

Potential of Mean Force (PMF)

(finishing lecture 9)

**A way how to evaluate free-energy profiles
along a reaction coordinate $Q(\mathbf{R})$ in an explicit solvation environment:**

Given a one-dimensional coordinate $Q(\mathbf{R})$, which has been expressed as a function of the Cartesian coordinates \mathbf{R} , its distribution in an equilibrium ensemble at temperature T can be written as:

$$P(Q) = \frac{Z(Q)}{Z}$$

where

Z is the overall configurational integral

$Z(Q)$ is the configurational integral over all coordinates orthogonal to $Q(\mathbf{R})$ at the section $Q(\mathbf{R})=Q$.

$$Z(Q) = \int \delta(Q(\mathbf{R}) - Q) e^{-V(\mathbf{R})/k_B T} d\mathbf{R} \quad \& \quad Z = \int Z(Q) dQ$$

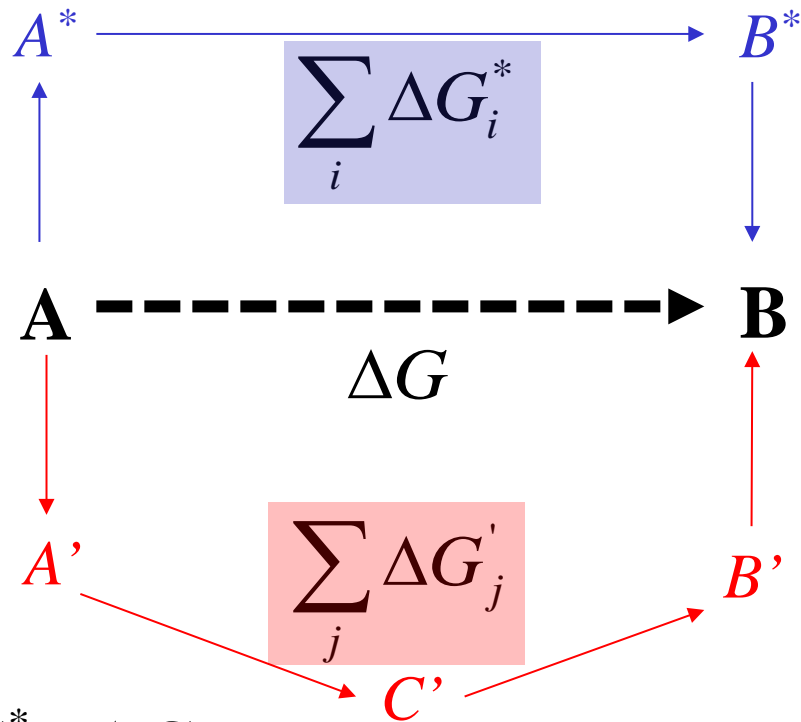
Free-energy profile is calculated as:

$$\Rightarrow G(Q) = -k_B T \ln Z(Q) = -k_B T \ln P(Q) + C$$

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

- lecture 10 -

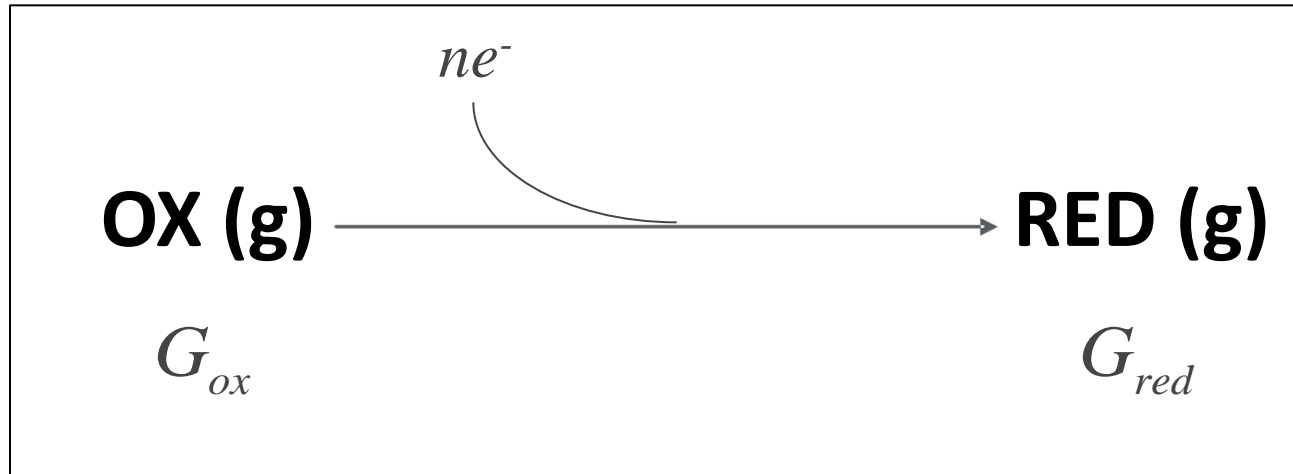
→ No dependence of (ΔG , ΔH , ΔS ...) on a pathway..



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

Case problem: Reduction potential

Half reaction



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



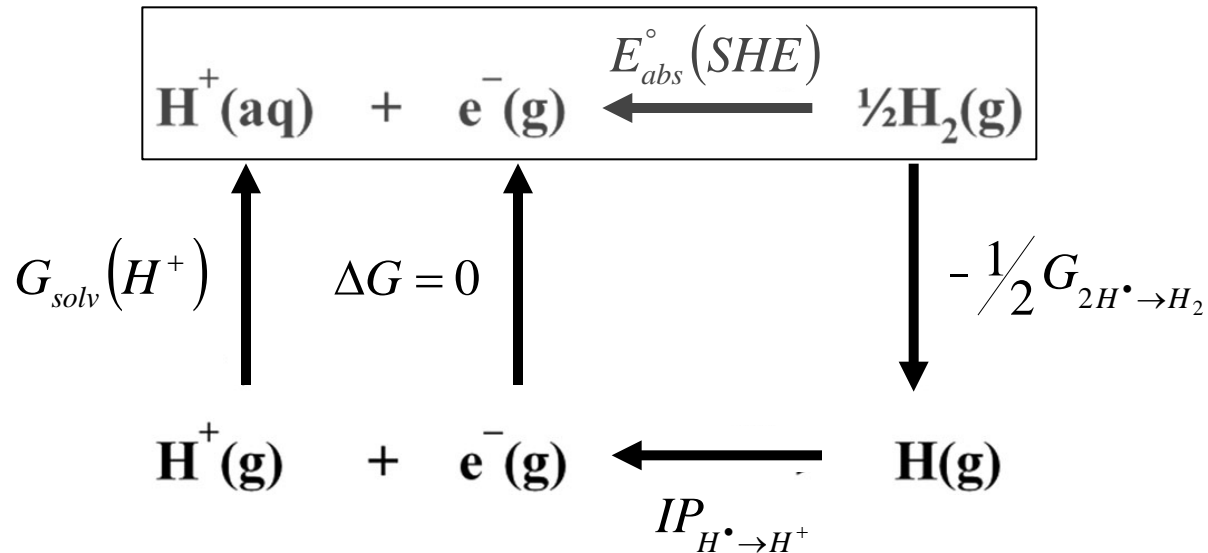
Absolute potential of a (reference) standard hydrogen electrode

Given as the sum of three terms:

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

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

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 ?

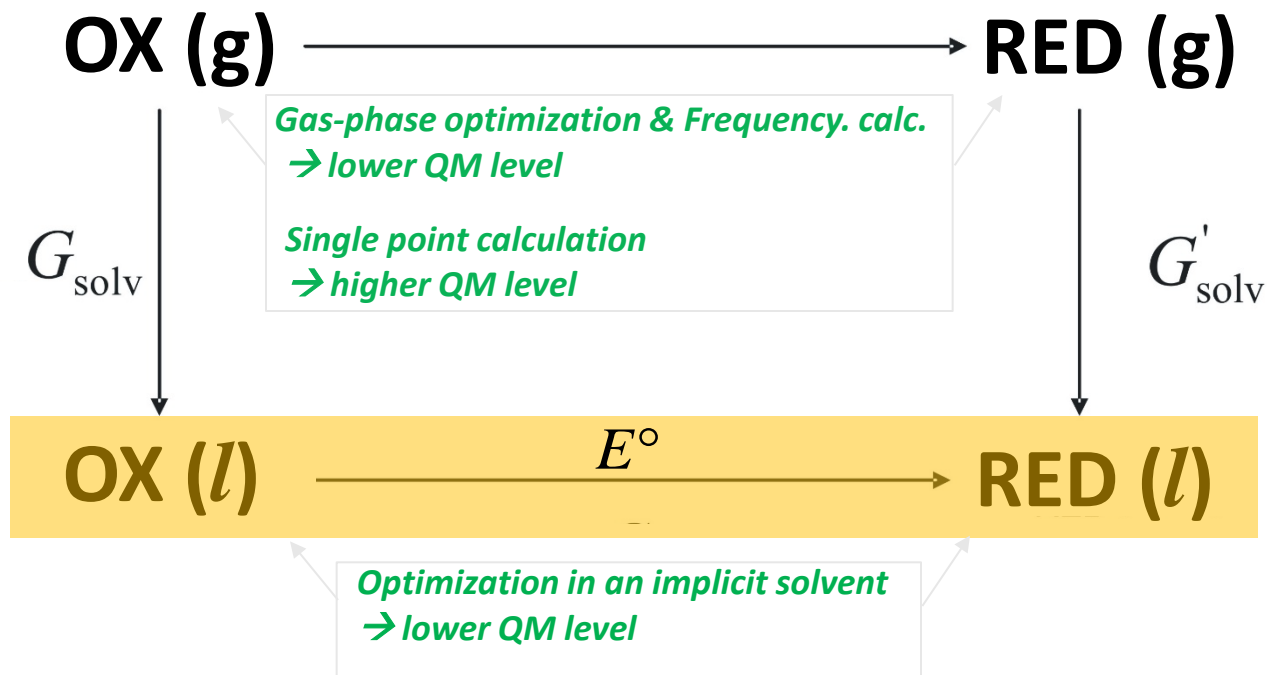
From lecture 5: *Ideal gas-phase, harmonic-oscillator, rigid-rotor approximation + protocol based on implicit-solvent model:*

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

- * *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)*

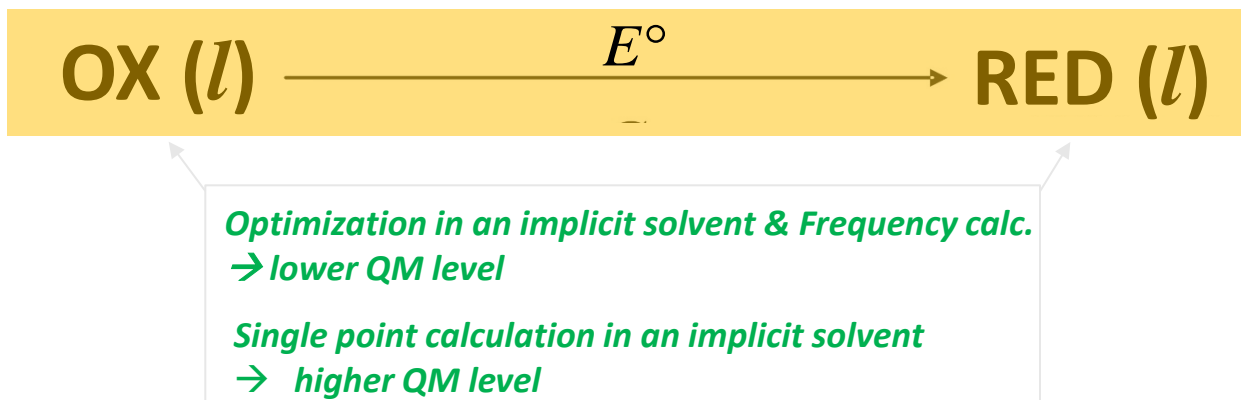
Calculation of reduction potentials using a thermodynamic cycle

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



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

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



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

= “*the standard approach*”

It was demonstrated for aminoacids 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

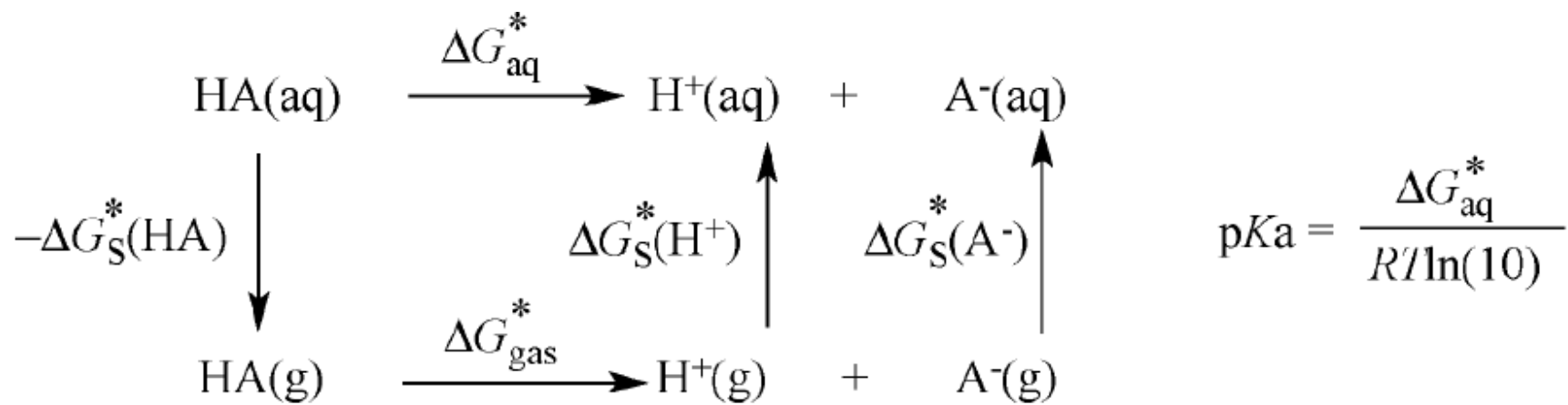
max. dev (exp/calc): 0.1 V

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

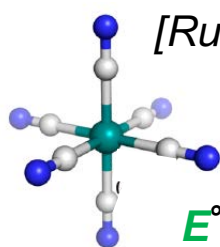
Thermodynamic cycle for calculating pK_a



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

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

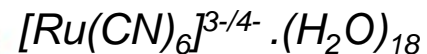
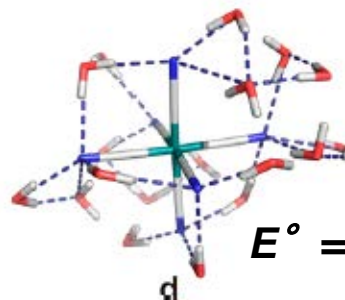
- *systems with a high molecular charge*
- *polar (and protic) solvents*



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

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

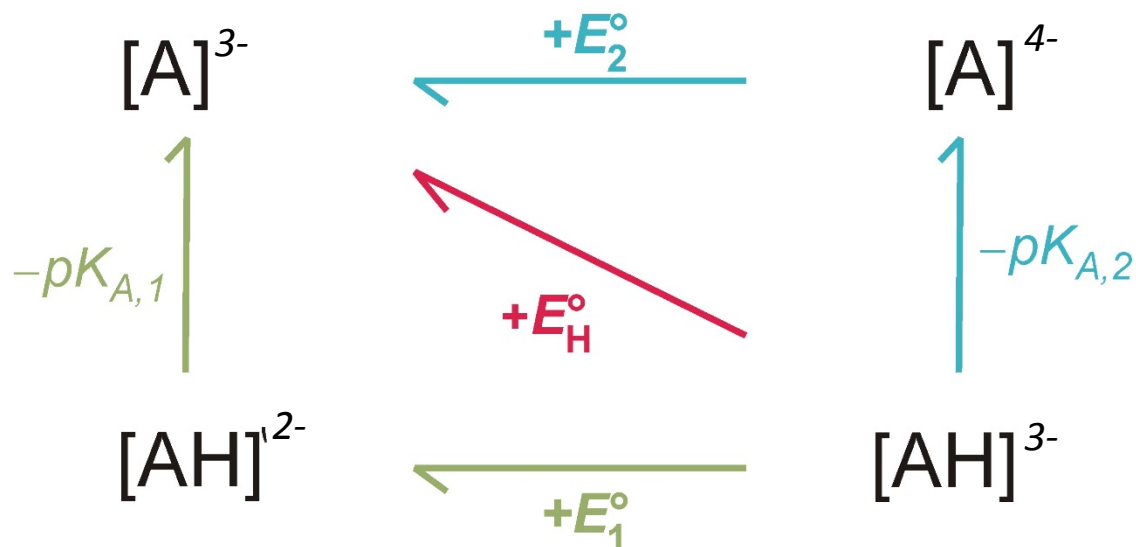
$$E^\circ = 0.12 \text{ V (SMD)}$$



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

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

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

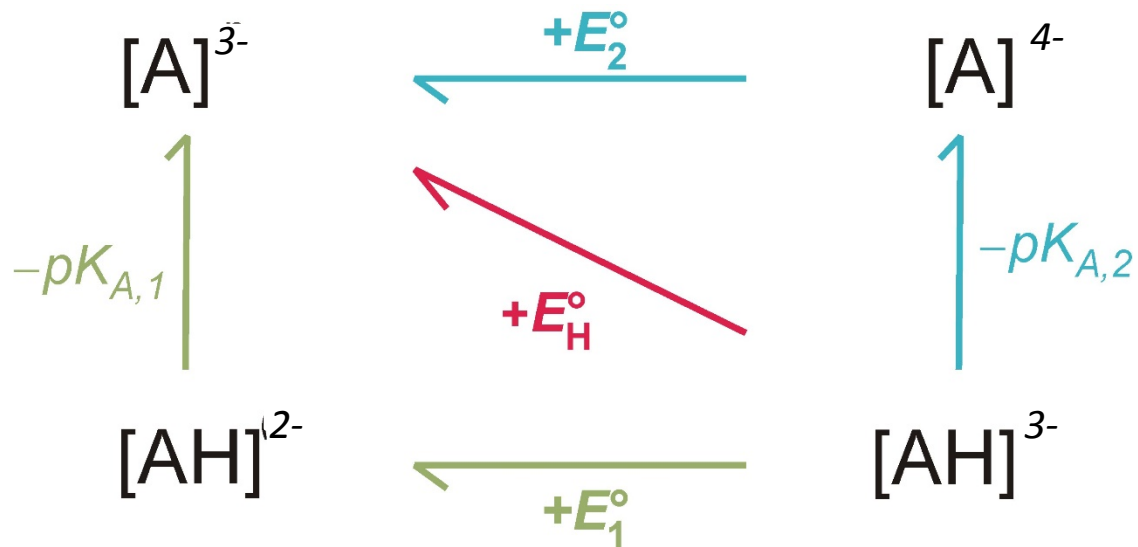


E_2° as a function of E_H° and E_1°

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.

VT-HAA : Derivation



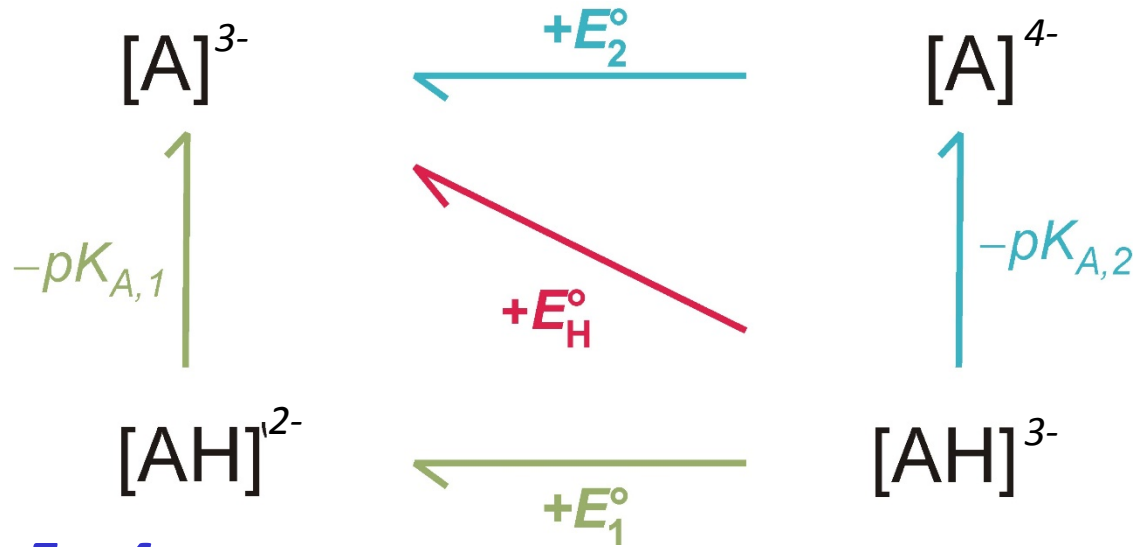
$$1. \quad \Delta E_H^\circ = \Delta G_{diag} + G_{solv}(H^+) - E_{abs}^\circ(SHE) \quad \text{Eq. 1}$$

$$2. \quad \Delta E_H^\circ = E_1^\circ - 2.3RTpK_{a,1} = E_2^\circ - 2.3RTpK_{a,2} \quad \text{Eq. 2}$$

$$\Rightarrow \Delta G_{diag} + G_{solv}(H^+) - E_{abs}^\circ(SHE) = \frac{1}{2}(E_1^\circ + E_2^\circ) - \frac{2.3}{2}RT(pK_{a,1} + pK_{a,2})$$

Eq. 3

VT HAA : Derivation



Eq. 3 → **Eq. 4**

$$\frac{\Delta G_{diag}(T)}{T} = \frac{\varepsilon}{T} - 2.3R \times pK_{a,eff}$$

with

$$\varepsilon = \frac{1}{2}(E_1^\circ + E_2^\circ) + E_{abs}^\circ(SHE) - G_{solv}(H^+) \quad \& \quad pK_{a,eff} = \frac{1}{2}(pK_{a,1} + pK_{a,2})$$

Eq. 5

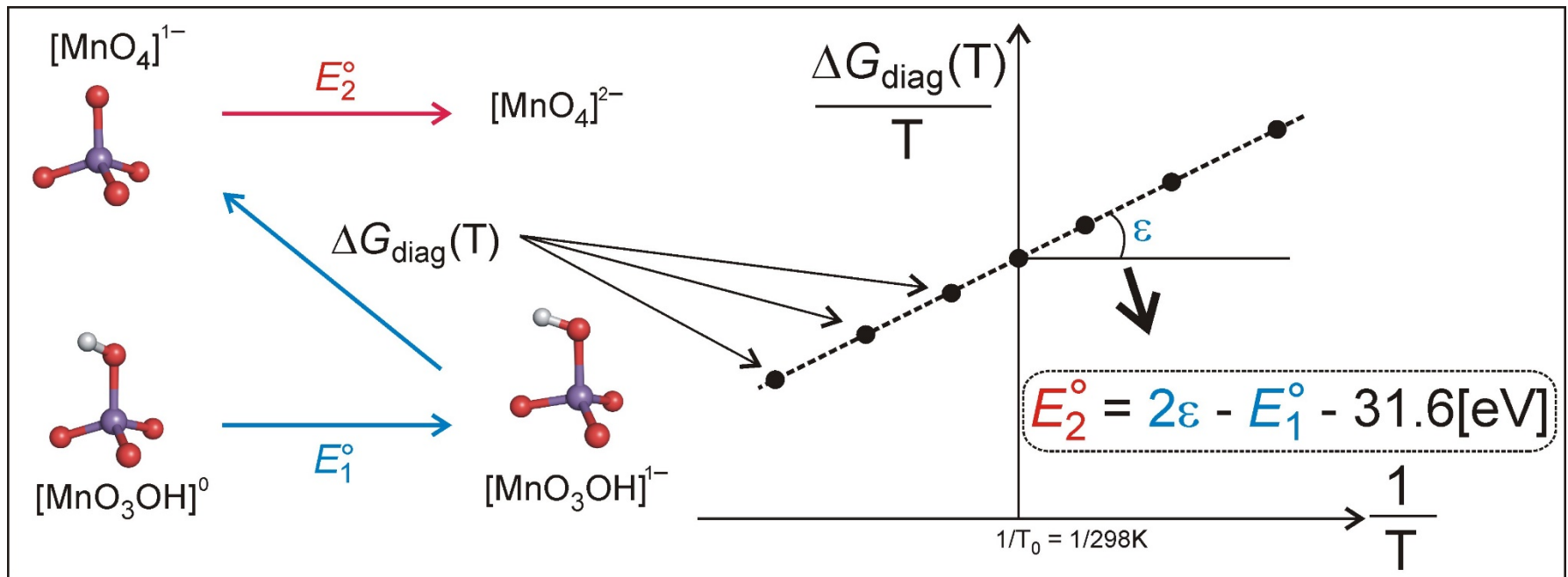
VT-HAA : Derivation

Derivation of Eq.4 with respect to T and using Eq.5:

$$E_2^\circ = 2 \left(\Delta G_{diag}(T_0) - T_0 \frac{d(\Delta G_{diag}(T))}{dT} \Big|_{T=T_0} \right) + 2G_{solv}(H^+) - 2E_{abs}^\circ(SHE) - E_1^\circ$$

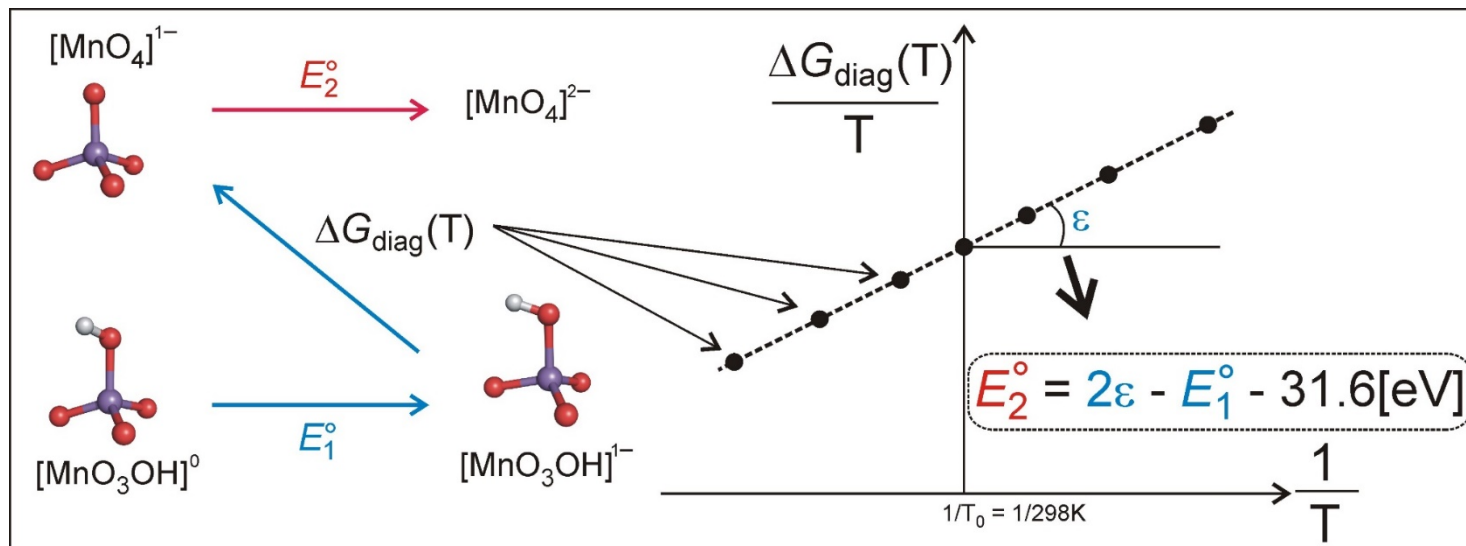
$$= -2 \times IP_{H^\bullet \rightarrow H^+} + G_{2H^\bullet \rightarrow H_2}$$

$$= \mathbf{-31.6 \text{ eV}}$$



VT HAA: Case System

	<i>Expt.</i>	<i>VT</i>	<i>Std.</i>
$[\text{MnO}_4]^{1-/2-}$	0.56 V	0.48 V	-0.18 V



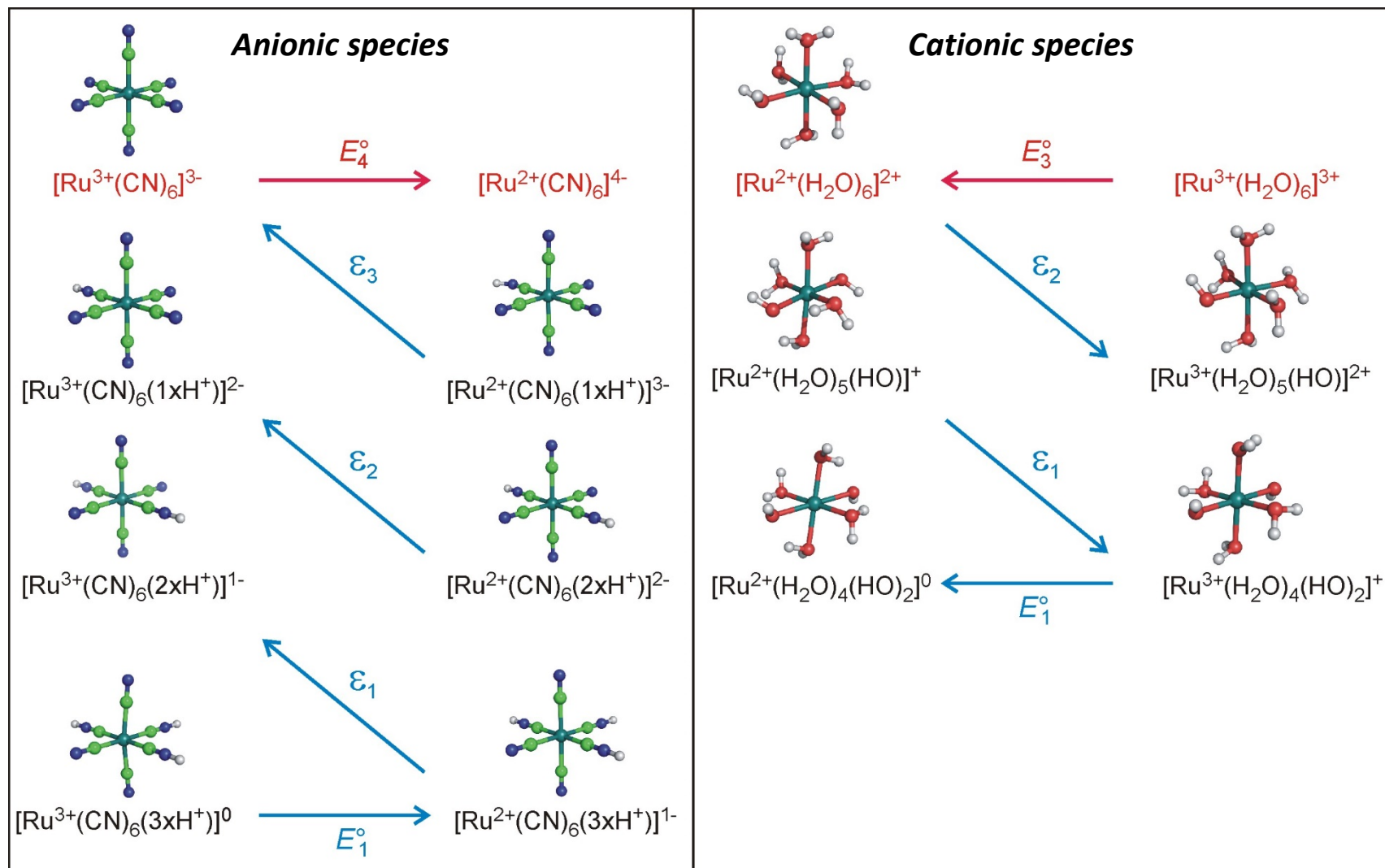
Geometry optimization and frequency calculation : BP86+D3 / def2-TZVPD / COSMO ($\epsilon=80.0$)

In vacuo energy: 2c-PBE+D3/dhf-TZVP-2c

solvation energy: 1) COSMO-RS: BP_TZVPD_FINE_HB2012_C30_1201.ctd for "VT-HA"
 or 2) COSMO($\epsilon=80.0$)

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

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



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

$$E_4^\circ = 2e_3 - 2e_2 + 2e_1 - E_1^\circ - 31.6 \quad \text{for } [\text{Ru}(\text{CN})_6]^{3-/4-}$$

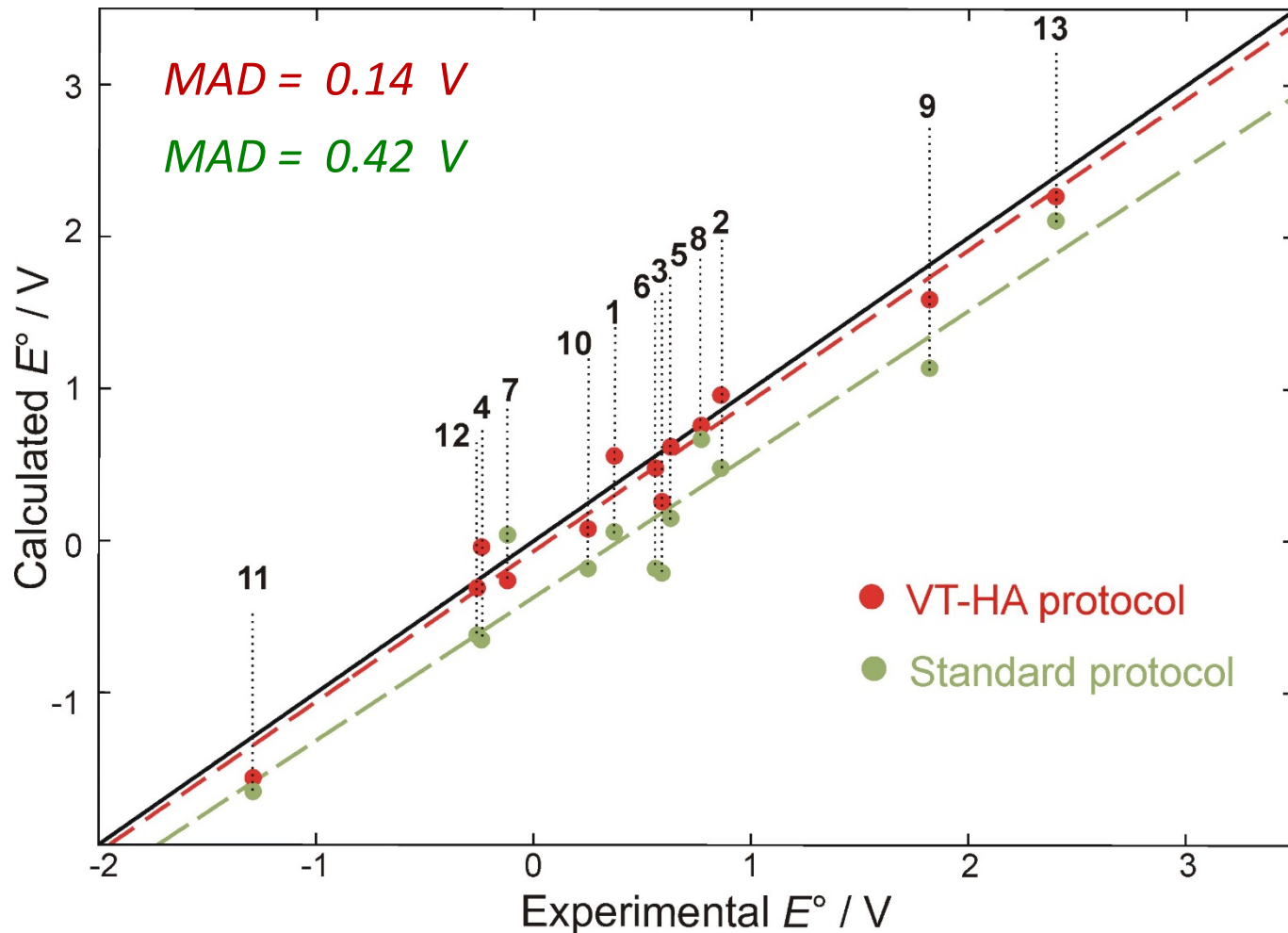
$$E_3^\circ - 2e_2 + 2e_1 + E_1^\circ \quad \text{for } [\text{Ru}(\text{H}_2\text{O})_6]^{3+/2+}$$

	<i>Expt.</i>	<i>VT</i>	<i>Std.</i>
$[\text{Ru}(\text{CN})_6]^{3-/4-}$	0.86 V	0.96 V	0.48 V
$[\text{Ru}(\text{H}_2\text{O})_6]^{2+/3+}$	0.25 V	0.08 V	-0.18 V

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)



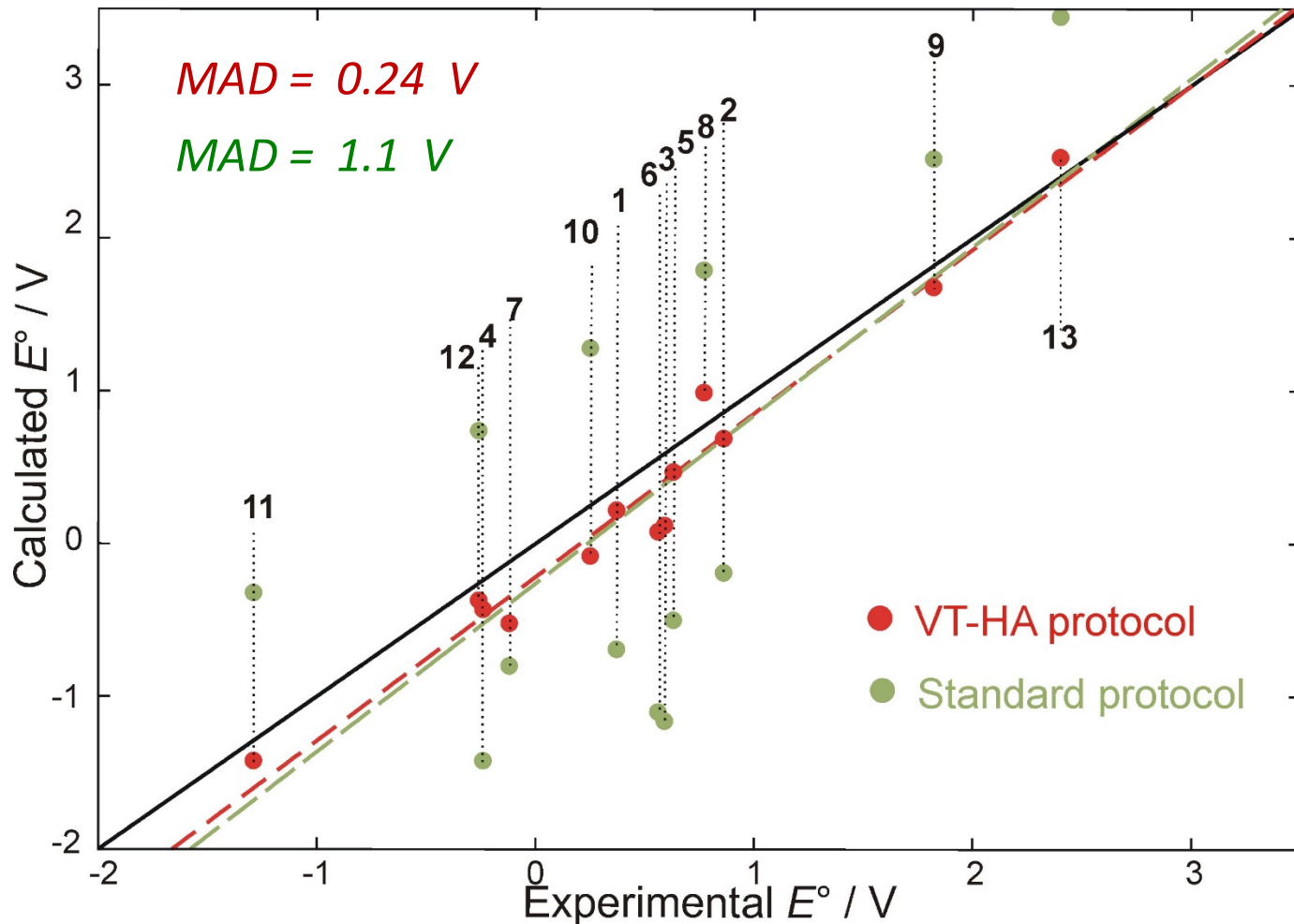
$$E^\circ_{\text{calc}} = 0.992E^\circ_{\text{exp}} - 0.067 \text{ V}$$
$$R^2 = 0.97$$

$$E^\circ_{\text{calc}} = 0.944E^\circ_{\text{exp}} - 0.371 \text{ V}$$
$$R^2 = 0.92$$

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

For COSMO 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)
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$[\text{Ru}(\text{H}_2\text{O})_6]^{3+/2+}$	(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)



$$E^{\circ}_{calc} = 1.072E^{\circ}_{exp} - 0.218 \text{ V}$$

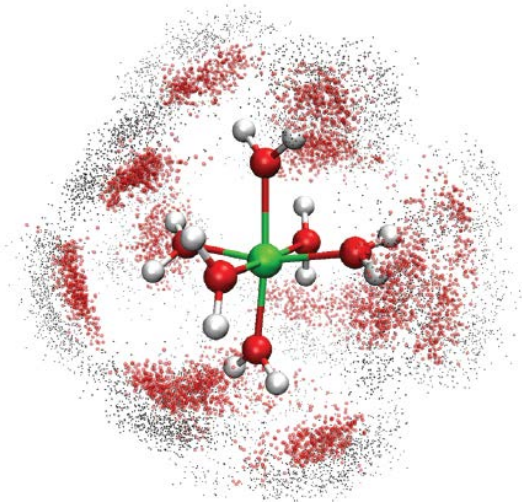
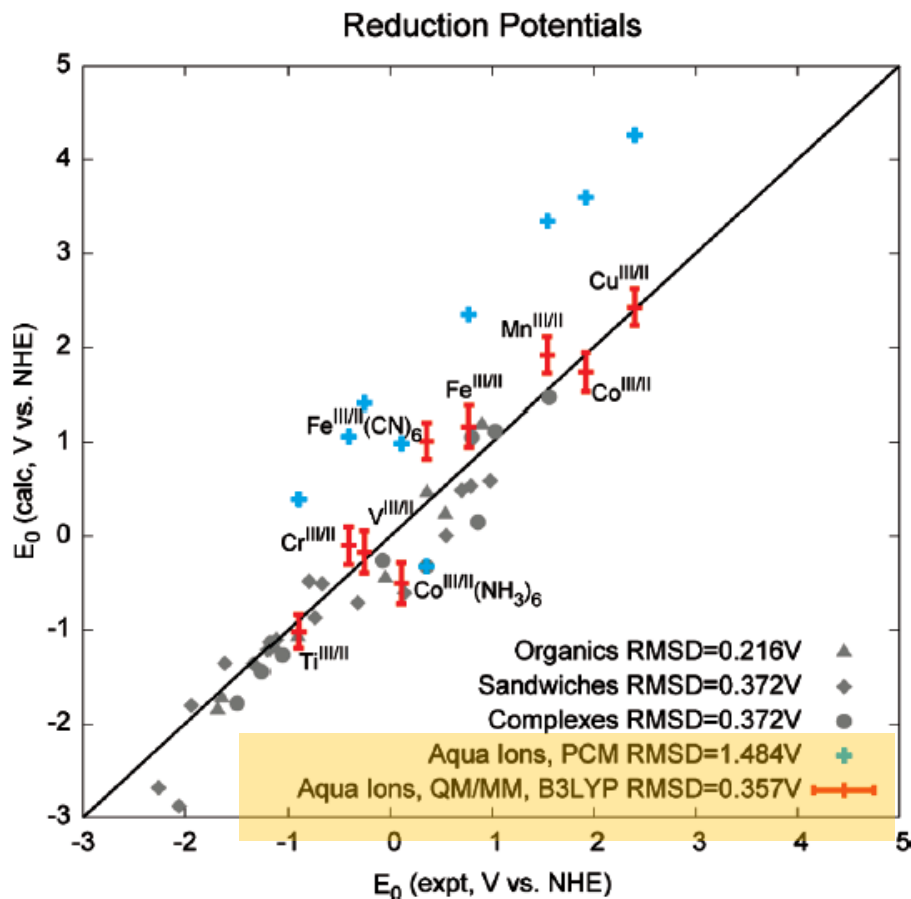
$$R^2 = 0.96$$

$$E^{\circ}_{calc} = 1.102E^{\circ}_{exp} - 0.261 \text{ V}$$

$$R^2 = 0.44$$

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)

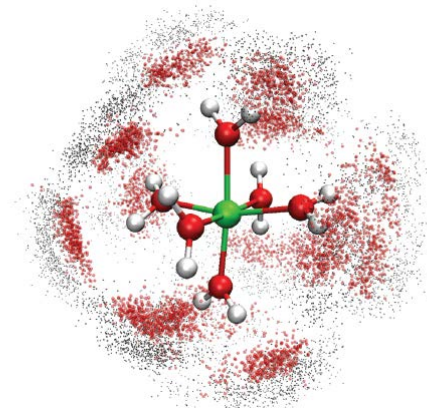
QM/MM MD Thermodynamic Integration

* 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) $\rightarrow E^\circ$

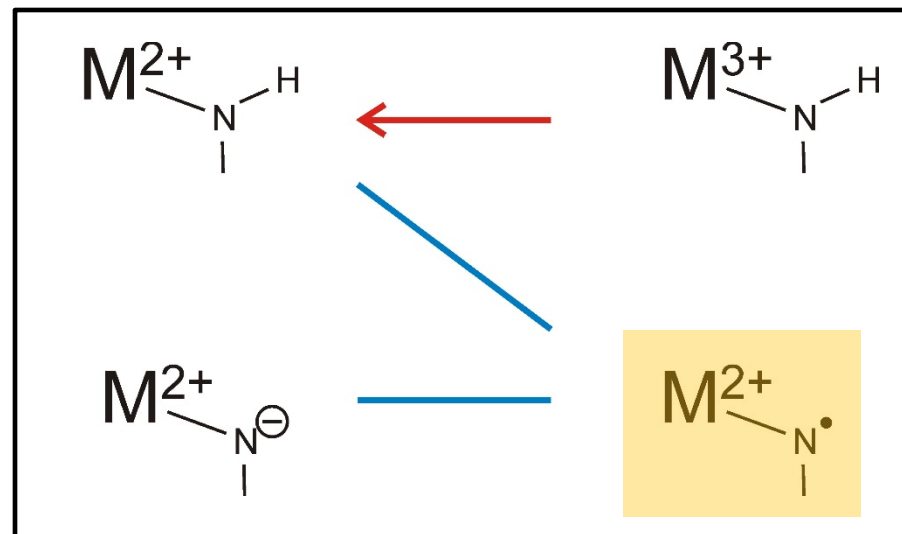
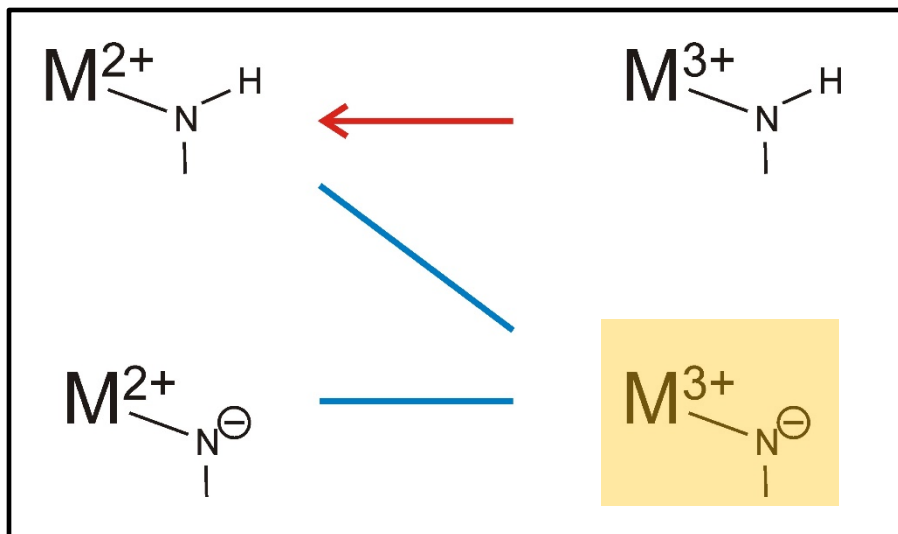
VT-HAA - Possible Failures

	<i>Expt.</i>	<i>VT</i>	<i>Std.</i>
$[\text{Ru}(\text{en})_3]^{2+/3+}$	0.21 V	-1.17 V	0.05 V

The correct "ideal" cycle

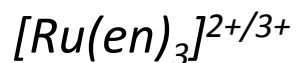


The incorrect cycle



VT HAA employing Cl⁻ counterions

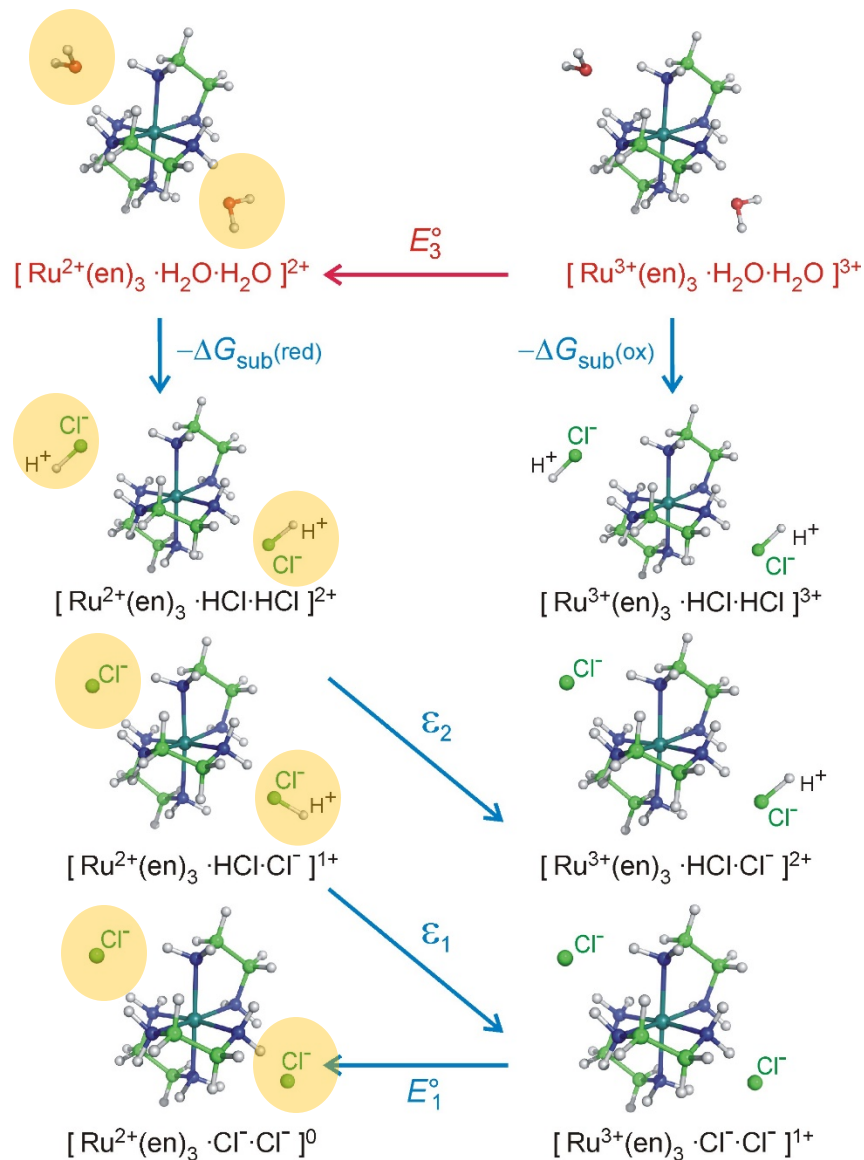
$$E_3^\circ = (\Delta G_{sub}(ox) - \Delta G_{sub}(red)) [eV] - 2e_2 + 2e_1 - E_1^\circ$$



Expt. 0.21 V

VT with Cl⁻ -0.18 V

VT without Cl⁻ -1.17 V



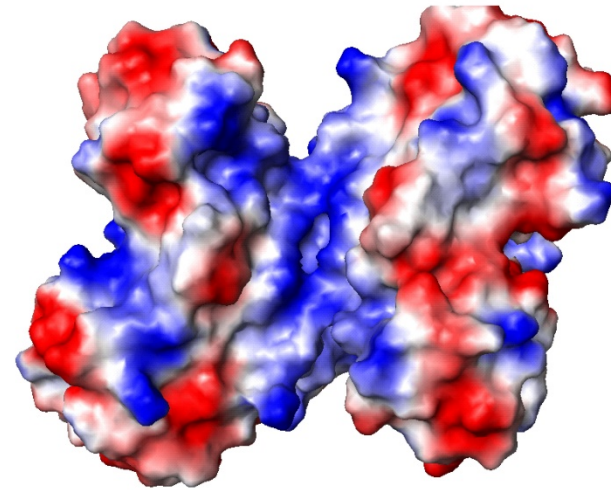
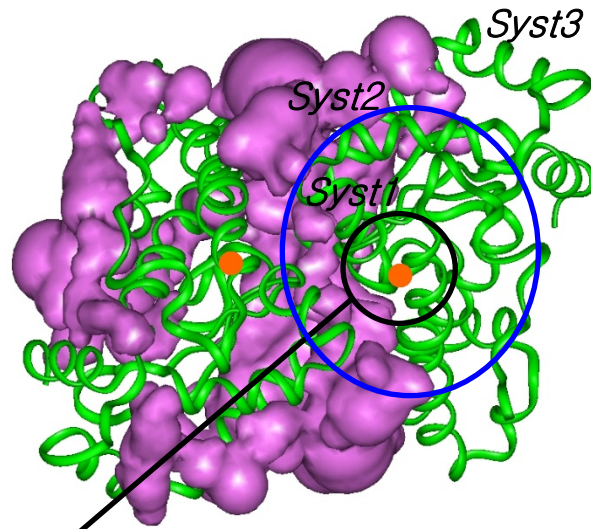
More elaborated thermodynamic cycles..

Reduction potential of an enzymatic complex: Manganese superoxide dismutase



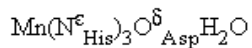
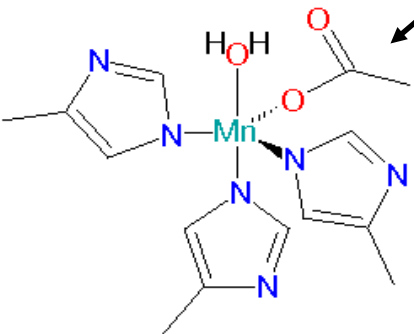
Entrance/Exit channel

Electrostatic potential map



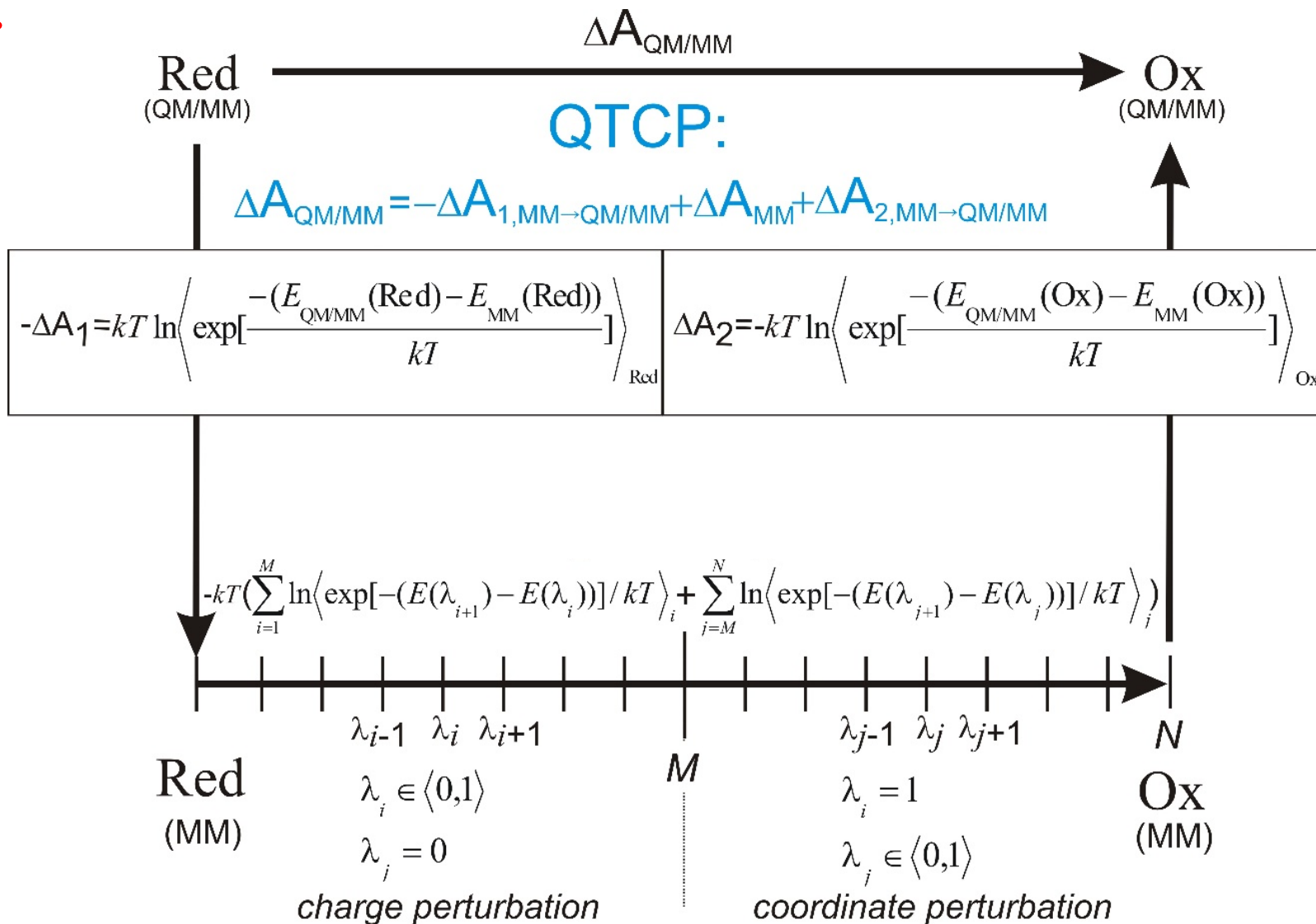
Magenta: entrance/exit channel
Green: protein backbone
Ball: active site

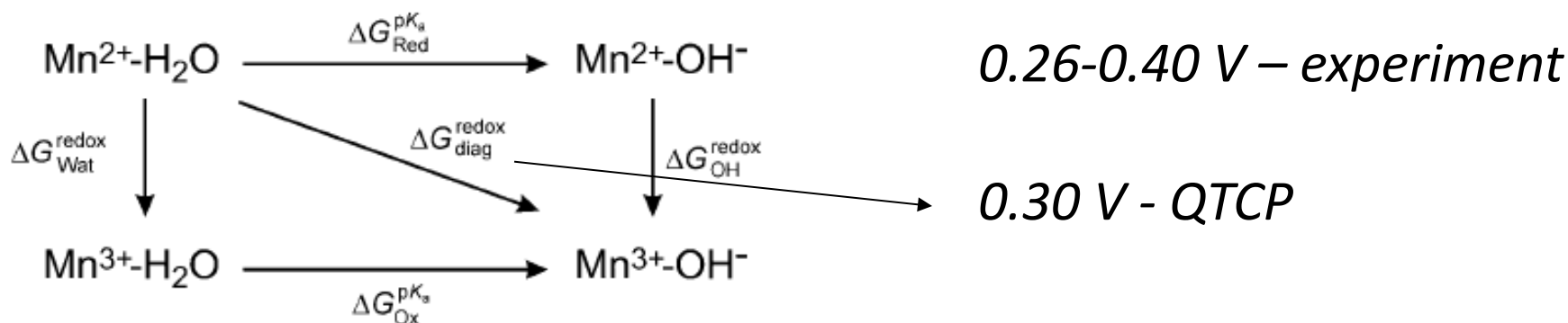
Blue: positively charged region
Red: negatively charged region



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.