New Theoretical Approaches to Study Raman Optical Activity:

Localized Vibrations, Intensity Carrying Modes, Intensity-Tracking

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Introduction

Raman Optical Activity (ROA) spectroscopy

$\longrightarrow$ measures difference in Raman scattering between right- and left-circularly polarized light

- sensitive to protein secondary structure
- spectra can be recorded in aqueous solution
- allows for the investigation of unfolded / disordered proteins
- ...

Goal: Development of theoretical methods and tools to calculate and understand ROA spectra,

... will also applicable to any other type of vibrational spectroscopy!

Why *Ab Initio* Calculation of (ROA) Spectra?

- direct connection between structure and ROA signal
- well-defined structural models can be investigated
- investigation of "artificial" structures possible
  e.g., switch on and off solvation
- allows for a detailed analysis of how (and why) structural changes affect the ROA spectra

Our Methodology for the Calculation of ROA Spectra

- semi-numerical calculations performed using SNF and TURBOMOLE

  
  J. Neugebauer, MR, C. Kind, B. A. Hess, JCC **23** (2002), 895.

- local version of TURBOMOLE includes $\boldsymbol{G}'$ and $\boldsymbol{A}$ tensors

  
  S. Luber, MR, Chem. Phys. **346** (2008), 212.

- **full ROA spectra calculated**

- density-fitting (TD-)DFT with BP86 functional
  (also B3LYP for transition metal complexes)

- Ahlrichs' TZVP and TZVPP basis sets

- generic structures studied first;
  afterwards solvent effects are considered

- For even larger calculations: MODE-TRACKING

  
  MR, J. Neugebauer, J. Chem. Phys. **118** (2003), 1634.

ROA Signatures of α-Helix and 3_{10}-Helix

Can ROA distinguish helical secondary structure elements?

Signatures of α-helix

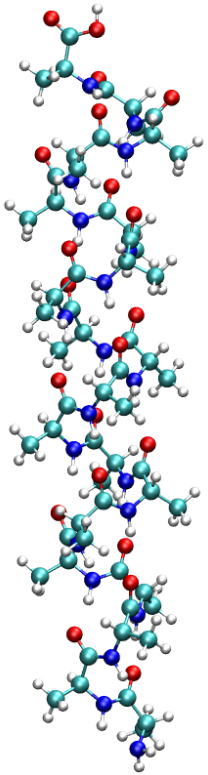
- several signatures have been identified experimentally
- amide I couplet (negative/positive) at about 1650 cm^{-1}
- extended amide III region sensitive to α-helix hydration state

Signatures of 3_{10}-helix

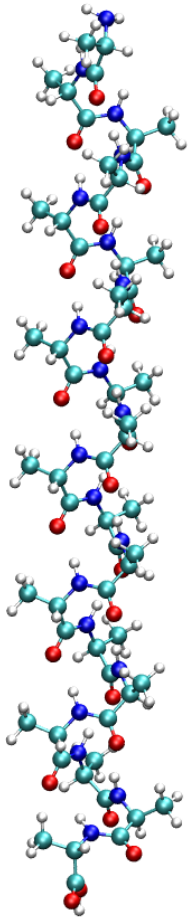
- no signatures identified so far

$\Rightarrow$ **calculations are essential for identifying ROA signatures**

Models of α-Helix and 3_{10}-Helix



α-helix



3_{10}-helix

Model system: (all-S)–$(Ala)_{20}$

- polypeptide containing 20 alanine (simplest chiral amino acid)
- 203 atoms
- two conformations:
  - α-helix
  - 3_{10}-helix
- geometry fully optimized
- solvent effects not considered

Ch. R. Jacob, S. Luber, MR, Chem. Eur. J. **15** (2009), 13491.

α-Helix: Comparison with Experimental Spectra

Amide I band

- excellent agreement of band position and intensities (amide I couplet)

CH_3 bending bands

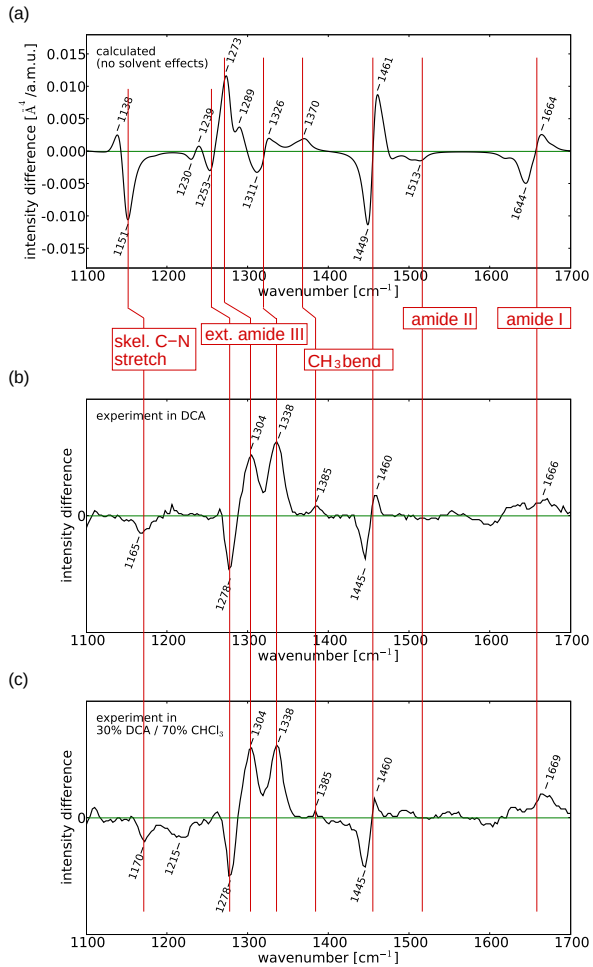
- excellent agreement of band position and intensities

Extended amide III region

- good agreement of band positions
- some differences for shapes and intensities

$\Rightarrow$ analyzed recently in more detail

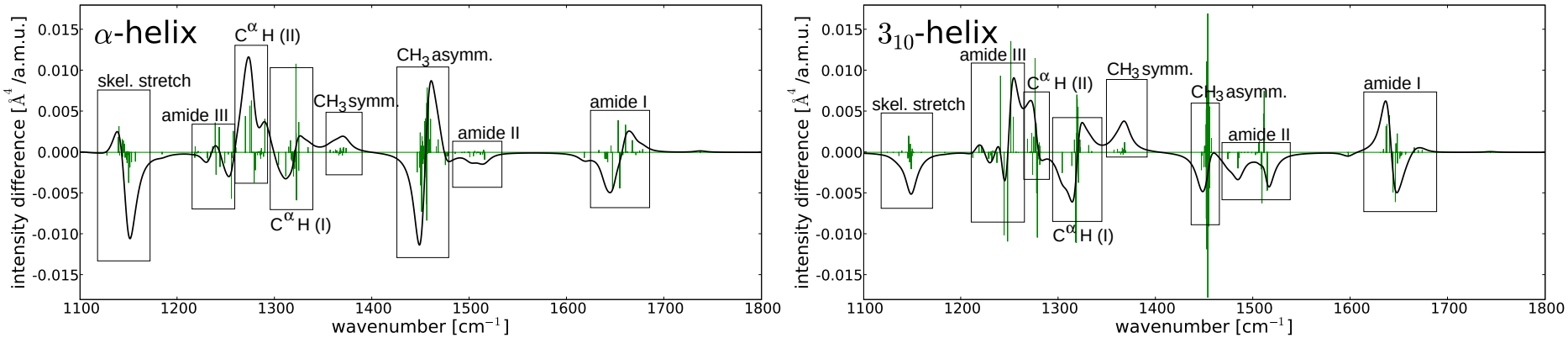
Th. Weymuth, Ch. R. Jacob, MR, J. Phys. Chem. B (2010), in press



experimental spectra from:

I.H. McColl *et al.*, J. Am. Chem. Soc. **126** (2004), 8181.

Calculated ROA Spectra of Helix Models



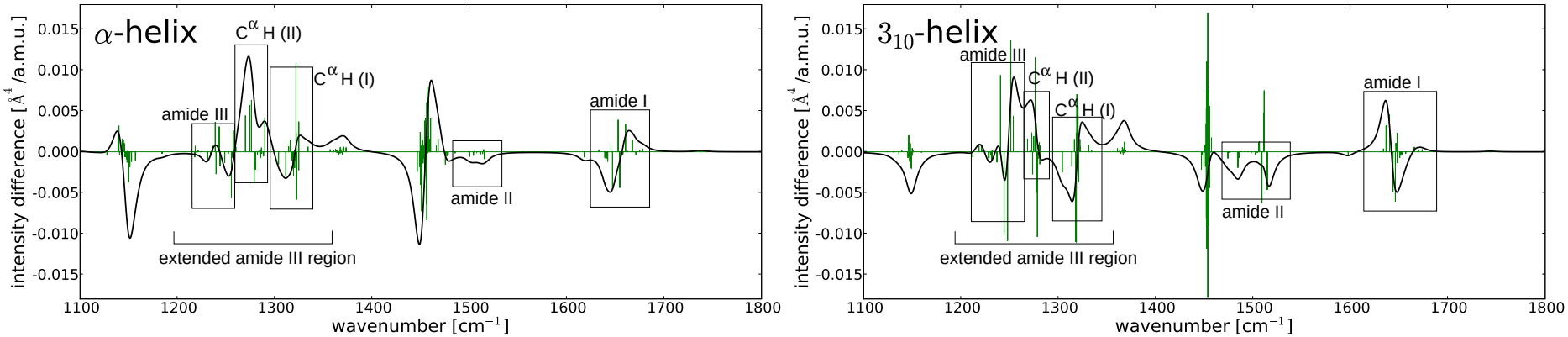
- spectra comprise large number of close-lying normal modes
- not resolved in experiment: only few number of ROA bands visible

$\longrightarrow$ calculated spectra plotted using line broadening

Assignment of normal modes to characteristic bands

- assignment based on:
  (a) wavenumbers and (b) contributions of certain atom types
- usually 20 normal modes contribute here for $(\mathrm{Ala})_{20}$ model systems

Analysis of Calculated ROA Spectra



How are changes in the ROA spectra related to helix structure?

- which vibrations and which atoms contribute to each band?
- how do the total band intensities arise?
- what determines the individual band shapes?

Problems with such an analysis

- several normal modes contribute to each band
- each of these normal modes is delocalized over the whole helix

$\Rightarrow$ **transformation to "localized modes"**

Localizing Normal Modes

1. consider a subset of normal modes $\boldsymbol{Q}^{\text{sub}}$
2. transform to new set of modes by unitary transformation $\boldsymbol{U}$

$$\tilde{Q}^{\text{sub}}_{i\alpha,p} = \sum_q U_{qp} Q^{\text{sub}}_{i\alpha,q}$$

3. define a criterion $\xi(\tilde{\boldsymbol{Q}}^{\text{sub}})$ that measures "how localized the transformed modes are", e.g.,

$$\xi_{\text{at}}(\tilde{\boldsymbol{Q}}^{\text{sub}}) = \sum_p \sum_i (\tilde{C}^{\text{sub}}_{ip})^2 \quad \text{with} \quad \tilde{C}^{\text{sub}}_{ip} = \sum_{\alpha=x,y,z} (\tilde{Q}^{\text{sub}}_{i\alpha,p})^2$$

4. determine $\boldsymbol{U}$ such that $\xi(\tilde{\boldsymbol{Q}}^{\text{sub}})$ is maximized (using consecutive Jacobi rotations)

Ch. R. Jacob, MR, J. Chem. Phys. **130** (2009), 084106.

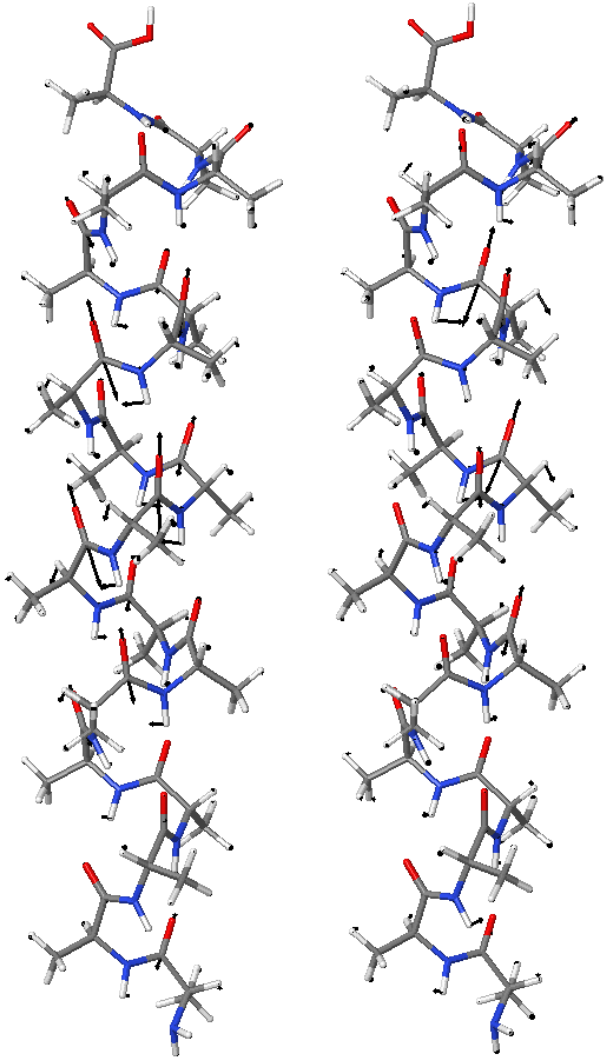
Localized Vibrations: Amide I Band

- Normal modes:
  - Delocalized combination of vibrations on several residues
- Localized modes:
  - Localized modes on different residues are very similar
  - Deviations only at the termini

  $\Rightarrow$ **it is sufficient to consider only one representative localized mode**

  - Vibration of a single residue

  $\Rightarrow$ **it is sufficient to show the atoms of only one residue**

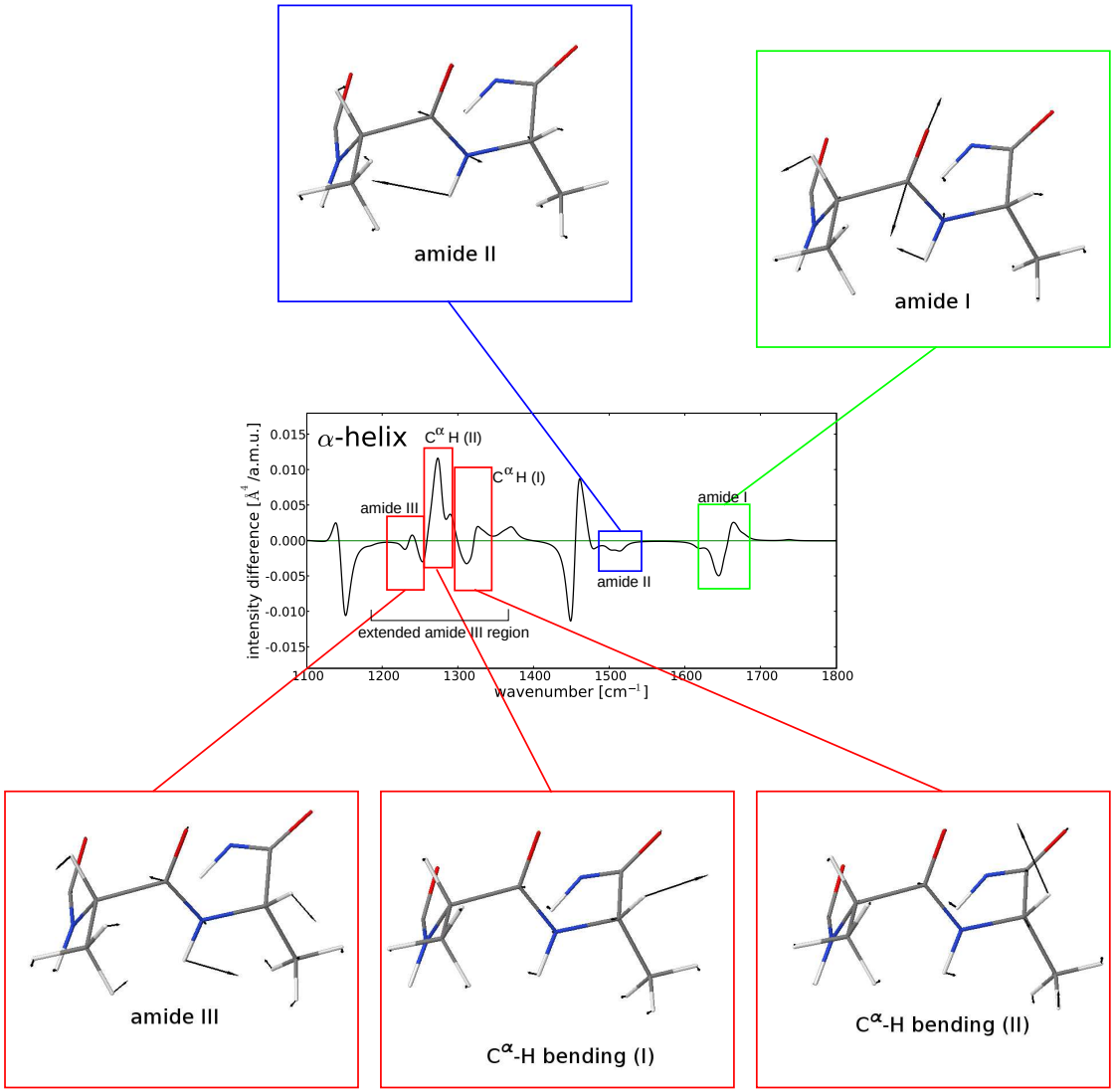


1660.4 cm^{-1} 1663.4 cm^{-1}

Ch. R. Jacob, MR, J. Chem. Phys. **130** (2009), 084106.

Visualization of Localized Modes

Consideration of only one representative localized mode necessary

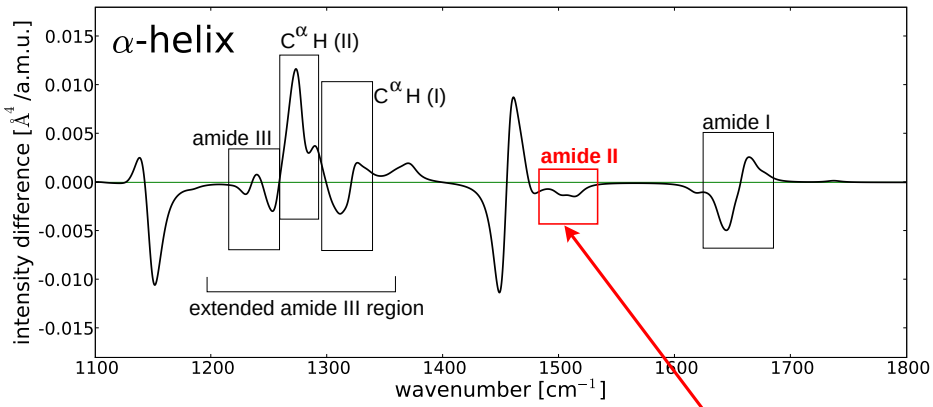


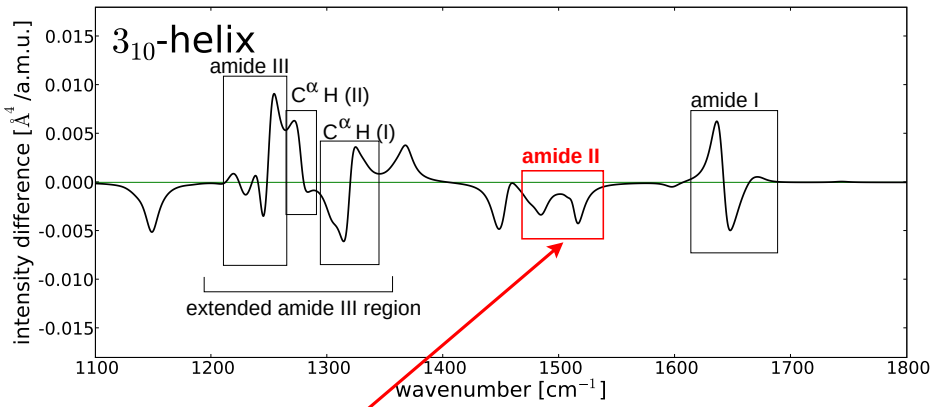
- Amide I:
  C=O stretching
- Amide II:
  N–H bending and
  C–N stretching
- Ext. Amide III:
  mixing between
  N–H bending and
  C^{α}–H bending

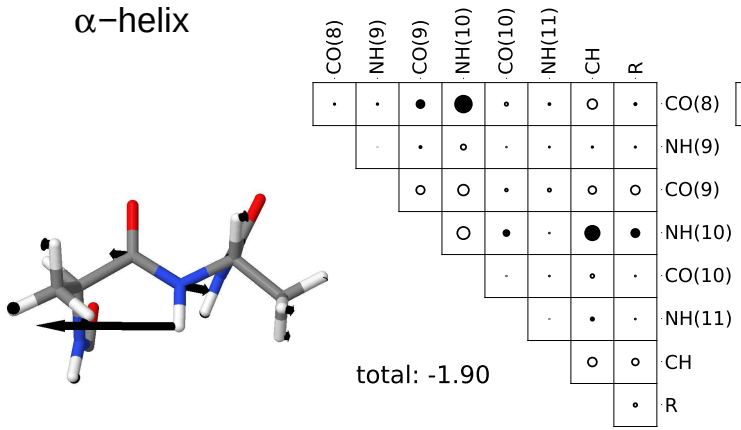
Note: Localized modes differ from normal modes of small model building blocks!

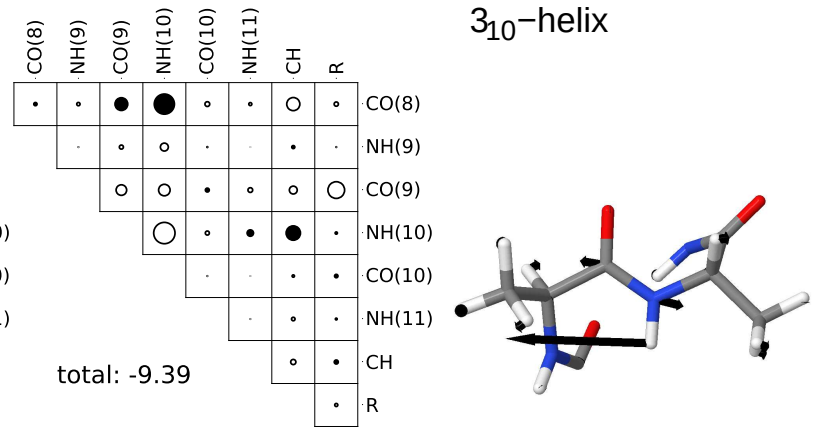
Analysis of Total Band Intensities

Why is the amide II band more intense for the 3_{10}-helix?





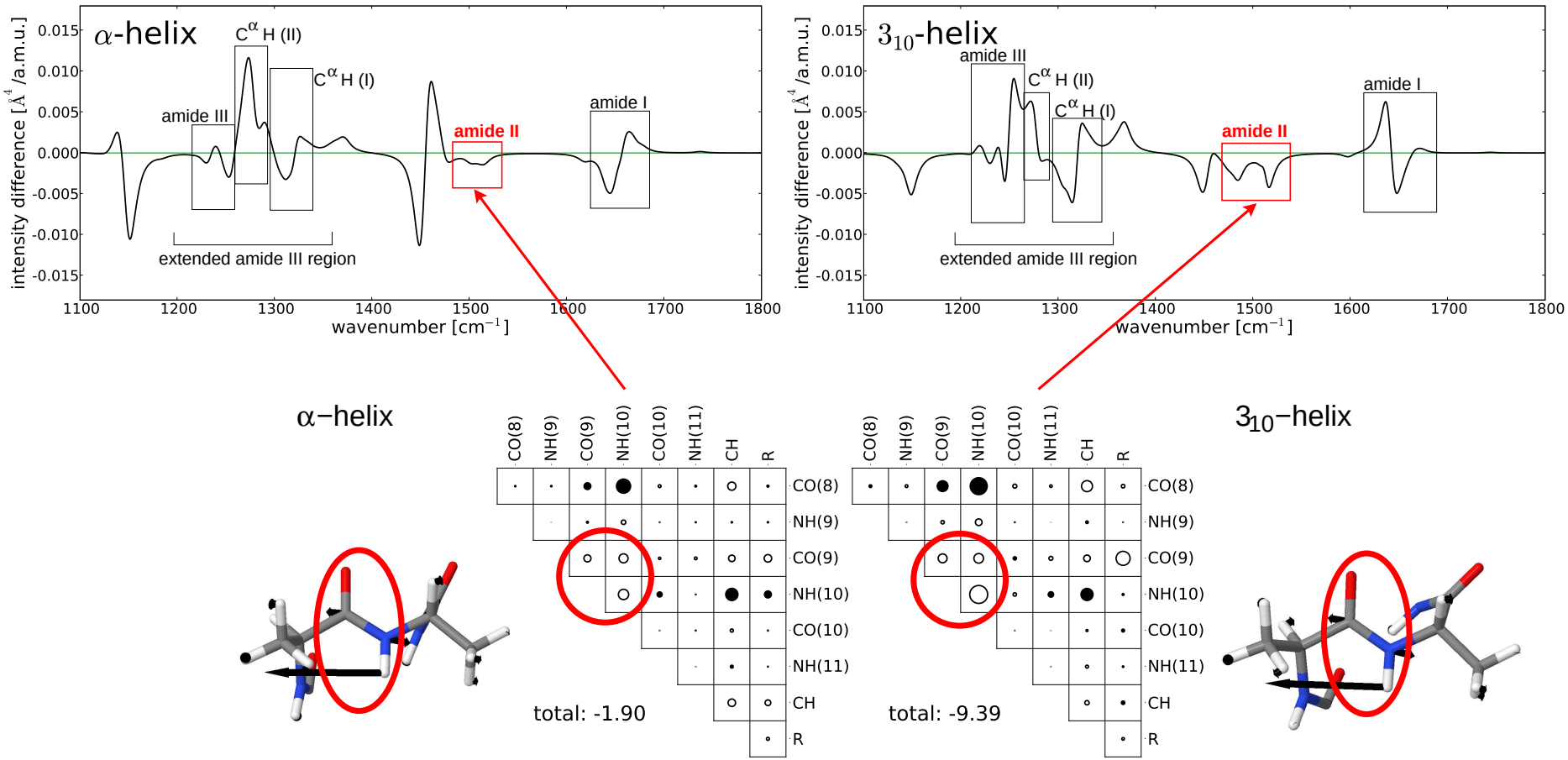




- increased total intensity is reflected by localized mode intensities
- localized modes are almost identical

Analysis of Total Band Intensities

Why is the amide II band more intense for the 3_{10}-helix?

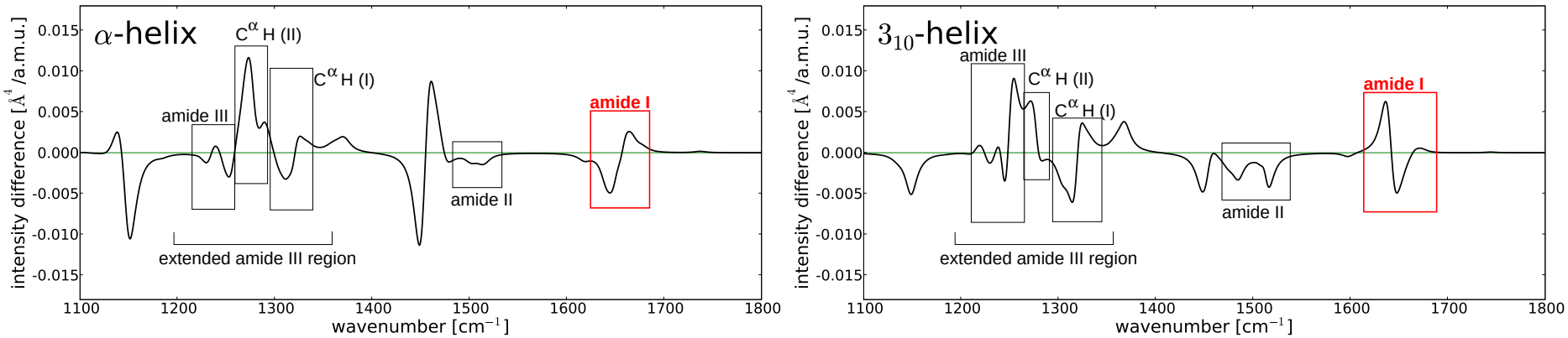


- changes in ROA intensity are mainly due to achiral amide group

$\longrightarrow$ relation to structure only indirect

Analysis of Band Shapes

Why is the amide I couplet opposite in the α-helix and the 3_{10}-helix?



- localized modes almost identical for α-helix and 3_{10}-helix
- intensities of localized modes and total intensities very similar

Decompose ROA intensities of normal modes

$$I_p = \sum_{qr} U_{pq} U_{pr} [\tilde{I}]_{qr}$$

- U_{pq}: coefficient of qth localized mode in pth normal mode
- $[\tilde{I}]_{qr}$: intensity coupling matrix

Analysis of Band Shapes

Amide I (vibrational) coupling matrices

- **α-helix:**

  nearest-neighbor coupling largest

  3rd nearest-neighbor coupling significant

α-helix

$$\begin{pmatrix} 1659.1 & 8.5 & -2.2 & -4.2 & -0.4 & -0.5 \\ 8.5 & 1655.9 & 7.9 & -2.3 & -4.2 & -0.4 \\ -2.2 & 7.9 & 1654.6 & 8.2 & -2.2 & -4.4 \\ -4.2 & -2.3 & 8.2 & 1654.9 & 8.3 & -2.1 \\ -0.4 & -4.2 & -2.2 & 8.3 & 1654.8 & 8.2 \\ -0.5 & -0.4 & -4.4 & -2.1 & 8.2 & 1655.8 \end{pmatrix}$$

- **3_{10}-helix:**

  2nd nearest-neighbor coupling largest

  3rd nearest-neighbor coupling small

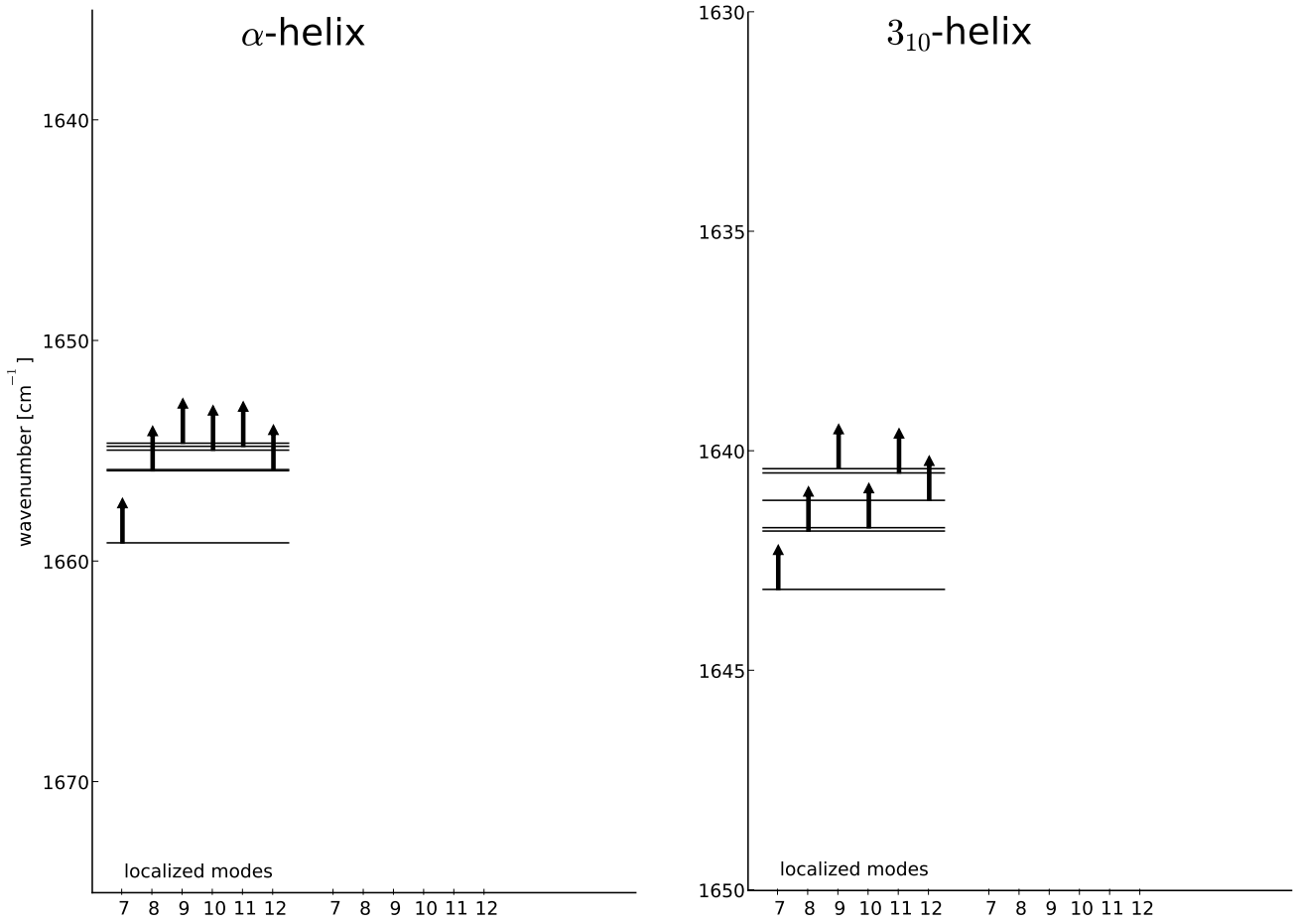
3_{10}-helix

$$\begin{pmatrix} 1643.1 & 2.5 & -3.7 & -0.7 & -0.6 & -0.6 \\ 2.5 & 1641.8 & 2.7 & -3.7 & -0.8 & -0.6 \\ -3.7 & 2.7 & 1640.4 & 2.8 & -3.8 & -0.8 \\ -0.7 & -3.7 & 2.8 & 1641.7 & 2.4 & -3.7 \\ -0.6 & -0.8 & -3.8 & 2.4 & 1640.5 & 2.5 \\ -0.6 & -0.6 & -0.8 & -3.7 & 2.5 & 1641.1 \end{pmatrix}$$

$\rightarrow$ **different coupling matrices directly related to helix structures**

Analysis of Band Shapes

Coupling of localized amide I modes



Analysis of Band Shapes

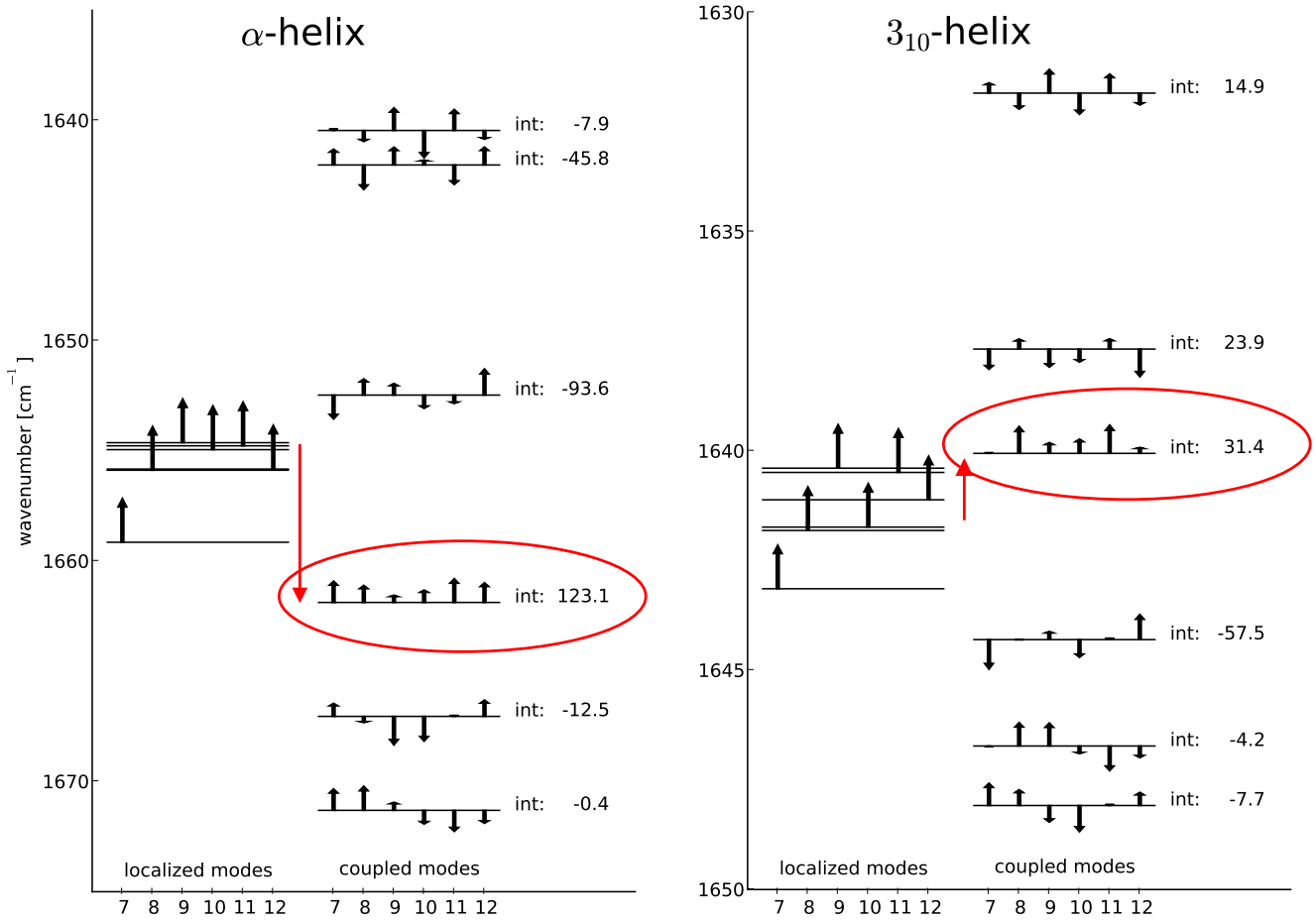
Coupling of localized amide I modes

α-**helix**:

in-phase combination shifted to **higher** wavenumbers

3_{10}-**helix**:

in-phase combination shifted to **lower** wavenumbers



⇒ **different structure of coupling matrix $\tilde{\Omega}$ explains opposite couplets**

Intensity-Carrying Modes (ICMs)

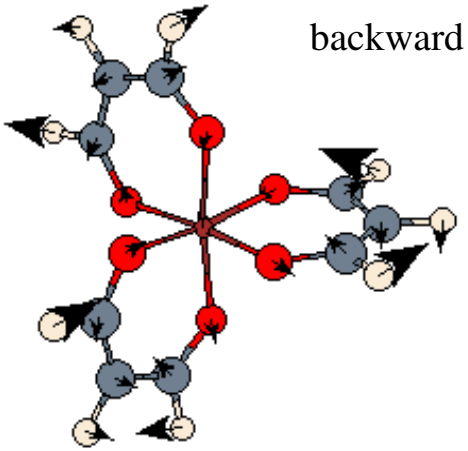
1. hypothetical modes $\boldsymbol{L}_k$ with maximum intensity
2. contain the total intensity of the spectrum
3. first derived for infrared spectroscopy
   
   H. Torii, *et al.*, J. Phys. Chem. A **103** (1999), 5557;
   S. Luber, J. Neugebauer, MR, J. Chem. Phys. **130** (2009), 064105.
4. most efficiently exploited for Resonance Raman
   
   K. Kiewisch, J. Neugebauer, MR, J. Chem. Phys. **129** (2008), 204103.
5. Raman- and ROA-ICMs determined by an eigenvalue problem:

   $$\boldsymbol{M}\boldsymbol{L}_k = a_k \boldsymbol{L}_k$$

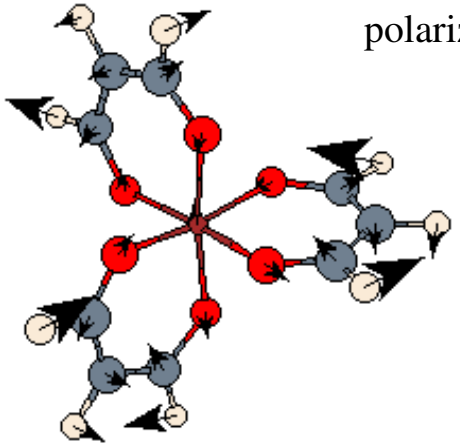
   eigenvalue a_k proportional to ROA intensity;

   $\boldsymbol{M}$ contains Cartesian derivatives of ROA tensor components
   
   S. Luber, MR, ChemPhysChem **10** (2009), 2049.

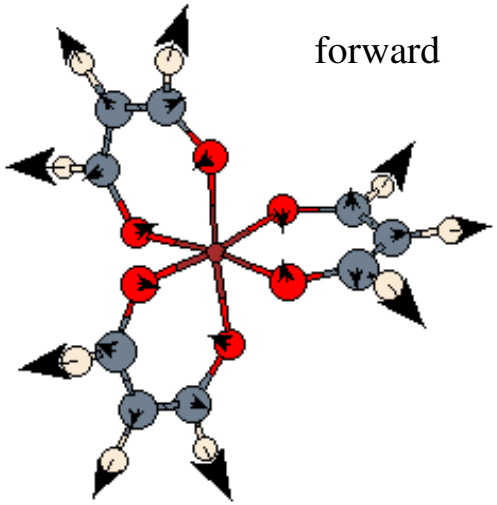
ROA-ICMs of Λ-Tris(propane-1,3-dionato)cobalt(III)



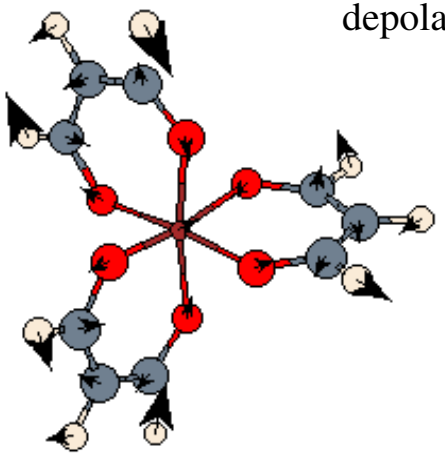
backward



polarized



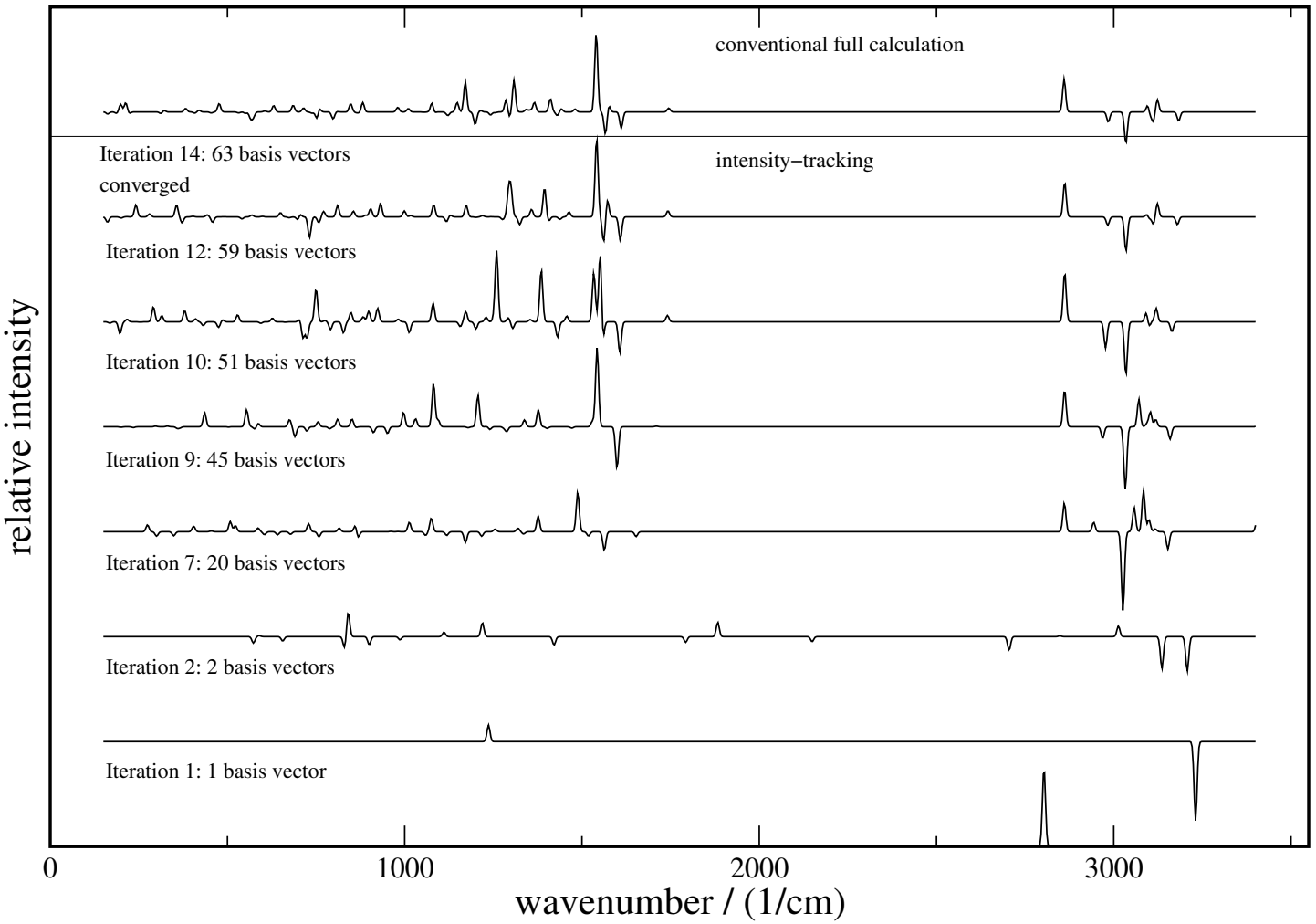
forward



depolarized

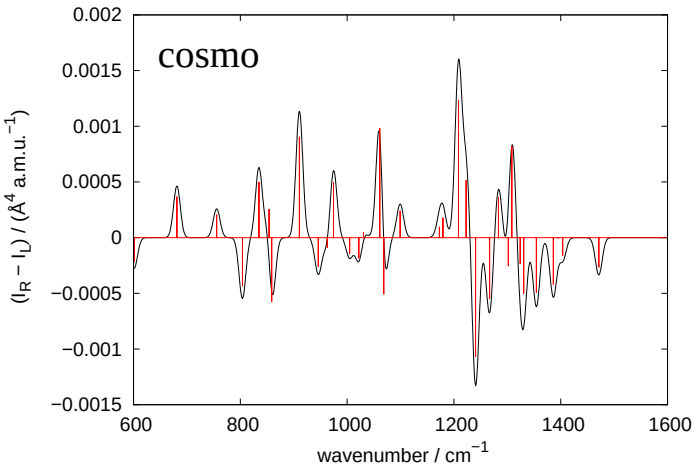
ROA Intensity-Tracking for L-Tryptophan

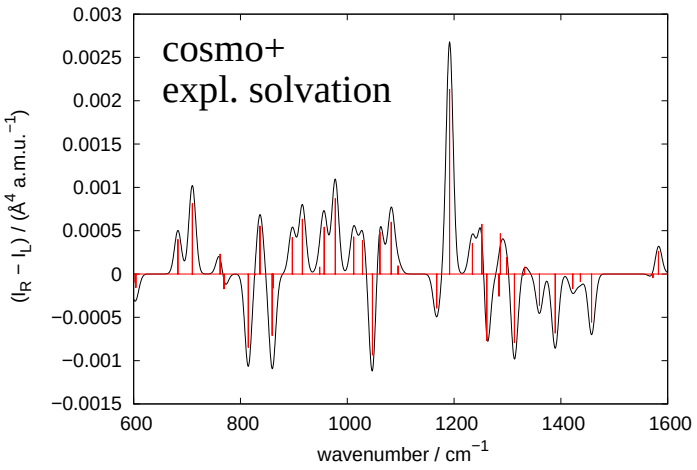
selective calculation of normal modes with high ROA intensity

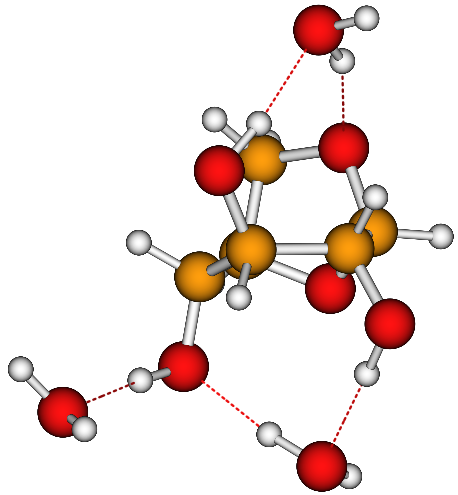


S. Luber, MR, ChemPhysChem **10** (2009), 2049.

Solvation Effects on ROA Spectrum of Sugar Molecules



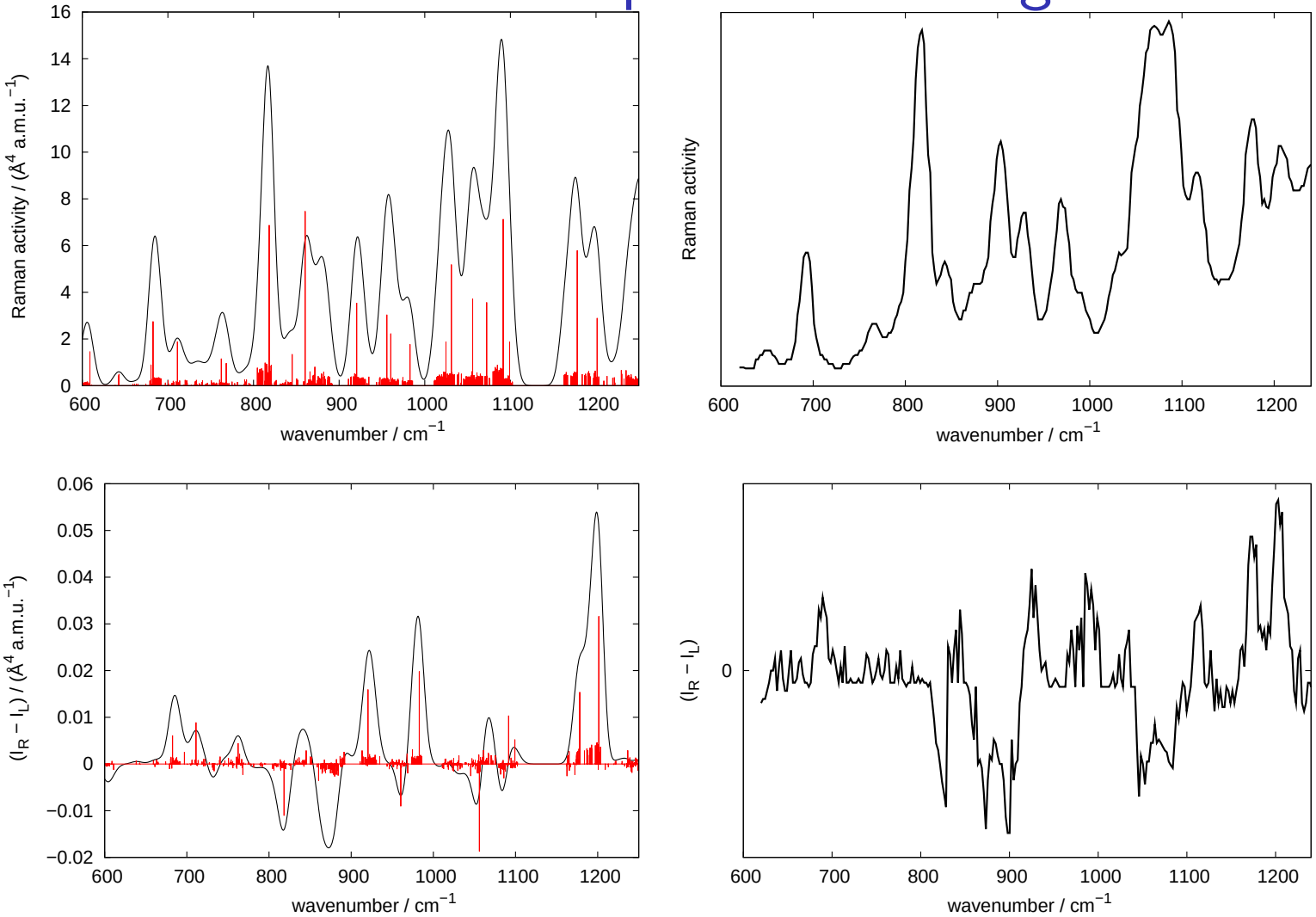




- sugar molecules are the most critical cases because of conformation and solvation effects
- our protocol: different conformations, COSMO and explicit solvation, Boltzmann weighting

  S. Luber, MR, J. Phys. Chem. A **113** (2009), 8268.
- other solvation protocols:
  - E. Blanch, P. Popelier, J. Cheeseman, talk at VOA-2
  - K. Ruud, talk at VOA-2
  - C. Johannessen, private communication

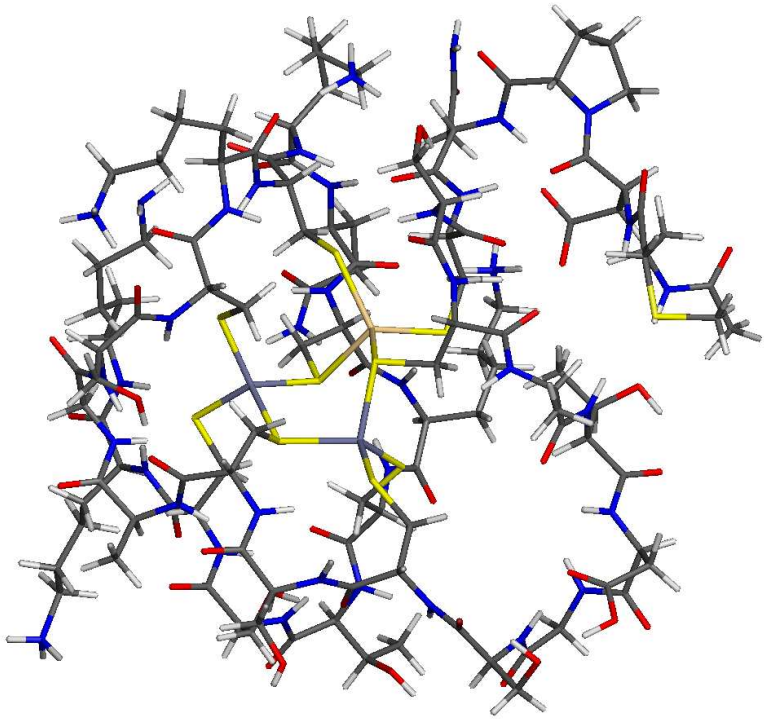
Solvation Effects on ROA Spectrum of Sugar Molecule

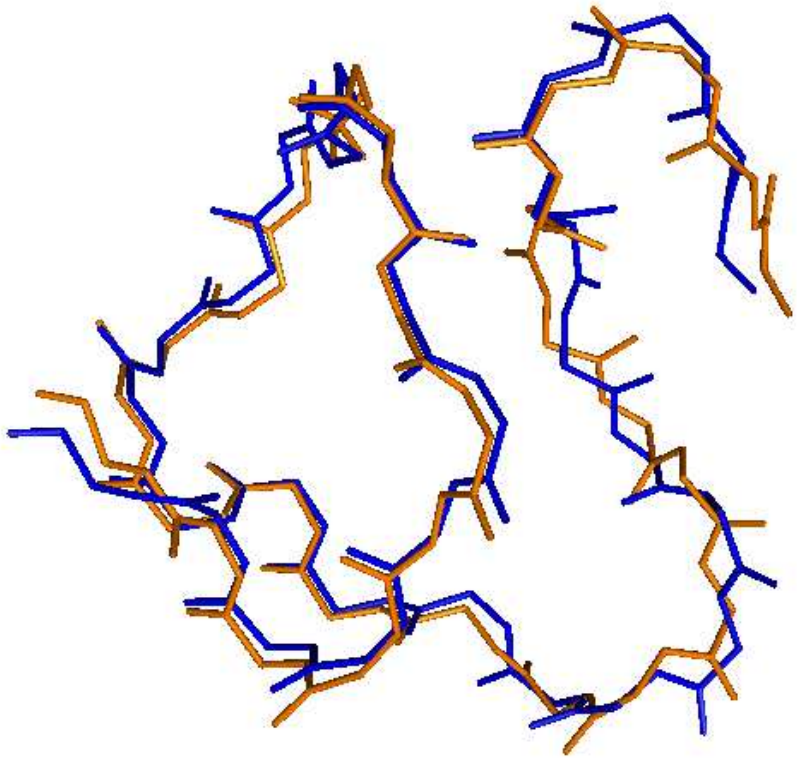


- overlay of all spectra of explicitly solvated chair conformers (left)
- Theory (left) / Exp. (right) ; Raman (top) / ROA (bottom)

Experiment: L. D. Barron et al., Carbohydr. Res. **210** (1991), 39.

ROA spectrum of β Domain of Rat Metallothionein



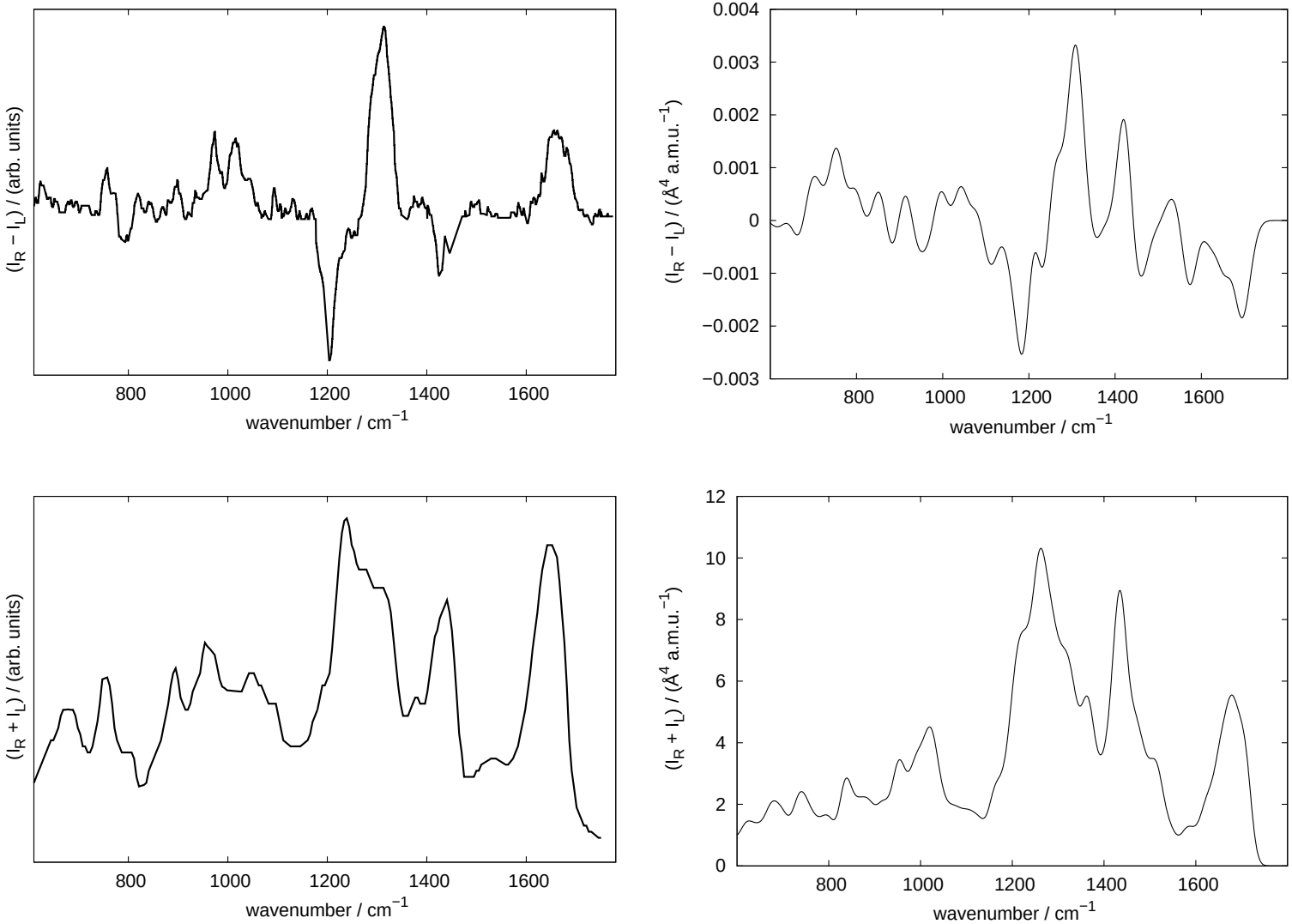


- >400 atoms, sulfur-rich, 2 Zn and 1 Cd atoms
- hardly any regular structures like α-helix or β-sheets, mostly β-turns

$\rightarrow$ identified signatures of β-turns

S. Luber, MR, J. Phys. Chem. B **114** (2010), 1057.

ROA spectrum of β Domain of Rat Metallothionein



- Exp. (left) / Theory (right) ; ROA (top) / Raman (bottom)

Experiment: E. Smyth et al., Biopolymers **58** (2001), 138.

Summary I

Localized Vibrations for the Analysis of Vibrational Spectra


J. Chem. Phys. **130** (2009), 084106.

Raman, IR and ROA Spectra of Helical Polypeptides


J. Phys. Chem. B **113** (2009), 6558.


Chem. Eur. J. **15** (2009), 13491.


+ older work in collaboration with K. Ruud (2003–2007)

Raman + ROA Intensity-Tracking and Intensity-carrying Modes


ChemPhysChem **10** (2009), 2049.

- also done for Resonance Raman and IR:


J. Chem. Phys. **129** (2008) 204103 + J. Chem. Phys. **130** (2009) 064105

ROA calculation for small metalloprotein


J. Phys. Chem. B **114** (2010), 1057.

Summary II + Outlook

Solvation effects on ROA spectra of sugar molecule


J. Phys. Chem. A **113** (2009), 8268.

Prediction for ROA spectra of chiral transition metal complexes


Chem. Phys. **346** (2008), 212.


ChemPhysChem **11** (2010), 1876.

Enhancement and De-Enhancement in Resonance ROA:


J. Chem. Phys. **132** (2010), 044113.

Dependence of Extended Amide III on Secondary Structure:


Th. Weymuth, Ch. R. Jacob, MR, J. Phys. Chem. B (2010), DOI: 10.1021/jp104542w

Identification of β-Turns with ROA:


Th. Weymuth, Ch. R. Jacob, MR, ChemPhysChem (2010), submitted.

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