Reactivity

Giovanni Bistoni, Ragnar Bjornsson, Dimitrios Pantazis

Max-Planck-Institut für
Kohlenforschung
Stifstr. 34-36
D-45470 Mülheim an der Ruhr
Germany

Key concepts and outline

1. Locate a Transition State

2. Methodological aspects (Solvation Methods, Conformational Sampling, Electronic Structure methods)

3. Accurate Energies for large systems (from CCSD(T) to DLPNO-CCSD(T))

4. Understanding (Qualitative and Quantitative interpretation methods)

5. Examples

Locate a Transition State

Chemistry and Potential Energy Surfaces

In computational chemistry, reactions are discussed by analyzing variations of the total energy with changes in the nuclear coordinates:
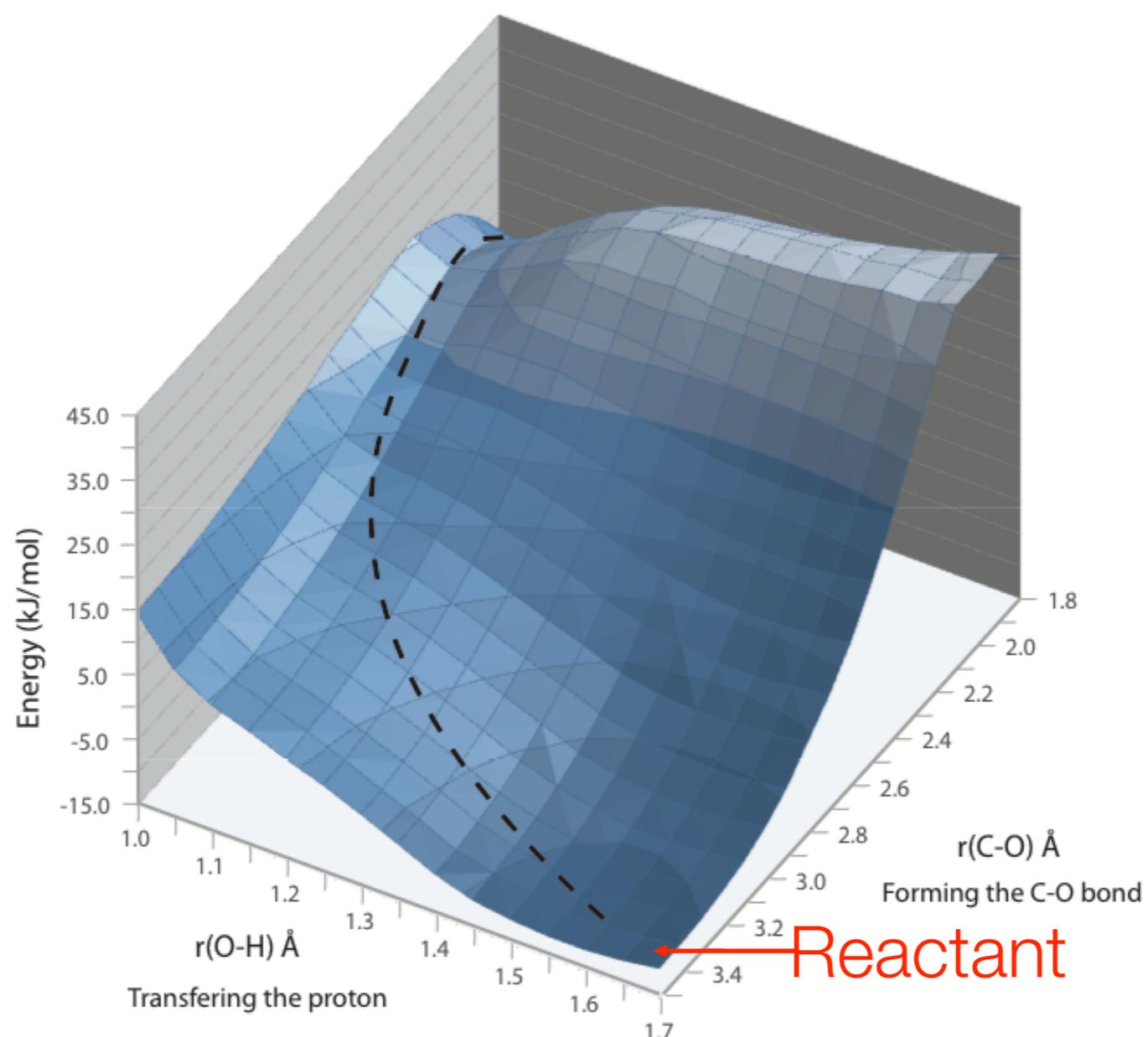
Transition State Theory

Consider a elementary reaction:
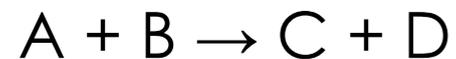
A + B → C + D

In TST, one assumes that the two reactants A and B have to pass through a special geometric arrangement [AB]≠ (the transition state, TS) before decaying to the products C and D, A + B→ [AB]≠ → C + D.

$$k_{\text{rate}} = \frac{kT}{h} e^{-\frac{\Delta G^{\neq}}{RT}} = \frac{kT}{h} e^{-\frac{\Delta H^{\neq} - T\Delta S^{\neq}}{RT}}$$
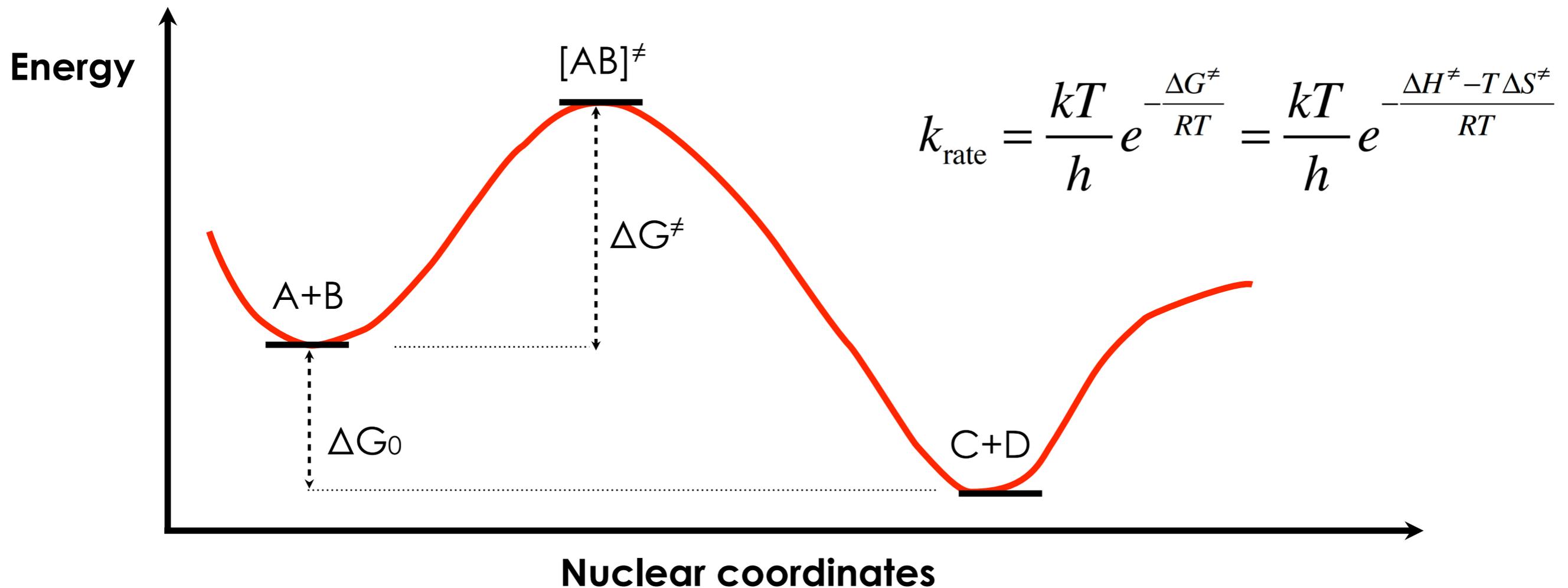
Finding a Saddle point

Use **chemical intuition** to buil an initial TS structure. If you provide a good estimate for the structure of the transition state structure, then you can find the respective transition state with the following keywords:

TS search

```
! PM3 OptTS
! Freq

%geom
Calc_Hess True
end

*xyz 0 1
Cartesian Coordinates
*
```

1. In ORCA, **analytic Hessian** evaluation is available for **SCF methods**, including the RI and RIJCOSX approximations and canonical **MP2**.

2. You need a good guess of the TS structure. **Relaxed surface scans** can help in almost all cases.

Finding a Saddle point: a simple case
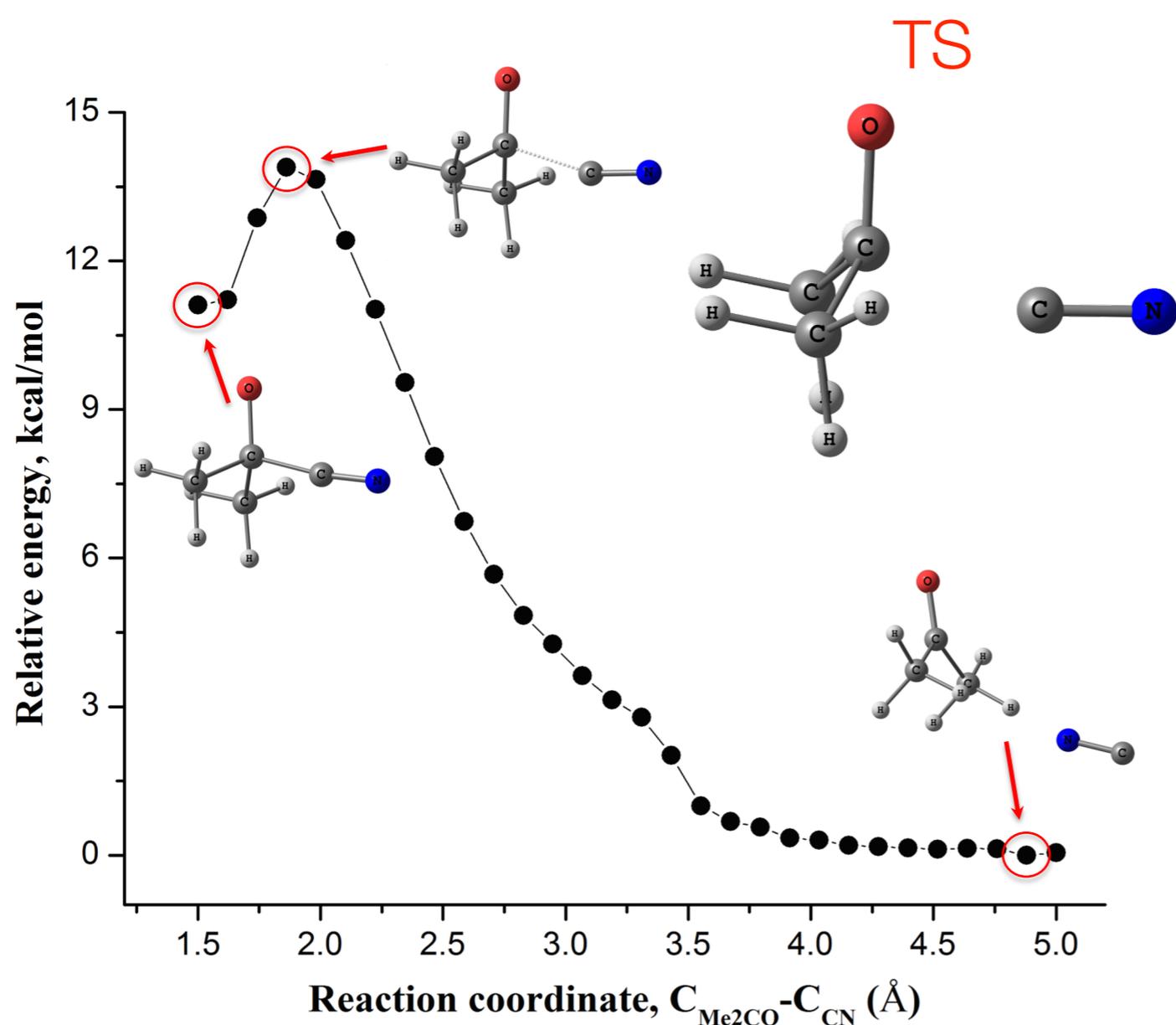
relaxed surface scan

```
!PM3
%geom scan B 1 10 = 1.50, 5.00, 30
        end
end
*xyz −1 1
Cartesian coordinate
*
```

TS search

```
! PM3 OptTS
! Freq

%geom
Calc_Hess True
end

*xyz −1 1
Cartesian Coordinates
*
```

After the optimization, **check the normal modes!**

The Intrinsic Reaction Coordinate (IRC) Method

The Intrinsic Reaction Coordinate (IRC) method finnds a path connecting a transition state (TS) with ist downhill-nearest intermediates.

Relative Energy along IRC
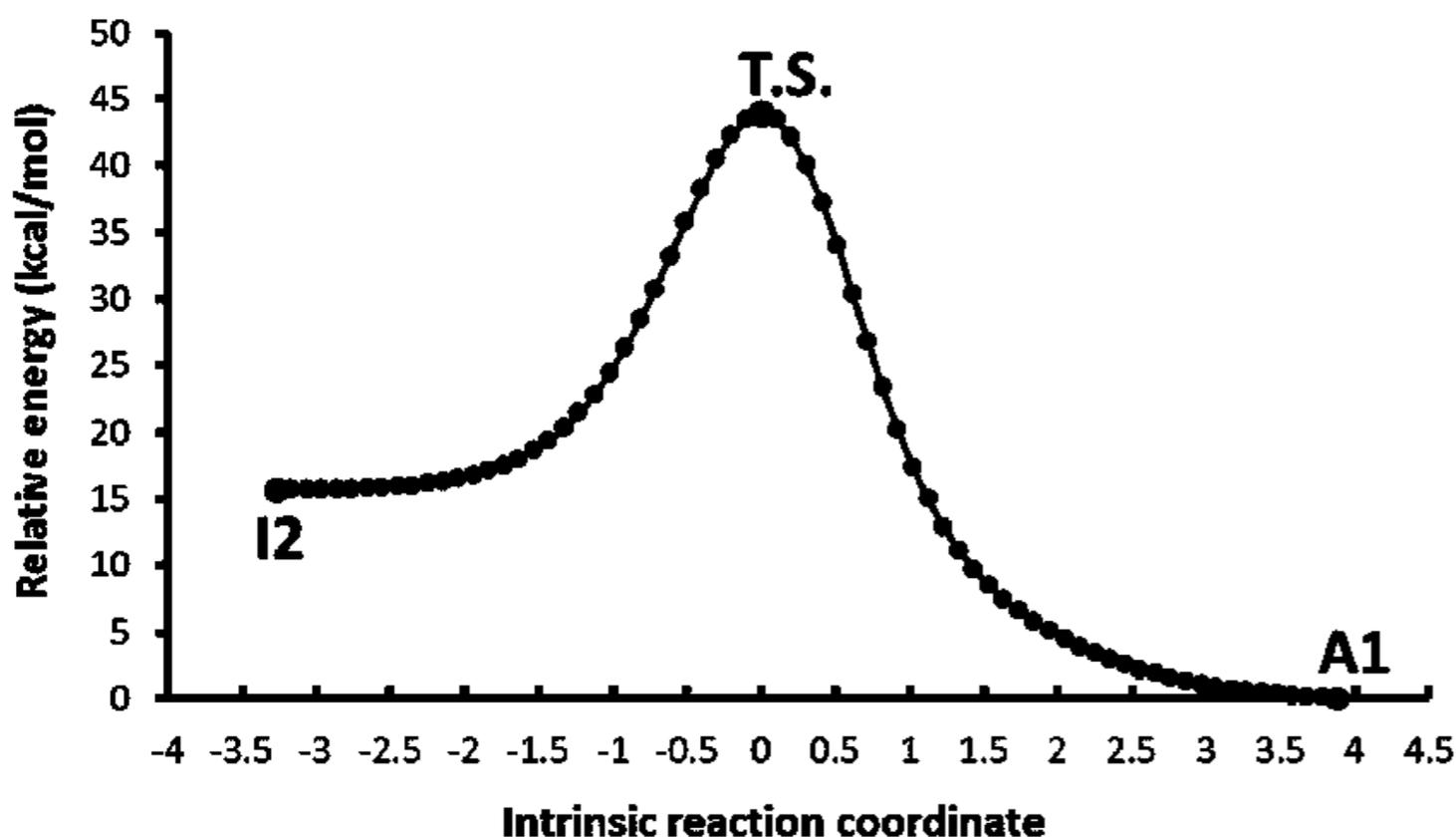

```
!B3LYP SV(P) TightSCF KDIIS Freq IRC
* xyz 0 2
C -0.000   0.001 -0.000
H  1.290   0.005 -0.006
H -0.330   1.050 -0.002
H -0.252 -0.532 -0.929
H -0.286 -0.545  0.911
O  2.499   0.220  0.065
H  2.509   1.085  0.525
*
```

A final trajectory (IRC Full.trj) is generated which contains both directions, forward and backward, by starting from one endpoint and going to the other endpoint, visualizing the entire IRC.

Difficult Cases: The Nudged Elastic Band method

Basic Idea: Find the TS from reactant and product only.

- Using reactant (**R**)and product (**P**) geometries, create an initial path (band) of intermediate geometries (images) by interpolation between **R** and **P**.
- Shift the set of images towards the minimum energy path, while maintaining the distribution of images, by minimizing the effective NEB force on each image
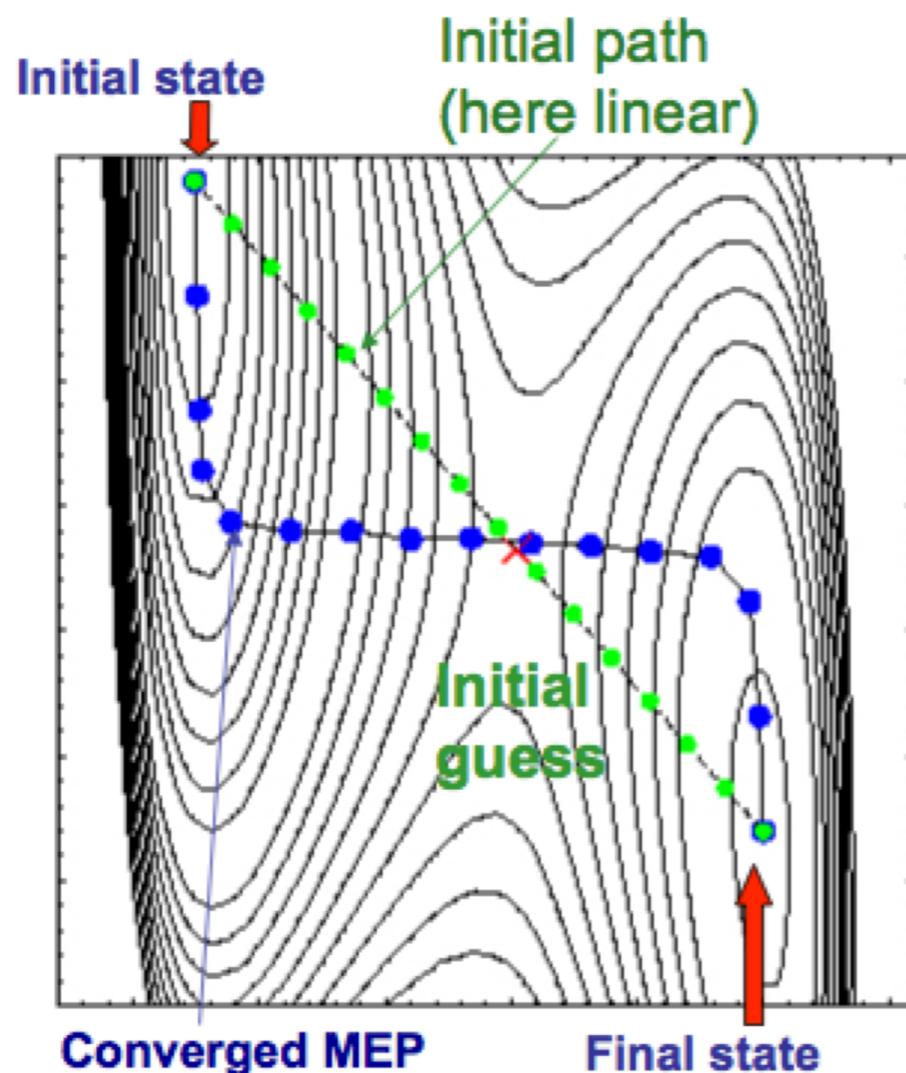

```
!PM3 NEB–TS TIGHTSCF FREQ

%neb
neb_end_xyzfile "product.xyz"
end

*xyzfile 0 1 reactant.xyz
```

Real-Life Chemistry
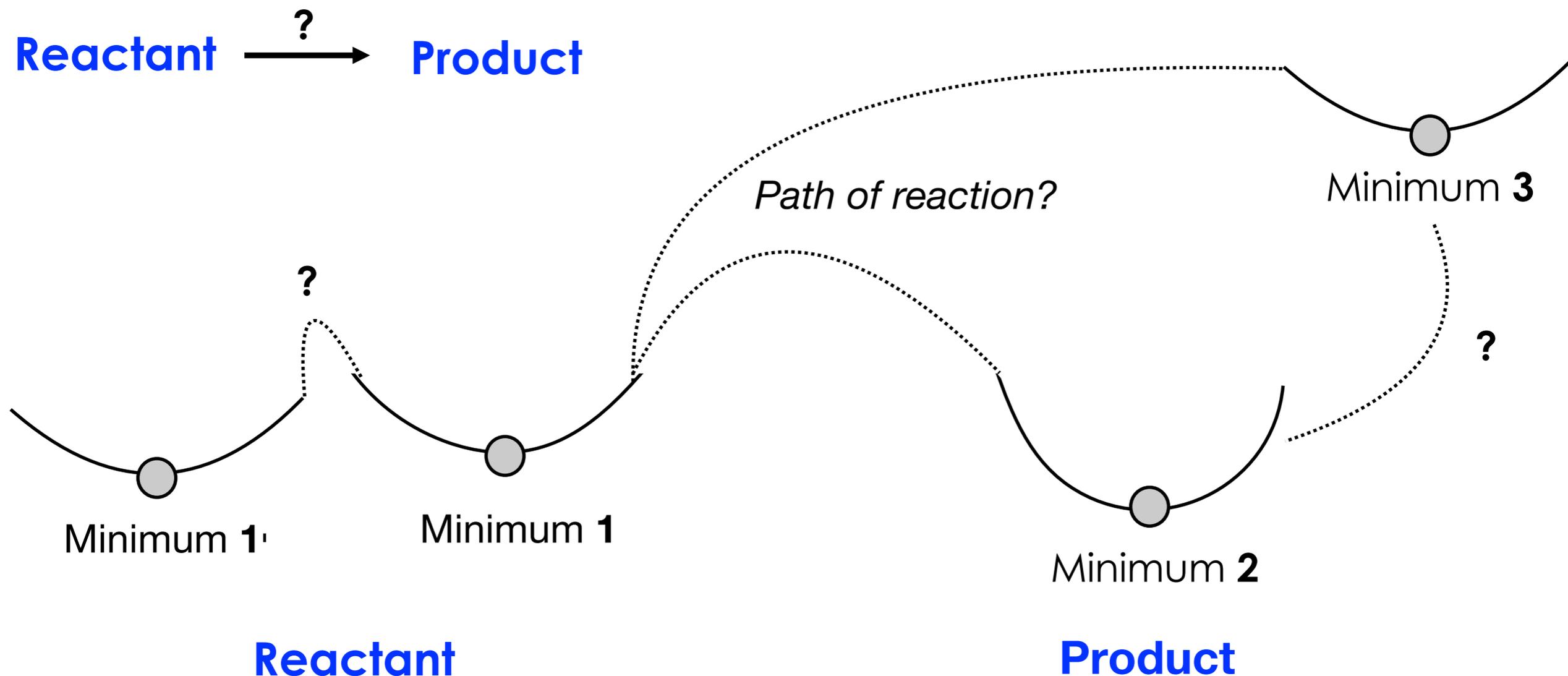
Chemical Intuition is **fundamental**, but it might not be enough.
We need **experimental information**. Need **good methods**.

Methodological Aspects

1. Solvation effects
2. Conformational Sampling
3. Electronic Structure Methods

Solvation Methods
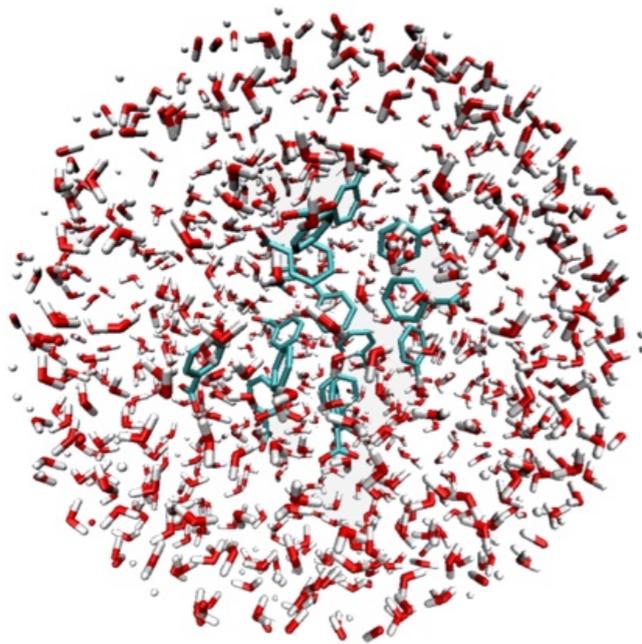
Explicit solvation

- Vacuum filled with solvent molecules
- Long-time MD

Implicit solvation
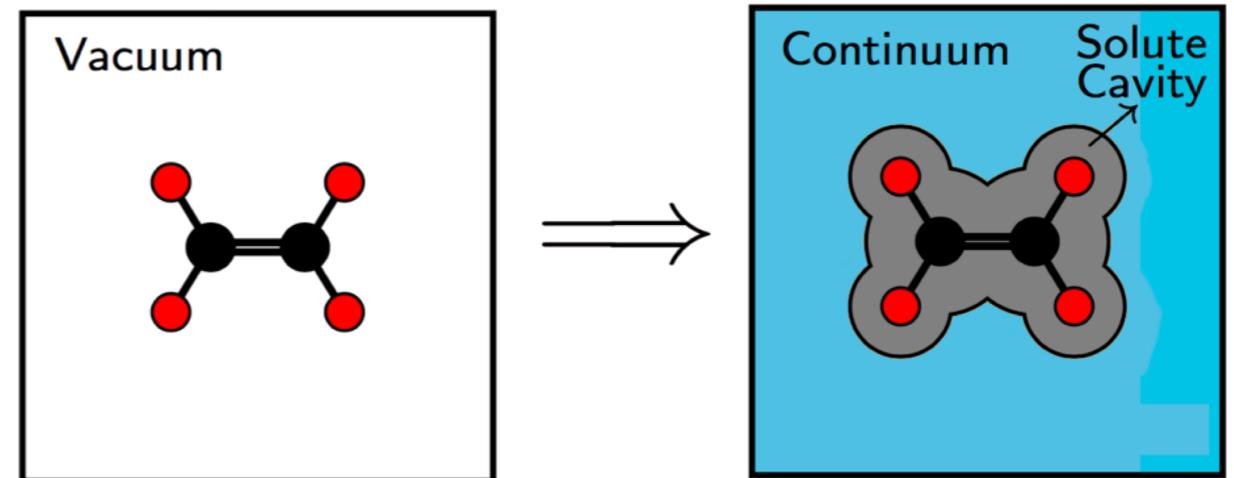
- Solvent replaced by dielectric medium
- Computational cost closer to that in vacuum
- Suitable for QM calculations

Solvation Methods
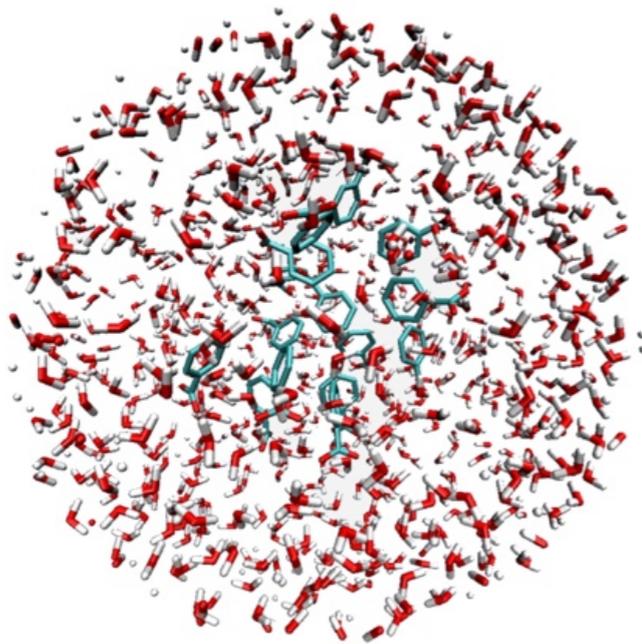
Explicit solvation

- Vacuum filled with solvent molecules
- Long-time MD

Implicit solvation
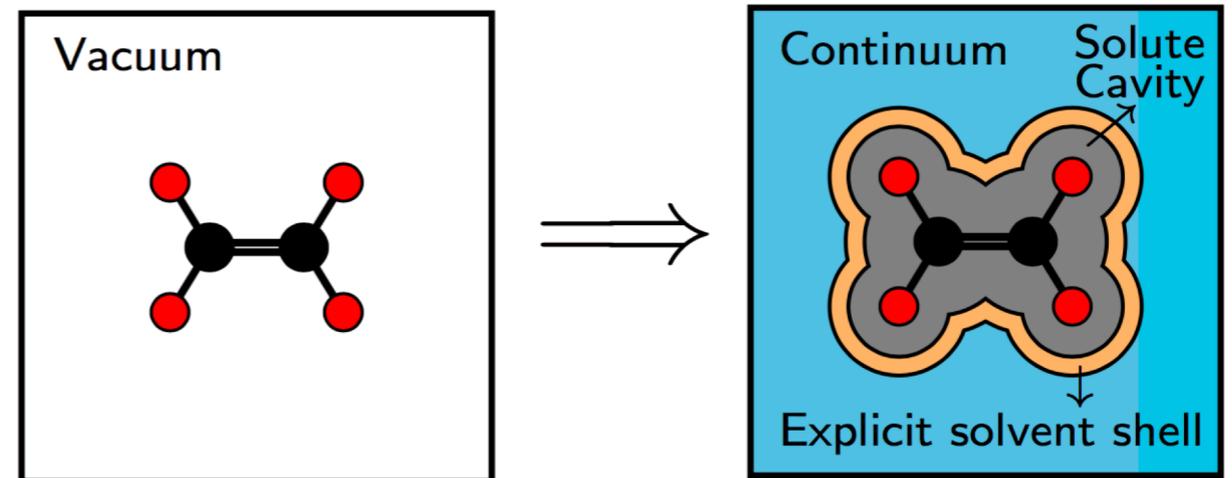
- Solvent replaced by dielectric medium
- Computational cost closer to that in vacuum
- Suitable for QM calculations

Implicit Solvation in ORCA

- Energies of molecules in solution (HF, DFT, MP2, CC (soon))

- Analytical Gradient (HF, DFT, MP2)

- Analytical Hessian (HF, DFT). Numerical Hessian for MP2

- Response properties like polarizabilities through coupled-perturbed SCF theory

- Solvent shifts or transition energies using TD-DFT or the CIS method

version **4.2.0**

Charge schemes: Point, Gaussian

Solv. models: C-PCM (SMD)

Addition of solv. schemes in ORCA

```
CPCM(Water)

%cpcm
epsilon 40.5
end
```

Conformational sampling
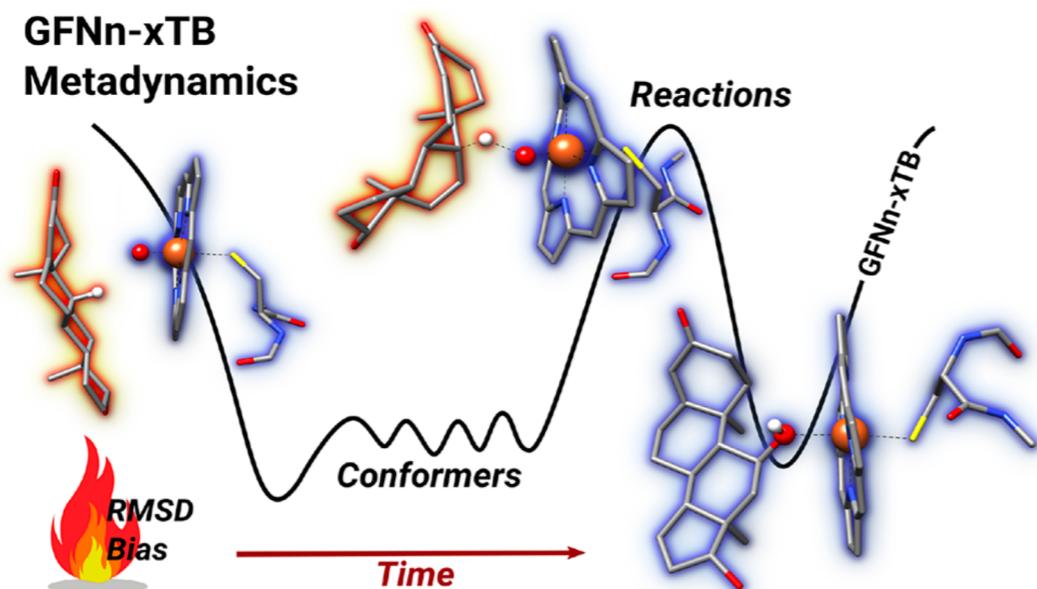
Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations

Stefan Grimme*

- A protocol to globally explore chemical compound, conformer and reaction space.

- Relies on cheap semi-empirical methods (GFN-xTB).

- Biased MD simulations (metadynamics) is used to systematically explore chemical space, locate multiple minima and distinguish between conformers, rotamers and reaction products.
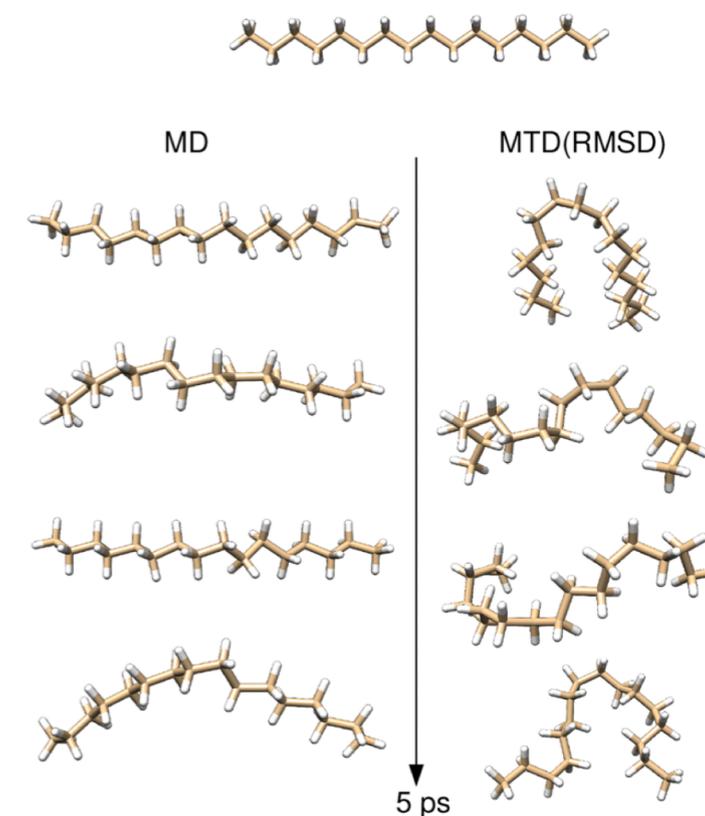
Personal View on the scope of Electronic structure methods

Semi-empirical Methods. Useful for preliminary investigations of PESs.

DFT: Popular cost effective methods in computational chemistry. **Which functional?** Nowadays, probably the best method for geometries for medium-sized systems.

MP2: Entry level correlation method. Not good for transition metals and open-shell systems. **Good for closed shell organic molecules.**

CCSD(T): **Robust and accurate**. It is considered as the "**gold standard**" of computational chemistry.

DLPNO-CCSD(T) : The local CCSD(T) in ORCA. It makes CCSD(T) applicable to large systems. No geometries.

CASSCF/CASPT2 and related methods: Good in case of static correlation (**e.g. transition metals with complex electronic structure**). Dynamic electron correlation included to some extent in CASPT2.

Accurate Energies For Large Systems

1. CCSD(T)
2. DLPNO-CCSD(T)

Gold Standard CCSD(T)

- CCSD(T) gives results that are better than chemical accuracy (1 kcal/mol for relative energies)

- Tremendous computational cost. Only few atoms and few hundreds basis functions.

Explosive cost
Wall clock time $\propto O(N^7)$

C. Riplinger, P. Pinski, U. Becker, E. F. Valeev, and F. Neese J. Chem. Phys. 144, 024109, **2016**
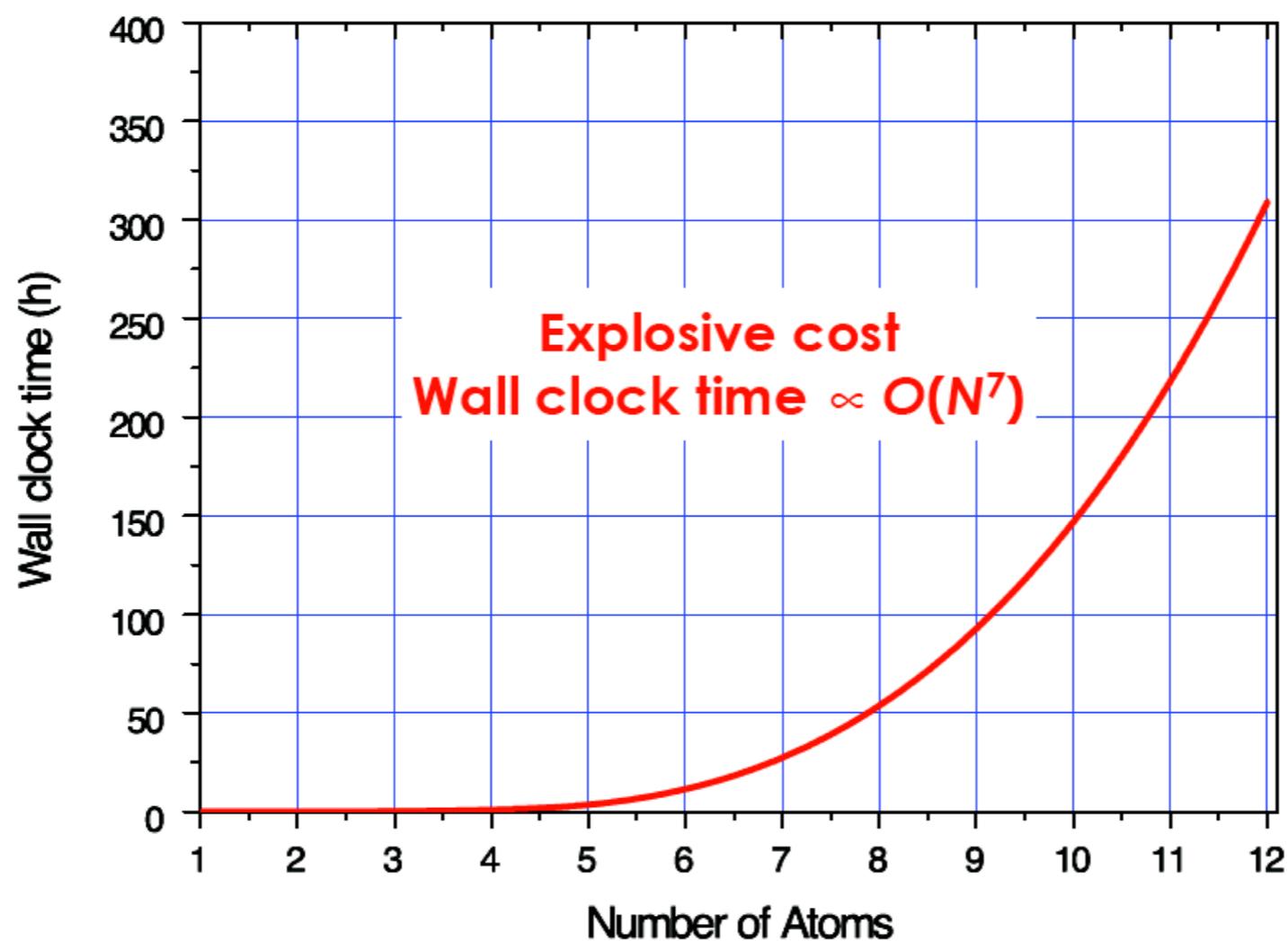
What about DLPNO-CCSD(T)?
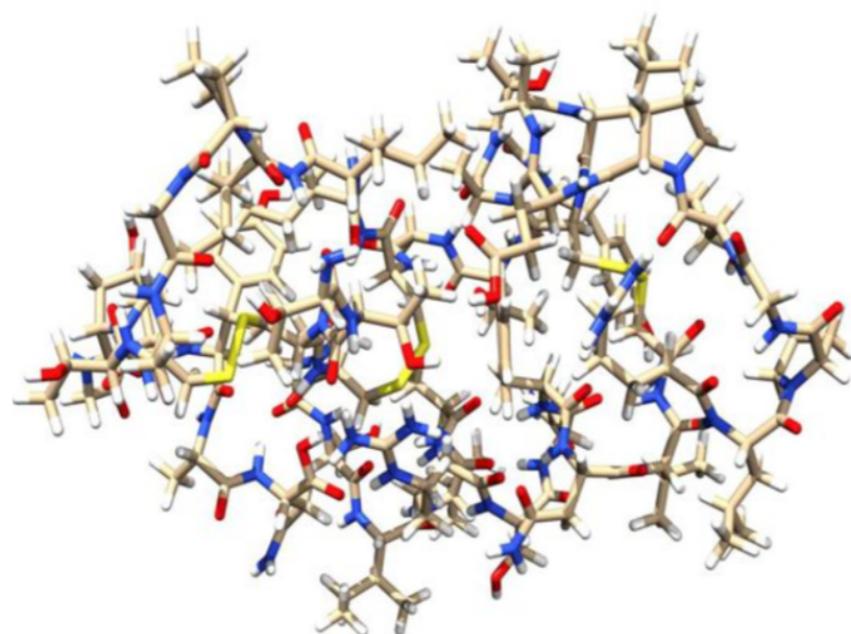
	Crambin
Atoms	644
Basis set	def2-TZVP
Basis functions	12075
DLPNO version	(2015)
Computing time	2 weeks (4 CPUs)
Disk space	1.6 TB

- Controllable accuracy

- Routinely applicable to systems with a few hundred atoms on common lab clusters.

- Single point energies, electron densities

4

C. Riplinger, P. Pinski, U. Becker, E. F. Valeev, and F. Neese J. Chem. Phys. 144, 024109, **2016**

Fundamentals of DLPNO-CCSD(T)

$$E_c = \sum_{i \geq j} \varepsilon_{ij}$$
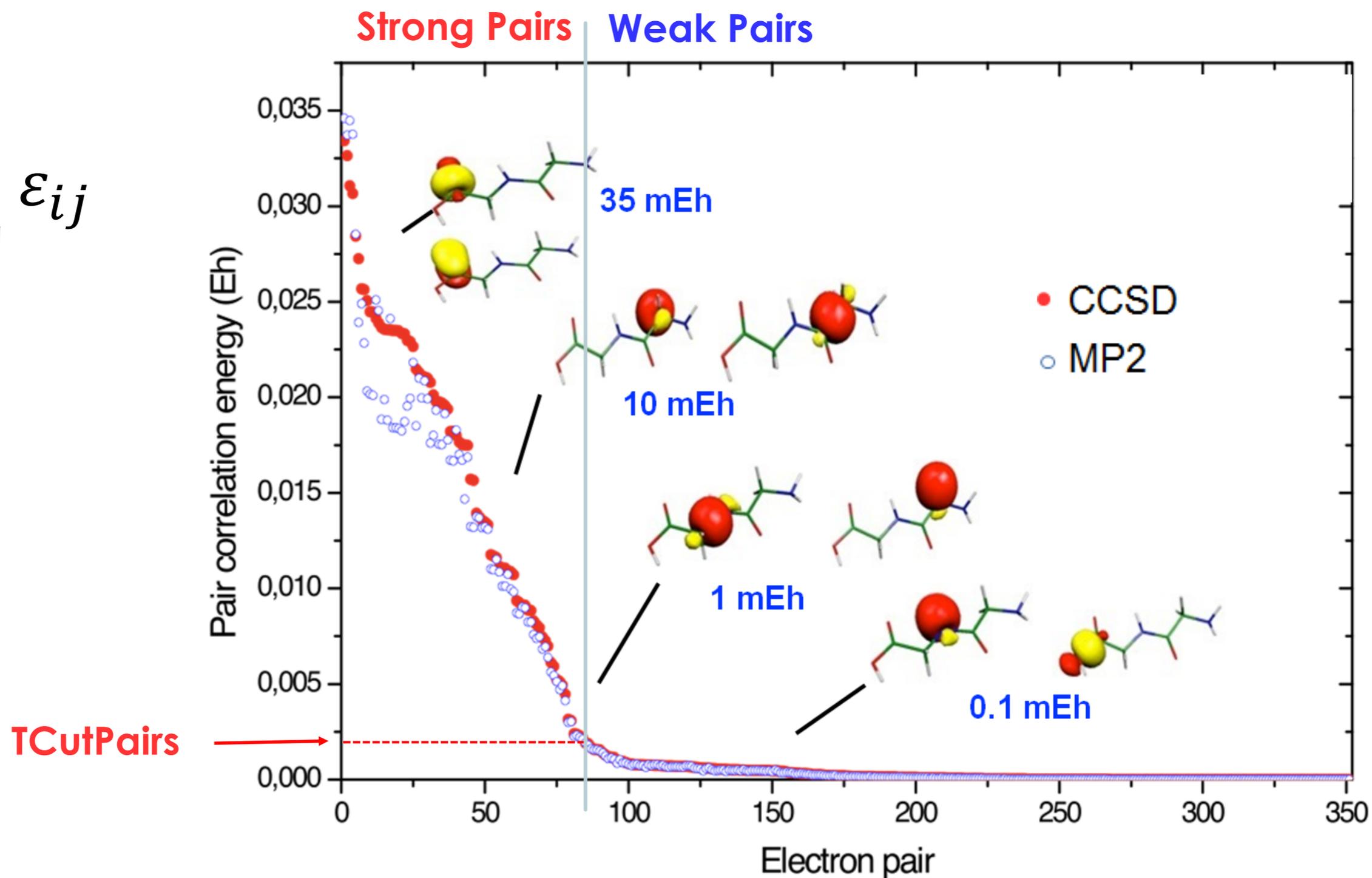
Fundamentals of DLPNO-CCSD(T)

PAOs (Projected Atomic Orbitals)→ ij pair domains → PNOs

$$\varepsilon_{ij} = \sum_{a,b} (ia \mid jb)\tau_{ab}^{ij}$$

$$\mathbf{D}^{ij}\mathbf{d}^{ij} = n^{ij}\mathbf{d}^{ij} \longrightarrow \text{PNOs}$$
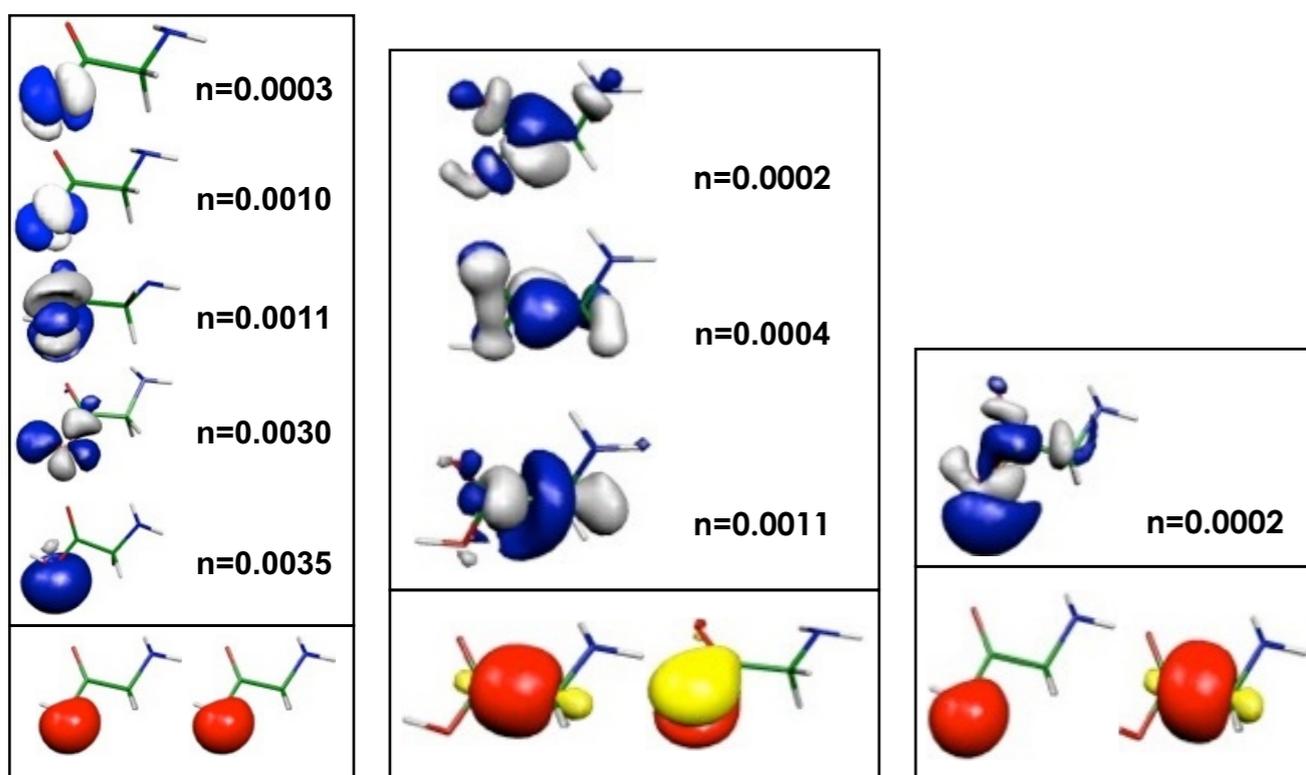
Diagonalization of the pair-density yields the PNOs and the corresponding occupations.

Small number of significant PNOs per electron pair.

Located in the same region of space as the internal pair but as delocalized as necessary.

Only PNOs with n_{ij} > **TCutPNO** are kept

F. Neese, F. Wennmohs, A. Hansen, J. Chem. Phys. **2009**, 130, 114108

DLPNO-CCSD(T) features and keywords

Key Features

- DLPNO-CCSD(T) energies and densities

- UHF-DLPNO-CCSD(T) energies and densities

- Multi-level Implementation

Important Keywords

- PNO settings: **TightPNO**, **NormalPNO**

- Iterative algorithm for triples: **DLPNO-CCSD(T1)**

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```
! dlpno-ccsd(t) cc-pvdz cc-pvdz/c verytightscf TightPNO

*xyz 1 1
C      0.1872   0.0821   0.1981
H      1.0712  -0.0022  -0.4600
H     -0.1552   1.1217   0.0432
O     -1.4750  -1.2935   2.2981
H     -0.8778  -0.9854   1.5898
H     -1.2239  -2.2052   2.4701
Na     2.224   -3.2213   3.1112
*
```

1

Multi-Level Implementation

- Idea: Region of interest (high accuracy) surrounded by assisting regions (lower accuracy required)

- Technical Realization:
  - Define fragments
  - Assign orbitals / electron pairs to fragments
  - Compute intra- and interfragment interactions on different levels of accuracy
    - DLPNO-CCSD(T) (TightPNO, NormalPNO, LoosePNO)
    - DLPNO-CCSD (open-shell n/a)
    - MP2 (open-shell n/a)
    - HF (open-shell n/a)
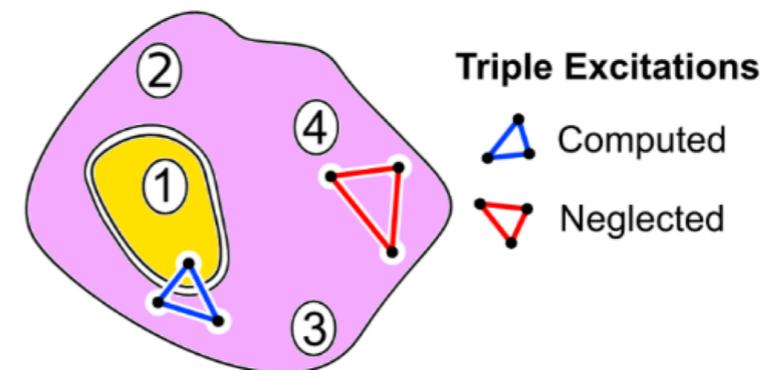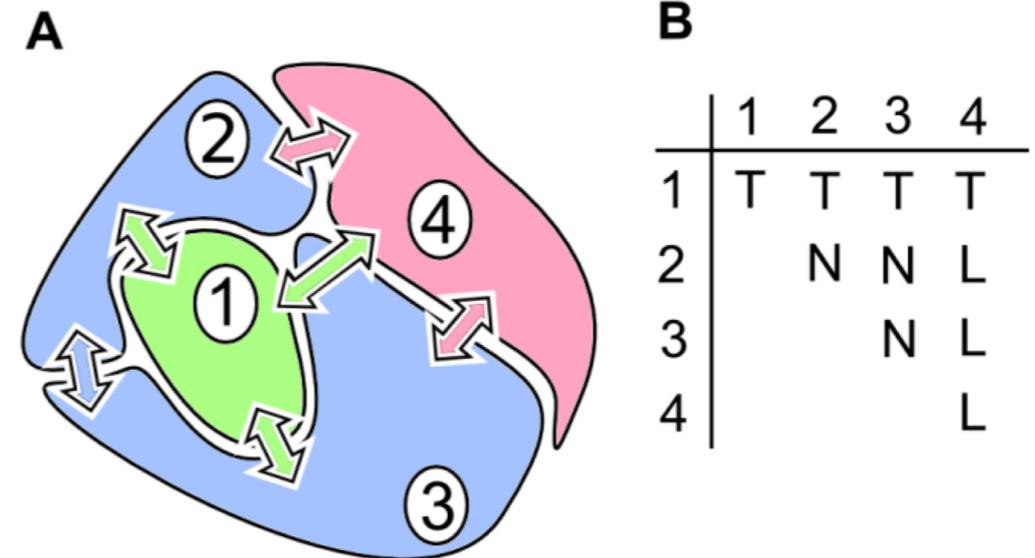
Example: Ellipticine Binding to DNA
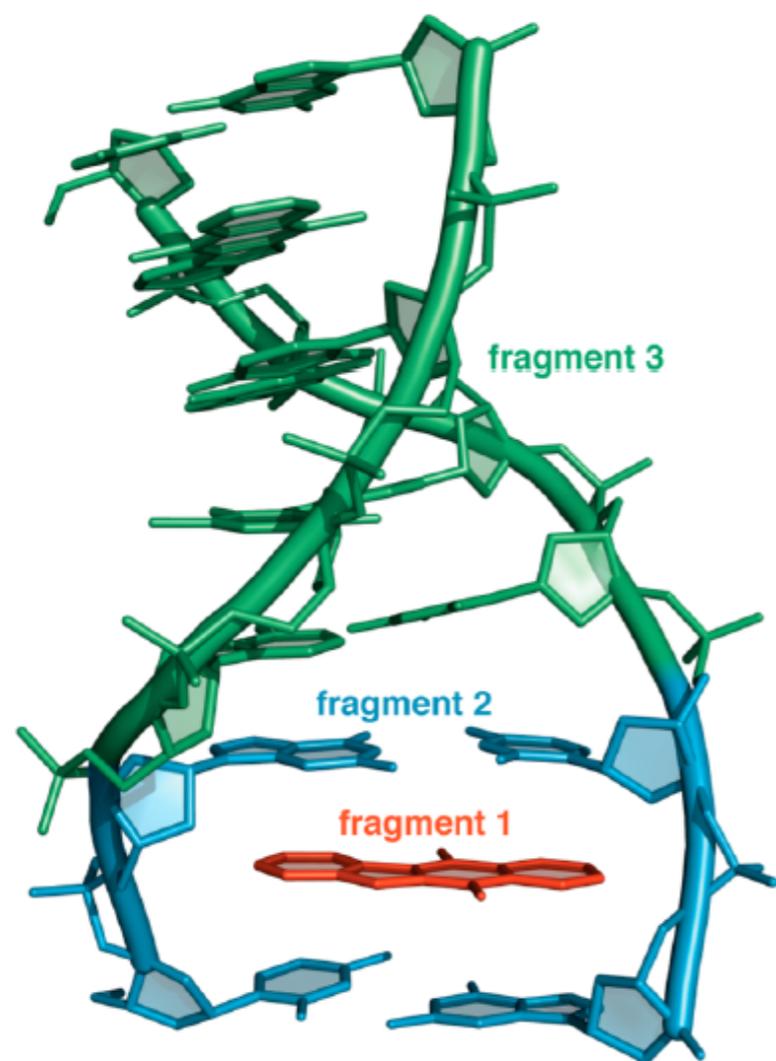
443 atoms

	ΔE [kcal/mol]
All TightPNO	-37.9
Mixed TightPNO - HF	-36.9

Mixed TightPNO - HF

	1	2	3
1	T	T	HF
2		T	HF
3			HF

M. Sparta et. al JCTC, 13, 1398 (**2017**)

Understanding

1. Qualitative Models
2. Quantitative Models

How to interpret theoretical results?

✓The primary goal of computational chemistry is to provide understanding, chemical insights, falsifiable predictions.

✓To Improve the activity or selectivity or new catalysts, one needs to understand chemical reactions at a deeper level.

✓Chemical reactivity is intimately connected with electronic structure, especially in Transition Metal Chemistry.

Neese, F.; Atanasov, M.; Bistoni, G.; Maganas, D.; Ye, S. *J. Am. Chem. Soc.* **2019**, *141*, 2814–2824.

Qualitative Models:
Population analyses/ Molecular Orbitals
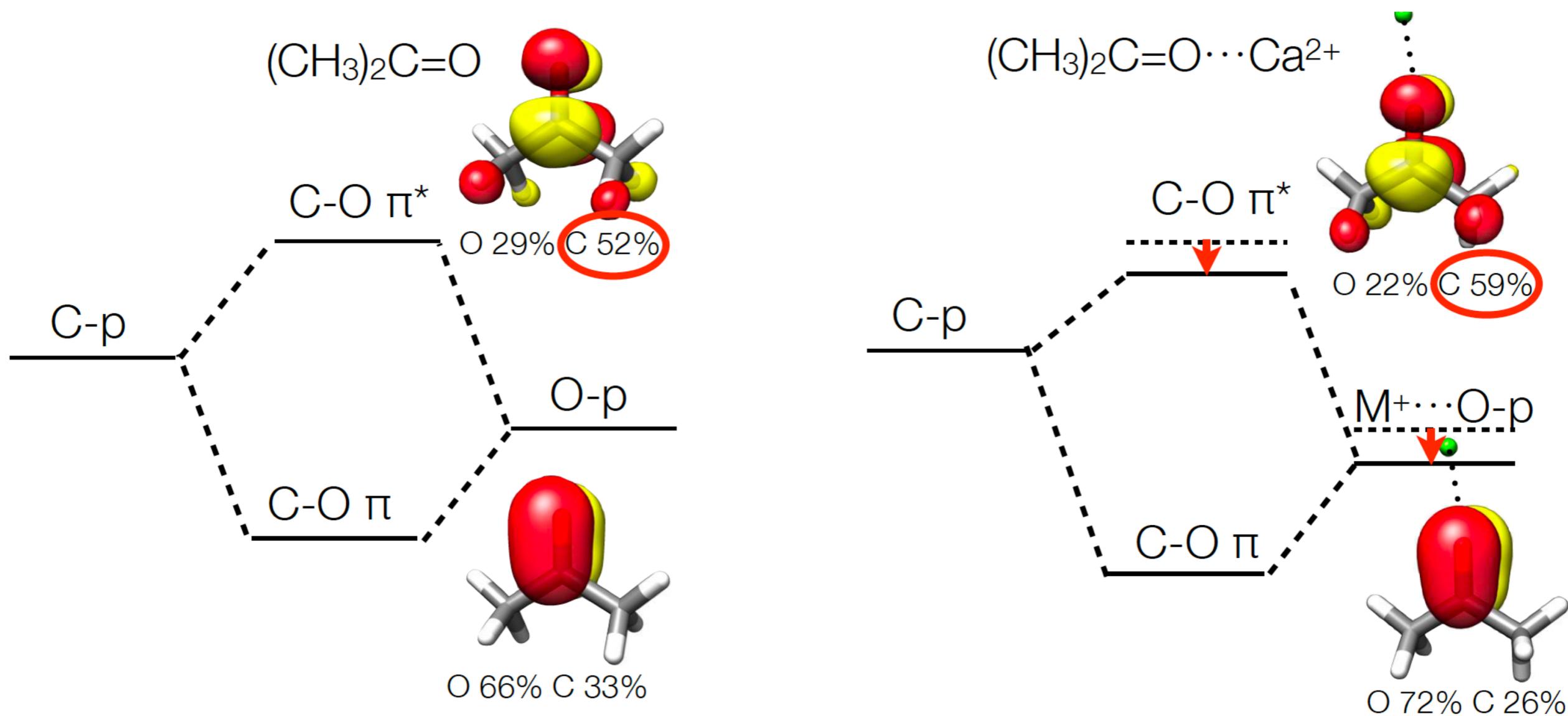
Local Energy Decomposition

User-defined fragments

Step 1. Localize the occupied orbitals ands assign them to fragments

Step 2. Localize the virtual (PNOs) and assign them to fragments

Step 3. Express the total DLPNO-CCSD(T) energy into **fragment-pairwise** contributions

Step 4. Further decomposition: additional physical insights

F1   F2   F1   F2
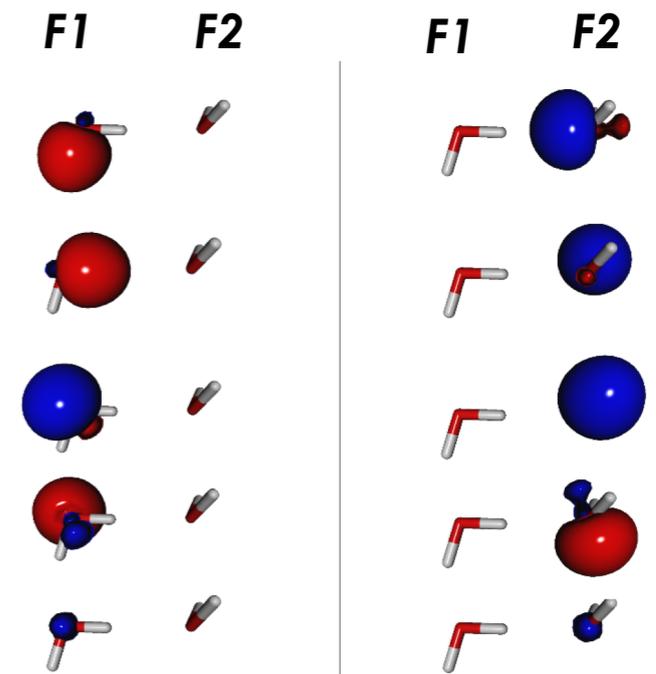
Illustrative Applications

Protein-Ligand Interactions
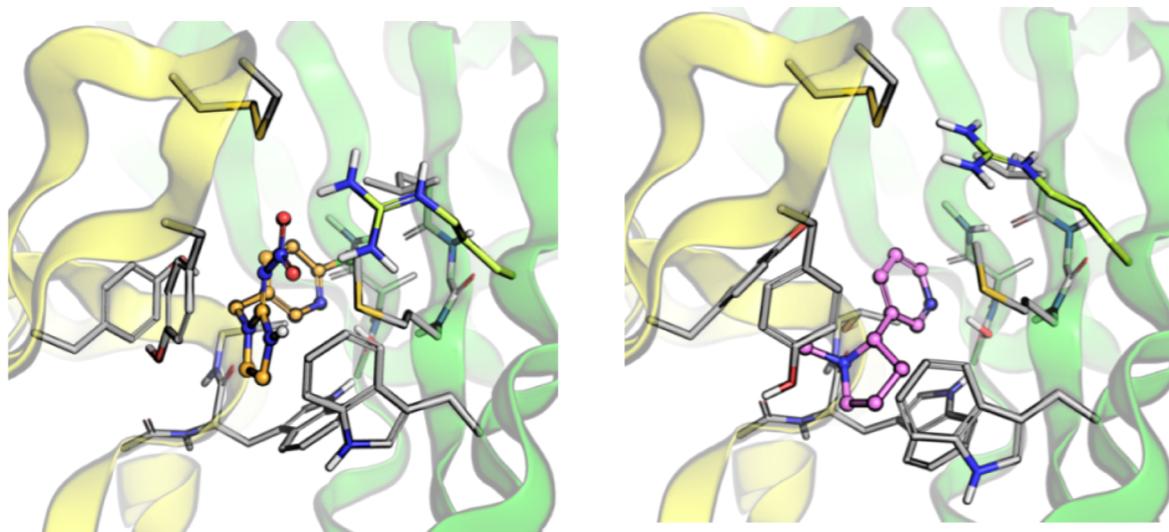
Transition Metal-Ligand Bonds
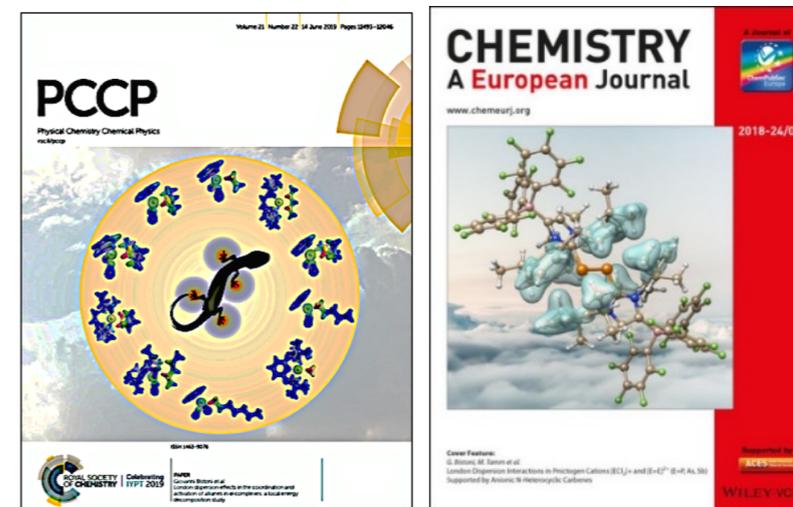
Angew. Chem. Int Ed. 57 , **2018**, *4760*
Phys. Chem. Chem. Phys., **2019**, *21, 11569*
Chem. Eur. J. **2018**, *24, 18922.*

Relative spin state energy stabilization
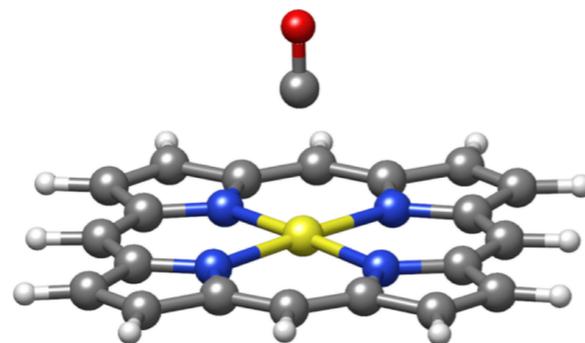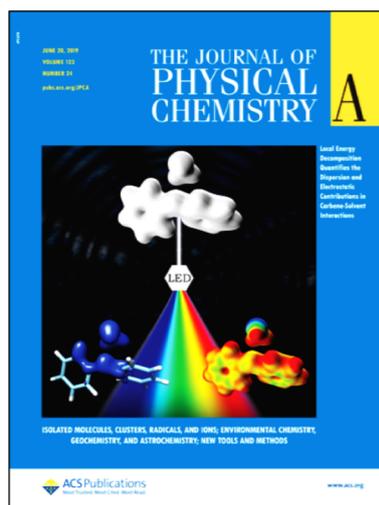
J. Phys. Chem. A, **2019**, *123, 24, 5081*
J. Chem. Theory Comput. **2019**, *15, 3, 1616*

NCIs in Catalysis
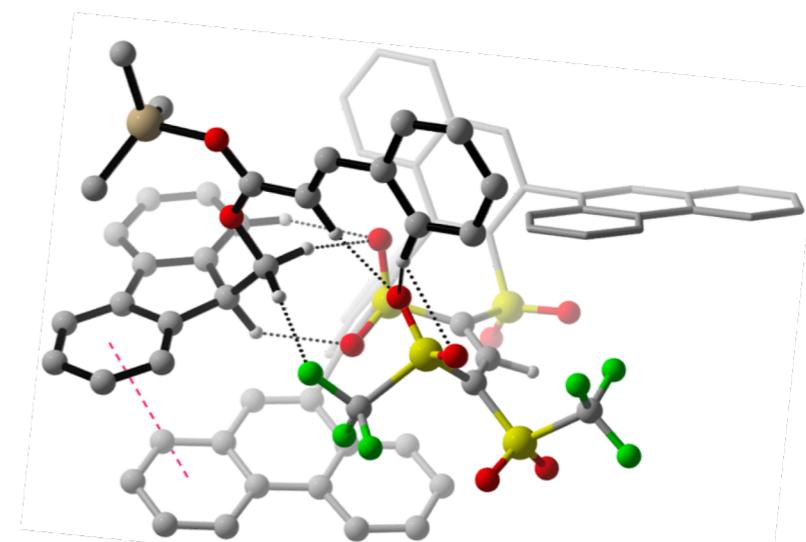
J. Am. Chem. Soc. **2018**, *140, 40, 12671*
J. Am. Chem. Soc. **2020**, *ASAP*

LED input

```
! dlpno-ccsd(t) cc-pvdz cc-pvdz/c cc-pvtz/jk rijk verytightscf TightPNO LED
*xyz 1 1
C(1)  0.1872  0.0821  0.1981
H(1)  1.0712 -0.0022 -0.4600
H(1) -0.1552  1.1217  0.0432
O(2) -1.4750 -1.2935  2.2981
H(2) -0.8778 -0.9854  1.5898
H(2) -1.2239 -2.2052  2.4701
Na(3) 2.224  -3.2213  3.1112
*
```

LED output

```
-------------------------------------------------
FINAL SUMMARY DLPNO-CCSD ENERGY DECOMPOSITION (Eh)
-------------------------------------------------

Intrafragment REF. energy:
Intra fragment 1 (REF.)                -38.842912491
Intra fragment 2 (REF.)                -76.006485450

Interaction of fragments 2 and 1:
Electrostatics (REF.)                   -0.054001249
Exchange (REF.)                         -0.009821569
Dispersion (strong pairs)               -0.001474706
Dispersion (weak pairs)                 -0.000015199

Sum of non dispersive correlation terms:
Non dispersion (strong pairs)           -0.349025658
Non dispersion (weak pairs)             -0.000003704
```

LED features

- Decomposition of DLPNO-CCSD(T)

- Decomposition of UHF-DLPNO-CCSD(T)

- Arbitrary number of fragments

- Automatic (or mix automatic/hybrid) fragmentation scheme

- DID plot: visualization of dispersion energy

- HFLD

ORCA

version **4.2.0**

Examples

A case study:
Organocatalytic Diels Alder reactions
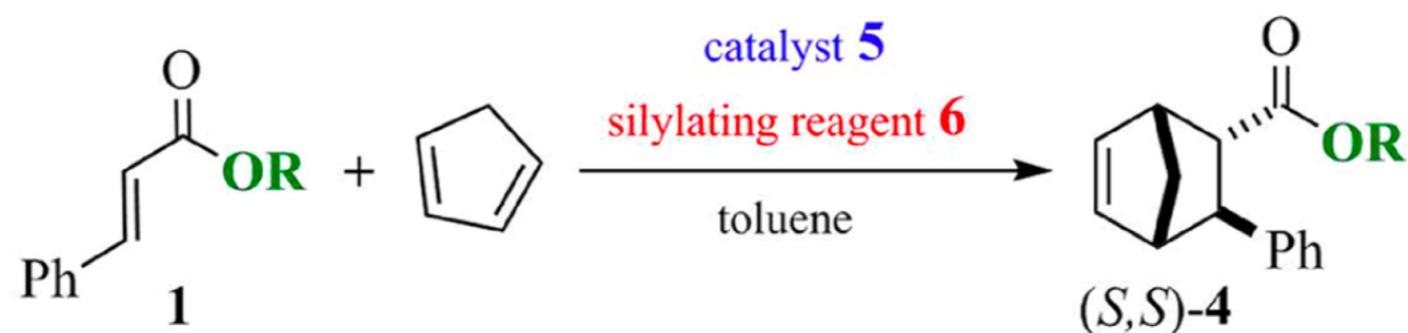
RB: (-40°C) 24h, 92%, d.r. 26:1 (endo/exo) e.r. 97:3 (endo)

1b R = Me   5b (S,S)-IDPi   6b
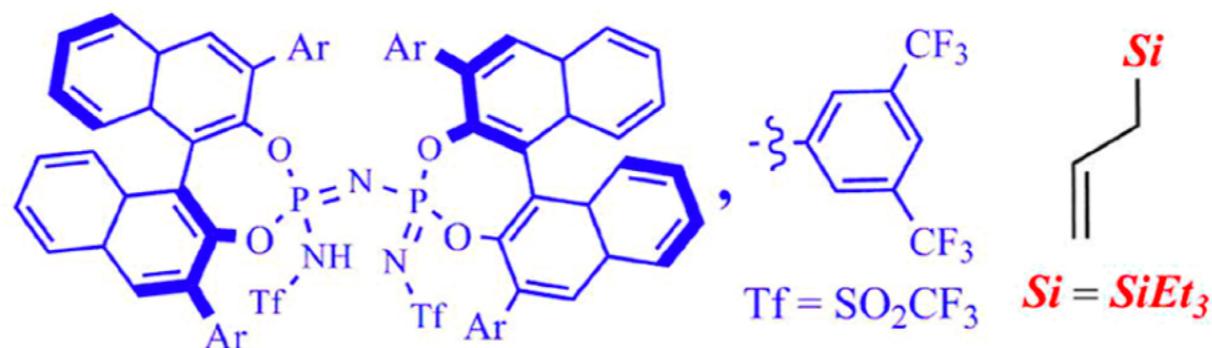
A case study:
Organocatalytic Diels Alder reactions

D. Yepes, F. Neese, B. List, G. Bistoni, S. J. Am. Chem. Soc. **2020**, *in press*
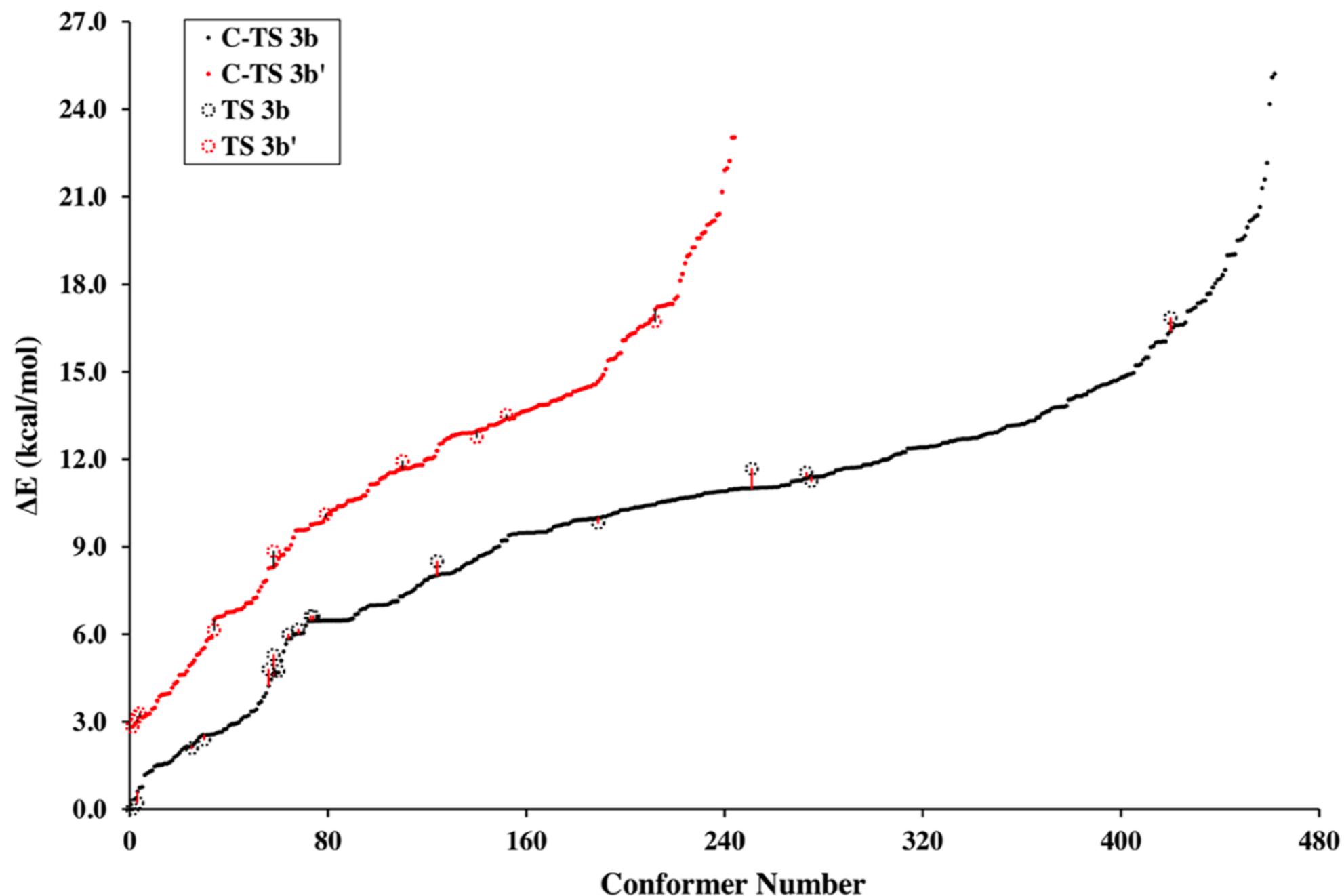
A case study:
Organocatalytic Diels Alder reactions
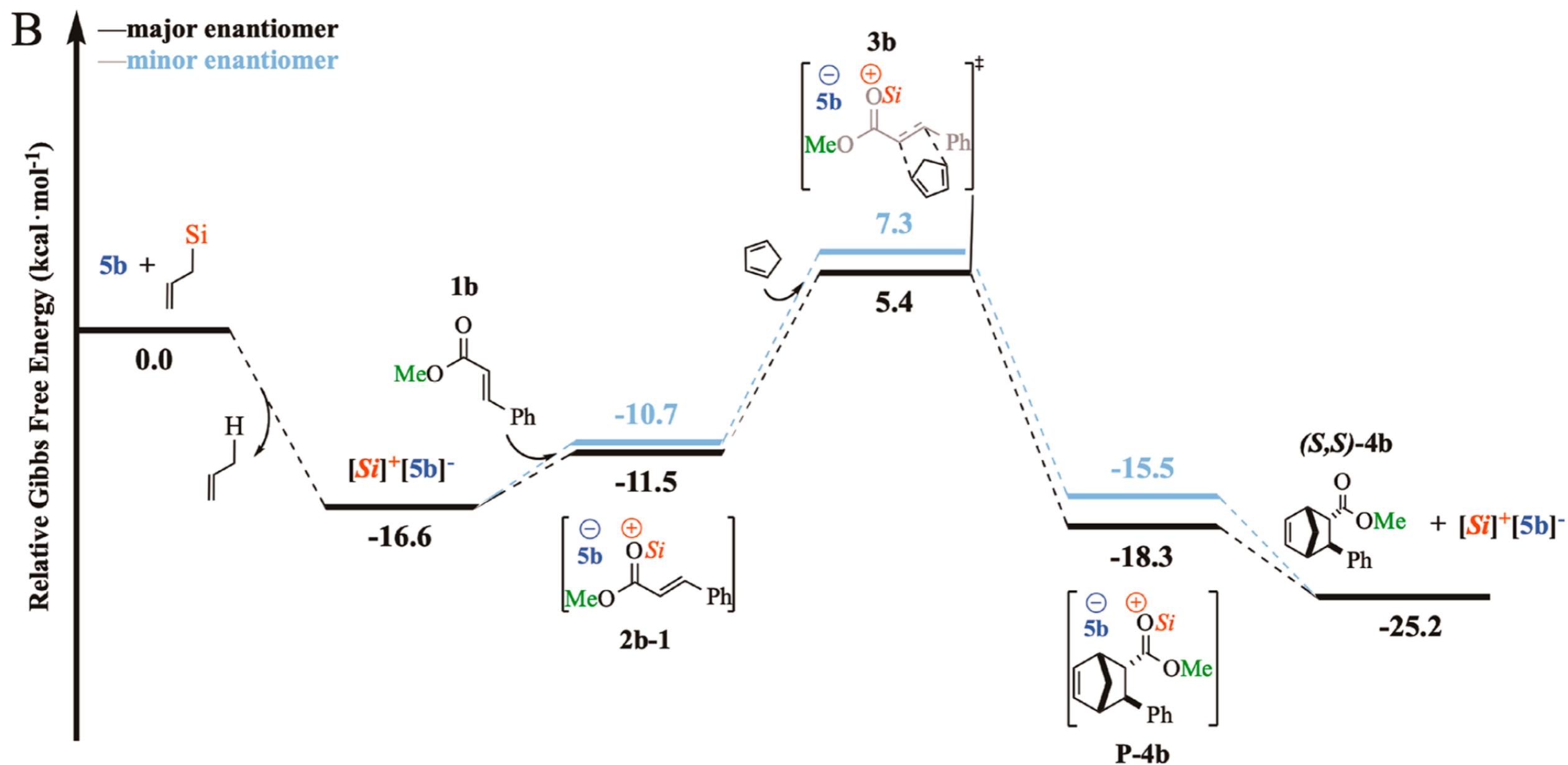
Figure 2. Proposed reaction mechanisms for **RA** (top) and **RB** (bottom) at the DLPNO-CCSD(T) + B3LYP(C-PCM) level.

D. Yepes, F. Neese, B. List, G. Bistoni, S. J. Am. Chem. Soc. **2020**, *in press*

A case study: Organocatalytic Diels Alder reactions

- Why is **3a** more stable than **3a'**? Difficult to answer. **Too many contacts/interactions!**

- LED can be used to decompose activation barriers into **geometric preparation** and **interaction** between Cp and diepnohile.

3a

3a'
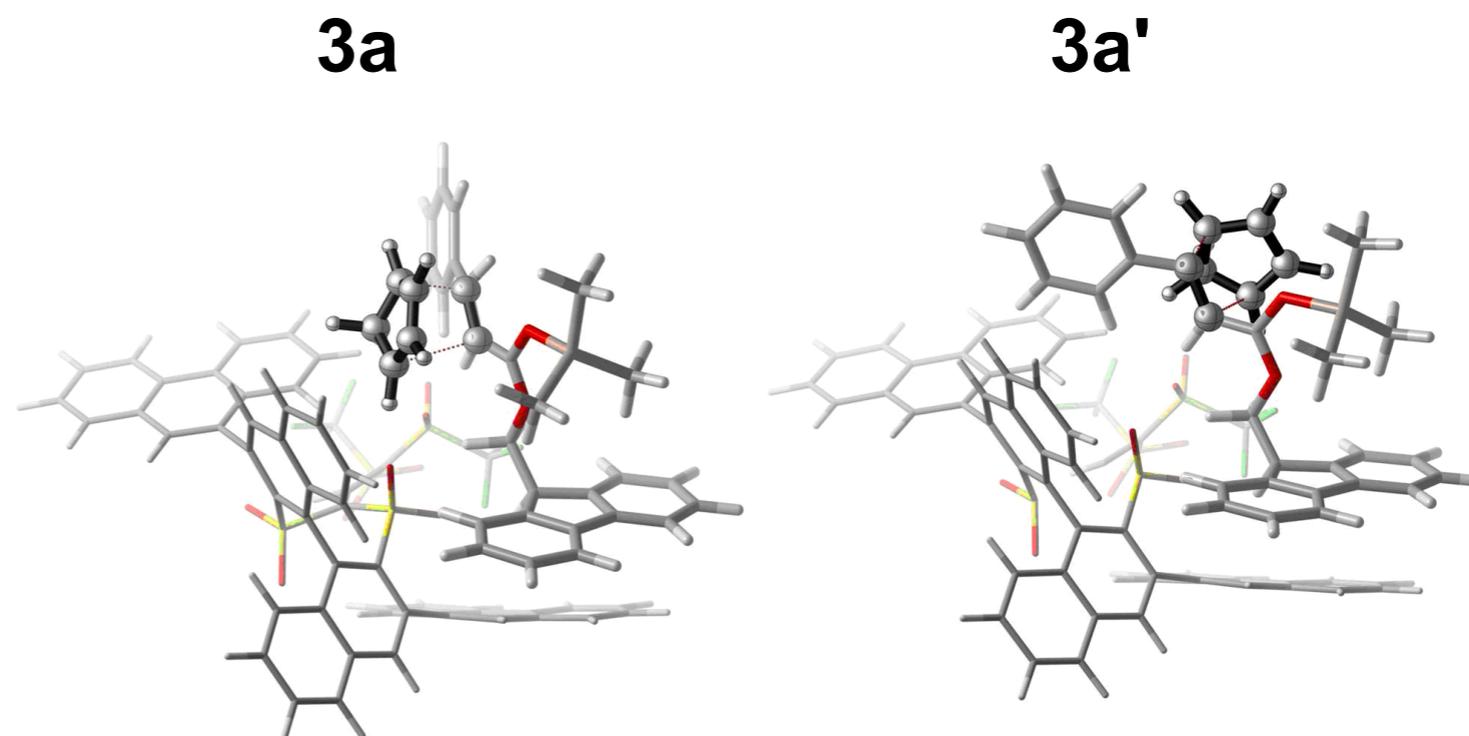
	RA		
	3a	**3a'**	**3a' − 3a**
$\Delta G^{\ddagger b,c}$	16.7	19.3	2.6 (exp 1.1^d)
$\Delta E^{\ddagger}$	−3.4	0.0	3.4
$\Delta E^{\ddagger}_{geo\text{-}prep}$	27.3	28.4	1.1
$\Delta E^{\ddagger}_{int}$	−30.7	−28.4	2.3
$\Delta E^{\ddagger}_{disp}$	−34.7	−29.6	5.1
$\Delta E^{\ddagger}_{no\text{-}disp}$	4.0	1.2	−2.8

D. Yepes, F. Neese, B. List, G. Bistoni, S. J. Am. Chem. Soc. **2020**, *in press*

From accurate numbers to chemical insights

D. Yepes, F. Neese, B. List, G. Bistoni, S. J. Am. Chem. Soc. **2020**, *in press*