Computer Modeling of Chemical Reactions and Enzyme Catalysis: *What Did We Learn?*

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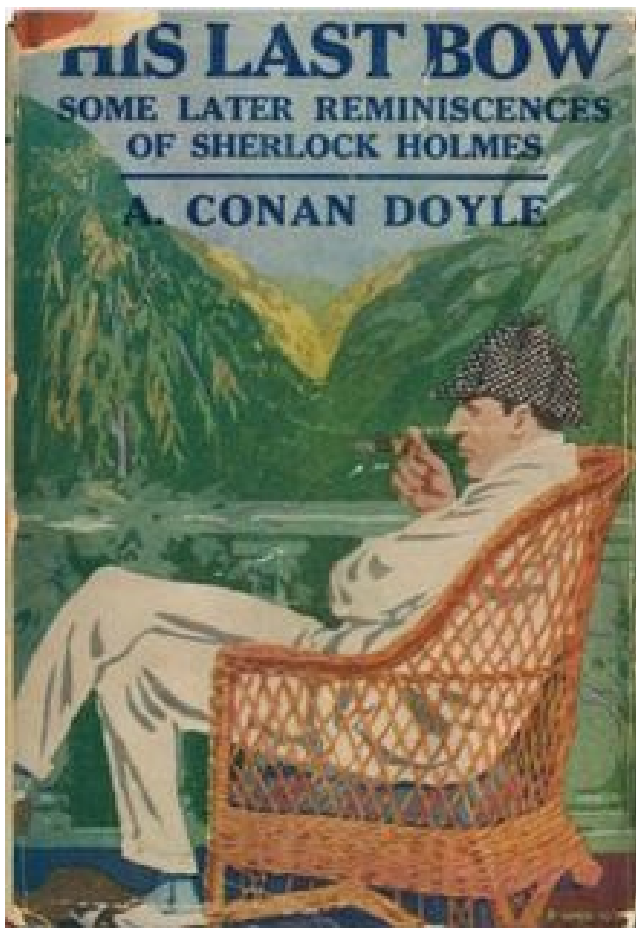
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Computer Modeling of Chemical Reactions and Enzyme Catalysis: *His Last Bow*

How often have I said to you that when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth?

"What's this?" It was a wax vesta half burned, which was so coated with mud that it looked at first like a little chip of wood.

"I cannot think how I came to overlook it," said the Inspector, with an expression of annoyance.

"It was invisible, buried in the mud. I only saw it because I was looking for it."

"What! You expected to find it?"

"I thought it not unlikely."

"Excellent!" I cried.
"Elementary," said he.
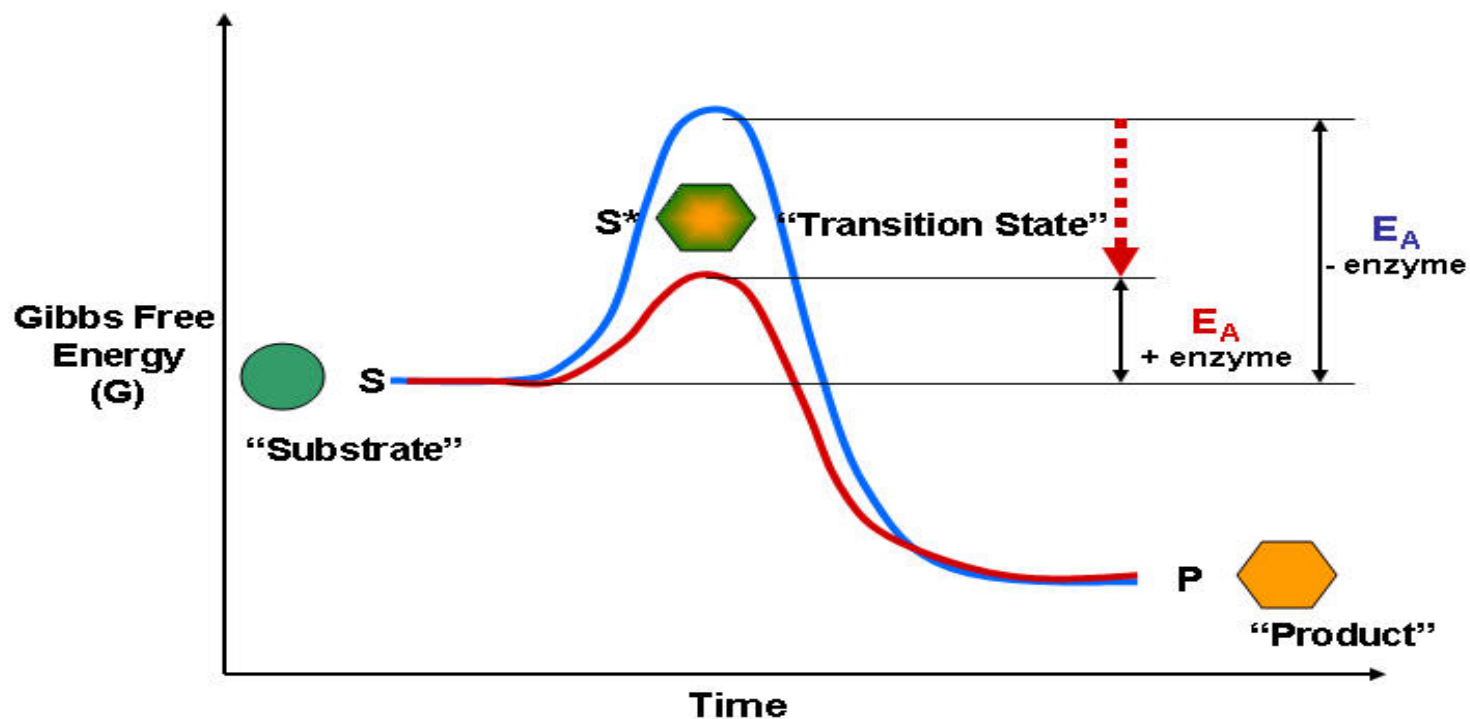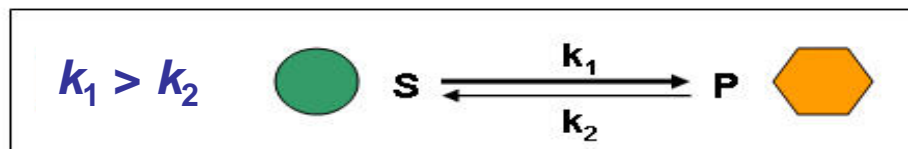
Lecture 1: Introduction

Chemical Reaction

IUPAC Gold Book: A process that results in the interconversion of **chemical species**. Chemical reactions may be elementary reactions or stepwise reactions (it should be noted that this definition includes experimentally observable interconversions of conformers). Detectable chemical reactions normally involve sets of molecular entities as indicated by this definition, but it is often conceptually convenient to use the term also for changes involving single molecular entities (i.e. 'microscopic chemical events').

Chemical Species: An ensemble of chemically identical molecular entities that can explore the same set of molecular energy levels on the time scale of the experiment. The term is applied equally to a set of chemically identical atomic or molecular structural units in a solid array

Chemical Reaction (graphical form)

$k_1 > k_2$

$$S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} P$$

"Substrate" — S

S* "Transition State"

E_A - enzyme

E_A + enzyme

Gibbs Free Energy (G)

Time

P "Product"

— Reaction in the presence of enzyme
— Reaction in the absence of enzyme
E_A = Activation energy

Computer Modeling in (Bio)Chemistry
## Computational Chemistry

Computational chemistry is rapidly emerging as a subfield of theoretical chemistry, where the primary focus is on solving chemically related problems by calculations.

For the newcomer to the field, there are three main problems:

(1) Deciphering the code. The **language of computational chemistry** is littered with acronyms, what do these abbreviations stand for in terms of underlying assumptions and approximations?

(2) Technical problems. How does one actually **run the program** and what to look for in the output**?**

(3) Quality assessment. **How good is the number that has been calculated?**

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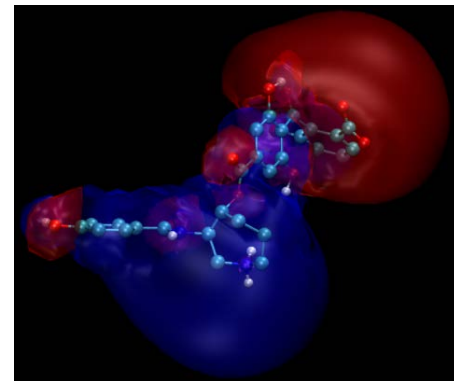
Quantum *vs.* Classical World
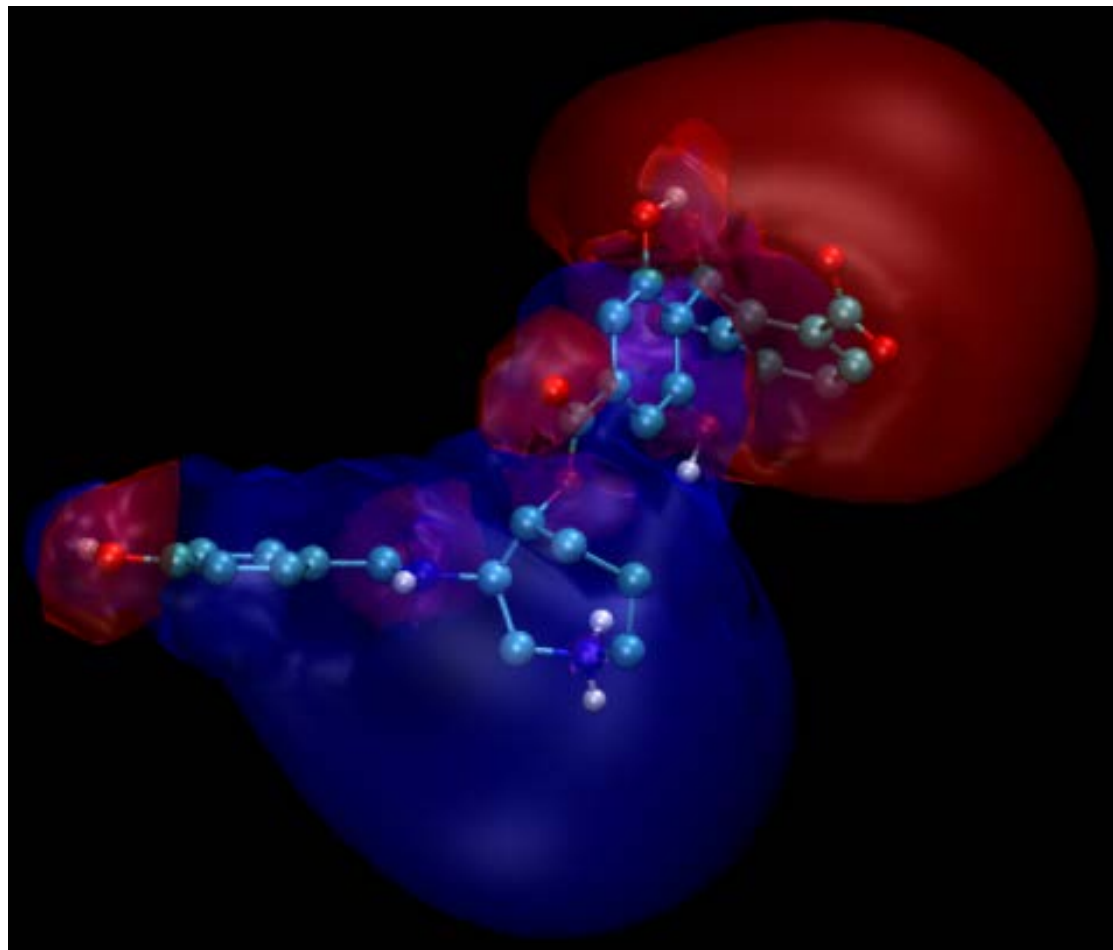
Lectures 2 and 3. Quantum Mechanics: *Key Concepts, Methods and Machinery*

Foundations of Quantum Chemistry

Molecular quantum mechanics

Electronic structure methods

Schrödinger Equation
Quantum Mechanics

$$\hat{H}\left|\Psi\right\rangle = i\hbar\frac{\partial}{\partial t}\left|\Psi\right\rangle$$

Free-Particle Dirac Equation
Relativistic Quantum Mechanics

$$\left(i\gamma^{\mu}\partial_{\mu} - m\right)\psi^{c} = 0$$

Six postulates in QM

I. **On quantum mechanical state**

The state of the system is described by the complex function of real variables, wave function $\Psi = \Psi(r,t)$

$$P(r,t) = \Psi^*(r,t)\ \Psi(x,t)\ dV = |\Psi(r,t)|^2\ dV$$ **(probabilistic interpretation)**

II. **On operator representation of mechanical quantities**

The mechanical quantities that describe the particle (energy, momentum, angular momentum etc.) are represented by linear operators acting on a wavefunction **CORRESPONDENCE PRINCIPLE**

The total energy operator, Hamiltonian: $\hat{H} = \hat{T} + \hat{V}$

The operator of the potential energy

The operator of the kinetic energy

Dirac notation:

$$\int \psi^* \hat{A} \phi\, d\tau \equiv \langle \psi \mid \hat{A} \mid \phi \rangle \qquad \int \psi^* \phi\, d\tau \equiv \langle \psi \mid \phi \rangle$$

Matrix element of the operator   Scalar product of two wavefunctions

III. **On time evolution of the state**

The time evolution of the wave function is given by the equation:

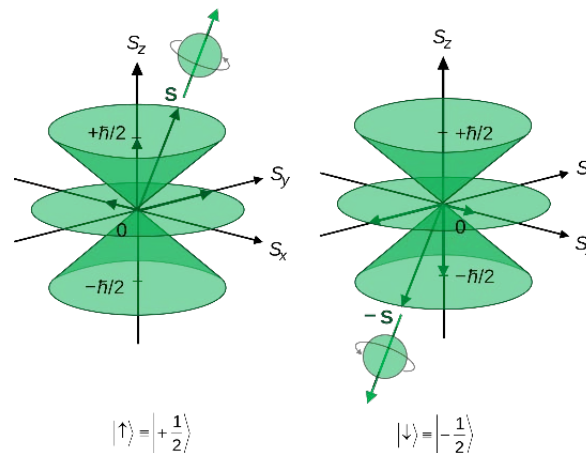$$\hat{H}\Psi(r,t) = i\hbar \frac{\partial \Psi(r,t)}{\partial t}$$

IV. **On interpretation of experimental measurements – not discussed here**

V. **Spin angular momentum** (in non-relativistic formulation of QM)

$$\hat{S}^2|\alpha\rangle = s(s+1)\hbar^2|\alpha\rangle$$

$$\hat{S}_z|\alpha\rangle = m_s\hbar|\alpha\rangle \ ; \ |\alpha\rangle \equiv |1/2\rangle$$

$$\hat{S}_z|\beta\rangle = m_s\hbar|\beta\rangle \ ; \ |\beta\rangle \equiv |-1/2\rangle$$

where the spin magnetic quantum number m_s = -s, -s+1,...,s

$$|\uparrow\rangle = \left|+\tfrac{1}{2}\right\rangle \qquad |\downarrow\rangle = \left|-\tfrac{1}{2}\right\rangle$$

VI. **On the permutational symmetry**

$$\Psi(1,2,...,i,....,j,....,N) = -\Psi(1,2,...,j,....,i,....,N)$$ -fermions (electrons, ...) – non-integer spin

$$\Psi(1,2,...,i,....,j,....,N) = \Psi(1,2,...,j,....,i,....,N)$$ -bosons - integer spin

Probability density of finding two identical fermions
in the same position and with the same spin coordinate equals to zero

Fermi correlation (Fermi hole)

Pauli exclusion principle

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Q-Chem World

Wave Function Theory

$$\hat{H}_e \Psi_e(\mathbf{r};\mathbf{R}) = E_e\, \Psi_e(\mathbf{r};\mathbf{R})$$

Ψ, ρ

Density Functional Theory (DFT)

$$E[\rho] = T_s[\rho] + V_{ext}[\rho] + V_H[\rho] + E_{xc}[\rho]$$

$$\left[-\frac{1}{2}\nabla^2 + V_{ext}(\mathbf{r}) + \int \frac{\rho(\mathbf{r'})}{|\mathbf{r}-\mathbf{r'}|}d\mathbf{r'} + V_{xc}(\mathbf{r}) \right]\phi_i(\mathbf{r}) = \varepsilon_i \phi_i(\mathbf{r})$$

Variational, perturbational treatment, (QMC)
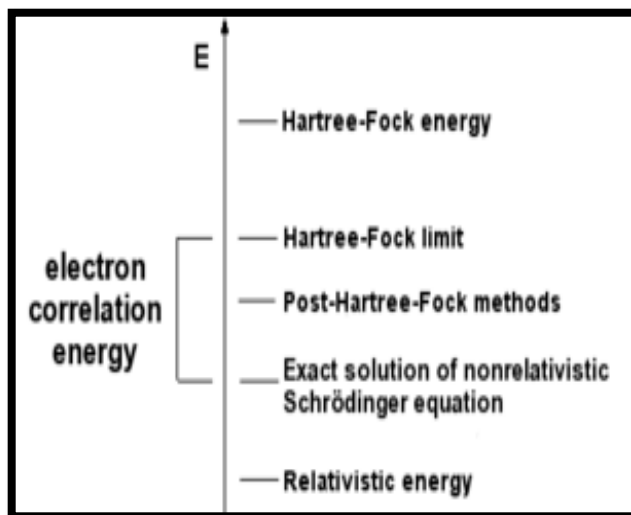
HF (Hartree–Fock) – MO-LCAO, basis set
MR-SCF (CASSCF)
CI
MP2
CASPT2
CCSD(T)
MR-CI
FCI

Hierarchy

E

electron correlation energy

— Hartree-Fock energy

— Hartree-Fock limit

— Post-Hartree-Fock methods

— Exact solution of nonrelativistic Schrödinger equation

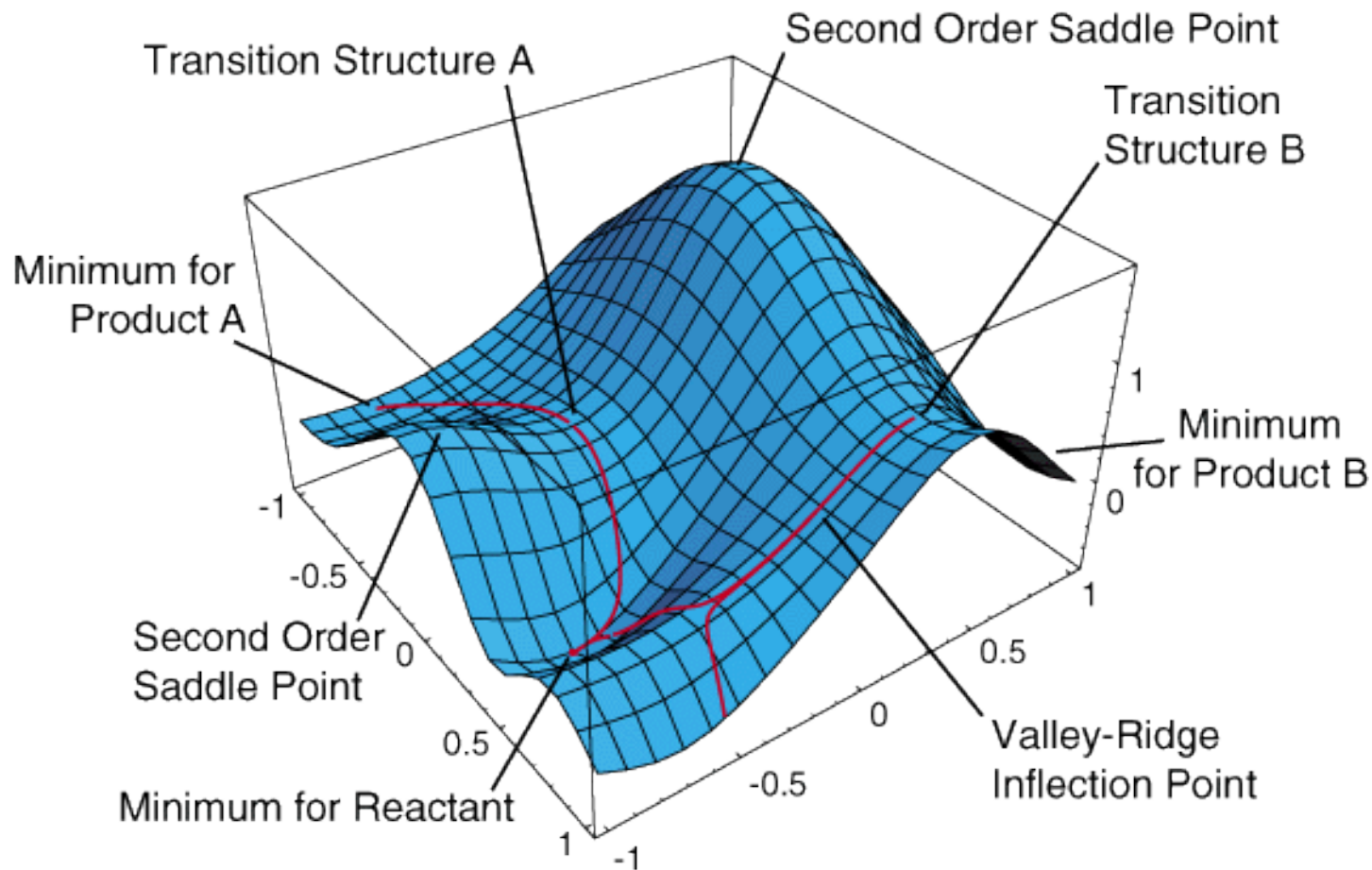— Relativistic energy

Hundreds of functionals available

- Local density approximation (LDA)
- Generalized gradient approx. (GGA)
- Meta-GGA
- Hybrid (+HF exchange)
+ (empirical dispersion, density-fitting)

John Perdew: Jaccob's Ladder?

"LR personal pick":
PBE, TPSS(h), B3LYP,
M06's, ωB97XD

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Potential Energy Surface

Hellmann–Feynman theorem (Bonus)

In quantum mechanics, the Hellmann–Feynman theorem relates **the derivative of the total energy with respect to a parameter**, to the **expectation value of the derivative of the Hamiltonian with respect to that same parameter**. According to the theorem, once the spatial distribution of the electrons has been determined by solving the Schrödinger equation, all the forces in the system can be calculated using classical electrostatics.

The theorem has been proven independently by many authors, including Paul Güttinger (1932), Wolfgang Pauli (1933), Hans Hellmann (1937) and Richard Feynman (1939).

$$\frac{dE}{d\lambda} = \int \psi_\lambda^* \frac{dH_\lambda}{d\lambda} \psi_\lambda \, dV$$

Properties as derivatives of the energy - Bonus

- **Consider a molecule in an external electric field ε.**

$$E(\varepsilon) = E(\varepsilon = 0) + \varepsilon \left.\frac{dE}{d\varepsilon}\right|_{\varepsilon=0} + \tfrac{1}{2}\varepsilon^2 \left.\frac{d^2E}{d\varepsilon^2}\right|_{\varepsilon=0} + \dots$$

- **Dipole moment** (μ) $\qquad \mu = -\left.\frac{dE}{d\varepsilon}\right|_{\varepsilon=0}$

- **Polarizability** (α) $\qquad \alpha = -\left.\frac{d^2E}{d\varepsilon^2}\right|_{\varepsilon=0}$

- **First hyperpolarizability** (ß) $\qquad \beta = -\left.\frac{d^3E}{d\varepsilon^3}\right|_{\varepsilon=0}$

$$\frac{dE}{d\varepsilon_\alpha}$$ **dipole moment; in a similar way also multipole moments, electric field gradients, etc.**

$$\frac{d^2E}{d\varepsilon_\alpha d\varepsilon_\beta}$$ **polarizability**

$$\frac{d^3E}{d\varepsilon_\alpha d\varepsilon_\beta d\varepsilon_\gamma}$$ **(first) hyperpolarizability**

$$\frac{dE}{dx_i}$$ **forces on nuclei**

$$\frac{d^2E}{dx_i dx_j}$$ **harmonic force constants; harmonic vibrational frequencies**

$$\frac{d^3E}{dx_i dx_j dx_k}$$ **cubic force constants; anharmonic corrections to distances and rotational constants**

$$\frac{d^4E}{dx_i dx_j dx_k dx_l}$$ **quartic force constants; anharmonic corrections to vibrational frequencies**

$$\frac{d^2E}{dx_i d\varepsilon_\alpha}$$ **dipole derivatives; infrared intensities**

$$\frac{d^3E}{dx_i d\varepsilon_\alpha d\varepsilon_\beta}$$ **polarizability derivatives; Raman intensities**

$$\frac{d^2E}{dB_\alpha dB_\beta}$$ **magnetizability**

$$\frac{d^2E}{dI_{i_\alpha} dB_\beta}$$ **nuclear magnetic shielding tensor; relative NMR shifts**

$$\frac{d^2E}{dI_{i_\alpha} dI_{j_\beta}}$$ **indirect spin-spin coupling constants**

$$\frac{d^2E}{dB_\alpha dJ_\beta}$$ **rotational g-tensor; rotational spectra in magnetic field**

$$\frac{d^2E}{dI_{i_\alpha} dJ_\beta}$$ **nuclear spin-rotation tensor; fine structure in rotational spectra**

$$\frac{dE}{dS_\alpha}$$ **spin density; hyperfine interaction constants**

$$\frac{d^2E}{dS_\alpha dS_\beta}$$ **electronic g-tensor**

…

and many more ...

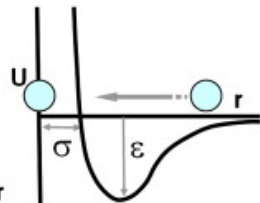# Lecture 4: Molecular Mechanics: Principles, Force Field, Optimization Methods
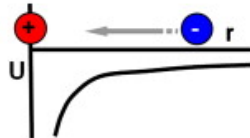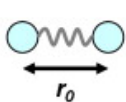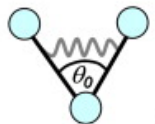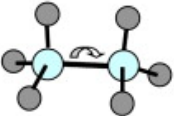
MM (molecular mechanics, force field) methods

QM: nuclei + electrons

MM: atoms

Potential Energy of Molecular System

$$U = \sum_{i<j} \sum 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right]$$

$$+ \sum_{i<j} \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

$$+ \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2$$

$$+ \sum_{angles} \frac{1}{2} k_a (\theta - \theta_0)^2$$

$$+ \sum_{torsions} k_\phi [1 + \cos(n\phi - \delta)]$$
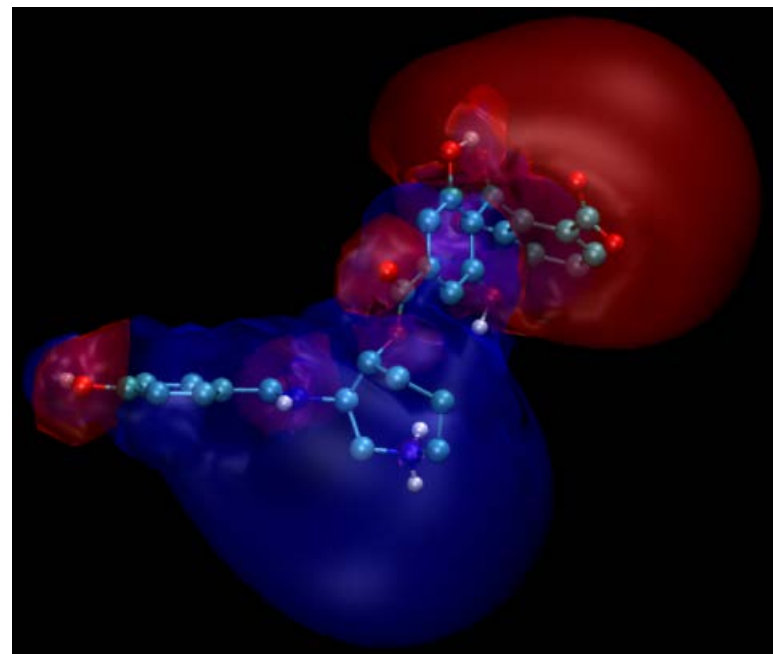
PARAMETRIZATION!

MM/MD (force field) methods: molecular simulations

Molecular mechanics (MM): optimization of molecular geometry

Molecular dynamics (MD): dynamical trajectory (t, T, …p, V, PBC)

Give atoms initial positions $r^{(t=0)}$, choose short Δt
Get forces $\mathbf{F} = -\nabla V(r^{(i)})$ and $\mathbf{a} = \mathbf{F}/m$
Move atoms: $r^{(i+1)} = r^{(i)} + v^{(i)} \Delta t + \frac{1}{2}\mathbf{a} \Delta t^2 + \ldots$
Move time forward: $t = t + \Delta t$
Repeat as long as you need
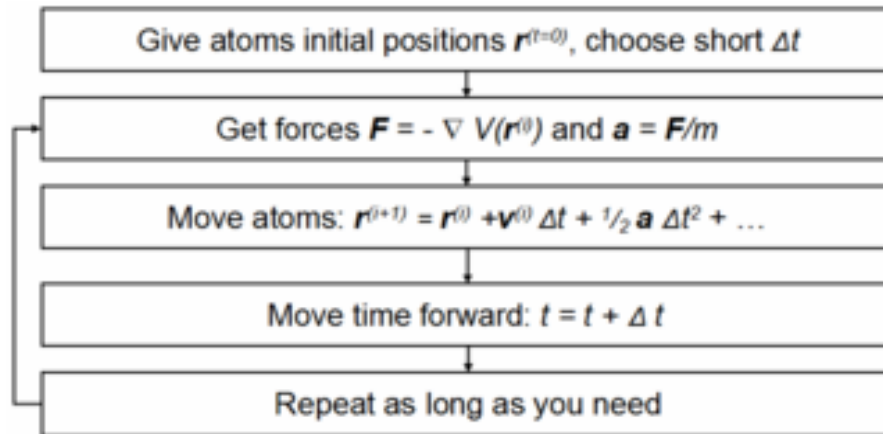
(Dis)advantages: universal parametrization

Systems: 100.000 atoms can be studied conveniently (more on the coarse-grained level

Limitations: *standard* force fields are not able to describe chemical reactions; heterocompounds poorly described

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Lecture 5: Statistical Thermodynamics
Essential Concepts
(Boltzmann Population, Partition Functions, Entropy, Enthalpy, Free Energy)

Toward the principles of statistical thermodynamics - Boltzmann distribution

Collection of thought systems

Canonical E_4	E_3	E_1	E_3
E_1	E_2	E_2	E_3
E_3	E_1	E_3	E_2
E_2	E_4	E_1	E_1

Microcanonical

Quantum states of systems and their energies: E_1, E_2, E_3, E_4....

n_i - number of systems having E_i.

Then:

$$\sum n_i = n_{tot} \qquad \sum n_i E_i = E_{tot}$$

$$W\{N\} = \frac{n_{tot}!}{\prod n_i!}$$

There exists the most probable configuration with the maximal weight..

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1) Stirling approximation

2) Method of Lagrange multipliers

$$\frac{n_i}{n_{tot}} = \wp_i = \frac{e^{-E_i/kT}}{\sum_{i=1}^{M} e^{-E_i/kT}}$$

Partition Function

$$Q = \sum_{i=1}^{M} e^{-E_i/kT}$$!

**Partition Function
for a classical system:**

$$Q = \iint e^{-E(\mathbf{p},\mathbf{q})/kT} d\mathbf{q} d\mathbf{p}$$!
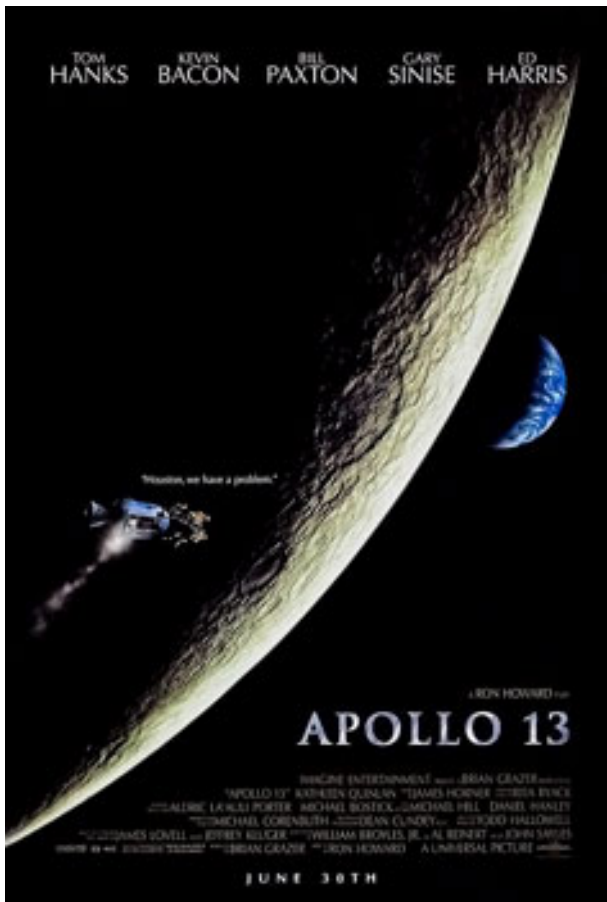
Lecture 6: Solvation Methods

Fundamentals (*Maxwell equation, Poisson(-Boltzmann) equation, Born, Onsager, Kirkwood*)
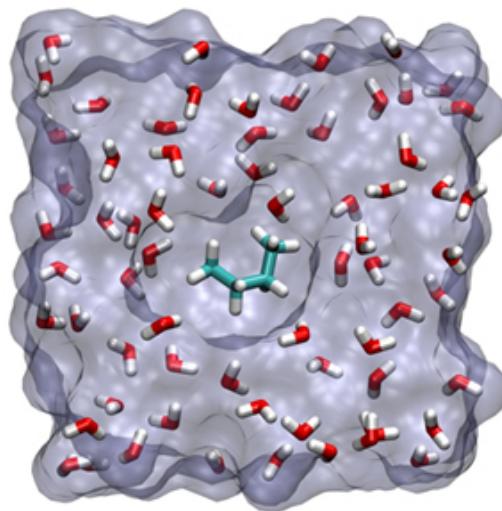
Continuum Solvation Models (*CSM, SCRF, PCM*)

COSMO-RS theory

http://mackerell.umaryland.edu/~chris/

Apollo 13 quote:

Power (Energy) is Everything
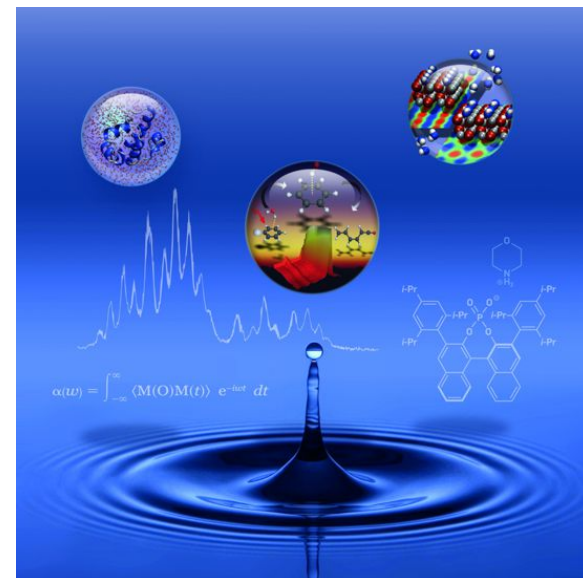
Modern Computational Chemistry:

Solvation Energy is (Almost) Everything

Fundamentals

Electrostatic interactions with Continuum

Work required to create charge distribution

$$G = -\frac{1}{2} \int\limits_{solute} \rho(\mathbf{r})\varphi(\mathbf{r})d\mathbf{r}$$

G_P (polarization free energy) … difference between the charging of the system in gas-phase and in the continuum

All that is needed $\varphi(\mathbf{r})$ in continuum and in the gas-phase

The Poisson Equation

$$\nabla^2 \phi\left(\mathbf{r}\right) = -\frac{4\pi\rho\left(\mathbf{r}\right)}{\varepsilon}$$

In non-homogenous medium

$$\nabla\varepsilon\left(\mathbf{r}\right)\cdot\nabla\phi\left(\mathbf{r}\right) = -4\pi\rho\left(\mathbf{r}\right)$$

Poisson-Boltzmann equation *(non-zero ionic strength)*

$$\nabla\varepsilon\left(\mathbf{r}\right)\cdot\nabla\phi\left(\mathbf{r}\right) - \varepsilon\left(\mathbf{r}\right)\lambda\left(\mathbf{r}\right)\kappa^2\frac{k_{\mathrm{B}}T}{q}\sinh\left[\frac{q\phi\left(\mathbf{r}\right)}{k_{\mathrm{B}}T}\right] = -4\pi\rho\left(\mathbf{r}\right)$$

With Debye-Hückel parameter

The Born Equation

$$G_P = -\frac{1}{2}\left(1 - \frac{1}{\varepsilon}\right)\frac{q^2}{a}$$

The Kirkwood-Onsager Equation

$$G_P = -\frac{1}{2}\left[\frac{2(\varepsilon-1)}{(2\varepsilon+1)}\right]\frac{\mu^2}{a^3} \qquad G_P = -\frac{1}{2}\sum_{l=0}^{L}\sum_{m=-l}^{l}\sum_{l'=0}^{L}\sum_{m'=-l'}^{l'} M_l^m f_{ll'}^{mm'} M_{l'}^{m'}$$

In the QM context: non-linear SchrEq, stationary dipole moment, Self-Consistent Reaction Field (SCRF) Calculations

$$\left\{H - \frac{1}{2}\left[\frac{2(\varepsilon-1)}{(2\varepsilon+1)}\right]\frac{\langle\Psi|\mu|\Psi\rangle}{a^3}\mu\right\}\Psi = E\Psi$$

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Polarized Continuum Models (PCM) = Self-Consistent Reaction Field (SCRF)

Seminal paper S. Miertus, E. Scrocco, J. Tomasi, "Electrostatic Interaction of a Solute with a Continuum. A Direct Utilization of Ab Initio Molecular Potentials for the Prevision of Solvent Effects." Chem. Phys. 1981, 55, 117.

Solute

Solvent (Polarized Continuum Dielectric)
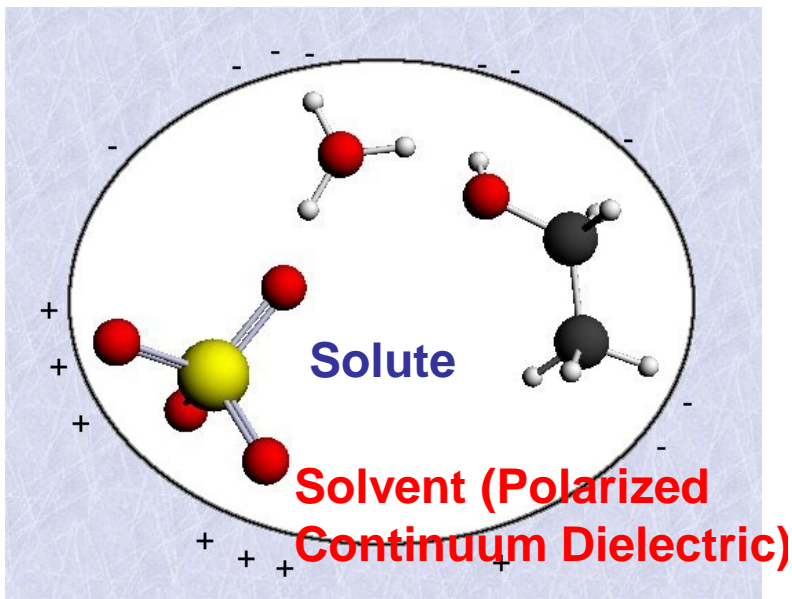
$$\Delta G_{sol} = \boxed{\Delta G_{el}} + G_{rep} + G_{dis} + G_{cav} + \Delta G_{tm} + P\Delta V$$

$$\hat{H}_{eff}^{FR}(\mathbf{f},\mathbf{r}) = \hat{H}^{F}(\mathbf{f}) + \hat{V}^{int}[\mathbf{f}, Q(\vec{r},\vec{r}\,')]$$

$$\vec{P} = \frac{\epsilon - 1}{4\pi}\vec{E}$$

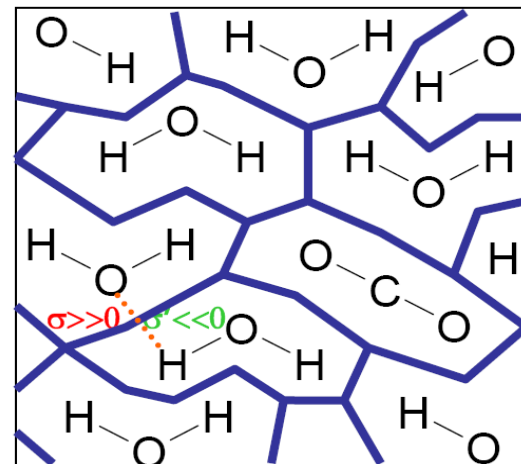$$-\nabla^2 V(\vec{r}) = 4\pi\rho_M(\vec{r}) \quad \text{within } C$$

$$-\epsilon\nabla^2 V(\vec{r}) = 0 \quad \text{outside } C$$

Tomasi,J.; Mennucci, B.; Cammi, R.: **Quantum Mechanical Continuum Solvation Models.** *Chem. Rev.* **2005,** *105*, 2999-3093.

COSMO-RS (conductor-like screening model for realistic solvation)

COSMO*therm* program suite
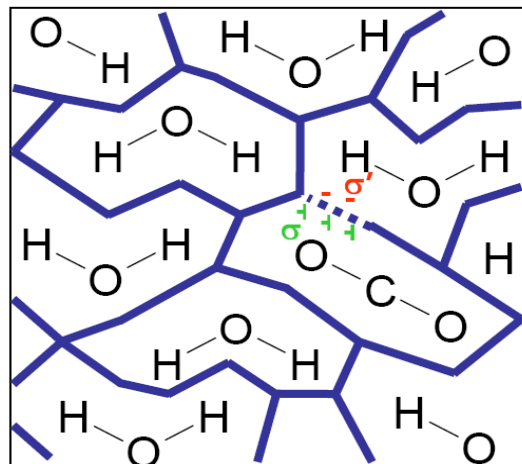
$$E_{misfit}(\sigma, \sigma') = a_{eff} \frac{\alpha'}{2}(\sigma + \sigma')^2$$

$$E_{HB} = a_{eff}\, c_{HB}\, \min\left(0; \min\left(0; \sigma_{donor} + \sigma_{HB}\right)\max\left(0; \sigma_{acceptor} - \sigma_{HB}\right)\right)$$

$$E_{vdW} = a_{eff}\left(\tau_{vdW} + \tau'_{vdW}\right)$$

$$\mu_S(\sigma) = -\frac{RT}{a_{eff}}\ln\left[\int p_S(\sigma')\exp\left(\frac{a_{eff}}{RT}\left(\mu_S(\sigma') - E_{misfit}(\sigma, \sigma') - E_{HB}(\sigma, \sigma')\right)\right)d\sigma'\right]$$

Andreas Klamt, COSMO*logic*

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Lecture 7: QM/MM Methods, Energy Minimization

QM/MM: Why not to couple QM and MM?

History: A. Warshel and M. Levitt, Theoretical Studies of Enzymatic Reactions: Dielectric Electrostatic and Steric stabilisation of the carbonium ion in the reaction of Lysozyme. *J. Mol. Biol.* **1976**, *103*, 227.
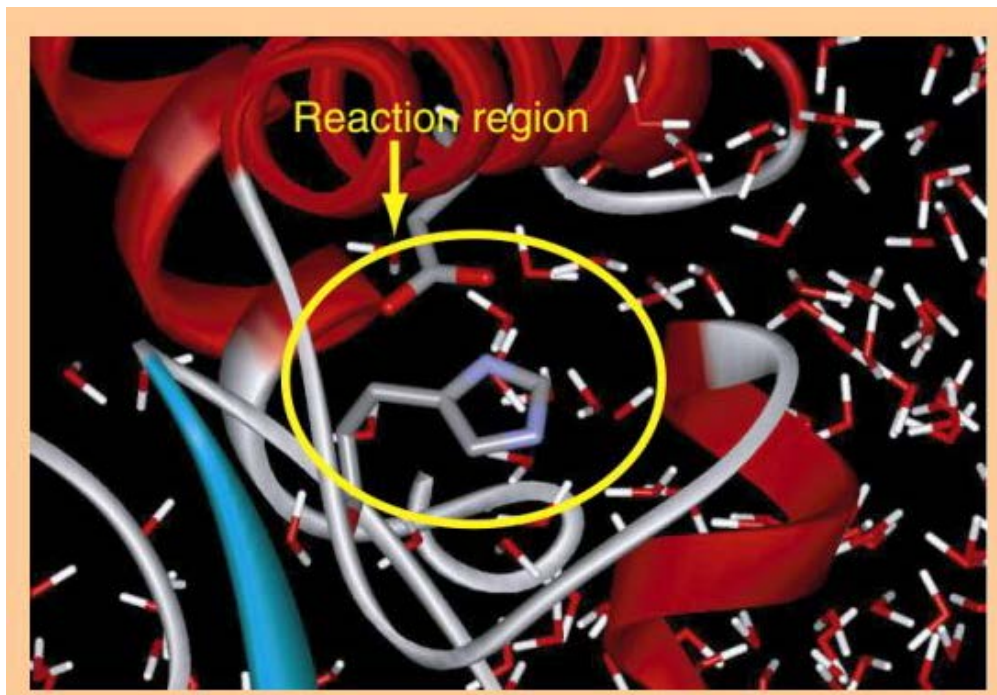
System is divided into 2 parts:

1/ Reaction region

described by QM methods

2/ The rest (spectator, bulk)

described by MM methods

The energy of the total system is given as :

$$E_{tot} = E_{QM} + E_{MM} + E_{coupling}$$

QM/MM (Example: ONIOM-like approach)
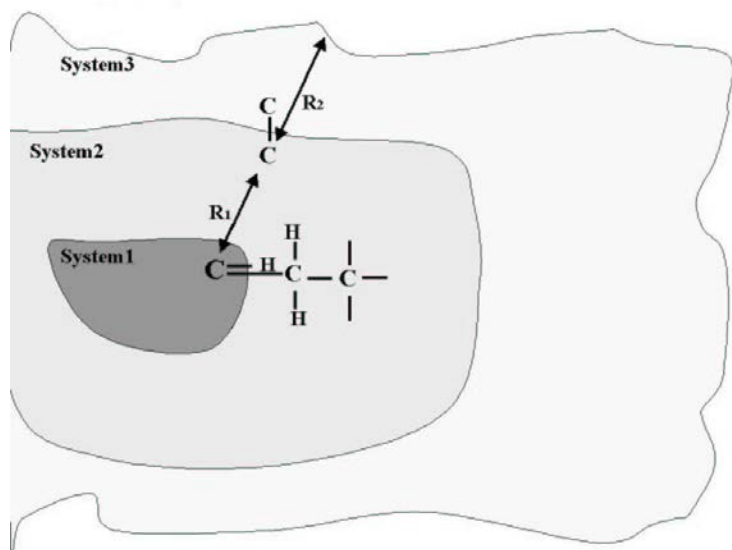
System 1 (S1) is treated at the QM level. It is truncated using link atoms. The positions of the link atoms are linearly dependent on the cooresponding heayy atoms (hydrogen link approach)

System 2 (S2) contains all amino acids and solvent molecules within a radius R1 of any atom in S1. It is treated with MM methods.

System 3 (S3) contains all amino acids and solvent molecules within a radius R2 of any atom in S2. It is also treated with MM methods.

The energy of the total system is given as :

$$E(QM/MM)=E(QM,S1) + E(MM,S3) - E(MM,S1),$$

where

$E(QM,S1)$ … QM energy of S1 in the field of point charges

$E(MM,S3)$ … MM energy of S3 with charges of S1 set to zero

$E(MM,S1)$ … MM energy of S1 with charges of S1 set to zero

U. Ryde and M. H. M. Olsson, *Int. J. Quantum Chem.* **2001**, *81*, 335-347.

Lecture 8: Transition State Theory

Eyring's Equation
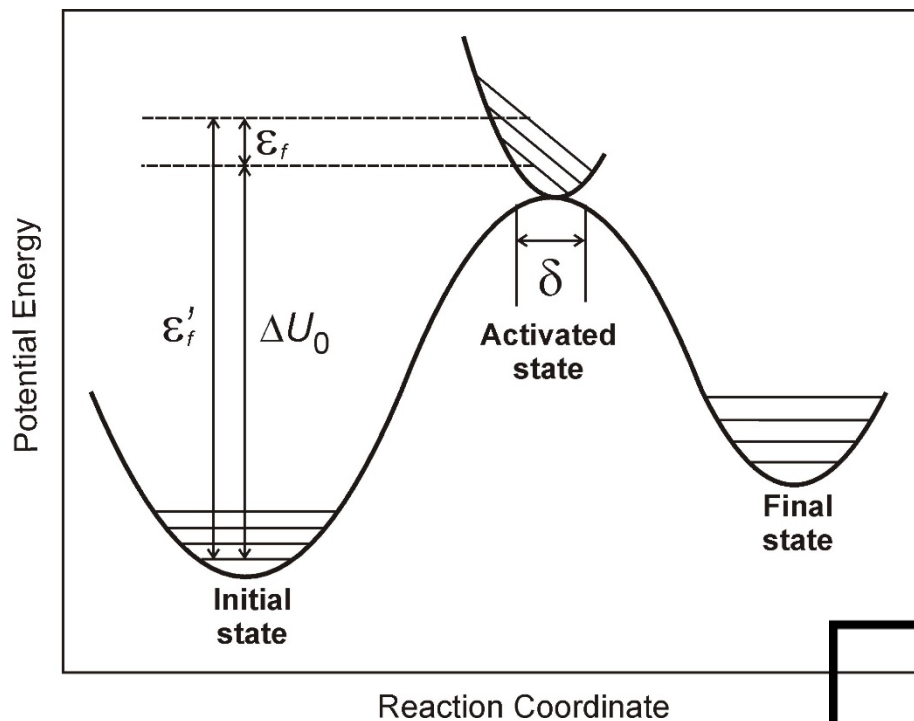
$$k = \frac{k_B T}{h} e^{-\Delta G^{\neq}/RT}$$

Limitations and assumptions of Eyring's transition state theory:

1. No recrossing considered

→ **Recrossing dynamics:**
  some trajectories reaching the top of the barrier return back to the reactant state,
  thus $k_{recrossing-corrected} \leq k_{Eyring}$

→ **No-recrossing condition:**
  "one-dimensional" motion normal to the TS (reaction mode) is separable from the tangent to the TS (bath modes)

2. No tunneling through the barrier considered

Wigner
Bell   **tunneling factors**
Eckart
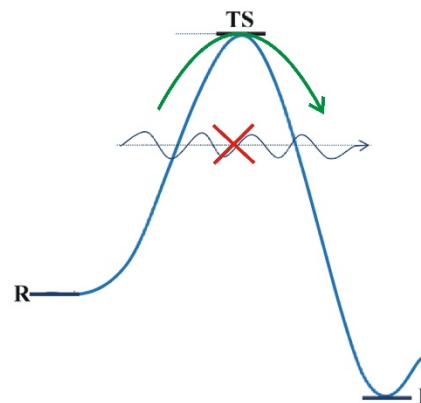
3. Assumption that the reaction system will pass over the lowest first-order saddle point on the potential energy system

4. Assumption of long-lived intermediates along a reaction coordinate (Boltzmann distribution of energies before continuing to the next step)

Lecture 9: Free-Energy Perturbation, Thermodynamic Integration, Potential of Mean Force

(+working examples on chemical reactivity)

Free Energy Perturbation (Zwanzig, 1954)

$$\langle A \rangle_{\mathrm{B}} - \langle A \rangle_{\mathrm{A}} = k_{\mathrm{B}} T \ln \left\langle e^{(E_{\mathrm{B}} - E_{\mathrm{A}})/k_{\mathrm{B}}T} \right\rangle_{\mathrm{A}}$$

In practice, a simulation windows for each coupling parameter

$$E(\lambda) = \lambda E_{\mathrm{B}} + (1 - \lambda) E_{\mathrm{A}}$$

$$\langle A \rangle_{\mathrm{B}} - \langle A \rangle_{\mathrm{A}} = \sum_{\lambda=0}^{1} k_{\mathrm{B}} T \ln \left\langle e^{(E_{\lambda+d\lambda} - E_{\lambda})/k_{\mathrm{B}}T} \right\rangle_{\lambda}$$

We may rewrite *U* as

$$U = \frac{\iint E(\mathbf{q},\mathbf{p})e^{-E(\mathbf{q},\mathbf{p})/k_B T}\,d\mathbf{q}d\mathbf{p}}{\iint e^{-E(\mathbf{q},\mathbf{p})/k_B T}\,d\mathbf{q}d\mathbf{p}}$$

$$= \iint E(\mathbf{q},\mathbf{p})P(\mathbf{q},\mathbf{p})\,d\mathbf{q}d\mathbf{p}$$

Carrying Monte Carlo or MD

$$\langle U\rangle_B - \langle U\rangle_A = \frac{1}{M_B}\sum_i^{M_B} E_i - \frac{1}{M_A}\sum_i^{M_A} E_i$$

$$= \langle E\rangle_B - \langle E\rangle_A$$

Lecture 10: Thermodynamic Cycles for Computation of a Free–Energy Change in Condensed Phase

Thermodynamic cycle for the absolute potential of the SHE:

$$
\begin{array}{ccccc}
\mathbf{H}^+(\mathbf{aq}) & + & \mathbf{e}^-(\mathbf{g}) & \xleftarrow{\ E^{\circ}_{abs}(SHE)\ } & \tfrac{1}{2}\mathbf{H}_2(\mathbf{g}) \\[2mm]
\Big\uparrow {\scriptstyle G_{solv}(H^+)} & & \Big\uparrow {\scriptstyle \Delta G = 0} & & \Big\downarrow {\scriptstyle -\tfrac{1}{2}G_{2H^\bullet \to H_2}} \\[2mm]
\mathbf{H}^+(\mathbf{g}) & + & \mathbf{e}^-(\mathbf{g}) & \xleftarrow{\ IP_{H^\bullet \to H^+}\ } & \mathbf{H}(\mathbf{g})
\end{array}
$$
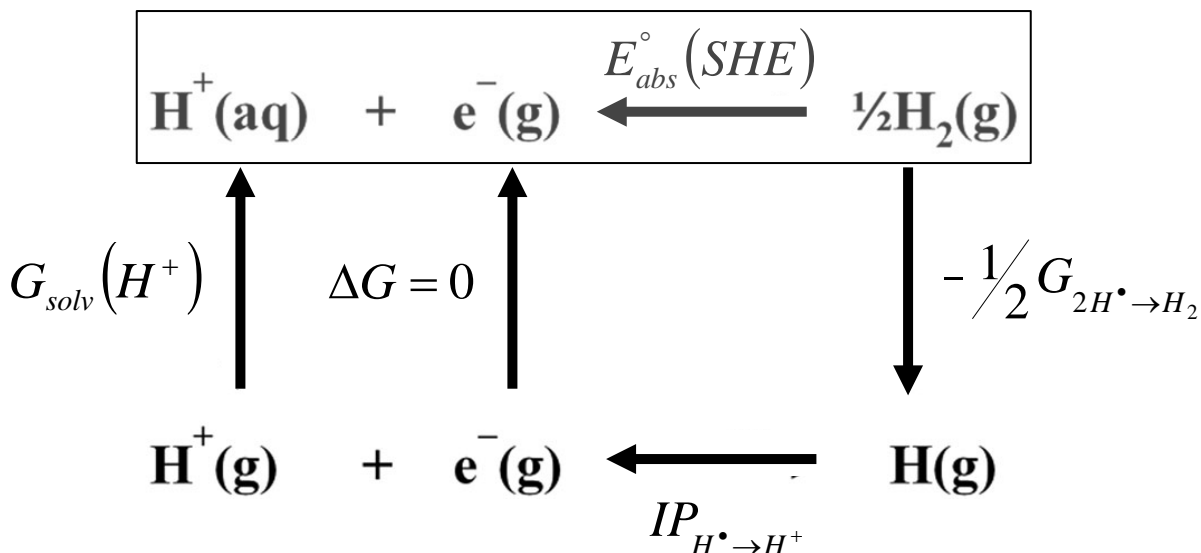
Thermodynamic cycle for calculating pK$_a$

$$HA(aq) \xrightarrow{\Delta G^*_{aq}} H^+(aq) + A^-(aq)$$

$-\Delta G^*_S(HA)$ $\Delta G^*_S(H^+)$ $\Delta G^*_S(A^-)$

$$HA(g) \xrightarrow{\Delta G^*_{gas}} H^+(g) + A^-(g)$$

$$pKa = \frac{\Delta G^*_{aq}}{RT\ln(10)}$$
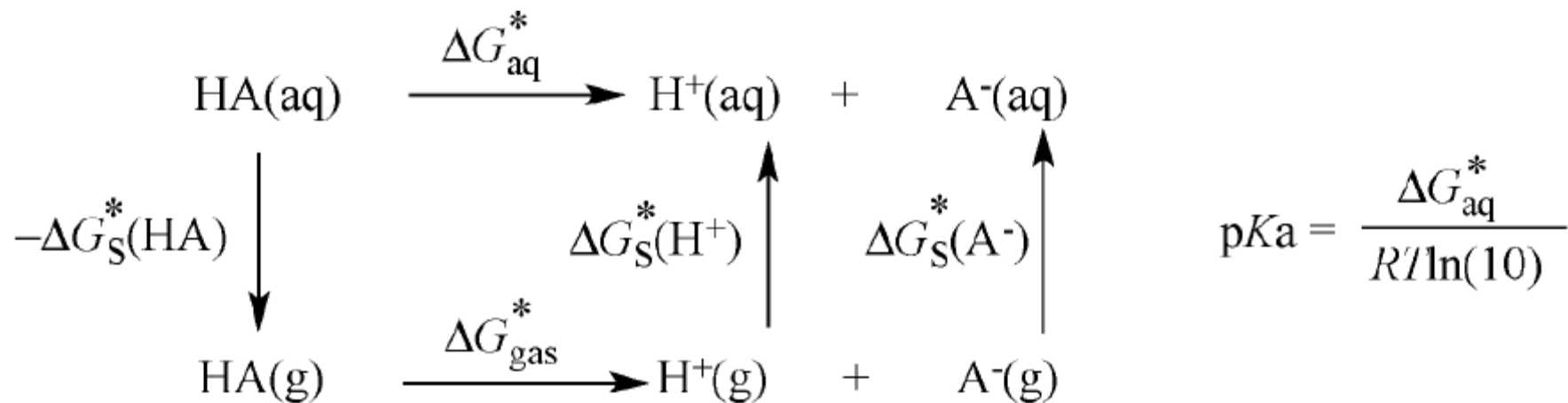
Solvation at the COSMO-RS level or PMF…

Variable Temperature H-atom Addition/Abstraction Approach ("VT-HAA")

$$[A]^{n-} \quad \xleftarrow{\;+E_2^\circ\;} \quad [A]^{(n+1)-}$$

$$-pK_{A,1} \qquad\qquad +E_H^\circ \qquad\qquad -pK_{A,2}$$

$$[AH]^{(n-1)-} \quad \xleftarrow{\;+E_1^\circ\;} \quad [AH]^{n-}$$
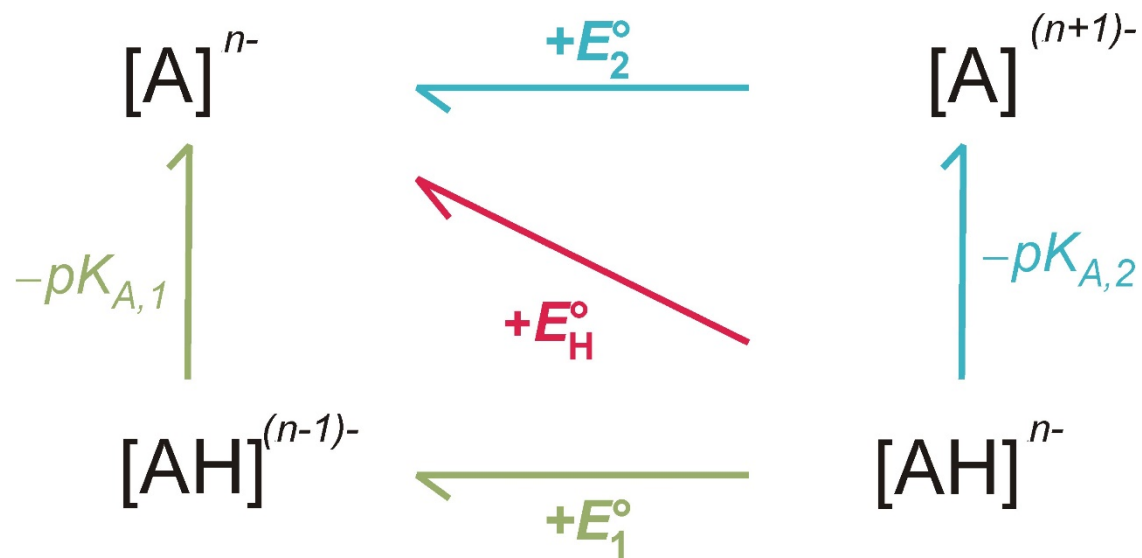
E_2° as a function of E_H° and E_1°

QM/MM thermodynamic cycle perturbation – QTCP (QM/MM-FEP)

Red (QM/MM) $\xrightarrow{\Delta A_{QM/MM}}$ Ox (QM/MM)

QTCP:

$$\Delta A_{QM/MM} = -\Delta A_{1,MM\to QM/MM} + \Delta A_{MM} + \Delta A_{2,MM\to QM/MM}$$

$$-\Delta A_1 = kT \ln\left\langle \exp\left[\frac{-(E_{QM/MM}(\text{Red}) - E_{MM}(\text{Red}))}{kT}\right]\right\rangle_{\text{Red}}$$

$$\Delta A_2 = -kT \ln\left\langle \exp\left[\frac{-(E_{QM/MM}(\text{Ox}) - E_{MM}(\text{Ox}))}{kT}\right]\right\rangle_{\text{Ox}}$$

$$\Delta A_{MM} = -kT \ln\left\langle \exp[-(E(\text{Red}) - E(\text{Ox}))]/kT\right\rangle_{\text{Ox}}$$

Red (MM) .... M .... Ox (MM)

λ_{i-1} λ_i $\lambda_{i}+1$ λ_{j-1} λ_j $\lambda_{j}+1$ N

$\lambda_i \in \langle 0,1 \rangle$ $\lambda_i = 1$

$\lambda_j = 0$ $\lambda_j \in \langle 0,1 \rangle$

charge perturbation   *coordinate perturbation*

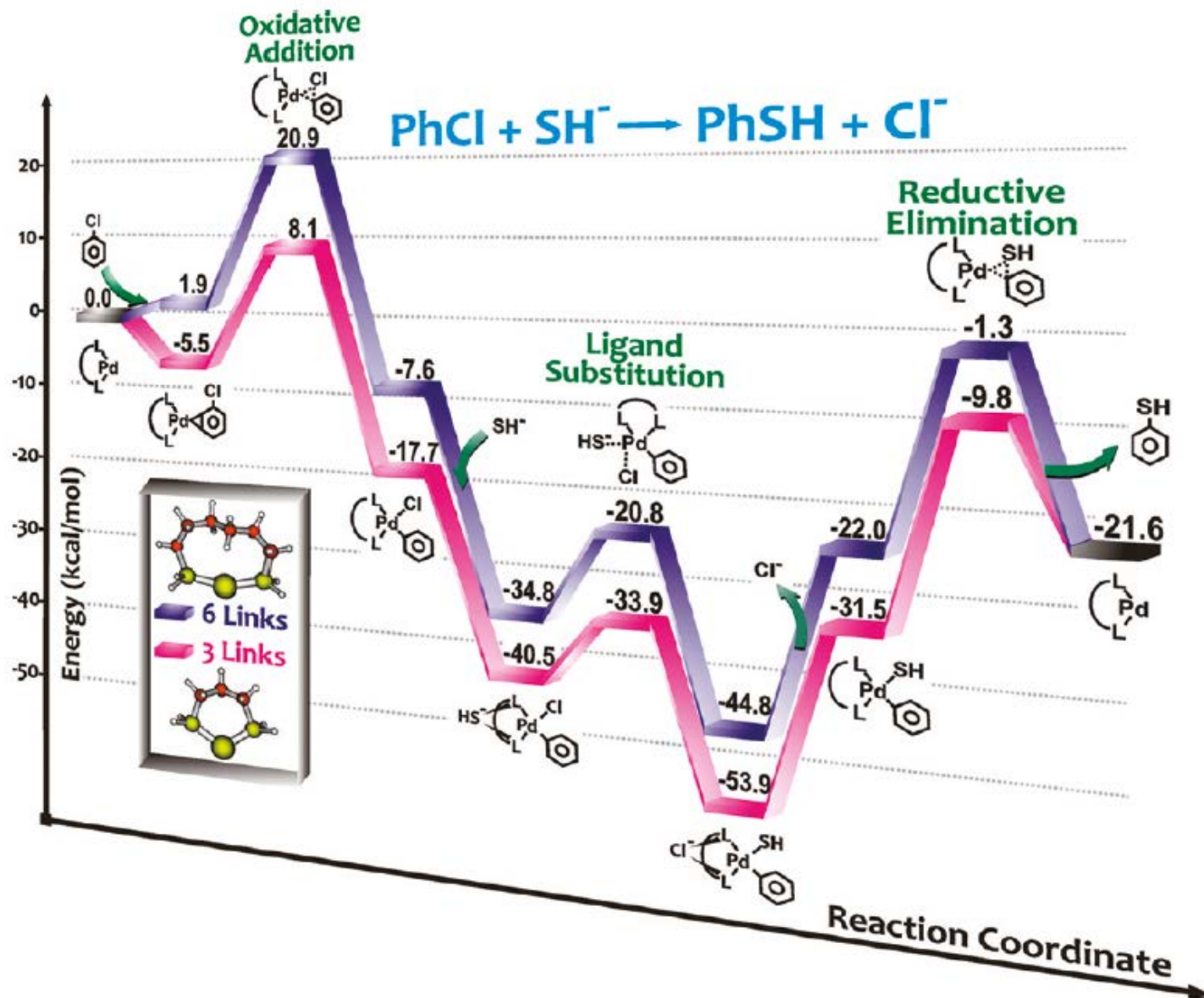Computer Modeling of Chemical Reactions and Enzyme Catalysis

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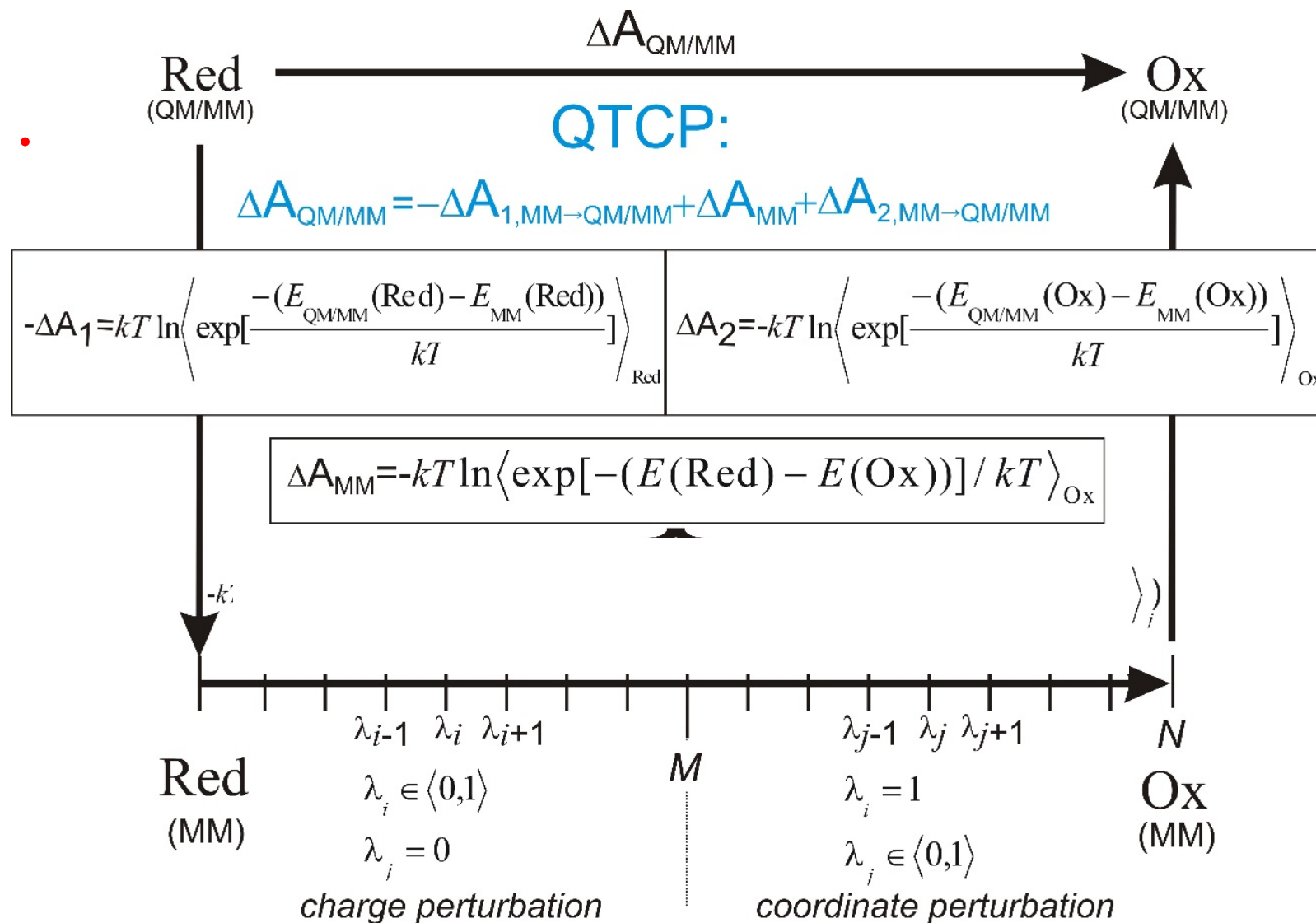
Lecture 11: Modelling Chemical Reactions in Solution: *Theory and Applications*
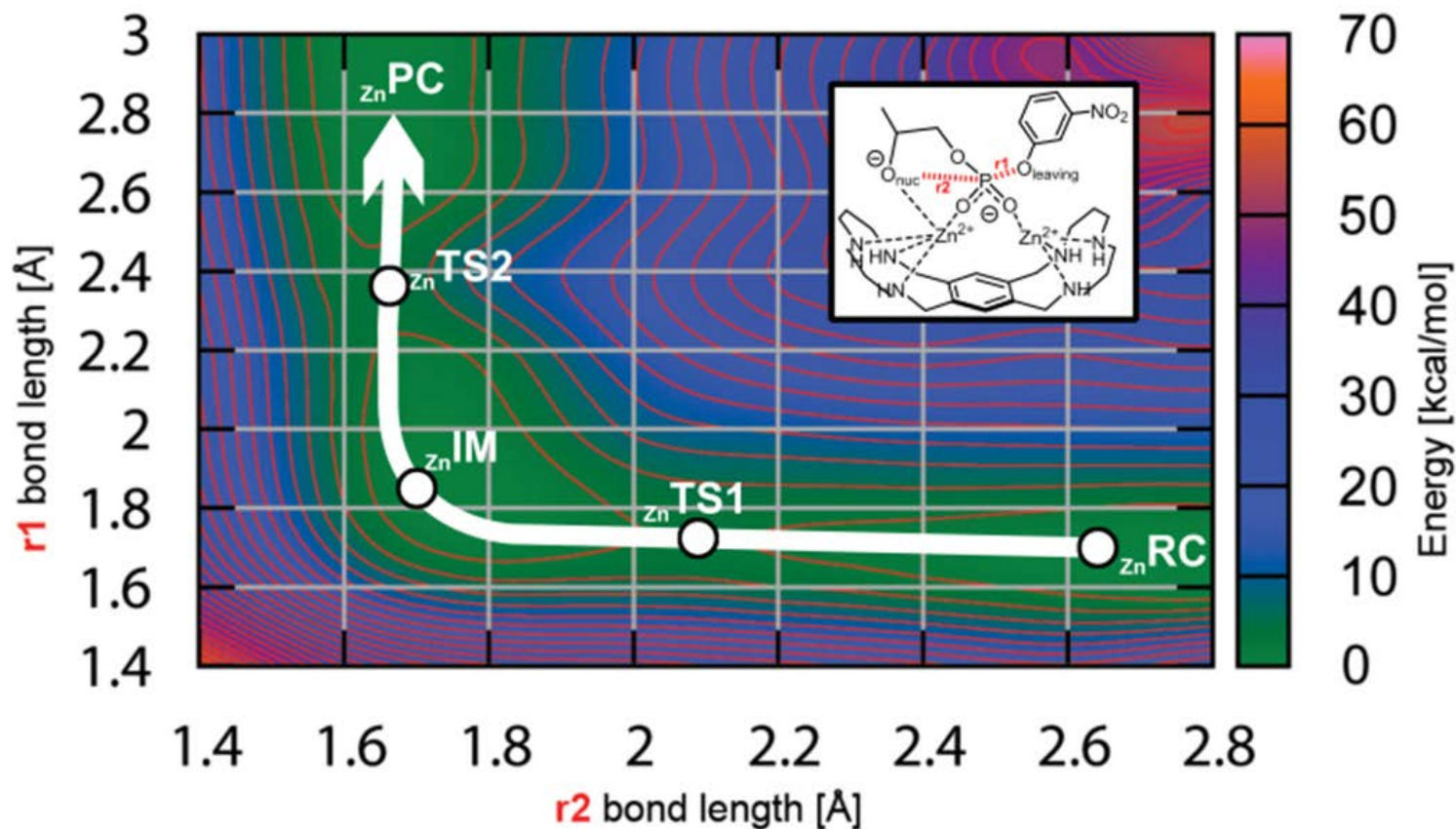
How to trap (meaning find and optimize) a "static" transition state using an easily definable reaction coordinate:

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-RTlnQ$^{\neq}$ contributions to Gibbs free energy of TS.
   (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).

Oxidative Addition

PhCl + SH⁻ → PhSH + Cl⁻

Ligand Substitution

Reductive Elimination

Energy (kcal/mol)

20.9

8.1

1.9

0.0

-5.5

-7.6

-17.7

-34.8

-40.5

-20.8

-33.9

-44.8

-53.9

-22.0

-31.5

-1.3

-9.8

-21.6

6 Links
3 Links

Reaction Coordinate

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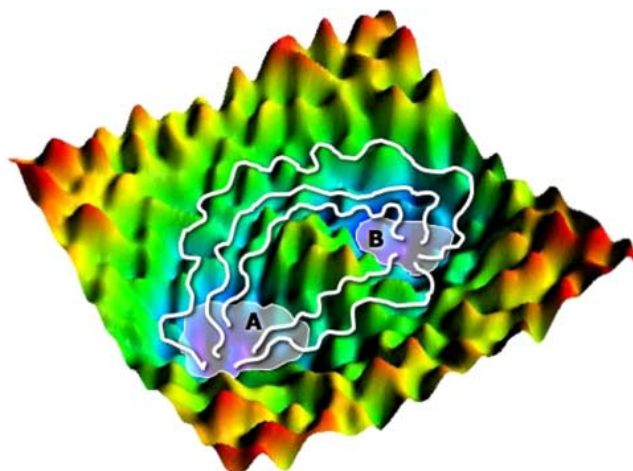
PMF ; QM/MM-FEP ; QM/MM-TI

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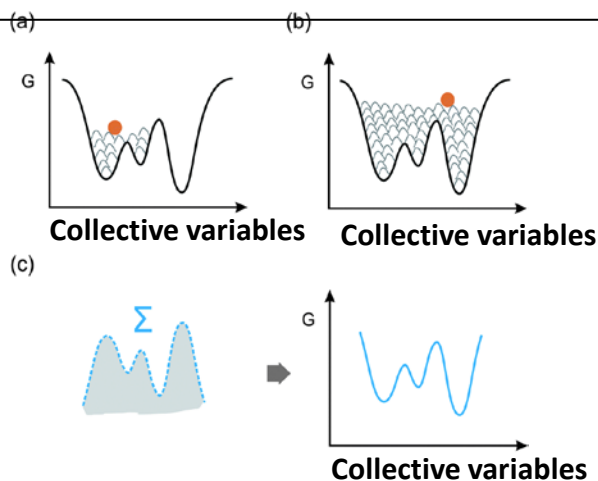
Collective variables (CVs) include for example bond lengths, dihedral angles, coordination numbers, etc.

QM/MM Transition Path Sampling

TPSs do not require prior knowledge of a reaction coordinate and do not rely on the indetification 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

Lecture 12: Computer Modeling (Physical Chemistry) of Enzyme Catalysis, Metalloenzymes

Leonor Michaelis (1875-1949)
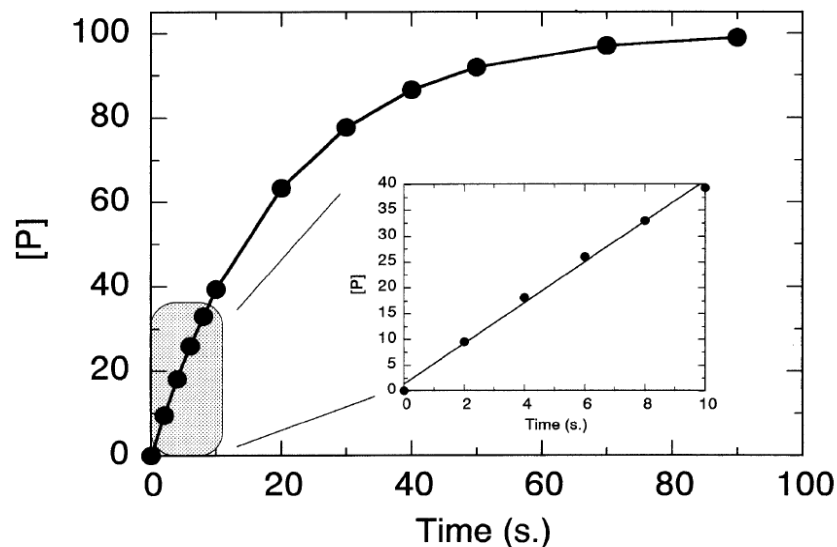
Maud Leonora Menten (1879-1960)

Figure 5.2 Reaction progress curve for the production of product during an enzyme-catalyzed reaction. Inset highlights the early time points at which the initial velocity can be determined from the slope of the linear plot of [P] versus time.

HMM Equation

$$v = k_2[\text{ES}]$$

$$\frac{d[\text{ES}]}{dt} = k_1[\text{E}]_f[\text{S}]_f \qquad \text{and} \qquad \frac{-d[\text{ES}]}{dt} = (k_{-1} + k_2)[\text{ES}]$$

$$k_1[\text{E}]_f[\text{S}]_f = (k_{-1} + k_2)[\text{ES}]$$

$$[\text{ES}] = \frac{[\text{E}]_f[\text{S}]_f}{K_m} \qquad \textbf{defining} \quad K_m = \frac{k_{-1} + k_2}{k_1}$$

replace $[\text{E}]_f$ by $([\text{E}] - [\text{ES}])$

$$v = k_{cat}[\text{E}] \frac{[\text{S}]}{[\text{S}] + K_m}$$

$$v = \frac{V_{max}[\text{S}]}{K_m + [\text{S}]} = \frac{V_{max}}{1 + \dfrac{K_m}{[\text{S}]}}$$

Protein Structure → Theoretical Model

full protein without conformational sampling
QM/MM
QM/MM/Exp (X-ray, EXAFS, NMR)
full protein with conformational sampling
QM/MD, QM/MM/FEP, QTCP
cluster model (active site only)
QM+solvation (COSMO-RS, SMD, ...)

Calculations vs. Experiment

spectroscopic properties
Absorption, CD, MCD, EPR, IR, Raman,
Mössbauer, NRVS,...
thermodynamic properties
reduction potentials, pK_a values,
equilibrium constants
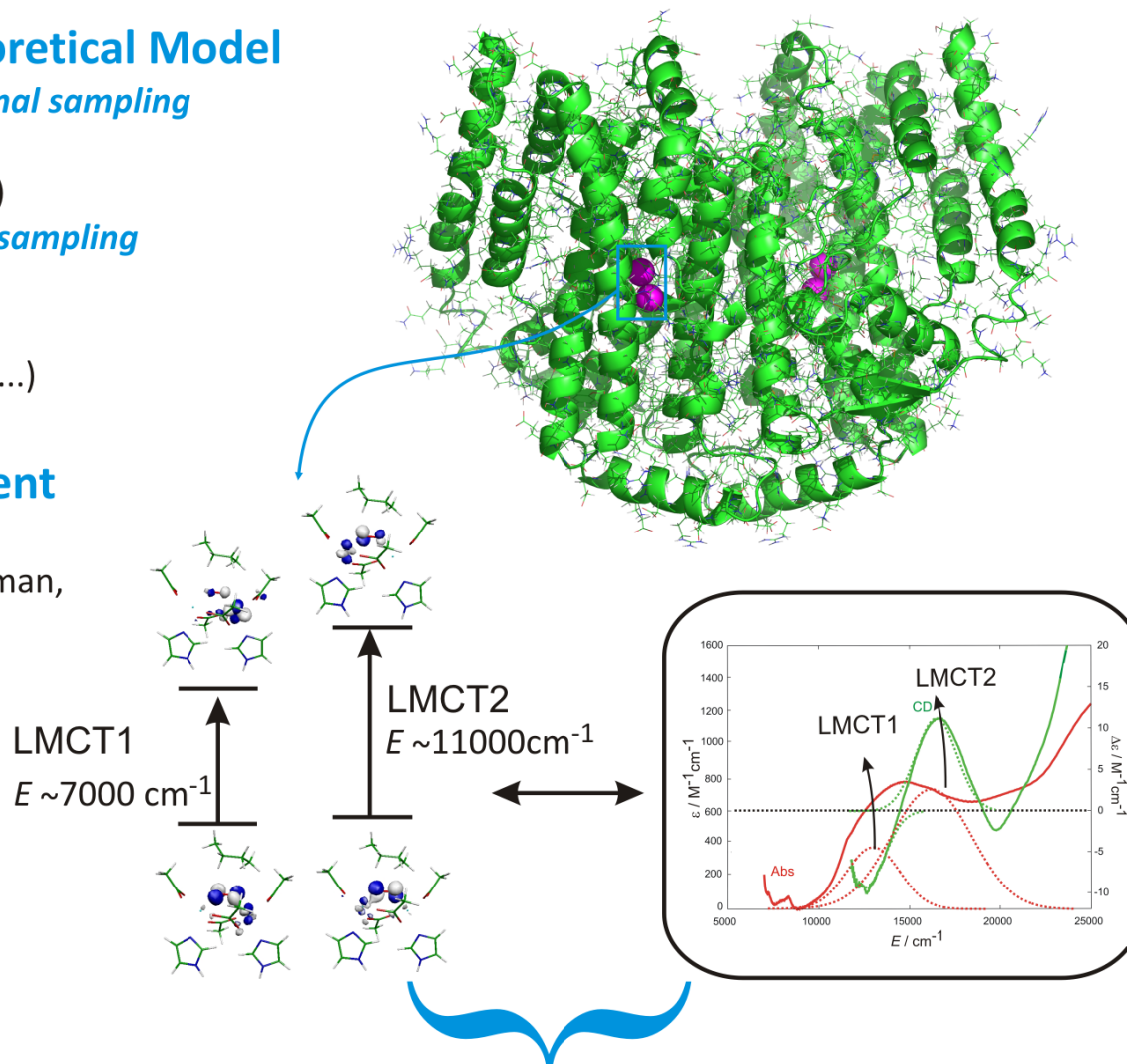*kinetic properties*
rate constants, isotope effect

QM Methods

wave function methods
MR-SCF, MR-PT2, MRCI, DMRG, ...
density functional theory (DFT) methods
DFT, DFT+D, ...

LMCT1
$E \sim 7000$ cm^{-1}

LMCT2
$E \sim 11000$cm^{-1}

Concepts and Mechanisms

adapted from Rokob, T. A.; Srnec, M.; Rulíšek, L.: *Dalton Trans.* **2012**, *41*, 5754-5768.

Lecture 13: Physical Chemistry
of Redox-Active Proteins / Enzymes :

Electron Transfer Kinetics, Marcus Theory, Adiabatic and Non-Adiabatic Reaction Dynamics, Landau-Zener model

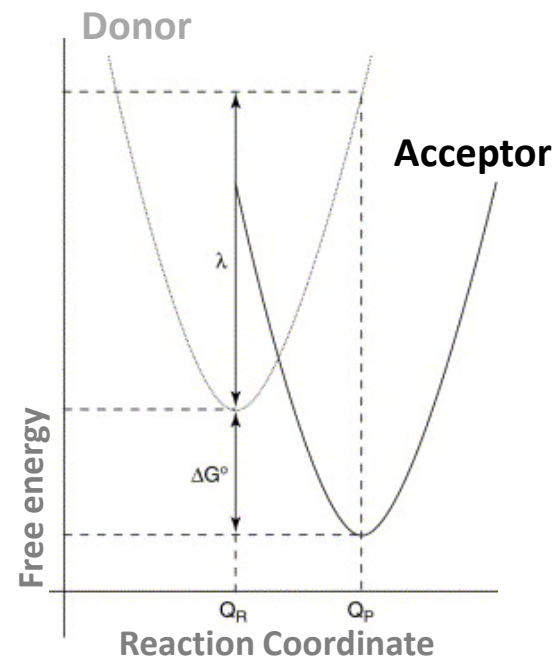# Classical Marcus theory (for outer-sphere ET)

1) Eyring's TST (lecture 8)

$$k = \tau_{el} \frac{k_B T}{h} \exp\left[-\frac{\Delta G^{\neq}}{k_B T}\right]$$

Electron Transmission coefficient

2) Reactant and product free-energy surfaces considered as two equivalent parabolas, then:

$$\Delta G^{\neq} = \frac{\left(\lambda + \Delta G^{\circ}\right)^2}{4\lambda}$$

$$k_{ET} = A \exp\left[-\frac{\left(\lambda + \Delta G^0\right)^2}{4\lambda k_B T}\right]$$

!

Donor

Acceptor

Free energy

λ

ΔG°

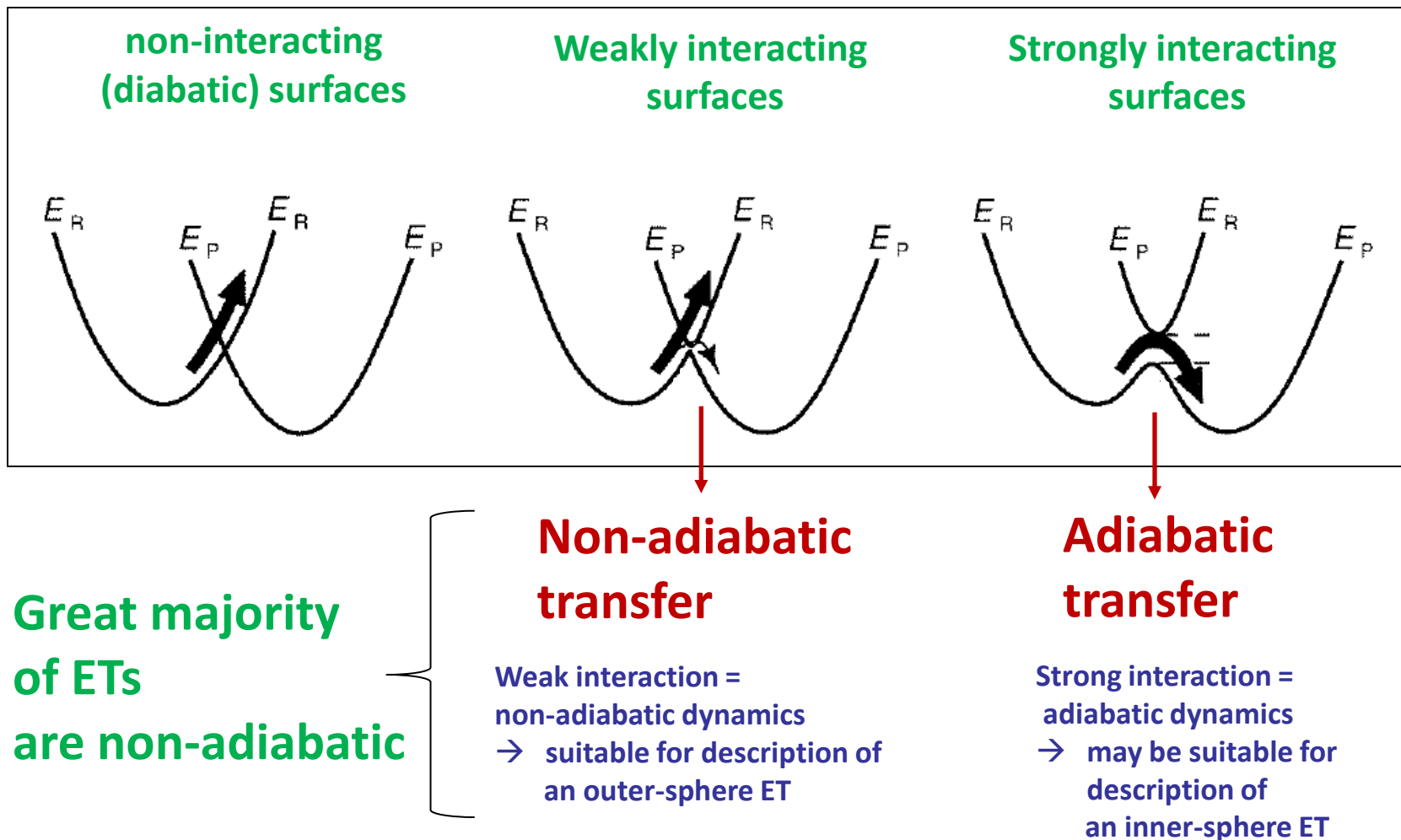Q_R Q_P

Reaction Coordinate

$\lambda -$ **reorganization energy** (always positive)
   (the free energy change due to the (R→P) nuclear rearrangement with no ET)

ΔG^0 **reaction free energy** (thermodynamic driving force)

$$\Delta G^0 = -F\Delta E^0 = -F\left(E_A^0 - E_D^0\right)$$

Adiabatic vs. non-adiabatic ETs

non-interacting (diabatic) surfaces

Weakly interacting surfaces

Strongly interacting surfaces

Great majority of ETs are non-adiabatic

Non-adiabatic transfer

Weak interaction = non-adiabatic dynamics
→ suitable for description of an outer-sphere ET

Adiabatic transfer

Strong interaction = adiabatic dynamics
→ may be suitable for description of an inner-sphere ET

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Vocabulary of Theoretical (Computer) Chemist

Ab Initio
Basis Set
Binding (Energy)
Binding Constants
Classical Mechanics
Computer Aided Ligand Design
Conformational Sampling
Continuum Solvation (PCM, COSMO)
Correlation Energy
Density Functional Theory (DFT)
Docking
Electrostatic Potential
Electron Transfer
Eyring's Equation
Free Energy
Free Energy Perturbation (FEP)
Homology Modelling
Metadynamics
Marcus Theory

Molecular Mechanics
Molecular Dynamics
Molecular Surface and Volume
Poisson-Boltzman/Surface Area (PBSA)
Potential Energy Surface
Potential of Mean Force
Protein Structure
QM/MM
Quantitative Structure-Activity Relationship
Quantum Chemical Methods
Semiempirical Methods
Schrodinger Equation
Solvation
Statistical Mechanics
Thermodynamic Integration (TI)
Thermodynamics
Trajectory
Tunneling
Wave Function (Methods)