



Computational Chemistry: An Organic Chemist's Perspective

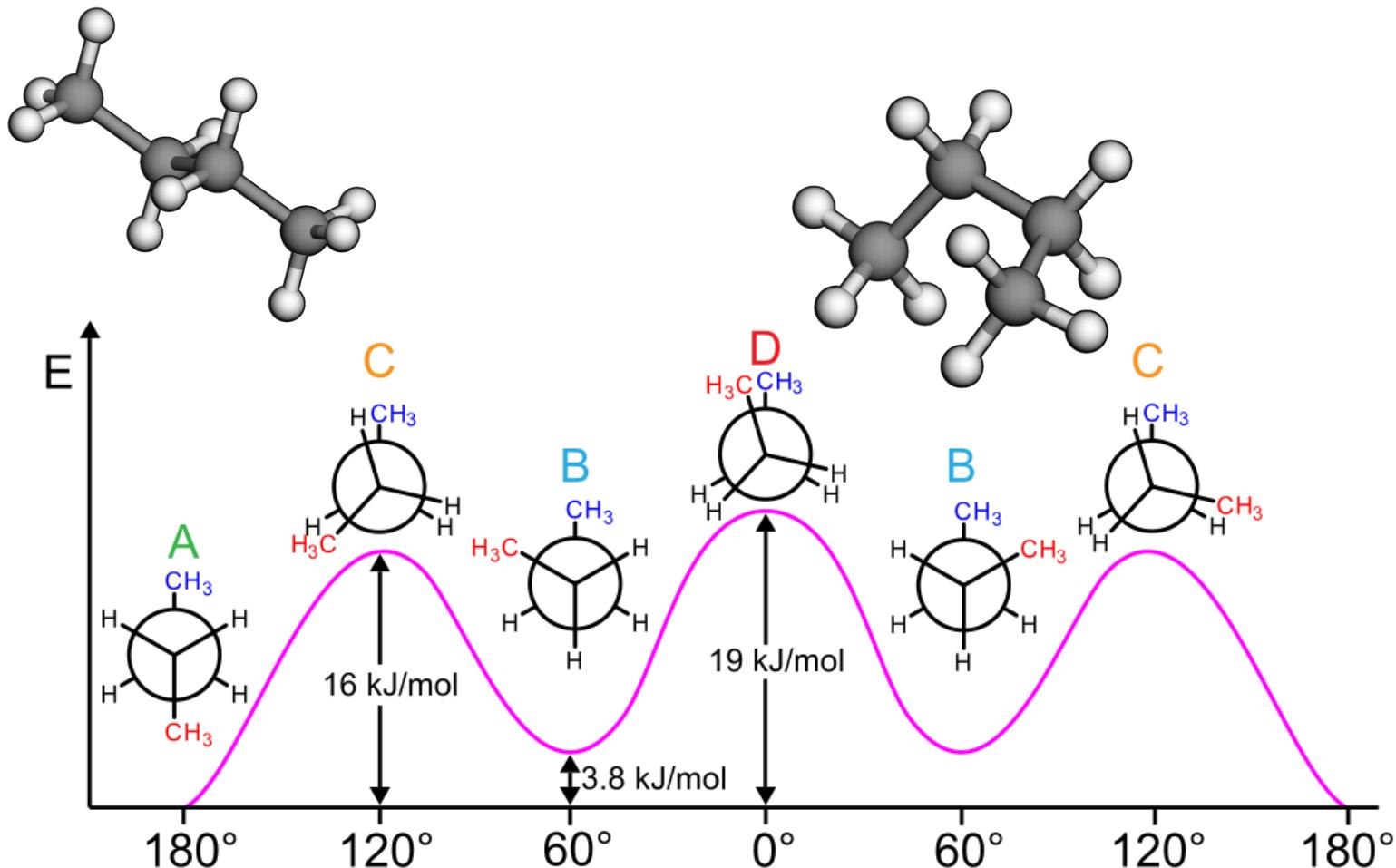
Assistant Professor Dr. **Dennis Svatunek**

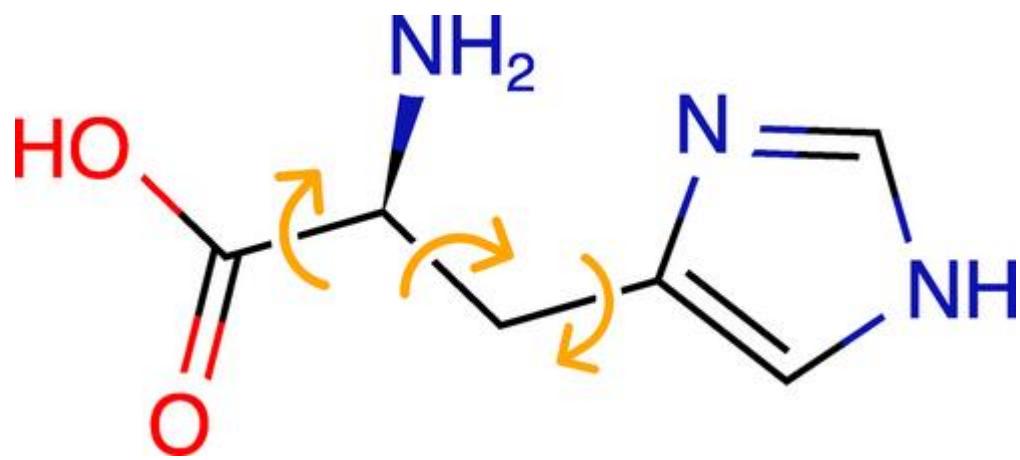
University of Malaya, 12th of November 2025

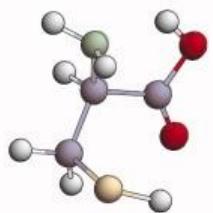
Conformer Searches

1. Conformer Searches

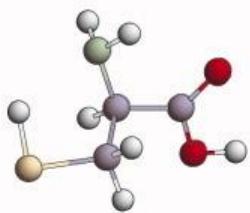
- **Conformers** are different spatial arrangements of a molecule → obtained by **rotation around single (σ) bonds**
- They have the **same connectivity**, only **different geometry**
- Often close in energy → can **interconvert at room temperature**



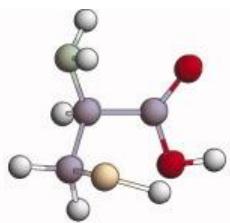




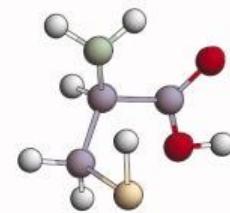
cys 1



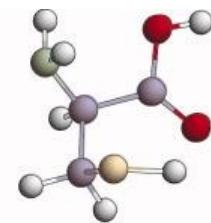
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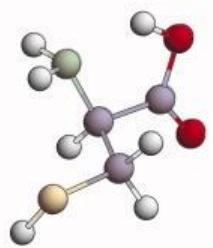
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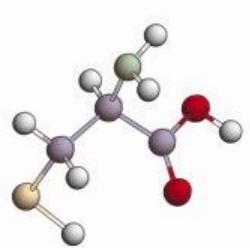
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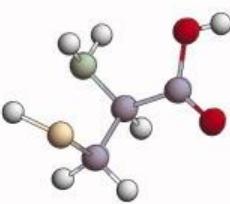
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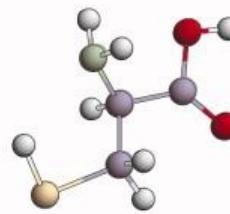
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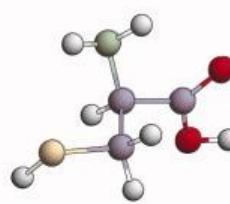
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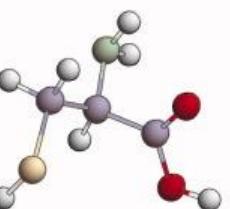
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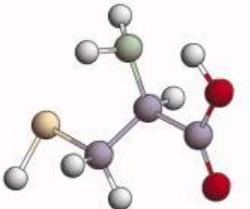
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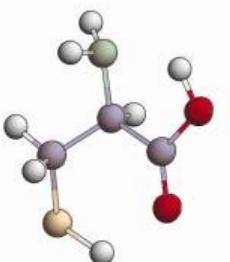
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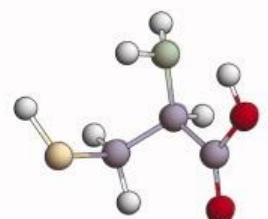
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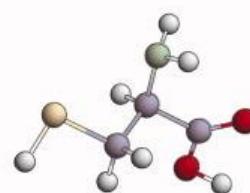
cys 12



cys 13



cys 14



cys 15

Why care about conformers?

- Conformers often have **different energies** → one (or more) ~~conformers dominates at equilibrium~~
 - Different **physical properties**, e.g.
 - Dipole moment
 - NMR chemical shifts
 - UV/Vis bondir.
-
- The graph plots the dipole moment μ in Debye (D) against the dihedral angle ϕ in degrees. The y-axis ranges from 0 to 14 D, and the x-axis ranges from 0 to 180 degrees. A black curve shows a deep minimum at $\phi = 90^\circ$. A light gray shaded area represents the range where the dipole moment is zero. A small molecular model with a cross-shaped dipole is shown above the graph at approximately $\phi = 120^\circ$.
- | Diederwinkel ϕ [°] | Dipolemoment μ [D] |
|-------------------------|------------------------|
| 0 | ~8.5 |
| 20 | ~7.0 |
| 40 | ~4.5 |
| 60 | ~2.5 |
| 80 | ~1.5 |
| 90 | 0 |
| 100 | ~1.5 |
| 120 | ~2.5 |
| 140 | ~4.5 |
| 160 | ~7.0 |
| 180 | ~8.5 |

Conformer Search

- Instead of optimizing one arbitrary conformer drawn by the researcher (introduces bias)
- **Goal:** identify the **lowest-energy conformer** or an **ensemble of low-energy conformers**
- Use the lowest-energy structure or a **Boltzmann-weighted ensemble** for further calculations and property predictions

Conformer Search

Step 1:

Generate potential conformers

Step 2:

Filter generated structures for unique conformers

- Energy threshold
- Geometric similarity threshold (RMSD)

and remove high energy conformers
(e.g., $\Delta E > 6$ kcal/mol)

Root-Mean-Square Deviation (RMSD)

- Quantifies **how similar** two molecular **geometries** are
- Calculated from the **average distance** between corresponding atoms after optimal alignment
- Commonly used to:
 - Detect duplicate conformers after a search
 - Compare a computed structure to an experimental geometry
 - Assess structural changes during optimization or dynamics
 - Typical threshold for duplicate filtering: $\text{RMSD} < 0.1\text{--}0.2 \text{ \AA}$

Root-Mean-Square Deviation (RMSD)

$$\text{RMSD} = \sqrt{\frac{1}{N} \sum_{i=1}^N \delta_i^2}$$

Systematic Search

- Rotate all **rotatable bonds** in fixed angle increments (e.g., 60° for C–C single bonds)
- Generate **all possible combinations** of torsions → set of trial geometries
- **Optimize each structure** to a local minimum
- Compare resulting energies **to identify low-energy conformers**
- Works well for **small and rigid molecules**, but becomes **combinatorially expensive** for flexible systems (**Combinatorial Explosion**)

Combinatorial Explosion

- 1 rotatable bond → 6 combinations
 - 3 bonds → $6^3 = \mathbf{216}$
 - 5 bonds → $6^5 = \mathbf{7,776}$
 - 10 bonds → $6^{10} = >\mathbf{60 \text{ million}}$
- **Systematic searches become impossible for flexible molecules**

Stochastic Conformer Searches

- Instead of testing all combinations, **sample selected regions** of conformational space
- Sampling can be:
 - **Random** → completely random torsion angles
 - **Guided** → biased toward chemically reasonable or low-energy regions
- Each generated structure is optimized to a local minimum
- Efficiently finds representative low-energy conformers without exhaustive search
- Works well for flexible or larger molecules

Random Sampling

- **Randomly assign torsion angles** for all rotatable bonds
- Each structure is energy-minimized to reach a nearby local minimum
- Repeat many times to explore different regions of conformational space
- Duplicates (similar RMSD or energy) are filtered out
- Efficiency improves with number of samples and quality of optimization

Monte Carlo Sampling

- Generates random conformations, but each step is **guided by probability**
- A **new structure** is accepted or rejected based on its **energy difference**
 - typically using the **Metropolis criterion**
- Allows both **downhill** (lower energy) and occasional **uphill** moves
 - helps escape local minima
- Repeated iterations explore conformational space efficiently
- Produces a set of **low-energy, statistically relevant conformers**

Metropolis Criterion

- Determines whether a **new (trial) structure** is accepted in Monte Carlo sampling
- Always accept if the **new structure has lower energy**
- If the **new structure is higher in energy**, accept it with a probability:

$$P = \exp \left(-\frac{\Delta E}{k_B T} \right)$$

Molecular Dynamics

- **Simulates atomic motion** over time by integrating Newton's equations of motion
- At each time step, forces are computed from the potential energy surface
- Atoms move according to $F=ma=-\nabla E$
- Generates a trajectory that samples many conformations naturally, we take **snapshots**
- Can explore conformational changes, flexibility, and equilibrium populations
- Requires a force field (e.g., AMBER, CHARMM) or a fast quantum mechanical potential

Problems with Classical MD

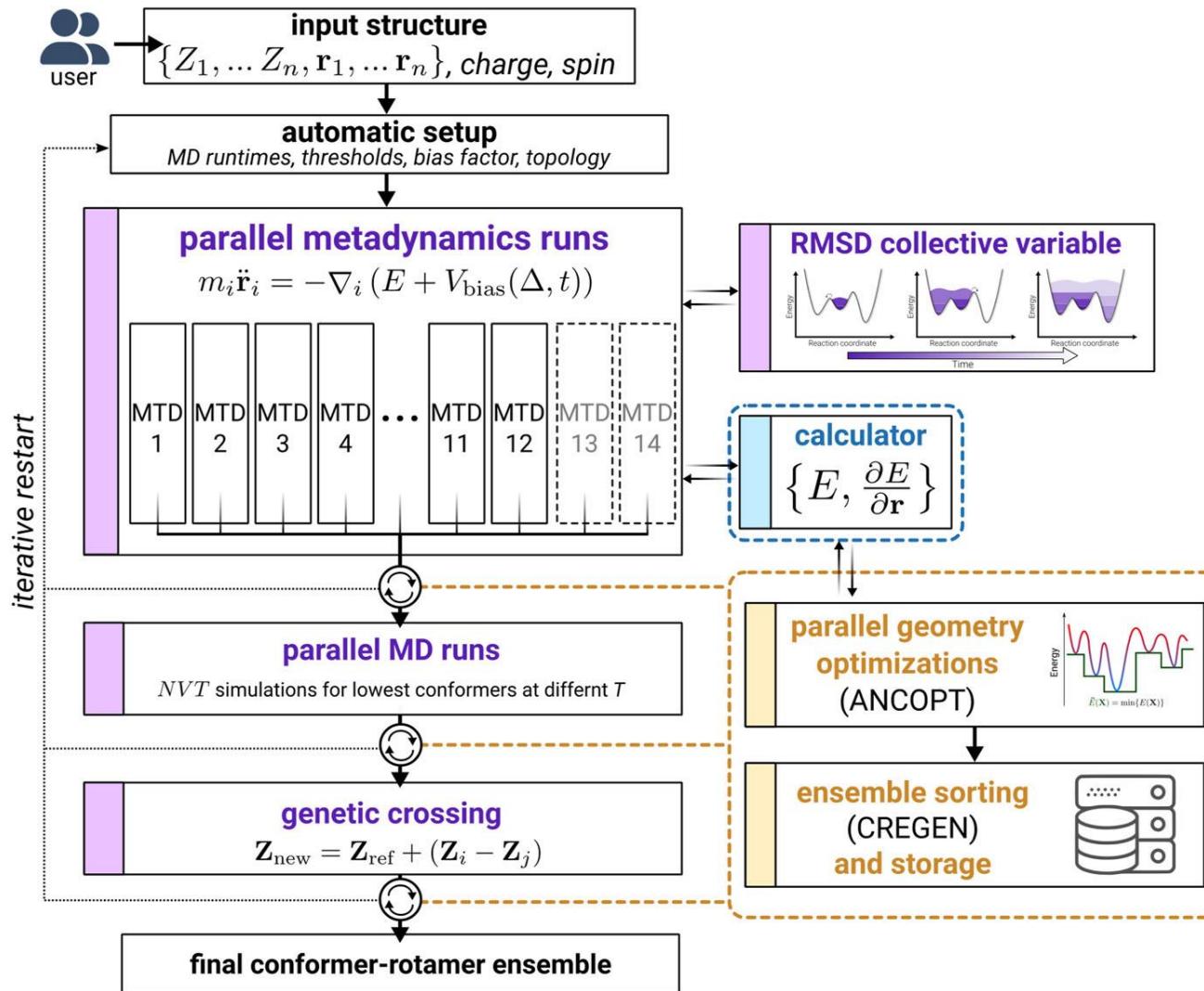
- MD explores conformational space through time evolution → **hard to cross high energy barriers**
- Reaching rare conformers may require very long trajectories
- Classical MD: fast but approximate (force field-dependent)
- Quantum MD (AIMD): accurate but computationally prohibitive

In practice → too slow or too costly for thorough conformer searches

CREST (Grimme Lab)

- Developed by Grimme and co-workers
- Combines efficient sampling with **semiempirical quantum mechanics** (GFN-xTB)
- Uses **metadynamics** and **genetic algorithms** to overcome energy barriers
- Continuously optimizes and refines conformers during the search
- Produces a Boltzmann-weighted ensemble of low-energy structures
- Strikes a balance between speed (sampling) and accuracy (QM forces)

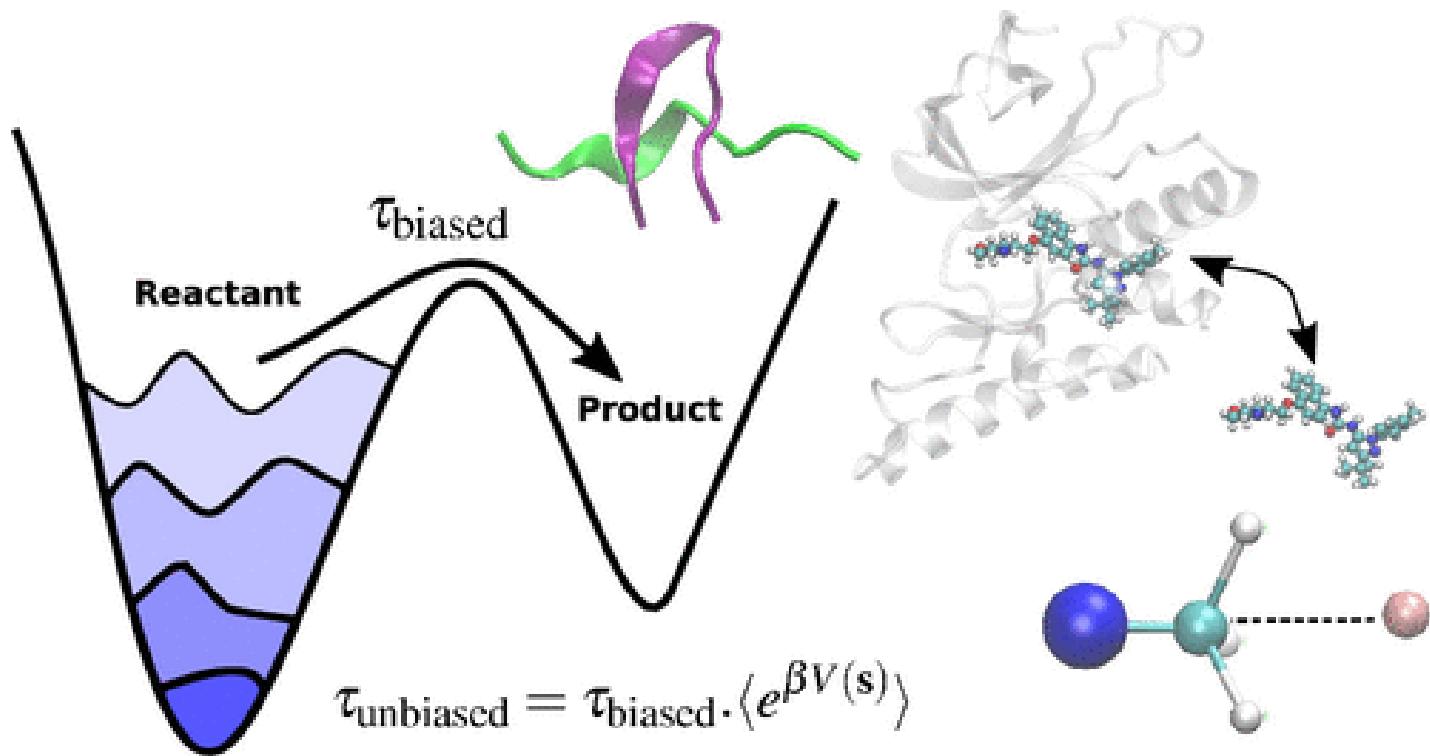
CREST (Grimme Lab)



Meta dynamics

- Sampling method that helps a system **escape local minima**
- Adds a **small biasing potential** (“hill”) to the energy surface at visited points → discourages revisiting the same region
- As simulation proceeds, the energy landscape is gradually flattened → allows exploration of new conformations and crossing of barriers
- Commonly used with molecular dynamics or semiempirical methods (e.g., GFN-xTB in CREST)
- Efficiently finds multiple minima without long MD times

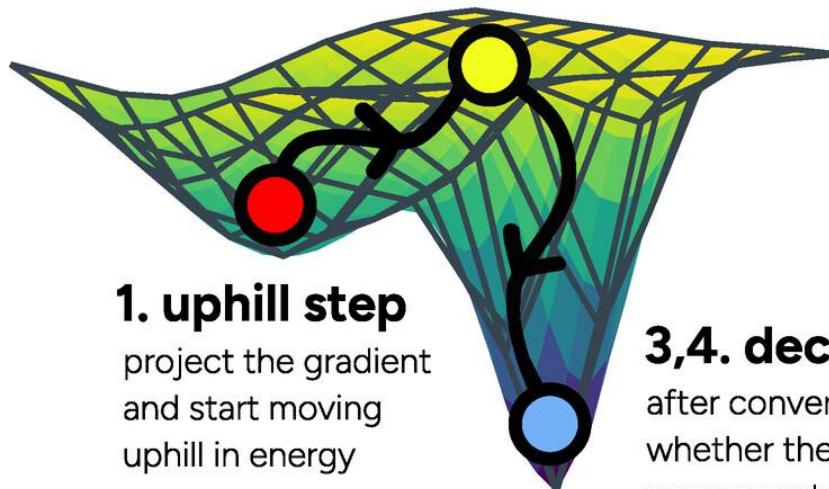
Metadynamics



GOAT: A Global Optimization Algorithm for Molecules and Atomic Clusters

- **New method within ORCA** → works with any FF or QM method
- Systematically explores the PES

**A GOAT
micro
iteration**

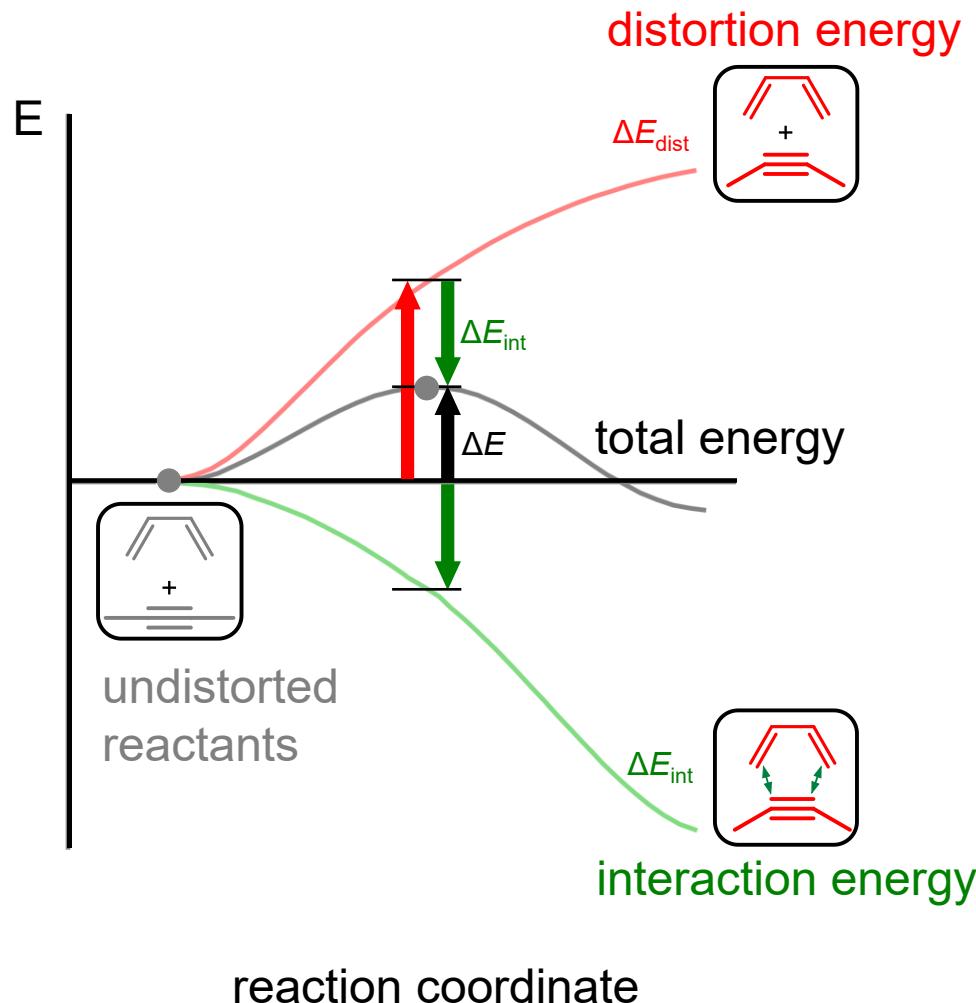


Energy Decomposition Analysis

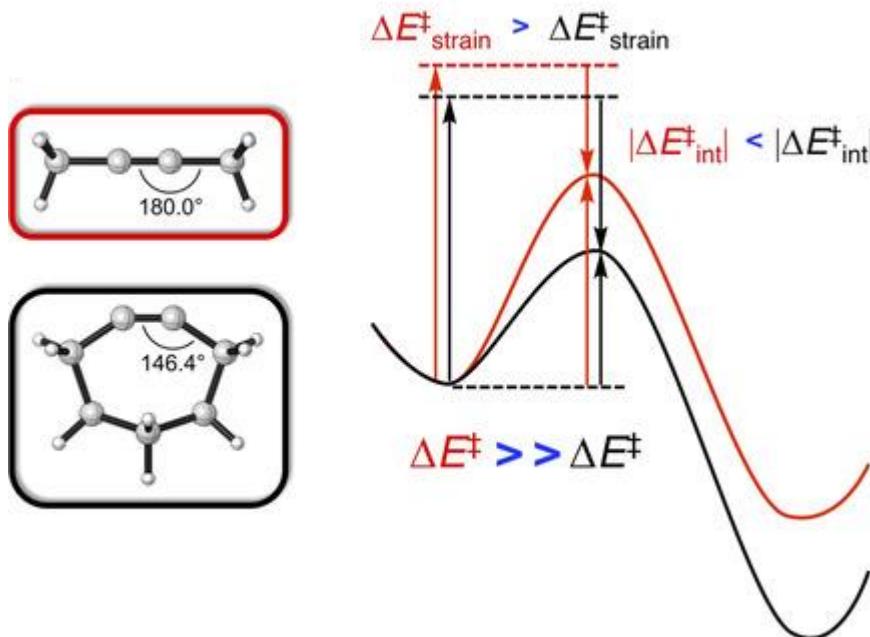
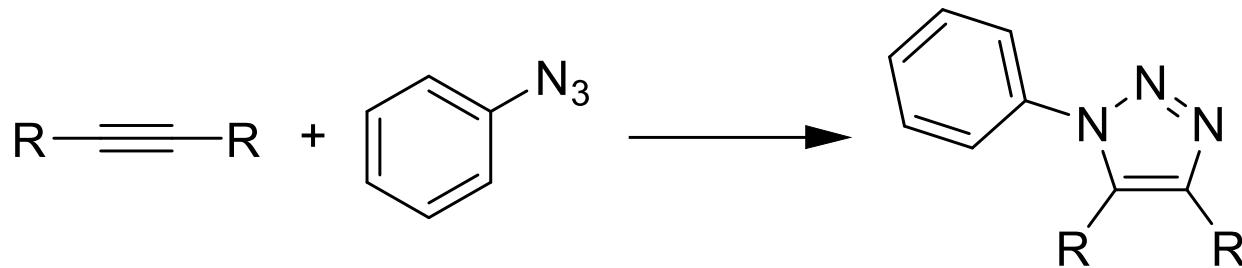
2. Energy Decomposition Analysis

- **Goal:** Understand molecular interactions by dividing total energies into **physically meaningful contributions**
- This helps connect **quantum-mechanical results** with **chemical intuition**
- Many different schemes exist, but they all begin with the **Distortion/Interaction Analysis (DIA)** as the first step

Distortion/Interaction Analysis



Distortion/Interaction Analysis



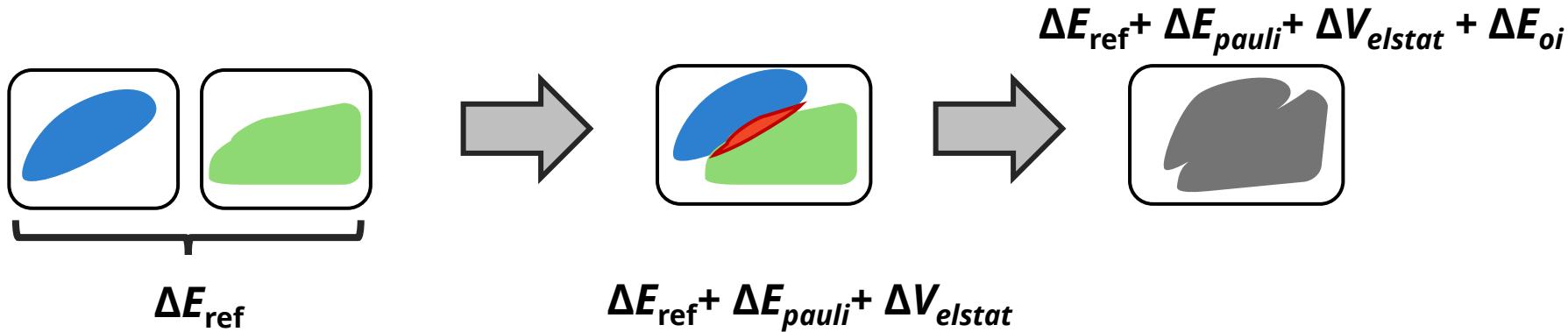
Energy Decomposition Analysis

- Further **decompose** E_{int} into meaningful terms
- Many different Schemes available. Most popular:
 - ALMO-EDA
 - SAPT
 - Rauk-Ziegler (canonical) EDA
- Each scheme refines E_{int} into quantitative terms that **link quantum mechanics with chemical concepts** like covalency, ionicity, and steric effects.

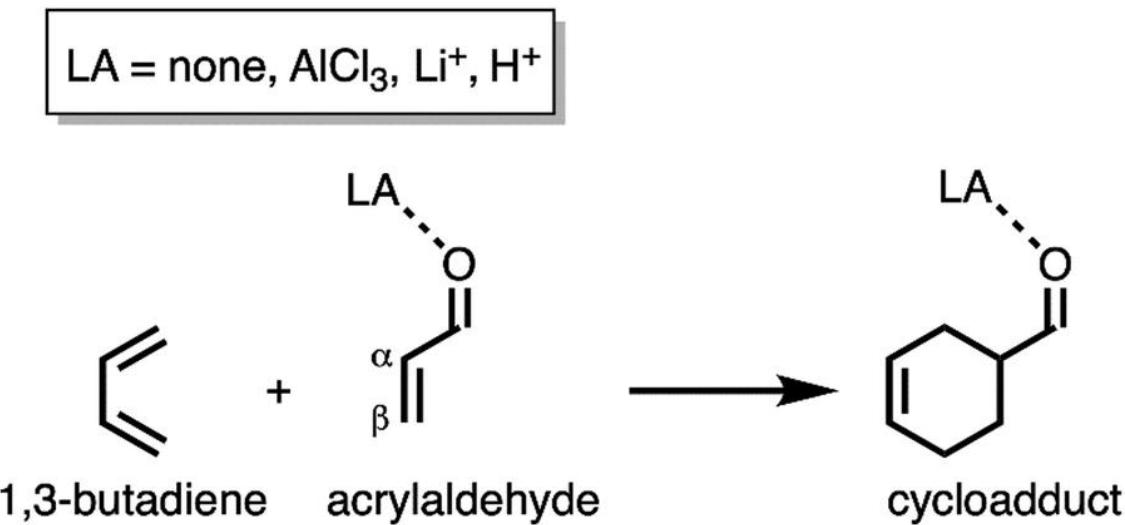
Rauk-Ziegler Energy Decomposition Analysis

Works within the DFT Kohn-Sham framework

$$\Delta E_{int} =$$



EDA in action: Catalysis in Diels-Alder reactions



	ΔE^*	ΔE_{strain}	ΔE_{int}	ΔV_{elstat}	ΔE_{Pauli}	ΔE_{oi}
O	12.1	19.3	-7.2	-38.9	82.9	-51.5
O- AlCl_3	1.5	14.9	-13.4	-34.5	73.5	-52.4
O- Li^+	-1.9	13.5	-15.4	-31.3	68.1	-52.2

Symmetry-Adapted Perturbation Theory (SAPT)

- Perturbation-based decomposition built from first principles
- Treats intermolecular interaction as perturbation of isolated monomers
- Energy terms:
 - Electrostatics
 - Exchange (Pauli repulsion)
 - Induction
 - Dispersion
- Widely used for noncovalent interactions and benchmarking

ALMO-EDA

- Uses **Absolutely Localized Molecular Orbitals** to define fragments
- Sequentially “turns on” electronic relaxation steps:
 - **Frozen interaction**
 - **Polarization** within fragments
 - **Charge-transfer (delocalization)**
- Ensures **strict separation** of polarization and charge transfer
- Implemented in **Q-Chem**, efficient for large systems
- Ideal for studying **hydrogen bonding, donor-acceptor, and solvation effects**

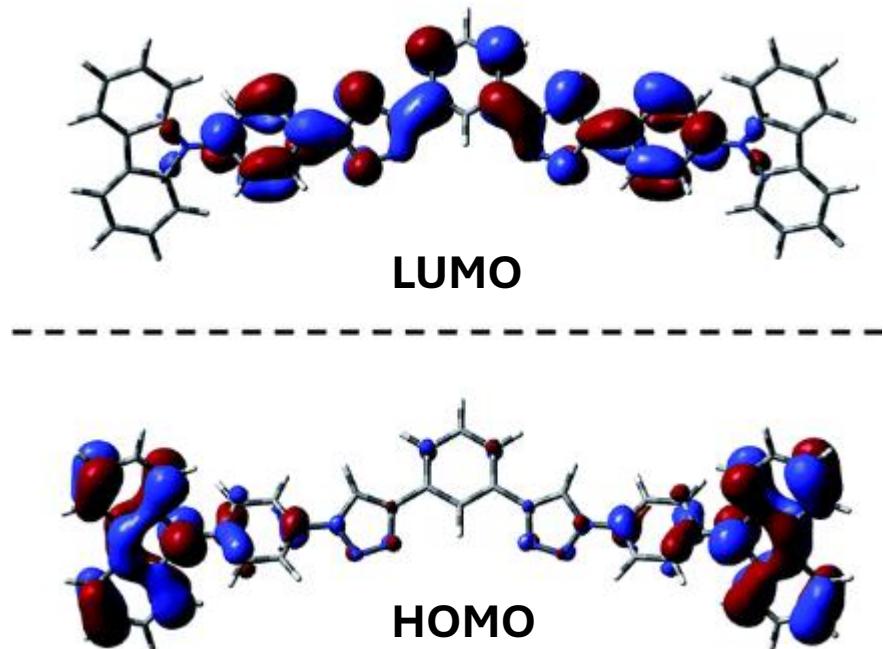
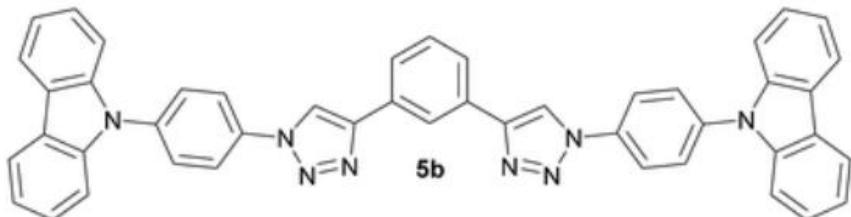
Orbitals

3. Orbitals

- One-electron functions $\psi_i(\mathbf{r})$ obtained from
 - Schrödinger equation (Hartree–Fock) or
 - Kohn–Sham equation (DFT)
- Each orbital describes a spatial electron distribution; $|\psi_i|^2$ = probability density
- Canonical orbitals are **orthogonal** and usually **delocalized**
- Energies ε_i ordered from lowest (core) to highest (virtual)

What are Orbitals used for?

- Approximate excitation energies
→ $\Delta E \approx \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}$
- Useful for interpreting photochemistry, donor–acceptor systems, $\pi - \pi^*$ transitions
- Predicting reactivity → (FMO) theory



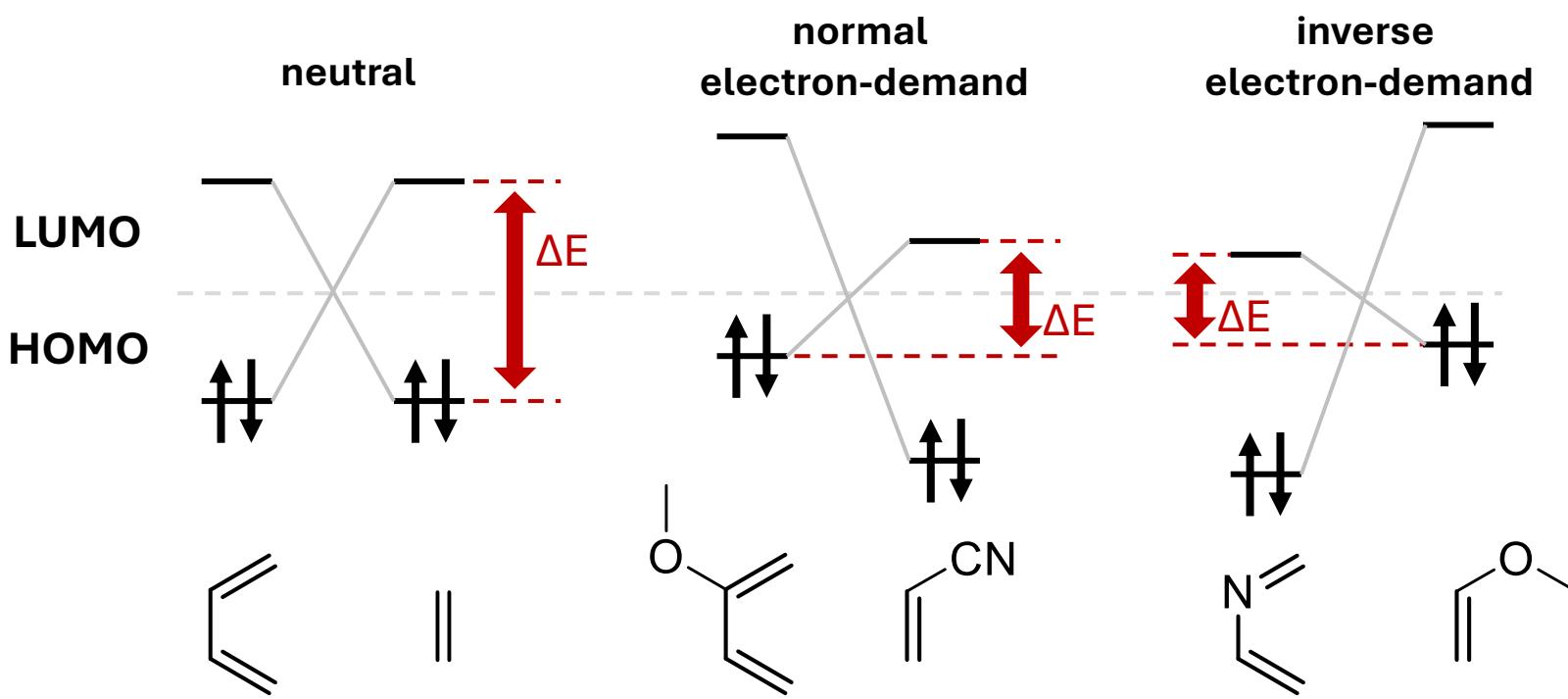
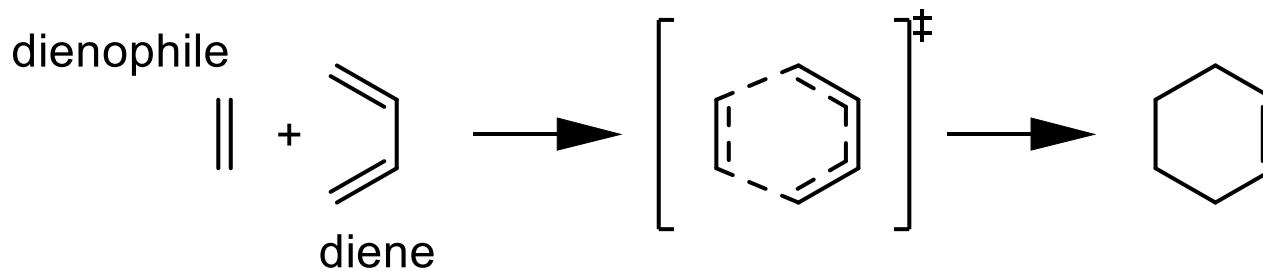
FMO Theory

- Developed by **Kenichi Fukui** (Nobel Prize 1981, with Roald Hoffmann)
- Key idea: *Only the outermost occupied and unoccupied orbitals, HOMO and LUMO, control chemical reactivity*
- **Interactions between HOMO (donor) and LUMO (acceptor)** determine reaction feasibility and selectivity

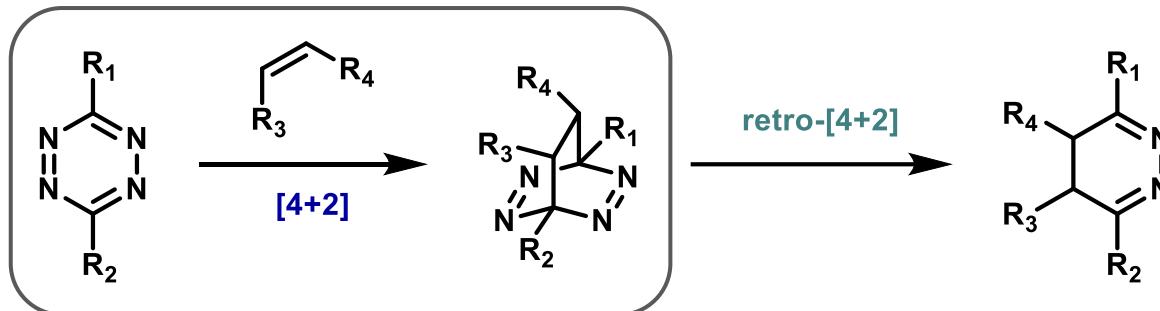
FMO Theory

- Reactivity governed by:
 - **Energy gap** ($\Delta E = \varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}$)
 - Orbital symmetry and overlap
- Explains outcomes of pericyclic reactions, donor–acceptor chemistry, and charge transfer

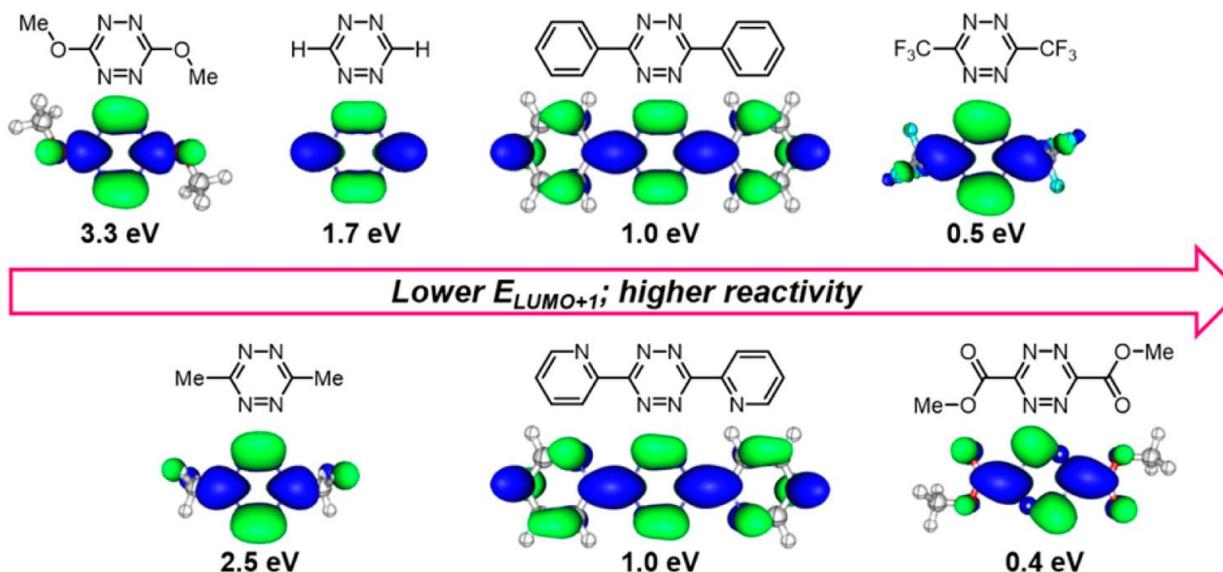
FMO Theory: Diels–Alder Reaction



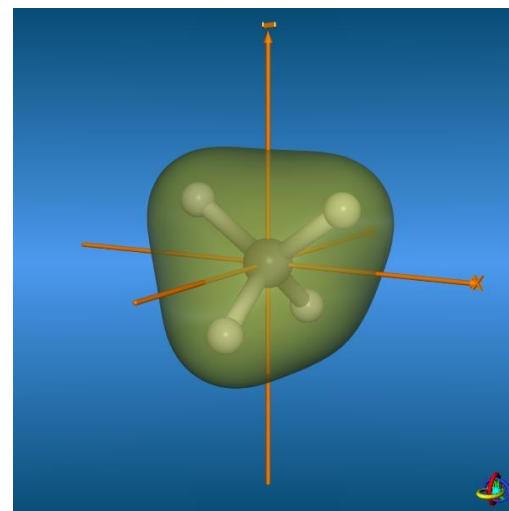
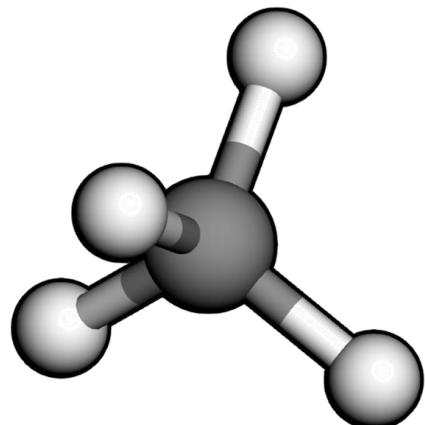
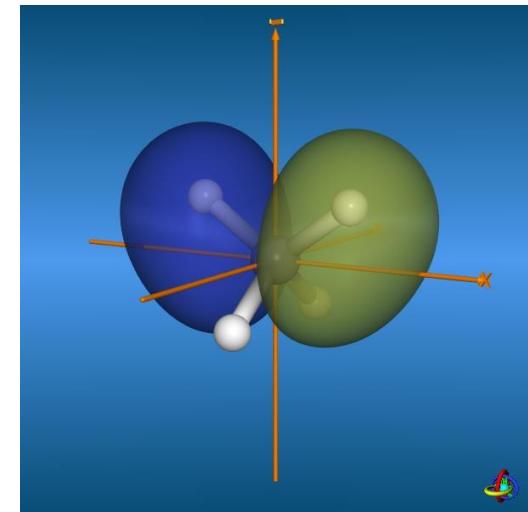
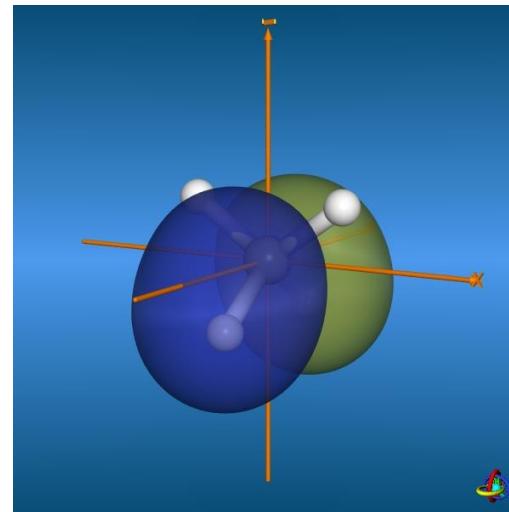
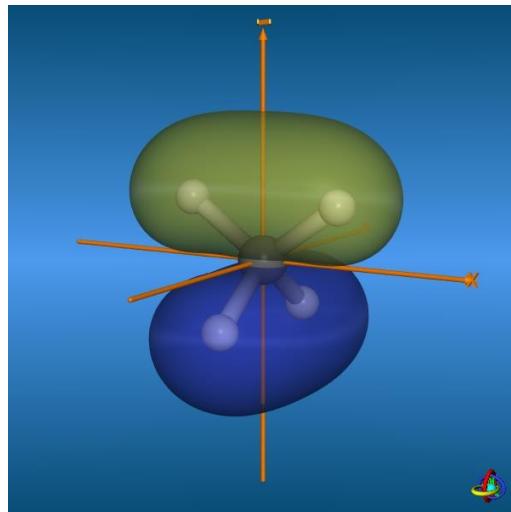
FMO Theory: Diels–Alder Reaction



rate limiting step

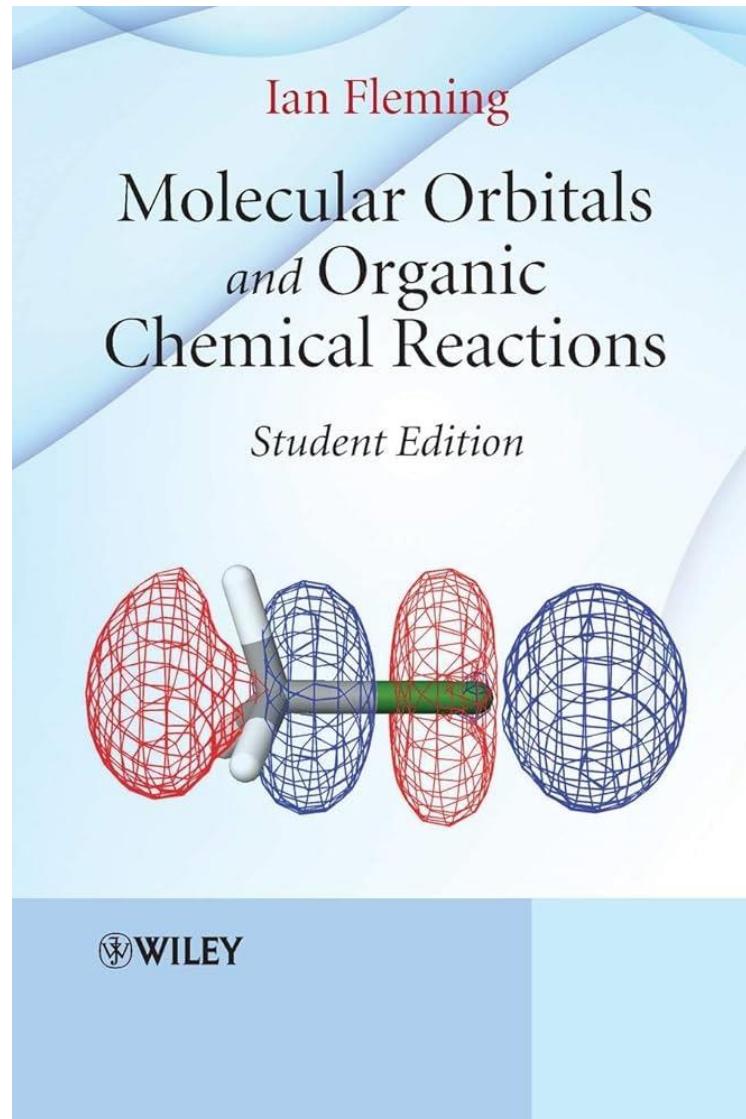


Canonical orbitals are delocalized



CH_4

Canonical orbitals are delocalized



Canonical orbitals are delocalized

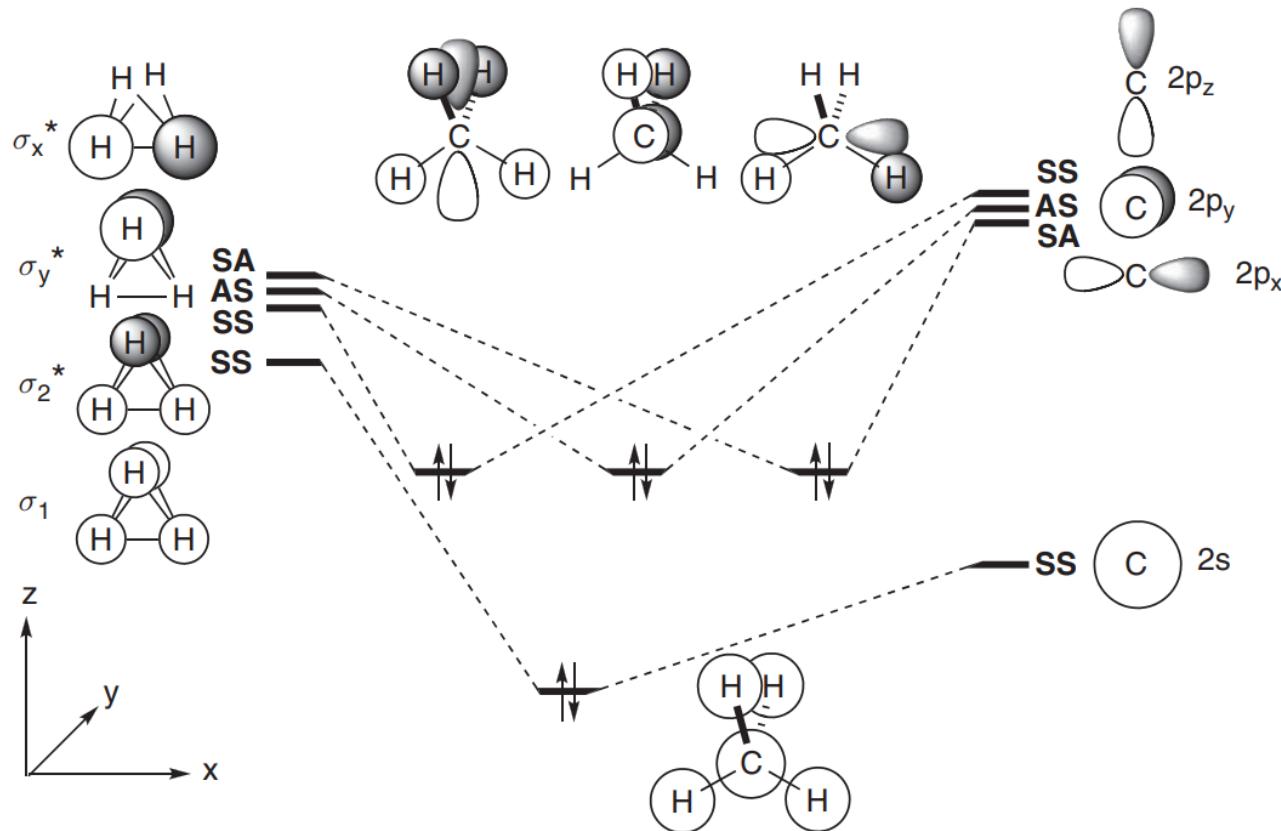
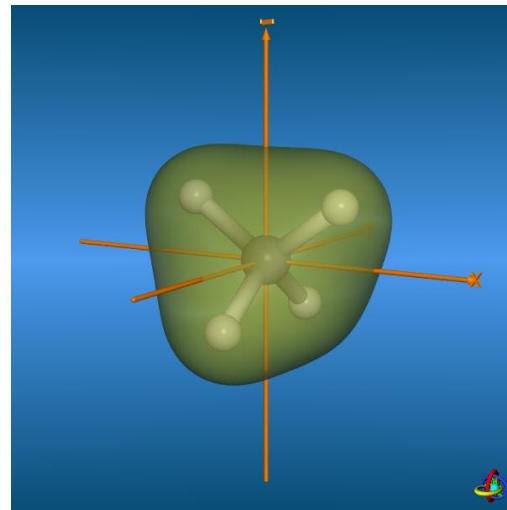
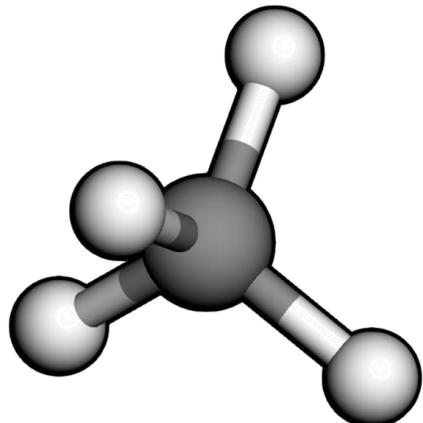
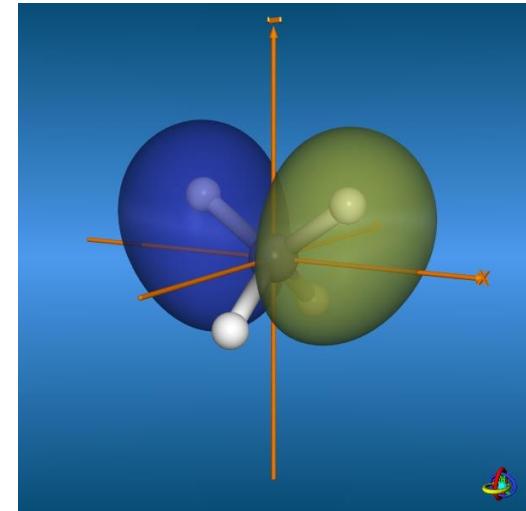
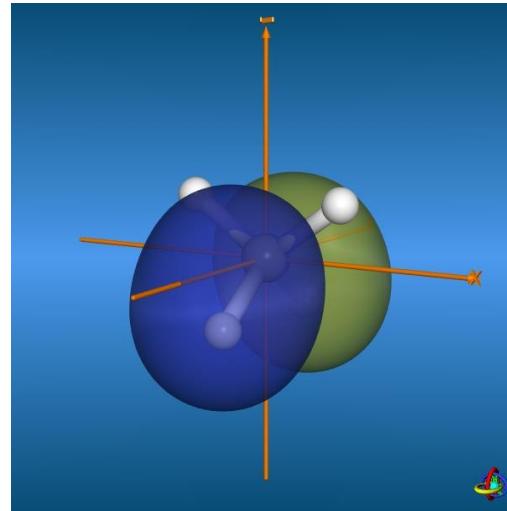
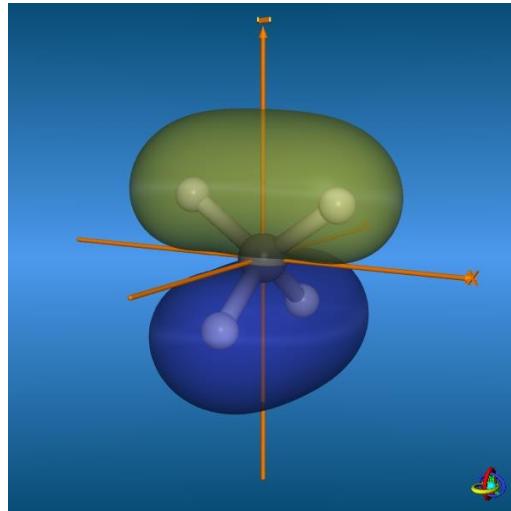


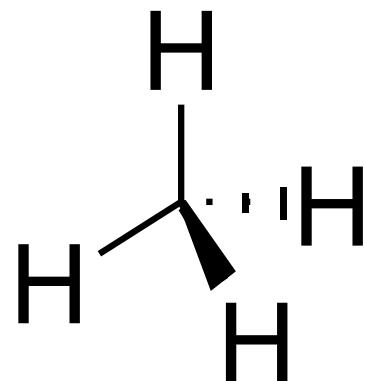
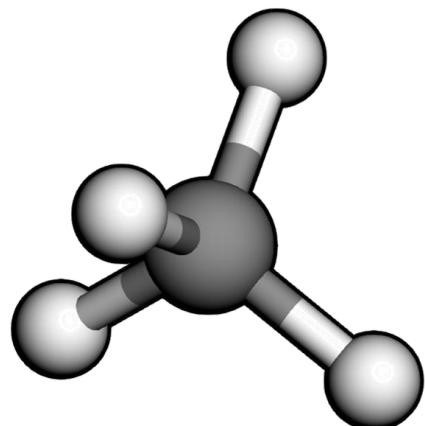
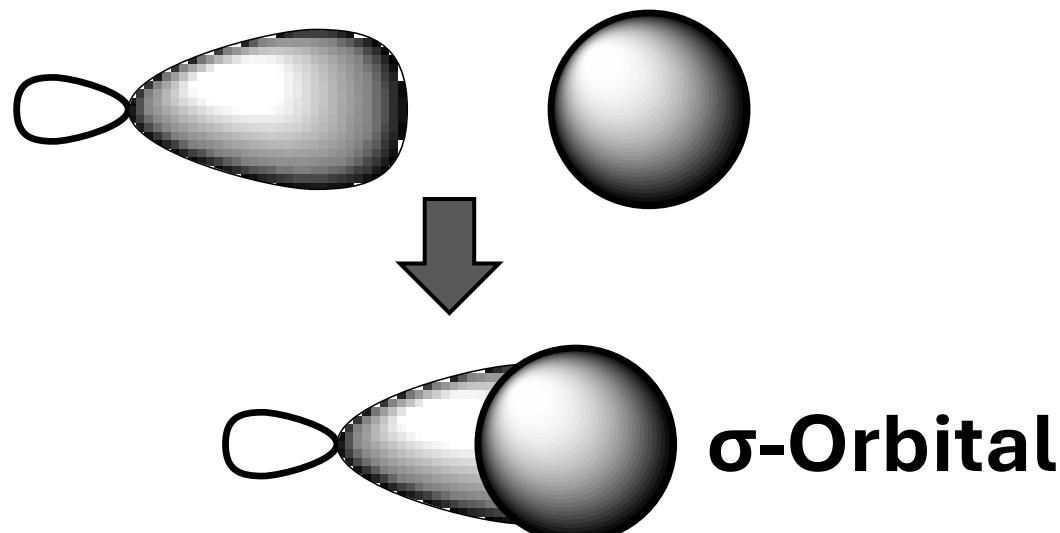
Fig. 1.12 The molecular orbitals of methane from the interaction of the orbitals of tetrahedral H_4 and a C atom

Canonical orbitals are delocalized



CH_4

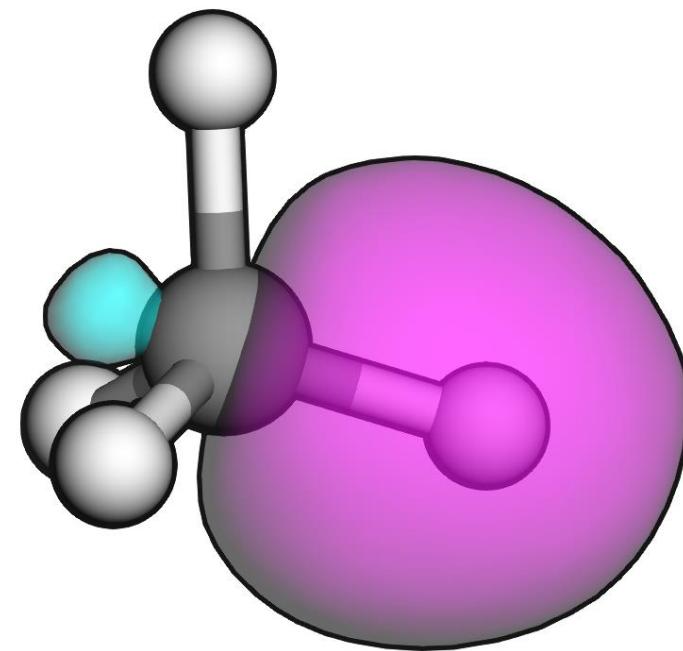
Canonical orbitals are delocalized



Localized Molecular Orbitals

- We are **allowed to make linear combinations** of occupied orbitals
- Such rotations **do not change total energy** or electron density
- We can choose these combinations so that **orbitals become spatially confined**
- These localized orbitals resemble bonds and lone pairs
- **Foster–Boys method (1950s):** minimize orbital spatial spread

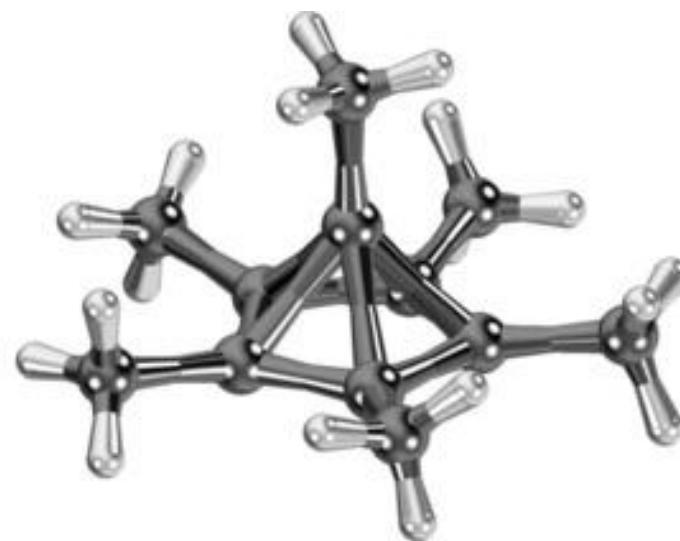
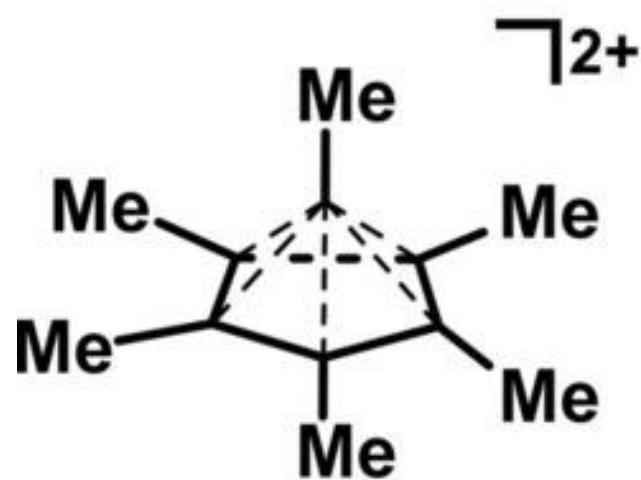
Localized Molecular Orbitals



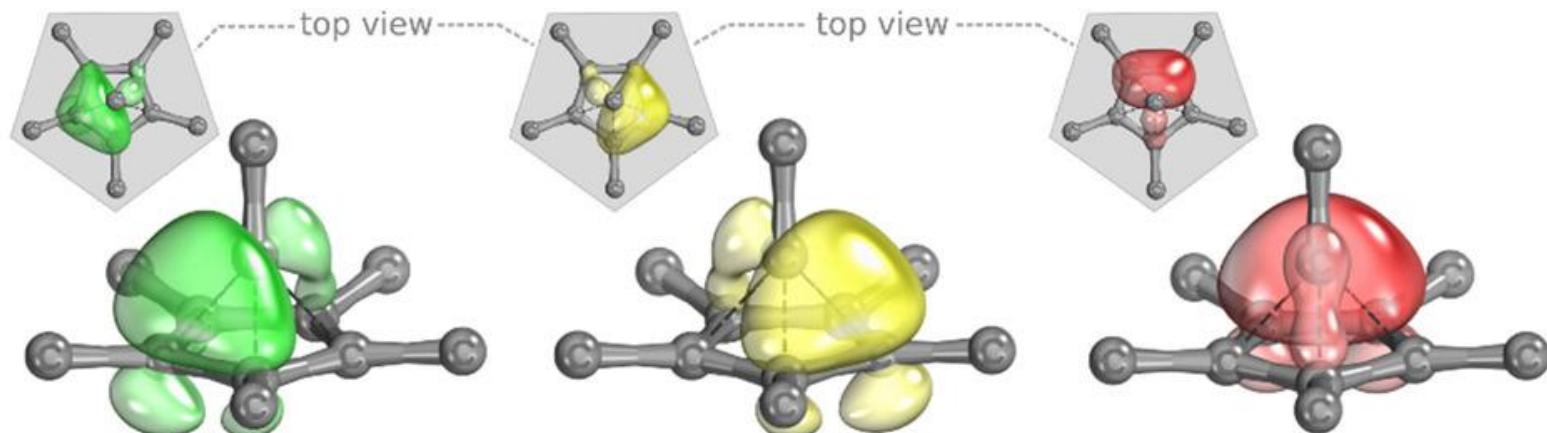
Localized Molecular Orbitals

- **Pipek–Mezey (1989)** – maximizes the *localization of charge* on individual atoms
- **Natural Bond Orbitals (NBOs)** – fits orbitals to an *idealized Lewis bonding pattern*
 - interprets density in terms of classical bonds, lone pairs, and donor–acceptor interactions
- **Intrinsic Bond Orbitals (IBOs, Knizia 2013)** – maximizes *occupancy in intrinsic atomic orbitals*
 - recovers clean σ and π bonds and lone pairs directly from the density

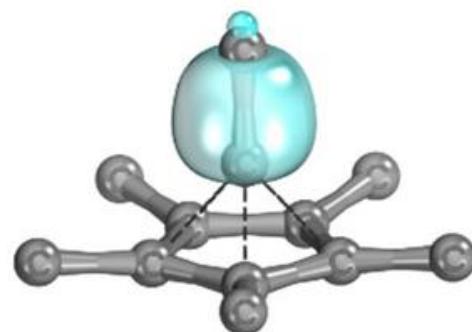
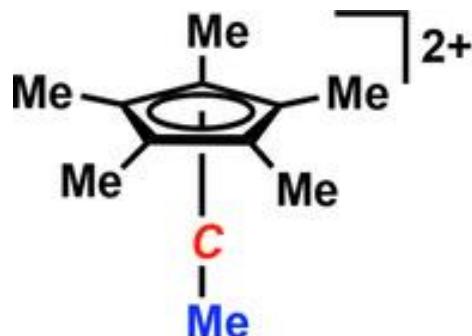
IBOs



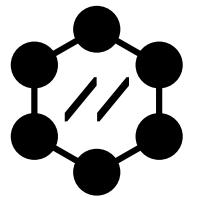
IBOs



π -interactions of C with Cp* ring in compound I



σ -interaction of C with CH₃ group



svatunek // lab

Computational Organic Chemistry

This teaching material is available at:
teaching.svatunek-lab.com



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