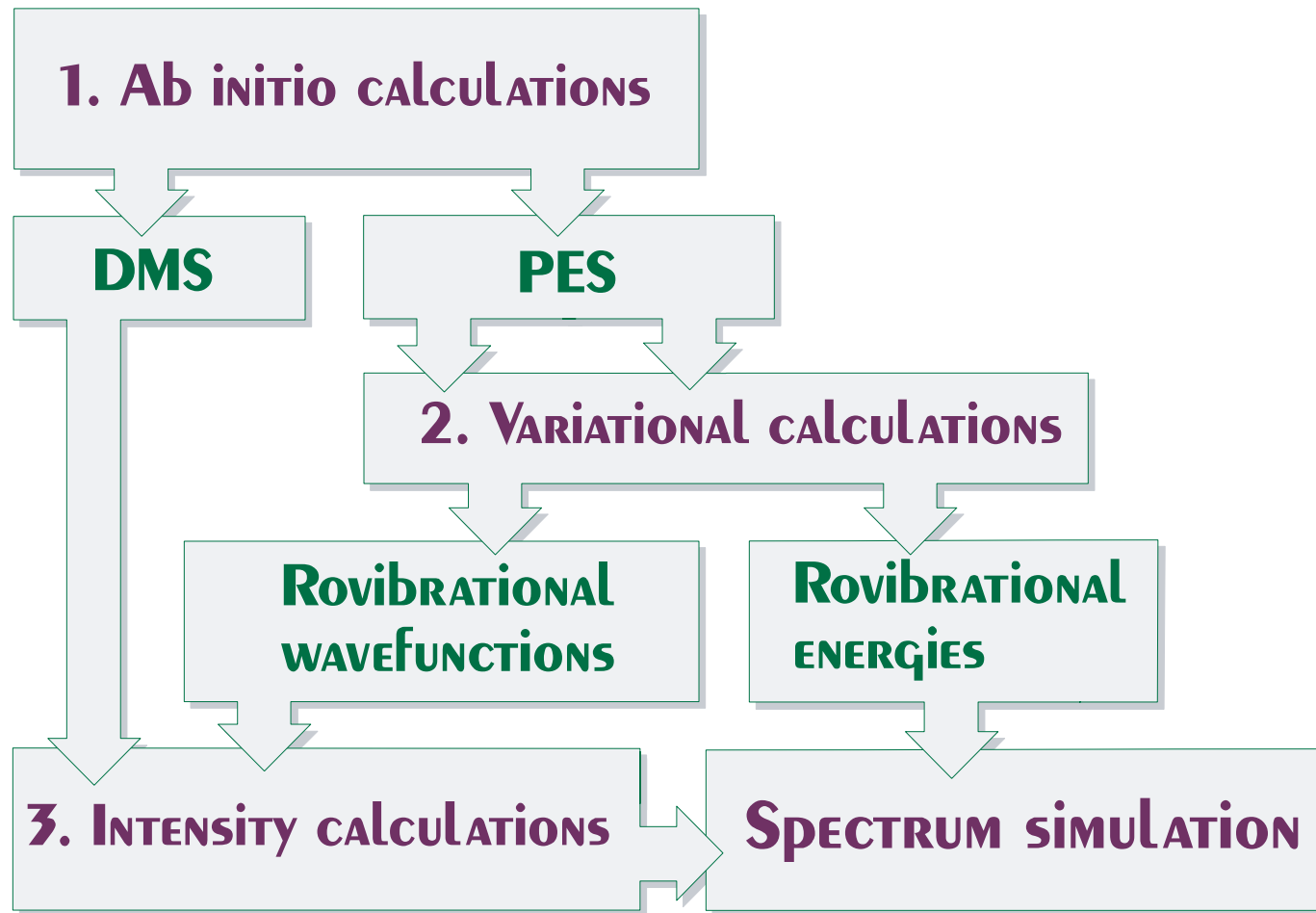




1. **Ab initio methods**
2. **Density functional methods**
3. **Semiempirical methods**
4. **Combined QM/MM methods**

Typical applications in our group:

1. **Small reactive molecules, spectroscopy**
2. **Transition metal compounds, catalysis**
3. **Electronically excited states, dynamics**
4. **Enzymes, biocatalysis**





Decisive factor: Quality of potential energy surface (PES)

Empirical finding:

- Variational calculations on CCSD(T)/CBS(fc) PES give wavenumbers (e.g., up to 6000 cm^{-1}) for all kinds of transitions typically to within 5 cm^{-1} .
- What is needed to get higher accuracy ?

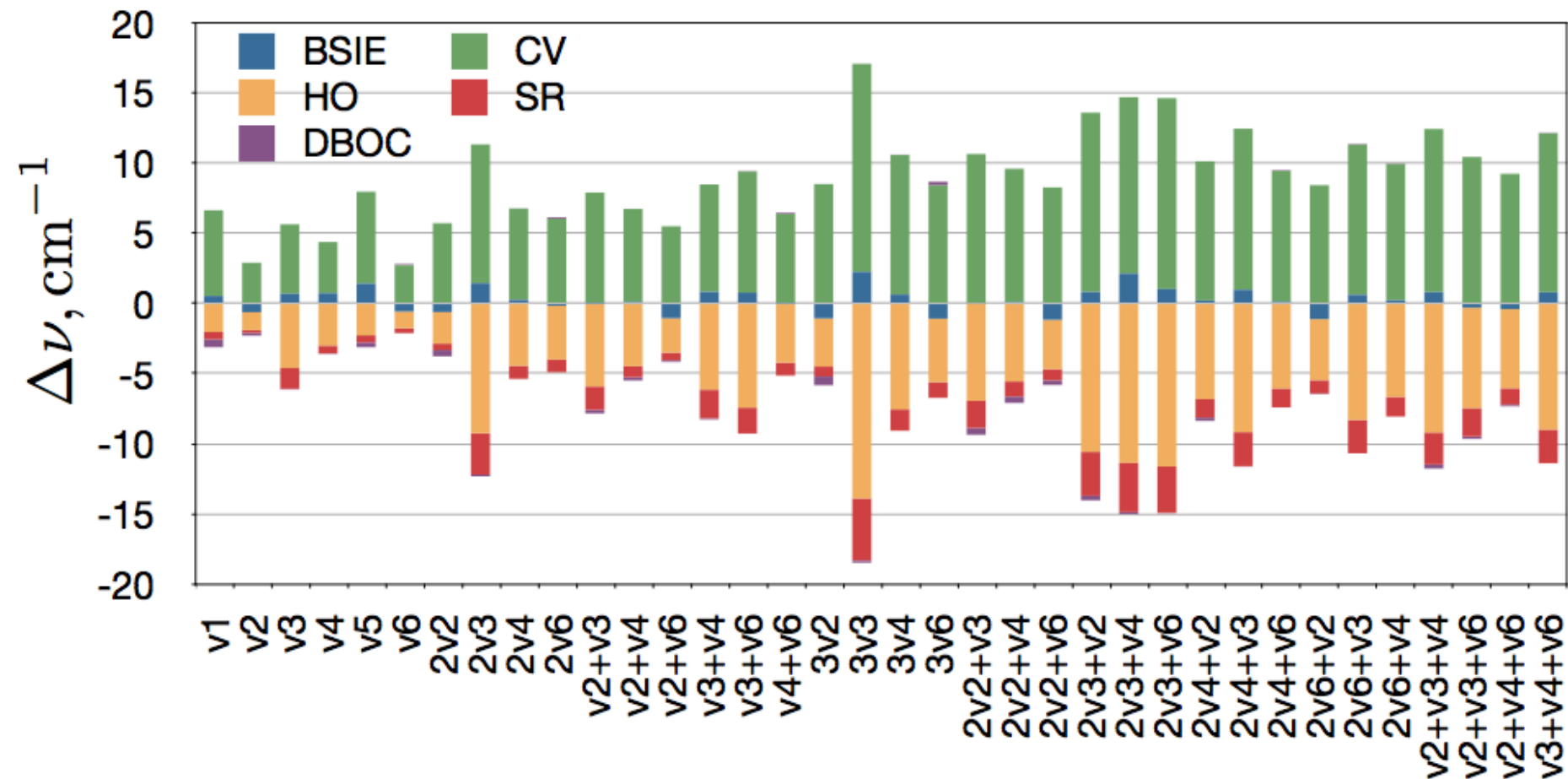
Systematic ab initio approach:

Start from CCSD(T)/CBS(fc) PES and add high-level (HL) corrections for

- high-order (HO) coupled cluster terms (typically up to CCSDTQP),
- core-valence (CV) correlation,
- scalar relativistic (SR) effects (typically from DKH2 or MVD1 calculations),
- diagonal Born-Oppenheimer contributions (DBOC),
- and possibly also other small terms (SO, QED).

Converge every single correction term in such an additive scheme.

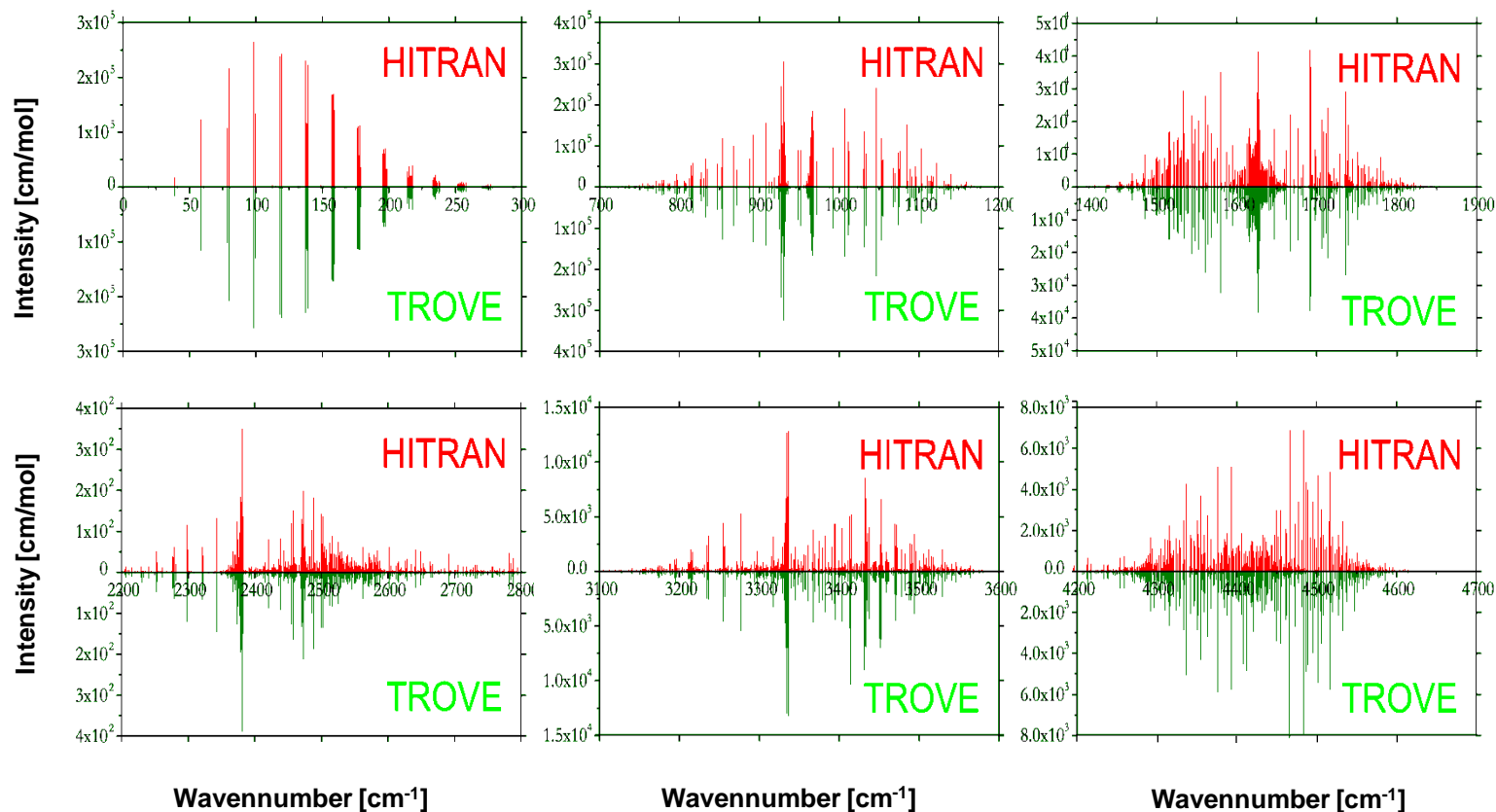
H₂CS: Compensation of high-level-terms



NH₃: rovibrational bands at T=300 K

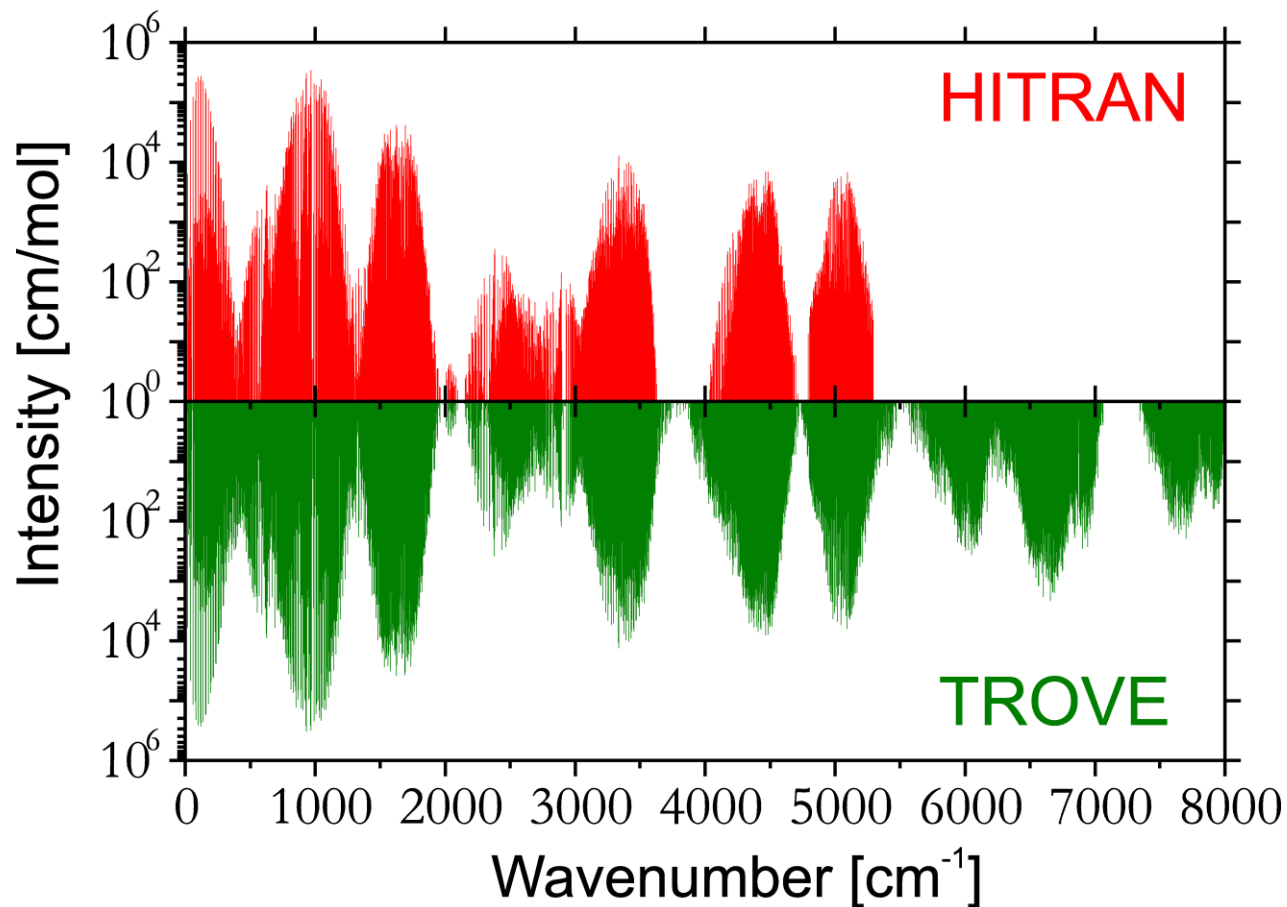


- 3.25 million transitions computed, comparison with HITRAN data base

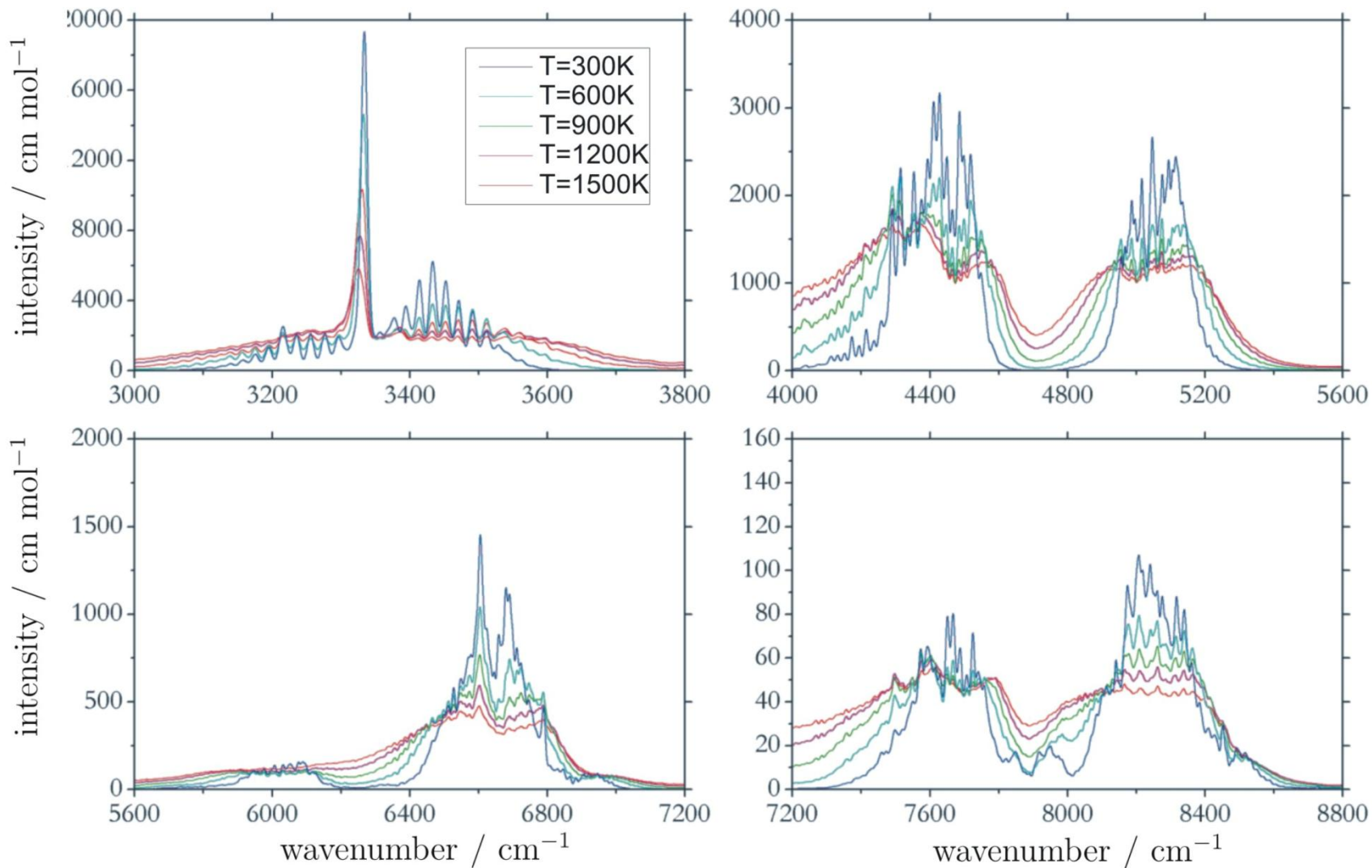




- 3.25 million transitions computed, comparison with HITRAN data base



Astrophysics: Hot NH₃ line lists





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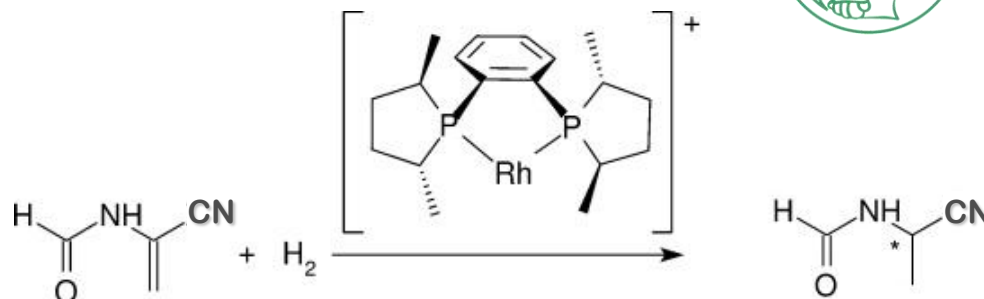
LPNO-CCSD: Rh-catalyzed asymmetric hydrogenation



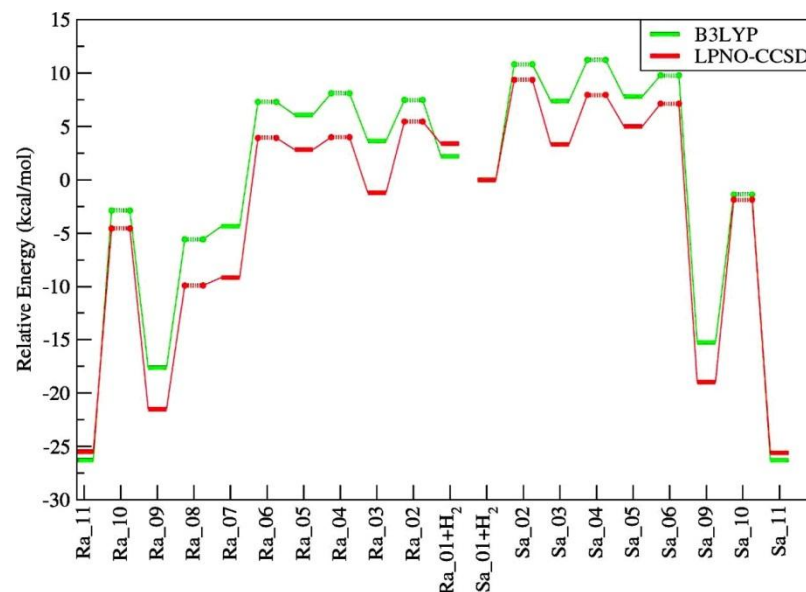
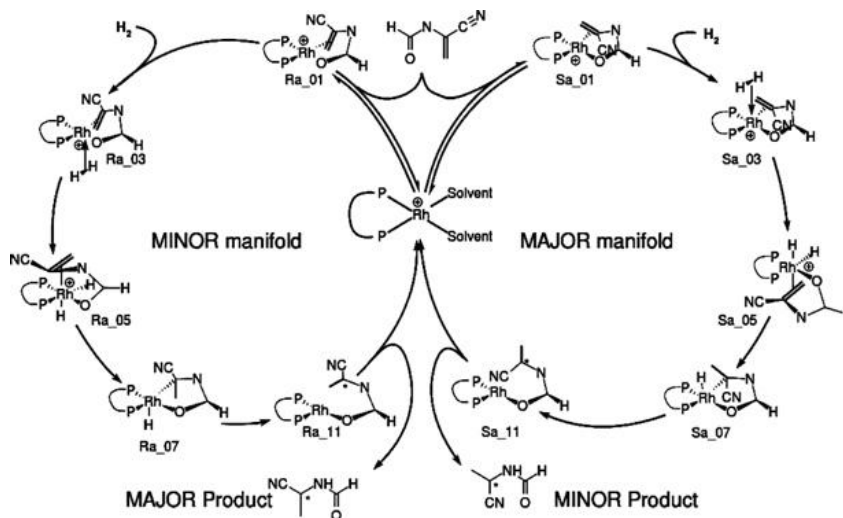
Substrate: α -formamidoacrylonitrile

Catalyst: [(*R,R*)-MeDuPHOS]⁺

System size: **62 atoms**



This reaction has been studied before at lower levels [1]. The full catalytic cycles (left) were recomputed using DFT(B3LYP) followed by single-point LPNO-CCSD calculations [2]. The resulting energy profiles (right) match quite well. The proposed origin of enantioselectivity [1] was confirmed.



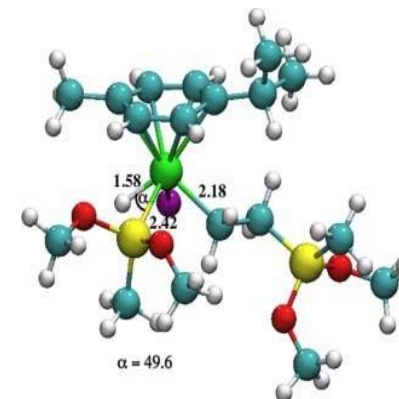
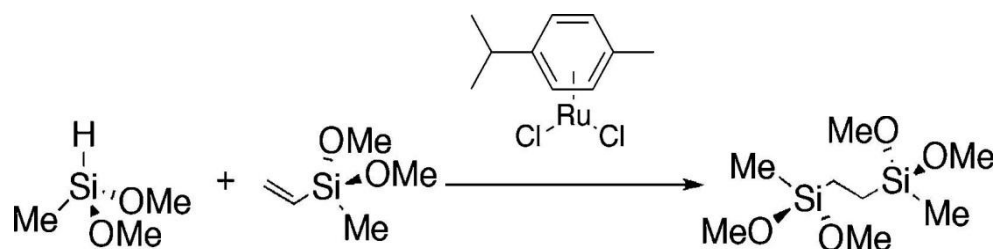
[1] S. Feldgus and C. S. Landis, J. Am. Chem. Soc. **122**, 12714 (2000).

[2] A. Anoop, W. Thiel, and F. Neese, J. Chem. Theory Comput. **6**, 3137 (2010).



Recently published DFT studies address

- the mechanism of asymmetric Rh-catalyzed **olefin hydrogenation** (Reetz)
- the electronic structure in **gold alkyne complexes** (Fürstner)
- acceptor and donor properties of **N-heterocyclic carbenes** (Fürstner)
- **carbon(0)** coordination compounds and their gold complexes (Fürstner)
- electron-rich **imines with an N(I) center** and two lone pairs (Alcarazo)
- the electronic structure in **iron-corrole complexes**
- the mechanism of Ru-catalyzed **olefin hydrosilylation**

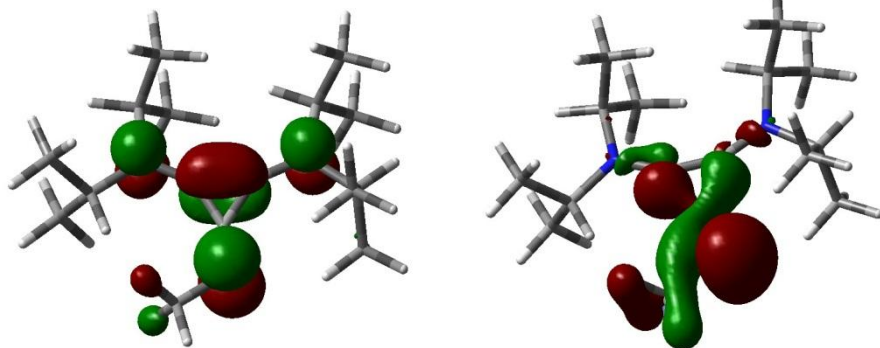


Chalk-Harrod intermediate

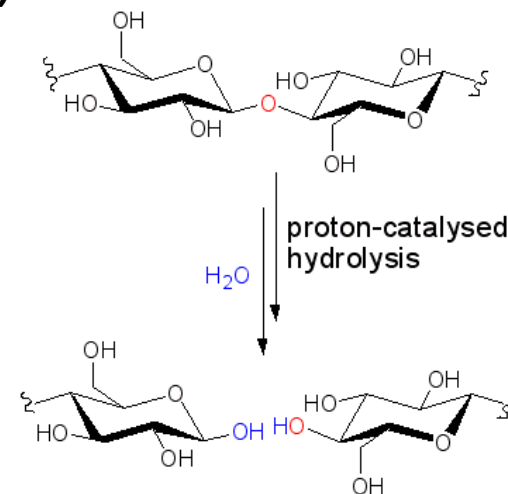


Ongoing DFT studies address

- the reaction mechanism in **Baeyer-Villiger cyclohexanone monooxygenase** (Reetz)
- the mechanism of Fe-catalyzed **cross coupling** reactions (Fürstner)
- the bonding in **carbeneimines** with an N(I) center (Alcarazo)
- the properties and reactivity of compounds with **frustrated Lewis pairs** (Alcarazo)
- the transition state in the organocatalytic **electrocyclization** of phenylhydrazone (List)
- the mechanism and stereoselectivity of Pd-catalyzed **allylic alkylation** (Maulide)
- the mechanism of **ylide transfer** reactions of sulfur reagents (Maulide)
- the mechanism of the conversion of **glucose** to 5-hydroxymethylfurfural (Schüth)
- the depolymerization reactions of **cellulose** (Rinaldi)



Molecular orbitals of N(I) compound:
HOMO(left) and HOMO-1 (right)



Depolymerization of cellulose



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Objective:

Efficient and realistic quantum-chemical treatment of large molecules

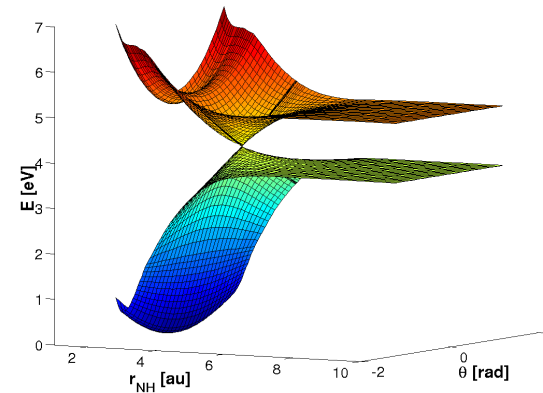
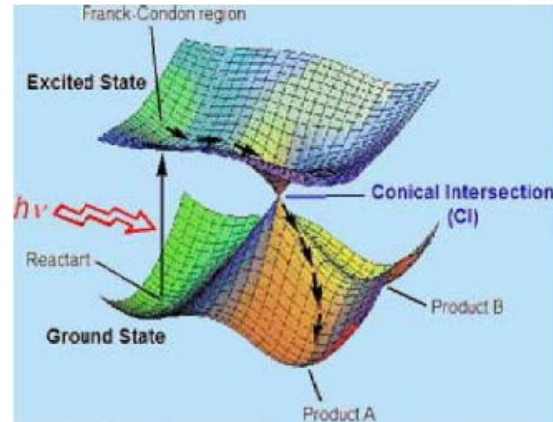
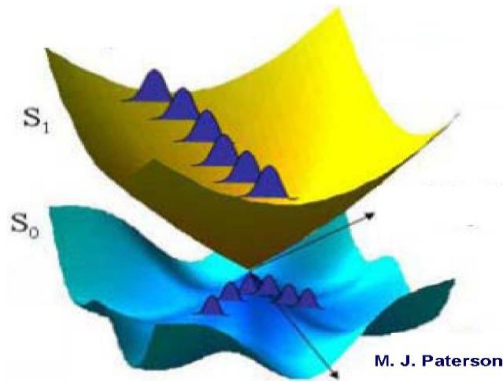
Our favored approach:

NDDO-based methods with orthogonalization corrections (OM1, OM2, OM3)

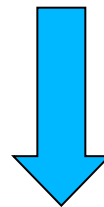
Recent excited-state activities:

- Validation of OMx/MRCI for electronically excited states
- Implementation of excited-state surface-hopping simulations
- Excited-state dynamics at the semiempirical QM and QM/MM level: Adenine, guanine, uracil, thymine, and cytosine in the gas phase; adenine and guanine in aqueous solution; adenine in solvated DNA strands; azobenzenes; retinal models; red fluorescent proteins; fluorene-based molecular motors; photoswitches; modified GFP chromophores.

Non-adiabatic dynamics: Overview



**Born-Oppenheimer approximation
breaks down !!**



**A self-consistent treatment of nuclear
and electronic degrees of freedom
is needed.**

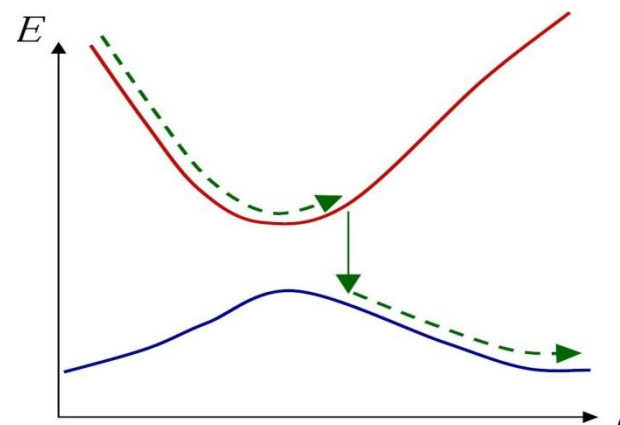


Methodology

A swarm of independent trajectories is considered.

Each trajectory evolves on a single potential energy surface.

Sudden hops between different potential energy surfaces are allowed.



Expansion of the electronic wavefunction

$$\Phi(\mathbf{r}, \mathbf{R}, t) = \sum_i c_i(t) \phi_i(\mathbf{r}, \mathbf{R})$$

Quantum amplitudes determine the time-dependent population of state i at time t

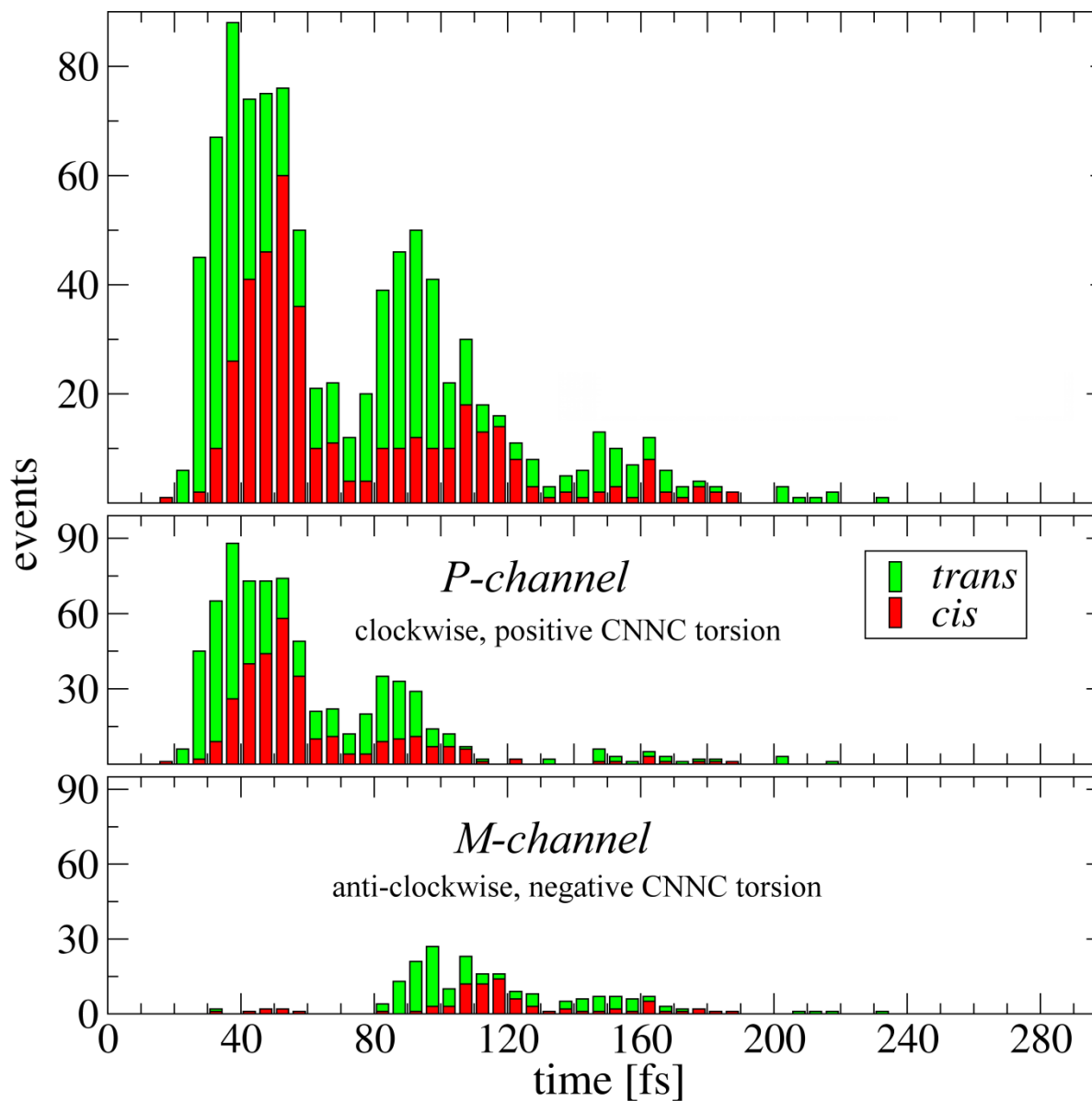
The electronic wavefunction is expanded as a superposition of independent adiabatic states.

Substitution into the time-dependent Schrödinger equation yields a set of coupled equations for the quantum amplitudes.

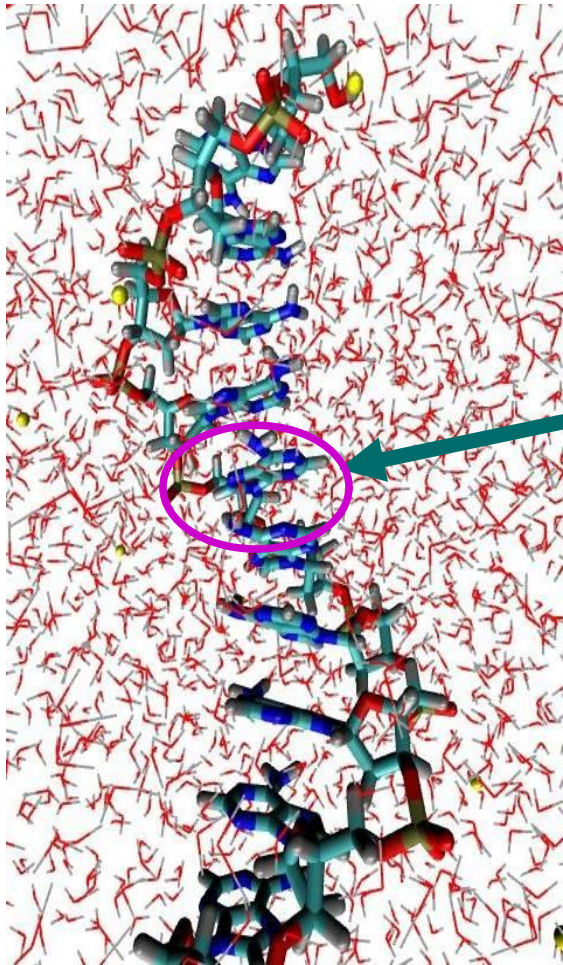
$$i\hbar \frac{dc_j(t)}{dt} = c_j(t)\epsilon_j - i\hbar \sum_i c_i(t) \dot{\mathbf{R}} \cdot \mathbf{d}_{ji}$$

nonadiabatic coupling

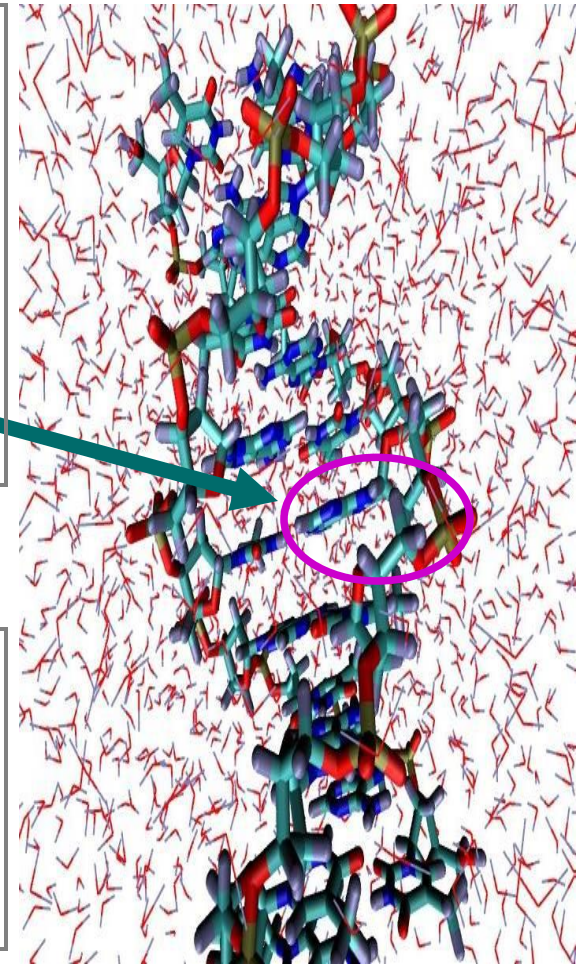
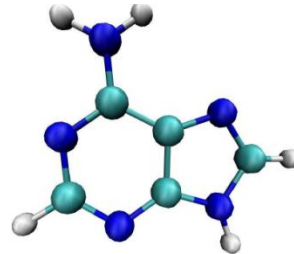
Photoisomerisation of *cis*-azobenzene: Lifetimes



Excited-state dynamics: Adenine in DNA strands



QM part
Single Adenine
OM2/GUGA-MRCI



MM part
All other atoms
CHARMM force-field
TIP3P water model

Decay dynamics of adenine in DNA strands



Adenine in single strand (dA)₁₀

Major decay channel: 6S_1

Out-of-plane NH₂

Secondary decay channel: E₂

Out-of-plane H2
and C2 puckering

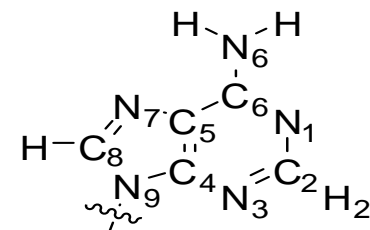
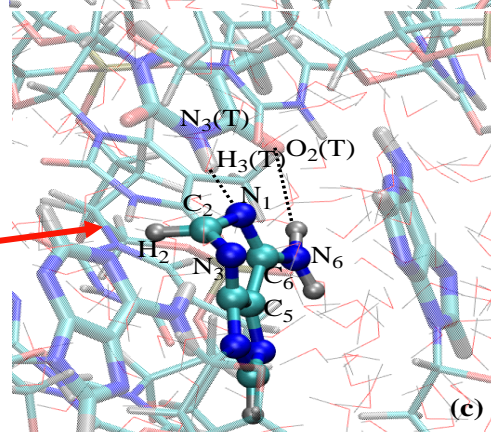
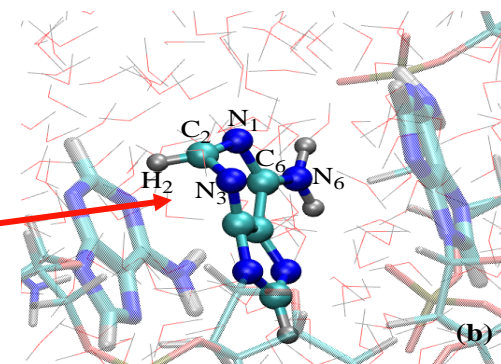
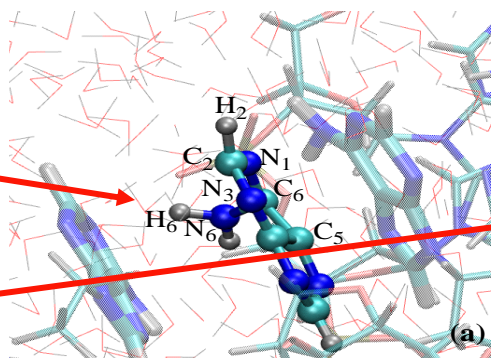
Adenine in double strands

(dA)₁₀(dT)₁₀

Major decay channel: E₂

Out-of-plane H2
and C2 puckering

The 6S_1 channel does not exist.



- For the $S_1 \rightarrow S_0$ decay of adenine in the gas phase, aqueous solution and single DNA strand (dA)₁₀, the major channel is governed by the 6S_1 conical intersection.
- For the $S_1 \rightarrow S_0$ decay of adenine in double DNA strands (dA)₁₀(dT)₁₀, the 6S_1 channel (out-of-plane motion of NH₂) is hindered by the A-T hydrogen bond. The major channel is now the E₂ conical intersection.



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QM/MM approach: General overview



QM: ab initio, DFT, semiempirical

MM: standard force field

QM – MM interactions:

„electronic embedding“

$$\hat{H}_{QM-MM}^{I,O} = -\sum_{i,J} \frac{q_J}{r_{ij}} + \sum_{i,J} \frac{q_J Z_A}{R_{AJ}} + \sum_{A,J} \left(\frac{A_{AJ}}{R_{AJ}^{12}} - \frac{B_{AJ}}{R_{AJ}^6} \right)$$

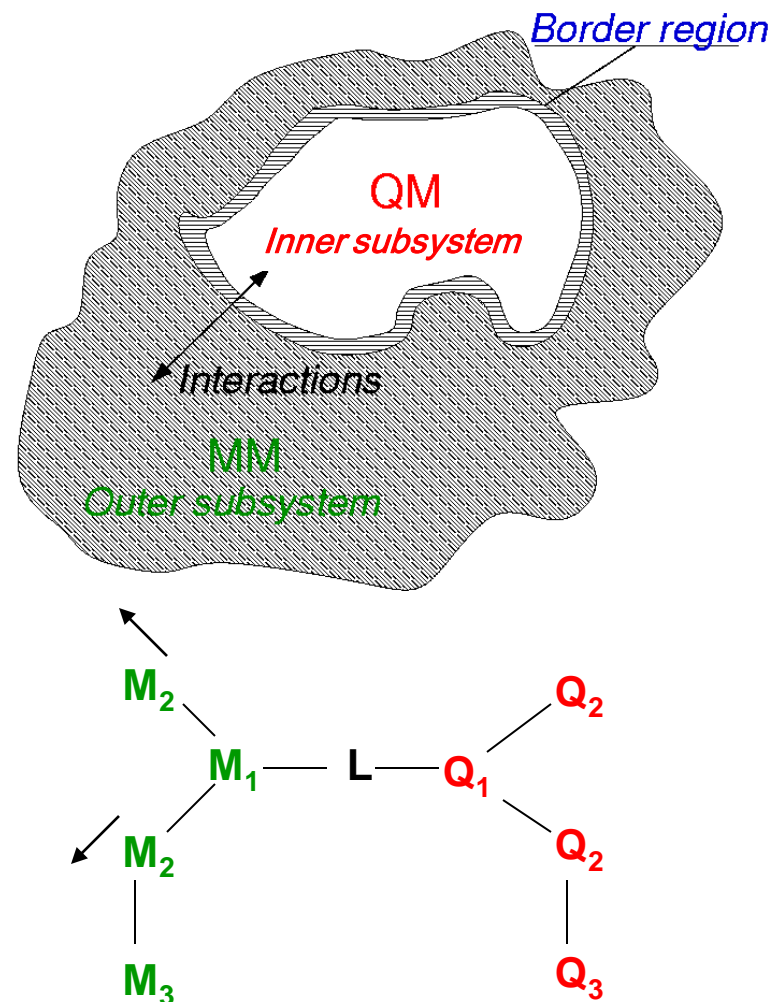
Border region:

- hydrogen link atoms **L**
- charge shift for $q(M_1)$

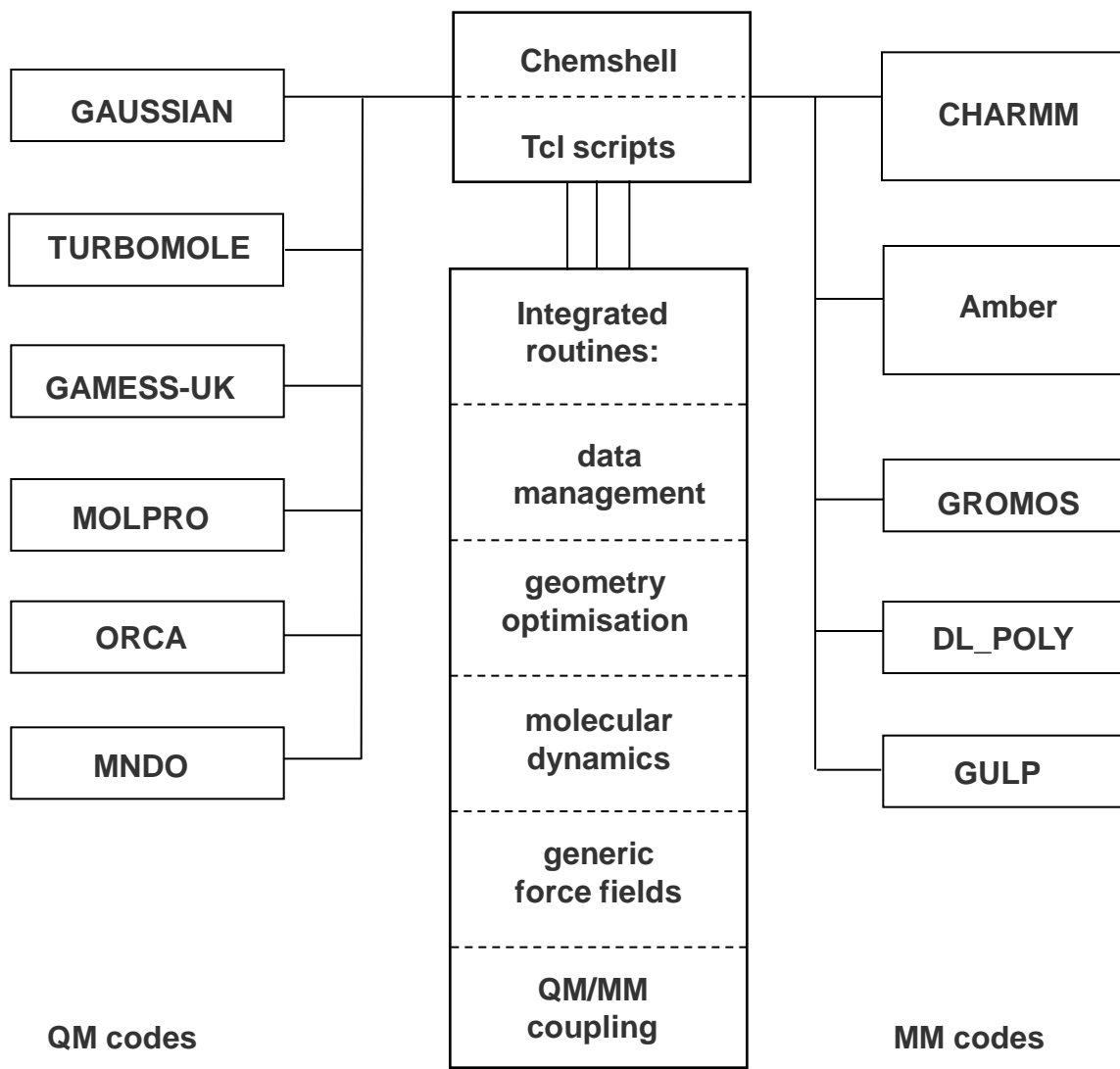
Codes:

ChemShell as control module

Interfaces to standard QM and MM codes



ChemShell: A modular QM/MM package





- Total **system size** of 10000-40000 atoms including solvent
- Active-site **QM region** of typically 50-100 atoms
- Standard **DFT** as QM component (typically B3LYP)
- Standard **force field** as MM component (CHARMM, GROMOS, AMBER, OPLS)
- Electrostatic QM/MM **embedding**
- QM/MM boundary treated by **link atom** scheme
- Geometry optimization of a limited number of **snapshots**
- Computation of reaction paths and **energy profiles**

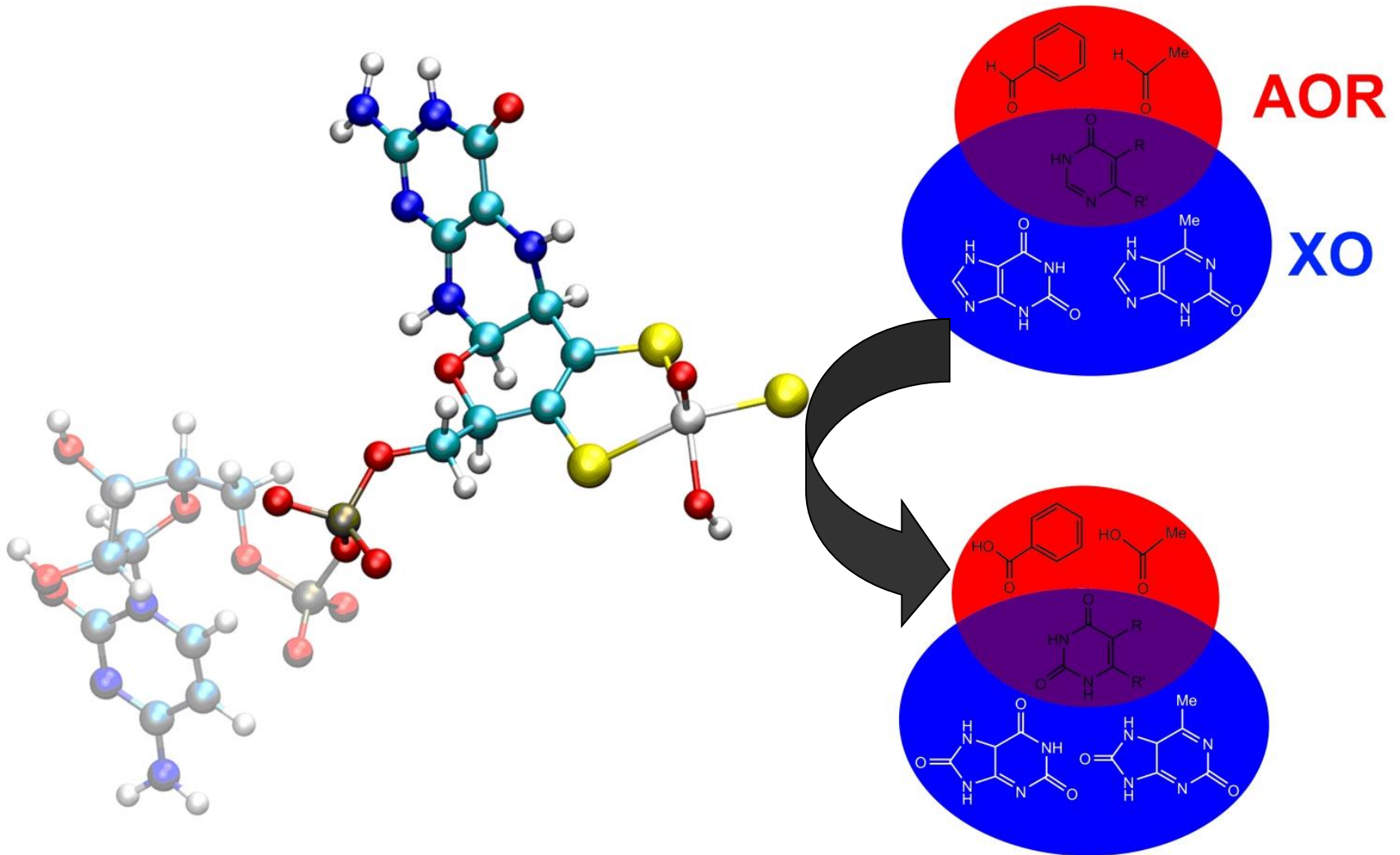


- High-level correlated **ab initio** methods as QM components
- **Polarized** force fields as MM component
- Polarized QM/MM **embedding**
- Proper **sampling** through molecular dynamics methods
- Computation of **free energy profiles**
- Extension to **excited-state** QM/MM modeling
- Extension to **three-layer** QM/MM/continuum approaches
- **Quantum refinement** of protein crystal structures

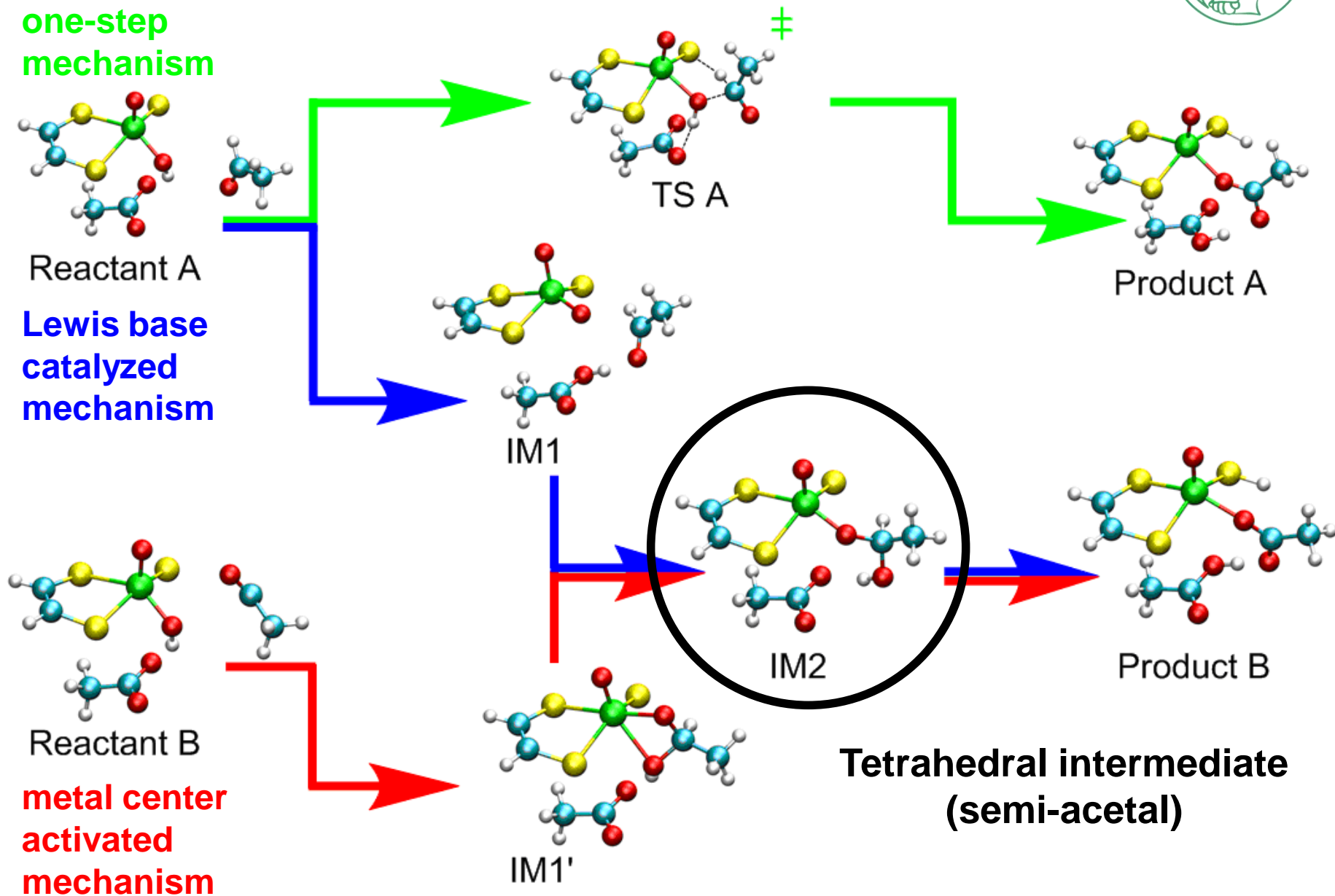
Molybdopterin containing enzymes: Structures



Molybdopterin cofactor



Aldehyde oxidoreductase: Pathways considered



Aldehyde oxidoreductase: Energies



QM(B3LYP/B1)/CHARMM results in kcal/mol

	Minimum	TS	barrier
One-step mechanism			
Concerted reaction	0.0	20.2	20.2
Metal center activated mechanism			
Substrate coordination and nucleophilic attack	0.0	15.4	15.4
Internal conversion IM1→IM2	5.8	6.8	1.0
Hydride transfer	-8.7	-0.2	8.5
Lewis base catalyzed mechanism			
Proton transfer from Mo-OH to Glu869	0.0	4.7	4.7
Nucleophilic attack	-2.8	2.8	5.6
Hydride transfer with proton recovery	-8.9	-0.4	8.5
Product	-21.5		

The favored Lewis base catalyzed mechanism involves an initial activation of the cofactor by proton transfer to the **active-site residue Glu869** and a final hydride transfer accompanied by a transfer of this proton from Glu869 to the forming acetic acid.