X-ray Circular Dichroism
A window to local chirality in molecules

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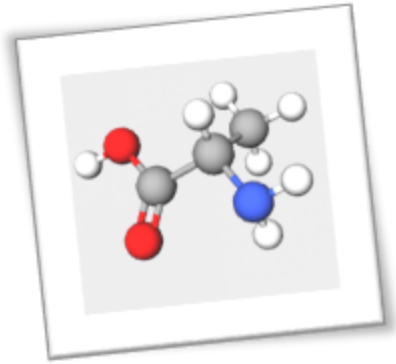
Chirality

A geometrical property characterizing those objects that can not overlap with their mirror image



10^{21} m

10^{5} m

10^{-1} m

10^{-9} m

10^{-10} m

Molecular chirality

- Molecular chirality:

- It is highly relevant in living organisms
- It impacts chemical and biological function
- It is essential for drug design
- The wrong enantiomer can be inert or even harmful
- Light can also be shaped into a chiral object
- Molecular chirality is detected by circular dichroism (CD) signals
- CD signals measure the difference in absorption between right and left circularly polarized light

Rotatory strengths

- Rotatory strength:

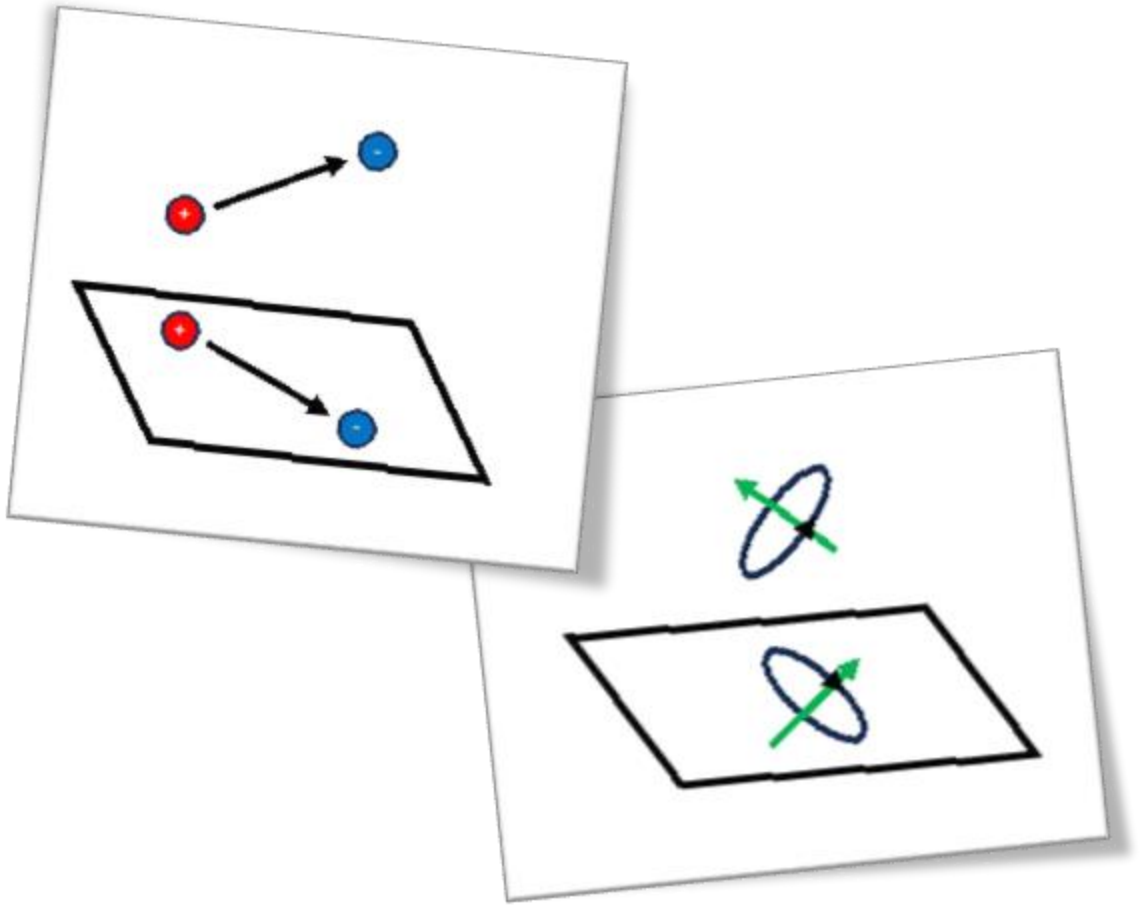
- After averaging over all the possible molecular orientations, CD signals become proportional to the rotatory strength:

$$S_{CD}(\omega) = A^{L}(\omega) - A^{R}(\omega)$$

$$S_{CD} \propto \sum_{m} R_{m0}\sigma_{m0}(\omega)$$

- Rotatory strength is given by the inner product between the electric and magnetic transition dipoles:

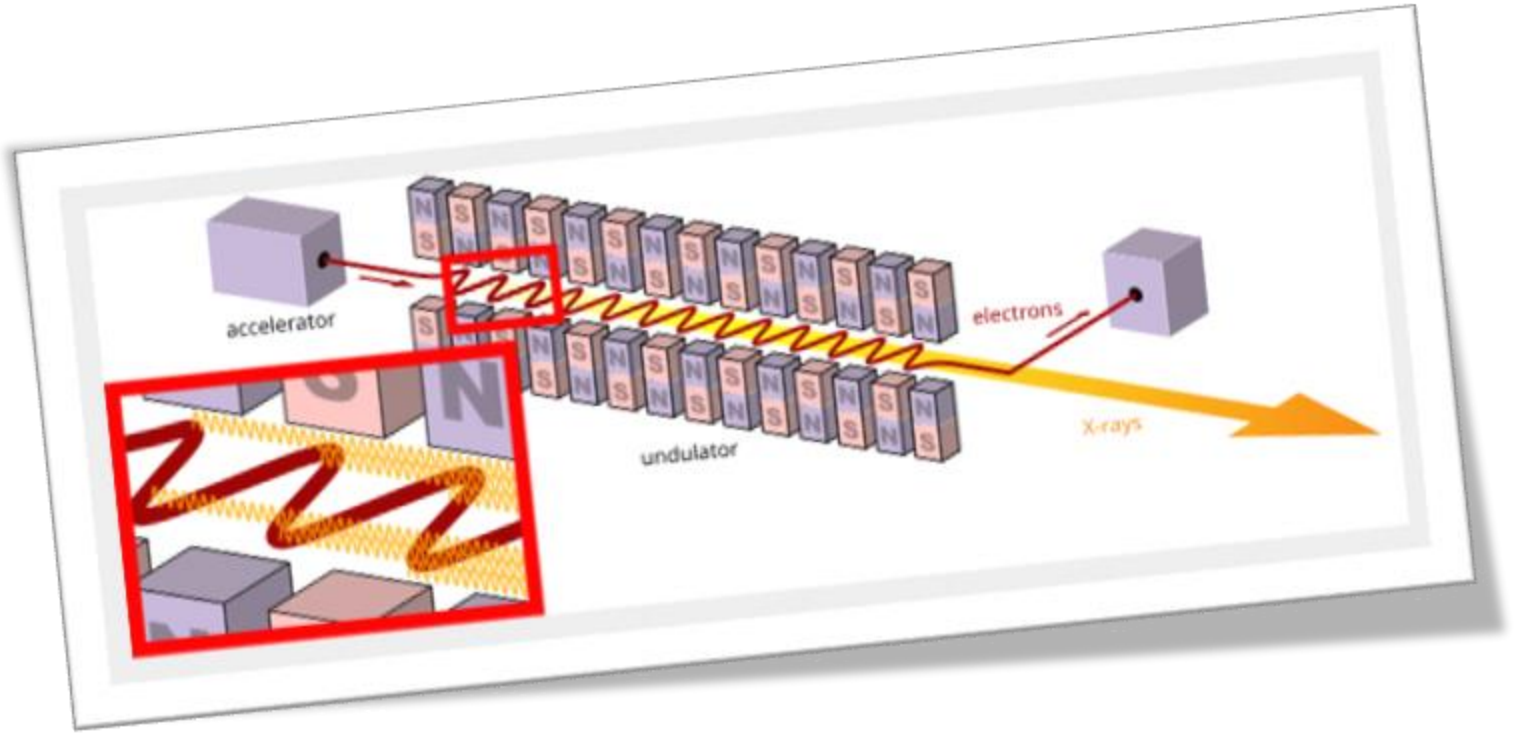
$$R_{m0} = \mathrm{Im}(\boldsymbol{\mu}_{m0} \cdot \boldsymbol{m}_{m0})$$



X-ray sources

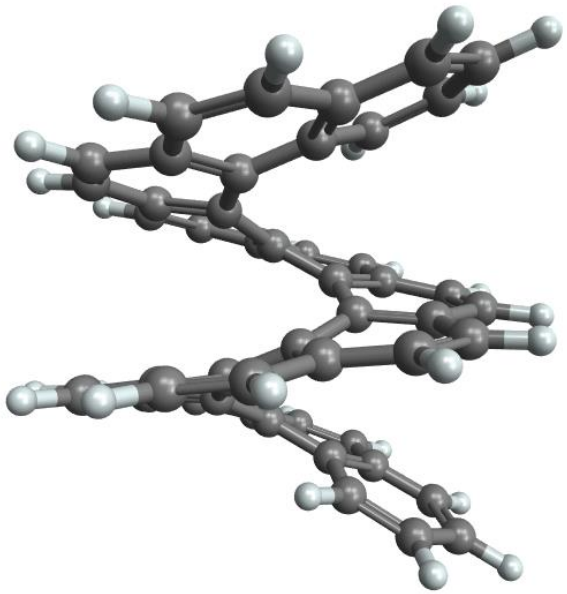
- X-ray laser sources:

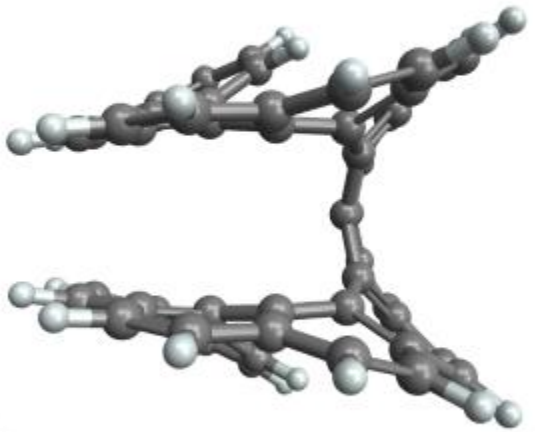
- Provide a better time resolution allowing to probe transient process
- Can be tuned to be resonant with specific X-ray chromophores electronic core transitions
- Allow to probe local information



- Recent advances in the control of the polarization and spatial structure of X-ray beams have paved the way for extending CD to the X-ray range (XCD)
- XCD can probe the local chirality of molecules and provides the time resolution required to probe transient chiral changes

Proof of concept example



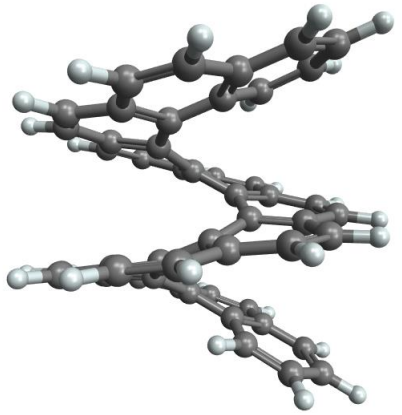


About Helicenes

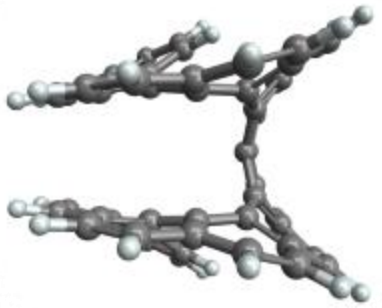
- Helicene molecules:

- Helicenes are twisted molecules usually having a Helix Shape (HS) conformation with a well defined global chirality
- While investigating helicenes melting point, it was discovered that they can racemize at high temperatures, going from one helix orientation to the opposite
- The racemization mechanism was determined to follow a conformational pathway, where a Transition State (TS) is located in the middle
- In the TS, helicene becomes globally achiral while retaining two opposite local chiralities

Helix shape (**HS**)



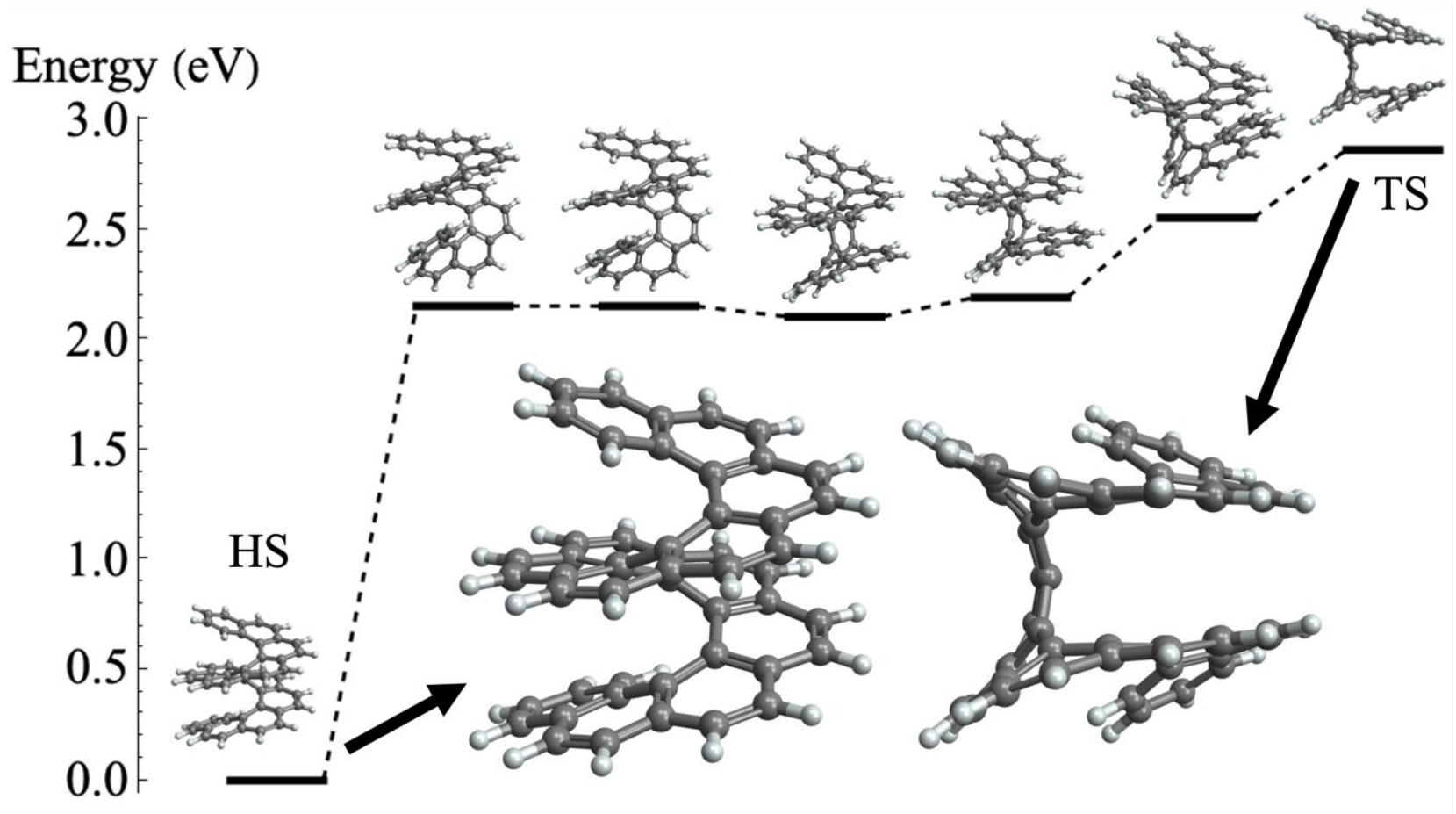
Transition State (**TS**)



[12]Helicene half racemization pathway

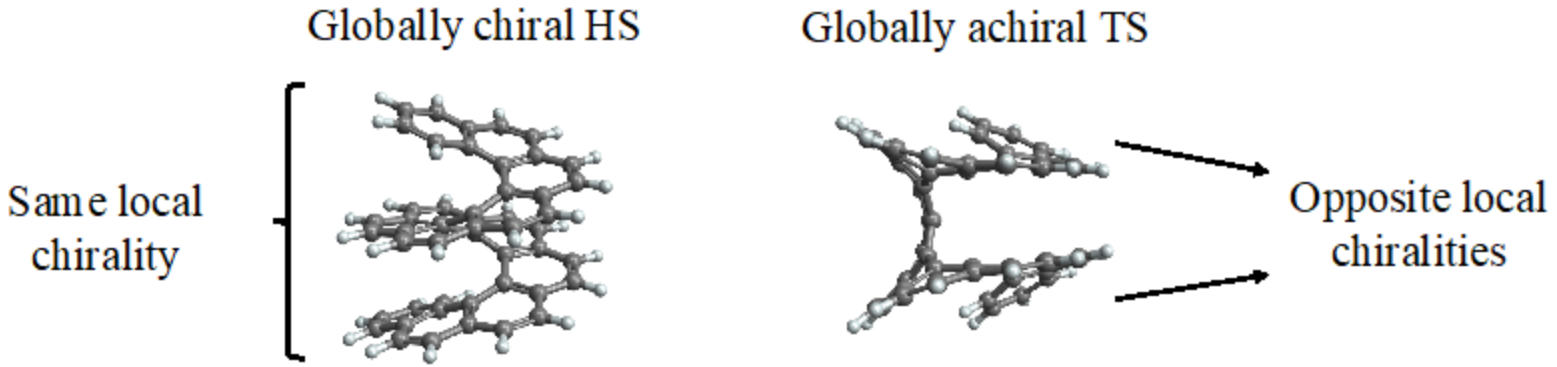
- Racemization pathway:

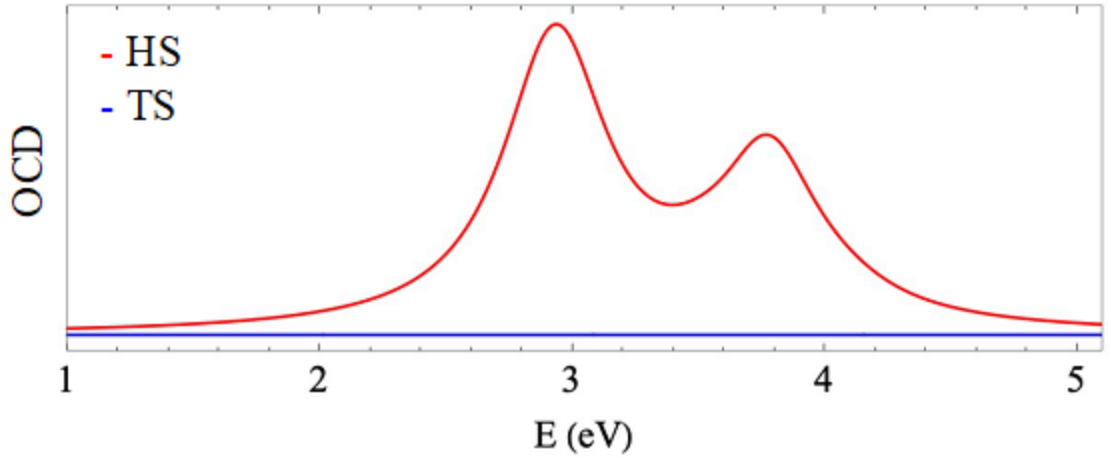
- Racemization of helicenes follows a conformational pathway [12] that is thermally activated



[12] Jorge Barroso *et al.*, *Chem. Comm. 2018,* 54(2), 188-191.

OCD for the HS and TS configurations

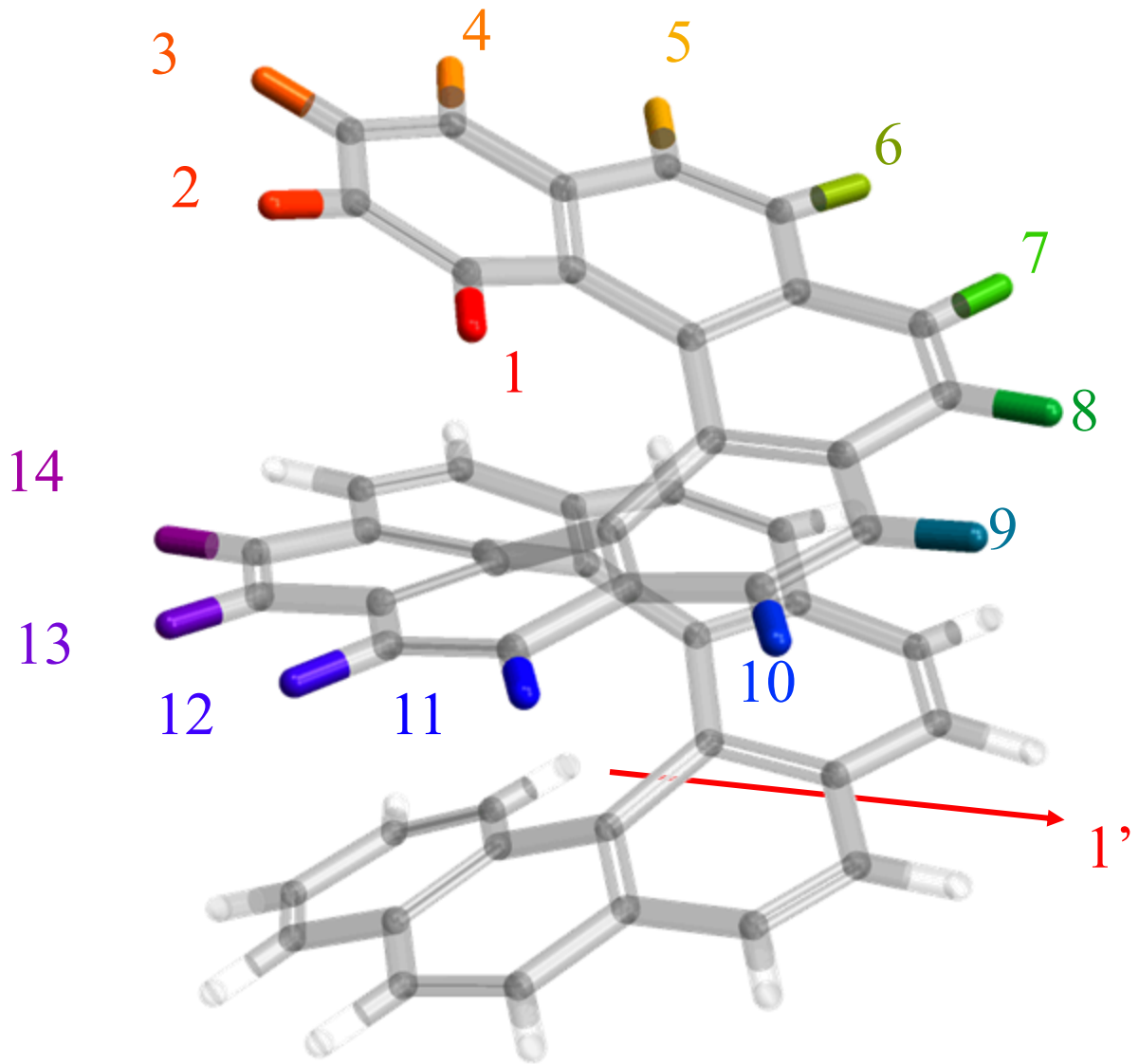




- OCD signals:

- OCD probes the global chirality of helicene
- The HS is globally chiral as probed by OCD
- The TS is globally achiral as probed by OCD

How to probe local chirality?



- XCD signals:

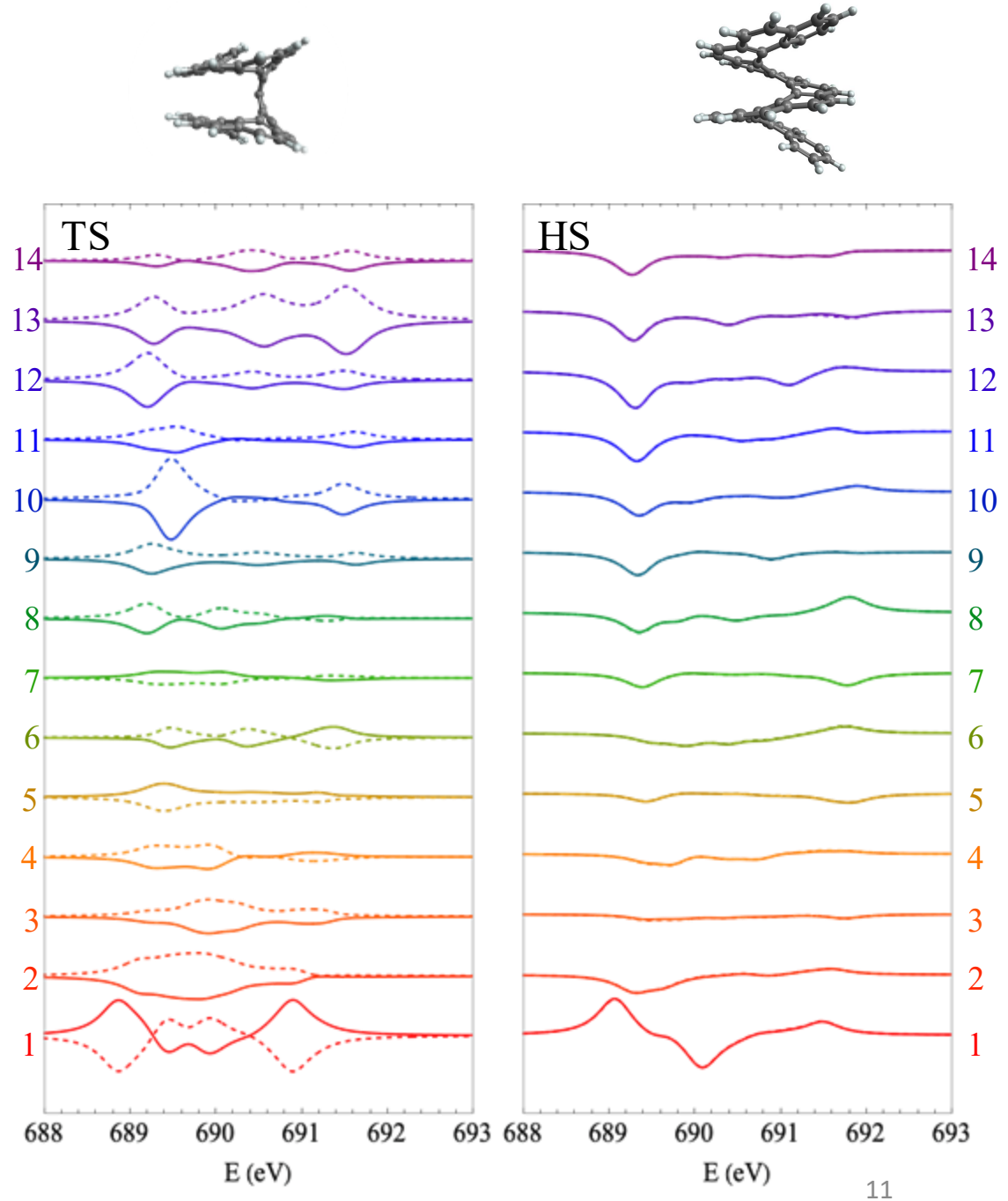
- XCD can be tailored for transitions that are well localized
- Carbon atoms have a small chemical shift for [12]helicene
- We can perform X-ray chromophore substitutions (e.g. F) to probe the local chirality at different substitution sites (as numbered in the sketch)[13]

[13] Freixas, V. M. *et al.*, *JACS. 2023,* 145(38), 21012-21019.

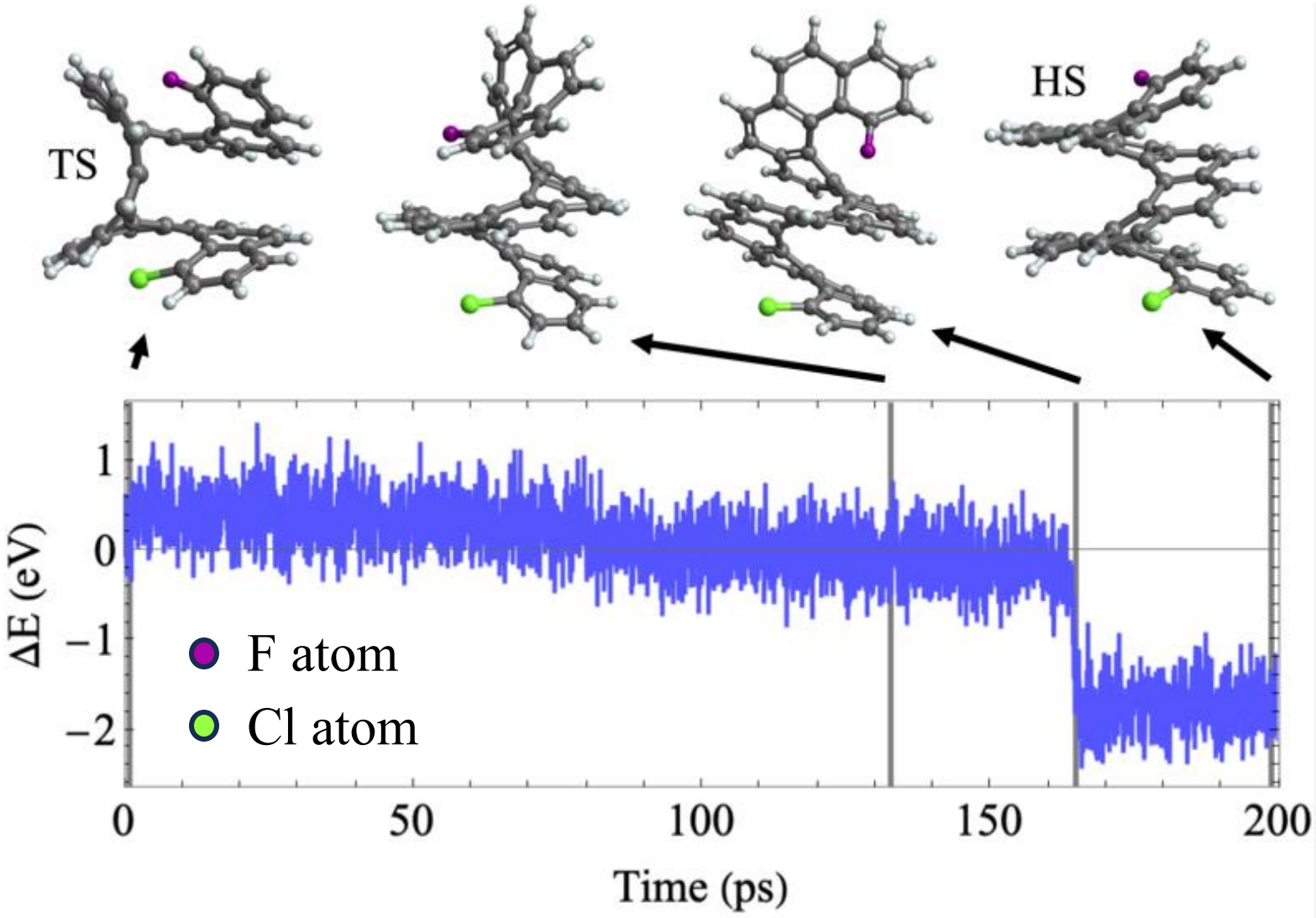
XCD for the F K-edge at different substitution sites

- XCD signals:

- For the TS conformation XCD detects the opposite local chirality on each side of the molecule
- For the HS conformation XCD detects the same local chirality on each side of the molecule



Molecular dynamics of the racemization pathway



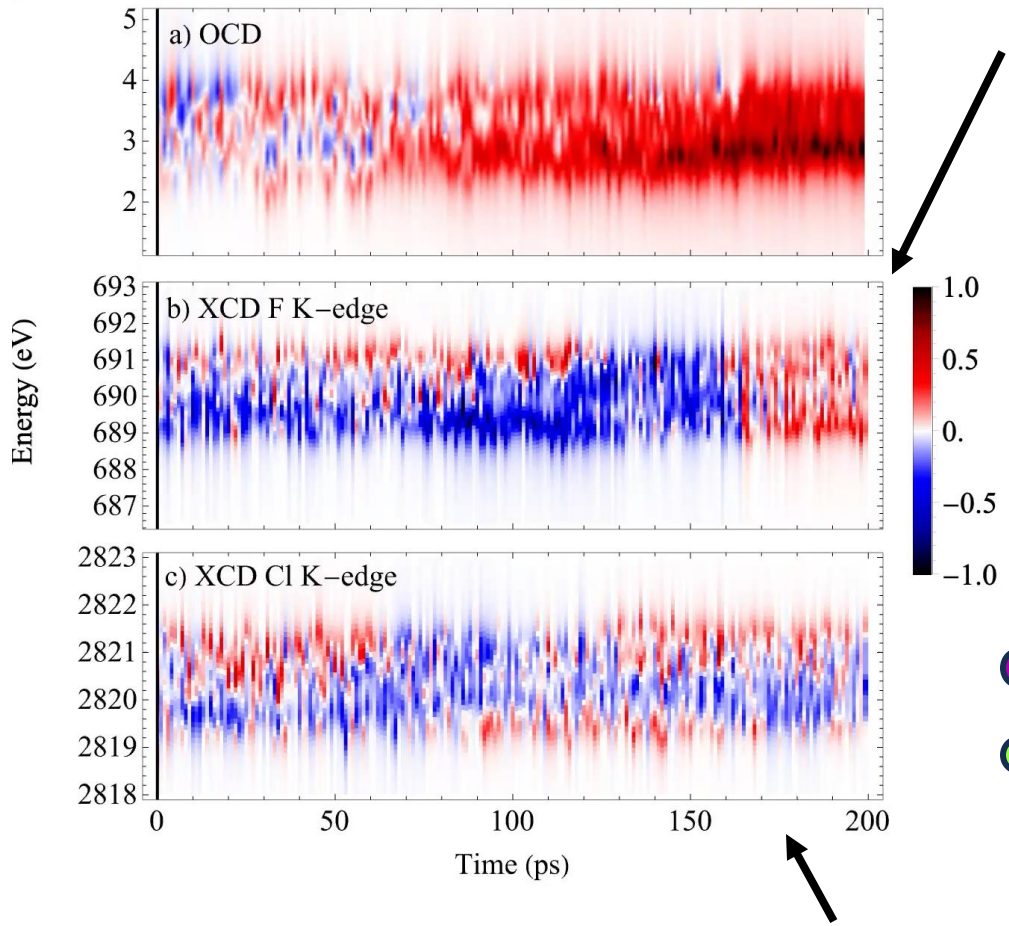
- Molecular dynamics simulation:

- Double substitutions were performed with different X-ray chromophores (F and Cl)
- Ground state molecular dynamics with the Langevin thermostat at 300 K starts from the TS conformation and evolves toward the HS conformation
- The potential energy drop (~165 ps) reflects the final transition to the HS conformation

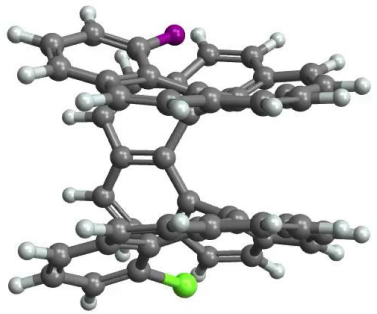
OCD vs. XCD at F and Cl K-edges

Globally chirality probed by OCD

Local chirality on the F side probed by XCD



Local chirality on the Cl side probed by XCD



- F atom
- Cl atom

- Molecular dynamics simulation:

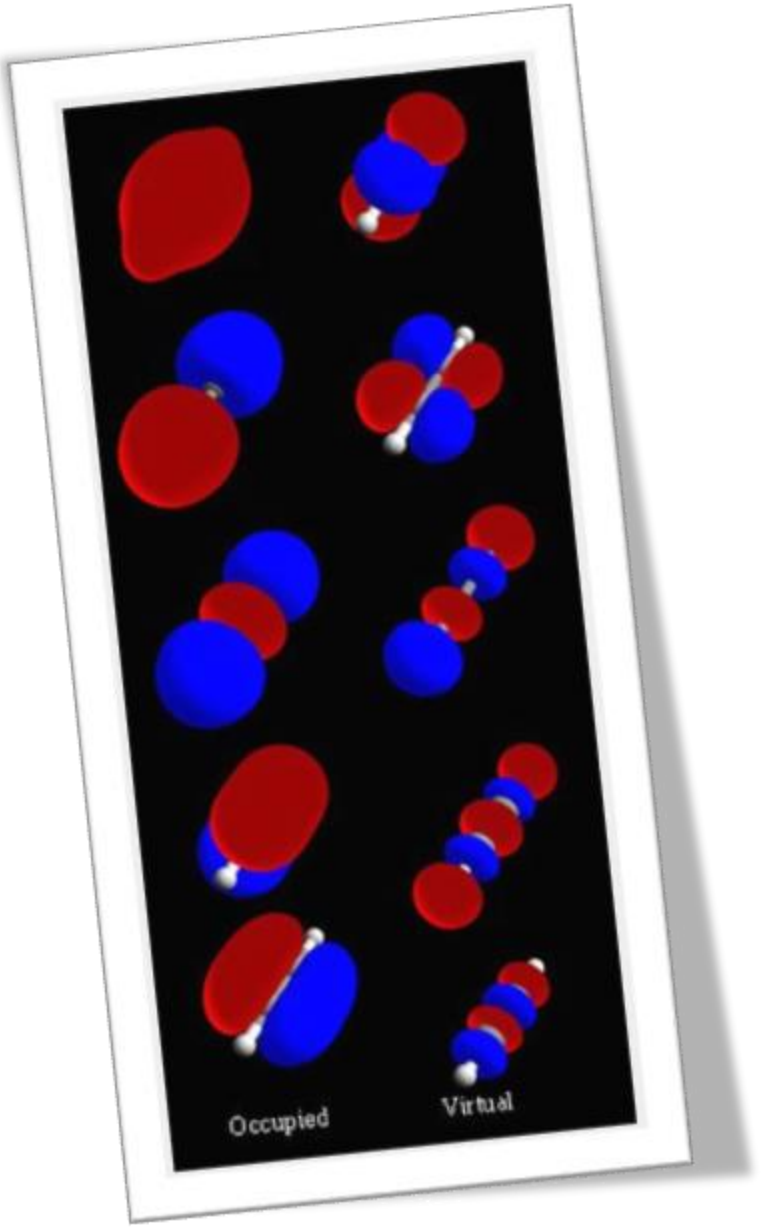
- The CD signal signs are represented by red vs. blue contributions
- a) OCD captures the global chirality as it grows from the globally achiral TS to the globally chiral HS
- b) The XCD signal on the F side shows a sudden sign flip at the local chirality transition (~165 ps)
- c) The chiral transition is not detected by the XCD signal on the Cl side

Can we connect chiral response to the atomic orbital picture in a systematic way?

Inspiration from traditional AO plots

- Isosurface plots:

- A 3D function is calculated by adding all atomic orbital (AO) contributions for a given point in space
- The AO are weighted according to the specific object represented
- Examples:
  - Molecular Orbitals (MOs) are given by linear combinations of AOs and these coefficients are used directly as the weights (see acetylene MOs on the right)
  - For excitonic states, diagonal elements of the transitioin density matrix (TDM), representing the transition charge density, can be used as the weights
  - For charge transfer states, a SVD of the TDM can be performed to get hole and particle components



Dissecting the rotatory strength

$$R = \sum_{ijkl} \left[\left(\vec{\mu}_{x\,ij} \rho_{ji} \right) \left(\vec{m}_{x\,kl} \rho_{lk} \right) + \left(\vec{\mu}_{y\,ij} \rho_{ji} \right) \left(\vec{m}_{y\,kl} \rho_{lk} \right) + \left(\vec{\mu}_{z\,ij} \rho_{ji} \right) \left(\vec{m}_{z\,kl} \rho_{lk} \right) \right]$$

$$R = \sum_{ijkl} \left[\vec{\mu}_{x\,ij} \vec{m}_{x\,kl} + \vec{\mu}_{y\,ij} \vec{m}_{y\,kl} + \vec{\mu}_{z\,ij} \vec{m}_{z\,kl} \right] \rho_{ji} \rho_{lk}$$

$$R = \sum_{ik} R_{ik}$$

$$R_{ik} = \sum_{jl} \left[\vec{\mu}_{x\,ij} \vec{m}_{x\,kl} + \vec{\mu}_{y\,ij} \vec{m}_{y\,kl} + \vec{\mu}_{z\,ij} \vec{m}_{z\,kl} \right] \rho_{ji} \rho_{lk}$$

R_{ik} represents contributions to the chiral response of electric dipole from AO i and magnetic dipole from AO k

Chiral population analysis

$$\boldsymbol{R} = \frac{1}{2}\left(\boldsymbol{R}^{(\mathrm{asym})} + \boldsymbol{R}^{(\mathrm{sym})}\right)$$

$$\boldsymbol{R}^{(\mathrm{asym})} = \frac{1}{2}(\boldsymbol{R} - \boldsymbol{R}^{T}) \longrightarrow \text{Has no contributions to the rotatory strength}$$

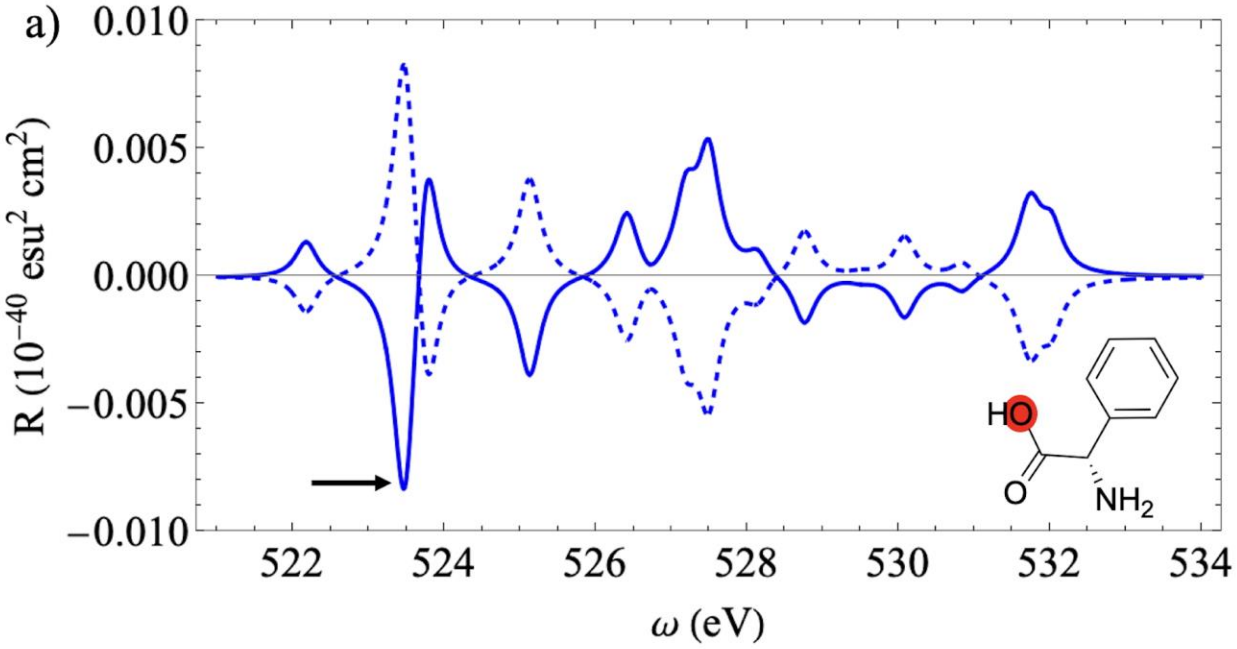
$$\boldsymbol{R}^{(\mathrm{sym})} = \frac{1}{2}(\boldsymbol{R} + \boldsymbol{R}^{T}) \longrightarrow \text{Retains the physically meaningful constructive contributions to the rotatory strength}$$

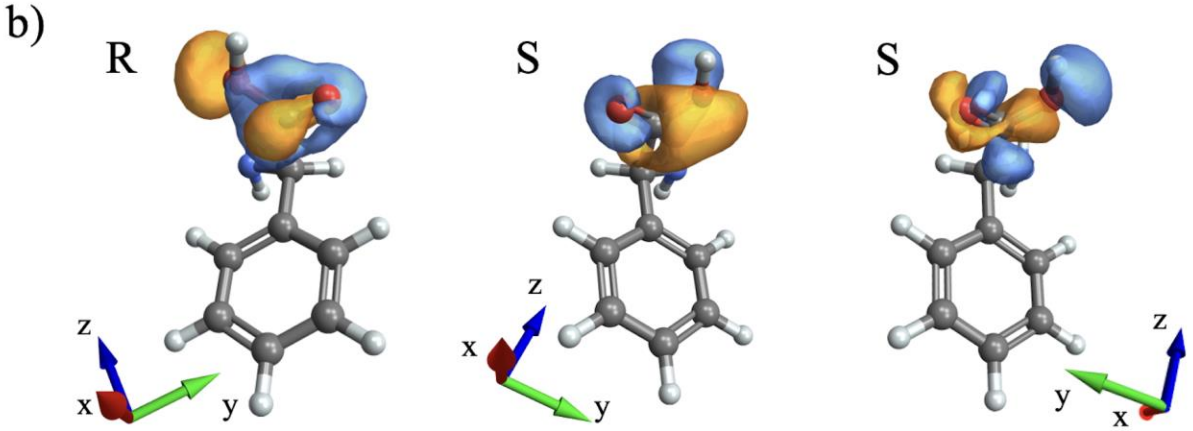
$$R_i^{(AO)} = \sum_k R_{ik}^{(\mathrm{sym})} \longrightarrow \text{Chiral populations}^{[14]} \text{ analogous to Mulliken charges}$$

$$\Phi(\vec{r}) = \sum_i R_i^{(AO)} \phi_i(\vec{r}) \longrightarrow \text{Chiral population orbitals}$$

[14] Freixas, V. M. *et al.*, *Chem. Sci*. 2025 (under revision)

Example of application: Phenylglycine

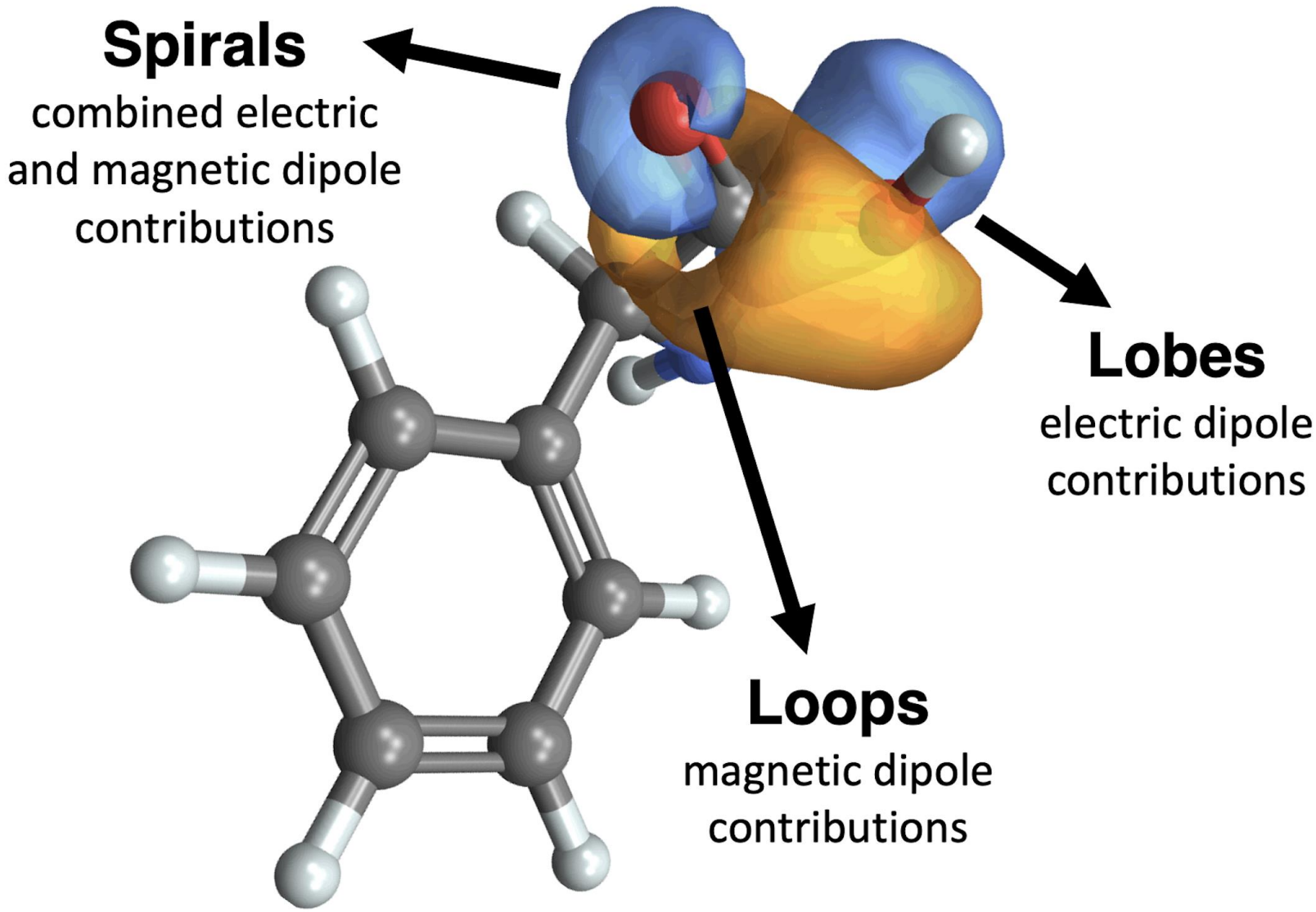




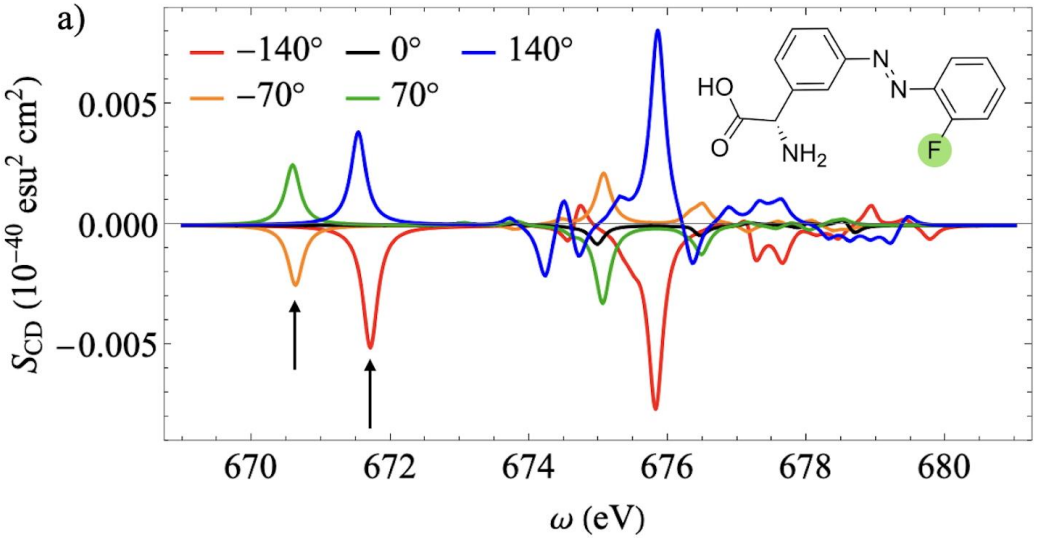
- Chiral Population Analysis:

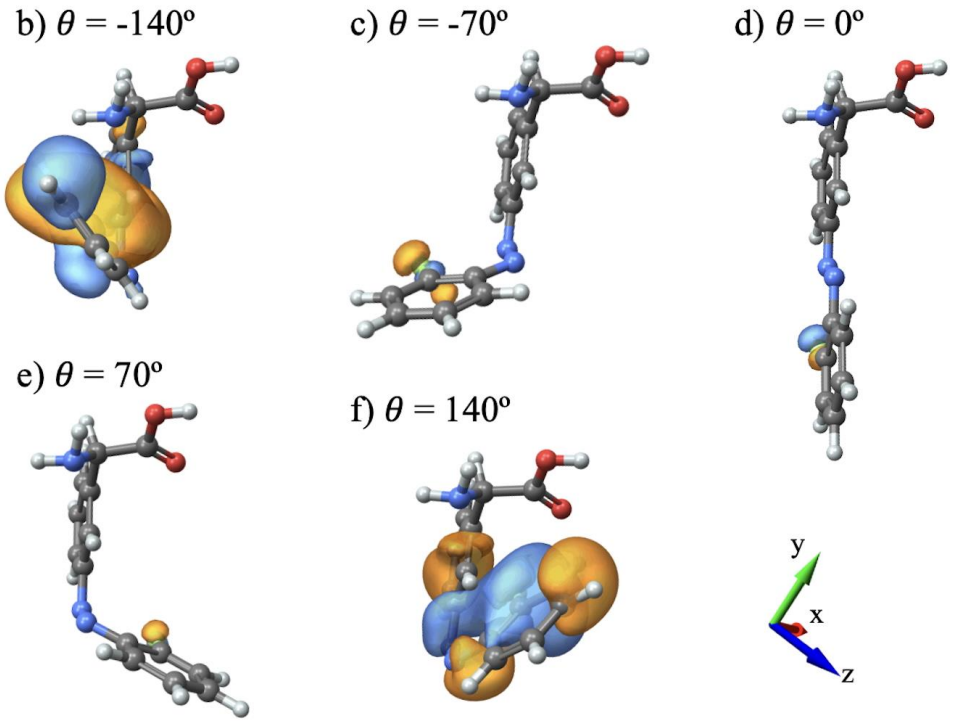
- XCD of the hydroxyl oxygen K-edge is shown in the top panel
- Chiral population orbitals corresponding to the second excitation of the manifold is shown in the lower panel
- Electric dipole induced displacements contributing to the chiral response appear as lobe features
- Magnetic dipole induced circulations contributing to the chiral response appear as loop features
- Spiral patterns emerge in regions where both electric and magnetic dipoles are relevant

Example of application: Phenylglycine



Example of application: Azobenzene-Phenylglycine

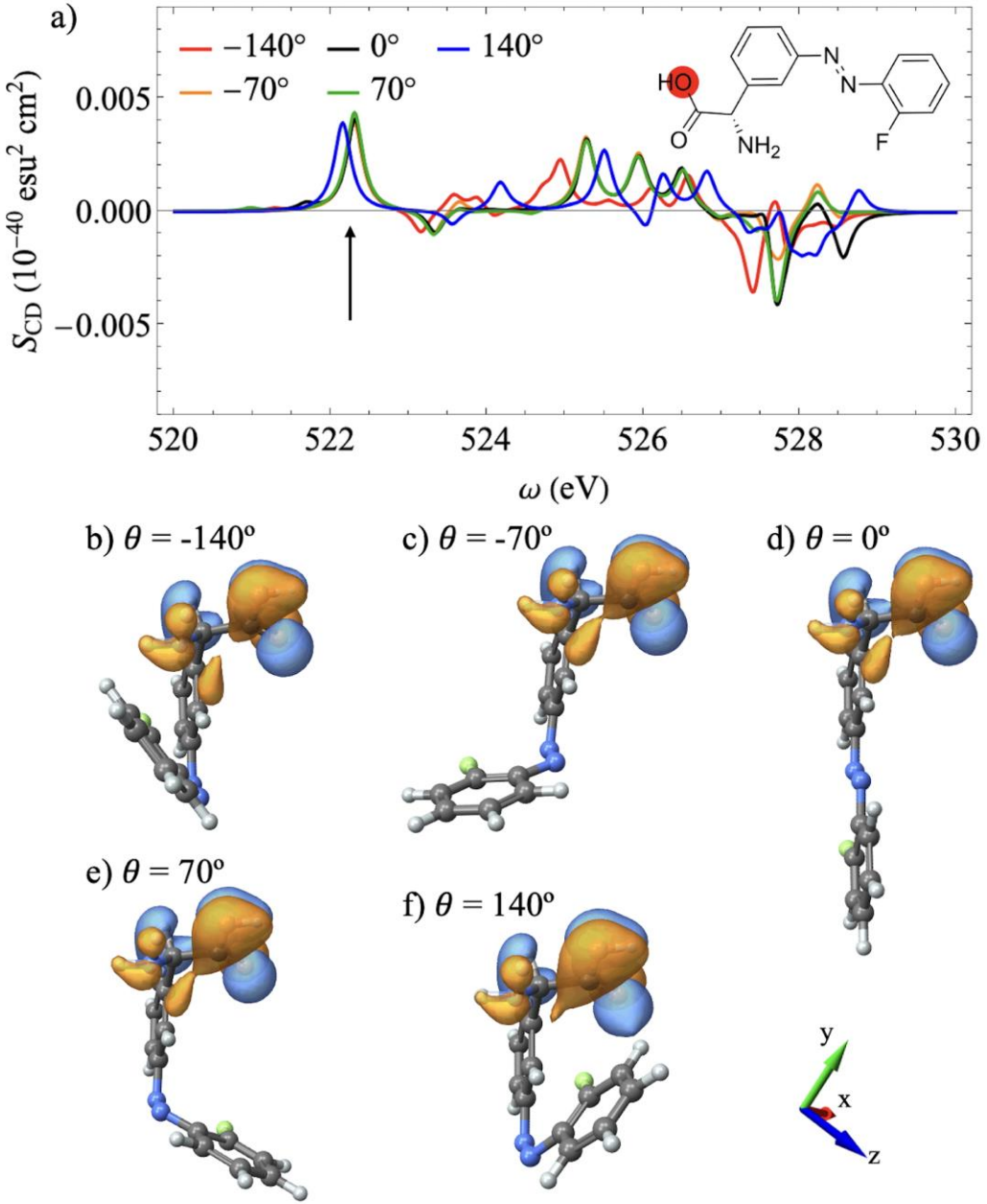




- Chiral Population Analysis:

- Azobenzene-phenylglycine provides a much interesting dichroic response as two different chiral sources interfere
- A F atom is added close to the azo bridge as an X-ray chromophere
- XCD at the F K-edge shows sensitivity only to the azobenzene twist
- Chiral population analysis is performed for the first excitation of the manifold
- The chiral population orbitals remain constrained to the azobenzene rings
- The isosurfaces extend to the neighboring ring for the bending angles of -140 and 140 degrees (b and f)

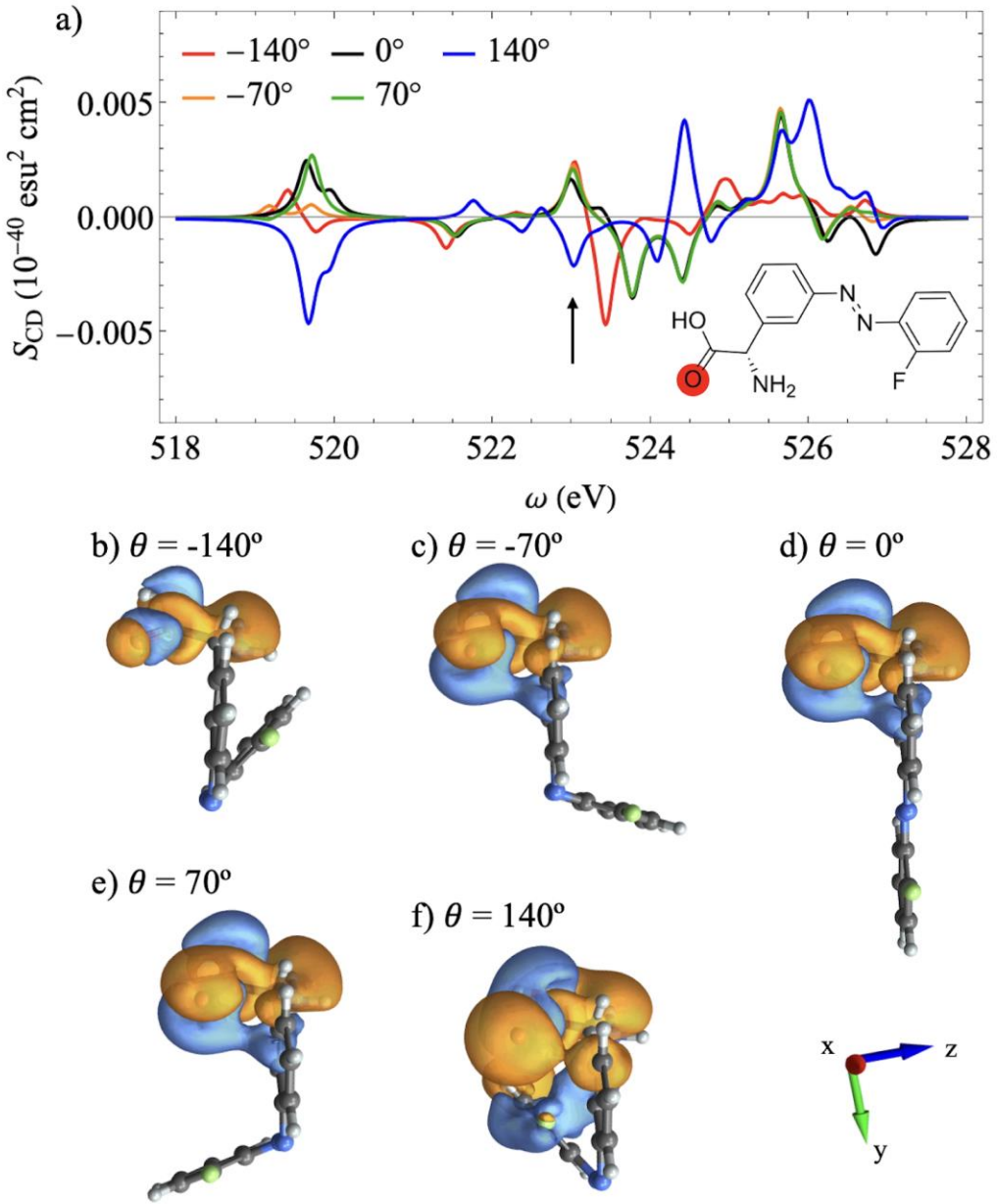
Example of application: Azobenzene-Phenylglycine



- Chiral Population Analysis:

- XCD at the hydroxyl oxygen K-edge
- Chiral population analysis is performed to the second transition of the manifold
- XCD in this range is independent of the azobenzene twist
- Chiral population analysis show similar orbitals located in the glycine moiety

Example of application: Azobenzene-Phenylglycine



- Chiral Population Analysis:

- XCD at the carboxyl oxygen K-edge
- Chiral population analysis is performed to the sixth and seventh transitions of the manifold
- The XCD signal changes suddenly for an azobenzene twist angle of 140, for which the corresponding chiral population orbital extends to the other ring

Conclusions

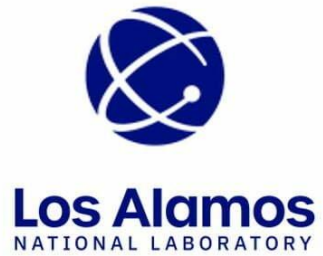
- X-ray circular dichroism is a promising candidate to obtain information about local chiral features within molecules
- X-ray circular dichroism also provides the time resolution required to probe ultrafast time-dependent chiral transitions
- Chiral population analysis is a promising tool for dissecting atomic orbital contributions to chiral response in a visually intuitive way

Aknowledgements

Shaul Mukamel

Niranjan Govind
Xu Lei

Jeremy Rouxel
Yeonsig Nam



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Ajay Khanna