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

→ 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
- local version of Turbomole includes $G'$ and $A$ tensors
- 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
Can ROA distinguish helical secondary structure elements?

Signatures of $\alpha$-helix

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

Signatures of $3_{10}$-helix

- no signatures identified so far

$\Rightarrow$ calculations are essential for identifying ROA signatures
Models of $\alpha$-Helix and $3_{10}$-Helix

Model system: $(\text{all-S})-(\text{Ala})_{20}$

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

α-Helix: Comparison with Experimental Spectra

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

CH₃ bending bands
- excellent agreement of band position and intensities

Extended amide III region
- good agreement of band positions
- some differences for shapes and intensities
⇒ analyzed recently in more detail


experimental spectra from:
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
  → 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 (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

⇒ transformation to “localized modes”
Localizing Normal Modes

1. consider a subset of normal modes $Q^{\text{sub}}$

2. transform to new set of modes by unitary transformation $U$

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

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

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

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

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

  \[ \Rightarrow \text{it is sufficient to consider only one representative localized mode} \]

- Vibration of a single residue

  \[ \Rightarrow \text{it is sufficient to show the atoms of only one residue} \]

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$^\alpha$–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

Theoretical Raman Optical Activity

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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
  → relation to structure only indirect
Analysis of Band Shapes

Why is the amide I couplet opposite in the \( \alpha \)-helix and the \( 3_{10} \)-helix?

- Localized modes almost identical for \( \alpha \)-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 \( q \)th localized mode in \( p \)th 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
  
  \[
  \begin{pmatrix}
  1659.1 & 8.5 & -2.2 & -4.2 & -0.4 & -0.5 \\
  8.5 & 1655.9 & 7.9 & -2.3 & -4.2 & -0.4 \\
  -2.2 & 7.9 & 1654.6 & 8.2 & -2.2 & -4.4 \\
  -4.2 & -2.3 & 8.2 & 1654.9 & 8.3 & -2.1 \\
  -0.4 & -4.2 & -2.2 & 8.3 & 1654.8 & 8.2 \\
  -0.5 & -0.4 & -4.4 & -2.1 & 8.2 & 1655.8
  \end{pmatrix}
  \]

- **3_{10}-helix:**
  - 2nd nearest-neighbor coupling largest
  - 3rd nearest-neighbor coupling small
  
  \[
  \begin{pmatrix}
  1643.1 & 2.5 & -3.7 & -0.7 & -0.6 & -0.6 \\
  2.5 & 1641.8 & 2.7 & -3.7 & -0.8 & -0.6 \\
  -3.7 & 2.7 & 1640.4 & 2.8 & -3.8 & -0.8 \\
  -0.7 & -3.7 & 2.8 & 1641.7 & 2.4 & -3.7 \\
  -0.6 & -0.8 & -3.8 & 2.4 & 1640.5 & 2.5 \\
  -0.6 & -0.6 & -0.8 & -3.7 & 2.5 & 1641.1
  \end{pmatrix}
  \]

→ different coupling matrices directly related to helix structures
Analysis of Band Shapes

Coupling of localized amide I modes

\( \alpha \)-helix:
in-phase combination shifted to higher wavenumbers

310-helix:
in-phase combination shifted to lower wavenumbers

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Analysis of Band Shapes

Coupling of localized amide I modes

$\alpha$-helix:

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

$3_{10}$-helix:

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

$\Rightarrow$ different structure of coupling matrix $\tilde{\Omega}$ explains opposite couplets
Intensity-Carrying Modes (ICMs)

1. hypothetical modes $L_k$ with maximum intensity
2. contain the total intensity of the spectrum
3. first derived for infrared spectroscopy
4. most efficiently exploited for Resonance Raman
5. Raman- and ROA-ICMs determined by an eigenvalue problem:
   \[ M L_k = a_k L_k \]
   eigenvalue $a_k$ proportional to ROA intensity;
   \[ M \] contains Cartesian derivatives of ROA tensor components
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

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
  

- 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)

ROA spectrum of $\beta$ Domain of Rat Metallothionein

- >400 atoms, sulfur-rich, 2 Zn and 1 Cd atoms
- hardly any regular structures like $\alpha$-helix or $\beta$-sheets, mostly $\beta$-turns
- identified signatures of $\beta$-turns

ROA spectrum of $\beta$ Domain of Rat Metallothionein

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

Summary I

Localized Vibrations for the Analysis of Vibrational Spectra

Raman, IR and ROA Spectra of Helical Polypeptides
- + older work in collaboration with K. Ruud (2003–2007)

Raman + ROA Intensity-Tracking and Intensity-carrying Modes

- also done for Resonance Raman and IR:

ROA calculation for small metalloprotein
Summary II + Outlook

Solvation effects on ROA spectra of sugar molecule

Prediction for ROA spectra of chiral transition metal complexes
Chem. Phys. 346 (2008), 212.

Enhancement and De-Enhancement in Resonance ROA:

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 $\beta$-Turns with ROA:
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