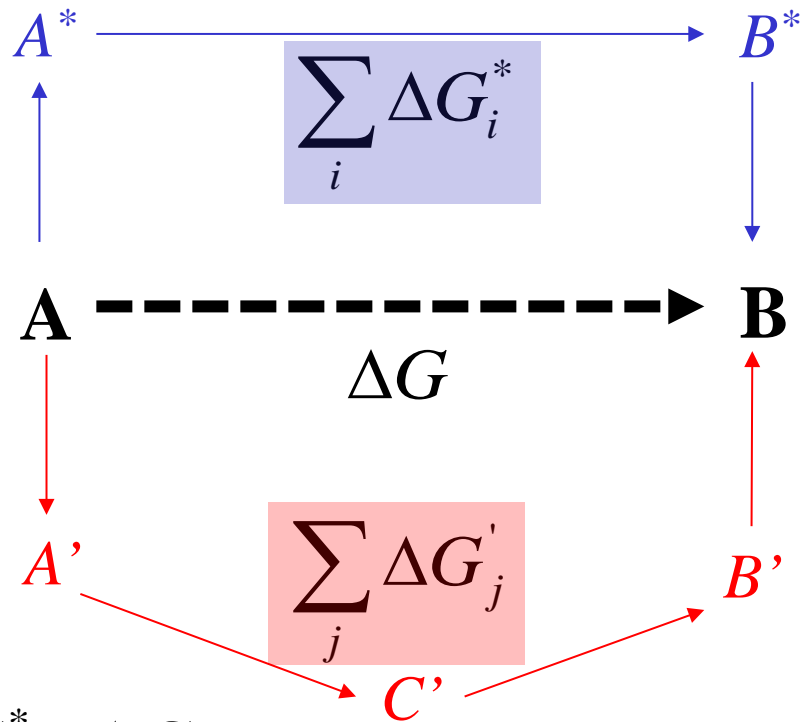


***Thermodynamic Cycles for Computation
of a Free-Energy Change
in Condensed Phase***

Computational Electrochemistry, pK_a 's

- lecture 10 -

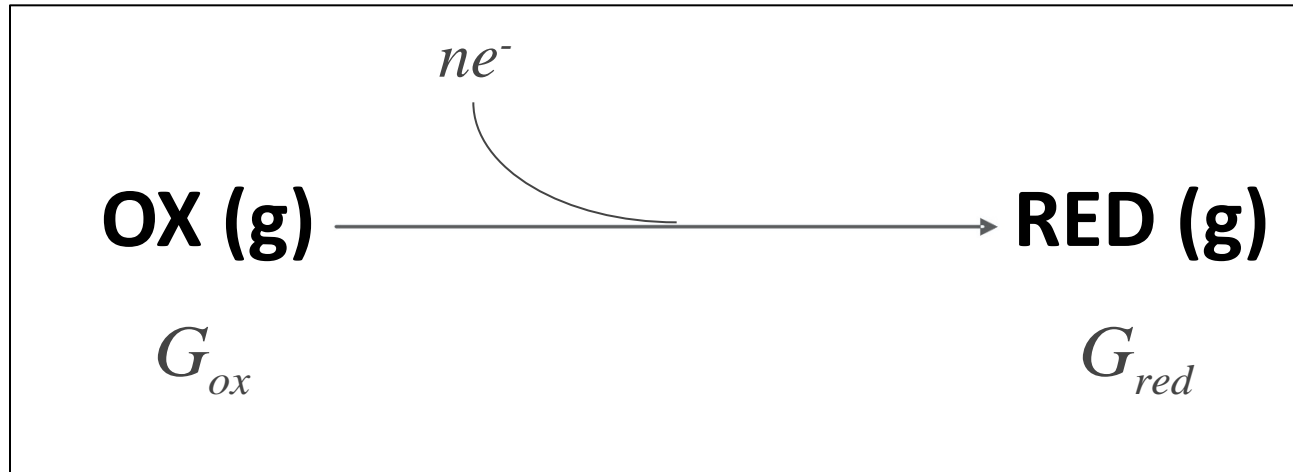
→ No dependence of (ΔG , ΔH , ΔS ...) on a pathway...
...since G , H , S are **state** functions



$$\sum_j \Delta G_j' = \sum_i \Delta G_i^* = \Delta G$$

Case problem: Reduction potential

Half reaction



$$E^\circ [V] = G_{ox} [eV] - G_{red} [eV] - nE_{abs}^\circ (\text{reference}) [V]$$



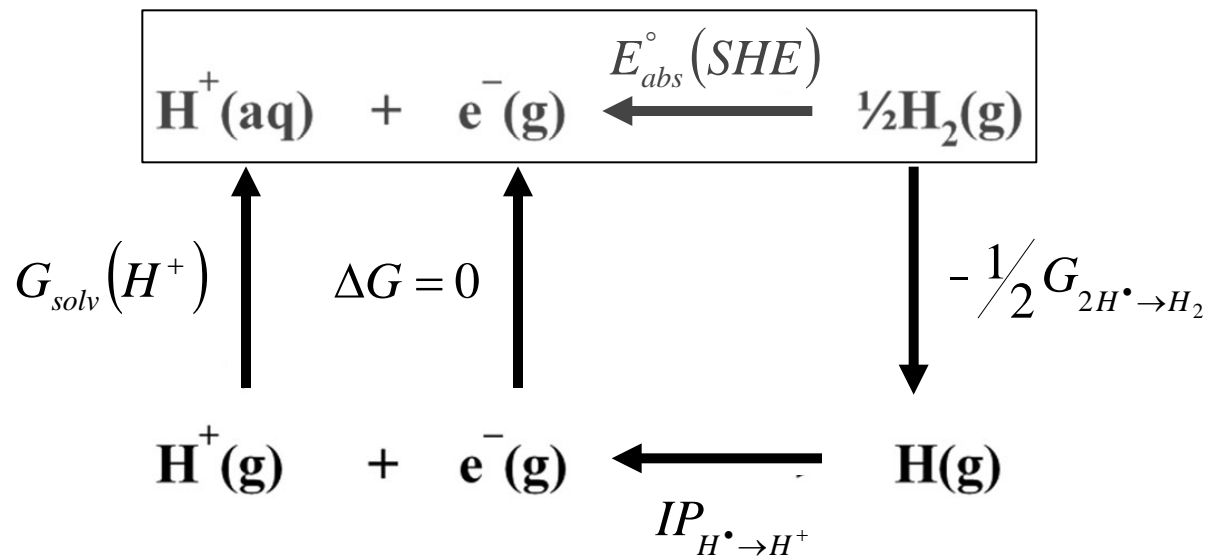
Absolute potential of a (reference) standard hydrogen electrode

Given as the sum of three terms:

$$G_{\text{solv}}(H^+) + IP_{H^\bullet \rightarrow H^+} - \frac{1}{2} G_{2H^\bullet \rightarrow H_2} = E_{\text{abs}}^\circ(\text{SHE})$$

$$\approx -11.6 \text{ eV} \quad \approx 13.6 \text{ eV} \quad \approx 2.3 \text{ eV} \quad \Rightarrow 4.3 \text{ V}$$

Thermodynamic cycle for the absolute potential of the SHE:



$$E^\circ [V] = G_{ox} [eV] - G_{red} [eV] - nE_{abs}^\circ (\text{reference}) [V]$$

How to evaluate G ?

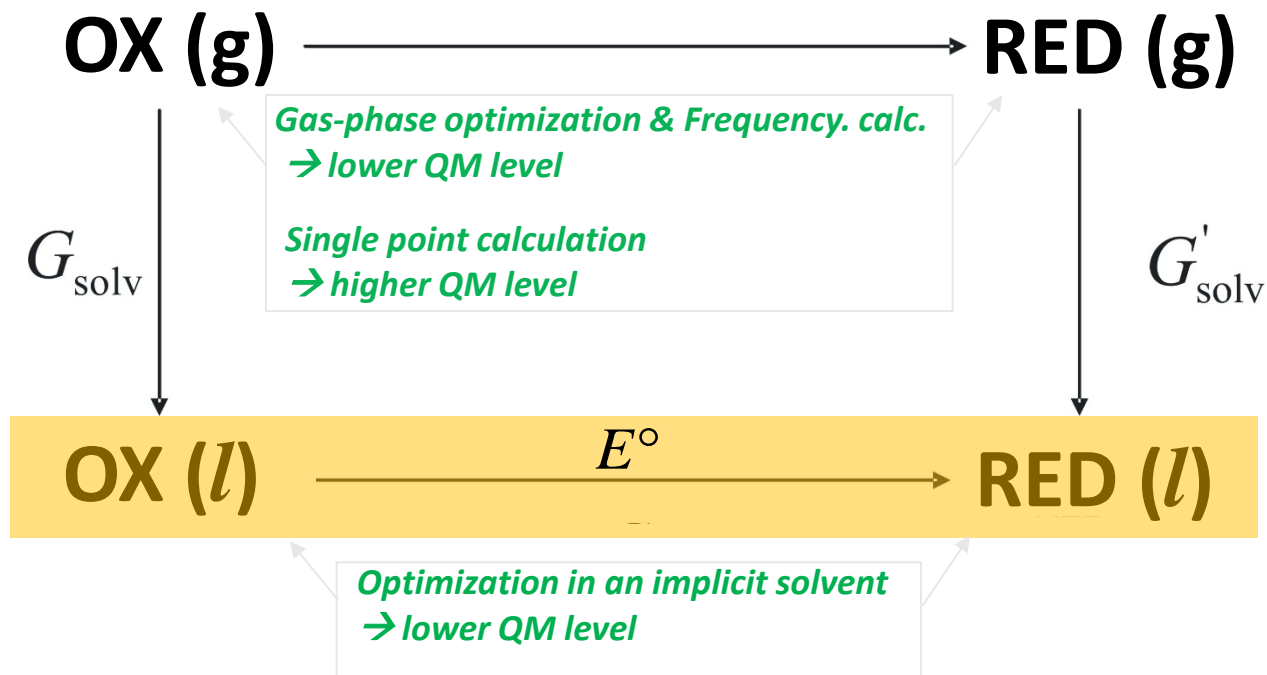
From lecture 5: *Ideal gas-phase, harmonic-oscillator, rigid-rotor approximation + protocol based on implicit-solvent model:*

$$G(T) = E_{el} + [E_{ZPVE} + RT - RT \ln Q(T)] + G_{solv}(T)$$

- * *the electronic energy*
- * *the thermal enthalpic and entropic contributions to the energy of solute*
- * *the free energy of solvation --- e.g. through an implicit solvation model such as COSMO-RS (COSMO)*

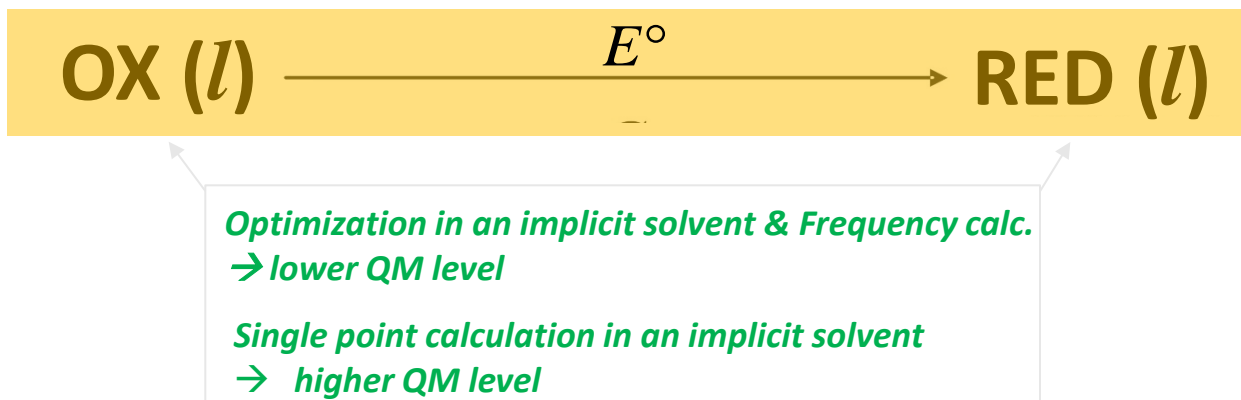
Calculation of reduction potentials using a thermodynamic cycle

$$G_{\text{OX,g}} = E_{el}^{\text{OX}} + \left[E_{\text{ZPVE}}^{\text{OX}} + RT - RT \ln Q_{\{\text{OX}\}} \right] \quad G_{\text{RED,g}} = E_{el}^{\text{RED}} + \left[E_{\text{ZPVE}}^{\text{RED}} + RT - RT \ln Q_{\{\text{RED}\}} \right]$$



$$E^{\circ} = \Delta E_{el}^{\text{OX-RED}} + \left[\Delta E_{\text{ZPVE}}^{\text{OX-RED}} - RT \ln \frac{Q_{\{\text{OX}\}}}{Q_{\{\text{RED}\}}} \right] + \Delta G_{\text{solv}}^{\text{OX-RED}} - nE^{\circ}(\text{SHE}) \quad !$$

$$- RT \ln \frac{\{q_{\text{vib}} q_{\text{rot}} q_{\text{trans}}\}_{\{\text{OX}\}}}{\{q_{\text{vib}} q_{\text{rot}} q_{\text{trans}}\}_{\{\text{RED}\}}} \approx \frac{q_{\text{vib}\{\text{OX}\}}}{q_{\text{vib}\{\text{RED}\}}}$$



$$E^\circ = \Delta E_{el,solv}^{\text{OX-RED}} + \left[\Delta E_{ZPVE}^{\text{OX-RED}} - RT \ln \frac{Q_{\{\text{OX}\}}}{Q_{\{\text{RED}\}}} \right] - nE^\circ(\text{SHE}) \quad !$$

= “*the standard approach*”

It was demonstrated for amino acids where the solution-phase geometries differ appreciably from the gas phase that carrying out high-level single-point calculations directly in the continuum model on the solution phase species gives rise to pKa's and reduction potentials that are in better agreement with experiment...

PCCP – 2015, 17, 2859-2868

Experimental and calculated reduction potentials of ferrocenes derivatives with respect to the Ag/AgCl 1M LiCl electrode

DFT(PBE/def2-TZVP) + COSMO-RS (acetonitrile):

E^0 range: 0.458 – 1.190 V

MAD (exp/calc): 0.03 V

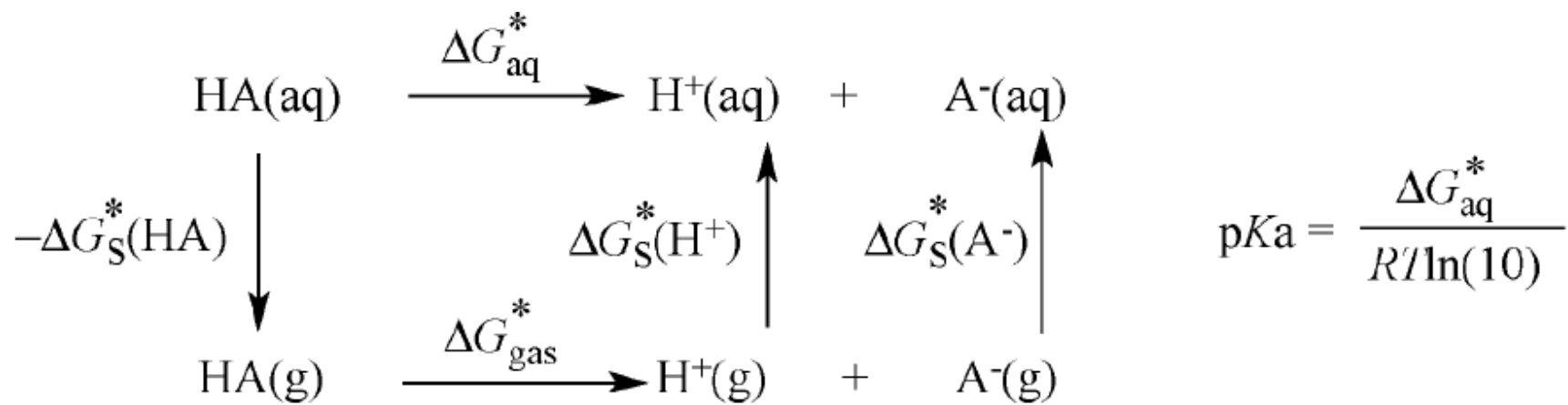
max. dev (exp/calc): 0.1 V

E_{abs} (SHE) = 4.291 V

Quantitative predictivity

Entry	Compound	E^0_{exp} [V]	E^0_{calc} [V]	IE [eV] ^[a]	$\Delta(E_{ZPVE} - RT\ln Q)$ ^[b] [eV]	$\Delta\Delta G_{solv}$ ^[c] [eV]
1	2i (CH ₂ Ph)	0.463	-	-	-	-
2	2b (COPh)	0.693	0.712	6.69	-0.028	-1.454
3	2a (CO ₂ <i>i</i> Pr)	0.704	0.702	6.80	-0.025	-1.576
4	2c (PPh ₂)	0.560	0.502	6.26	-0.003	-1.259
5	2k (POPh ₂)	0.713	0.700	6.57	-0.049	-1.318
6	2d (PO ₃ Et ₂)	0.695	0.708	6.65	-0.004	-1.436
7	2e (SPh)	0.610	0.567	6.40	0.003	-1.340
8	2l (SOPh)	0.783	0.735	6.75	-0.016	-1.495
9	2m (SO ₂ Ph)	0.847	0.823	6.84	-0.008	-1.507
10	2f (Cl)	0.624	0.633	6.82	-0.008	-1.679
11	2g (Br)	0.630	0.668	6.83	-0.001	-1.657
12	2h (I)	0.635	0.640	6.77	-0.003	-1.626
13	3i (CH ₂ Ph) ₂	0.458	0.501	6.38	0.012	-1.387
14	3b (COPh) ₂	0.917	0.952	6.77	-0.038	-1.274
15	3a (CO ₂ <i>i</i> Pr) ₂	0.914	0.933	6.88	-0.024	-1.399
16	3c (PPh ₂) ₂	0.653	0.554	6.07	0.016	-1.036
17	3k (POPh ₂) ₂	0.946	1.000	6.50	0.001	-1.001
18	3d (PO ₃ Et ₂) ₂	0.903	0.917	6.53	-0.017	-1.095
19	3e (SPh) ₂	0.681	0.671	6.28	0.050	-1.157
20	3l (SOPh) ₂	0.983	0.994	6.79	-0.005	-1.290
21	3m (SO ₂ Ph) ₂	1.190	1.165	6.94	-0.007	-1.266
22	3f (Cl) ₂	0.771	0.765	6.92	0.003	-1.661
23	3g (Br) ₂	0.797	0.828	6.93	0.016	-1.620
24	3h (I) ₂	0.741	0.768	6.85	-0.009	-1.574

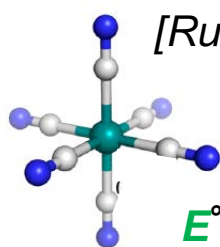
Thermodynamic cycle for calculating pK_a



Solvation at the COSMO-RS level or PMF...

Cases difficult for the standard approach (from the implicit solvation point of view):

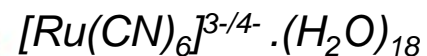
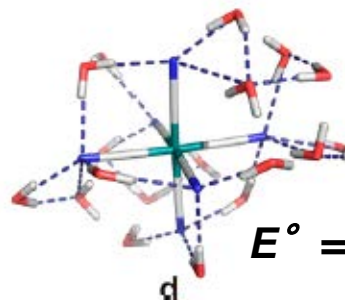
- *systems with a high molecular charge*
- *polar (and protic) solvents*



$E^\circ(\text{exp}) = 0.86 \text{ V}$

$E^\circ = 1.94 \text{ V (COSMO-RS)}$

$E^\circ = 0.12 \text{ V (SMD)}$

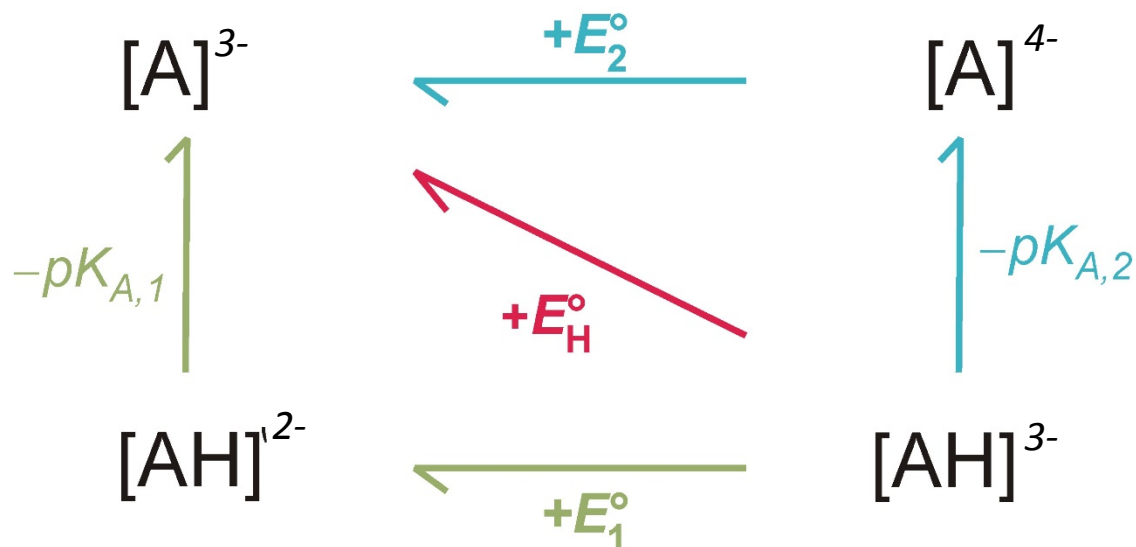


$E^\circ = 1.26 \text{ V (COSMO-RS)}$

*Employing a thermodynamic cycle
in a different way...*

Bím, D.; Rulíšek, L.; Srnec, M.: Accurate Prediction of One-Electron Reduction Potentials in Aqueous Solution by Variable-Temperature H-Atom Addition/Abstraction Methodology. *J. Phys. Chem. Lett.* **2016**, 7, 7-13.

Variable Temperature H-atom Addition/Abstraction Approach (“VT-HAA”) : Idea



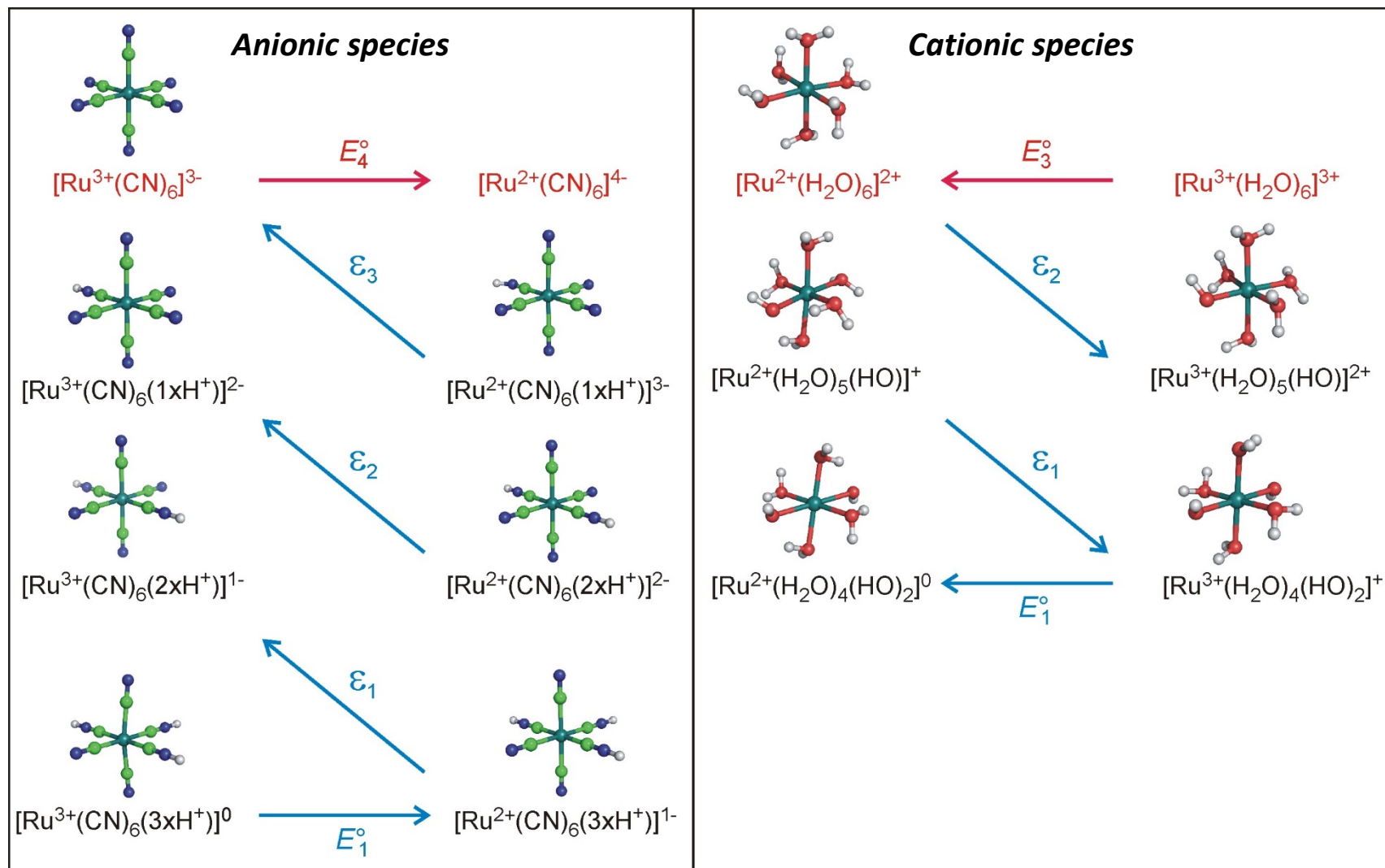
E_2° as a function of E_H° and E_1°

Two assumptions

- Within the implicit solvation model, solvation (electrostatic) interactions of a **less** charged species are described more accurately than those of a **more** charged cognate
- Equivalently charged molecular cognates have comparable solvation (electrostatic) energies, implying small errors in prediction of their solvation energy difference.

Extension to multiple thermodynamic cycles $[\text{Ru}(\text{CN})_6]^{4-/3-}$ & $[\text{Ru}(\text{H}_2\text{O})_6]^{2+/3+}$

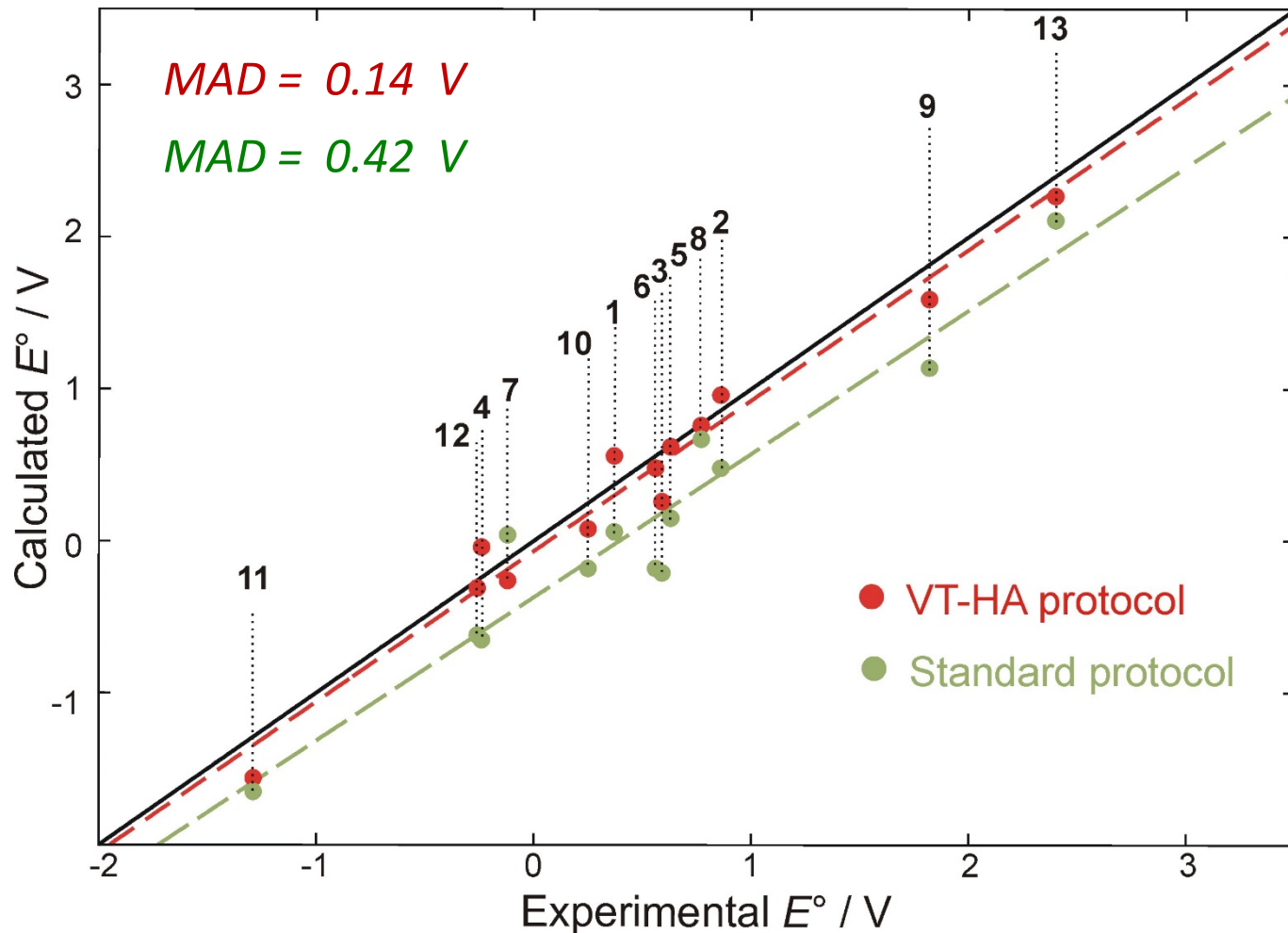
$$E_{n+1}^\circ = 2 \sum_{i=1}^n (-1)^{n-i} \varepsilon_i + (-1)^n E_1^\circ - 31.6 \times \delta \begin{cases} \delta = 0 & \text{if } n \text{ is even} \\ \delta = 1 & \text{if } n \text{ is odd} \end{cases}$$



Experiment vs. "VT-HAA" vs. "Standard approach"

For COSMO-RS solvation model

$[\text{Fe}(\text{CN})_6]^{3-/4-}$	(1)
$[\text{Ru}(\text{CN})_6]^{3-/4-}$	(2)
$[\text{Os}(\text{CN})_6]^{3-/4-}$	(3)
$[\text{Mn}(\text{CN})_6]^{3-/4-}$	(4)
$[\text{RuO}_4]^{1-/2-}$	(5)
$[\text{MnO}_4]^{1-/2-}$	(6)
$[\text{Fe}(\text{EDTA})]^{1-/2-}$	(7)
$[\text{Fe}(\text{H}_2\text{O})_6]^{3+/2+}$	(8)
$[\text{Co}(\text{H}_2\text{O})_6]^{3+/2+}$	(9)
$[\text{Ru}(\text{H}_2\text{O})_6]^{3+/2+}$	(10)
$[\text{Ti}(\text{H}_2\text{O})_6]^{3+/2+}$	(11)
$[\text{V}(\text{H}_2\text{O})_6]^{3+/2+}$	(12)
$[\text{Cu}(\text{H}_2\text{O})_6]^{3+/2+}$	(13)



$$E^{\circ}_{calc} = 0.992E^{\circ}_{exp} - 0.067 \text{ V}$$

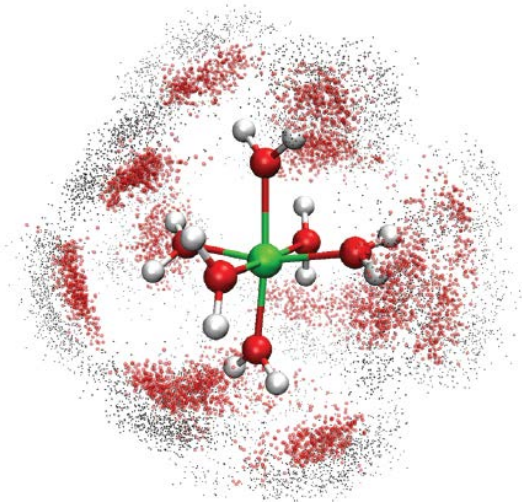
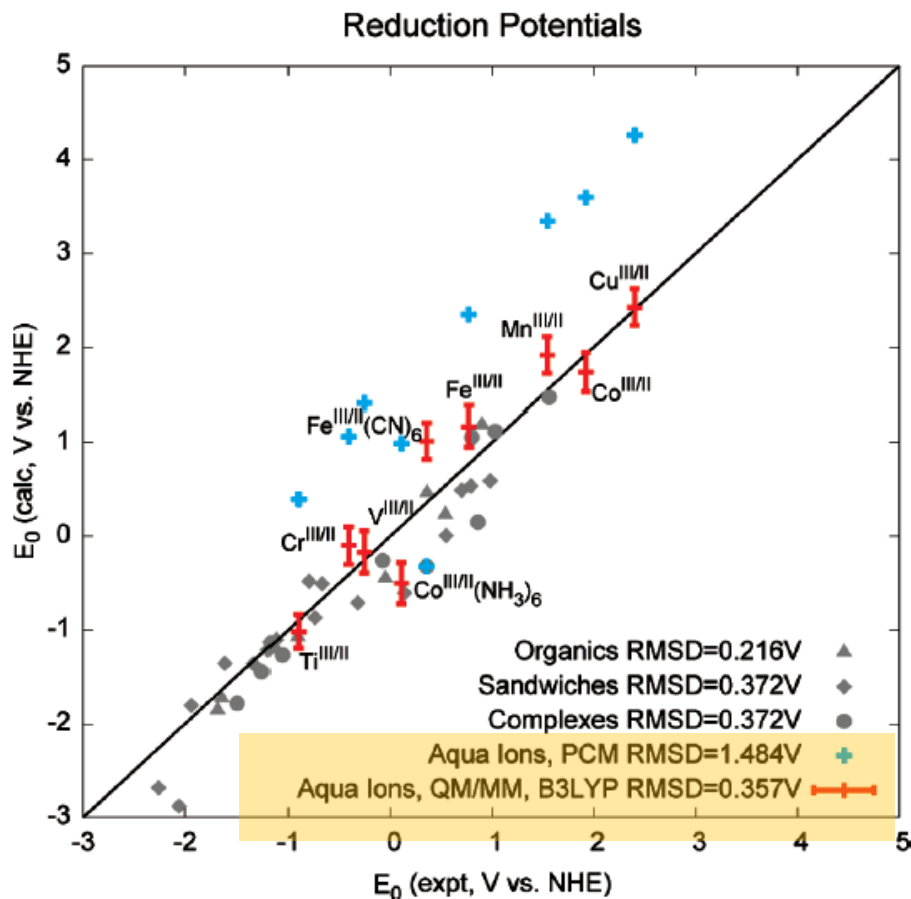
$$R^2 = 0.97$$

$$E^{\circ}_{calc} = 0.944E^{\circ}_{exp} - 0.371 \text{ V}$$

$$R^2 = 0.92$$

Comparison with more advanced QM/MM MD Thermodynamic Integration

Wang & Van Voorhis *J. Chem Theory and Comput.* 2012, 8,610:



RMSD = 0.357 V

versus

our "VT-HAA" approach: **RMSD = 0.035 V (COSMO-RS)**

RMSD = 0.270 V (COSMO)

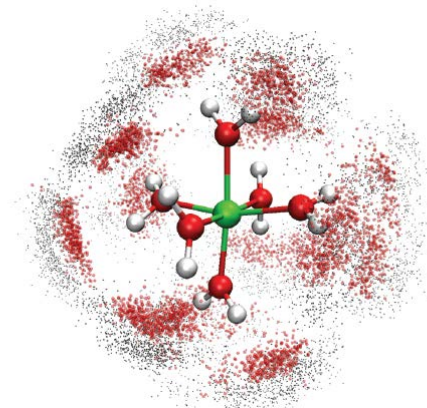
QM/MM MD Thermodynamic Integration

* A Polarizable QM/MM

$$* E(\lambda) = \lambda E_{ox} + (1 - \lambda) E_{red}$$

Potential energy
of the oxidized state

Potential energy
of the reduced state



* Thermodynamic Integration

Coconfiguration function
("classical" partition function in coordinate space)

$$\frac{dA}{d\lambda} = \frac{d}{d\lambda} -k_b T \ln Z = \frac{1}{Z} \sum_i \frac{dE_i(\lambda)}{d\lambda} e^{-E_i(\lambda)/k_B T} = \left\langle \frac{dE(\lambda)}{d\lambda} \right\rangle$$

* Linear response approximation ($dA/d\lambda$) is linearly dependent on λ)

$$\Delta A = \int_{\lambda=0}^1 \left\langle \frac{dE}{d\lambda} \right\rangle d\lambda = \frac{1}{2} \left(\langle E_{ox} - E_{red} \rangle_{ox} + \langle E_{ox} - E_{red} \rangle_{red} \right)$$

$\Delta A \sim \Delta G$ (if ΔpV is negligible) $\rightarrow E^\circ$

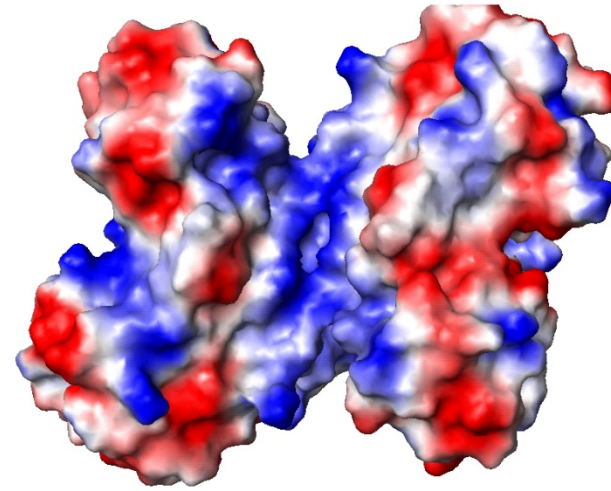
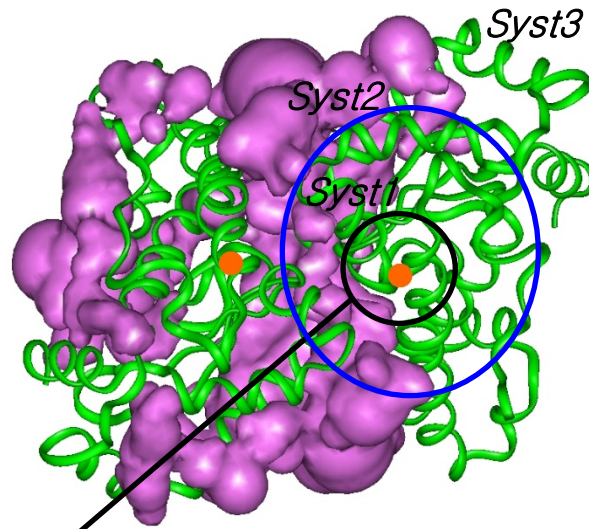
More elaborated thermodynamic cycles..

Reduction potential of an enzymatic complex: Manganese superoxide dismutase



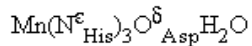
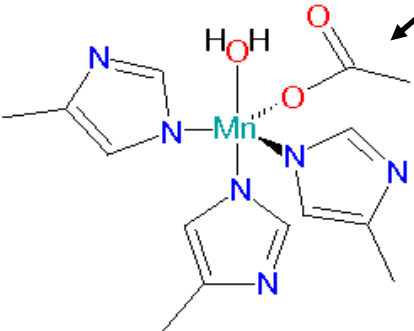
Entrance/Exit channel

Electrostatic potential map



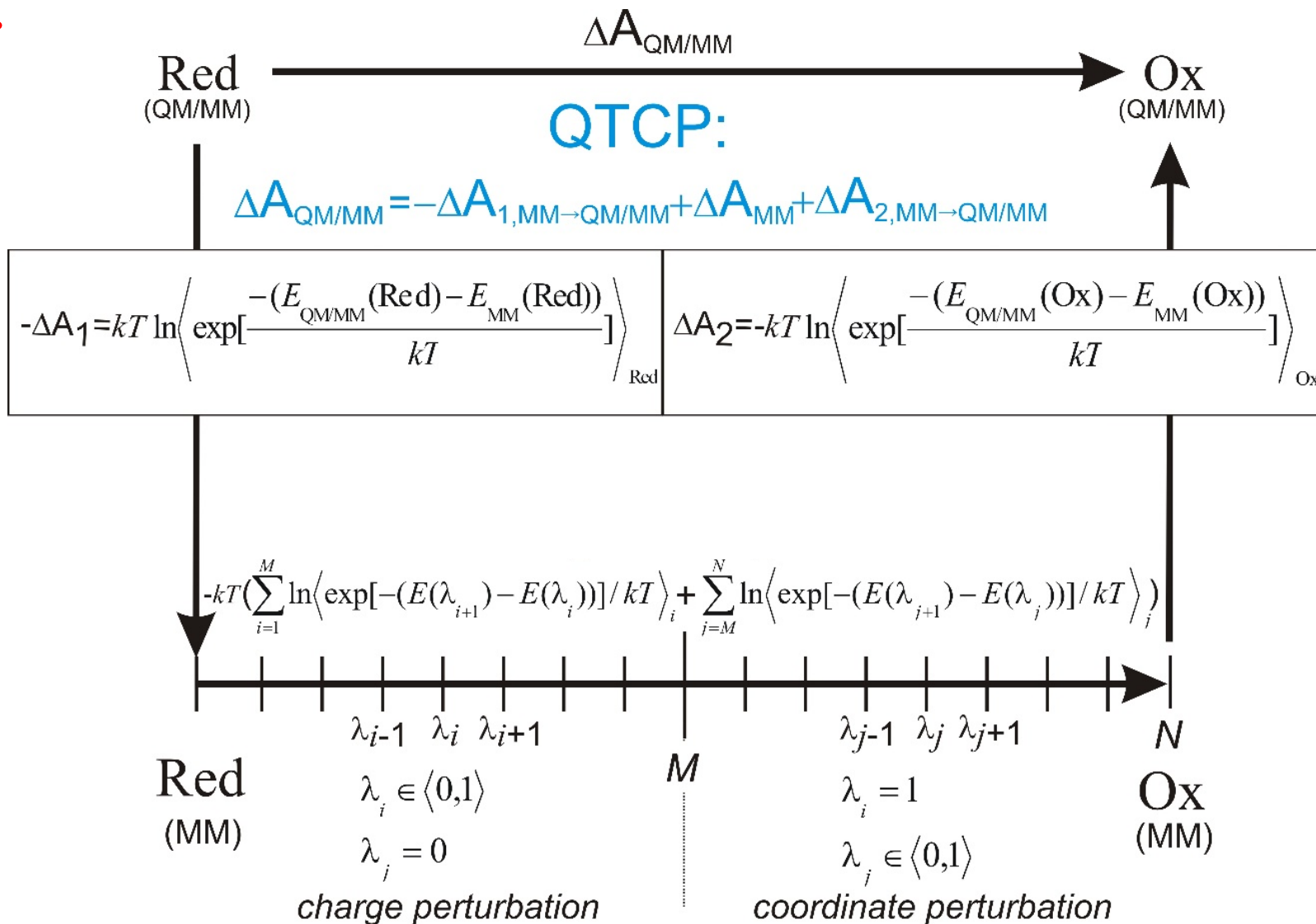
Magenta: entrance/exit channel
Green: protein backbone
Ball: active site

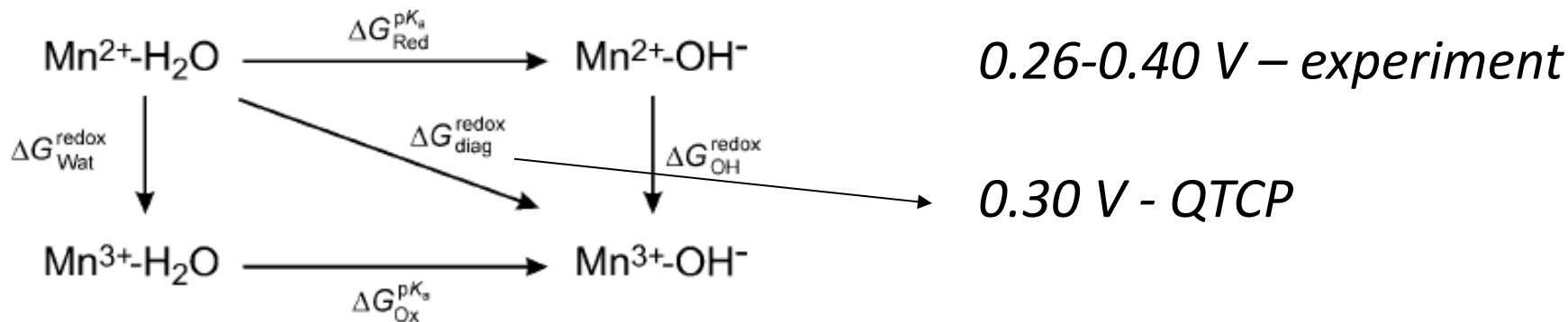
Blue: positively charged region
Red: negatively charged region



QM/MM thermodynamic cycle perturbation - QTCP

ΔA of a reduction process:





In the case of metalloproteins, the explicit protein environment may have a significant effect on the calculated reduction potentials, as it was demonstrated on the examples of plastocyanin and rusticyanin. Despite the high similarities between the copper-containing active sites of both proteins, their reduction potentials differ by more than 300 mV. This phenomenon was found to arise from the long-range electrostatic interactions of the active sites with amino-acid residues, the resulting shift in plastocyanin and rusticyanin being -166 mV and $+170$ mV.

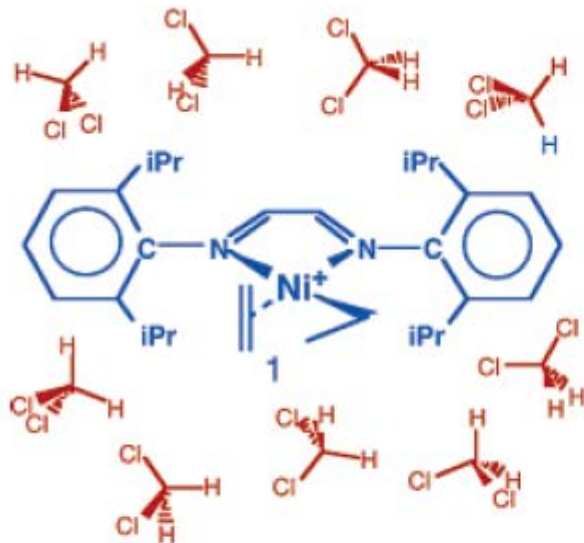
QM/MM-FEP ; QTCP... - suitable techniques to study reduction potentials and $\text{p}K_a$ in enzymes.

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

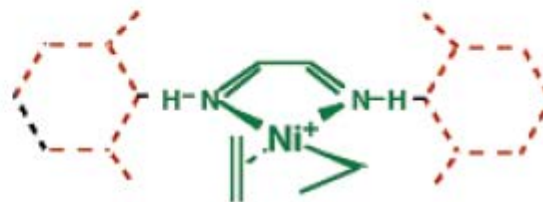
- lecture 11 -

Various types of models used for modelling chemical reactions in solutions

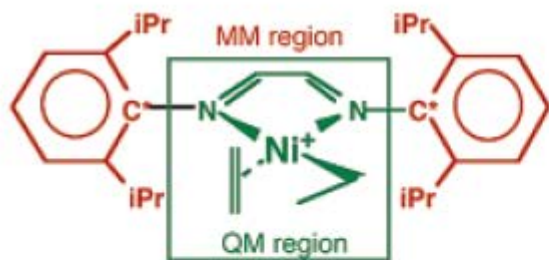
a. Real System



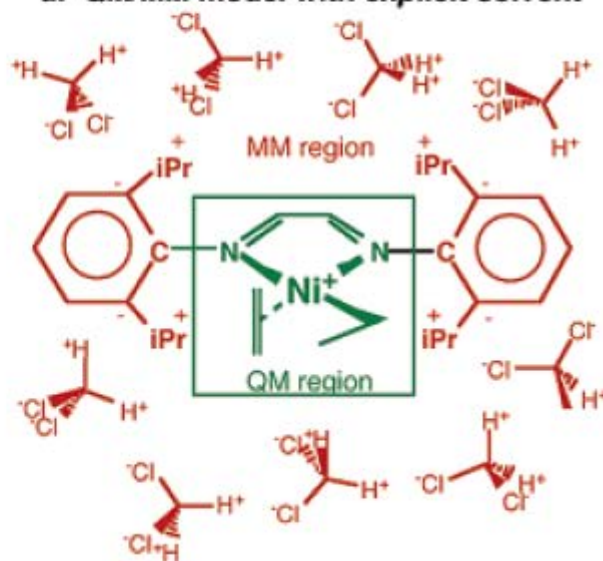
b. Most Pure QM Calculations & QM model system



c. QM/MM Model



d. QM/MM model with explicit solvent

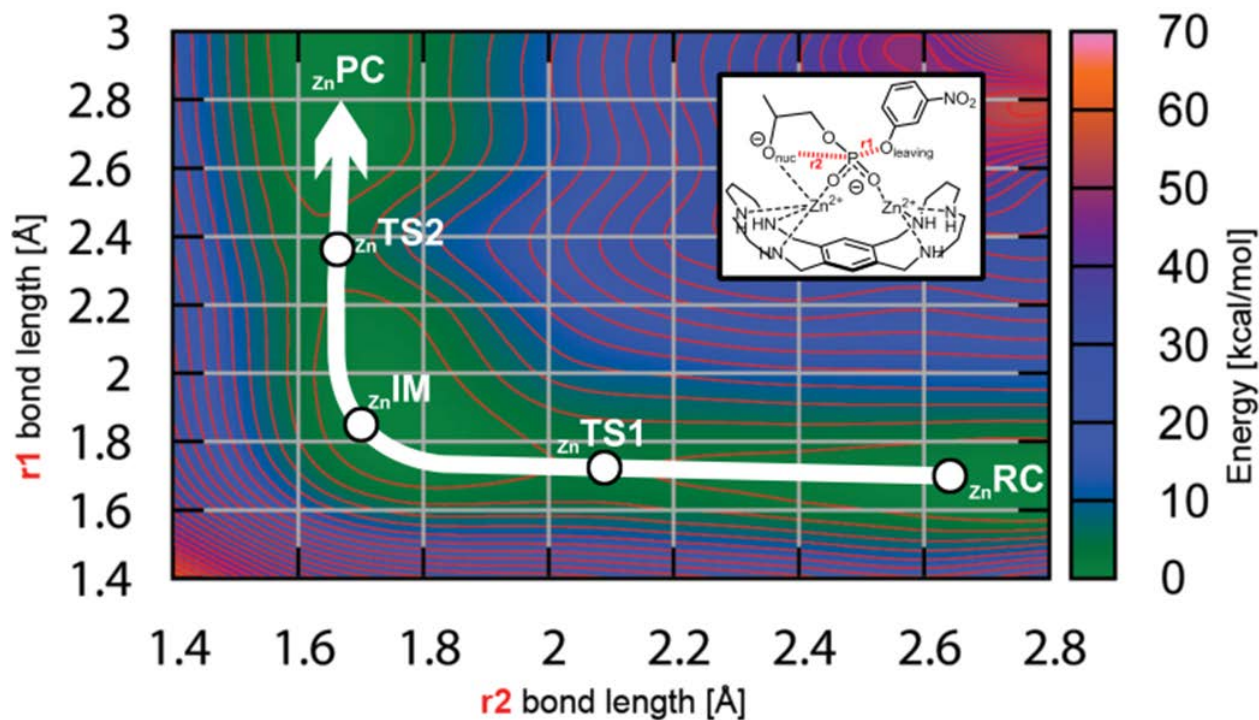


Key concept of a reaction coordinate and search for TS's

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:

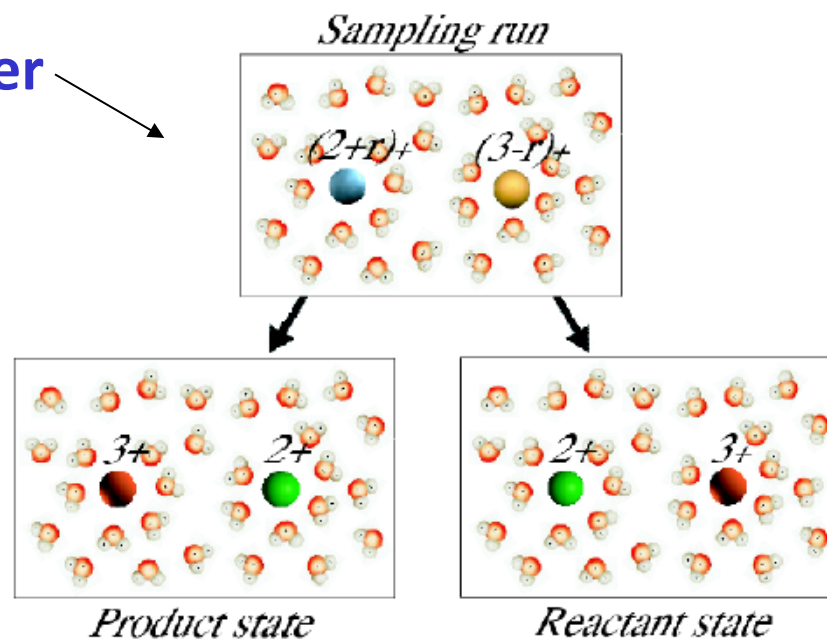
- **Collective (non-intuitive) reaction coordinate**

e.g.:

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

- **Electron transfer**

etc...



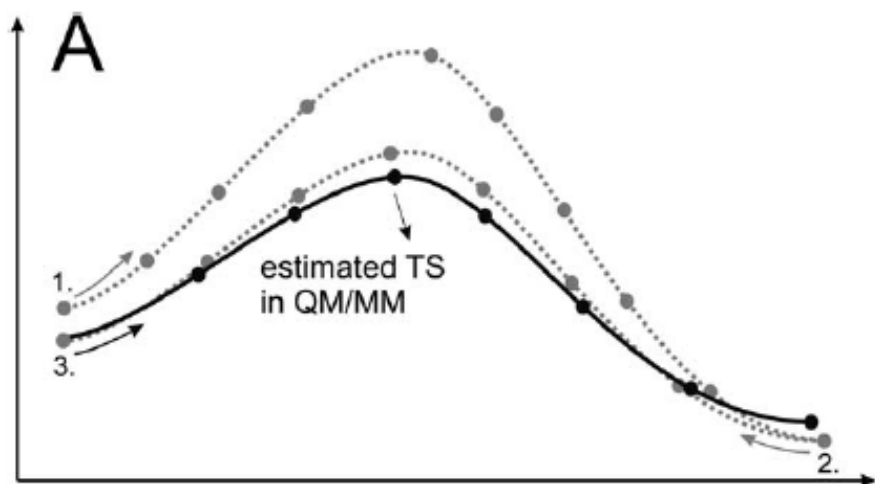
How to trap (meaning find and optimize) a “static” transition state using an easily definable reaction coordinate:

- 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).

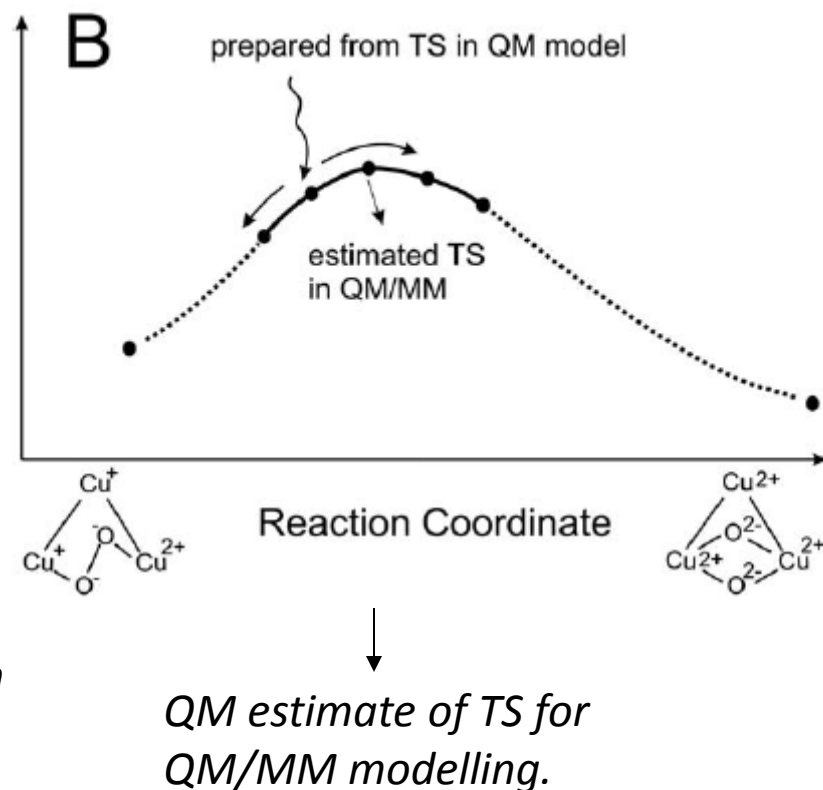
Alternative strategies in searching relevant TS's (next lecture)

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.

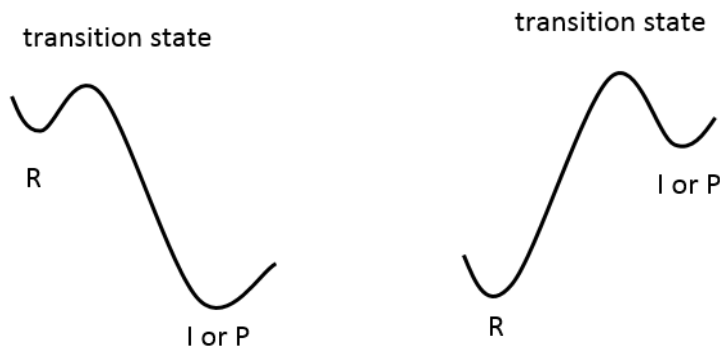


Transition State, its characterization in terms of its position along a reaction coordinate

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)*

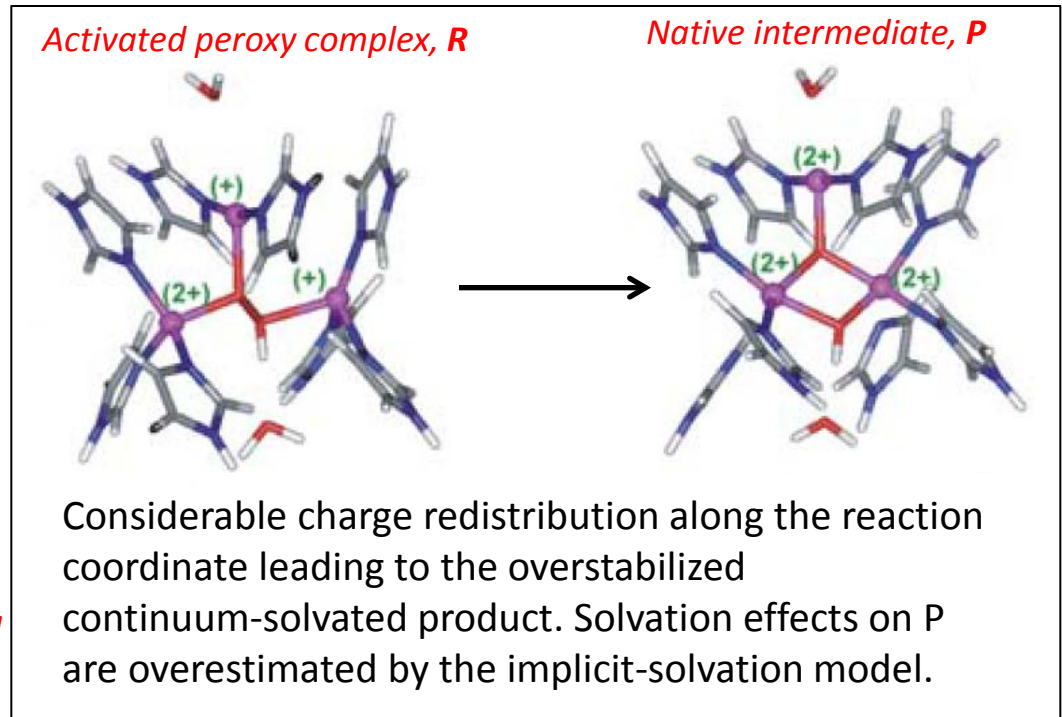
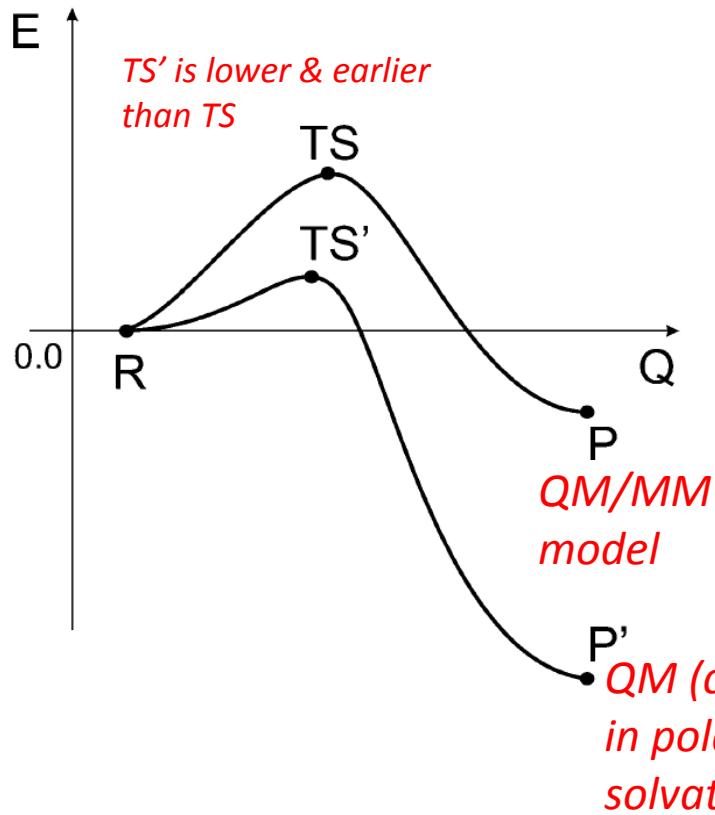
⇒ This resemblance/position with **R** or **P** is also reflected by the relative free energy of TS with respect to the reactant /product state



Hammond postulate
(kinetic-thermodynamic connections)

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

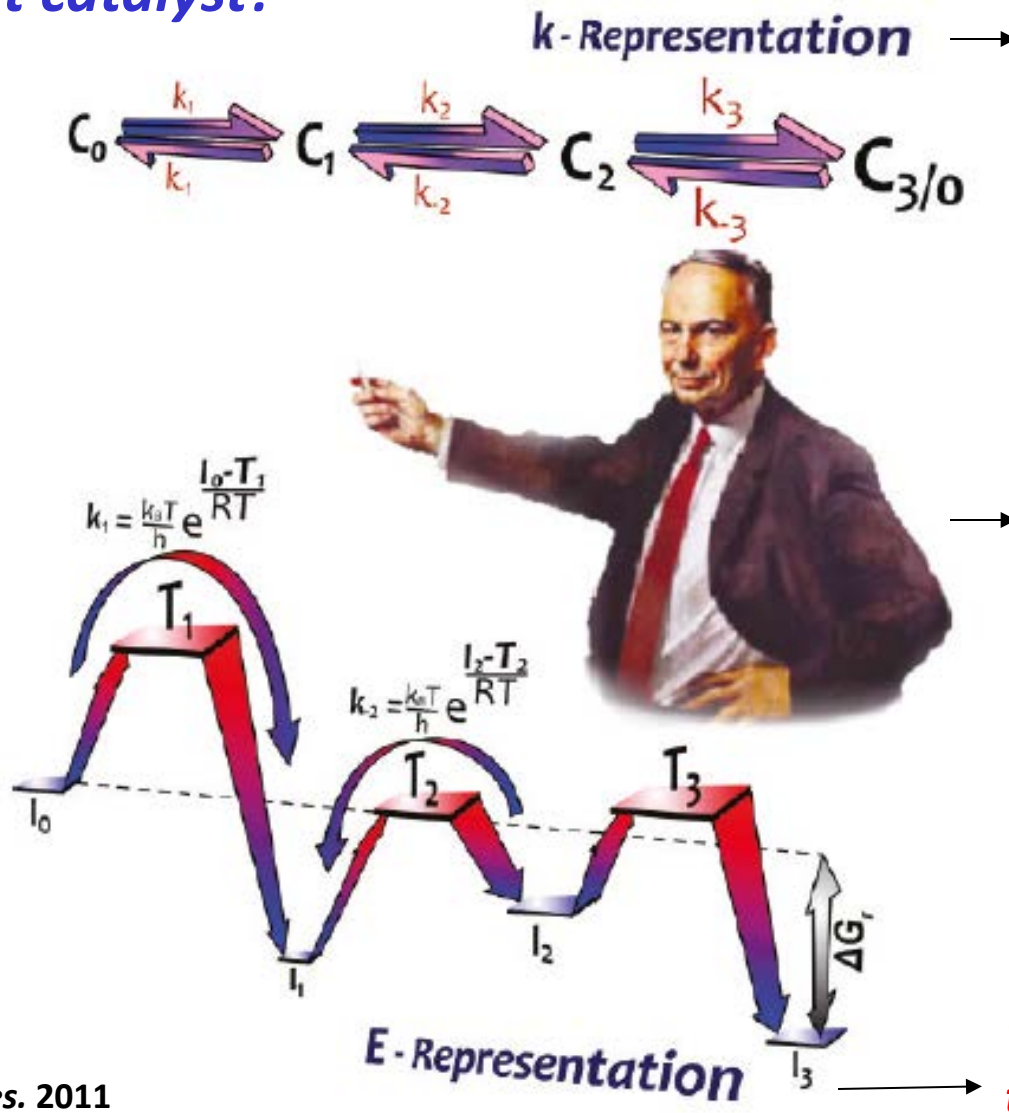
Case of the O_2^{2-} reduction in the active site of multi-copper oxidase:



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

Catalyzed reactions – prominent reactions in chemistry

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

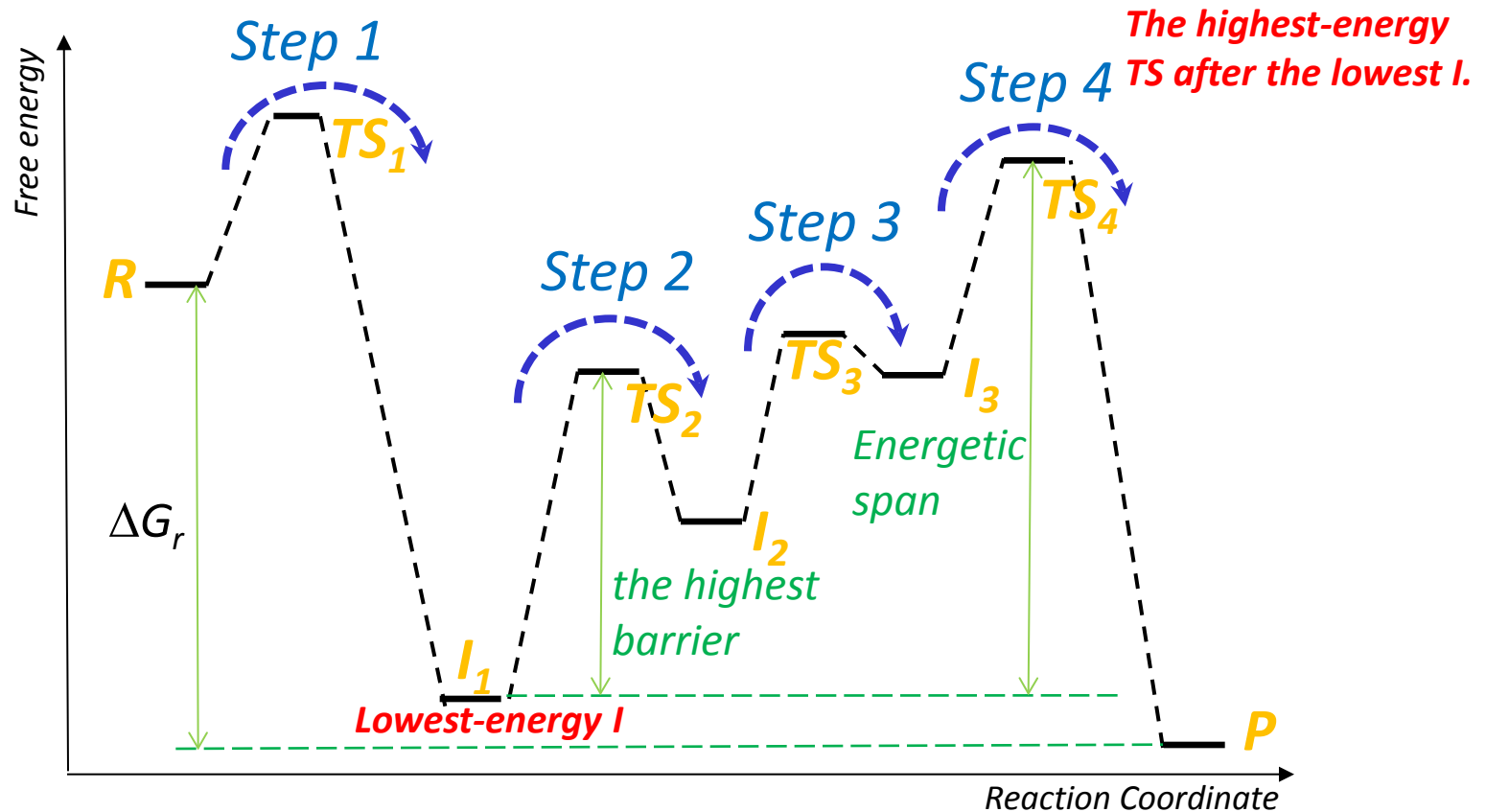


World of an experimentalist

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.

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

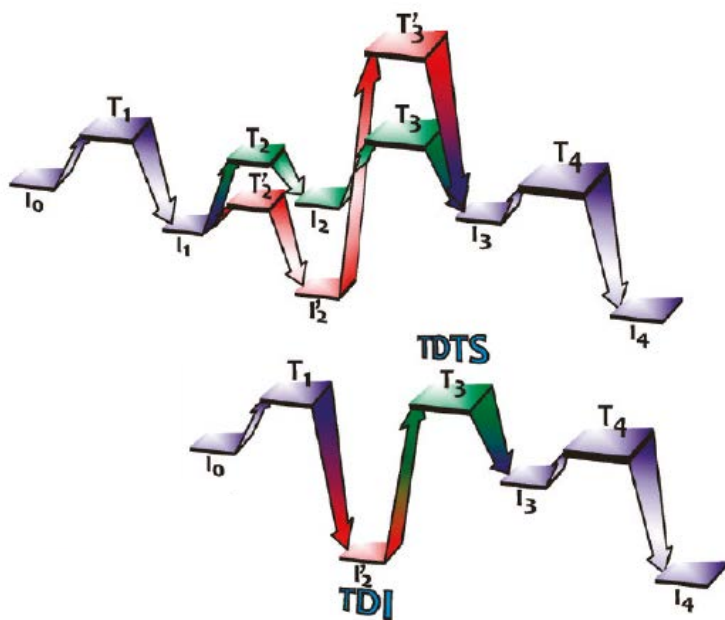
Eq. 1 can be simplified if the denominator M is dominated by a single term of the summation:

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

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

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

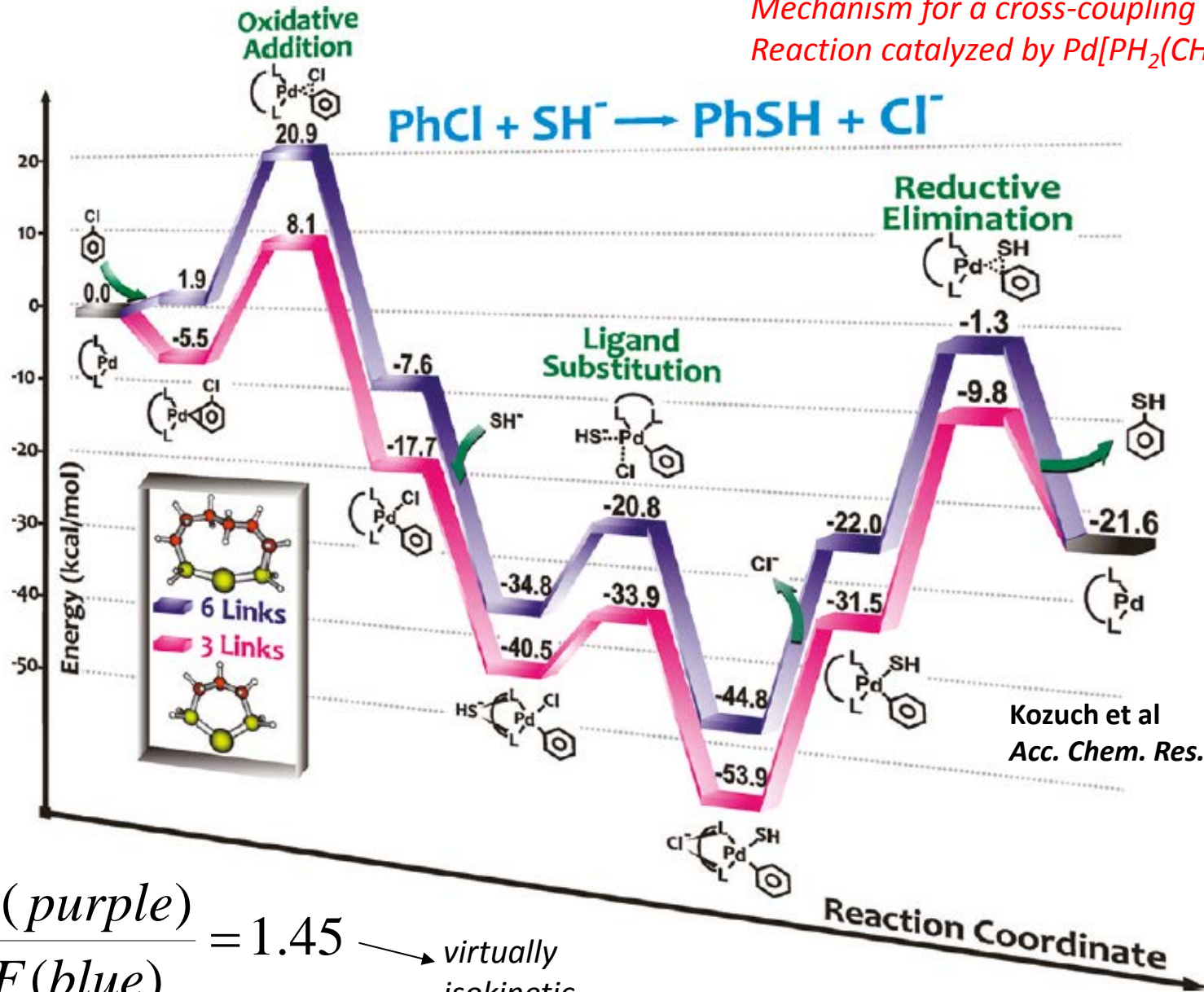
but

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 $\text{Pd}[\text{PH}_2(\text{CH}_2)_n\text{PH}_2]$



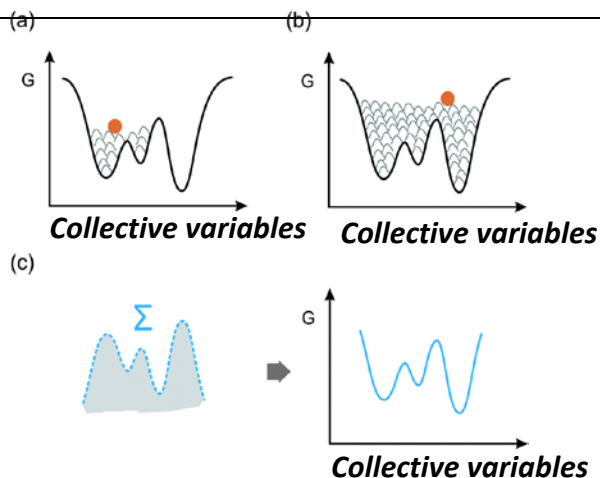
$$\frac{\text{TOF}(\text{purple})}{\text{TOF}(\text{blue})} = 1.45 \rightarrow \text{virtually isokinetic}$$

*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

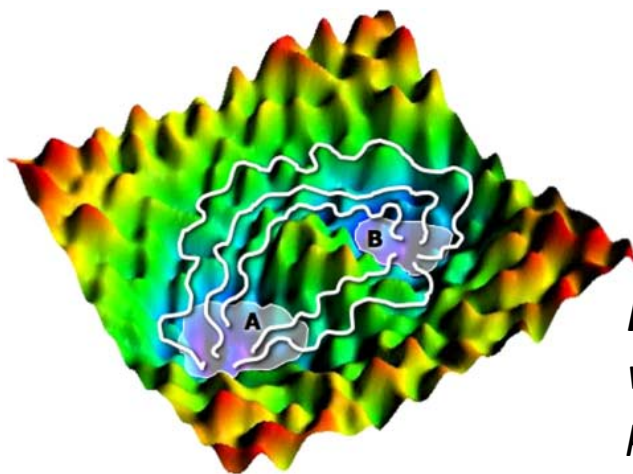
PMF ; QM/MM-FEP ; QM/MM-TI

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**.

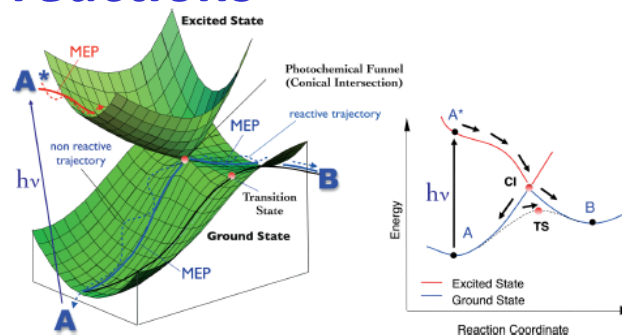
...and free energy profile of diabatic state 1 is given by:

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

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:

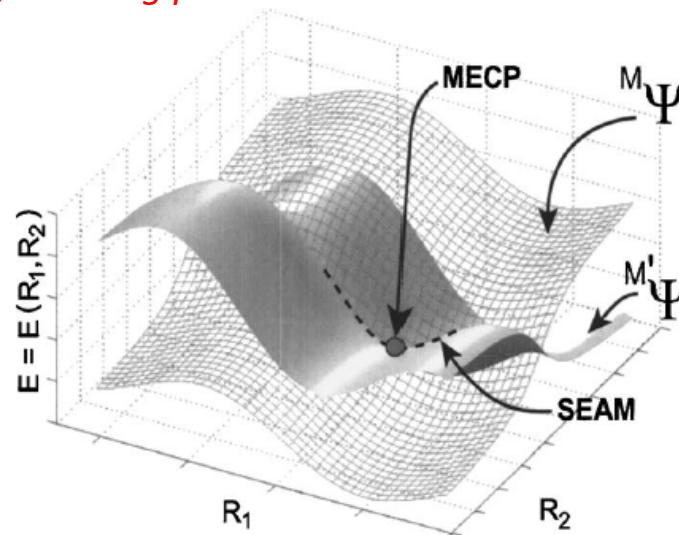
- these states are diabatic (=non-interacting) from the non-relativistic quantum-chemical perspective
- There is no a “classical” TS with one unstable mode along a reaction coordinate but rather the “minimum” on the crossing seam is searched.

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



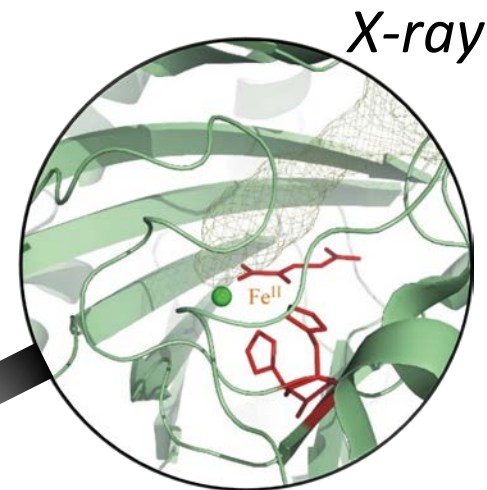
(CASSCF, CASPT2
methods suitable)

Modelling chemical reactions

through correlation of theory and spectroscopy

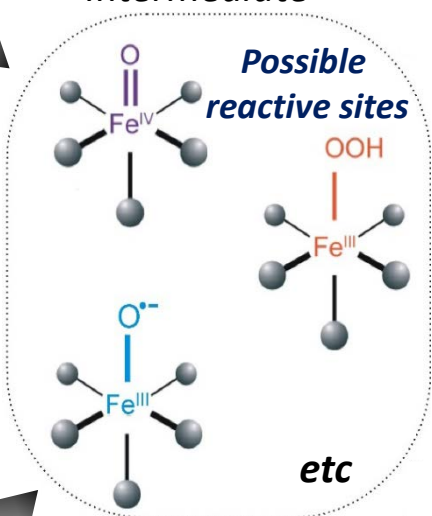
Calculations of physico-chemical properties of biomimetic, synthetic Complexes (e.g. reduction potential..)

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..)

