

svatunek // lab  
Computational Organic Chemistry

# Computational Chemistry: An Organic Chemist's Perspective

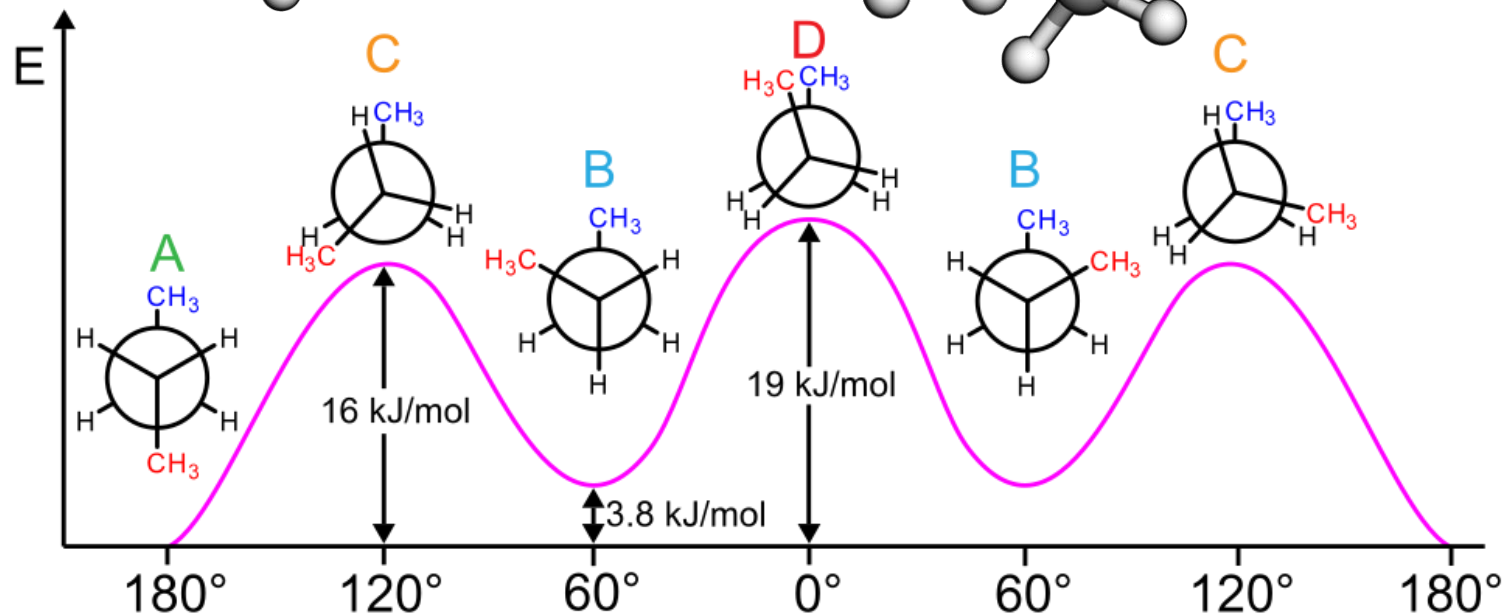
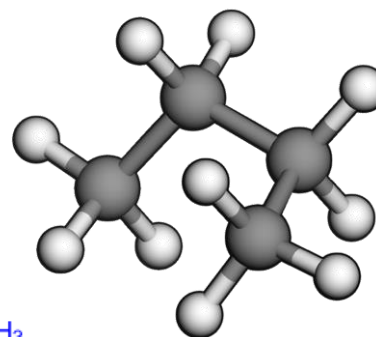
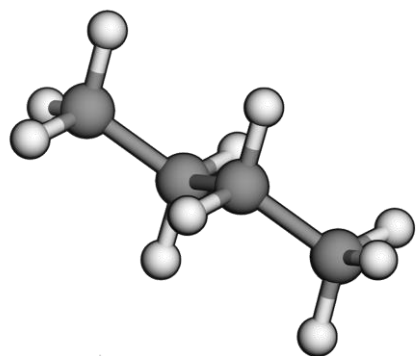
Assistant Professor Dr. **Dennis Svatunek**

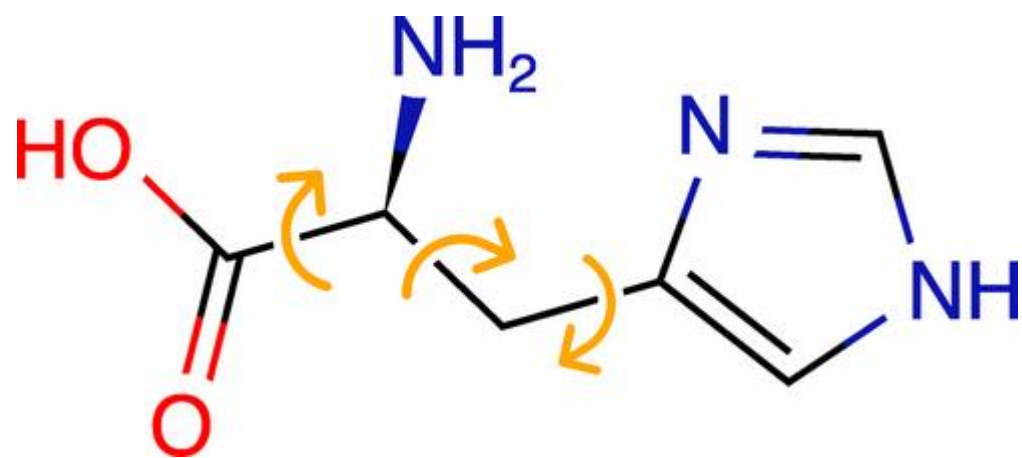
University of Malaya, 12<sup>th</sup> of November 2025

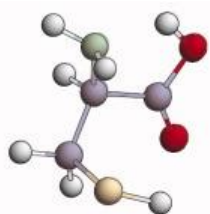
# **Conformer Searches**

# 1. Conformer Searches

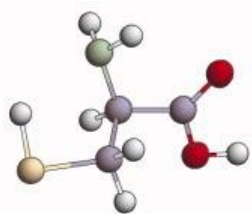
- **Conformers** are different spatial arrangements of a molecule → obtained by **rotation around single ( $\sigma$ ) bonds**
- They have the **same connectivity**, only **different geometry**
- Often close in energy → can **interconvert at room temperature**



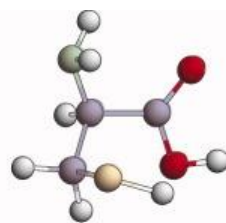




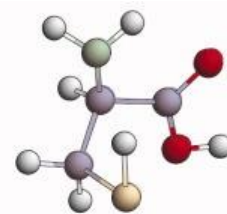
cys 1



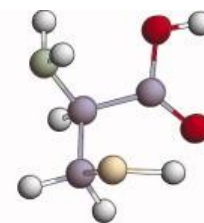
cys 2



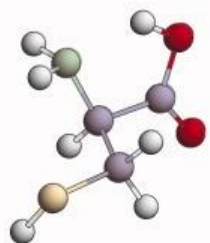
cys 3



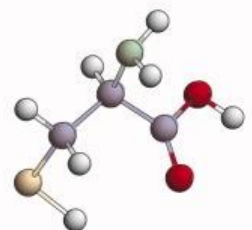
cys 4



cys 5



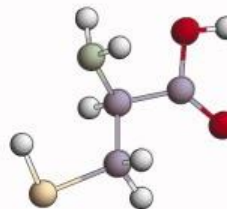
cys 6



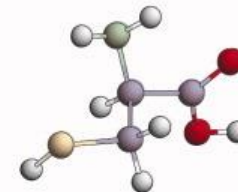
cys 7



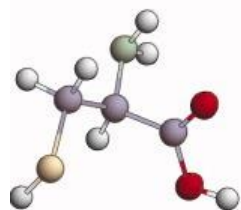
cys 8



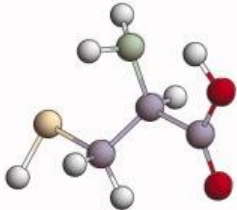
cys 9



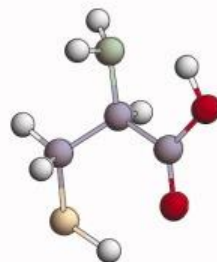
cys 10



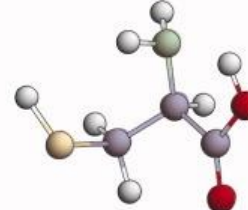
cys 11



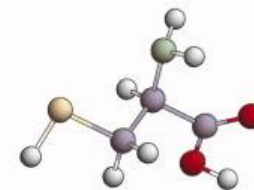
cys 12



cys 13



cys 14



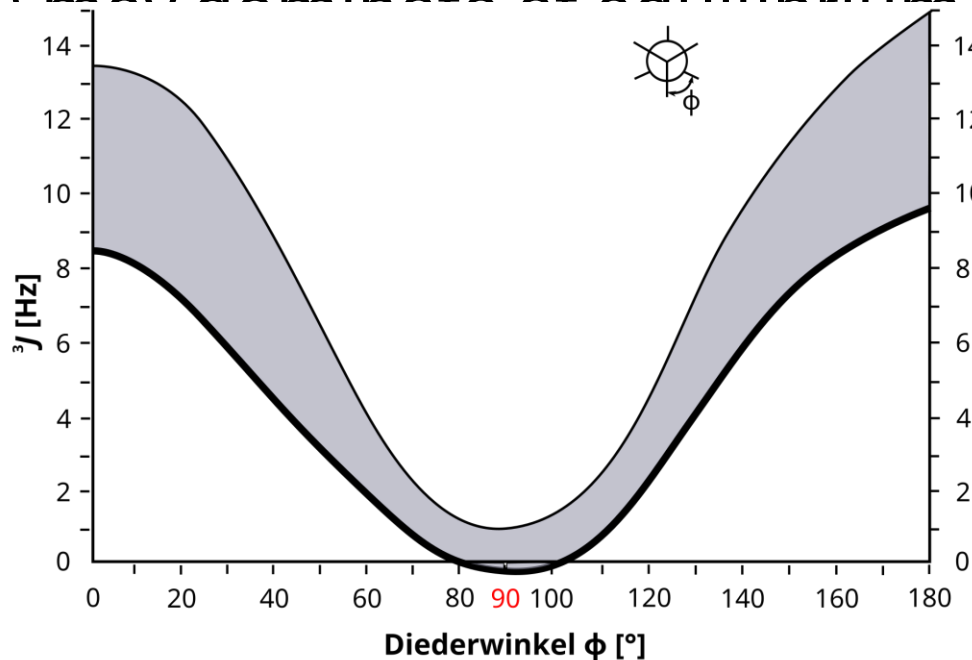
cys 15

# Why care about conformers?

- Conformers often have **different energies** → one (or more) may dominate at equilibrium

- Different **physical**

- Dipole intens
- NMR c angles
- UV/Vis bondir.



it  
e.g.  
ty, IR  
edra

ry and H-

# 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 (RMSE)

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.,  $60^\circ$  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  $\rightarrow$  6 combinations
- 3 bonds  $\rightarrow 6^3 = \mathbf{216}$
- 5 bonds  $\rightarrow 6^5 = \mathbf{7,776}$
- 10 bonds  $\rightarrow 6^{10} = \mathbf{>60 \text{ million}}$

**$\rightarrow$  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

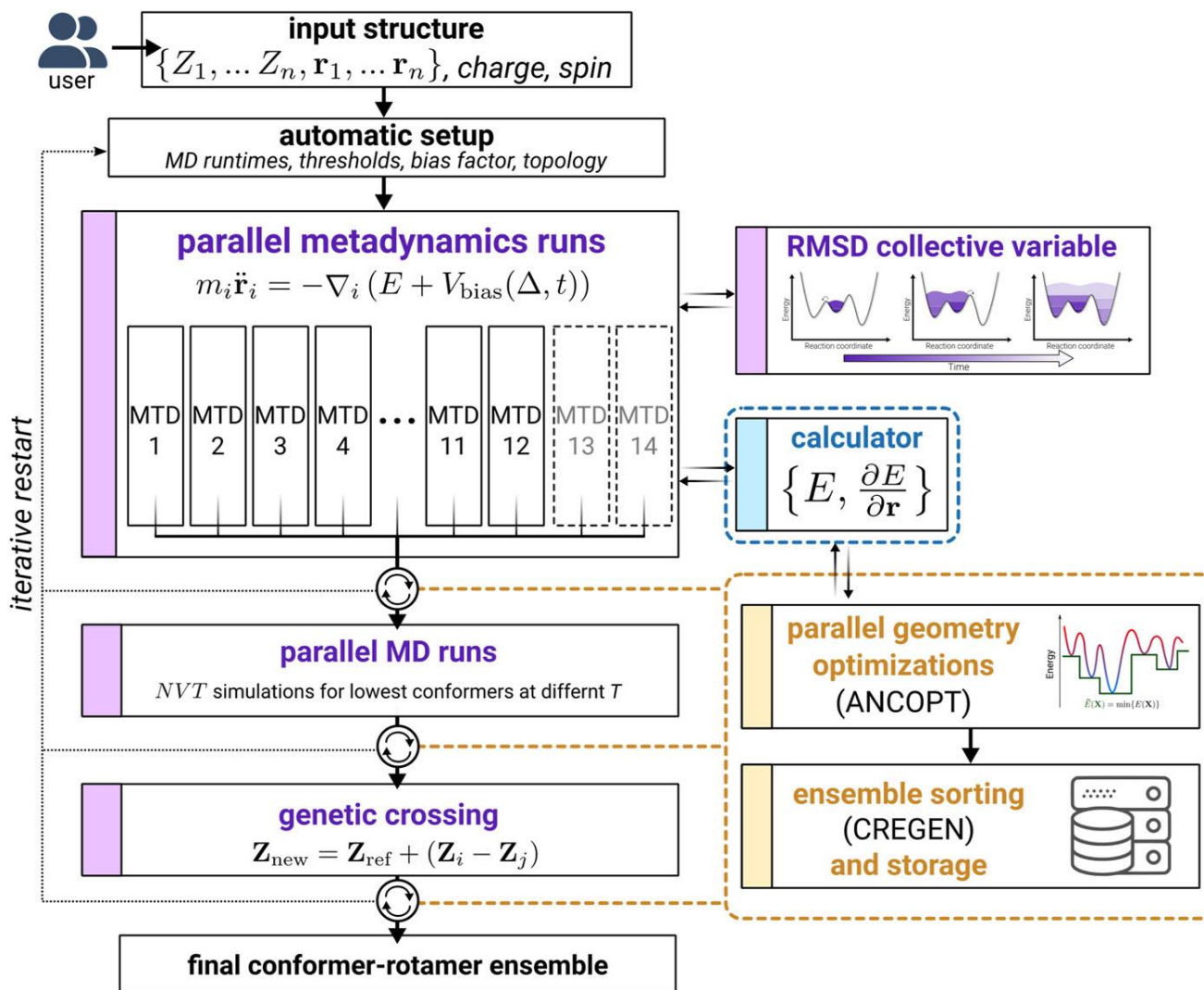
- MD explores conformational space through time evolution → **hard to cross high energy barriers**
- Reaching rare conformers may require very long trajectories
- Classical MD: fast but approximate (force field-dependent)
- Quantum MD (AIMD): accurate but computationally prohibitive

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)

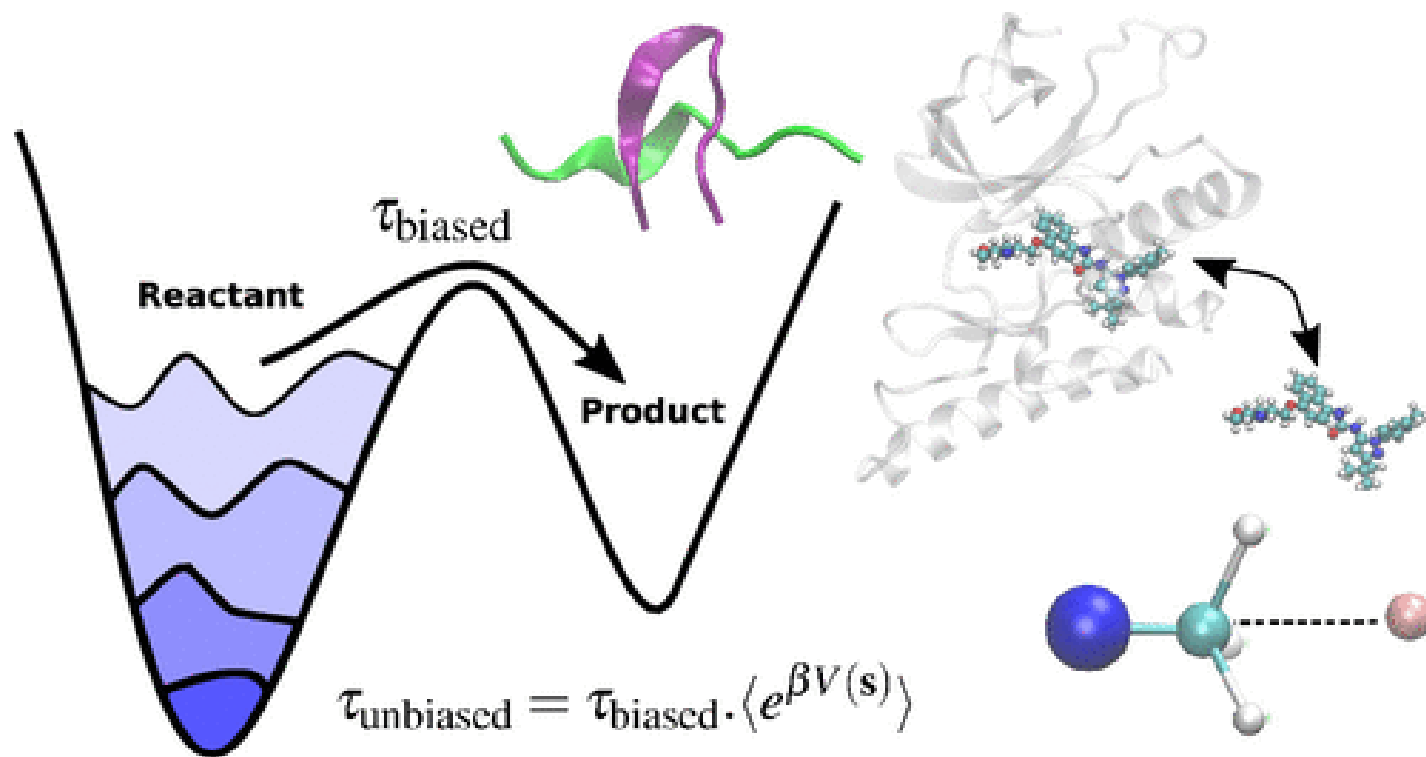
# CREST (Grimme Lab)



# 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***

### **2. stop and optimize**

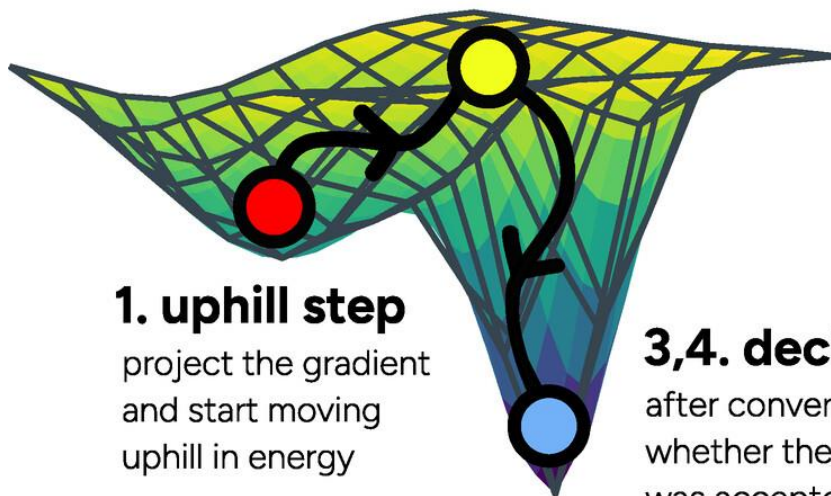
once a barrier was crossed  
or stop criteria were met,  
do a regular optimization

### **1. uphill step**

project the gradient  
and start moving  
uphill in energy

### **3,4. decide and sort**

after convergence, decided  
whether the new minimum  
was accepted, sort and repeat



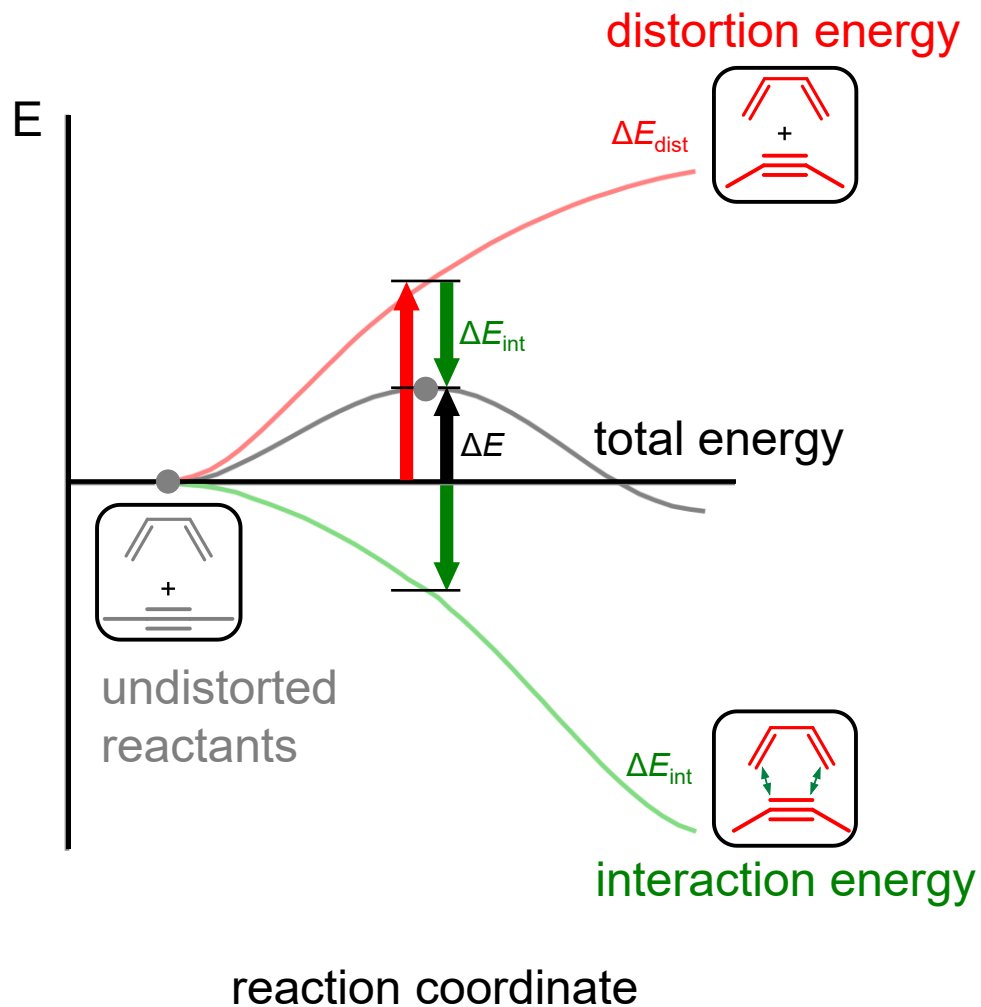


# **Energy Decomposition Analysis**

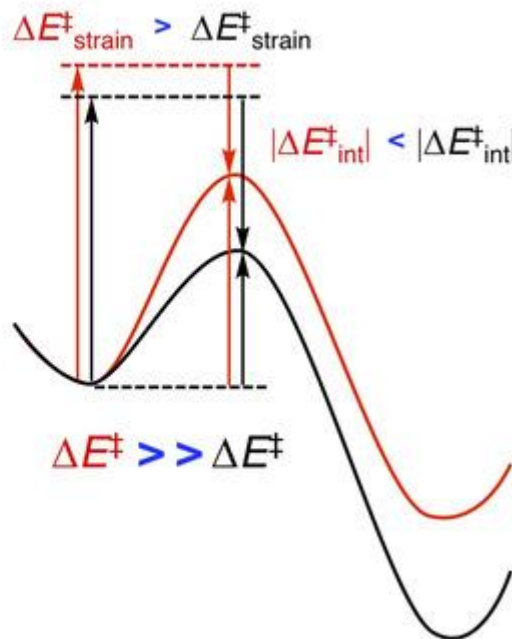
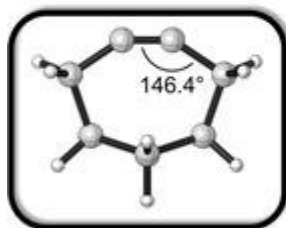
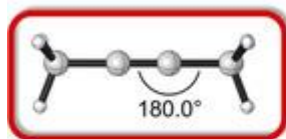
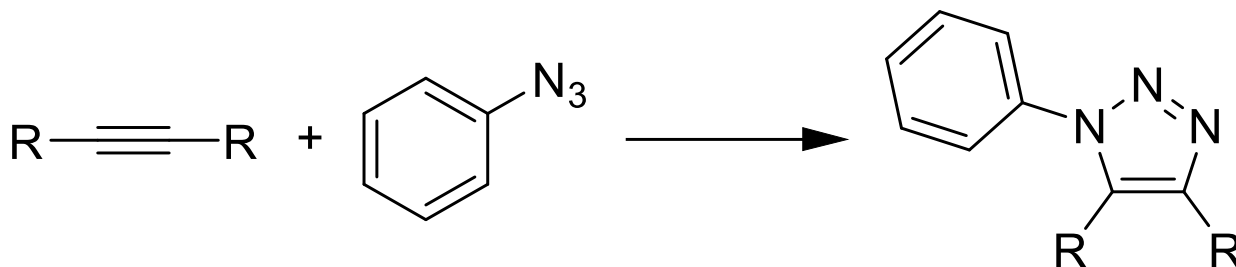
## 2. Energy Decomposition Analysis

- **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



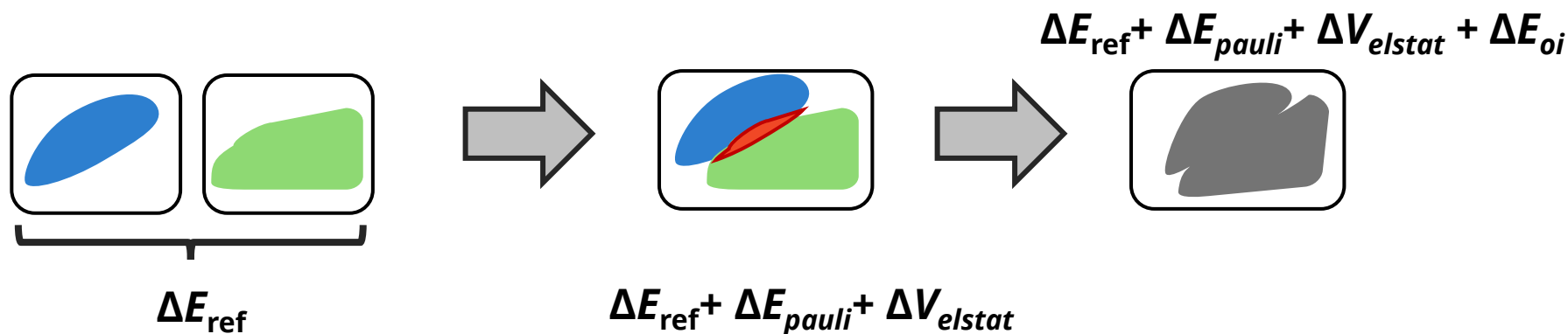
# Energy Decomposition Analysis

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

# Rauk-Ziegler Energy Decomposition Analysis

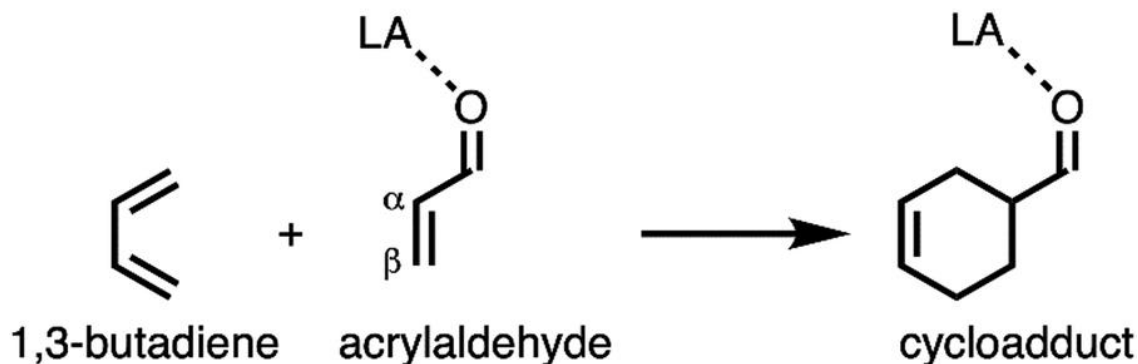
Works within the DFT Kohn-Sham framework

$$\Delta E_{int} =$$



# EDA in action: Catalysis in Diels-Alder reactions

LA = none, AlCl<sub>3</sub>, Li<sup>+</sup>, H<sup>+</sup>



|                           | $\Delta E^*$ | $\Delta E_{\text{strain}}$ | $\Delta E_{\text{int}}$ | $\Delta V_{\text{elstat}}$ | $\Delta E_{\text{Pauli}}$ | $\Delta E_{\text{oi}}$ |
|---------------------------|--------------|----------------------------|-------------------------|----------------------------|---------------------------|------------------------|
| <b>O</b>                  | 12.1         | 19.3                       | -7.2                    | -38.9                      | <b>82.9</b>               | -51.5                  |
| <b>O-AlCl<sub>3</sub></b> | 1.5          | 14.9                       | -13.4                   | -34.5                      | <b>73.5</b>               | -52.4                  |
| <b>O-Li<sup>+</sup></b>   | -1.9         | 13.5                       | -15.4                   | -31.3                      | <b>68.1</b>               | -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**

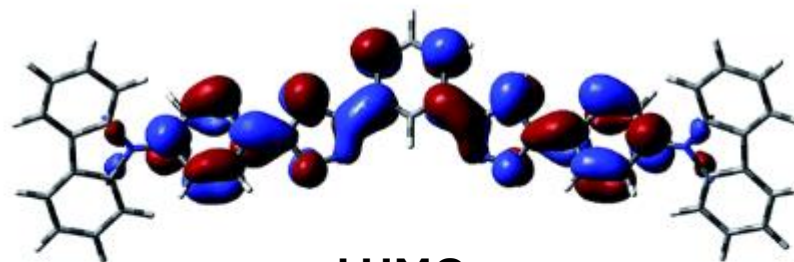
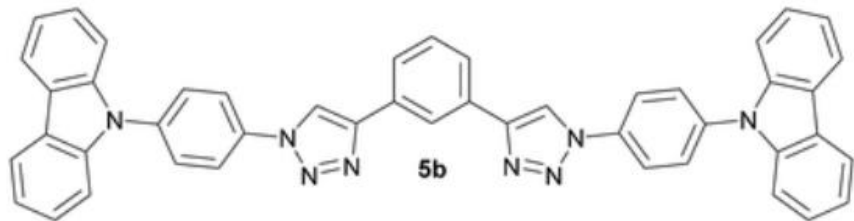
# Orbitals

# 3. Orbitals

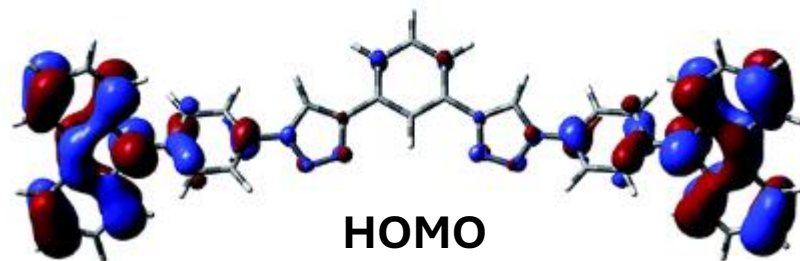
- One-electron functions  $\psi_i(\mathbf{r})$  obtained from
  - Schrödinger equation (Hartree–Fock) or
  - Kohn–Sham equation (DFT)
- Each orbital describes a spatial electron distribution;  $|\psi_i|^2$  = probability density
- Canonical orbitals are **orthogonal** and usually **delocalized**
- Energies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

# What are Orbitals used for?

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



LUMO



HOMO

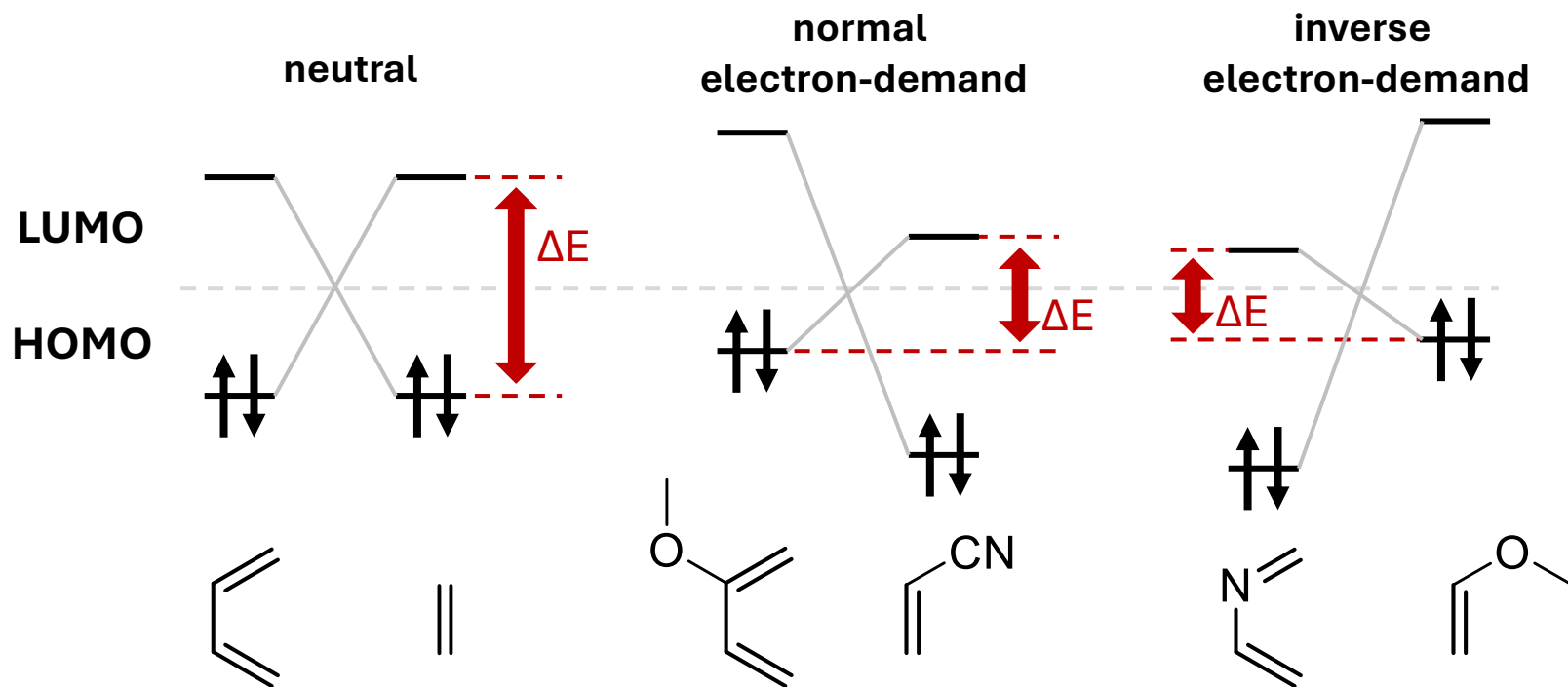
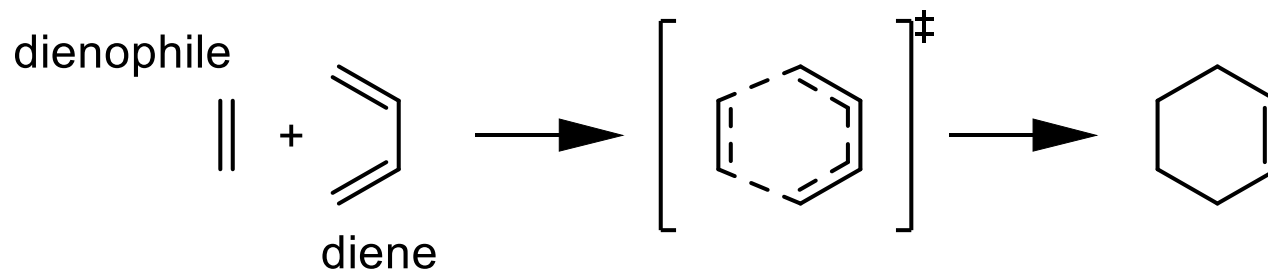
# FMO Theory

- 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

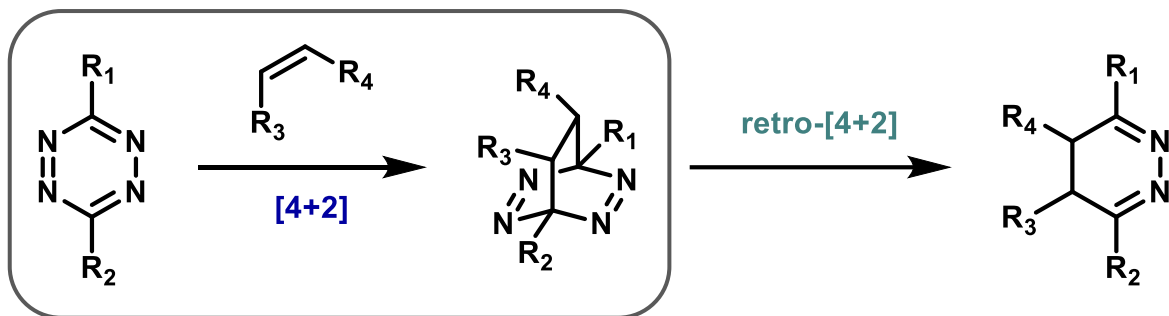
# FMO Theory

- 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

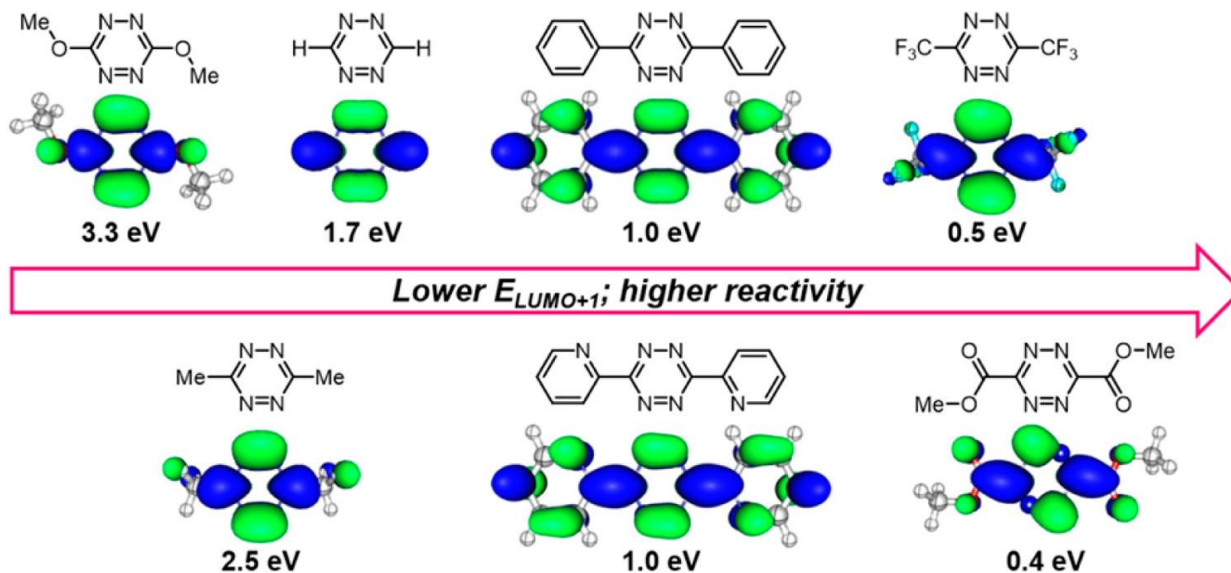
# FMO Theory: Diels–Alder Reaction



# FMO Theory: Diels–Alder Reaction

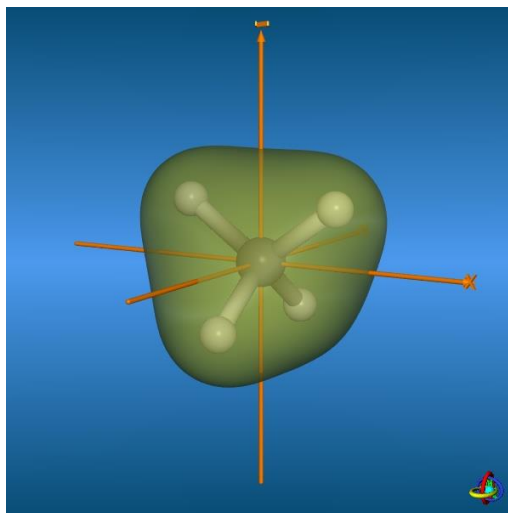
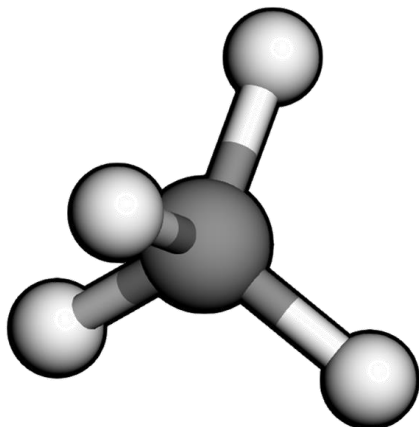
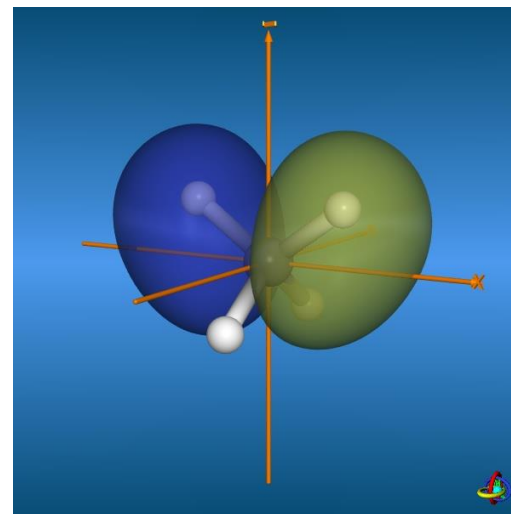
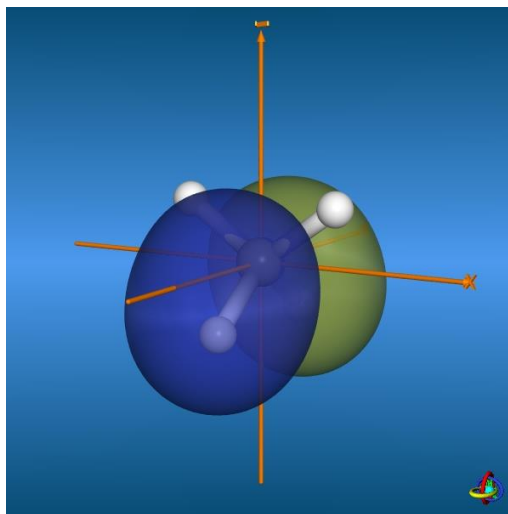
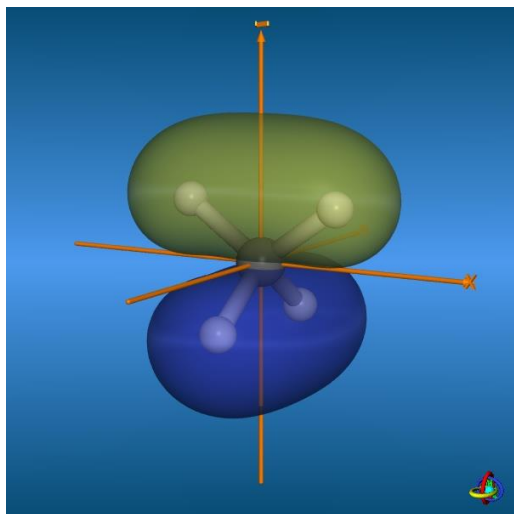


rate limiting step

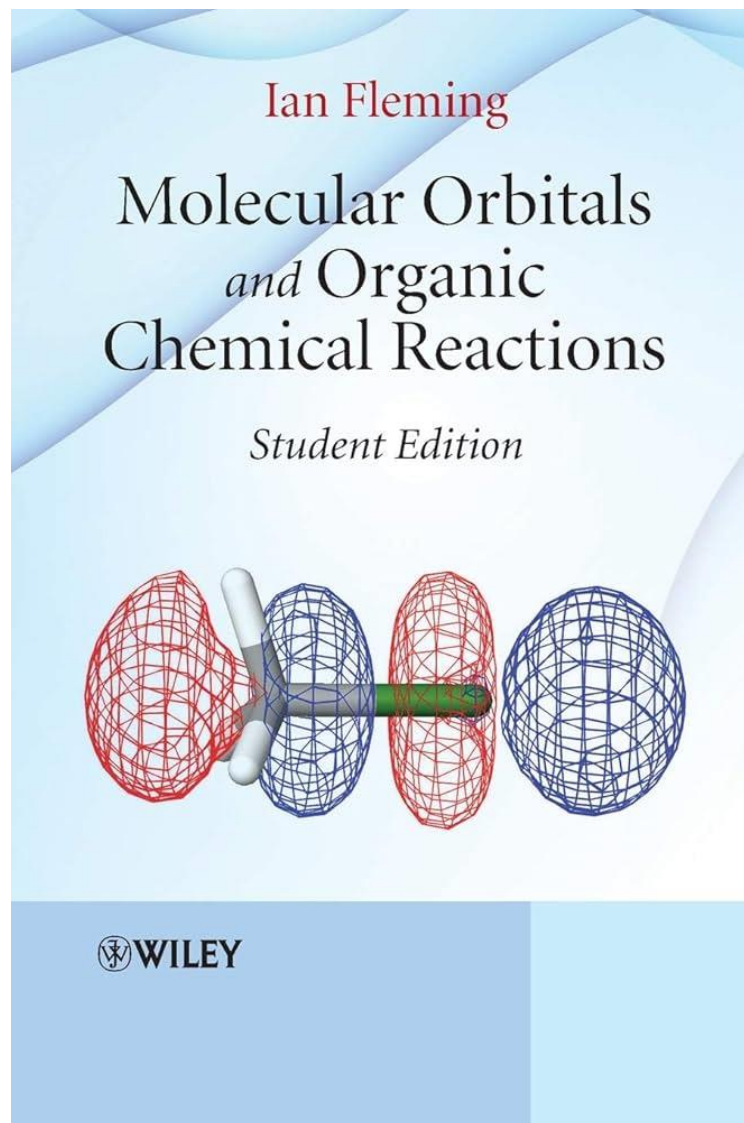




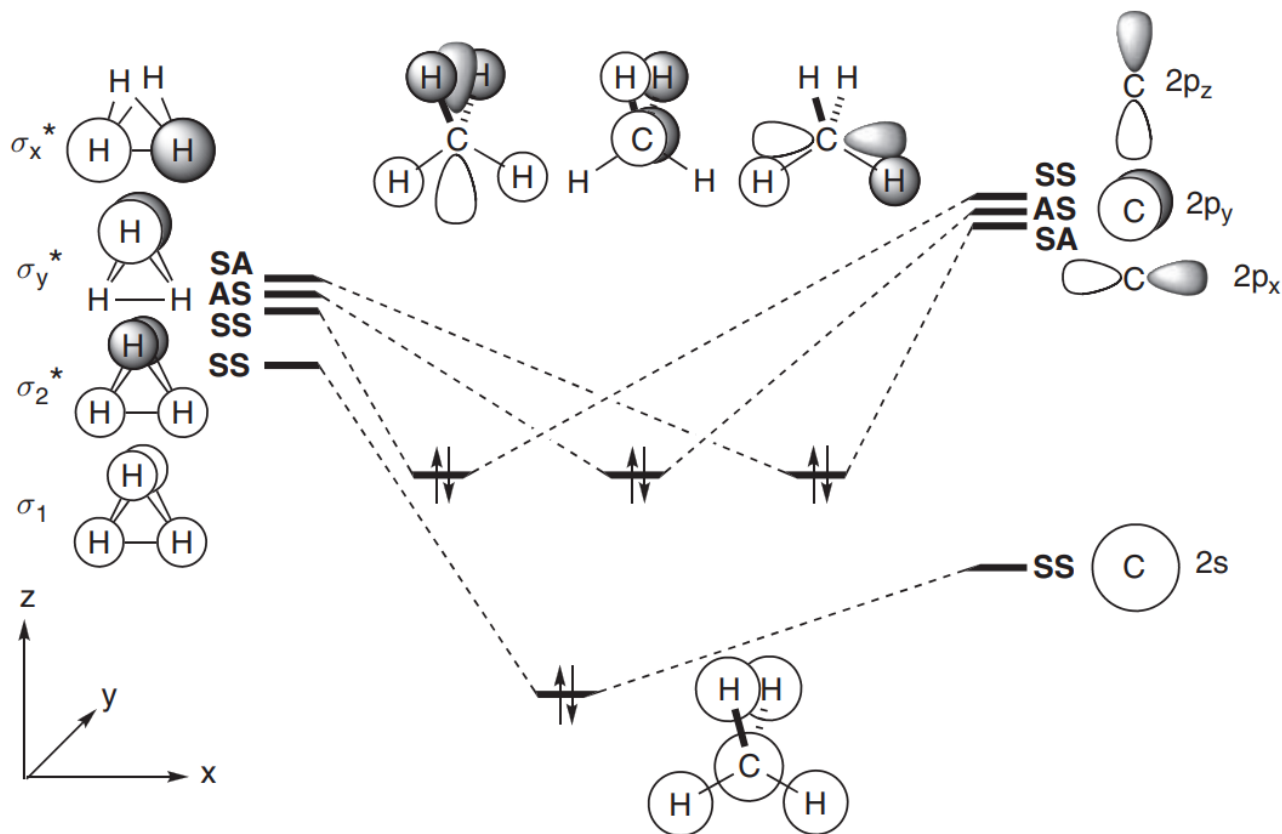
# Canonical orbitals are delocalized



# Canonical orbitals are delocalized

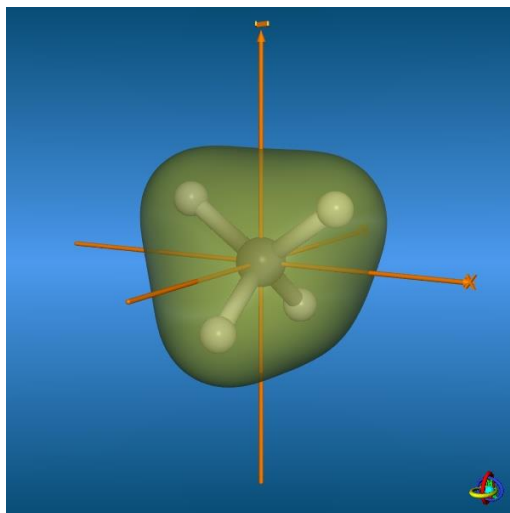
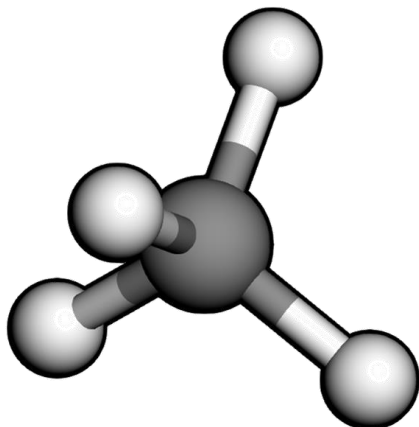
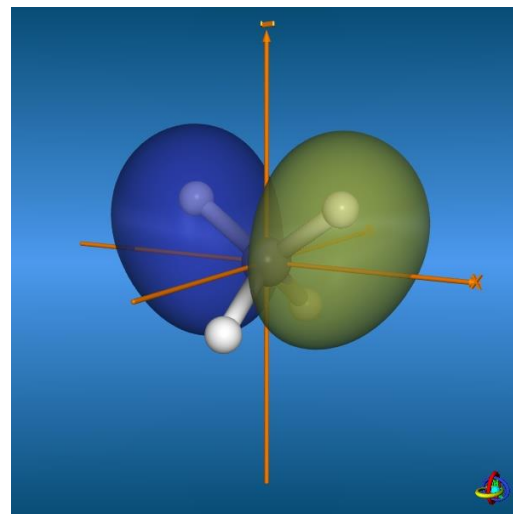
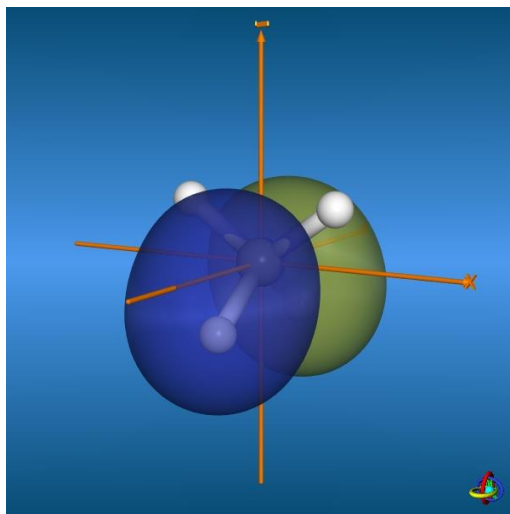
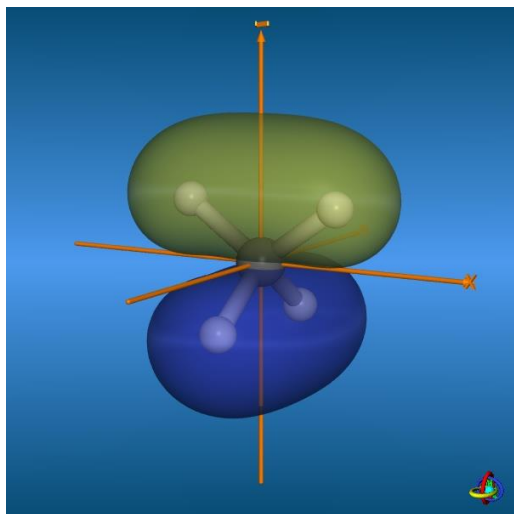


# Canonical orbitals are delocalized

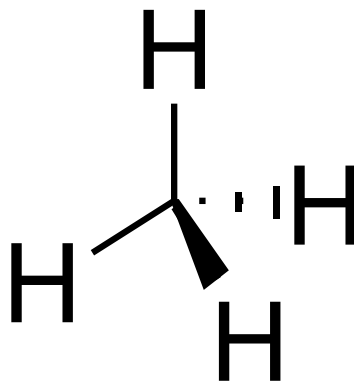
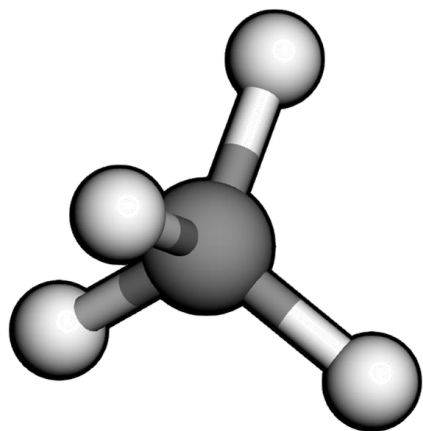
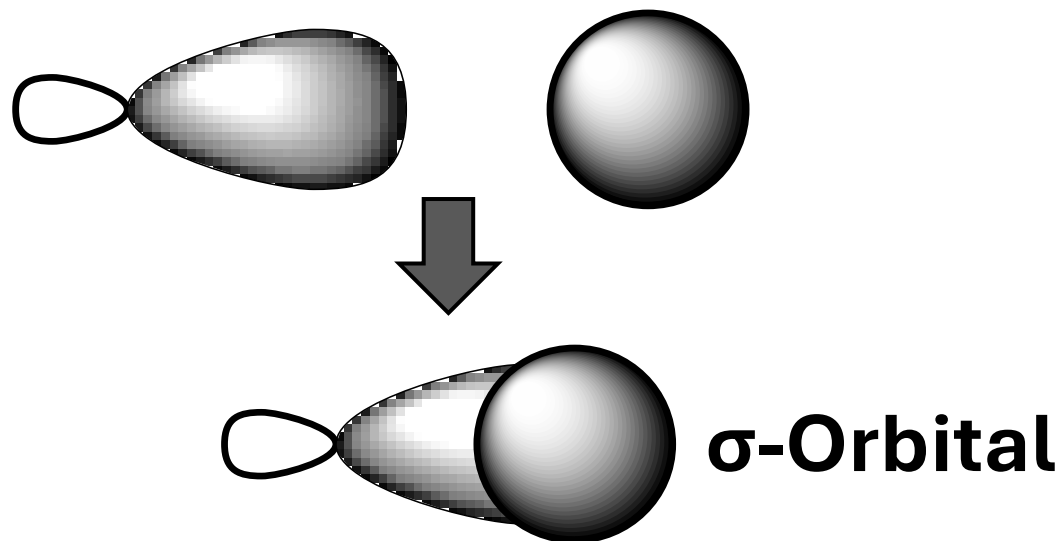


**Fig. 1.12** The molecular orbitals of methane from the interaction of the orbitals of tetrahedral  $\text{H}_4$  and a C atom

# Canonical orbitals are delocalized



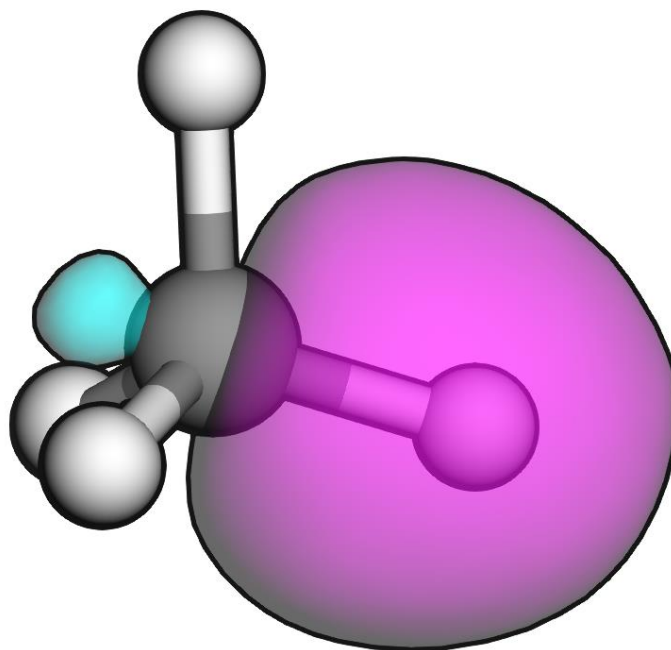
# Canonical orbitals are delocalized



# 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

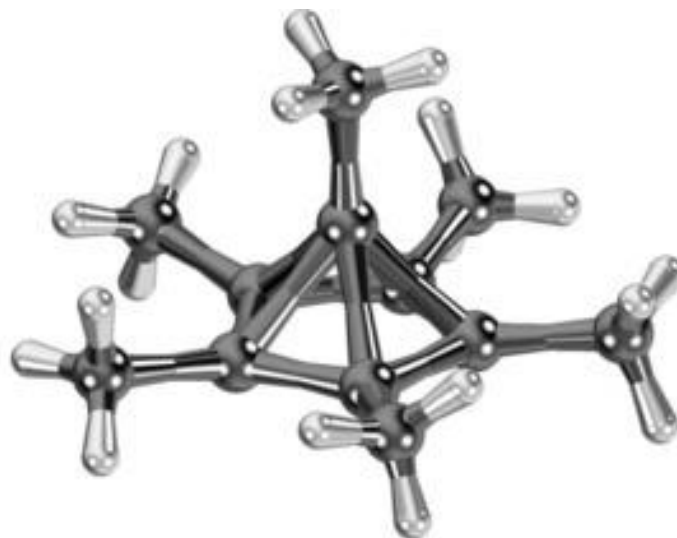
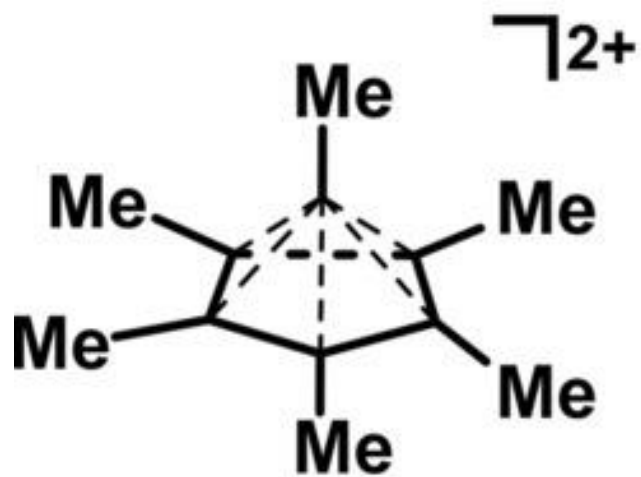


# Localized Molecular Orbitals

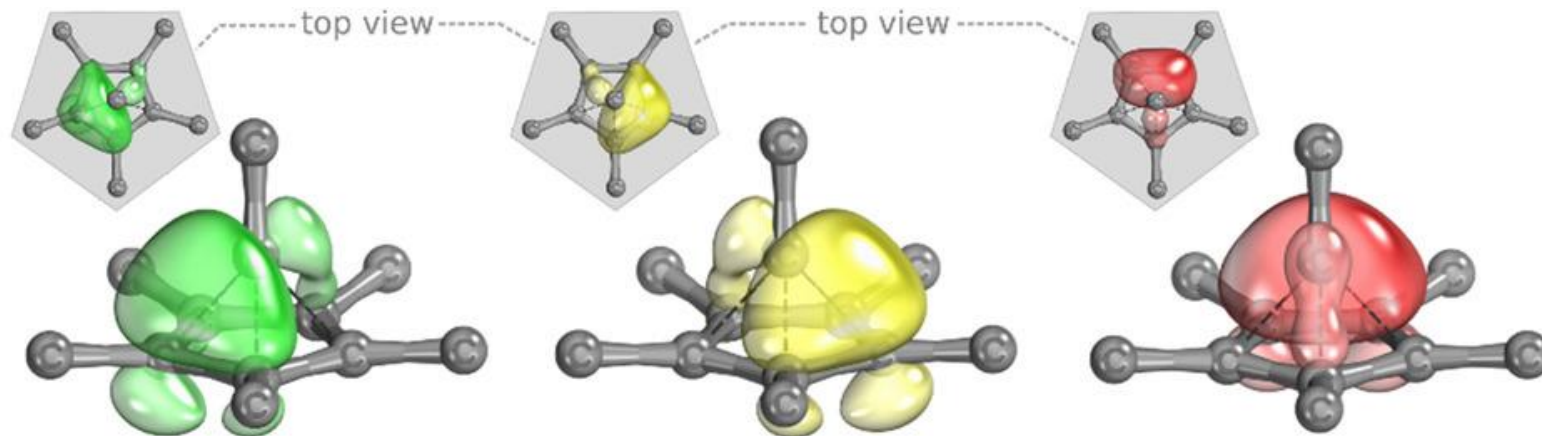
- **Pipek–Mezey (1989)** – maximizes the *localization of charge* on individual atoms
- **Natural Bond Orbitals (NBOs)** – fits orbitals to an *idealized Lewis bonding pattern*
  - interprets density in terms of classical bonds, lone pairs, and donor–acceptor interactions
- **Intrinsic Bond Orbitals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



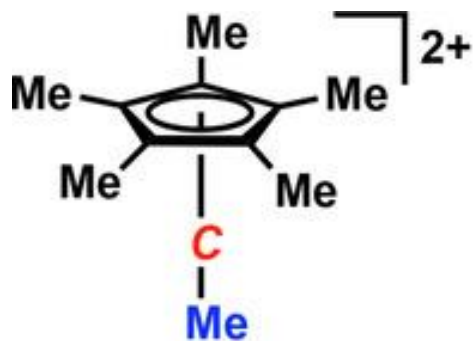
# IBOs



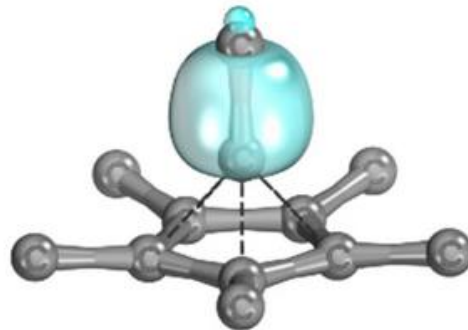
# IBOs



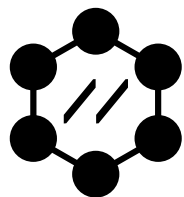
$\pi$ -interactions of C with Cp\* ring in compound I



I  $[C_6(CH_3)_6]^{2+}$



$\sigma$ -interaction of C with CH<sub>3</sub> group



svatunek // lab

Computational Organic Chemistry

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



svatunek-lab.com



dennis.svatunek@tuwien.ac.at