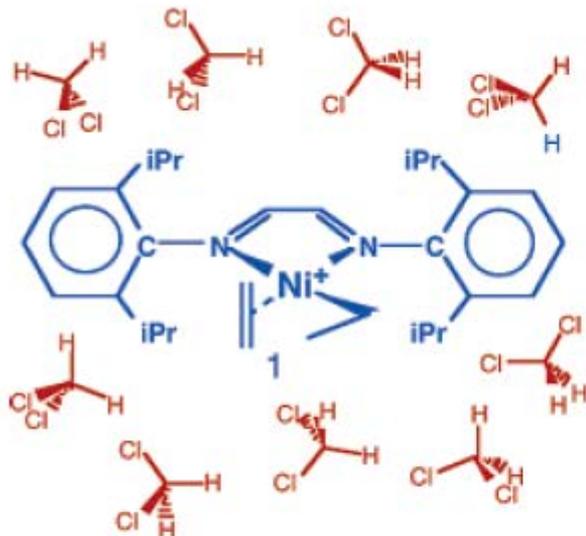


***Modelling Chemical Reactions in Solution:
Theory and Applications***

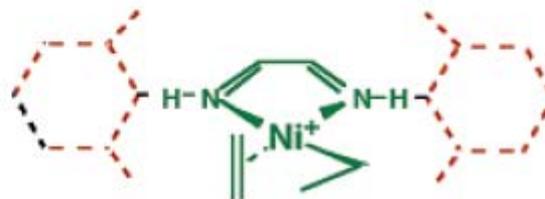
- lecture 11 -

Various types of models used for modelling chemical reactions in solutions

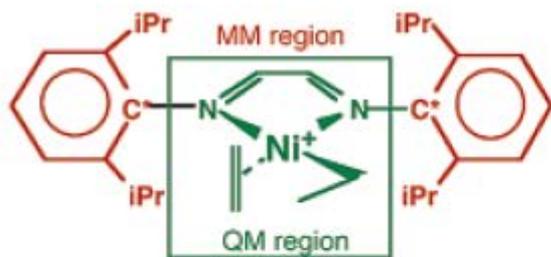
a. Real System



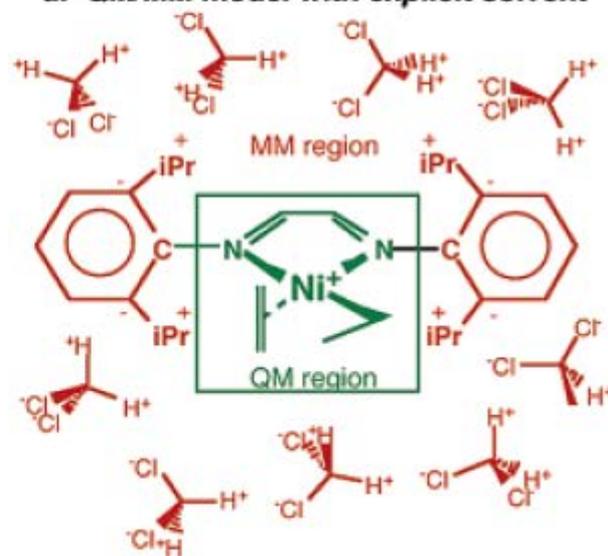
b. Most Pure QM Calculations & QM model system



c. QM/MM Model



d. QM/MM model with explicit solvent

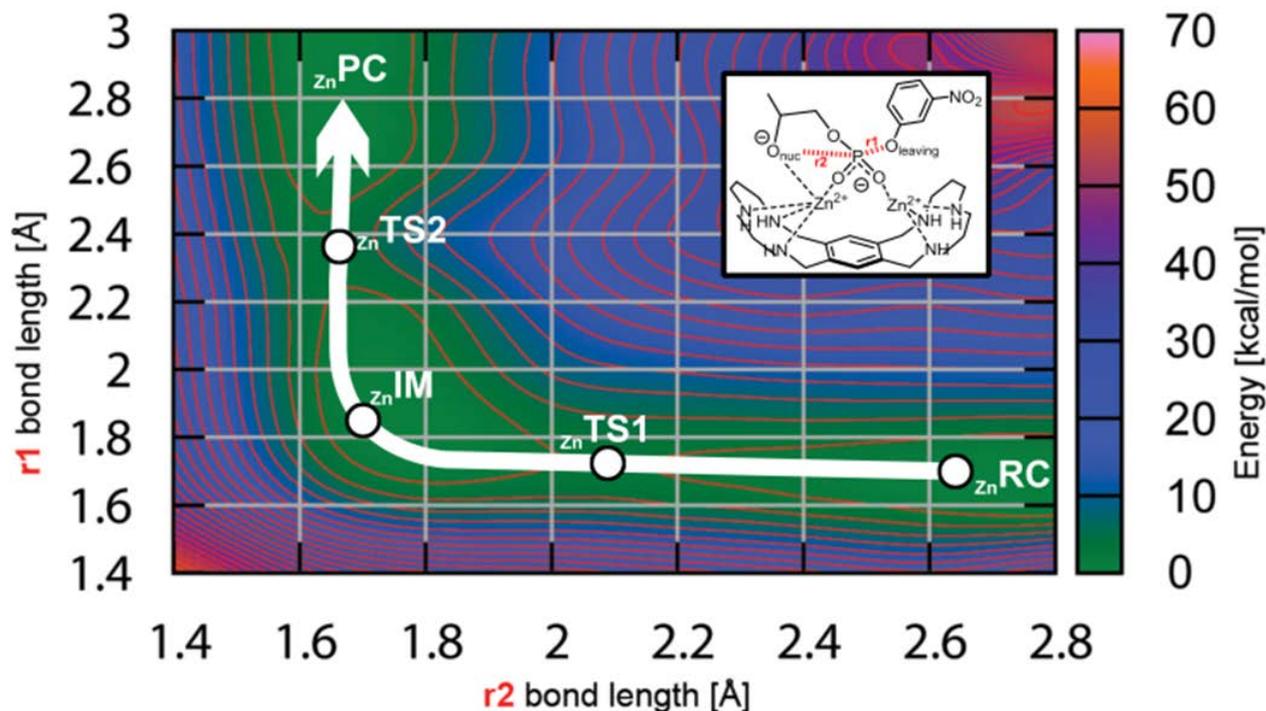


Key concept of a reaction coordinate and search for TS's

A reaction coordinate is a function of the configurational degrees of freedom of the system that should be capable of characterizing the progress of a transition through the dynamical bottleneck region.

Reaction coordinate can be as *simple* as:

- **One or two (intuitive) geometric parameter:**



Sometimes other than geometric parameters are more suitable as descriptors of a reaction coordinate: bond order, spin-density etc..

Reaction coordinate can be as **difficult** as:

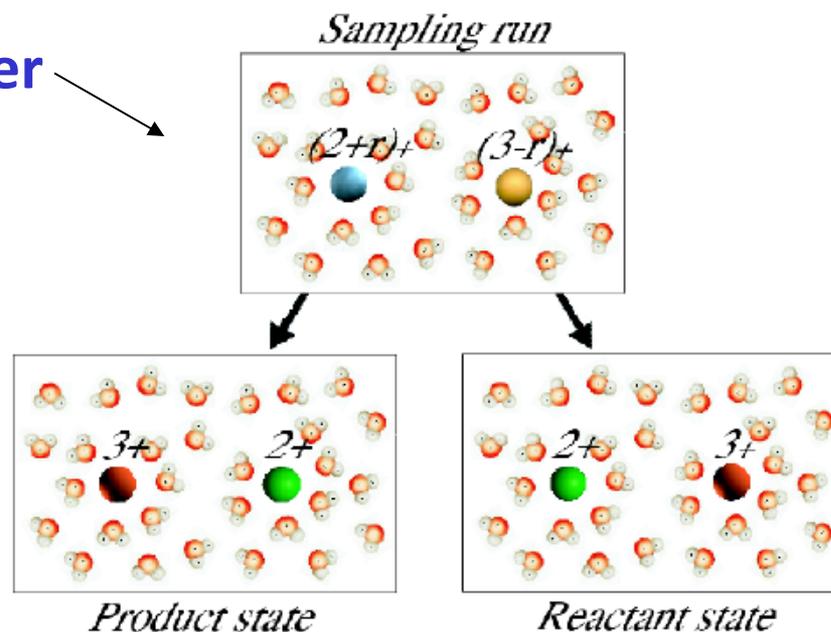
- **Collective (non-intuitive) reaction coordinate**

e.g.:

- **Peptide/Protein folding**
 - generic reaction coordinate unknown

- **Electron transfer**

etc...



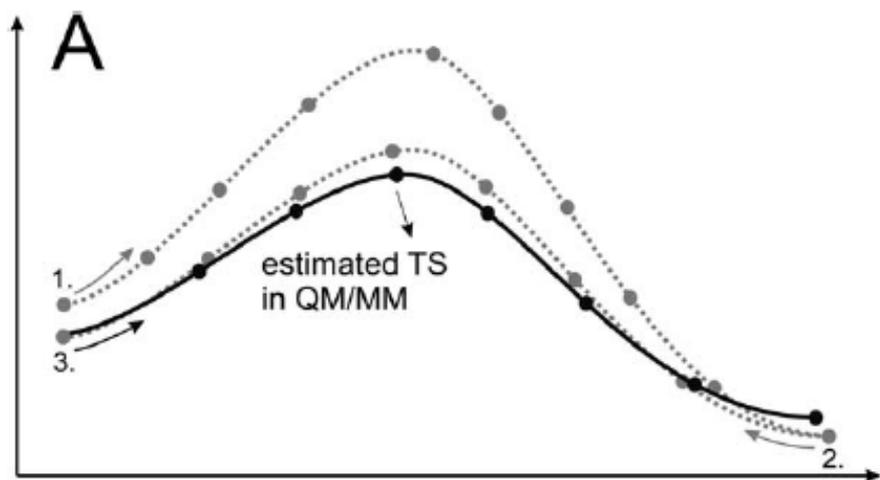
How to trap (meaning find and optimize) a “static” transition state using an easily definable reaction coordinate:

- 1) Define chemically reasonable reaction coordinate** (bond formation / breaking)
- 2) Perform a potential-energy surface (PES) scan**
along the defined reaction coordinate starting from a reactant
(1D or 2D scans => maximum in 1D or
saddle point in 2D → a good **guess for a “real” TS**)
- 3) Do a TS optimization** (structure stable in 3N-7 dimension)
starting from the guess obtained by a PES scan.
- 4) Frequency calculation** (to confirm that TS is stable in the 3N-7 space and
to calculate $RT-RT\ln Q^\ddagger$ contributions to **Gibbs free energy of TS**. [see **lecture 10**]
(the unstable mode is reaction coordinate at TS)
- 5) Perform intrinsic reaction coordinate (IRC) analysis** to
show that the TS is directly connected to the reactant state (backward step) &
and allows to reach the product state (forward step).

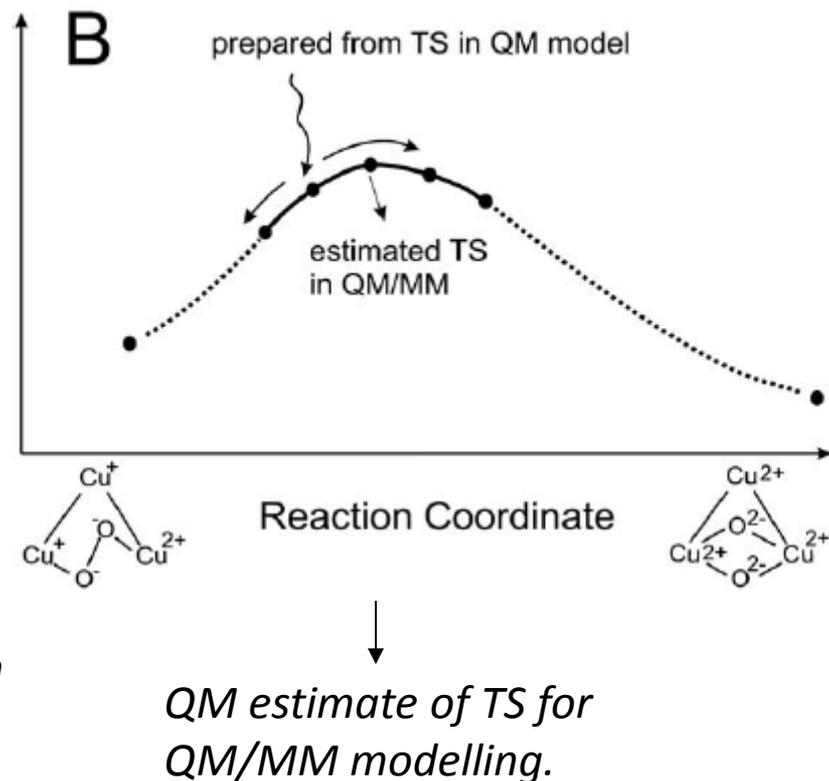
Alternative strategies in searching relevant TS's (next lecture)

A remark on “static” QM/MM modelling of chemical reactions

If the **analytic second derivatives of $E_{\text{QM/MM}}$** with respect to coordinates are **not implemented (available)** then the PES 1D (or 2D) scans along a reaction coordinate is the method of choice for “locating” relevant TS’s.



“Back-and-Forth” strategy
(scanning from R to P and back and forth). Slow convergence of the scan to the “stable” PES profile due to slow convergence to a “stable” configuration in the MM space.

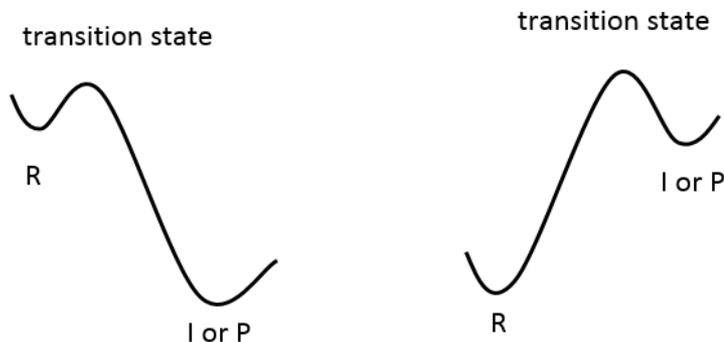


Transition State, its characterization in terms of its position along a reaction coordinate

From the geometric/electronic structure point of view the transition state can be characterized as:

- *Reactant-like TS (called “early” TS)*
- *Product-like TS (called “late” TS)*

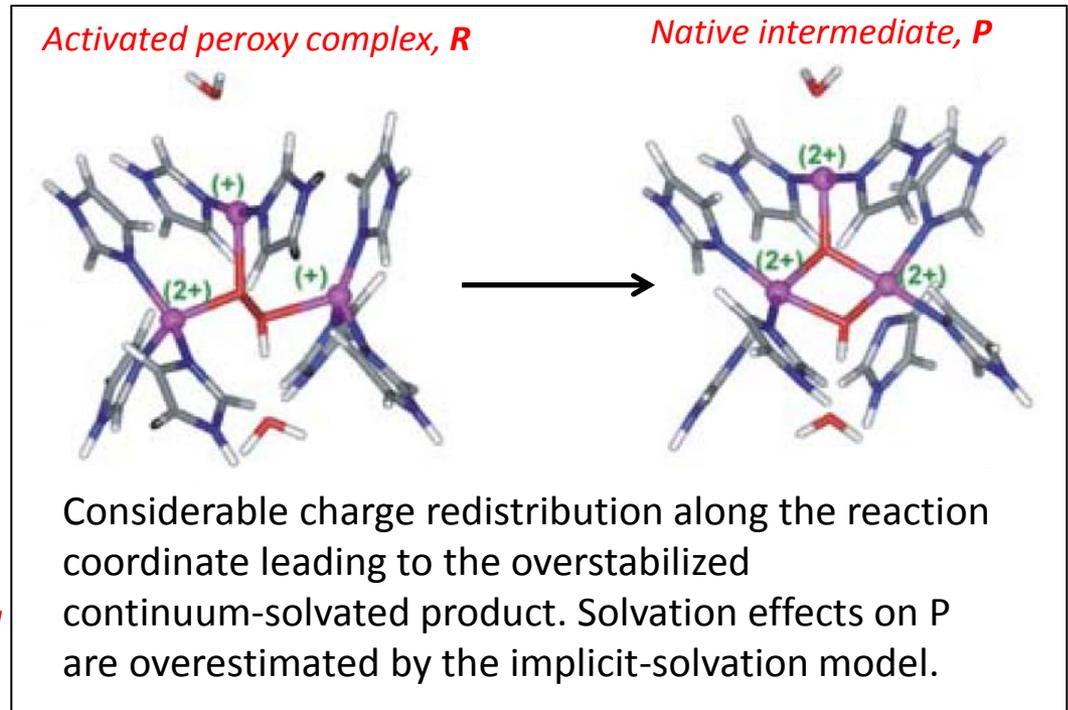
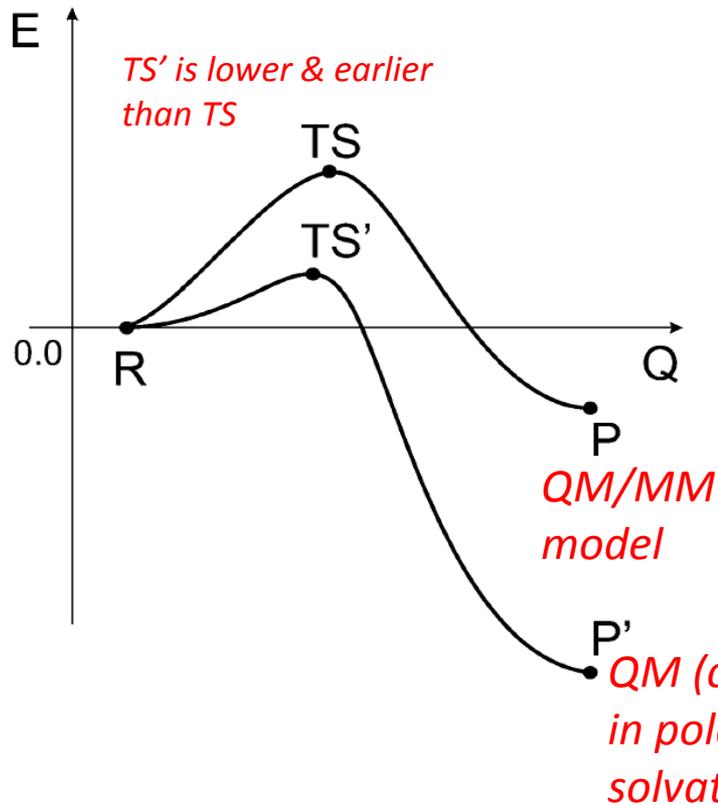
⇒ This resemblance/position with **R** or **P** is also reflected by the relative free energy of TS with respect to the reactant /product state



Hammond postulate
(kinetic-thermodynamic connections)

Practical consequences of the Hammond postulate related to the inappropriate description of solvation effects

Case of the O_2^{2-} reduction in the active site of multi-copper oxidase:

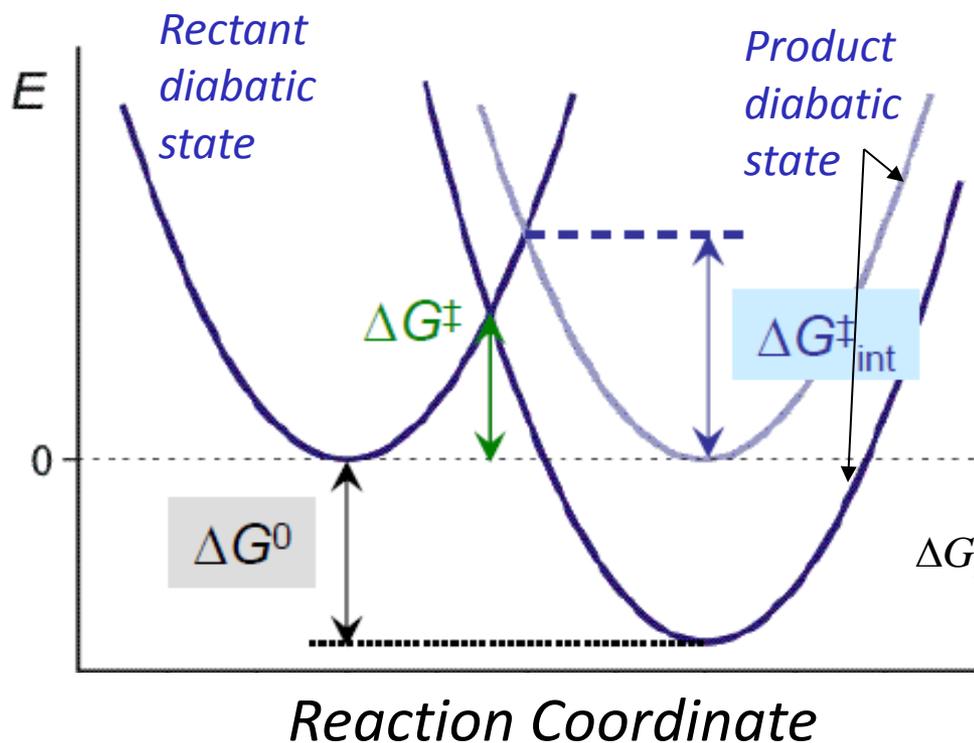


The overstabilization of the product state may lead to an artificial lowering of the activation barrier

Kinetic-thermodynamic connections

How the overstabilization of the product state may lead to an artificial lowering of the activation barrier..

Marcus theory (that was originally developed for electron-transfer reactions; more in [lecture 13](#)) provides the insight into kinetic-thermodynamic connections:



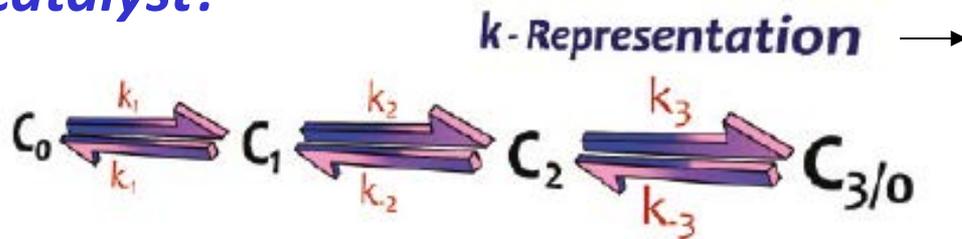
Within this theory the “real” thermodynamic effect on the the activation free-energy barrier can be (analyzed) decoupled through the equation:

$$\Delta G_{\text{intrinsic}}^\ddagger = \frac{1}{2} \left(\Delta G^\ddagger - \frac{1}{2} \Delta G^0 + \sqrt{\Delta G^{\ddagger 2} - \Delta G^\ddagger \Delta G^0} \right)$$

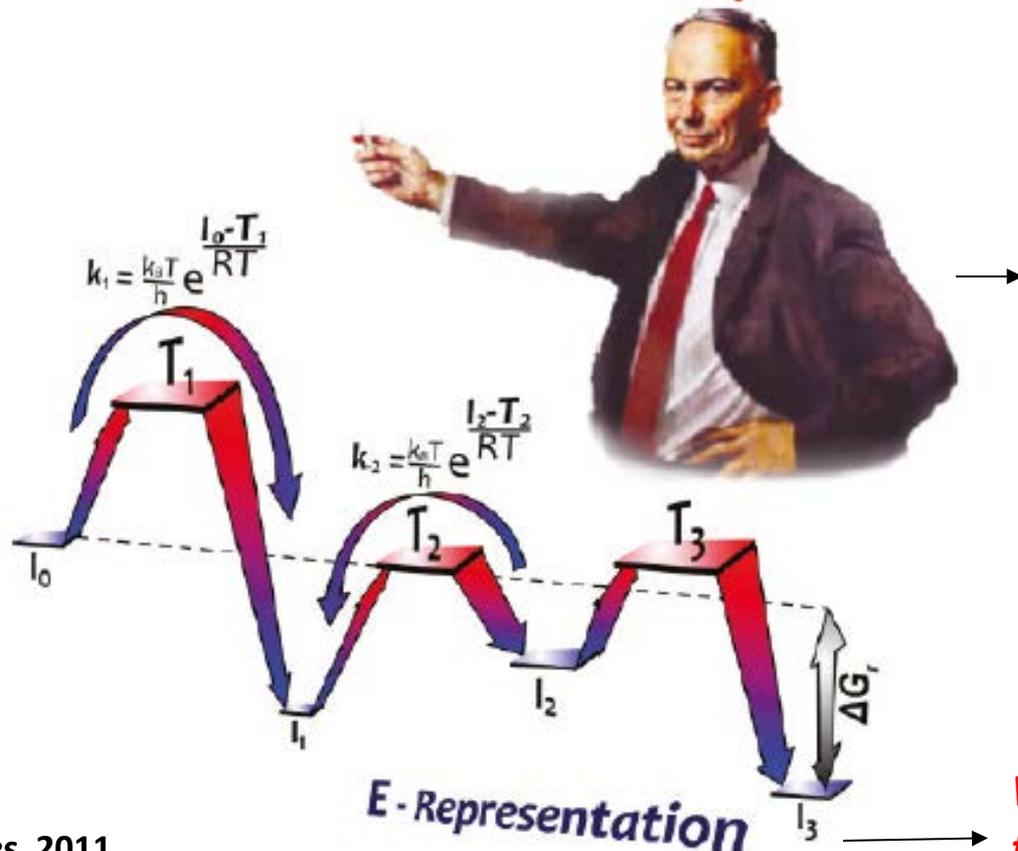
Simplification in MT: Parabolic behavior

Catalyzed reactions – prominent reactions in chemistry

What is a discriminating factor in a search of the most efficient catalyst?



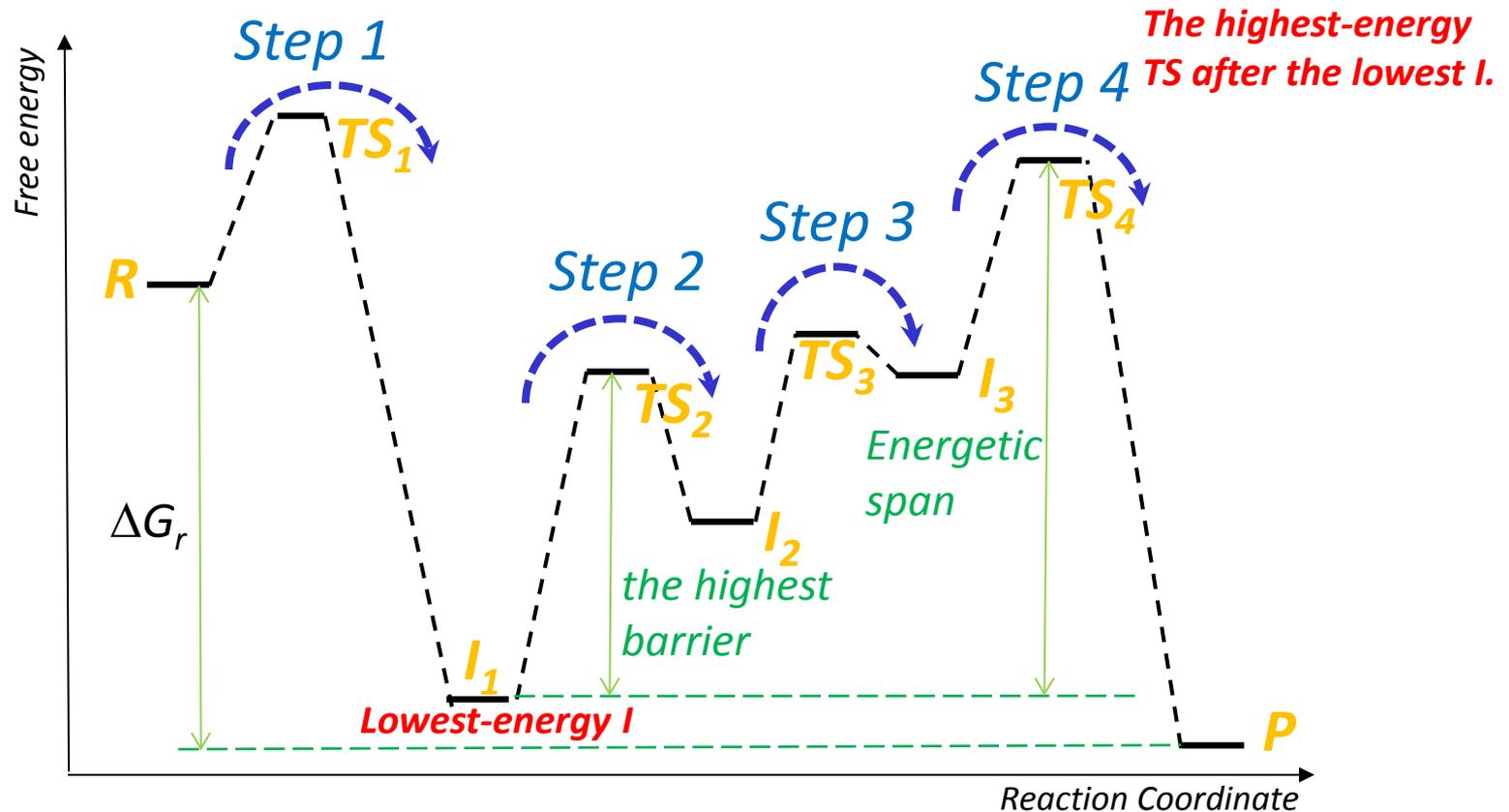
World of an experimentalist



Henry Eyring as a translator between k- and E-representation of a reaction

World of a theoretician

**How to calculate the efficiency of the catalytic cycle
(= its frequency turnover - TOF) from the theoretically obtained energy profile:**



Which step is the rate-determining step?:

Step 1 with the highest TS?

Step 2 with the highest barrier?

Step 4 with the highest TS that is after the lowest I along a reaction coordinate?

TOF - turnover frequency of the cycle is given as the number of cycles (N) per catalyst concentration (C) per time (time)

$$TOF = \frac{N}{Ct}$$

[reaction is first-order in catalyst and in a steady state]

Energetic Span Approximation for a catalytic cycle – based on Eyring's TST

Eq. 1

$$TOF = \frac{k_B T}{h} \frac{e^{-\Delta G_r / RT} - 1}{\sum_{i,j} e^{(G[T_i] - G[I_j] - A) / RT}} = \frac{\Delta}{M}$$

“Potential of the process”

“the resistance to the chemical flow” given as the sum of exponentials of Gibbs free-energy differences between all combinations of intermediates and transition states.

$$A = \begin{cases} \Delta G_r & \text{if } i > j \\ 0 & \text{if } i \leq j \end{cases}$$

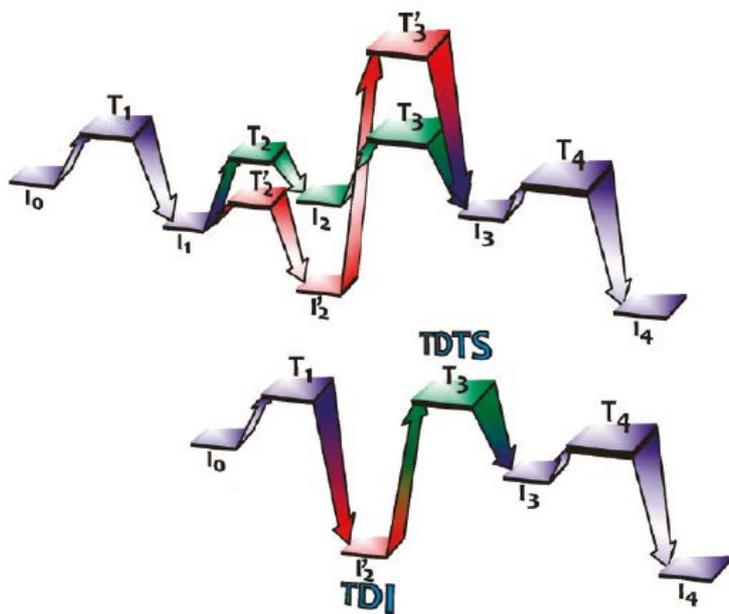
Eq. 1 can be simplified if the denominator M is dominated by a single term of the summation:

$$TOF = \frac{k_B T}{h} e^{-\delta G / RT}$$

$$\delta G = \begin{cases} G[\text{highest TS}] - G[\text{lowest I}] & \text{if highest TS after lowest I} \\ G[\text{highest TS}] - G[\text{lowest I}] + \Delta G_r & \text{if highest TS before lowest I} \end{cases}$$

3 assumptions considered in the Energetic Span Approximation:

- Transition state theory is valid
- Steady state regime is applicable
- Intermediates undergo fast relaxation



Two possible mechanisms with “red one” unlikely

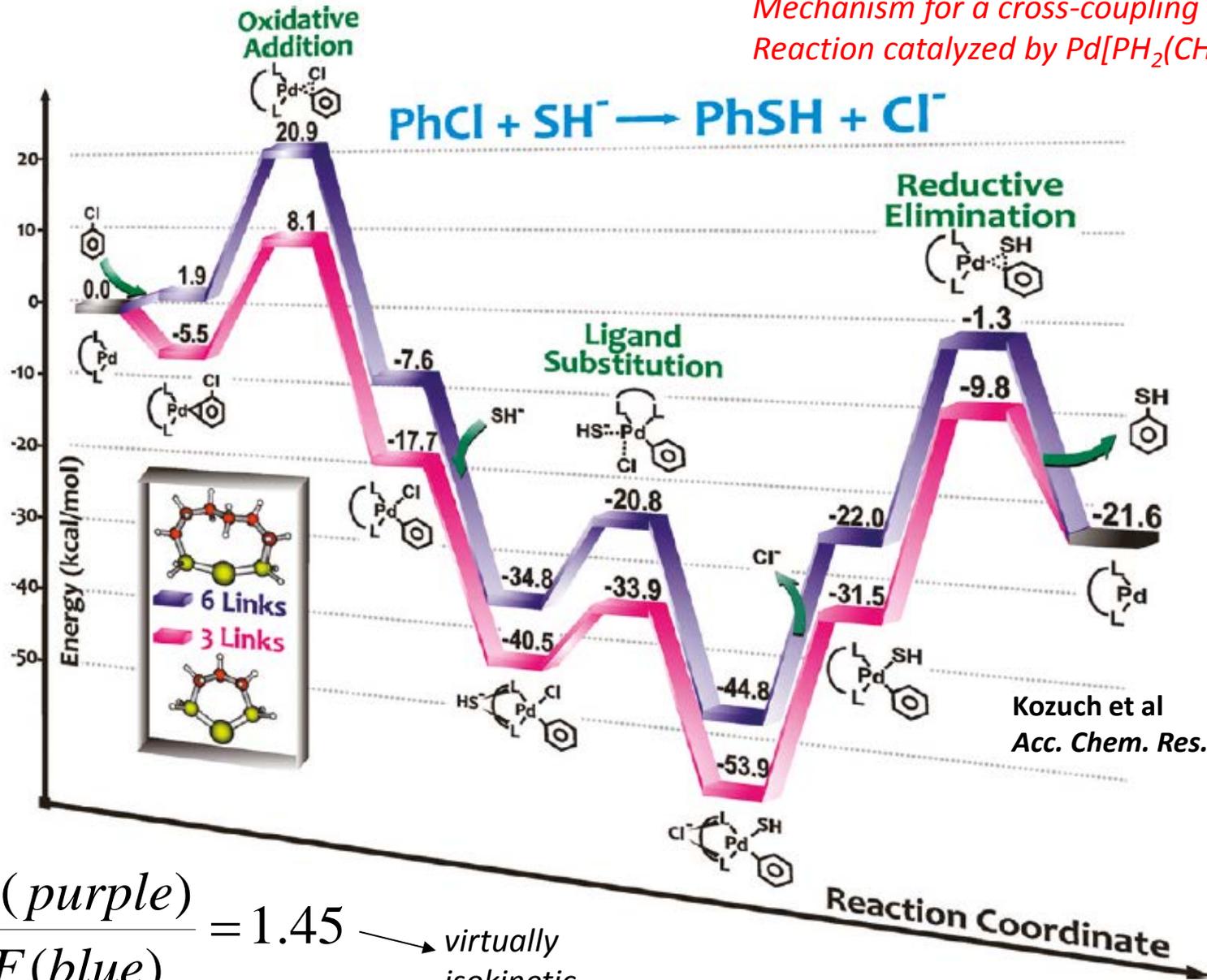
but

Kinetic TOF is a combination of both

There are no rate-determining steps but there are rate-determining states!

Which of these two catalysts is more efficient?

Mechanism for a cross-coupling
Reaction catalyzed by $\text{Pd}[\text{PH}_2(\text{CH}_2)_n\text{PH}_2]$



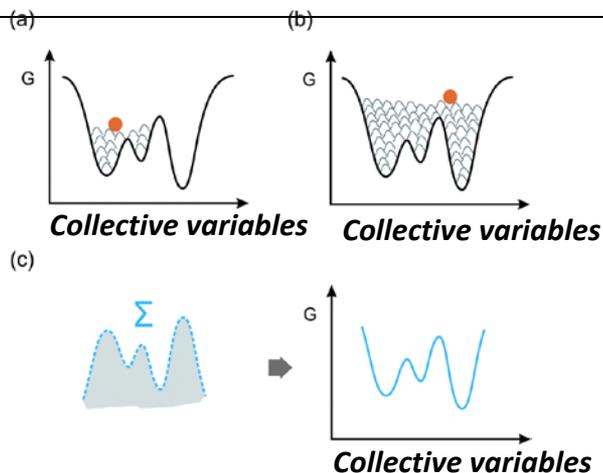
$$\frac{\text{TOF}(\text{purple})}{\text{TOF}(\text{blue})} = 1.45 \rightarrow \text{virtually isokinetic}$$

*Modelling chemical reactions in solutions
considering all-atom solvent environment*

MD- MC-based techniques suitable for the study of “rare transitions” such as a chemical reaction in a complex system with a huge number of degrees of freedom

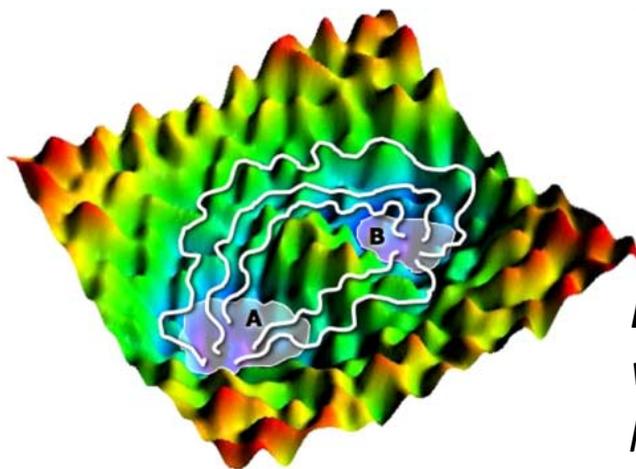
PMF ; QM/MM-FEP ; QM/MM-TI

QM/MM
Metadynamics



Collective variables (CVs) include
for example bond lengths,
dihedral angles, coordination
numbers, etc.

QM/MM
Transition Path
Sampling



TPSs do not require **prior knowledge of a reaction coordinate** and do not rely on the identification of particular features of the potential energy surface

Idea: to generate reactive trajectories with a frequency proportional to their probability in the transition path ensemble

Semiempirical EVB (=QM/MM) MD Approach (pioneered by A. Warshel)

EVB – empirical valence bond – is a QM/MM method. It mixes resonance (=diabatic) states (valence bond structures), which describes reactant, intermediate and product states.

The potential energy of an i -th “resonance” state is represented by the MM force field of the form:

1)

$$\epsilon_i = \epsilon_{gas}^i + V_{solute}^i(R, Q) + V_{solute, surrounding}^i(R, Q, r, q) + V_{surrounding}(r, q)$$

atomic coordinates → (R, Q) (R, Q, r, q) → charges

gas-phase energy of the i -th state (when all fragments are taken to be at infinity) → calibrated by a high-level QM calc. or experiment

ϵ_i forms the diagonal element of the EVB Hamiltonian:

2)

Assumed to be independent of the solvent environment

represented by simple exponential (Morse-like) functions of the distances between the reacting atoms (fitted to experimental or high-level QM data)

$$\begin{pmatrix} \epsilon_{11} & \epsilon_{12} \\ \epsilon_{21} & \epsilon_{22} \end{pmatrix}$$

↓ solution:

Lowest-energy eigenvalue ← $E_{GS} = \frac{1}{2}(\epsilon_{11} - \epsilon_{22}) - \sqrt{\frac{1}{2}(\epsilon_{11} - \epsilon_{22})^2 + \epsilon_{12}^2}$

Semiempirical EVB (=QM/MM) MD Approach *(pioneered by A. Warshel)*

3)

EVB evaluates the relevant activation energies (ΔG^\ddagger) by changing one diabatic state (=reactant) into another one (=product) through:

$$\varepsilon_m = (1 - \lambda_m) \varepsilon_1 + \lambda_m \varepsilon_2$$

The free energy, ΔG_m , associated with changing λ is evaluated by **FEP-umbrella sampling**.

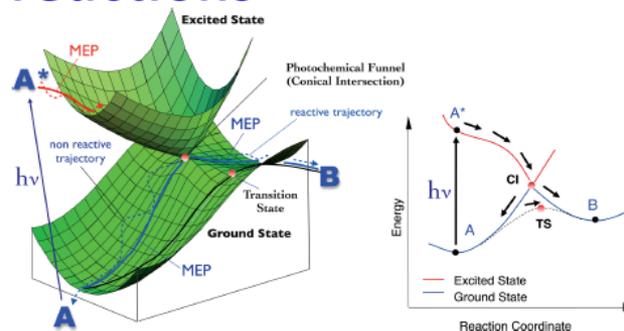
...and free energy profile of diabatic state 1 is given by:

$$\Delta G_1(x') = \Delta G_m - k_B T \ln \left\langle \delta(x - x') \exp \left[\frac{\varepsilon_m(x) - \varepsilon_1(x)}{k_B T} \right] \right\rangle_{\varepsilon_m}$$

with x – reaction coordinate ($\varepsilon_1 - \varepsilon_2$)

- **Modelling “photochemical” chemical reactions**

Reactions involving conical intersections
(crossing seam between two states is of $3N-8$ dimension if these states have the same spin)



- **Modelling “spin-forbidden” chemical reactions**

Reaction barrier can be given by a crossover of two spin states:

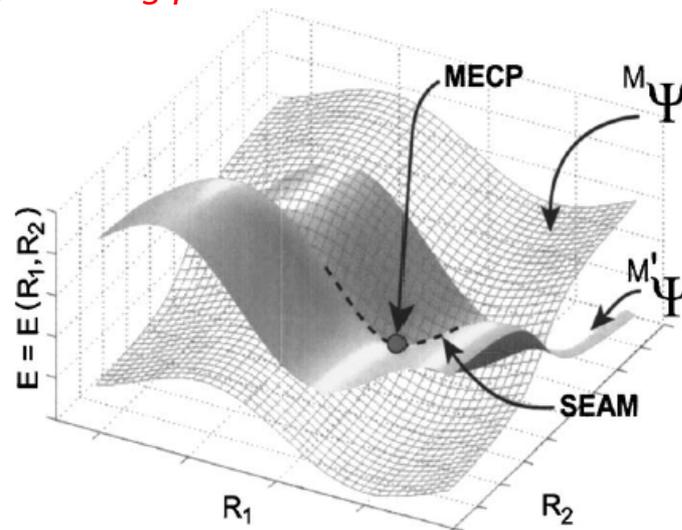
- these states are diabatic (=non-interacting) from the non-relativistic quantum-chemical perspective
- There is no a “classical” TS with one unstable mode along a reaction coordinate but rather the “minimum” on the crossing seam is searched.

Search algorithms
(e.g., Harvey’s approach)
or constrained PES scans

Minimum energy crossing point
(MECP)

Then, k (rate constant) can
be calculated within the non-
adiabatic TS theory.

More in lecture 13



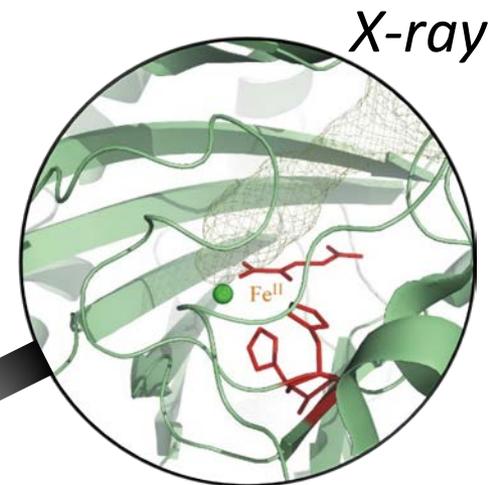
(CASSCF, CASPT2
methods suitable)

Modelling chemical reactions

through correlation of theory and spectroscopy

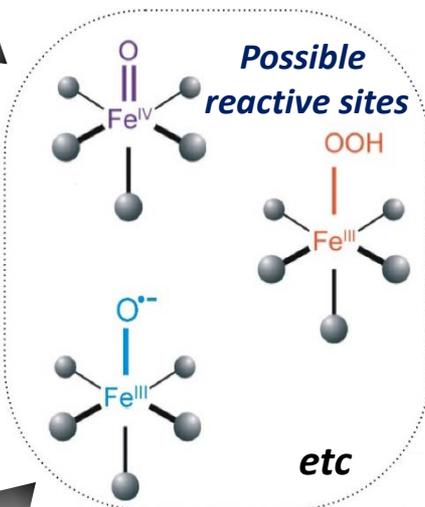
Calculations of physico-chemical properties of biomimetic, synthetic Complexes (e.g. reduction potential..)

generation by structural models for "experimentally trapped" intermediate



Trapped Intermediate

(QM(DFT)/MM ; QM models
QM cluster models..)



Reaction mechanism

Is compatible with kinetic data?

Calculations correlated with spectroscopic parameters
→ Complex electronic-structure properties (CCSD[T], CASPT2, DMRG-CASPT2, DFT...)

Spectroscopic characterization & analysis
(MCD, NRVS, Mössbauer, EPR Resonance Raman..)

