

Determination of Vibrational Circular Dichroism spectra of fluxional molecules through classical polarisable molecular dynamics

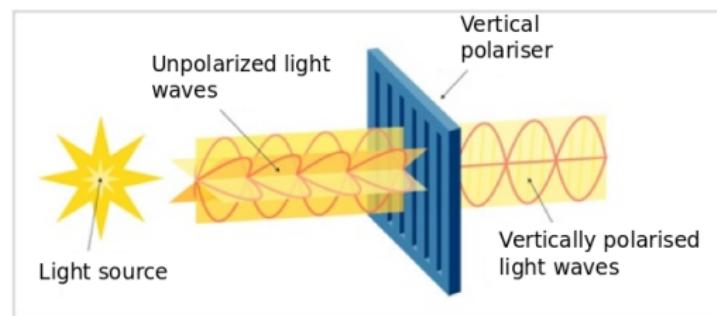
Jessica Bowles

ICP, Université Paris Saclay

16th March 2022

Polarisation of light to study chirality

Light travels in **all directions**, with a polariser, we can choose **one direction** (for example: vertically):

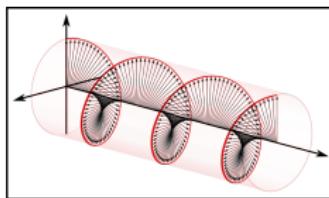


Example: Sunglasses

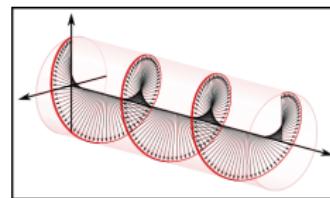


Circular polarisation of light to study chirality

Our chiral probe is **circular polarised light**.



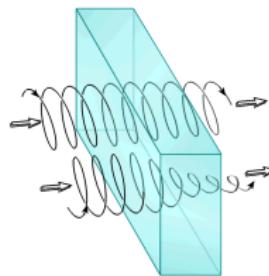
Left-handed circular polarisation



Right-handed circular polarisation

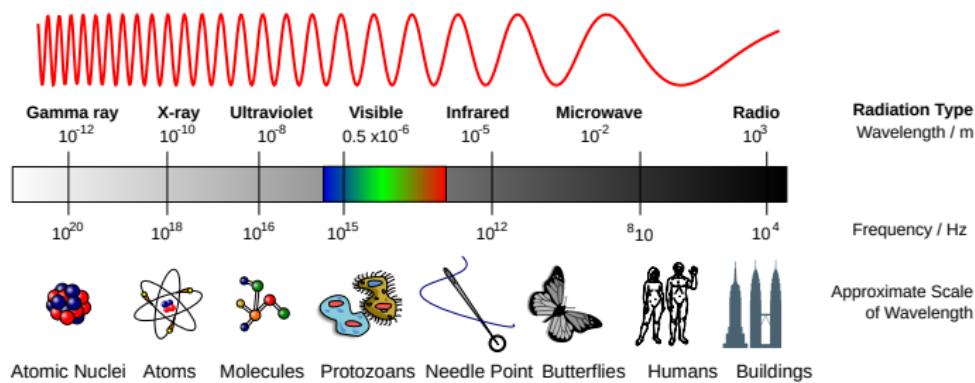
Depending on the direction of polarisation, the **chiral molecule absorbs the light differently**.

This phenomenon is called circular dichroism (CD)



Infra-Red light to study chirality

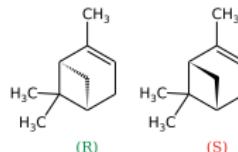
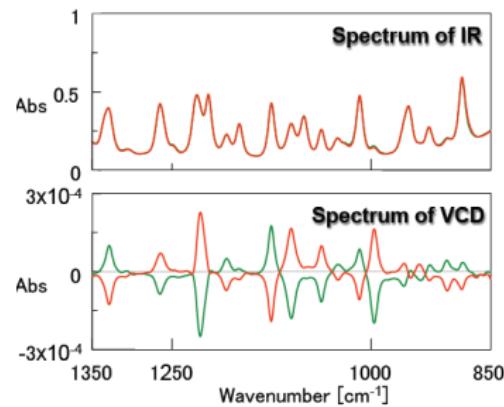
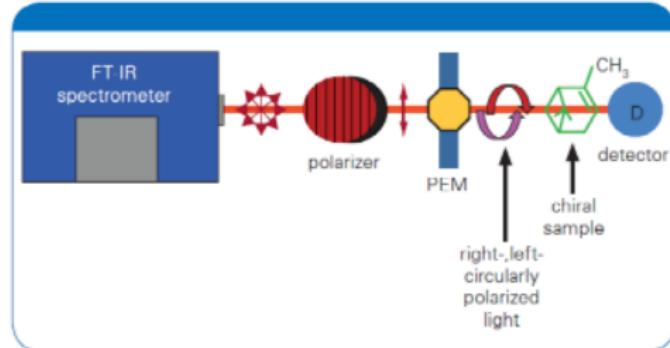
We use Infra-Red light to probe the vibrations of chiral molecules.



⇒ Vibrational Circular Dichroism (VCD)

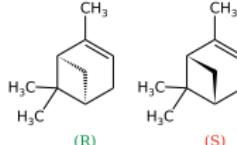
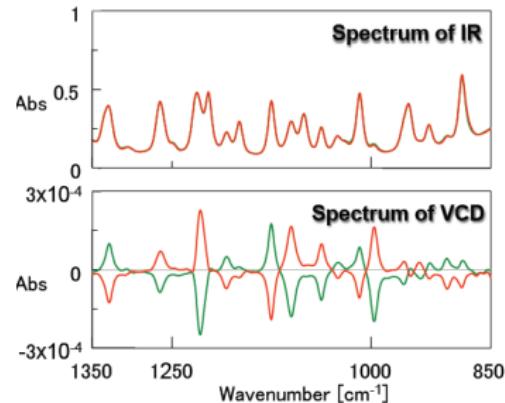
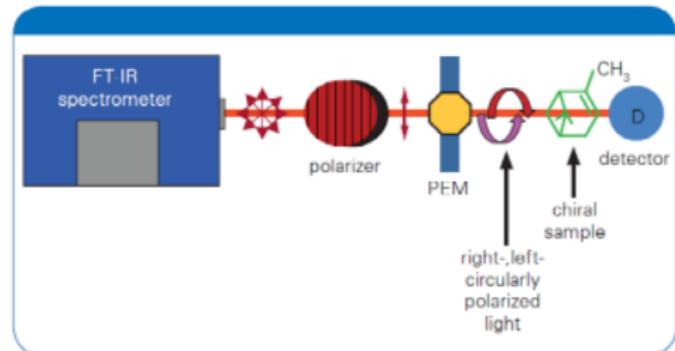
Spectrometer

Scheme of a **spectrometer** used to obtain VCD absorption spectra



Spectrometer

Scheme of a **spectrometer** used to obtain VCD absorption spectra



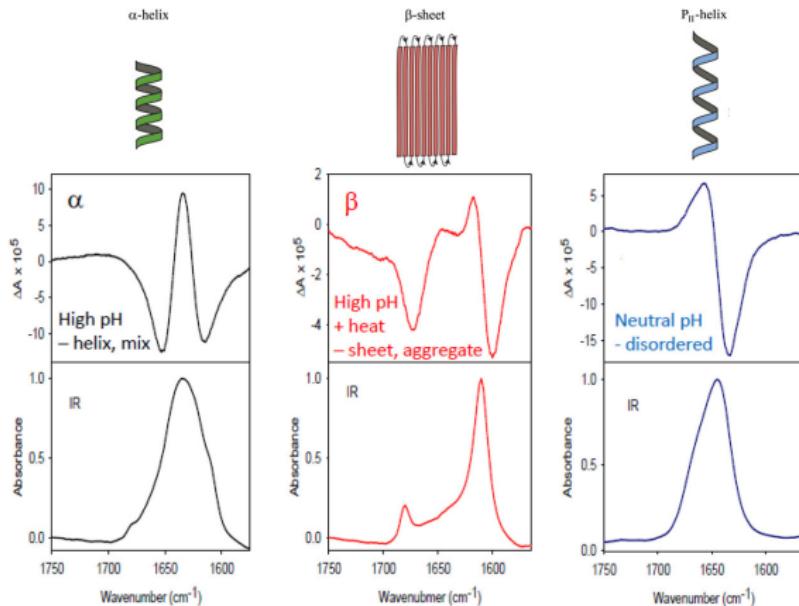
For each peak in the IR spectrum, there is a corresponding peak at the same frequency for the VCD spectrum.

PEM : Photo elastic modulator

<https://jascoinc.com>

Applications of VCD spectroscopy

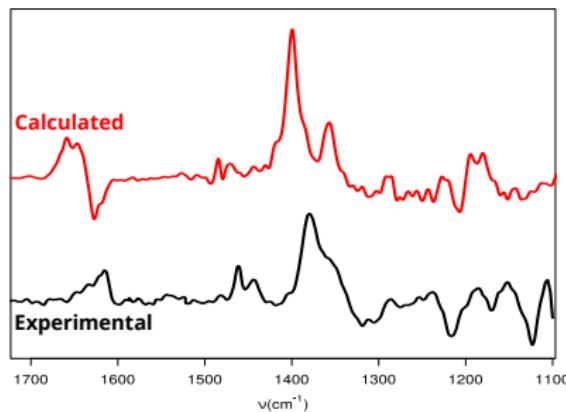
VCD spectroscopy can be used to differentiate between R and S enantiomers or between different polypeptide conformations (here poly-L-lysine).



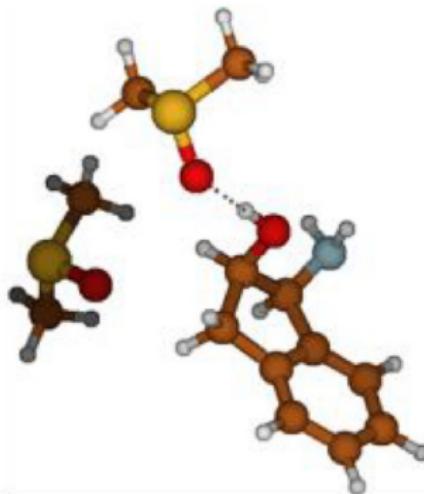
VCD spectroscopy in theoretical chemistry

Calculations can allow us to:

- Obtain spectra that are impossible to get experimentally (ex: temperature too high or low),
- Do tests before a costly experiment,
- Help interpret results.



Method 1: DFT, a static approach

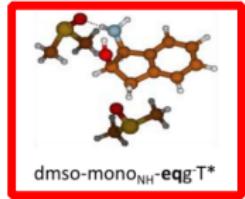
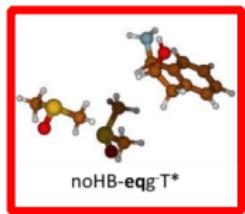
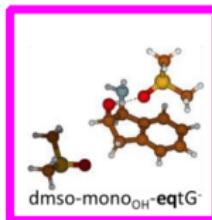
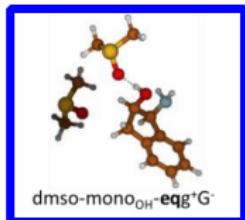


Structure of (1 S ,2 R)-(-)-cis-1-amino-2-indanol in DMSO

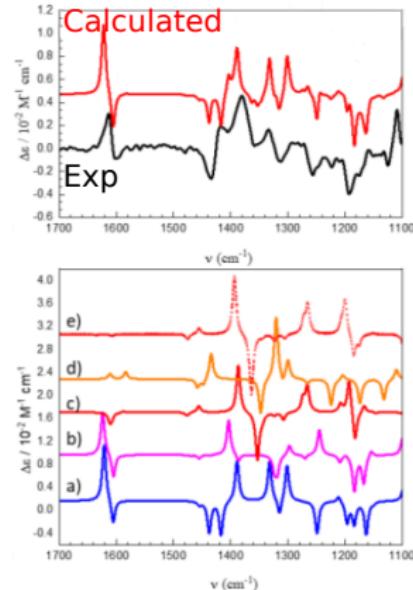
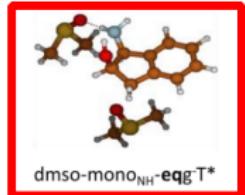
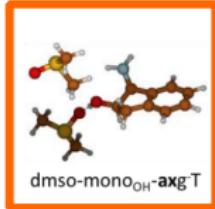
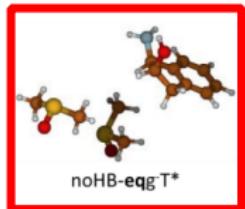
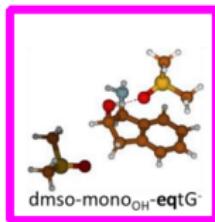
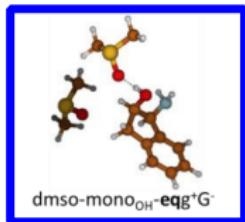
B3LYP/6-311G++(d,p)

Katia Le Barbu-Debus, Anne Zehnacker. *Competition between inter and intramolecular hydrogen bond evidenced by vibrational circular dichroism spectroscopy: The case of (1 S ,2 R)-(-)-cis-1-amino-2-indanol.* Chirality (2021).

Method 1: DFT, a static approach



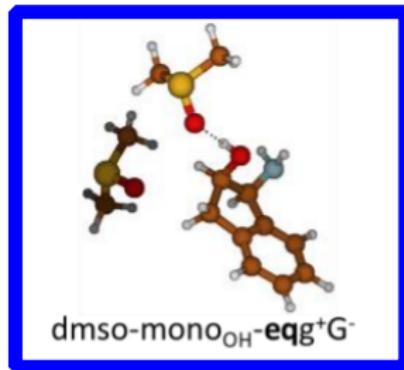
Method 1: DFT, a static approach



Top: Experimental VCD spectrum compared with the simulation resulting from Boltzmann averaged contributions of the 1:2 complexes
Bottom: Individual VCD contributions

Method 1: DFT, a static approach

Most likely structure:



Flexibility is accounted for indirectly by a Boltzmann distribution of the most stable conformers .

This is not accurate for very floppy molecules or ones which have a strong interaction with their environment.

Method 2: Ab-initio molecular dynamics

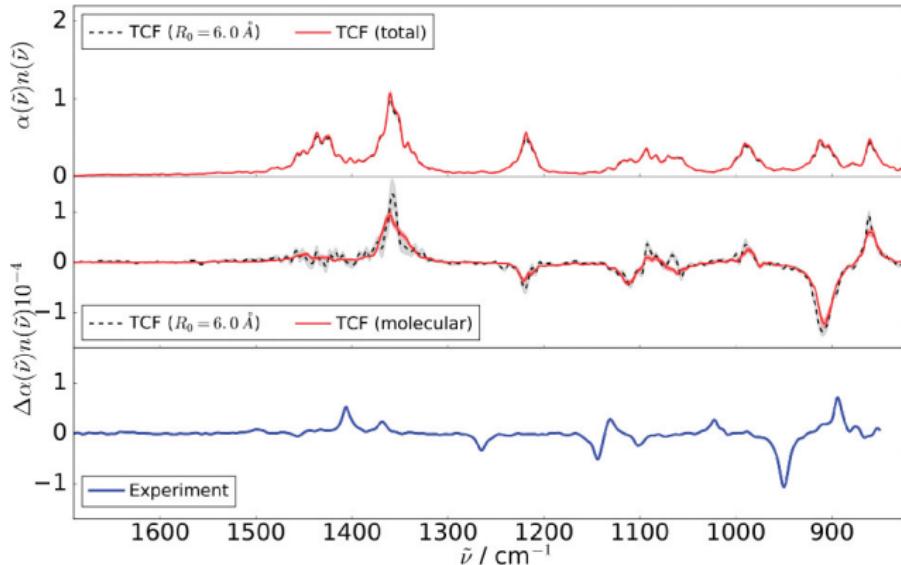
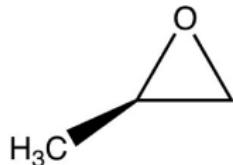


Figure: Dynamical IRA and VCD spectra of (R)-propylene-oxide (RPO) solvated in water at 340 K. The intensities are in units of km cm mol^{-1} .

7 RPO molecules in 34 H_2O , 2 trajectories of 20 ps

Method 2: Ab-initio molecular dynamics

- Flexibility and anharmocity are accounted for through the molecular dynamics simulation.
- But molecular interactions are treated by a continuum and/or very few solvent molecules.
- The calculations are expensive so only explore for a short period of time. (<100ps)

Method 3: Classical molecular dynamics

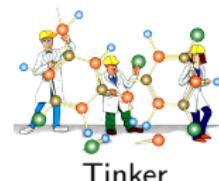
Goal: VCD spectra of flexible molecules in an explicit solvent ⇒ Novel approach with classical MD



- The system is described with a force field
- Calculations are less expensive so it is possible to explore for longer periods of time and with an explicit solvent

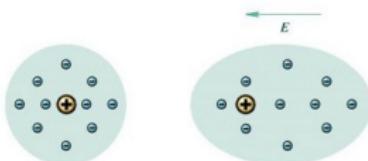
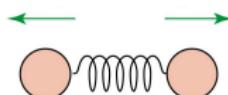
Method 3: Classical molecular dynamics

Goal: VCD spectra of flexible molecules in an explicit solvent ⇒ Novel approach with classical MD



We use the AMOEBA force field which has:

- Anharmonic bond stretch and angle terms,
- Multipoles on each atom (charges, dipoles and quadripoles),
- Polarisable dipoles on each atom, which deform the atom according to the electric field of the other charges.



Implementation to obtain VCD spectra with classical molecular dynamics (Method 3)

From the **molecular dynamics** simulations we can **retrieve** the electric and magnetic **moments** throughout time.

The **Fourier transform** of the **cross-correlation** between the electric and magnetic **moments**:

$$\Delta I \propto \int_0^{+\infty} \left\langle \dot{\vec{\mu}}(0) \cdot \vec{m}(t) \right\rangle e^{-i\omega t} dt \quad (1)$$

where $\dot{\vec{\mu}}(t)$ is the **electric** moment and $\vec{m}(t)$ the **magnetic** moment at time t .

Implementation to obtain VCD spectra with classical molecular dynamics (Method 3)

From the **molecular dynamics** simulations we can **retrieve** the electric and magnetic **moments** throughout time.

The **Fourier transform** of the **cross-correlation** between the electric and magnetic **moments**:

$$\Delta I \propto \int_0^{+\infty} \left\langle \dot{\vec{\mu}}(0) \cdot \vec{m}(t) \right\rangle e^{-i\omega t} dt \quad (1)$$

where $\vec{\mu}(t)$ is the **electric** moment and $\vec{m}(t)$ the **magnetic** moment at time t .

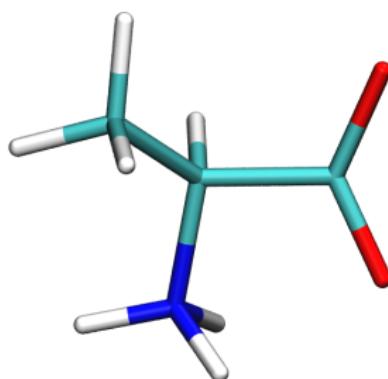
$$\vec{\mu}(t) = \sum_i^N (q_i \vec{r}_i(t) + \vec{\mu}_{ind}(t)) \quad (2)$$

$$\vec{m}(t) = \frac{1}{2} \sum_i^N [q_i \vec{r}_i(t) + \vec{\mu}_{ind}(t)] \times \vec{v}_i(t) + \vec{\mu}_{ind}(t) \times \vec{r}_i(t) \quad (3)$$

These **moments** of the molecule will **predict** the way it will **turn** circular polarized **light**.

Alanine in the gas phase

The cross-correlation and Fourier transform are carried out in **ChirPy**. ChirPy (chiral python) is a python package for analysing supramolecular and electronic structure, chirality and dynamics.



Zwitterionic form of L-alanine

Compare moments: ab-initio/classical (Methods 2 and 3)

To check our classical MD method:

From the same trajectory, we calculate the moments using the two molecular dynamics methods.

Compare moments: ab-initio/classical (Methods 2 and 3)

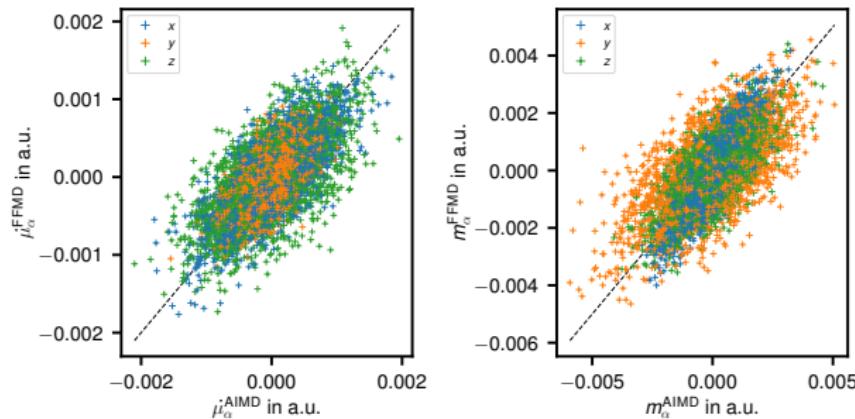
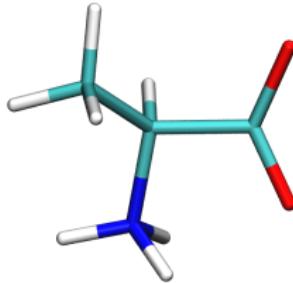


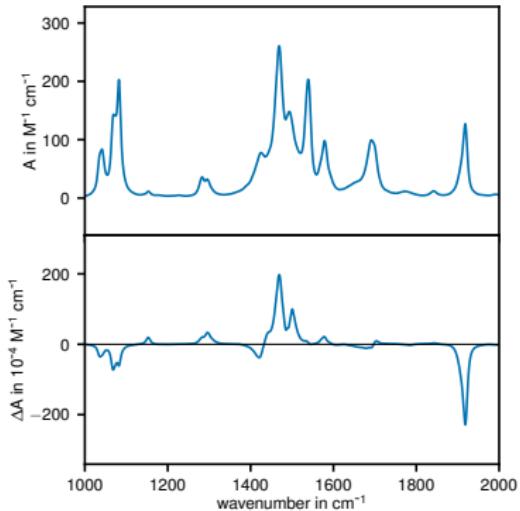
Figure: Comparison between ab-initio and classical MD for the velocity form of the electric moments $\frac{\partial \mu}{\partial t}$ and the magnetic moments m

The moments and time correlation functions are similar.

Alanine in the gas phase



Zwitterionic form of L-alanine



(a) IR and VCD spectra of Alanine in the gas phase averaged over 40 trajectories of 200 ps

Compare spectra: ab-initio/classical (Methods 2 and 3)

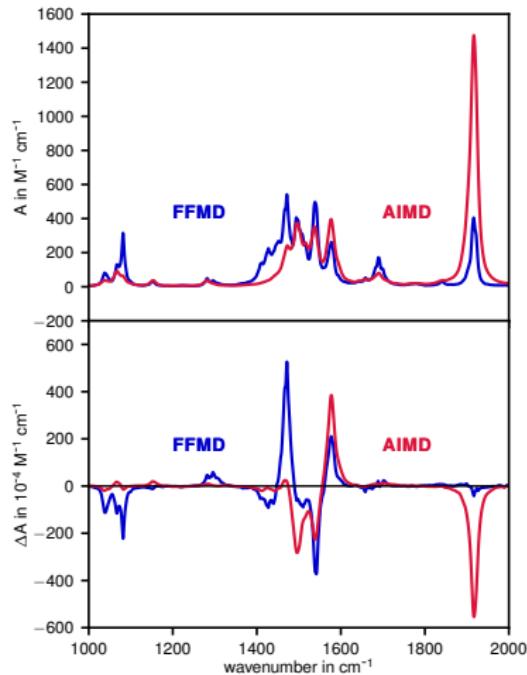
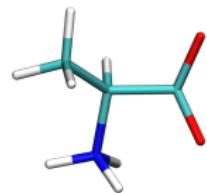


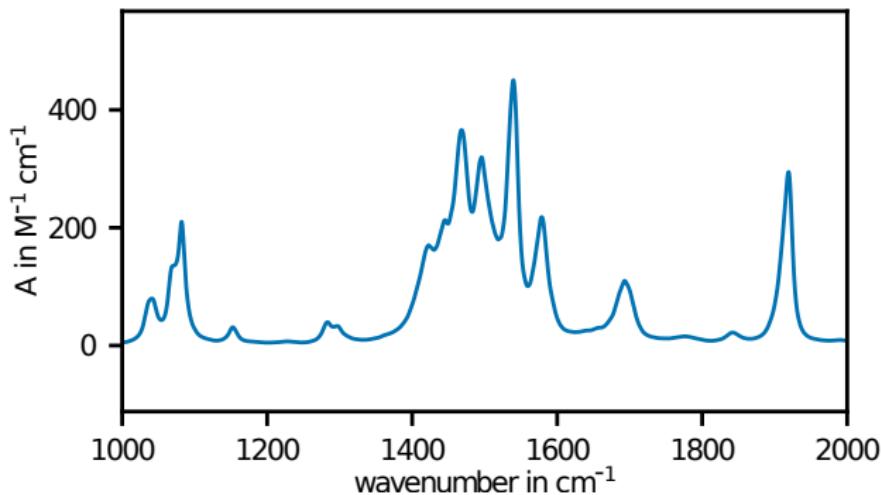
Figure: Comparison between ab-initio and classical MD for the IR and VCD spectra

The spectra are similar though there is a slight difference in the IR and VCD activities in the range $1410\text{--}1450 \text{ cm}^{-1}$.

Decomposing IR spectrum



Zwitterionic form of L-alanine



(a) IR spectrum of alanine in the gas phase

We expect for each peak of the IR spectrum, a peak in the VCD spectrum at the same frequency.

We decompose the spectrum into effective modes.

Decomposition of the IR spectrum

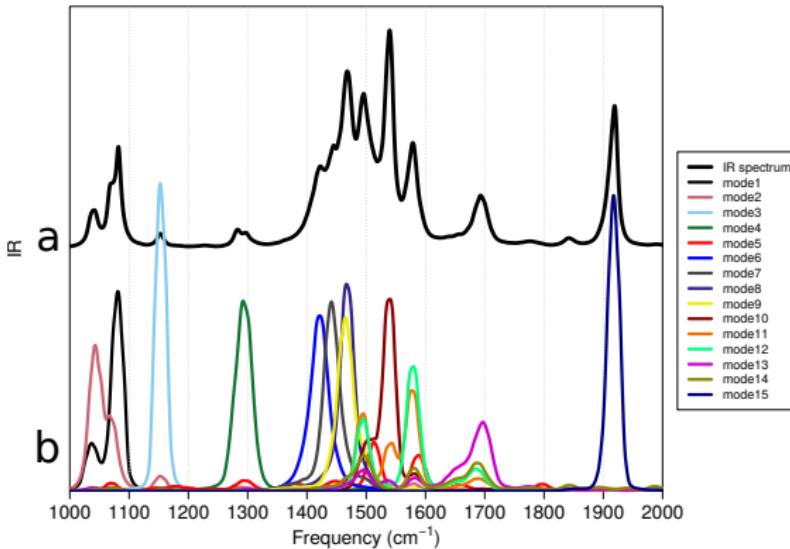
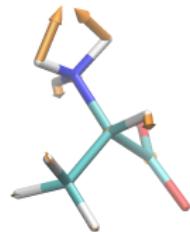
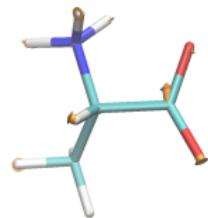


Figure: a-IR spectrum of alanine in the gas phase at 300K
b-Decomposition of this spectrum



(a) Effective Mode 11 -
1580 cm⁻¹: NH₃ bend



(b) Effective Mode 15 -
1918 cm⁻¹: C = O stretch

We can determine which molecular **vibrations** are included in each peak.

Federica Agostini, Rodolphe Vuilleumier, Giovanni Ciccotti. *Infrared spectroscopy of small protonated water clusters at room temperature: an effective modes analysis.* J. Phys. Chem. 2011, 134, 084302.

Decomposition of the IR spectrum

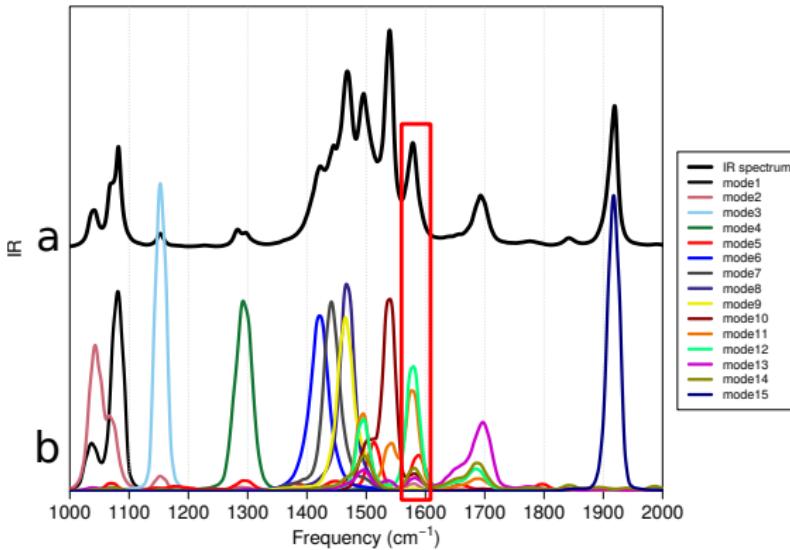
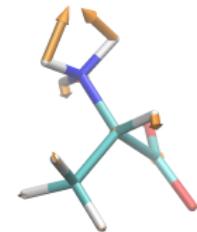
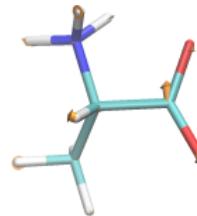


Figure: a-IR spectrum of alanine in the gas phase at 300K
b-Decomposition of this spectrum



(a) Effective Mode 11 -
1580 cm⁻¹: NH₃ bend



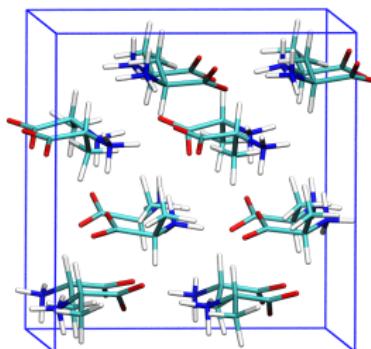
(b) Effective Mode 15 -
1918 cm⁻¹: C = O stretch

We can determine which molecular **vibrations** are included in each peak.

Federica Agostini, Rodolphe Vuilleumier, Giovanni Ciccotti. *Infrared spectroscopy of small protonated water clusters at room temperature: an effective modes analysis*. J. Phys. Chem. 2011, 134, 084302.

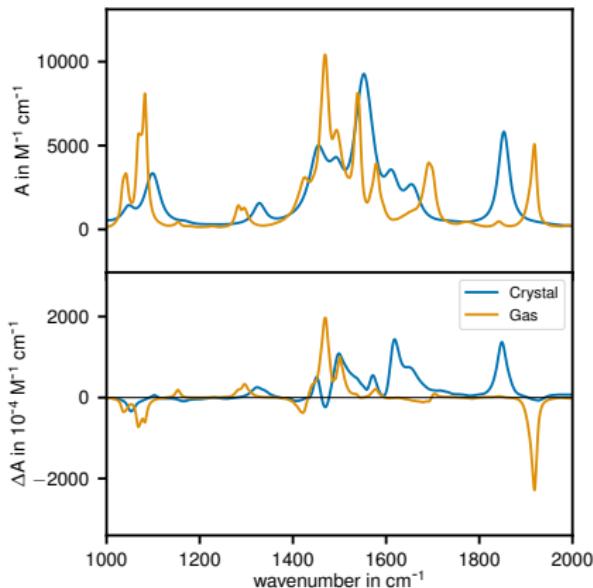
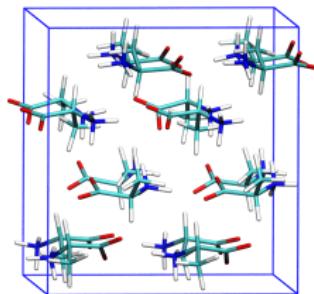
Alanine in the crystal phase

From the **crystallographic data**, a **crystal** of 16 alanine molecules was **constructed** and placed in a periodic box of $12.073 * 12.342 * 11.577 \text{ \AA}$.



The electric and magnetic moments of this system are calculated to obtain the IR and VCD spectra.

Alanine in the crystal phase



(a) IR and VCD spectra of alanine in the zwitterionic form for crystal and gas phase

Alanine in the crystal phase - convergence

We need to **sample enough configurations** to have a representative description of the molecule.

We have enough when the new conformations do not **change the spectra significantly**.

Alanine in the crystal phase - convergence

We need to **sample enough configurations** to have a representative description of the molecule.

We have enough when the new conformations do not **change the spectra significantly**.

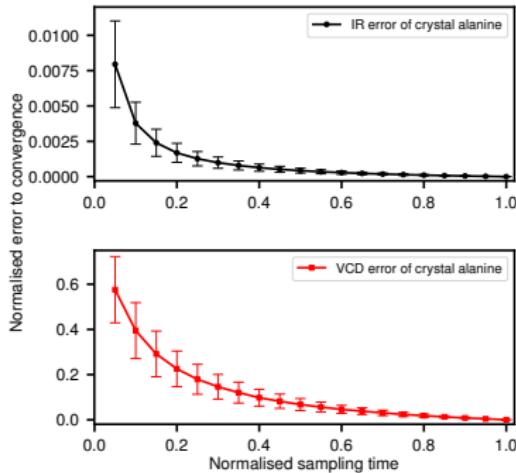
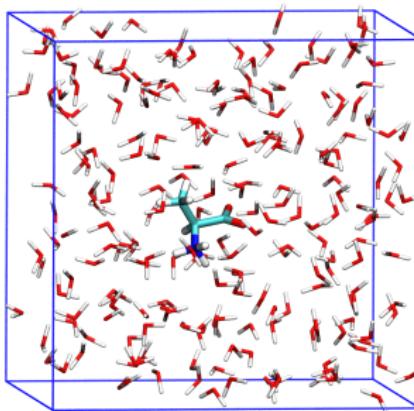


Figure: Normalised error of the average of X trajectories compared to the average of 20 trajectories of 40ps

The IR spectrum converges quicker than the VCD spectrum.

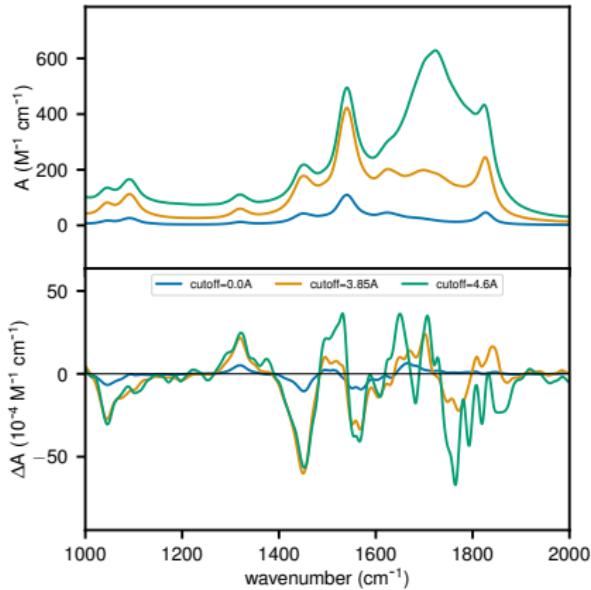
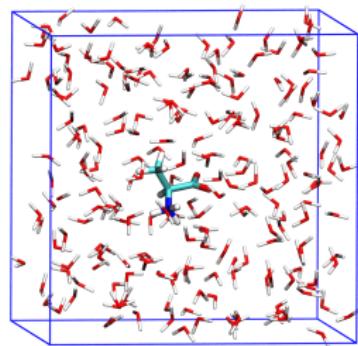
Alanine in water

The molecule of alanine is inserted in a **periodic boundary condition box** of 18.6 Å containing 211 **water** molecules.



The electric and magnetic moments of this system are calculated to obtain the IR and VCD spectra.

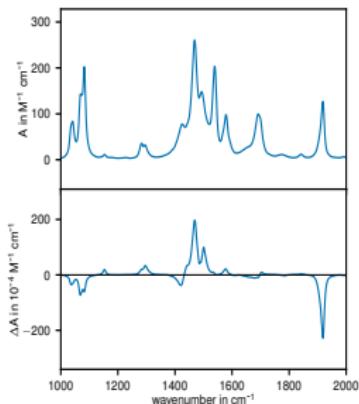
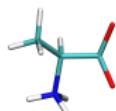
Alanine in water



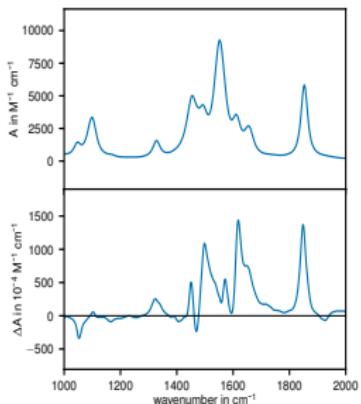
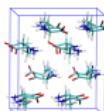
(a) IR and VCD spectra of Alanine in water, average of 20 trajectories of 40ps

Conclusion

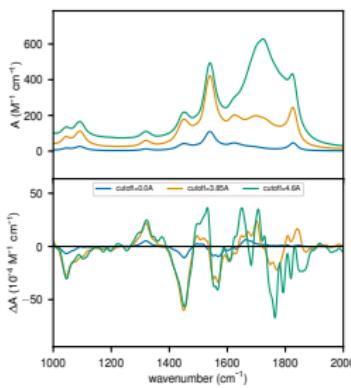
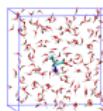
The VCD spectra of Alanine in the gas, crystal and liquid phases can be calculated in classical polarisable molecular dynamics.



(a) IR and VCD spectra of Alanine in the gas phase



(b) IR and VCD spectra of alanine in the crystal phase



(c) IR and VCD spectra of Alanine in water

The convergence is long for the system that is studied.

Thank you!



ANR Dichroprobe:

Carine Clavaguéra *ICP, Université Paris-Saclay*
Federica Agostini *ICP, Université Paris-Saclay*



Florent Calvo *LiPhy, Université Grenoble Alpes*



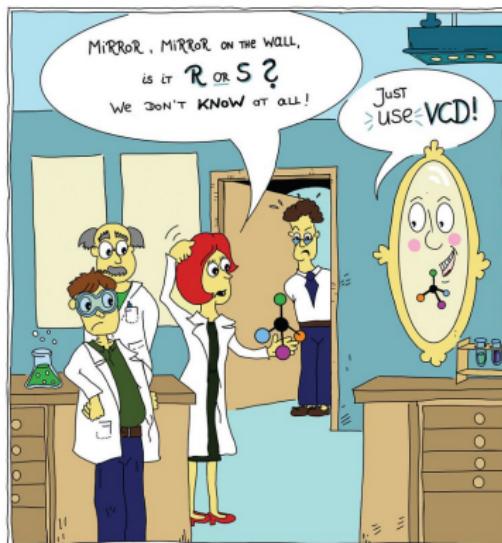
Anne Zehnacker *ISMO, Université Paris-Saclay*
Katia Le Barbu-Debus *ISMO, Université Paris-Saclay*
Sascha Jänigen *ISMO, Université Paris-Saclay*



Rodolphe Vuilleumier *PASTEUR, ENS Paris*



Thank you for your attention!



Decomposing IR spectrum

- Transform the trajectory (position & velocities) of **Cartesian coordinates** obtained from a TINKER simulation into a trajectory of **internal coordinates**: ζ_j ($j \in \{1, \dots, 3N - 6\}$)
- The **Effective modes** are :

$$k_i = \sum_{j=1}^{3N-6} Z_{ij}^{-1} \zeta_j \quad (4)$$

Decomposing IR spectrum

- Transform the trajectory (position & velocities) of **Cartesian coordinates** obtained from a TINKER simulation into a trajectory of **internal coordinates**: ζ_j ($j \in \{1, \dots, 3N - 6\}$)
- The **Effective modes** are :

$$k_i = \sum_{j=1}^{3N-6} Z_{ij}^{-1} \zeta_j \quad (4)$$

- To find the transformation matrix Z_{ij} , $\Omega^{(m)}$ is **minimized** with respect to the elements of Z :

$$\Omega^{(m)} = \sum_{i=1}^{3N-6} \left[\frac{\beta}{2\pi} \int_{-\infty}^{+\infty} d\omega \omega^{2m} P_{ii}^{(k)}(\omega) - \left(\frac{\beta}{2\pi} \int_{-\infty}^{+\infty} d\omega \omega^m P_{ii}^{(k)}(\omega) \right)^2 \right]$$

with $P_{ii}^{(k)}(\omega)$ the power spectrum:

$$P_{ii}^{(k)}(\omega) = \int_{-\infty}^{+\infty} dt e^{-i\omega t} \langle \dot{k}_i(t) \dot{k}_i(0) \rangle \quad (5)$$

Decomposing IR spectrum

- Transform the trajectory (position & velocities) of **Cartesian coordinates** obtained from a TINKER simulation into a trajectory of **internal coordinates**: ζ_j ($j \in \{1, \dots, 3N - 6\}$)
- The **Effective modes** are :

$$k_i = \sum_{j=1}^{3N-6} Z_{ij}^{-1} \zeta_j \quad (4)$$

- Equation for the **IR spectrum**:

$$I_m^{(\omega)} = \frac{\beta N_A}{6c\epsilon_0} \sum_{i=1}^{3N-6} \left\langle \left| \frac{\partial \vec{\mu}}{\partial k_i}(0) \right|^2 \right\rangle P_{ii}^{(k)}(\omega) \quad (5)$$

Origin dependence of \vec{m} in periodic boundary conditions

Minimum image convention : Each **particle interacts** with the **closest image** of the remaining particles, through a common origin. (Black lines) This gives different values of \vec{r} depending on the origin.

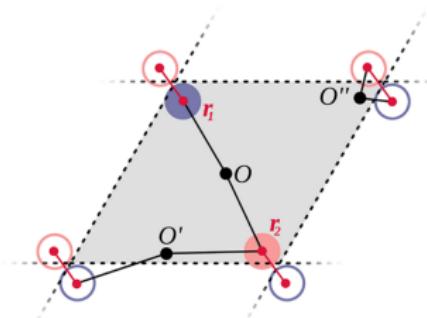


Figure: Sketch illustrating the common origin problem within periodic boundaries.

Origin dependence of \vec{m} in periodic boundary conditions

Minimum image convention : Each **particle interacts** with the **closest image** of the remaining particles, through a common origin. (Black lines) This gives different values of \vec{r} depending on the origin.

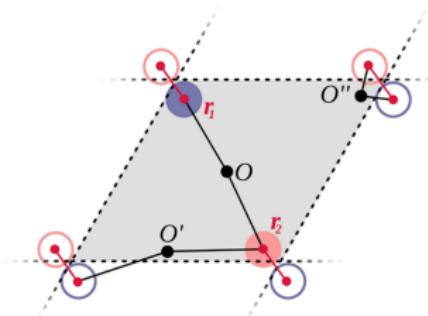
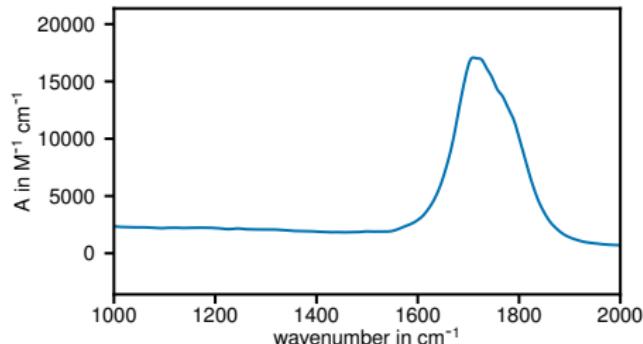


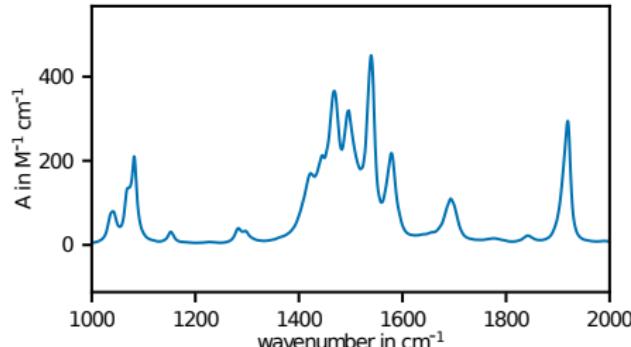
Figure: Sketch illustrating the common origin problem within periodic boundaries.

Novel approach: **Evaluate** the nearest image directly **between particles** so the VCD spectrum is origin invariant (**Red lines**)
Moments are retrieved for each molecule.

Problem: strong intensities of water



(a) IR spectrum of water



(b) IR spectrum of alanine in the gas phase

The moments of water are **big** compared to those of alanine!

We use a **cutoff function** that **includes** the **nearest water** molecules from the alanine.