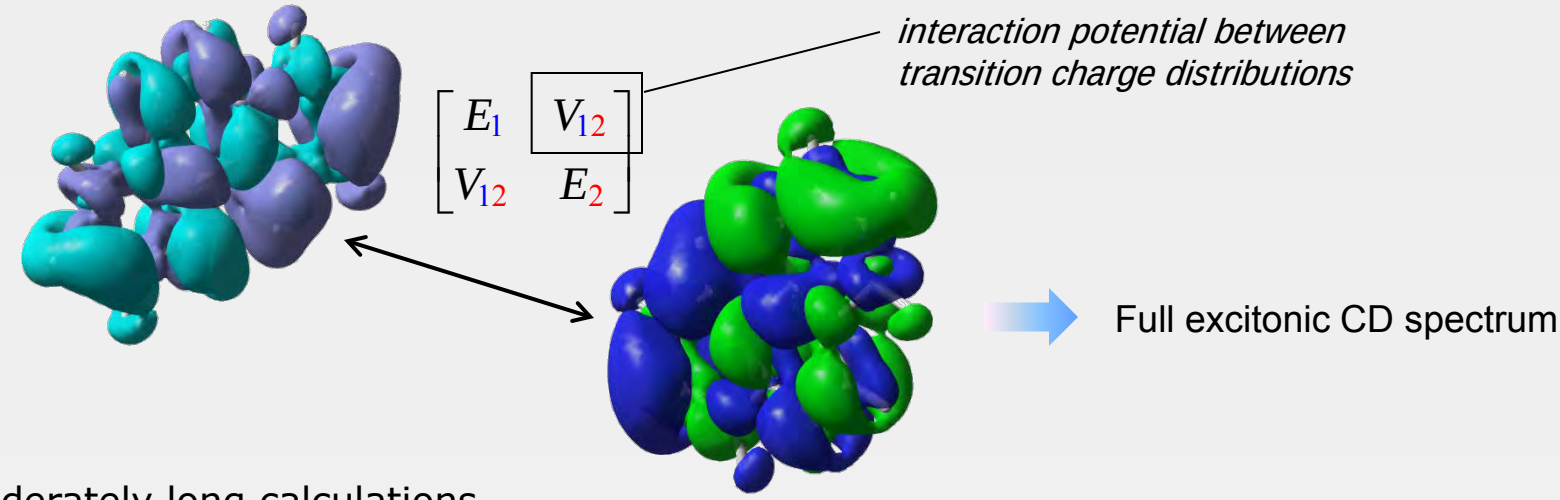
Eigenvectors:
dipolar & rotational strengths

- Very fast calculation
- May treat magnetic-allowed transitions as well (e.g. carbonyl n-π*)
- Chromophores to be known or separately investigated
- Provides full spectra

Superchi et al. Chirality 2004, 422

Exciton-coupled CD evaluation

- "Visual" estimation: exciton chirality rule
- Semi-classical calculation approaches: matrix-method, DeVoe
- Quantum-mechanics fragmentation methods
  - QM description of transition densities
  - Density interaction by classical physics
- Full quantum-mechanics calculations

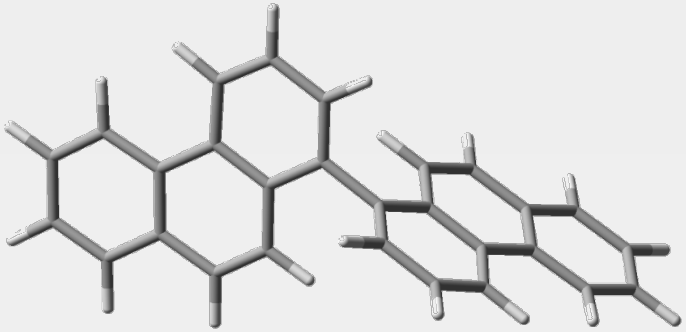


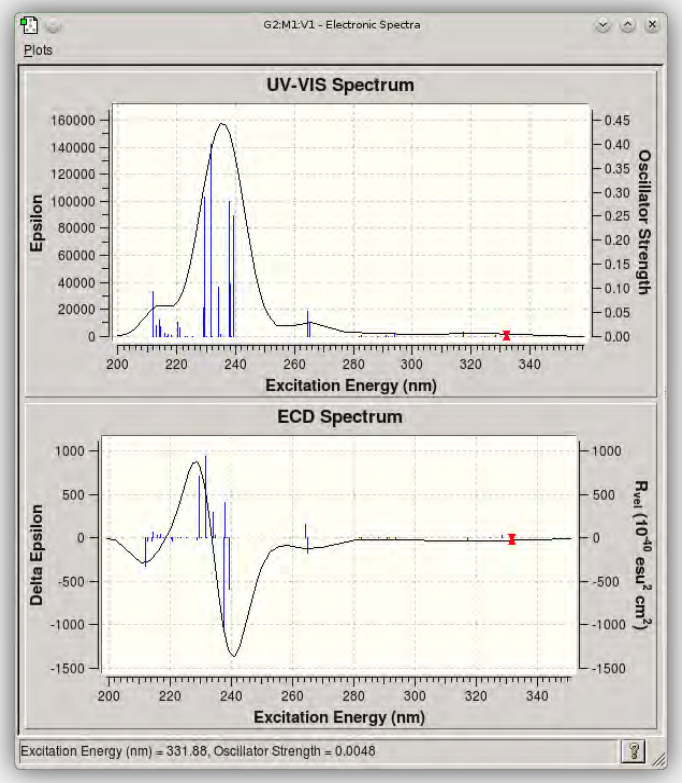
- Moderately long calculations
- No previous knowledge of chromophores is needed
- May require a selection of electronic transitions
- Provides full spectra

PCCP 2014, 16407

Exciton-coupled CD evaluation

- "Visual" estimation: exciton chirality rule
- Semi-classical calculation approaches: matrix-method, DeVoe
- Quantum-mechanics fragmentation methods
- Full quantum-mechanics calculations
  - Time-dependent density functional theory (TDDFT) B3LYP, CAM-B3LYP, PBE0 etc.





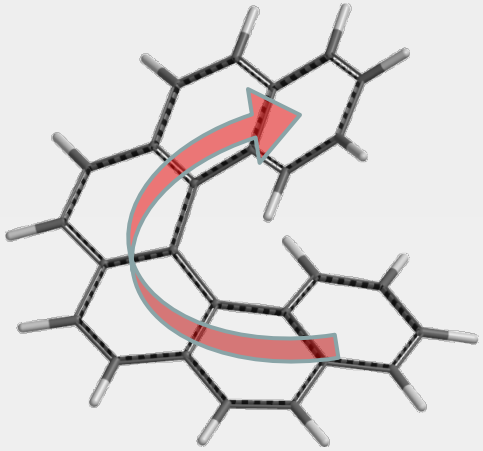
- Long or very long calculations (brute force)
- Black-box calculations
- Potentially applicable to any structure, no approximation
- Provides full spectra

Autschbach et al. Top Curr Chem 2011, 1

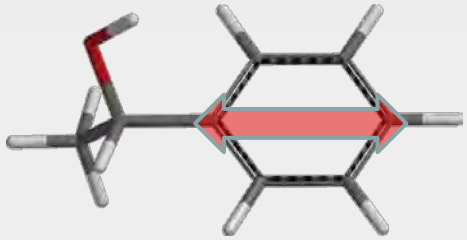
Quantifying CD spectra: the g-factor

Dissimmetry ratio or Kuhn's ratio or g-factor:

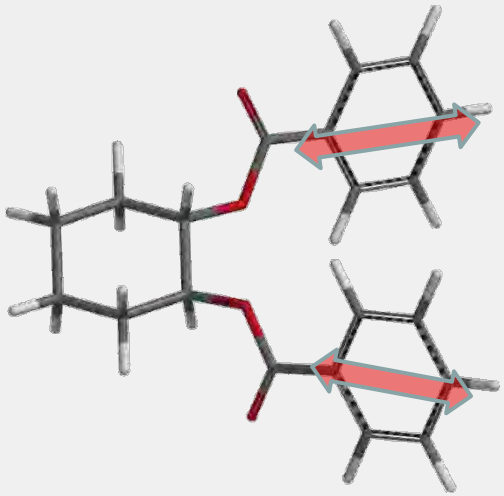
$$g = \frac{\Delta\varepsilon}{\varepsilon} = \frac{\Delta Abs}{Abs} \propto \frac{\mathbf{m}_{i0}}{\boldsymbol{\mu}_{0i}}$$



inherently chiral chromophore
(π-twisted)
$g \approx 10^{-2}$



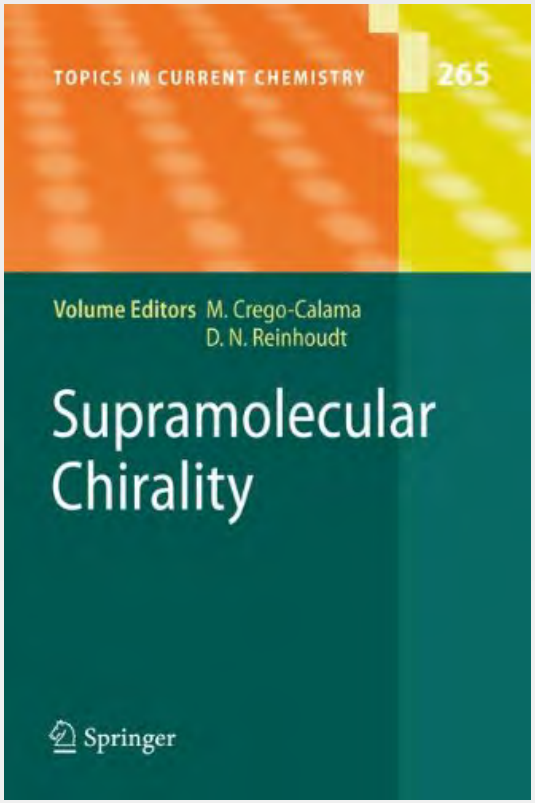
achiral chromophore
in a chiral framework
$g \approx 10^{-4}$



two exciton-coupled
chromophores
$g \approx 10^{-3}$

Supramolecular chirality

- Many supramolecular architectures inspired by Nature, or designed following a bio-mimetic approach
- Necessarily related to chiral symmetry-breaking

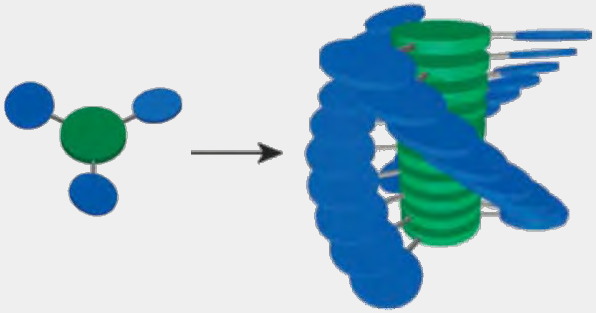


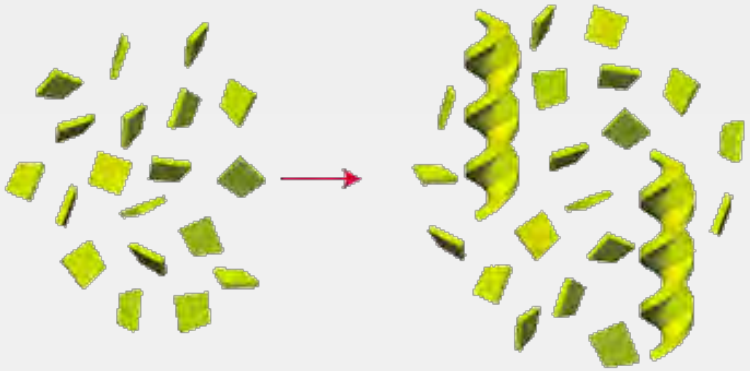
Themed issue: Nanoscale chirality

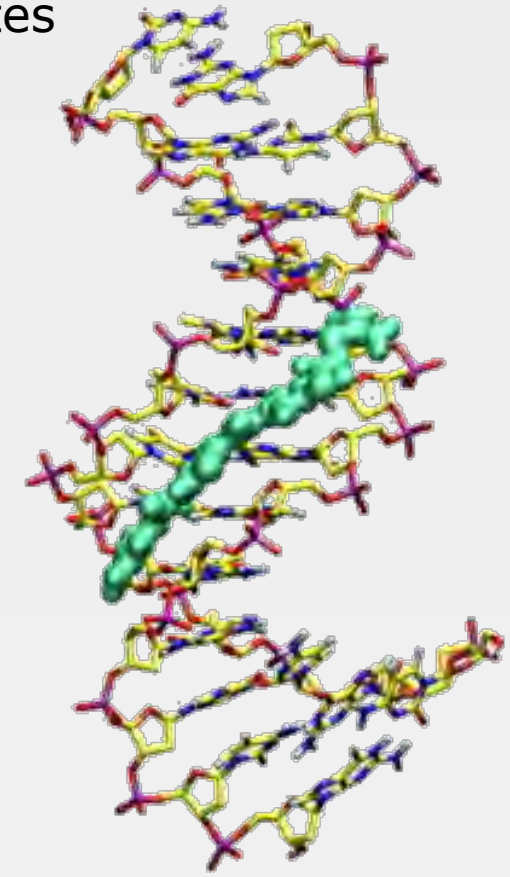
Supramolecular chirality

Classification based on chirality source:

1. Aggregates of chiral entities
2. Complexes between chiral and achiral partners
3. Spontaneous resolution: chiral aggregates from achiral objects



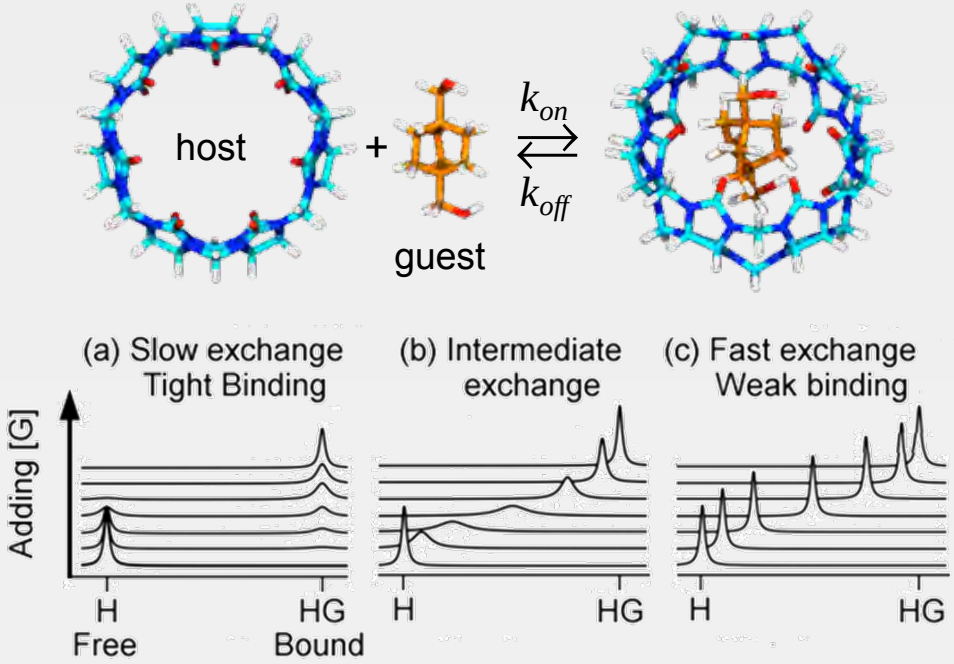


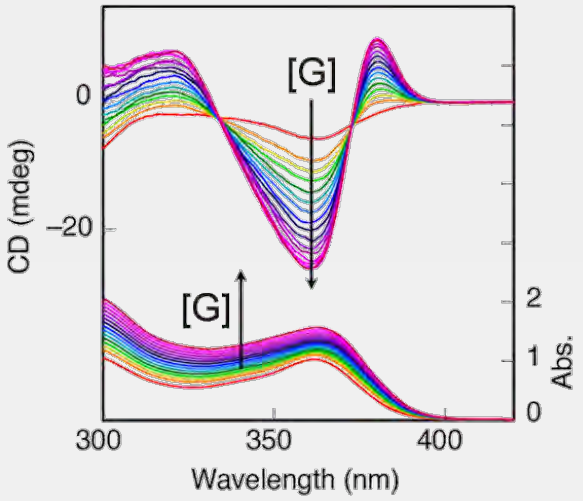


Detection of supramolecular species

Optical spectroscopies: Absorption, ECD, Fluorescence

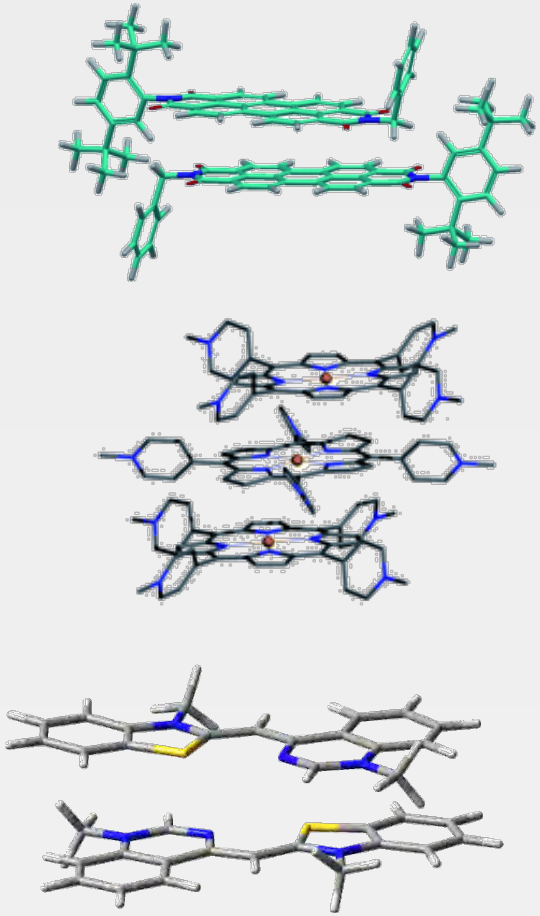
- "Fast" spectroscopies
- Suitable for very large systems
- Low resolution
- Need chromophores (and chirality)
- Offer chromophore viewpoint

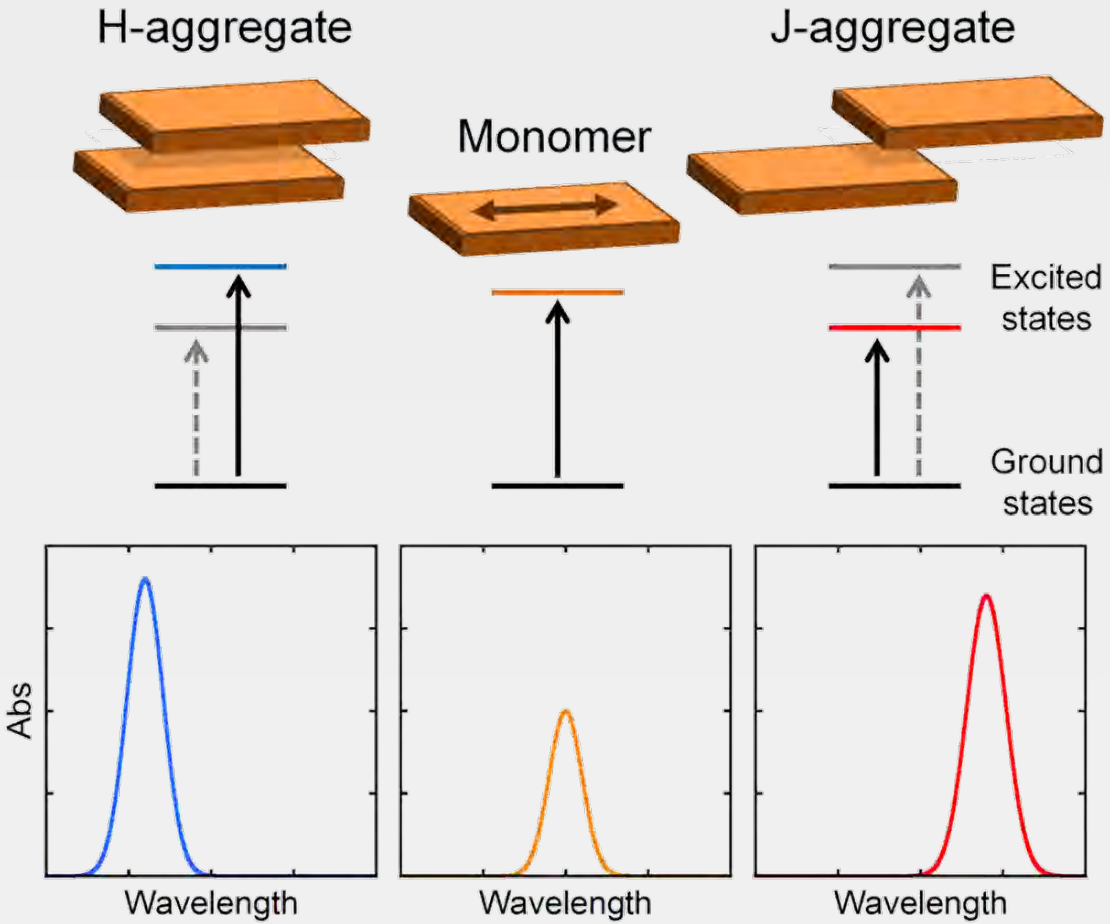




H- and J-aggregates: absorption spectra

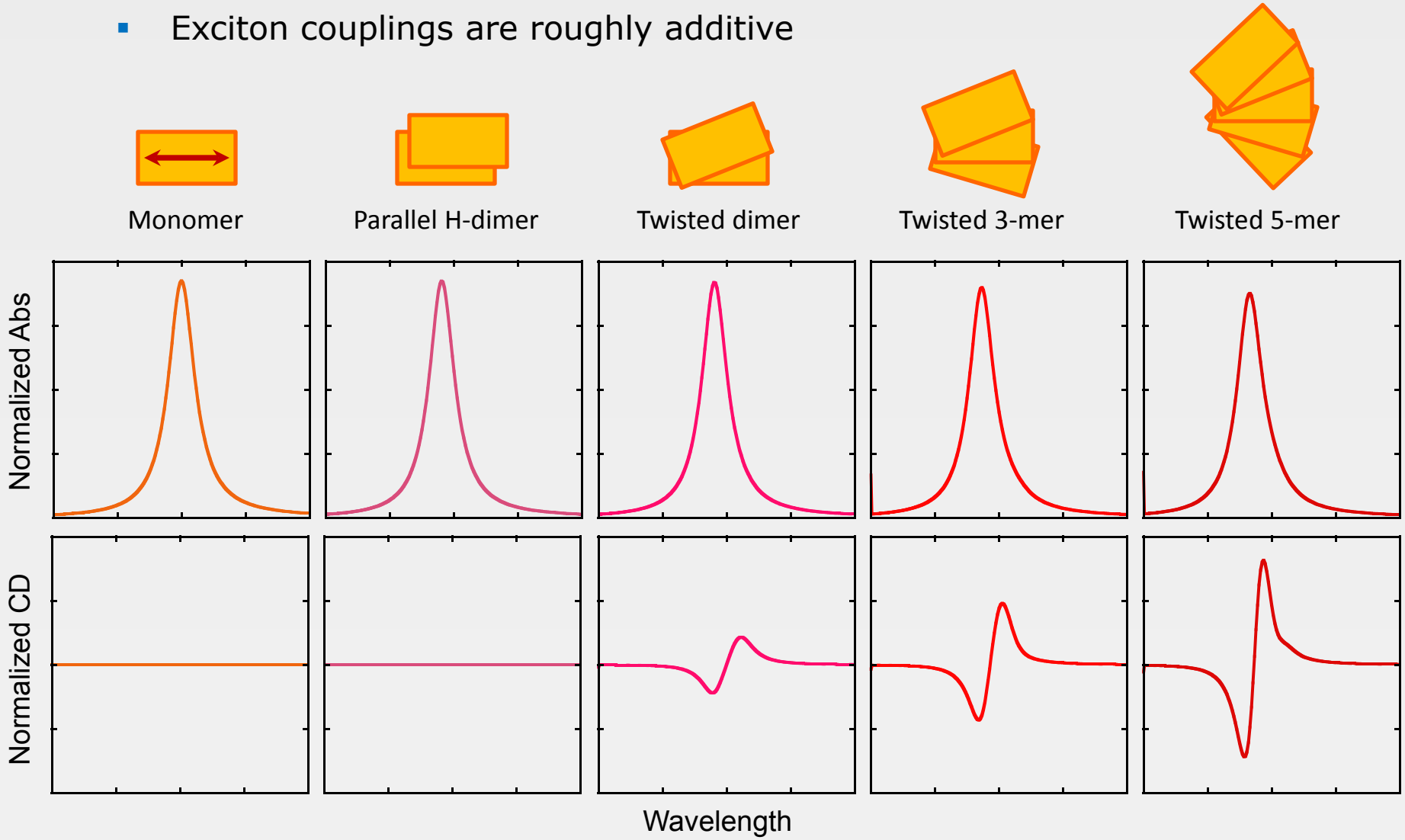
- Typical response to aggregation due to π-stacking
- In- and out-of-phase combinations of transition dipole moments





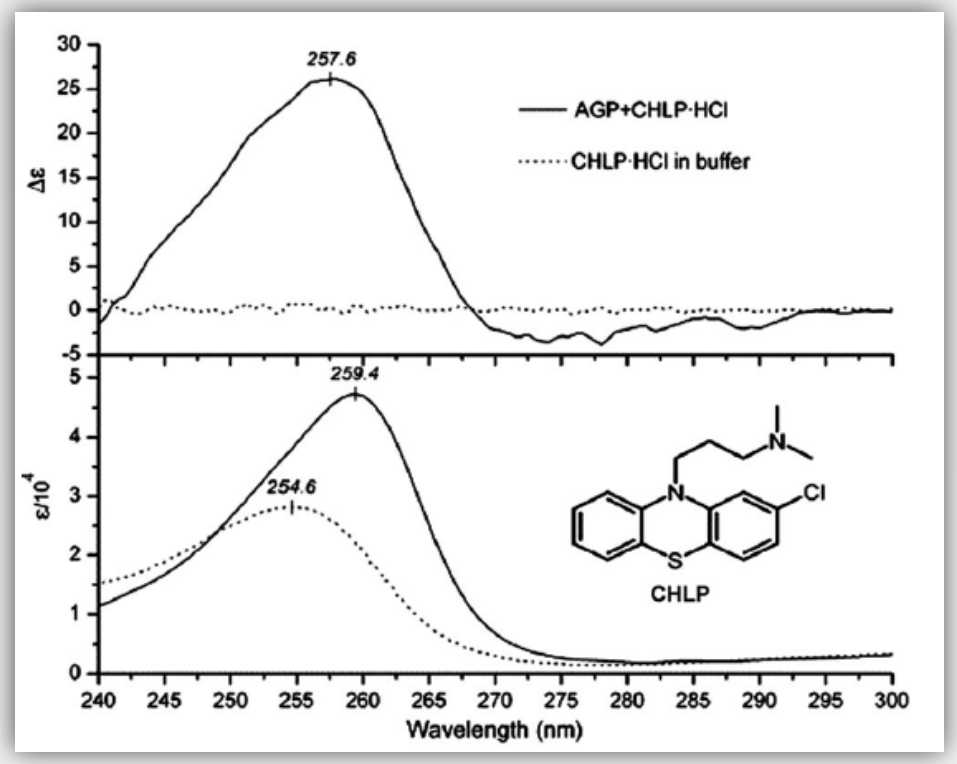
H- and J-aggregates: CD spectra

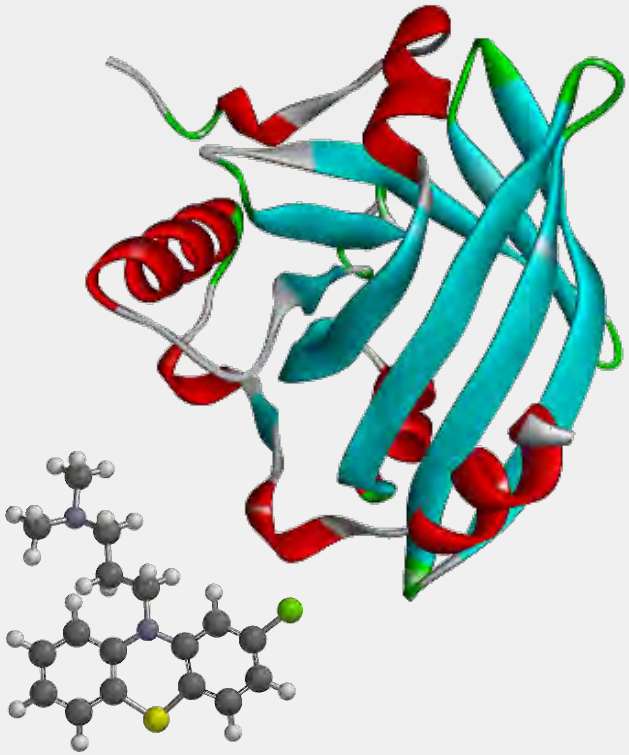
- Exciton coupling scales with R^{-2}, first-neighbor couplings dominate
- Exciton couplings are roughly additive



Induced Circular Dichroism (ICD)

- Any chiral, chromophoric supramolecular object is expected to give a CD signal
- Its components may not: **induced** CD (ICD)
- Example: the AC/CN case
  achiral chromophoric guest (**AC**) + chiral non-chromophoric host (CN)





Chem Soc Rev 2014, 5211

CD and supramolecular chirality

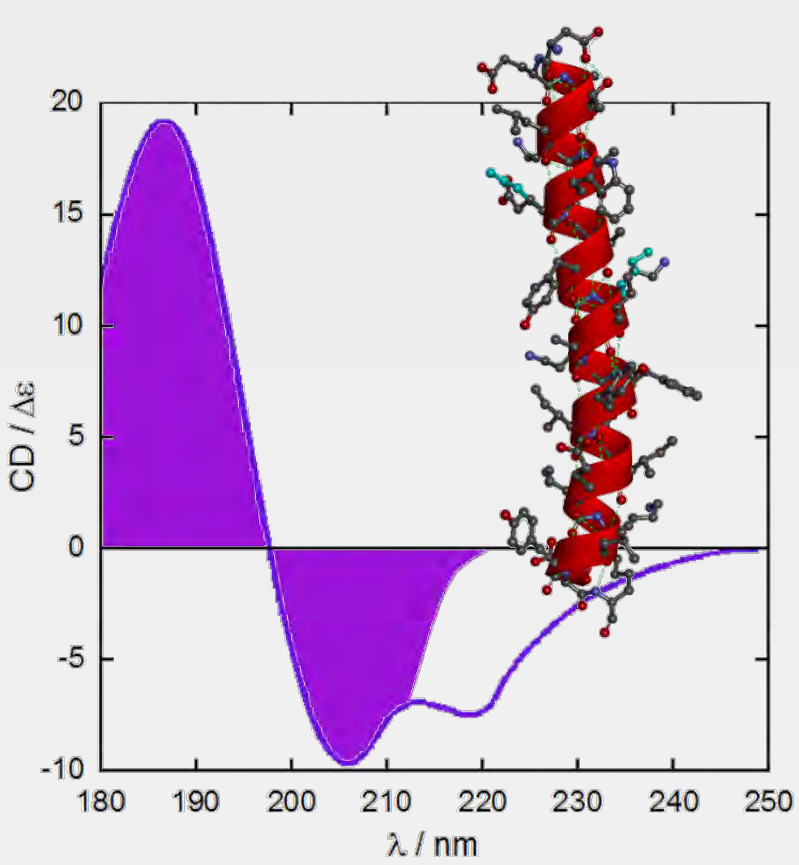
Main applications:

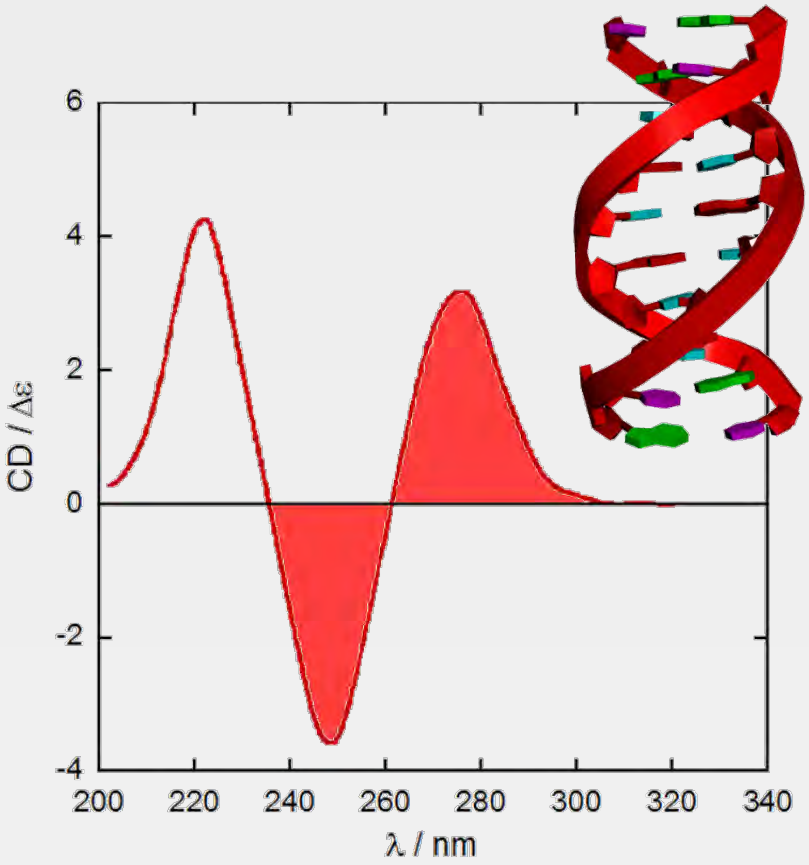
1. As an analytical tool
   - Detection of chiral supramolecular objects
   - Quantification of chiral supramolecular object
     - binding isotherms, K_{eq}, ΔH^0 / ΔS^0
     - stoichiometries and Hill coefficients
     - $T_{sol/gel}$ and other transition parameters
2. Qualititative structure/property relationships
   - Assignment of supramolecular helicity
   - Geometry of host/guest complexes
   - Geometry of biomacromolecule/dye adducts
3. Quantitative structural information

Chem Soc Rev 2014, 5211

CD and (supra)molecular helicity

- No universal relation between CD sign and helix handedness
- Right-handed protein α-helix and B-DNA have opposite "couplets"
- Nature of CD signals and orientation of transition moments needed





Chiral conjugated polymers

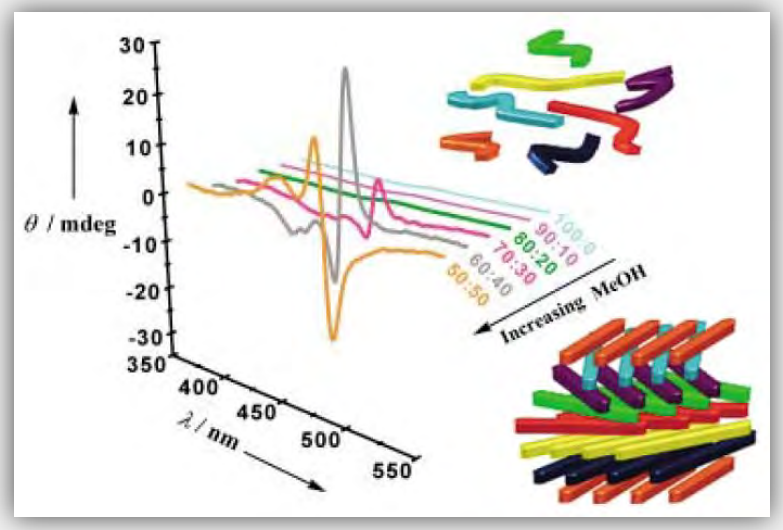
- Favorable (?) impact of chirality on material properties

Parallel
Efficient exciton transport
but dipole-dipole cancellation
leads to fluorescence quenching

Oblique
Compromise between
efficient exciton transport
and luminescence

Orthogonal
High luminescence but
minimal interchain
exciton migration

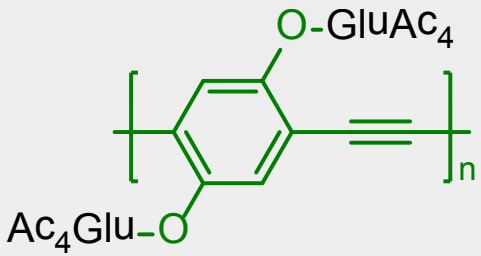
- CD used for detection and structural characterization (especially of aggregated states)



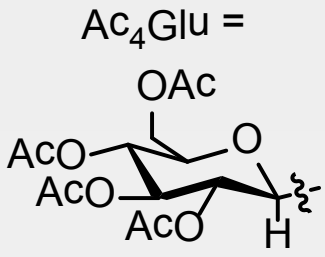
Swager et al. Polym Phys 2011, 476

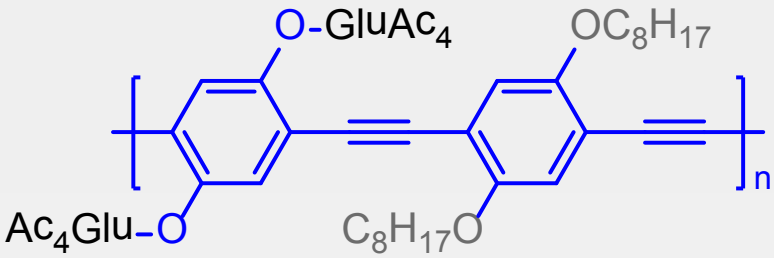
Chiral conjugated polymers

- Glucose-appended poly(phenyleneethylidene) (PPE)
- Used for chirality sensing
- Two analogs with different density of chiral moieties



Homooligomer **HO** ($n \approx 10$)



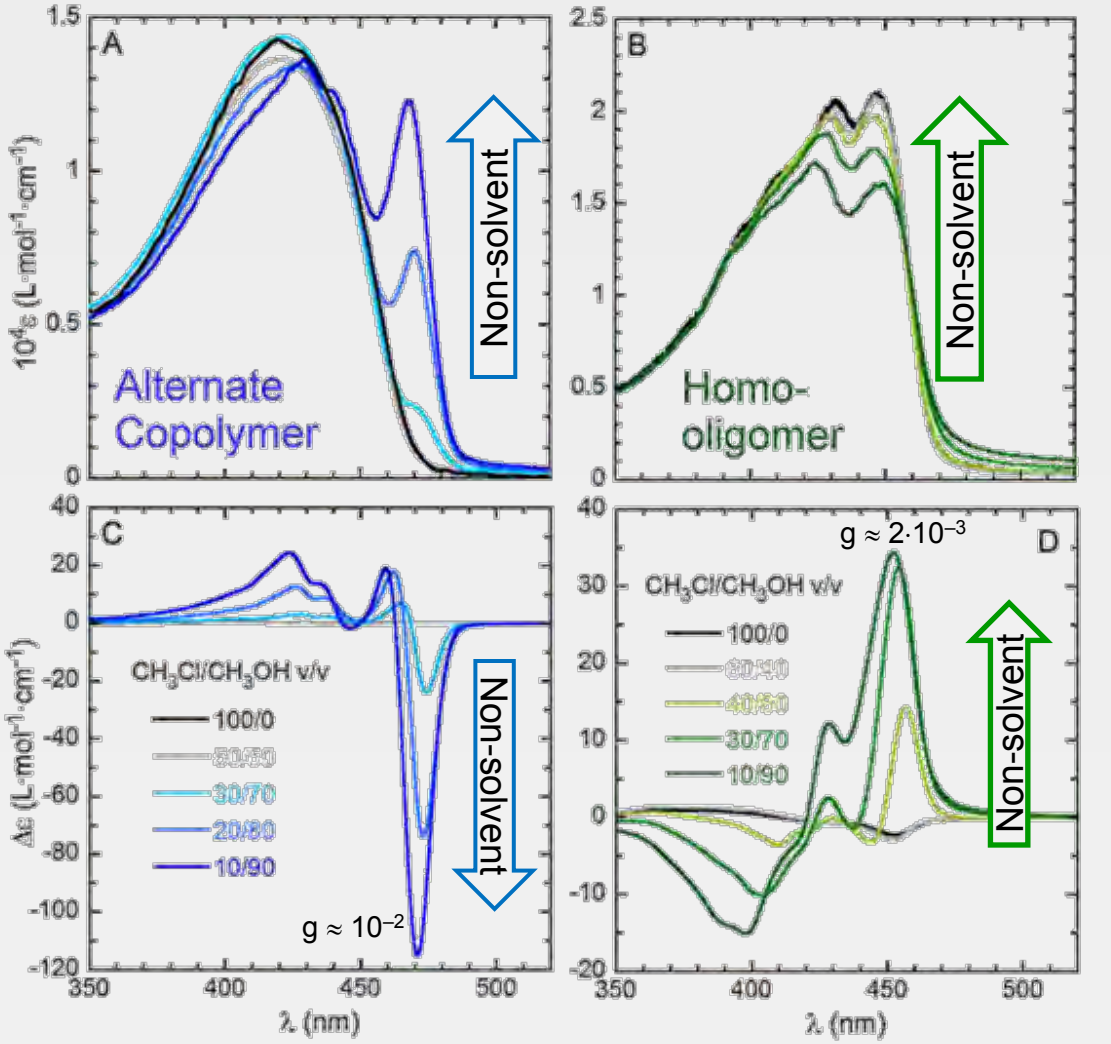


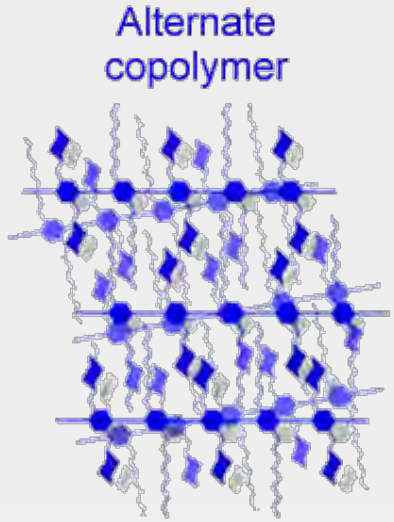
Alternate copolymer **AP** ($n \approx 40$)

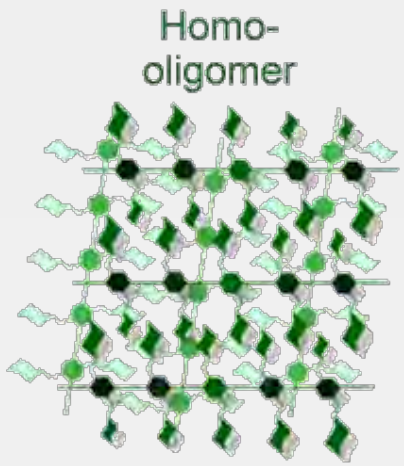
Macromolecules 2012, 9626

Chiral conjugated polymers

- Solvent-induced aggregation (solvochromism)
- Solution aggregate mimic solid-state aggregates



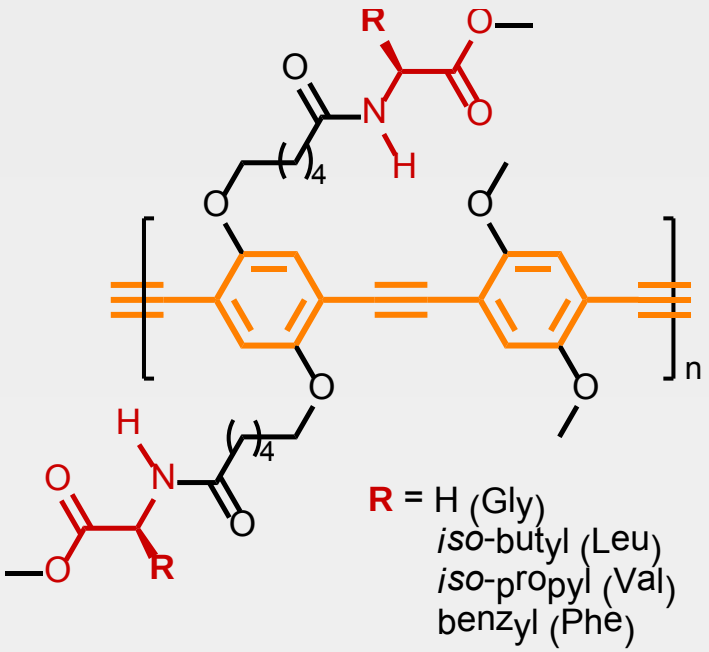


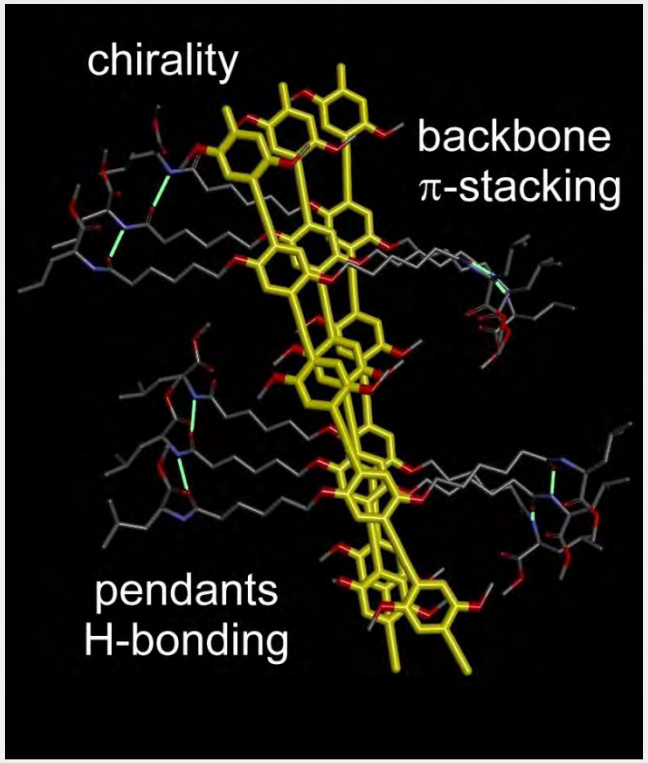


Macromolecules 2012, 9626

Chiral conjugated polymers

- Aminoacid-appended poly(phenyleneethylidene) (PPE)
- Role of chirality, steric hindrance, hydrogen bonds





Leu, Val, Phe

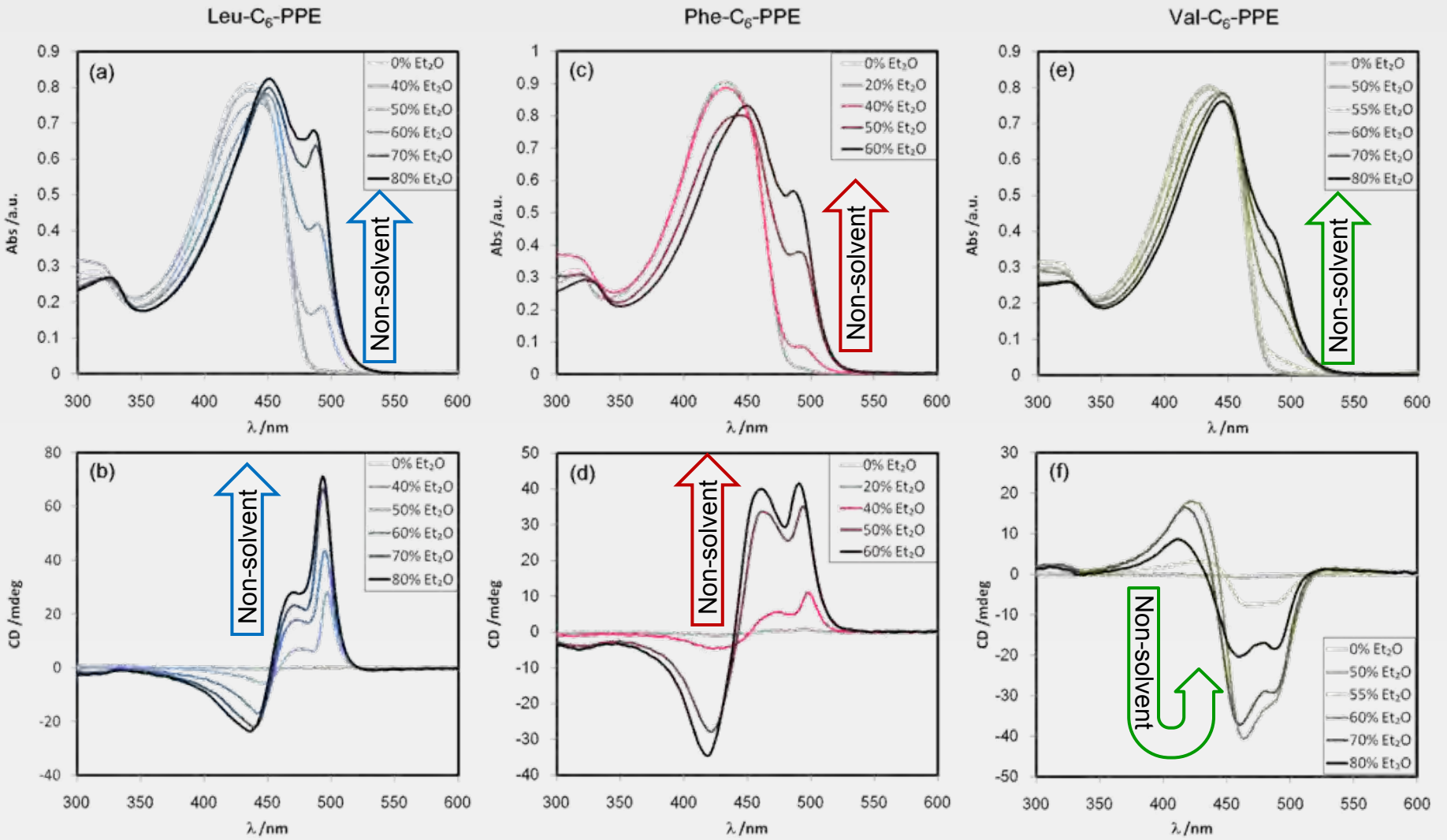
vs

Gly, *N*-Me-Leu

Macromolecules 2014, 7052

Chiral conjugated polymers

- Role of aminoacid side-chain: aggregate CD spectra

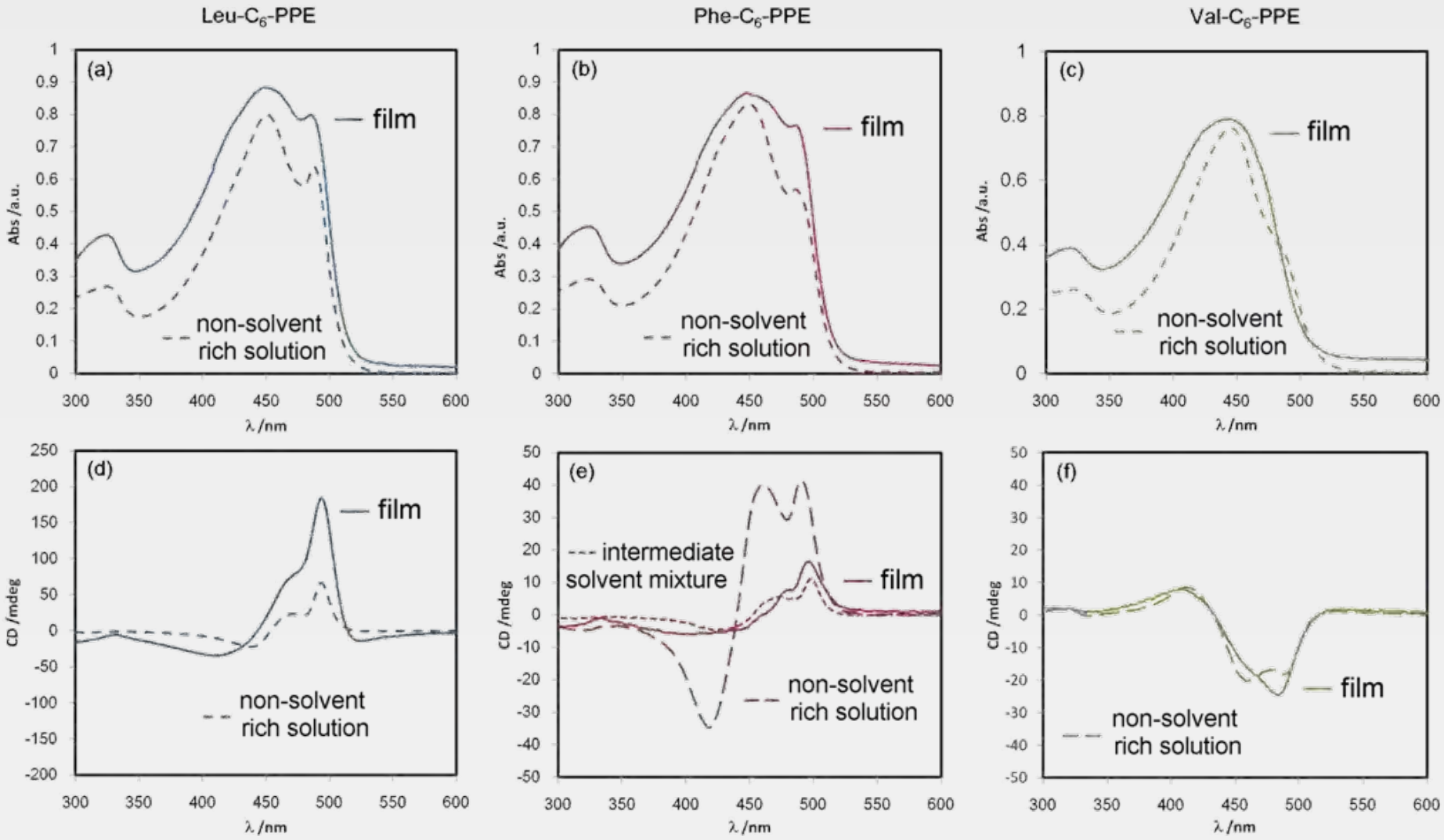


CH_2Cl_2/ether mixtures

Macromolecules 2014, 7052

Chiral conjugated polymers

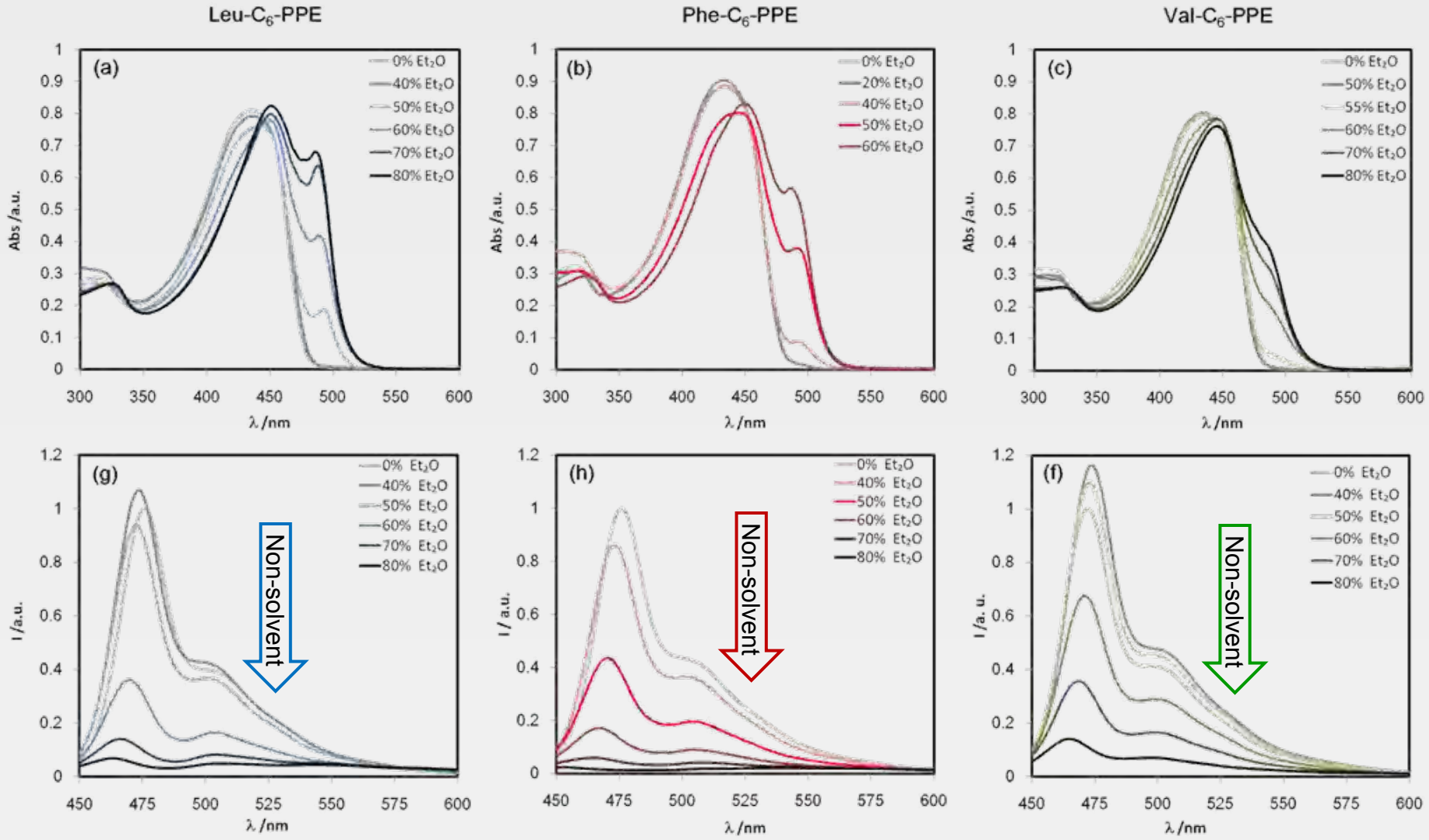
- Role of aminoacid side-chain: thin film spectra



Macromolecules 2014, 7052

Chiral conjugated polymers

- Role of aminoacid side-chain: fluorescence quenching



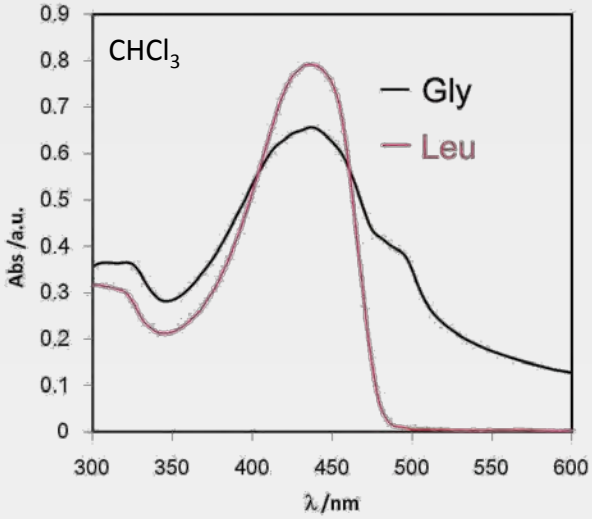
CH_2Cl_2/ether mixtures

Macromolecules 2014, 7052

Chiral conjugated polymers

- Aminoacid-appended poly(phenyleneethylidene) (PPE)
- Role of chirality and hydrogen bond

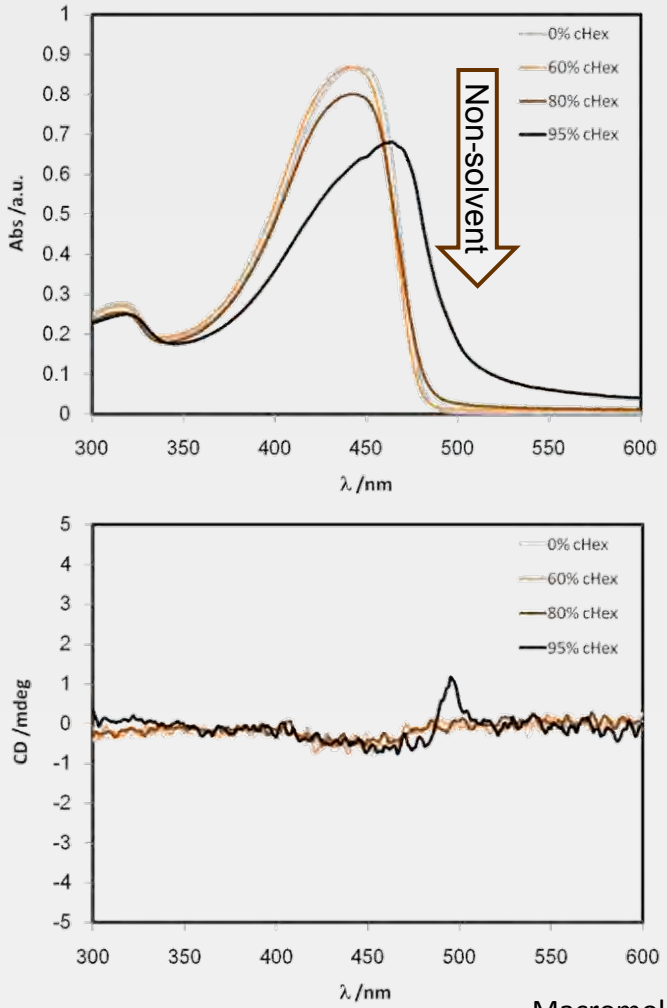
Gly-C6-PPE vs Leu-C6-PPE



Propensity to aggregate:

Gly ≫ Phe ≳ Leu > Val

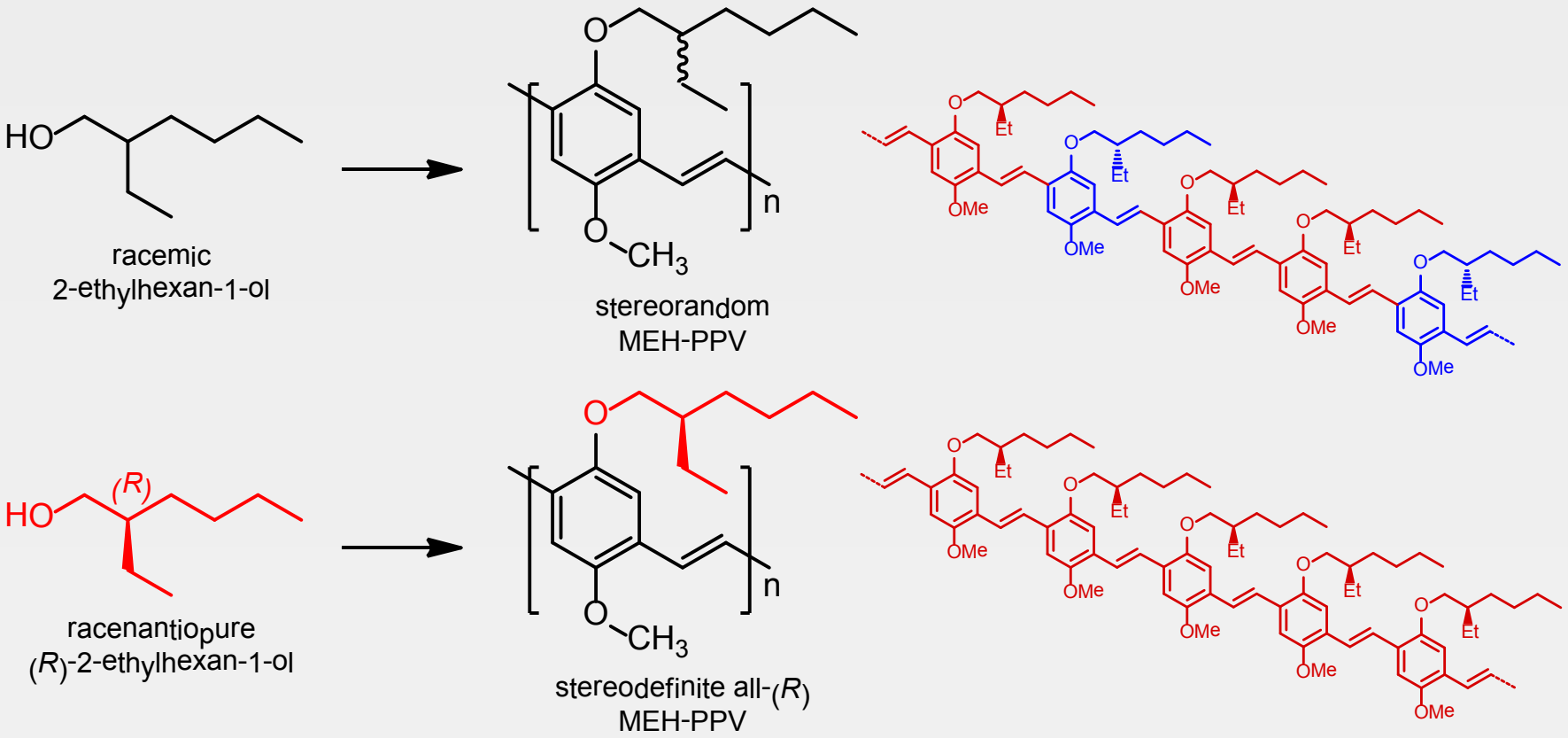
***N*-methyl-Leu-C6-PPE**



Macromolecules 2014, 7052

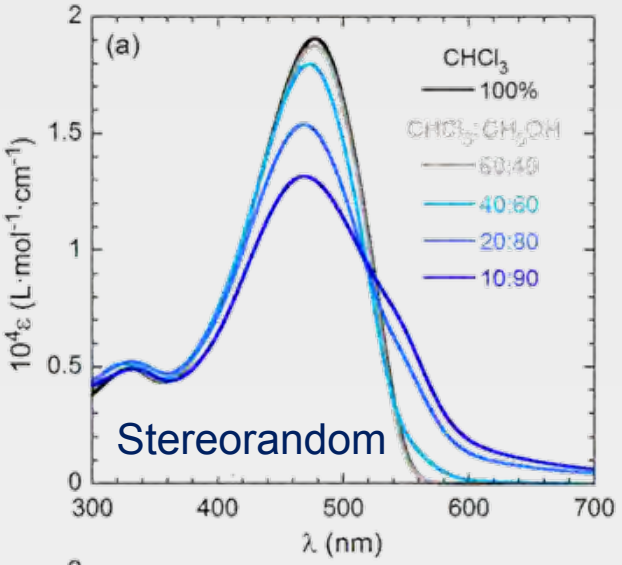
Chiral conjugated polymers

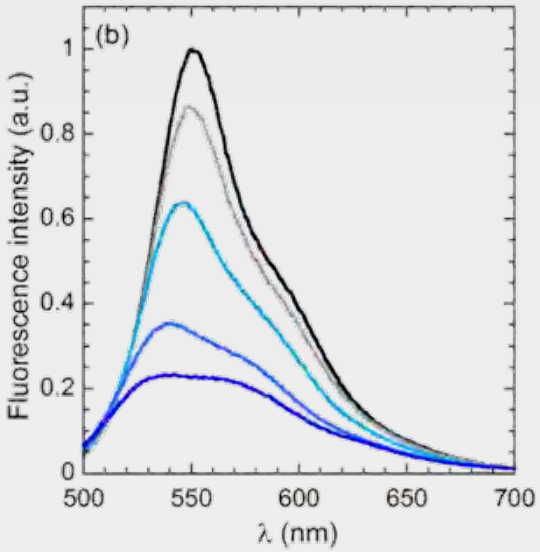
- Soluble poly(phenylenevinylene) (MEH-PPV)
- The first successful PPV used in sensors, field-effect transistors, LEDs
- Never described in stereodefinite form!

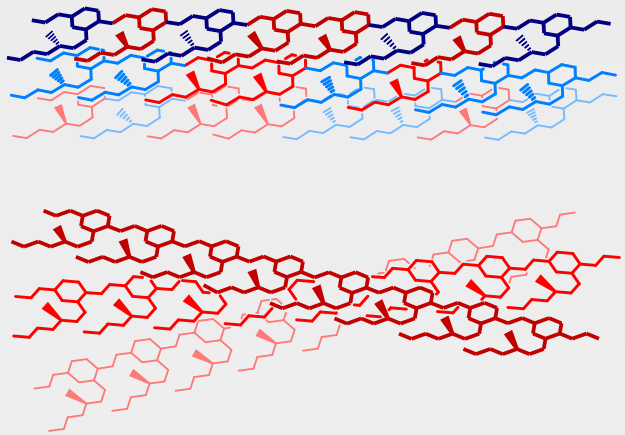


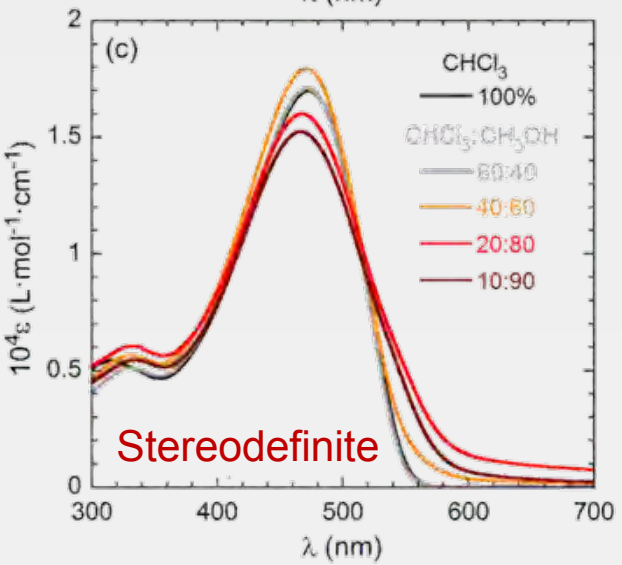
Macromolecules 2014, 4847

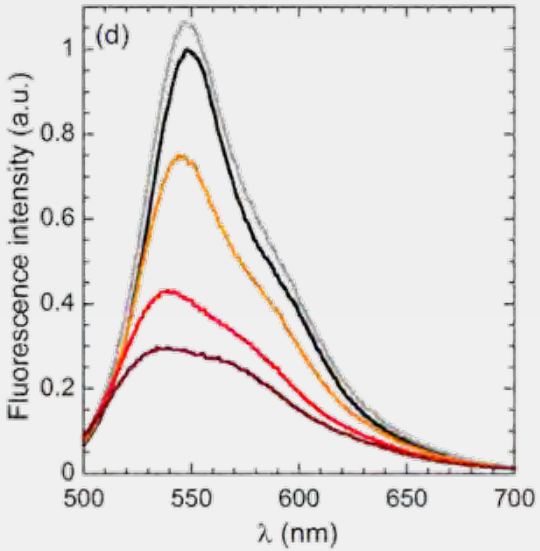
Chiral conjugated polymers

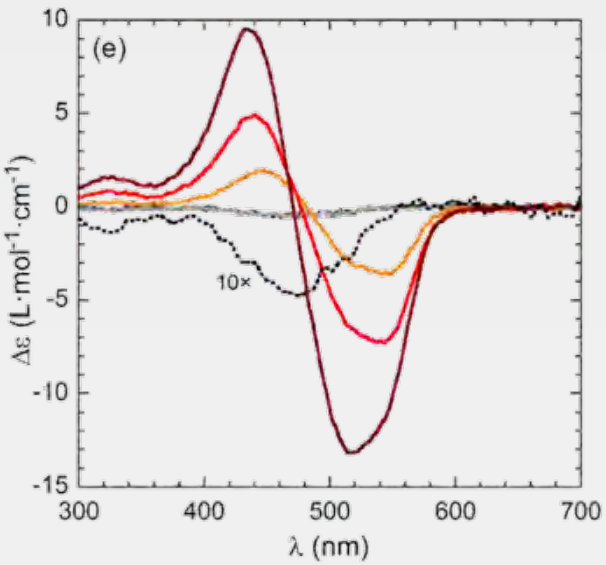








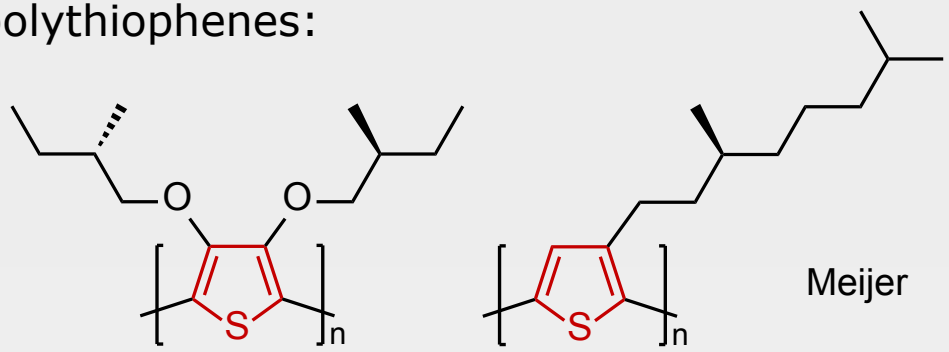




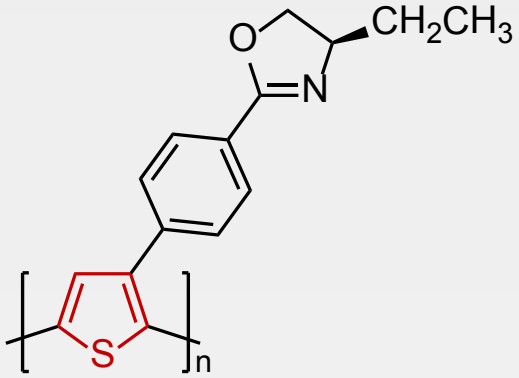
Macromolecules 2014, 4847

Chiral conjugated polymers

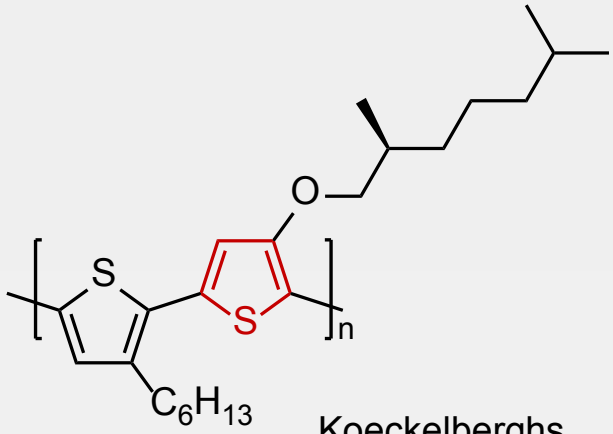
- Regioregular polythiophenes are among the most successful conjugated polymers for optoelectronic materials
- Chiral polythiophenes:



Meijer



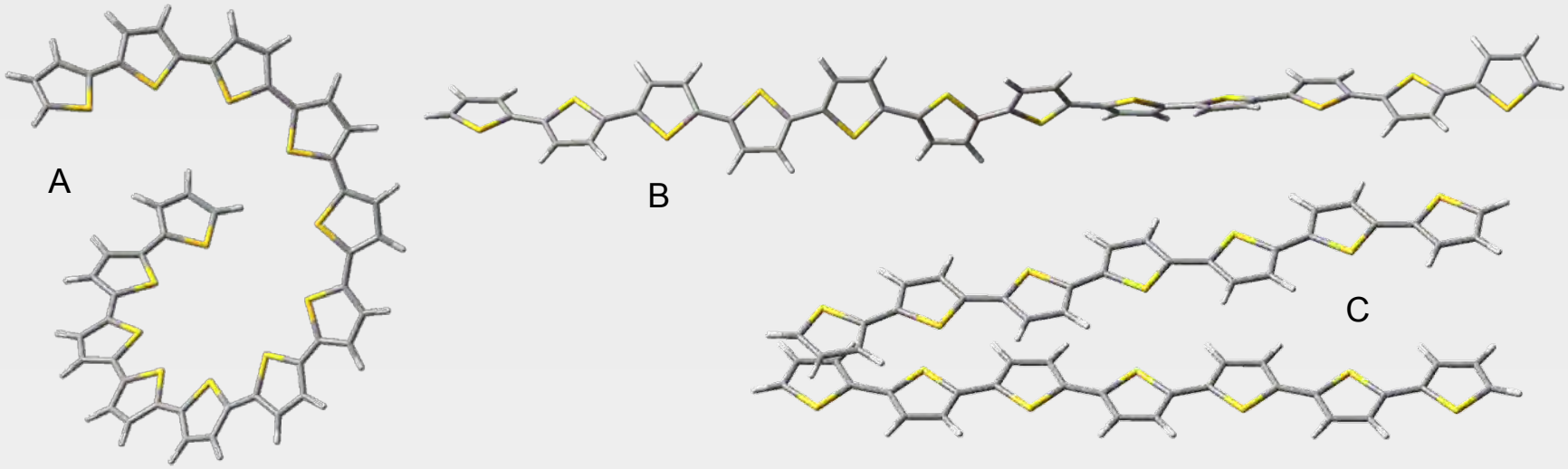
Yashima

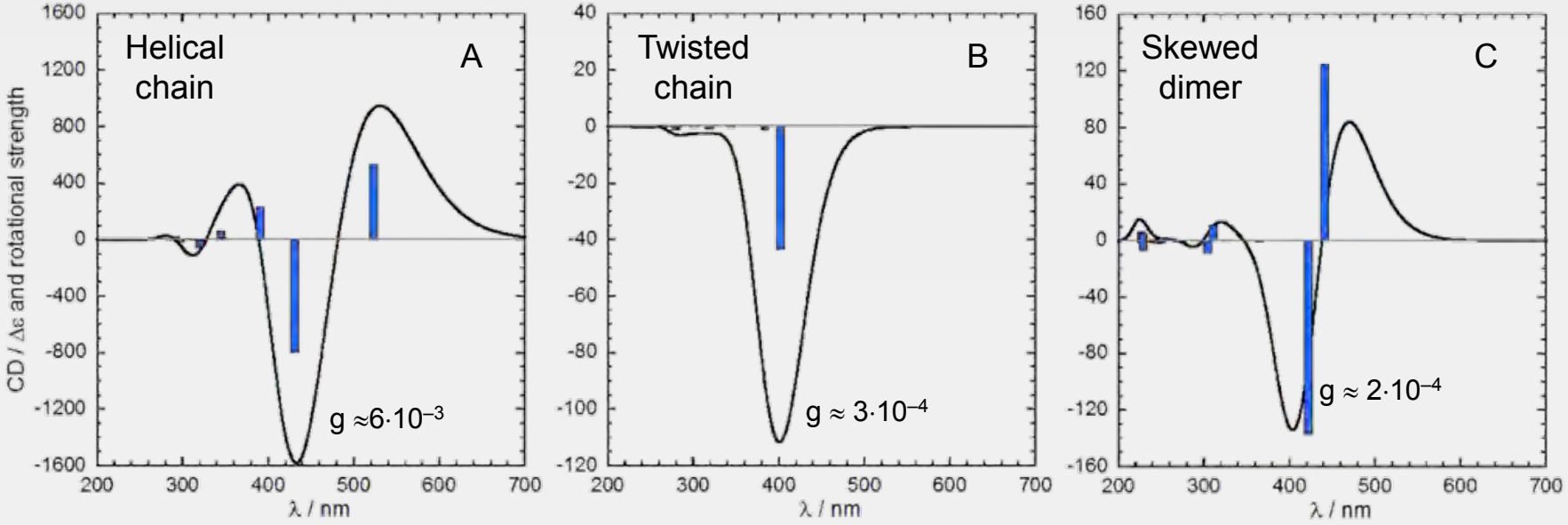


Koeckelberghs

Janssen et al. J Mol Struct 2000, 285

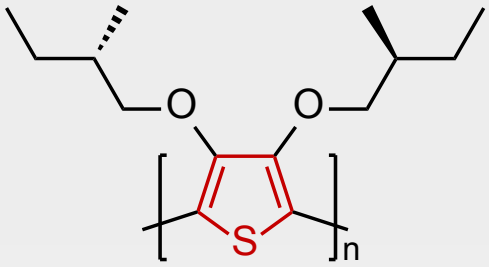
Intrachain vs. interchain chirality



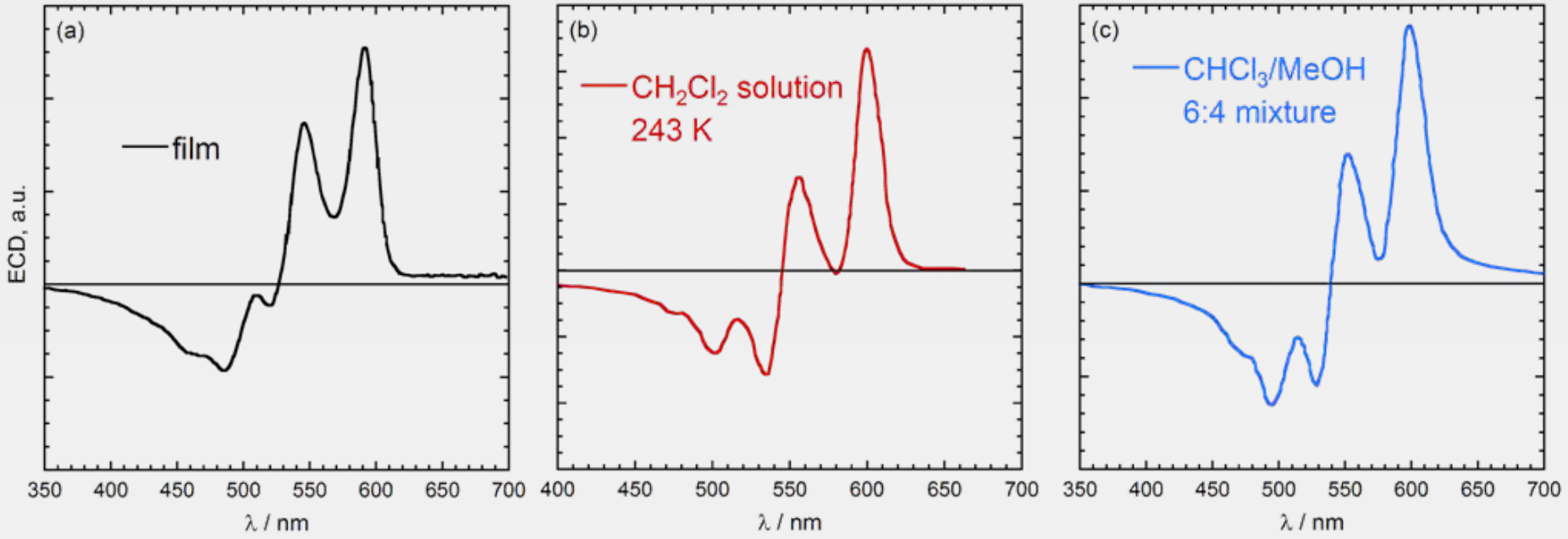


Chiral conjugated polymers

- Aggregate CD spectra often show pronounced vibronic features
- Vibronic exciton-coupled CD spectra are a fingerprint of aggregation



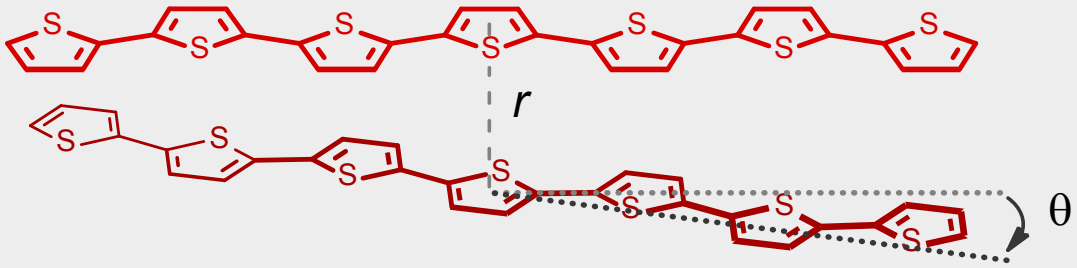
poly{3,4-bis[(S)-2-methylbutoxy]thiophene}
(PBMBT)

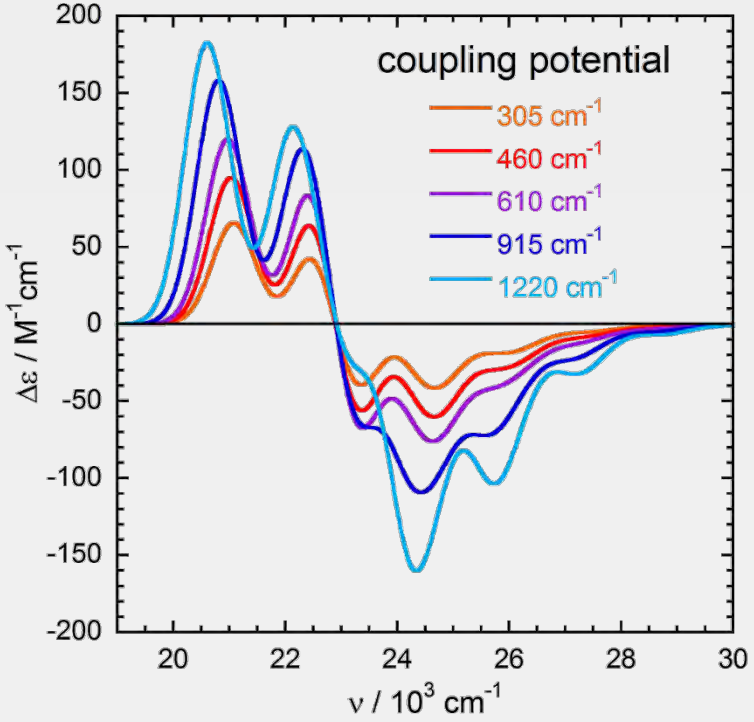


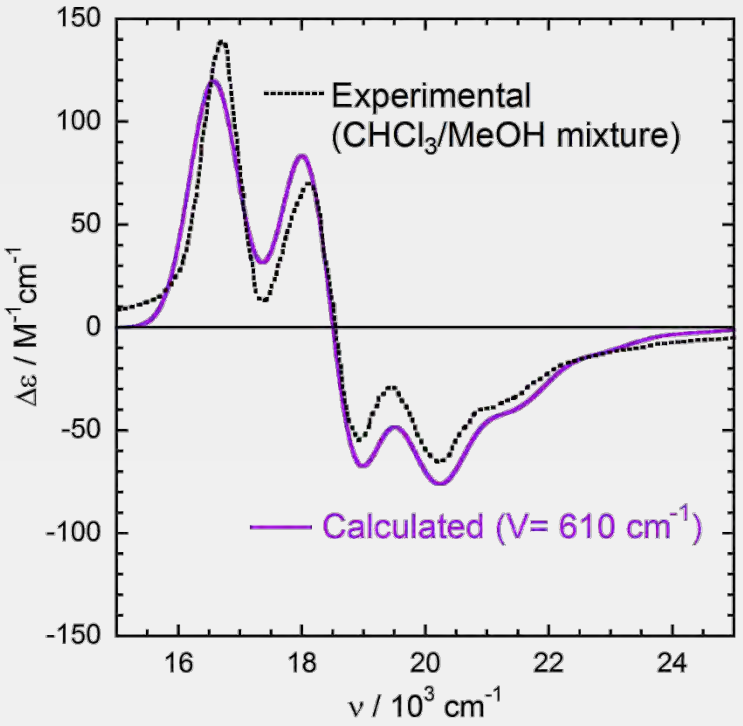
Janssen et al. J Mol Struct 2000, 285

Chiral conjugated polymers

- A simple dimeric model may reproduce the fingerprint CD spectra
- The coupling potential V_{12} is sampled by varying distance and angle



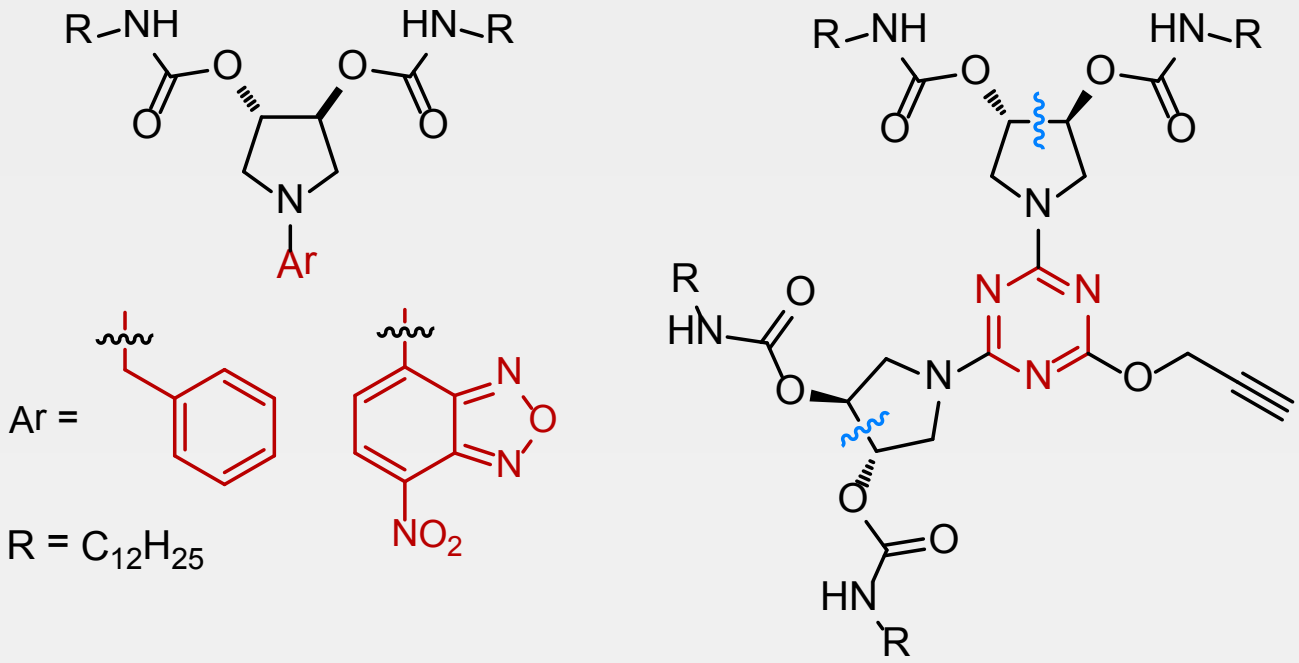




Harshly rejected

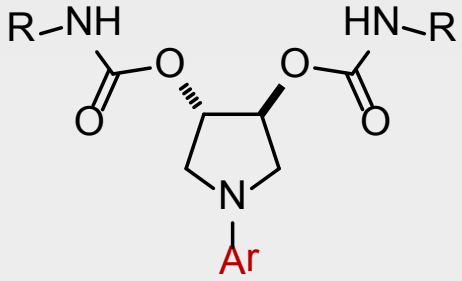
Chiral organogels

- Organogels are often based on chiral scaffolds
- Gelling properties due to long alkyl chains
- Aggregates formed by π-interactions and hydrogen bonds
- Self-sorting phenomena (racemate vs enantiopure gelation)
- CD detection of phase transitions and structural information



Chiral organogels

- Pyrrolidine + carbamate + benzofurazane



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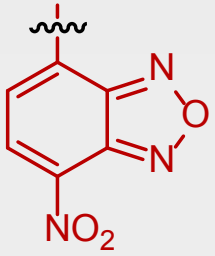
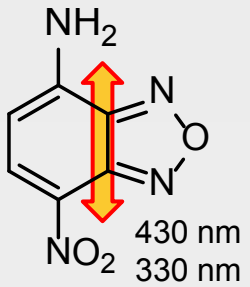
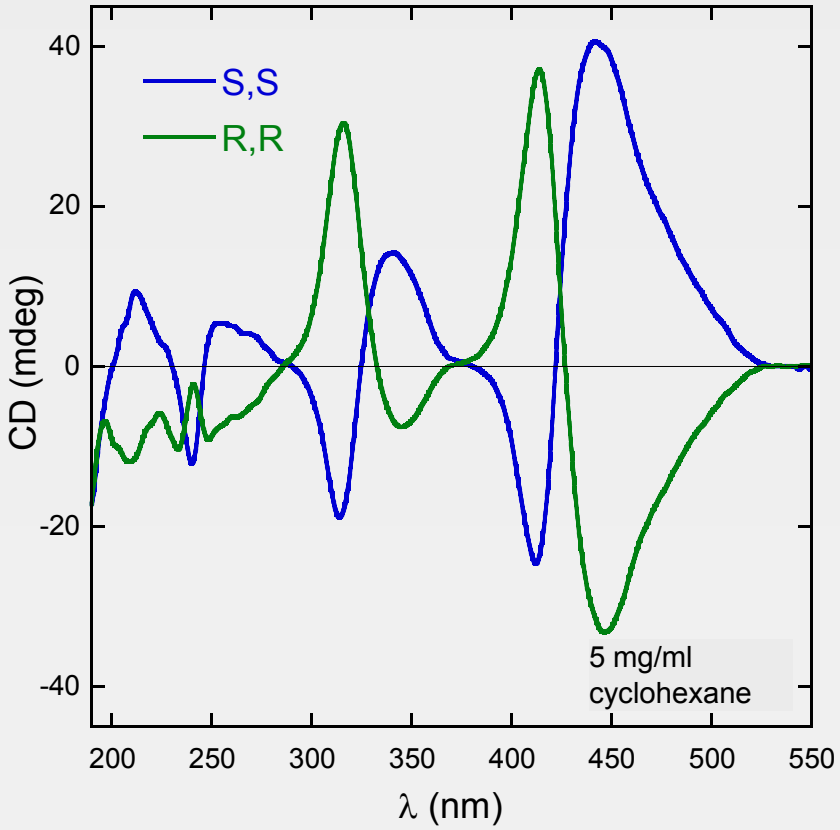
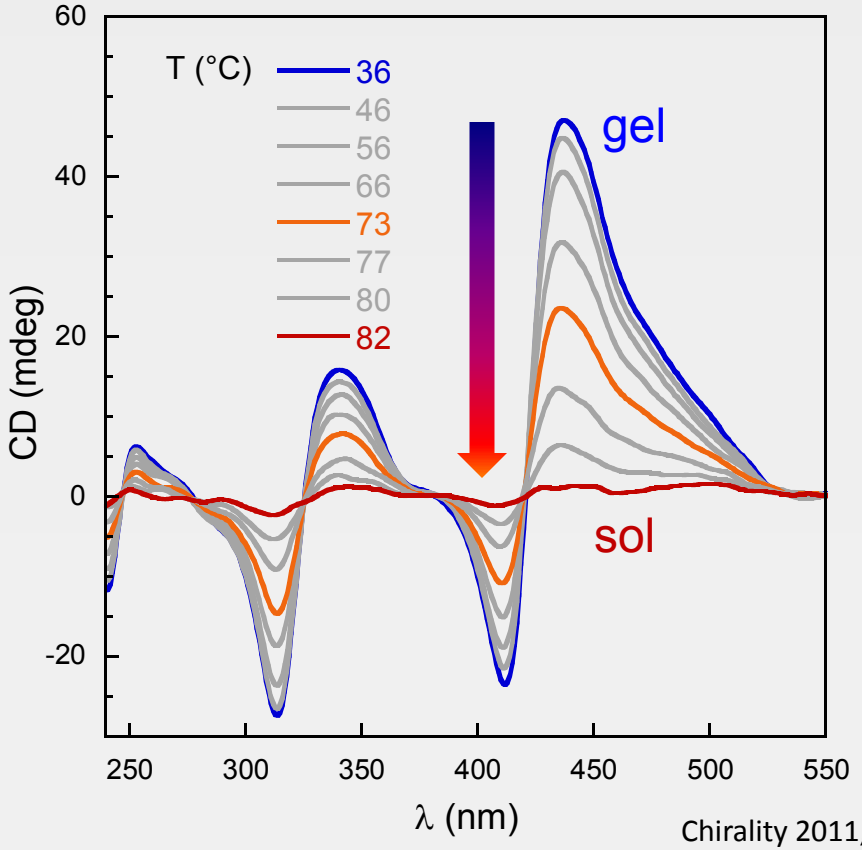


R = $C_{12}H_{25}$



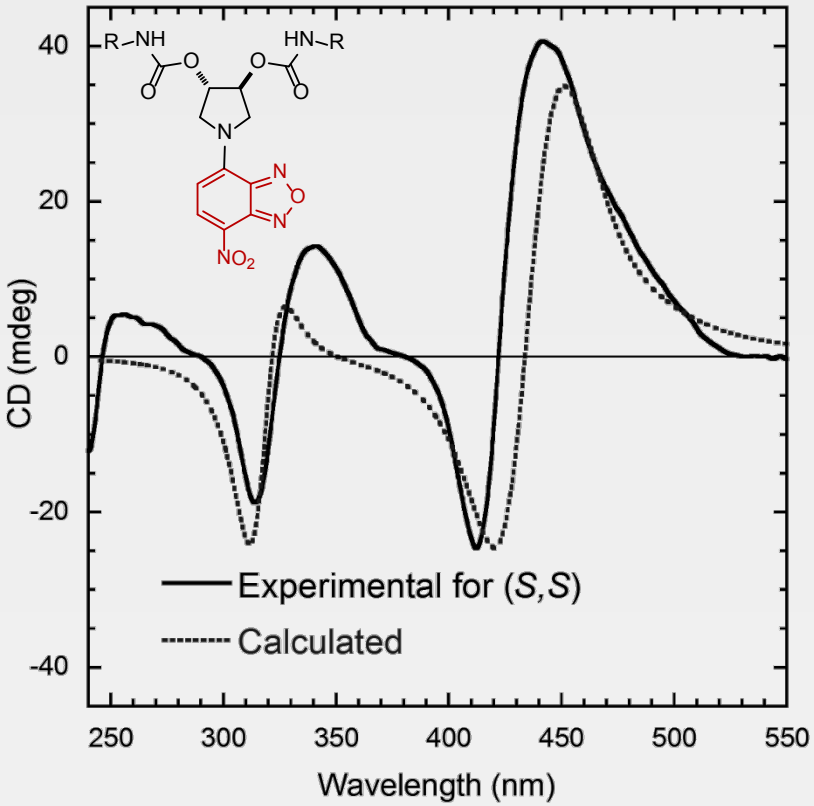


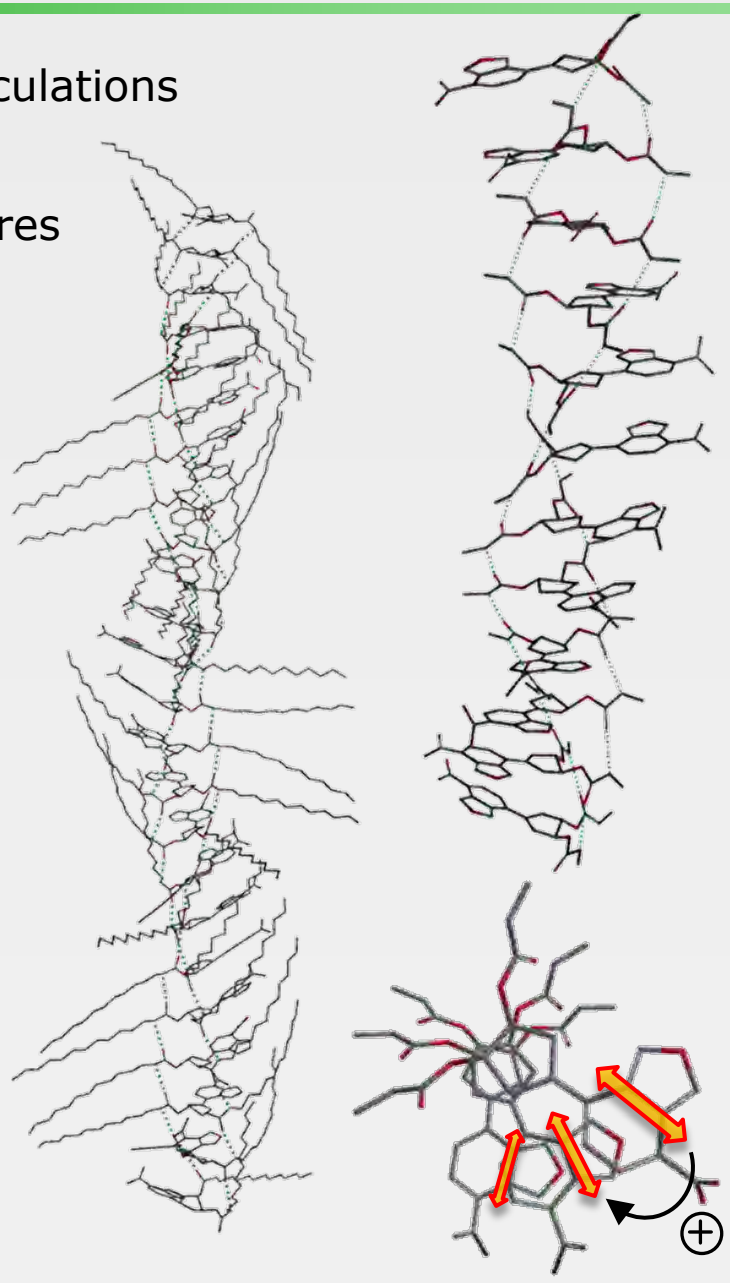


Chirality 2011, 833

Chiral organogels

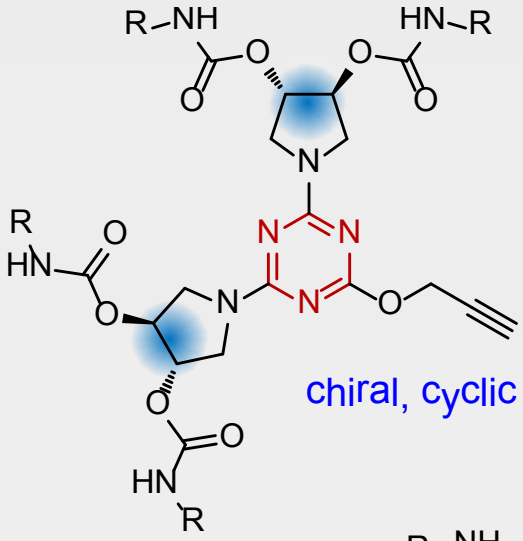
- Quantitative exciton coupled-CD calculations (DeVoe method)
- Validation of supramolecular structures (from MM or MD simulations)





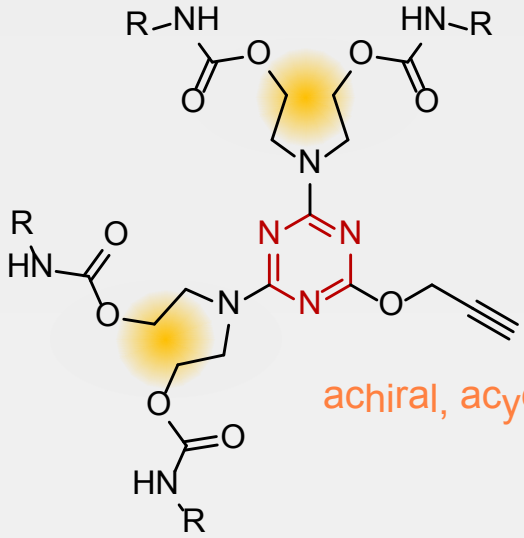
Chiral organogels

- Pyrrolidine + carbamate + triazine

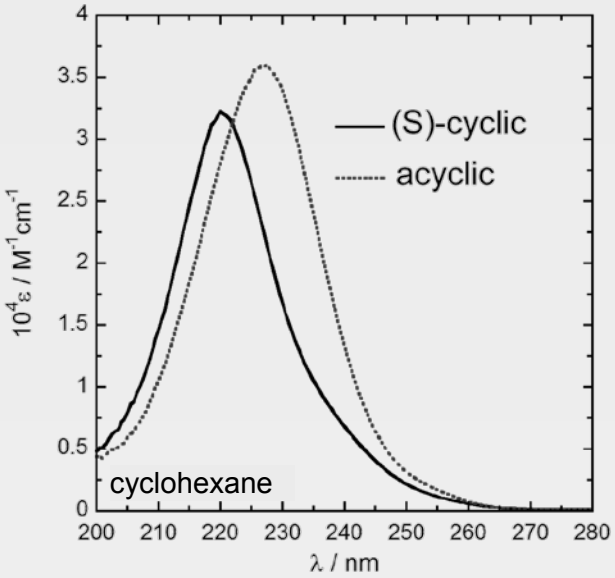


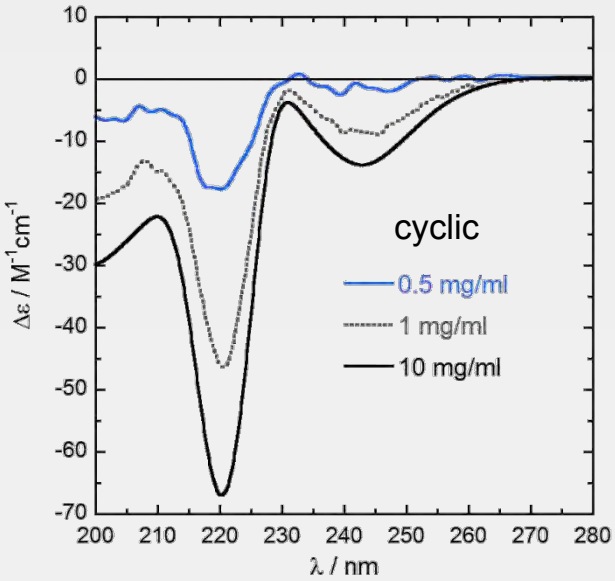
chiral, cyclic

R = $C_{12}H_{25}$



achiral, acyclic

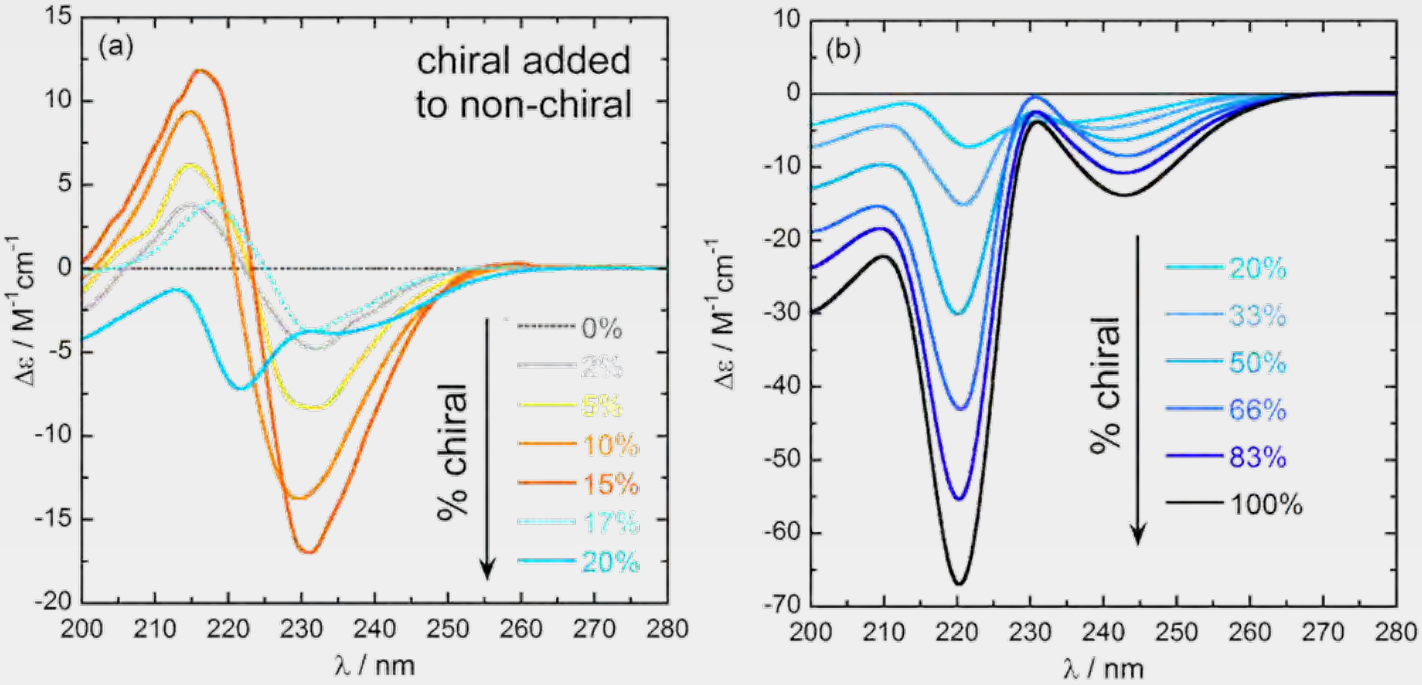


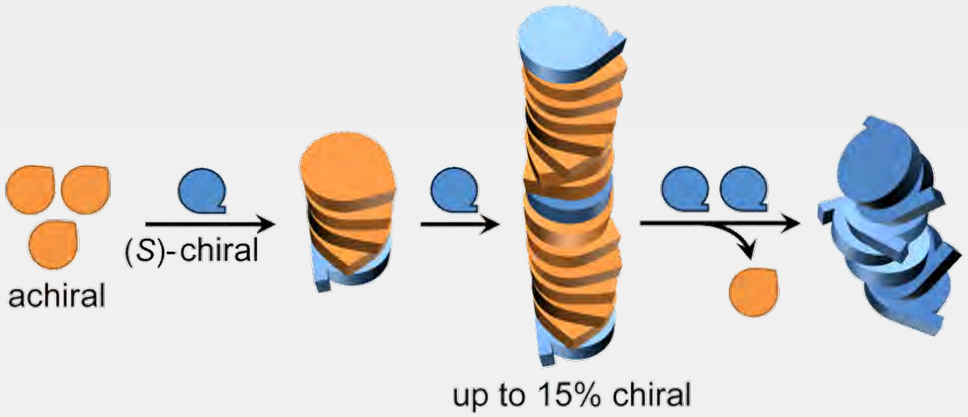


Soft Matter 2014, 3762

Chiral organogels

- Chiral + Achiral mixtures: amplification of chirality

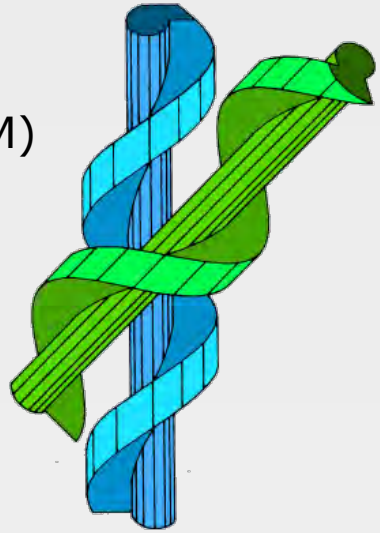


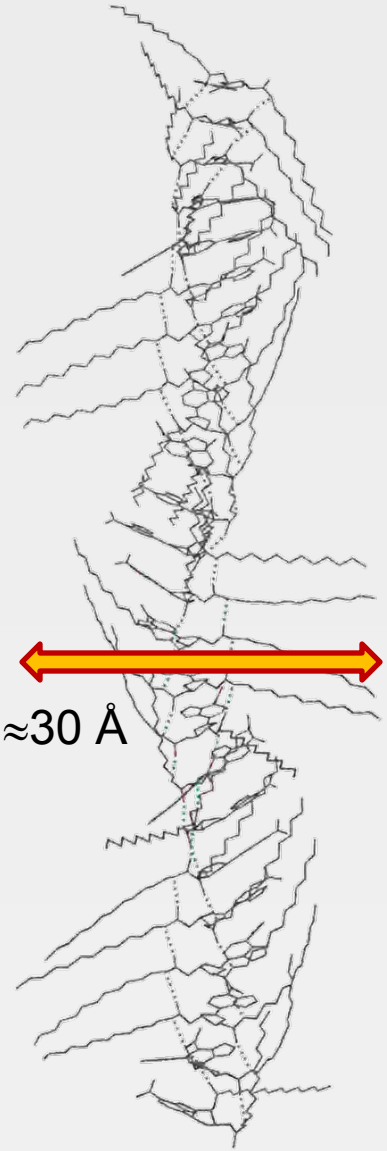


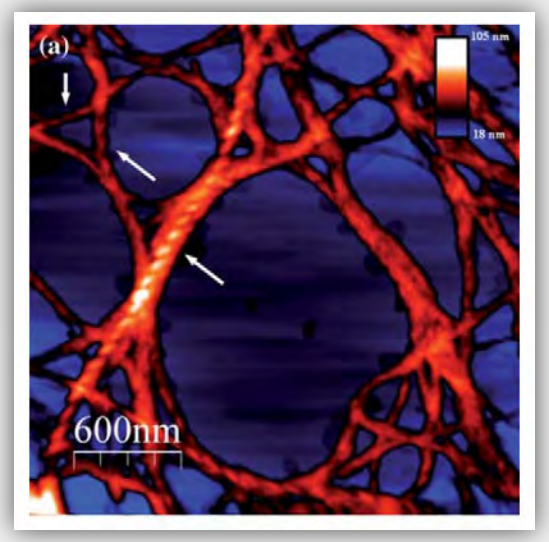
Soft Matter 2014, 3762

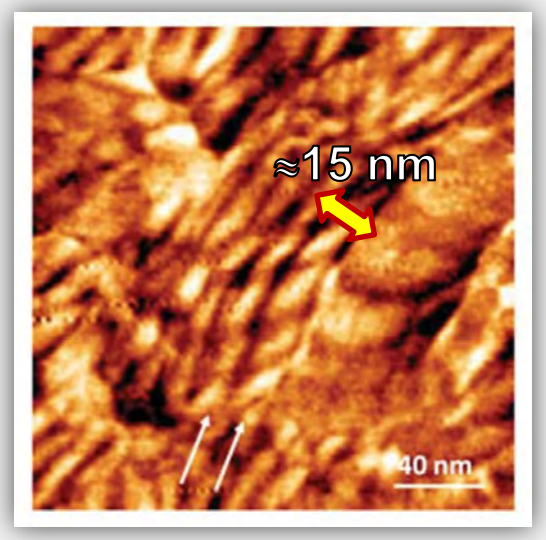
Helicity at different scales

- Nano-scale helical fibers detected by microscopy techniques (AFM, SEM, TEM) are usually a bundle of several molecular-scale helical structures
- The sense of helicity at the two levels is not immediately correlated



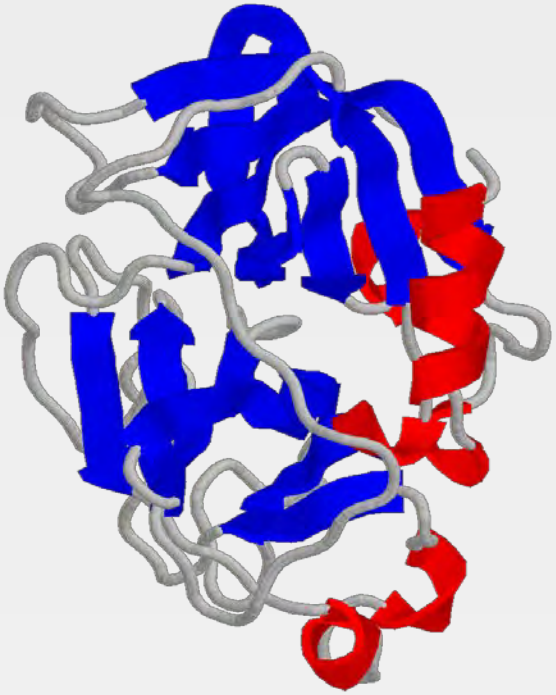


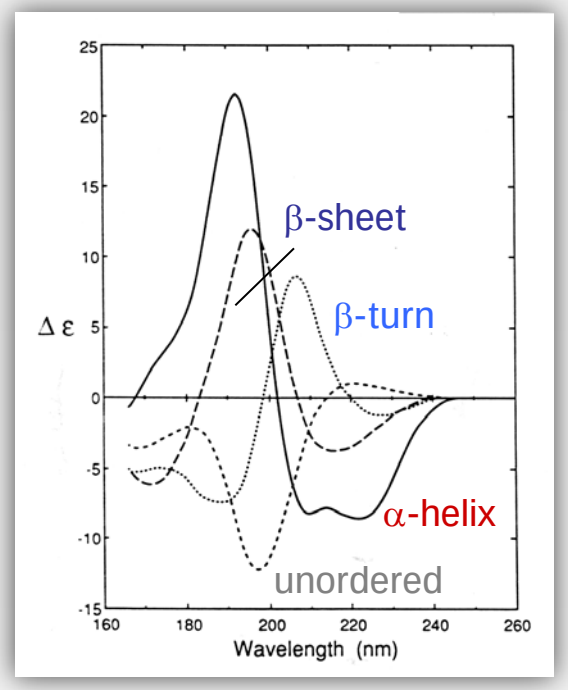


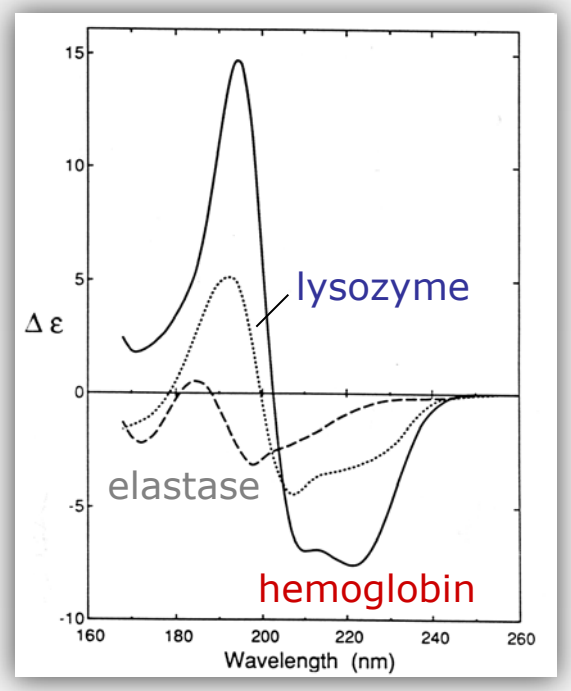


Proteins and CD

- CD of peptides and proteins is very sensitive to secondary structure
- Used as a tool for secondary structure fraction estimation





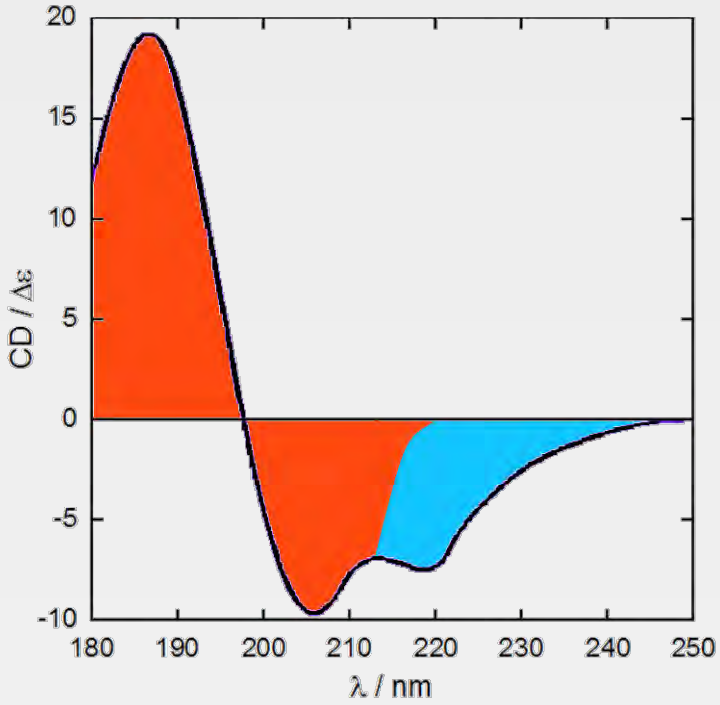


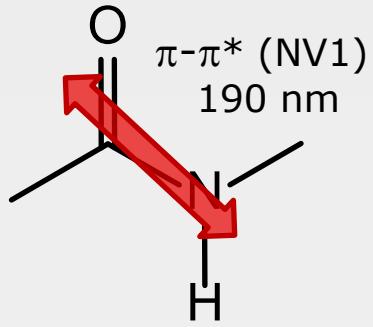
hemoglobin	76% α	0% β	10% turn	14% random
lysozyme	42% α	6% β	30% turn	22% random
elastase	11% α	34% β	21% turn	34% random

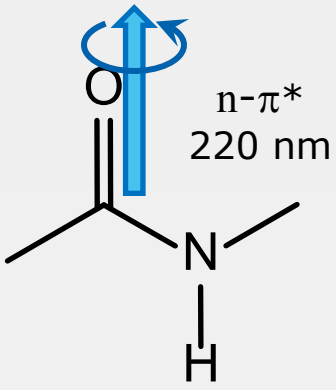
Woody et al. Meth Enzymol 2004, 318

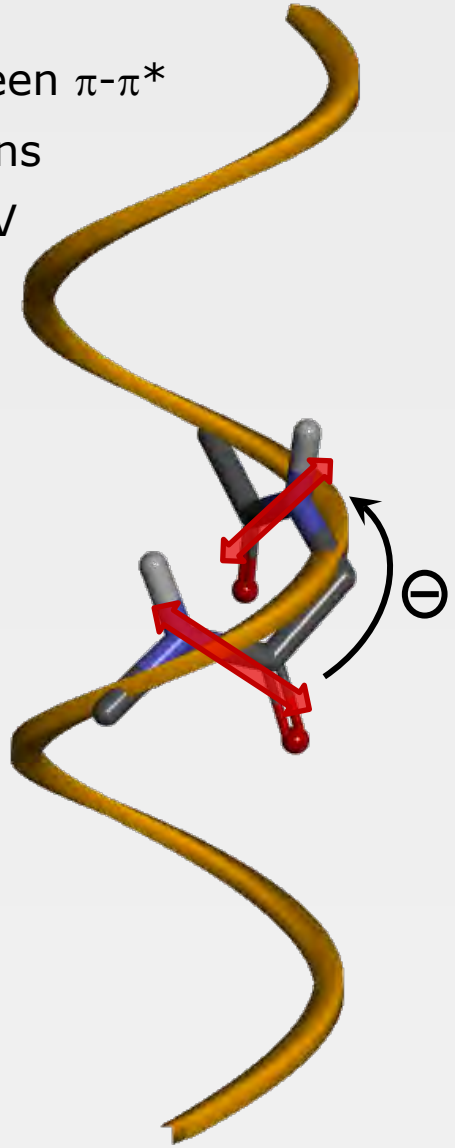
Proteins and CD

- α-Helix CD is dominated by exciton coupling between π-π* transitions, plus a contribution from n-π* transitions
- Side-chain chromophores contribute in the near-UV





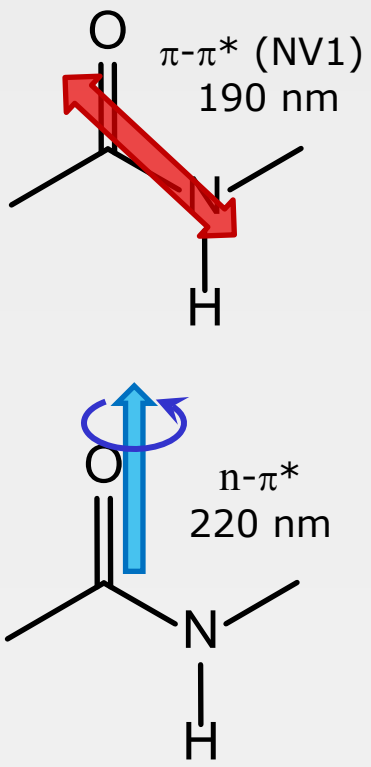


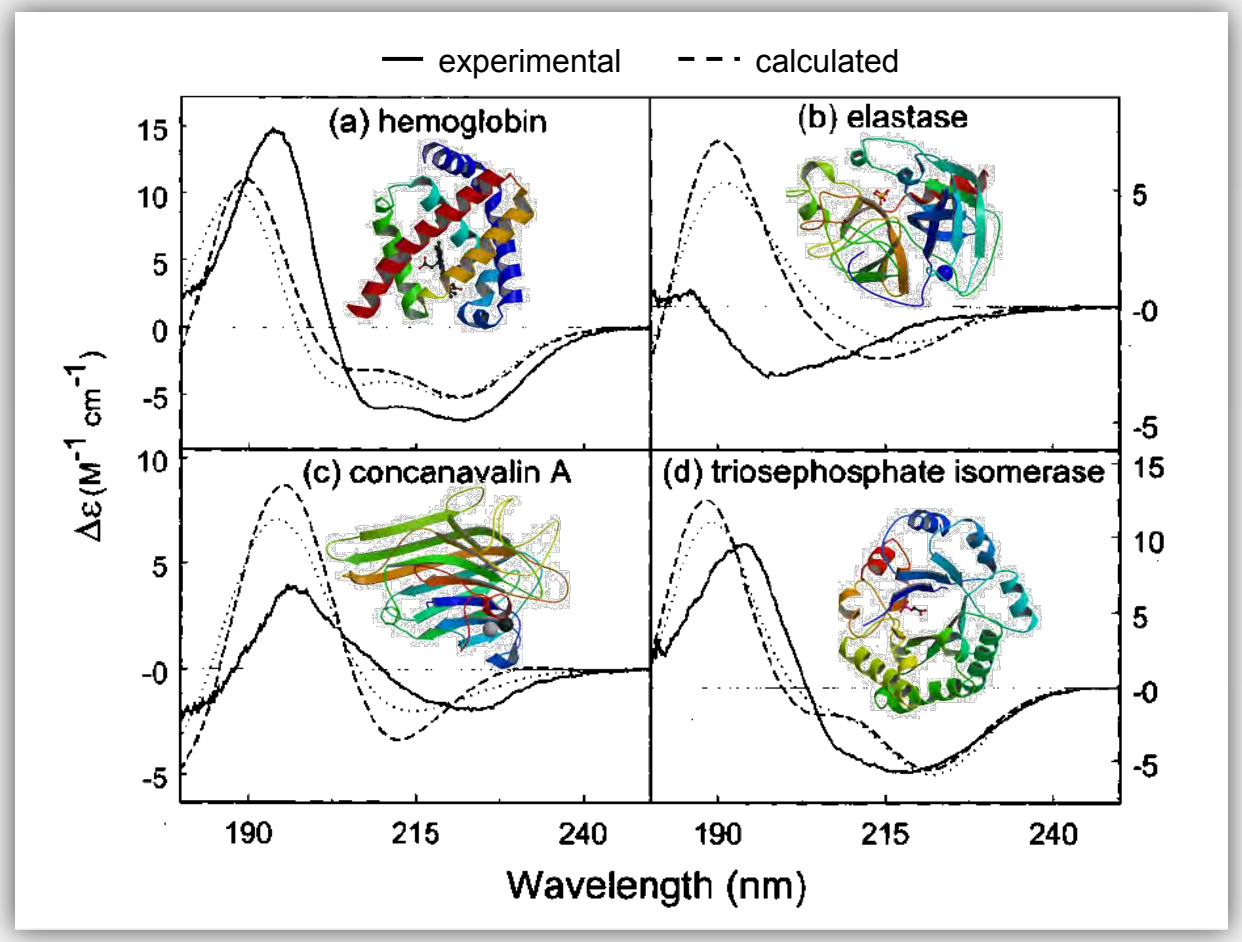


Woody et al. Meth Enzymol 2004, 318

Proteins and CD

- A full calculation of protein CD is accomplished by matrix methods
- Choice of parameters (energy, direction, intensity) is crucial
- Additional transitions: amide NV2 (140 nm), side-groups

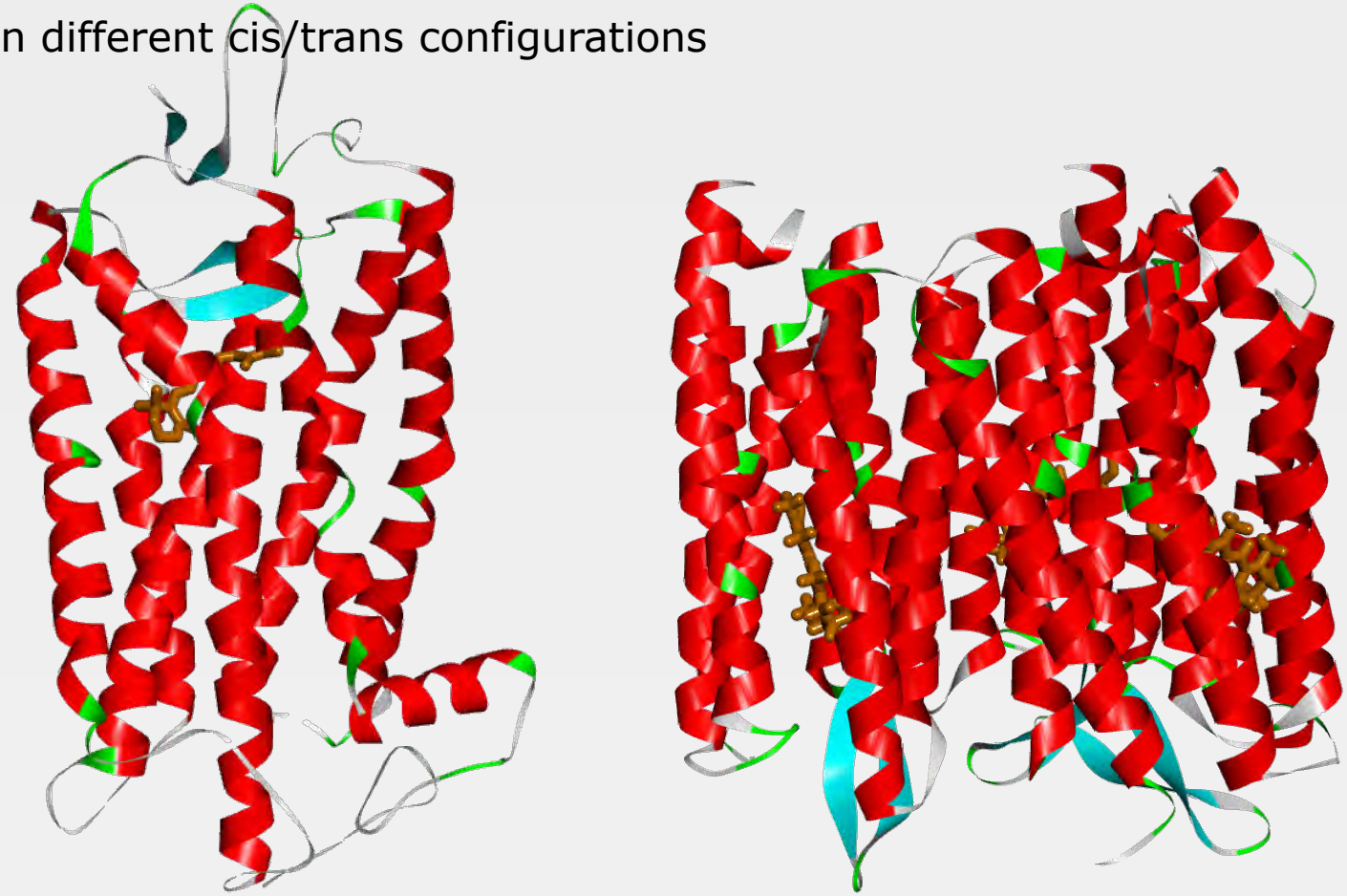




Woody et al. Meth Enzymol 2004, 318

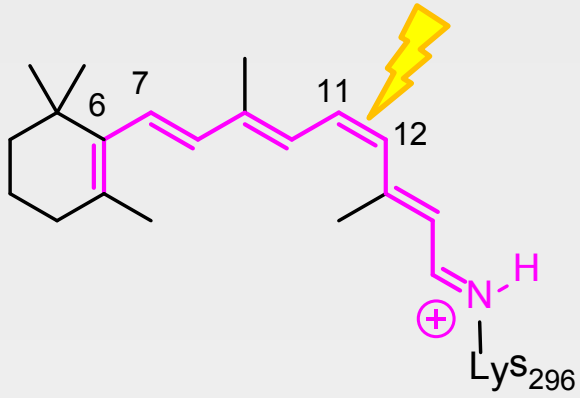
Retinylidene proteins (opsins)

- A family of G-protein coupled receptor (GPCR) proteins
- Protein structure: 7 transmembrane α-helices
- Chromophore: retinal protonated Schiff-base (retPSB) in different cis/trans configurations

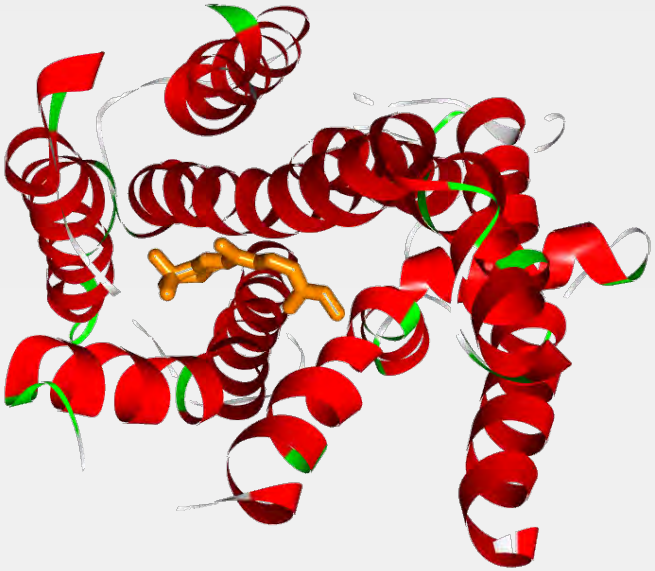


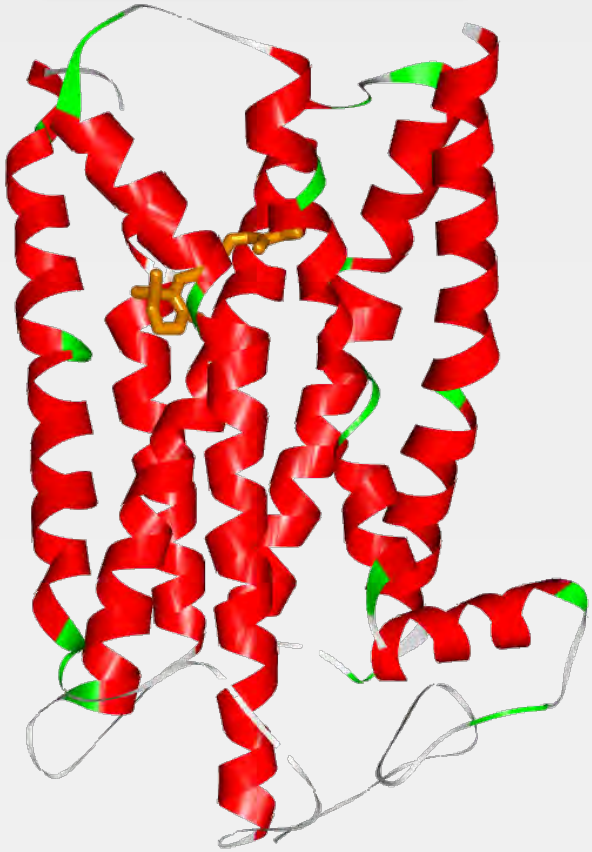
Type II opsin: rhodopsin

- Rhodopsin: visual protein

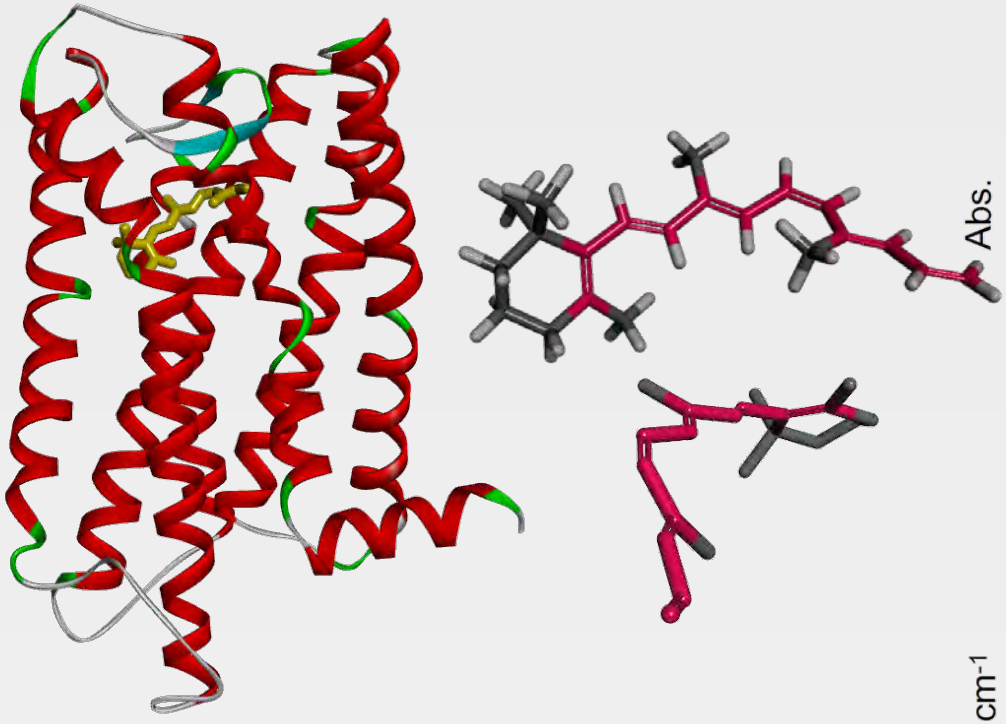


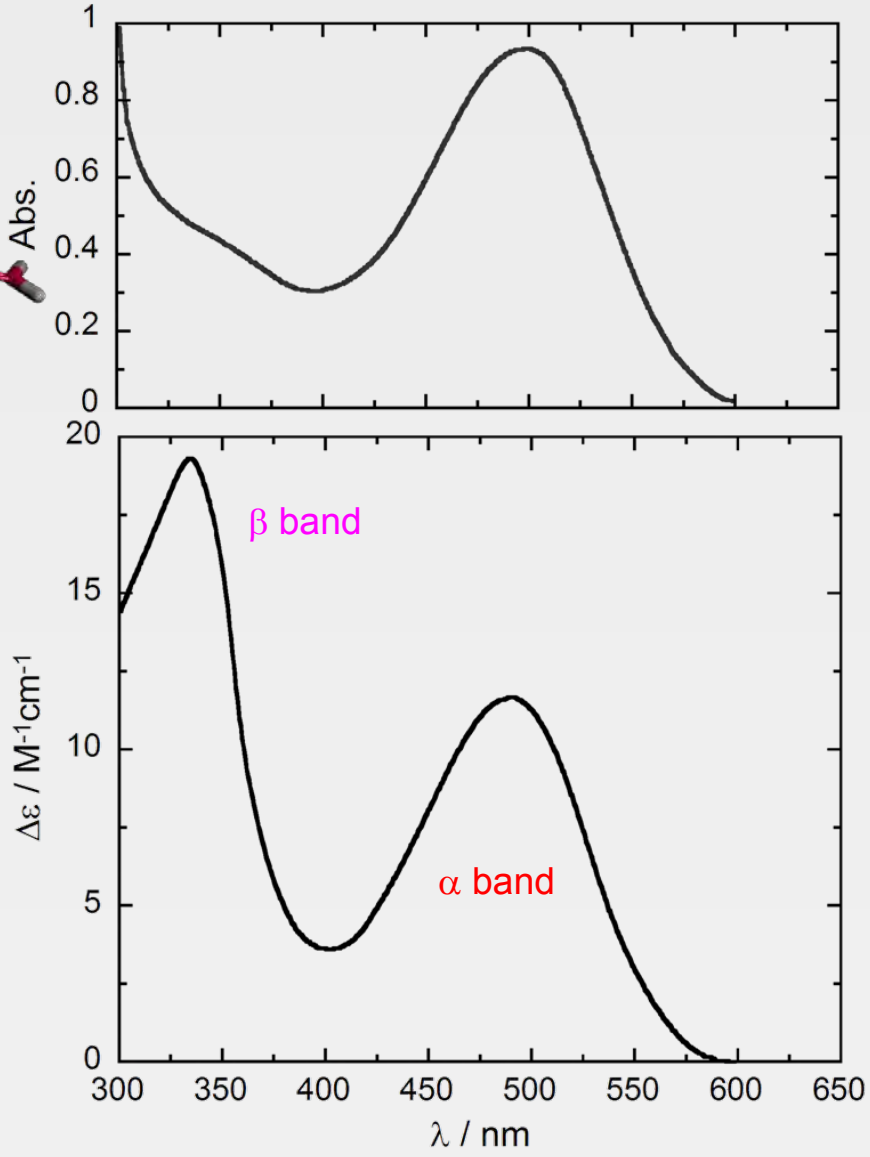
6-*s*-cis-11-trans-retinal protonated Schiff base (retPSB)





Type II opsin: rhodopsin





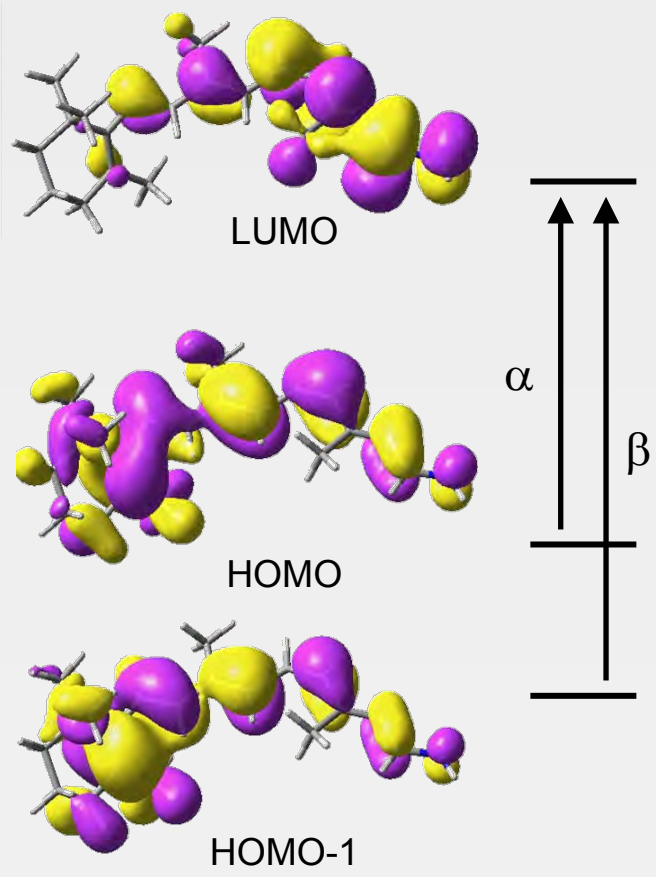
Possible contributions to visible-CD spectrum:

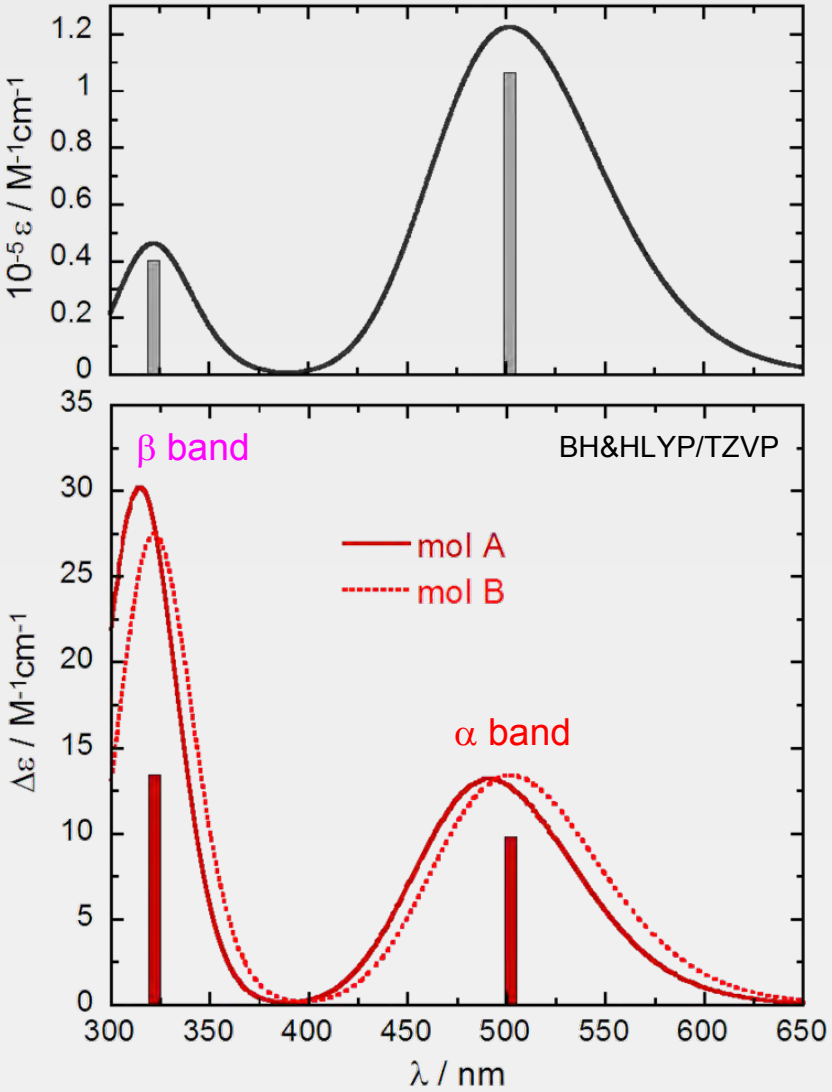
- Intrinsic chirality of RetPSB
- RetPSB / peptide couplings
- RetPSB / aromatic couplings

X-ray: Palczewski, et al. Science 2000, 6171; Okada et al. PNAS 2002, 5982

Type II opsin: rhodopsin

- TDDFT calculations on retPSB
- Geometry taken from X-ray structure (2.2 Å, two mols/unit cell)

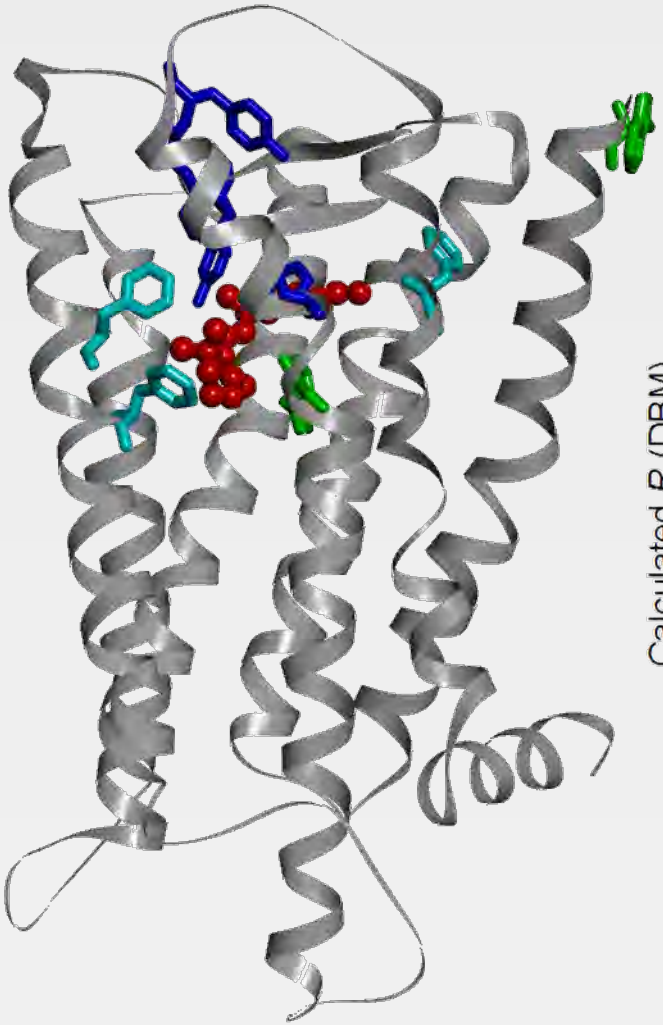


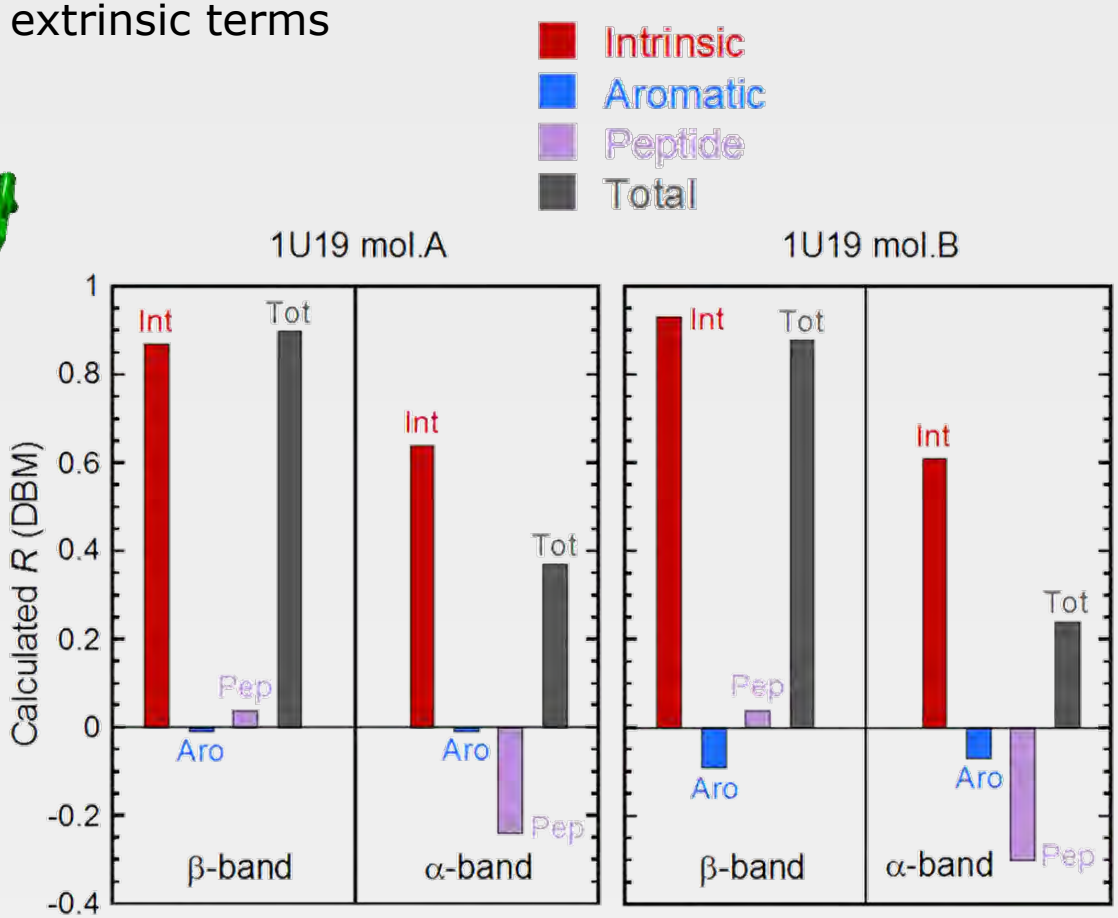


JACS 2008, 6170

Type II opsin: rhodopsin

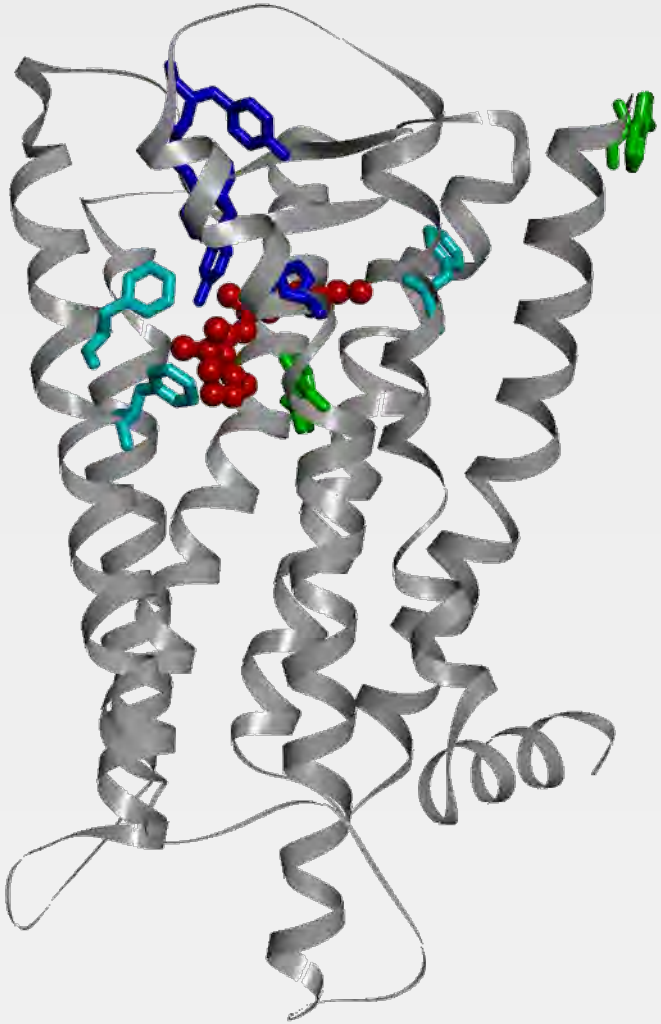
- Matrix calculations of extrinsic terms

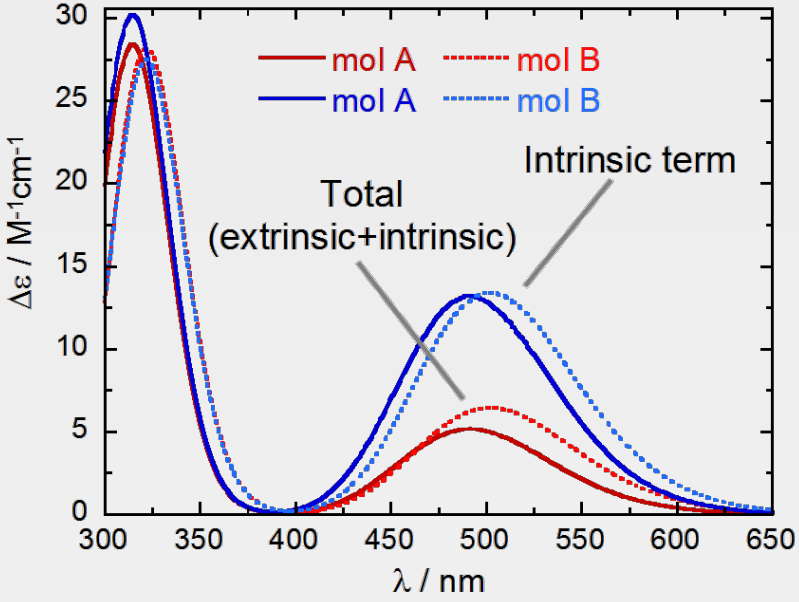




JACS 2008, 6170

Type II opsin: rhodopsin



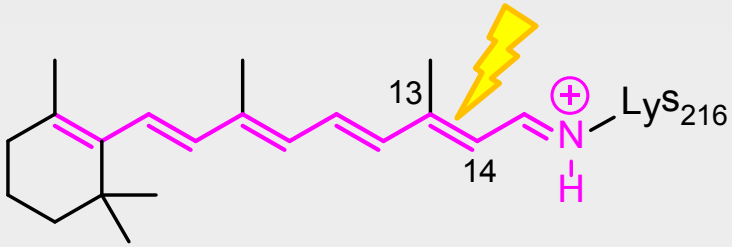


The near UV/vis-CD of rhodopsin is largely determined by the intrinsic chirality of the retPSB chromophore

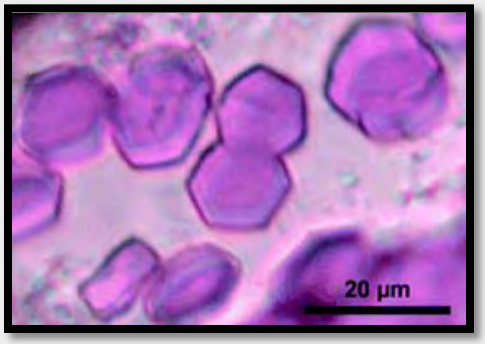
JACS 2008, 6170

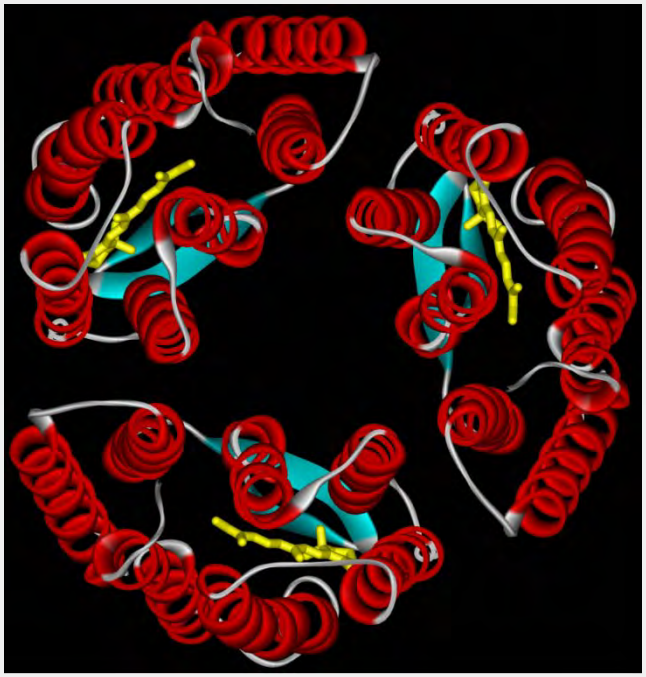
Type I opsin: bacteriorhodopsin

- Bacteriorhodopsin: purple membrane protein

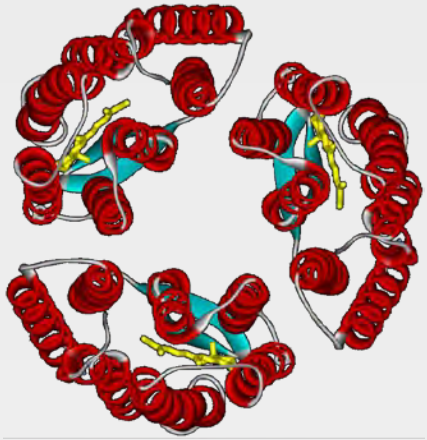


all-trans retinal protonated Schiff base (retPSB)



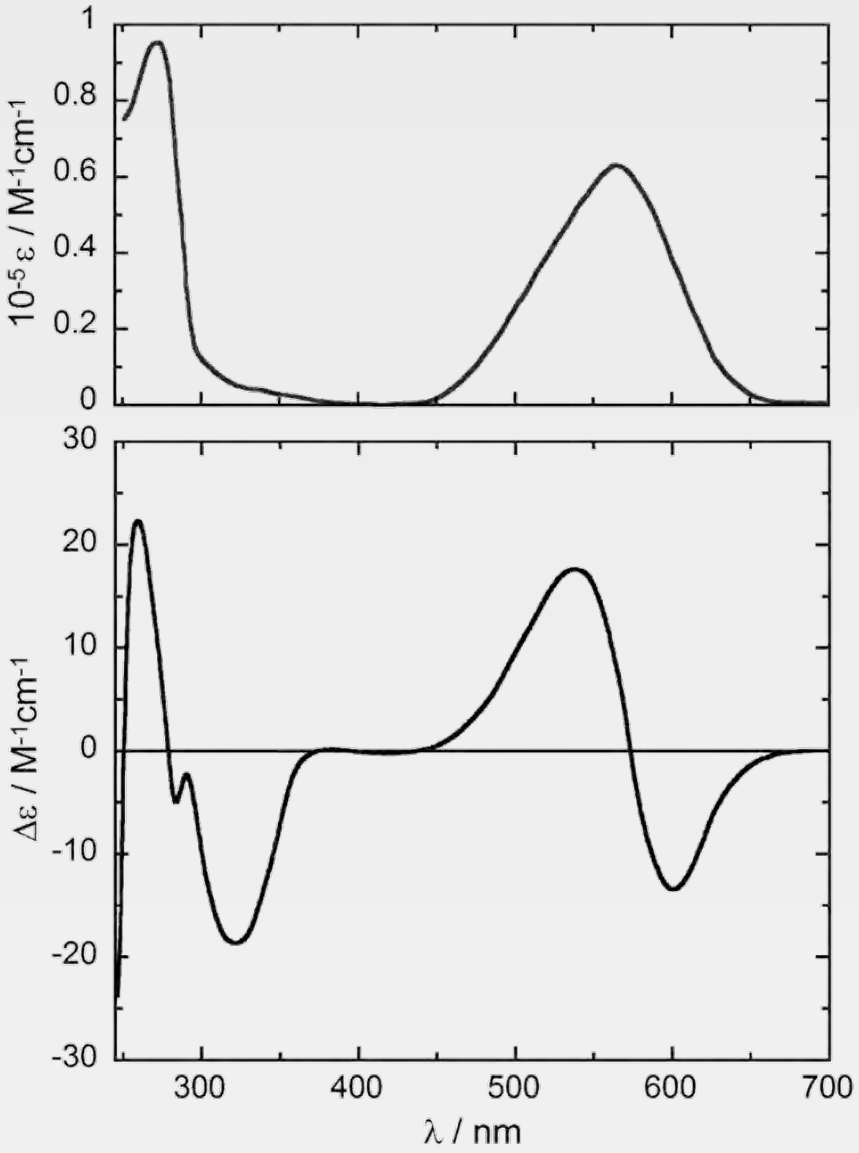


Type I opsin: bacteriorhodopsin



Possible contributions to visible-CD spectrum:

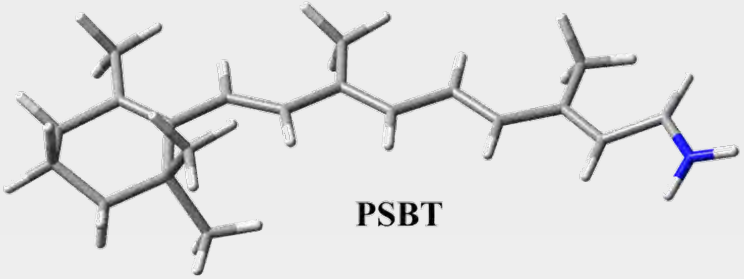
- Exciton-coupling in-trimer
- Exciton coupling between trimers
- Intrinsic chirality of RetPSB
- RetPSB / peptide couplings
- RetPSB / aromatic couplings

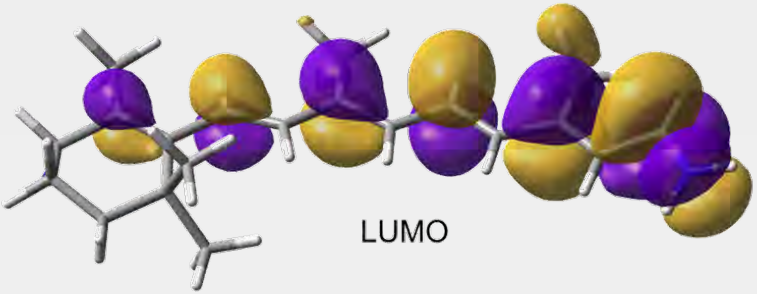


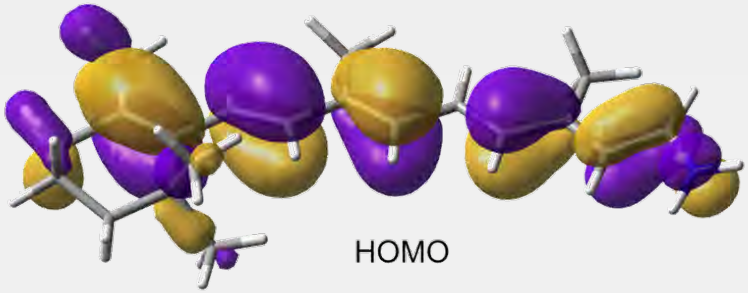
X-ray: Luecke et al. J Mol Biol 1999, 899

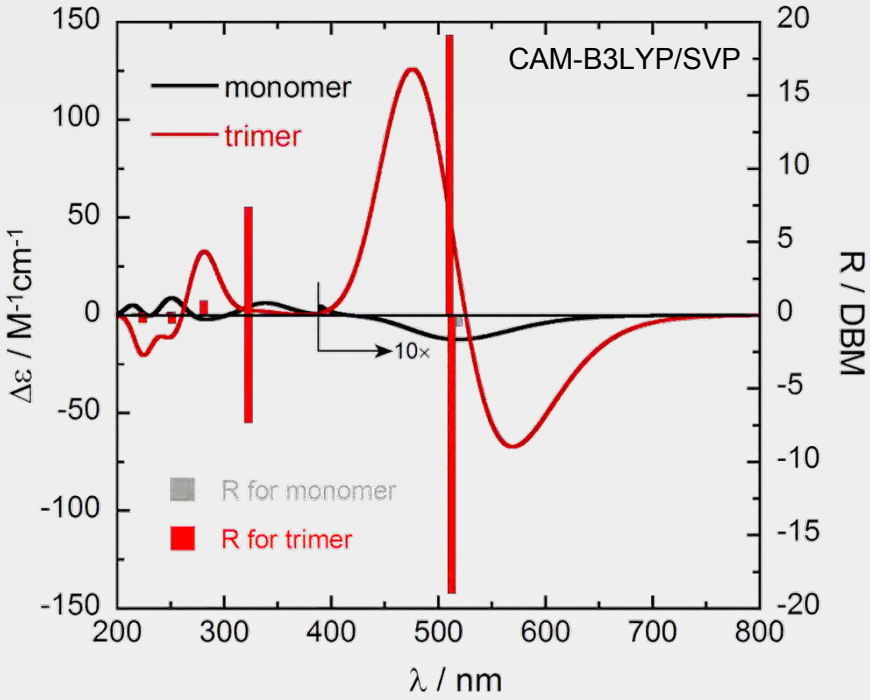
Type I opsin: bacteriorhodopsin

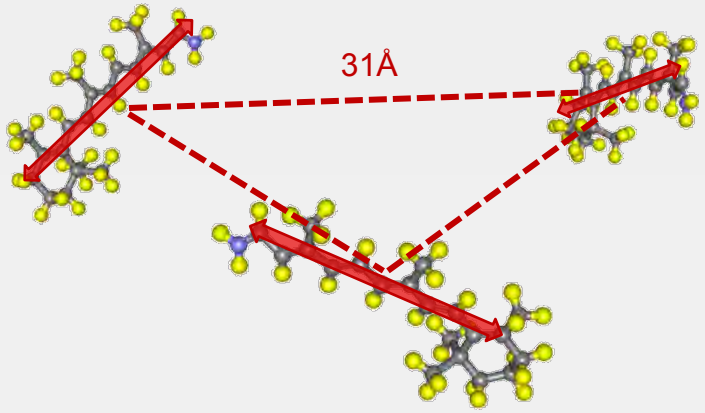
- TDDFT calculations on PSBT monomer and trimer











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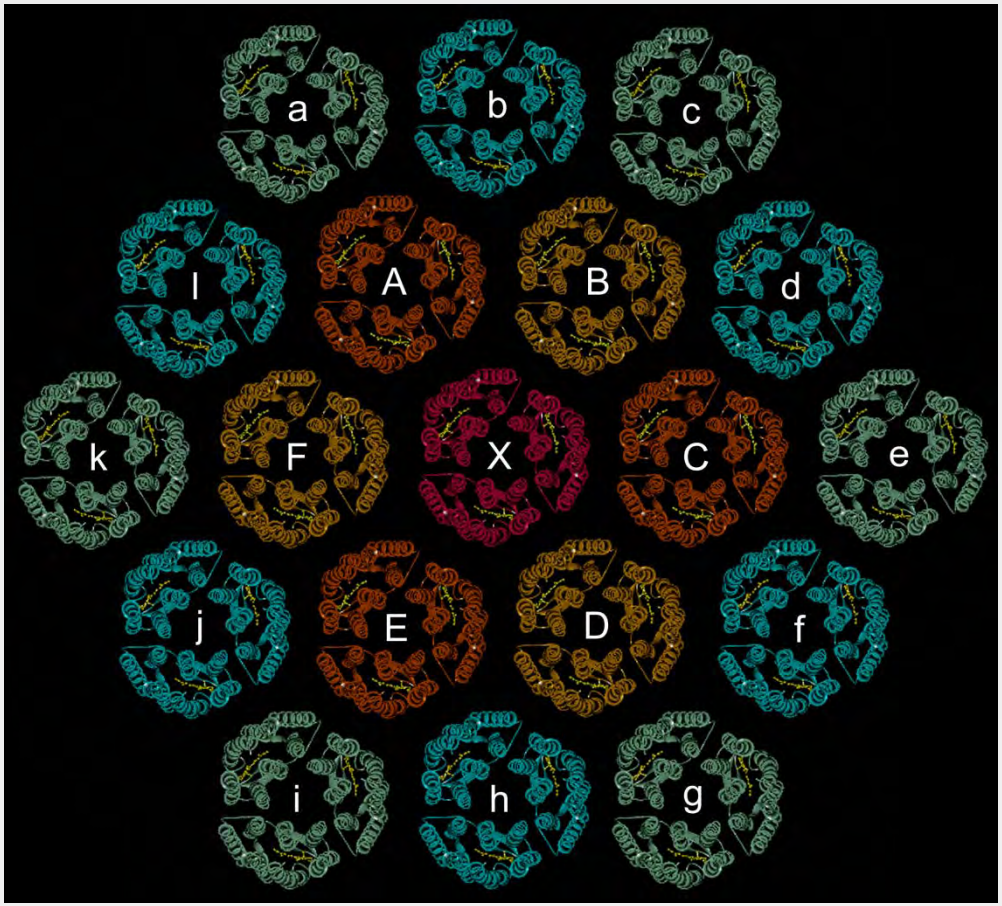
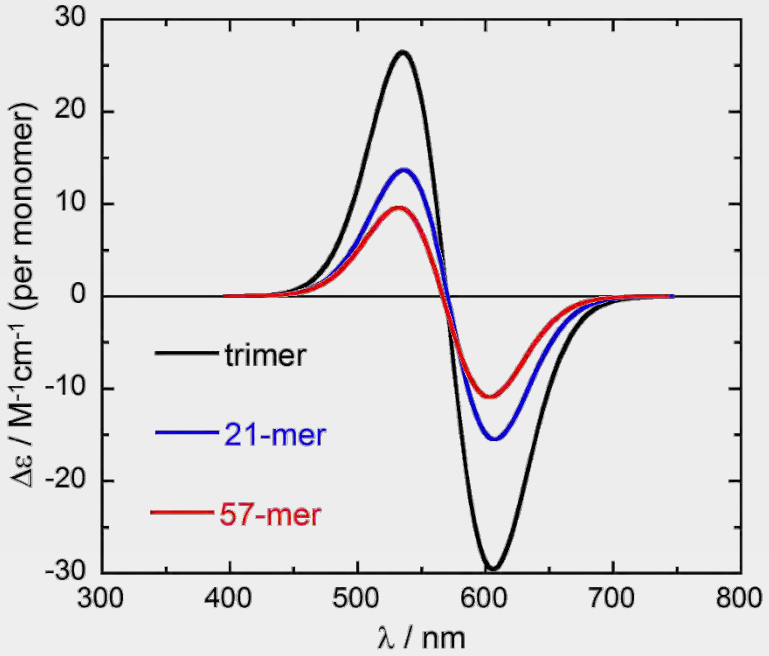
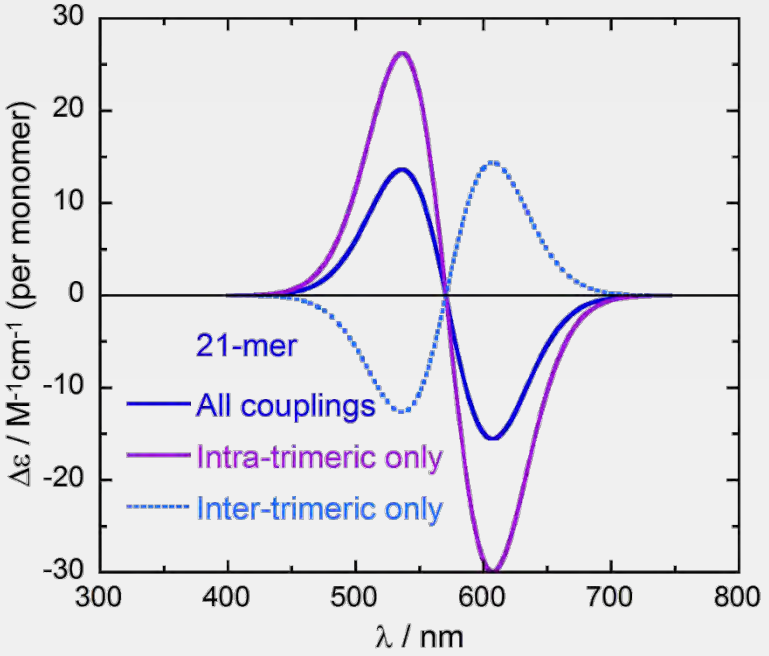
Bacteriorhodopsin

- DeVoe calculations on PSBT oligomers: inter-trimer couplings







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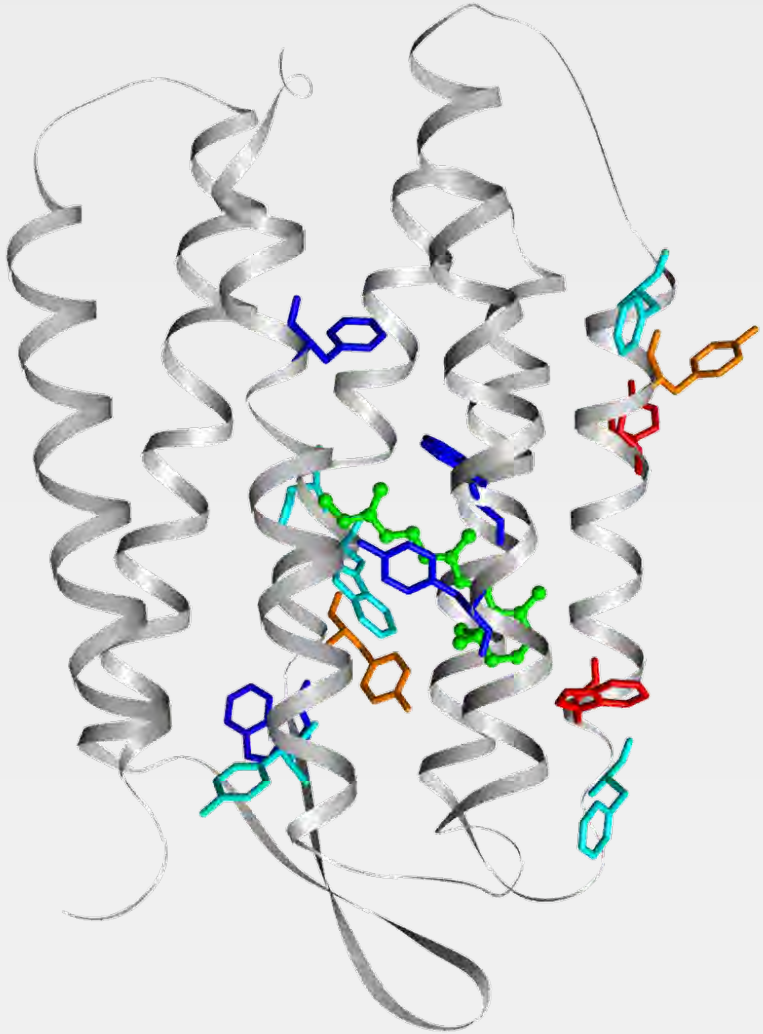
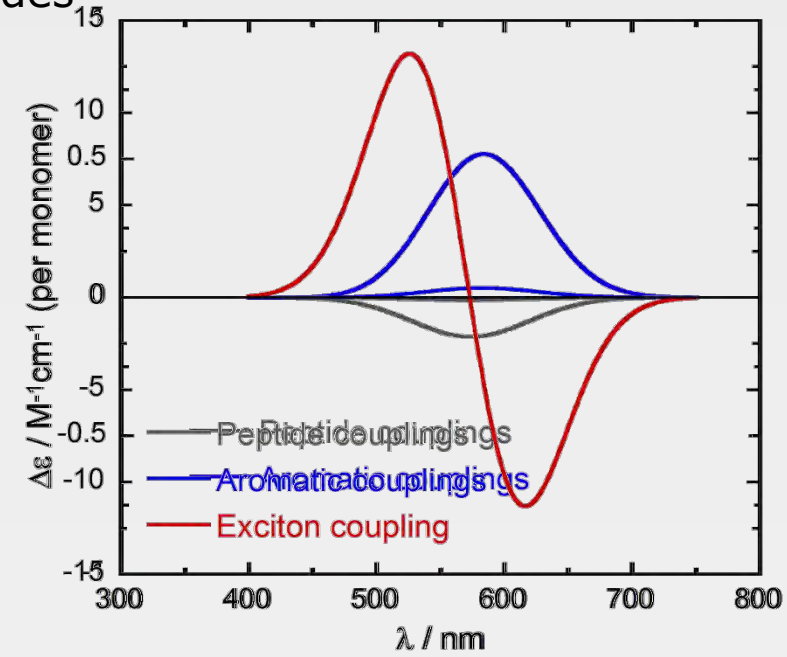
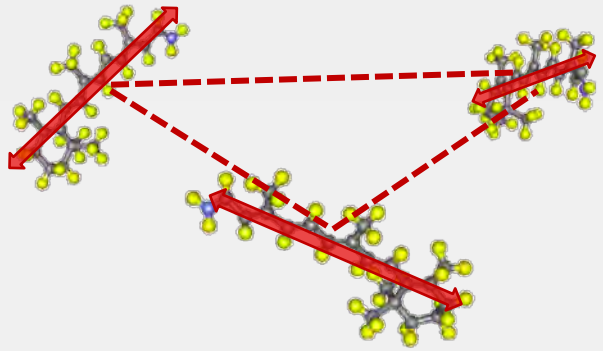
Type I opsin: bacteriorhodopsin

- Matrix calculations of extrinsic terms: couplings with aromatics and peptides







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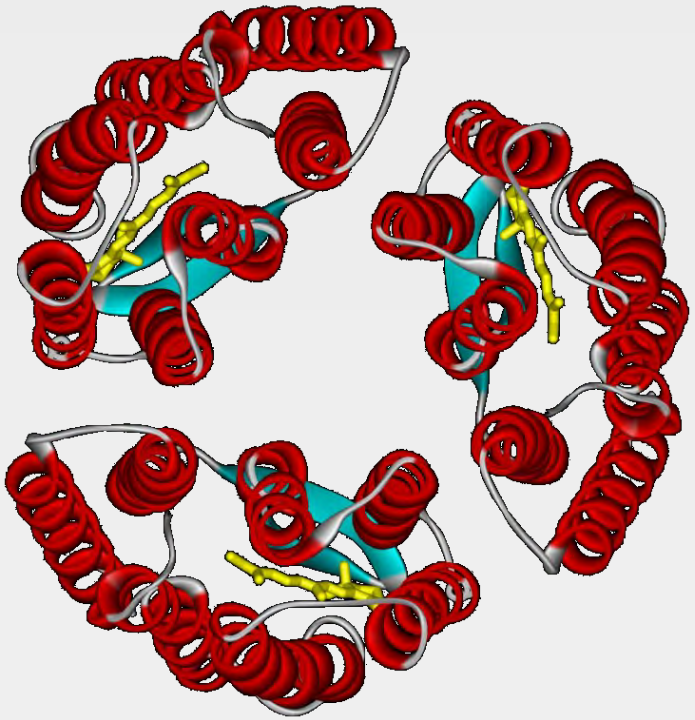
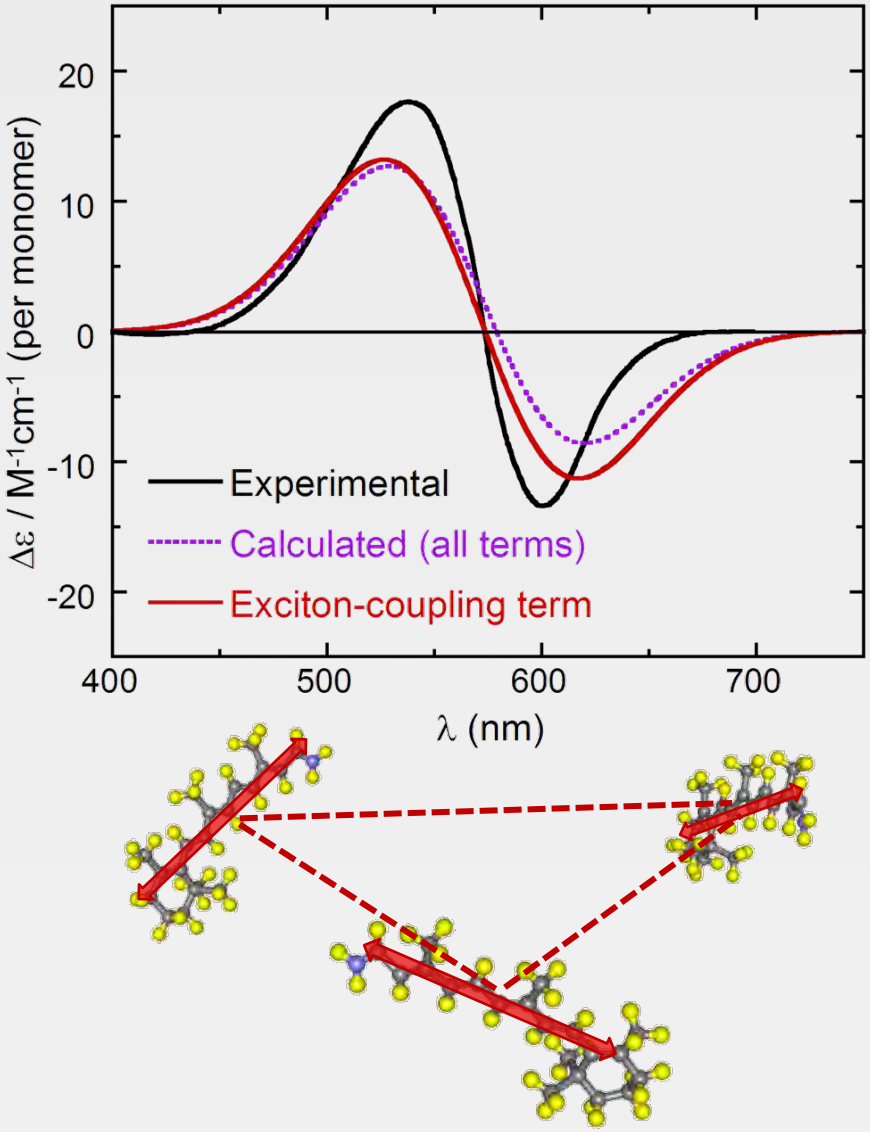
Type I opsin: bacteriorhodopsin





The vis-CD of purple membrane is (by far) dominated by in-trimer exciton coupling between ret-PSB chromophores

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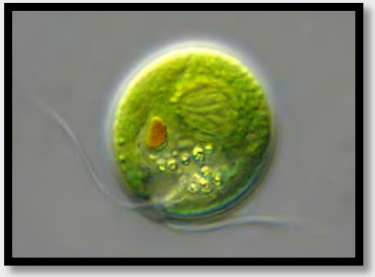
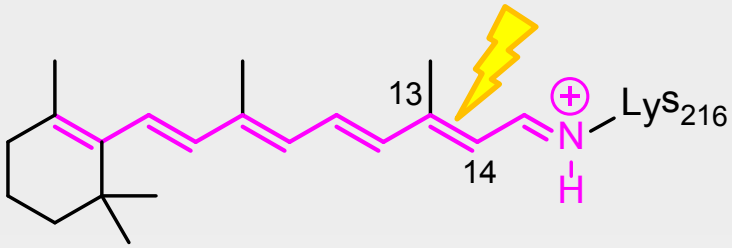
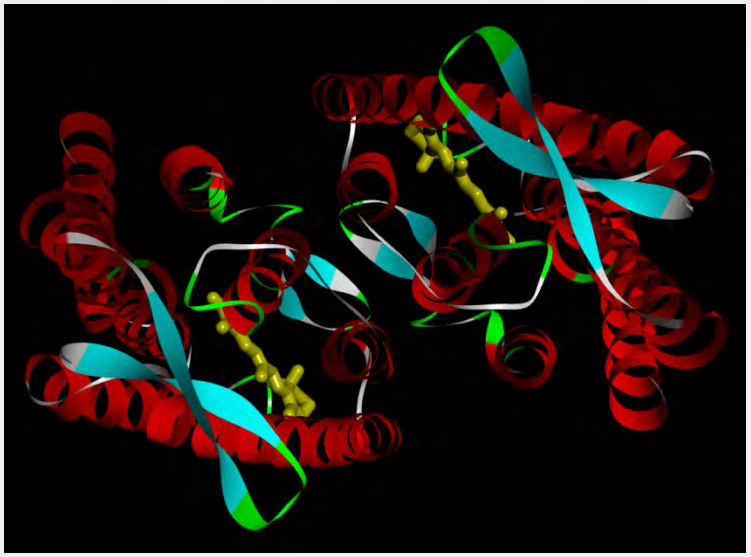
Type I opsin: channelrhodopsin

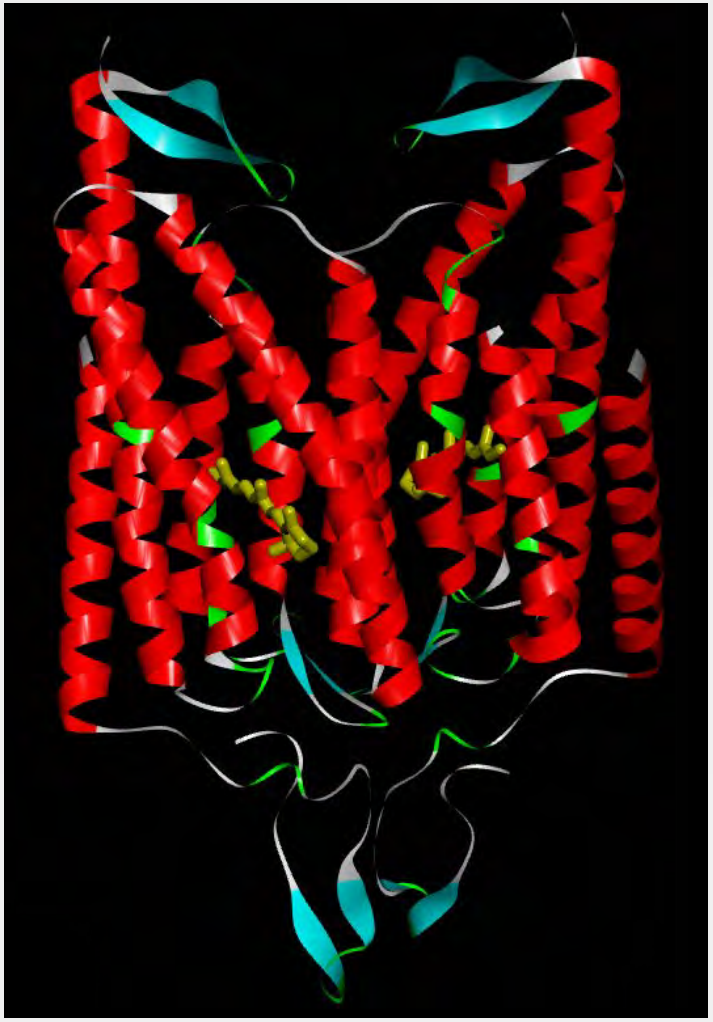


- C1C2 Channel Rhodopsin: a chimera of ChR1 and ChR2 cation channels



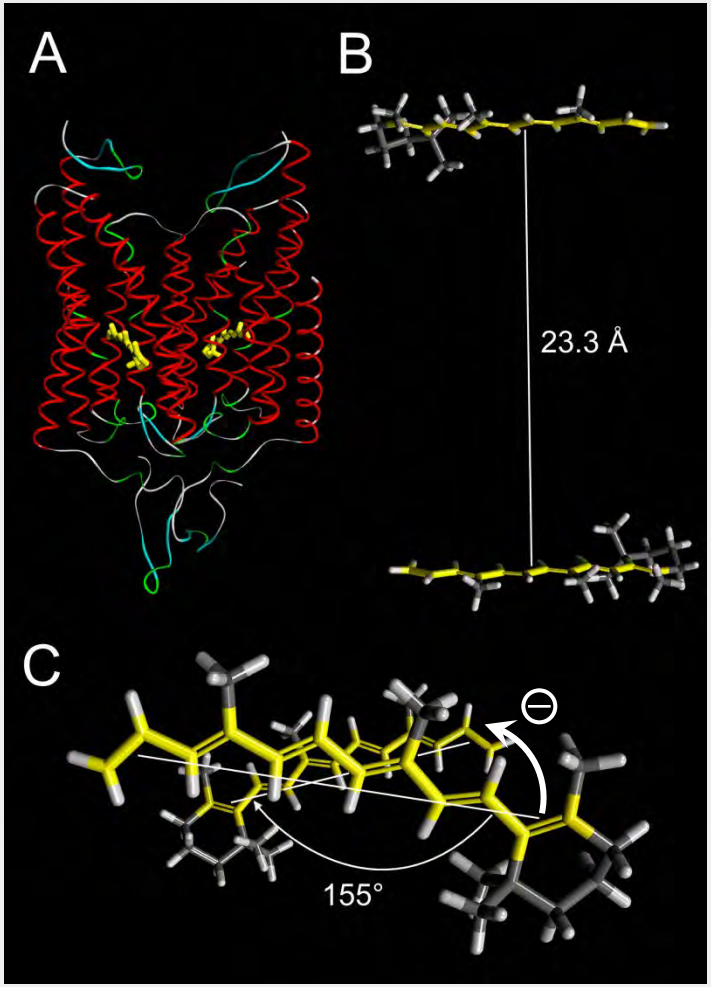
all-trans retinal protonated Schiff base (retPSB)

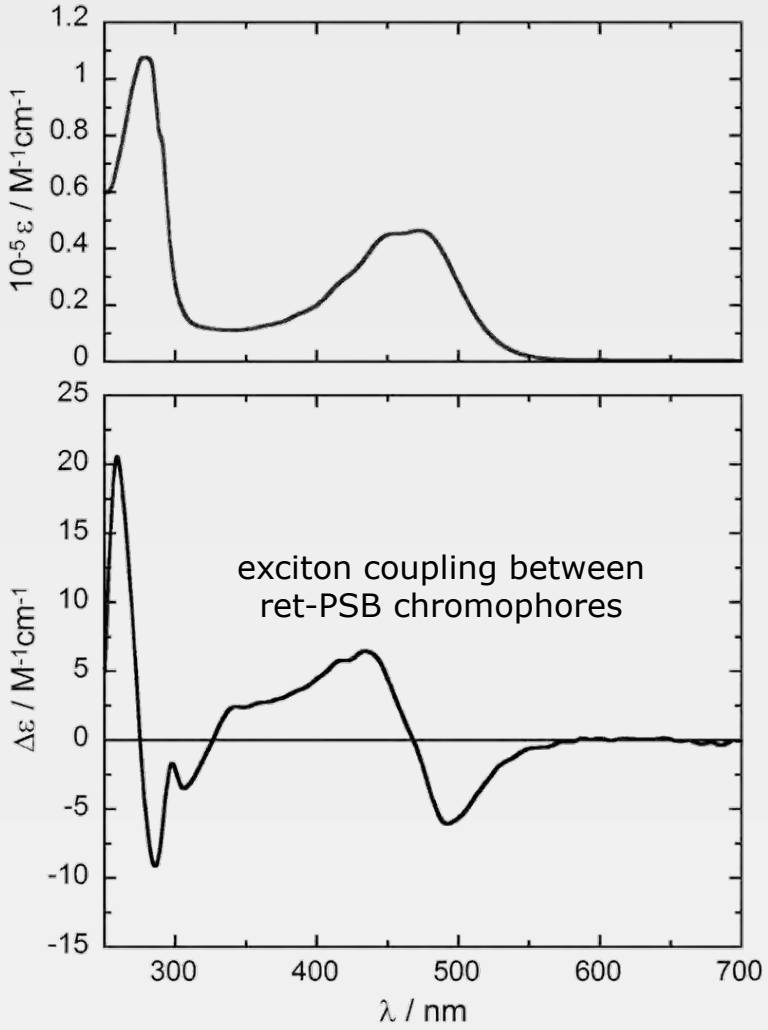




Syntheis and X-ray: Kato et al. Nature 2012, 369

Type I opsin: channelrhodopsin





J Phys Chem B 2014, 11873

Conclusions

- Electronic CD offers unique advantages in the study of chiral supramolecular species
- Any chiral supramolecular arrangement of chromophoric molecules is expected to give an exciton-coupled CD response
- Exciton-coupled CD spectra may be calculated at different levels of theory
- CD lends itself as a versatile tool for characterizing chiral assemblies
- Possible applications range from selective detection to (semi-)quantitative structural studies