Computer Modeling of Chemical Reactions and Enzyme Catalysis

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Lecture 1

Chemical Reaction

Computational Chemistry

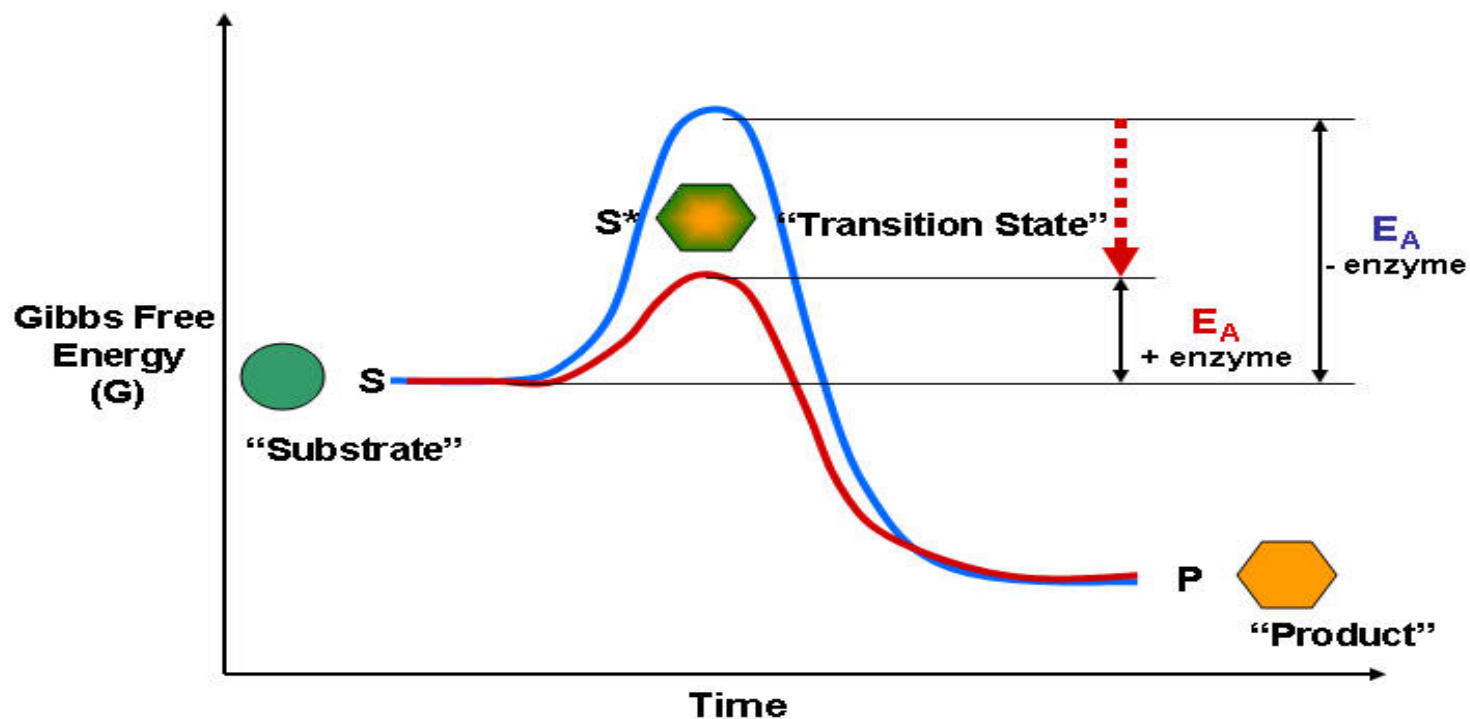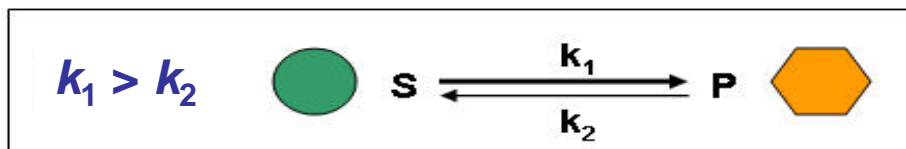**Historical Development**

Motivation/Aims (Syllabus)

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

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Chemical Reaction (graphical form)

$k_1 > k_2$ S $\xrightleftharpoons[k_2]{k_1}$ P

Gibbs Free Energy (G)

S* "Transition State"

S "Substrate"

E_A - enzyme

E_A + enzyme

P "Product"

Time

⎯⎯ 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?**

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
Free Energy
Free Energy Perturbation
Homology Modelling
Molecular Mechanics

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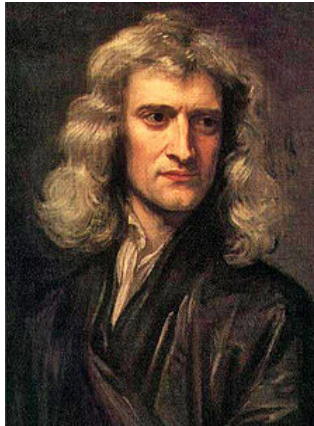Thermodynamics
Trajectory
Wave Function

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1. Introduction to Molecular Modeling:

Historical Developments, Literature

History of classical mechanics:

Galileo Galilei (1564-1642)

Sir Isaac Newton (1642-1727)

the three laws of motion

the law of inertia $\qquad \vec{F} = m\vec{a}$

the law of action and reaction

1687 - Philosophiae Naturalis Principia Mathematica

History of classical mechanics:

1738 - **Daniel Bernoulli: fluid flow in Hydrodynamica**

1739 - **Leonhard Euler** solves the ordinary differential equation for a forced harmonic oscillator and notices the resonance phenomenon

1764 - Leonhard Euler examines the partial differential equation for the vibration of a circular drum and finds one of the Bessel function solutions

1776 - John Smeaton publishes a paper on experiments relating power, work, momentum and kinetic energy, and supporting the conservation of energy

1788 - **Joseph Louis Lagrange** **presents Lagrange's equations of motion in Mécanique Analytique**

1789 - Antoine Lavoisier states the law of conservation of mass

1813 - Peter Ewart supports the idea of the conservation of energy in his paper On the measure of moving force

1834 - Carl Jacobi discovers his uniformly rotating self-gravitating ellipsoids

1835 - **William Hamilton** **states Hamilton's canonical equations of motion**

1835 - Gaspard Coriolis examines theoretically the mechanical efficiency of waterwheels, and deduces the Coriolis effect.

1842 - Christian Doppler proposes the Doppler effect

1847 - Hermann von Helmholtz formally states the law of conservation of energy
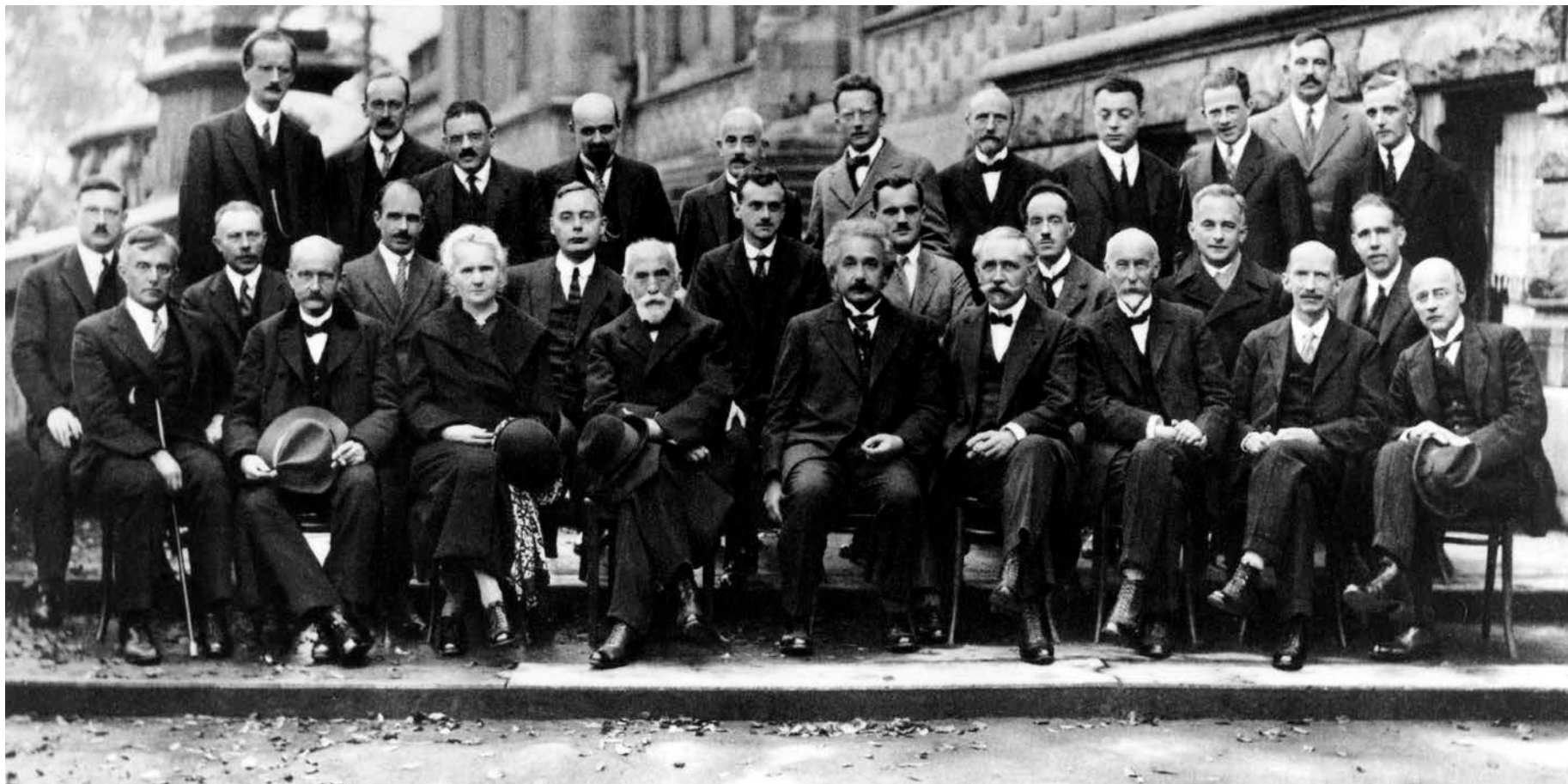
History of quantum mechanics (Top 10?)

??	
??	
??	

Computer Modeling of Chemical Reactions and Enzyme Catalysis

History of quantum mechanics (Top 10?)

Max Planck	Albert Einstein
Niels Bohr	Louis de Broglie
Max Born	Paul Dirac
Werner Heisenberg	Wolfgang Pauli
Erwin Schrödinger	Richard Feynman

Left-to right: Top row: A. Piccard, E. Henriot, P. Ehrenfest, Ed. Herzen, Th. De Donder, E. Schrödinger, E. Verschaffelt, W. Pauli, W. Heisenberg, R.H. Fowler, Léon Brillouin. **Middle:** P. Debye, M. Knudsen, W.L. Bragg, H.A. Kramers, P.A.M. Dirac, A.H. Compton, Louis de Broglie, Max Born, Niels Bohr. **Front row:** I. Langmuir, Max Planck, Marie Curie, H.A. Lorentz, A. Einstein, P. Langevin, Ch. E. Guye, C.T.R. Wilson, O.W. Richardson.

1900 – Max Planck black-body radiation (experimentally discovered 1862)

1905 (Annus Mirabilis)– Albert Einstein - the photoelectric effect (reported in 1887 by Heinrich Hertz)

1912 – Henri Poincaré publishes an influential mathematical argument in support of the essential nature of energy quanta.

1922 – Arthur Compton - Compton effect or Compton scattering, demonstrates the particle concept of electromagnetic radiation.

1922 – Bohr updates his model of the atom presaging orbital theory.

1923 – Louis de Broglie extends wave–particle duality to particles, postulating that electrons in motion are associated with waves. He predicts that the wavelengths are given by Planck's constant h divided by the momentum of the $mv = p$ of the electron: $\lambda = h / mv = h / p$

1924 – Wolfgang Pauli outlines the "Pauli exclusion principle"

1925 – George Uhlenbeck and Samuel Goudsmit- electron spin.

1925 – Friedrich Hund outlines Hund's rule of Maximum Multiplicity

1925 – Werner Heisenberg, Max Born, and Pascual Jordan develops the matrix mechanics formulation of Quantum Mechanics.

1926 – Oskar Klein and Walter Gordon state their relativistic quantum wave equation, later called the Klein–Gordon equation.

1926 – Erwin Schrödinger - "wave equation" also introduces the Hamiltonian operator in quantum mechanics.

1927 – Werner Heisenberg formulates the quantum uncertainty principle.

1927 – Max Born develops the Copenhagen interpretation of the probabilistic nature of wavefunctions.

1927 – Born and J. Robert Oppenheimer introduce the Born–Oppenheimer approximation, which allows the quick approximation of the energy and wavefunctions of smaller molecules.

1927 – Walter Heitler and Fritz London introduce the concepts of valence bond theory and apply it to the hydrogen molecule.

1927 – Thomas and Fermi develop the Thomas–Fermi model for a gas in a box.

1927 – Dirac states his relativistic electron quantum wave equation, the Dirac equation.

1927 – Walter Heitler uses Schrödinger's wave equation to show how two hydrogen atom wavefunctions join together, with plus, minus, and exchange terms, to form a covalent bond.

1927 – Robert Mulliken works, in coordination with Hund, to develop a molecular orbital theory: σ bond, π bond, and δ bond.

1928 – Linus Pauling outlines the nature of the chemical bond: uses Heitler's quantum mechanical covalent bond model; "resonance" (1931)

1928 – Friedrich Hund and Robert S. Mulliken introduce the concept of molecular orbitals.

1930 – Erich Hückel - Hückel molecular orbital method - energies of orbitals of π electrons in conjugated hydrocarbon systems.

1930 – Fritz London explains van der Waals forces as due to the interacting fluctuating dipole moments between molecules

1931 – John Lennard-Jones proposes the Lennard-Jones interatomic potential

1931 – Erich Hückel redefines the property of aromaticity in a quantum mechanical context by introducing the 4n+2 rule, or Hückel's rule, which predicts whether an organic planar ring molecule will have aromatic properties.

1932 – Werner Heisenberg applies perturbation theory to the two-electron problem to show how resonance arising from electron exchange can explain exchange forces.

1935 – Eyring equation: Henry Eyring, Meredith Gwynne Evans and Michael Polanyi

1938 – Charles Coulson makes the first accurate calculation of a molecular orbital wavefunction with the hydrogen molecule.

1950 – Barton (later Pitzer) conformational analysis

1953 – Watson Crick DNA structure

1954 – Zwanzig Free Energy Perturbation

1965 - Wiberg steepest descent algorithm

1964 – Hohenberg-Kohn theorem (foundations of modern DFT)

1965 - Kohn, Sham method

1968 – Boyd's implementation of Newton-Raphson method

1970's- the major force field formulations were being reported: Scheraga, Lifson, Allinger, Schleyer, Boyd, Bartell

1993 – Axel Becke - B3LYP ☺

1998- Nobel Prize Walter Kohn, John Pople

2013 – Nobel Prize Arieh Warshel, Martin Karplus, Michael Levitt

2. Quantum Mechanics: *Key Concepts, Methods, and Machinery*

Quantum *vs*. Classical World
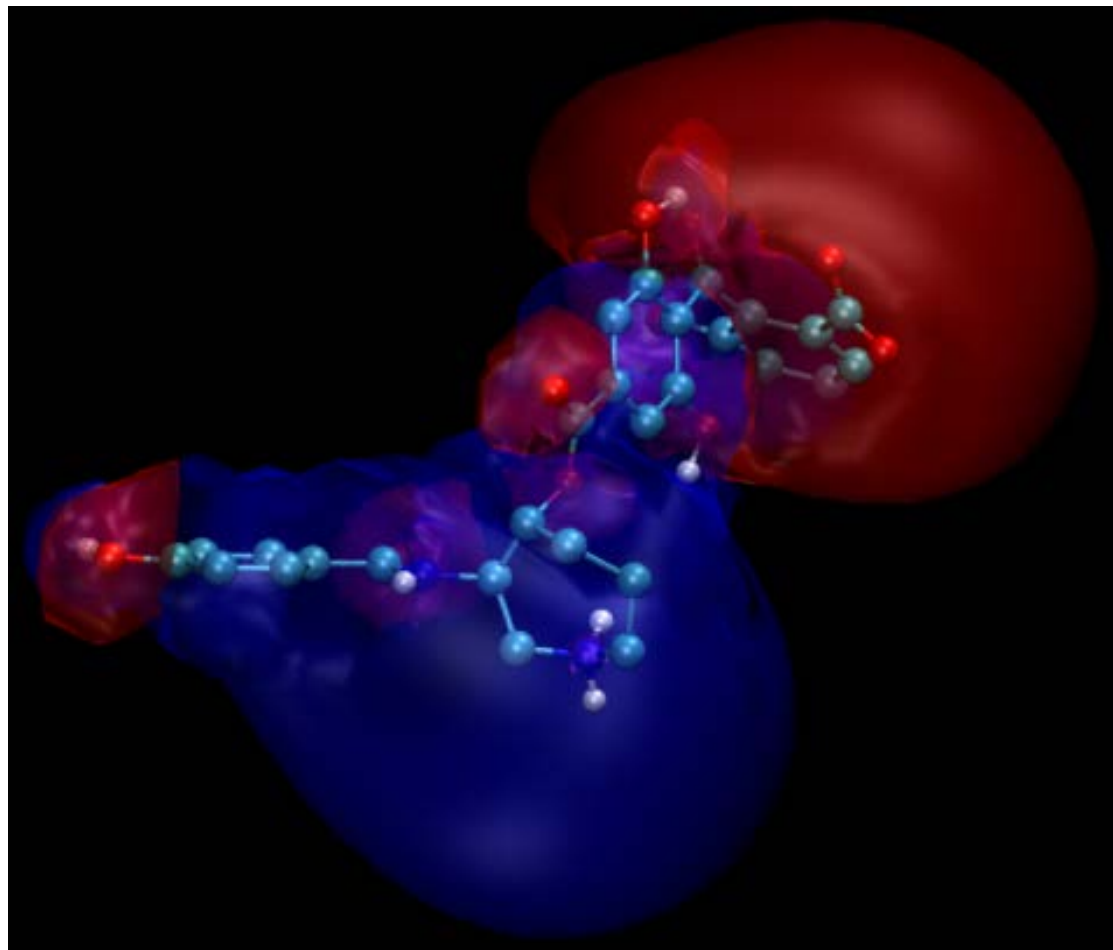
Foundations of Quantum Chemistry

Molecular quantum mechanics

Electronic structure methods
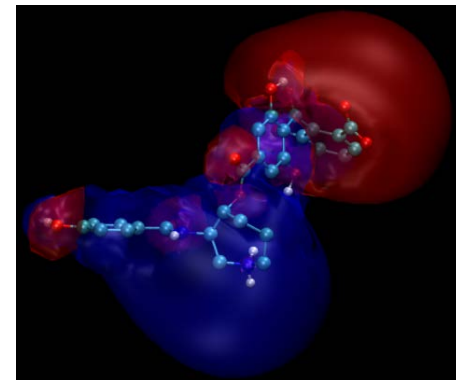
Schrödinger Equation
Quantum Mechanics

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

Free-Particle Dirac Equation
Relativistic Quantum Mechanics

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

Q-Chem World

Density Functional Theory (DFT)

Wave Function Theory

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

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

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

Variational, perturbational treatment, (QMC)

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

Hierarchy

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":
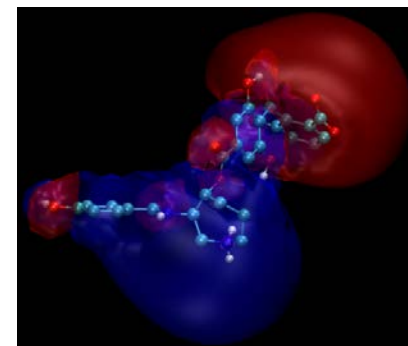PBE, TPSS(h), B3LYP,
M06's, ωB97XD

E

electron
correlation
energy

— Hartree-Fock energy

— Hartree-Fock limit

— Post-Hartree-Fock methods

— Exact solution of nonrelativistic Schrödinger equation

— Relativistic energy

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3. Molecular Mechanics: *Key Concepts, Methods, and Machinery*

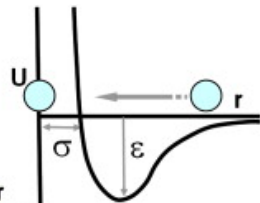# MM (molecular mechanics, force field) methods

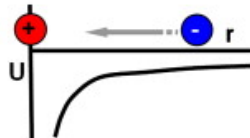**QM: nuclei + electrons**
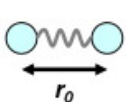
MM: atoms

Potential Energy of Molecular System

$$U = \sum_{i<j} \sum 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$
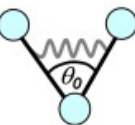
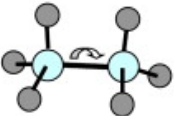$$+ \sum_{i<j} \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

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

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

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

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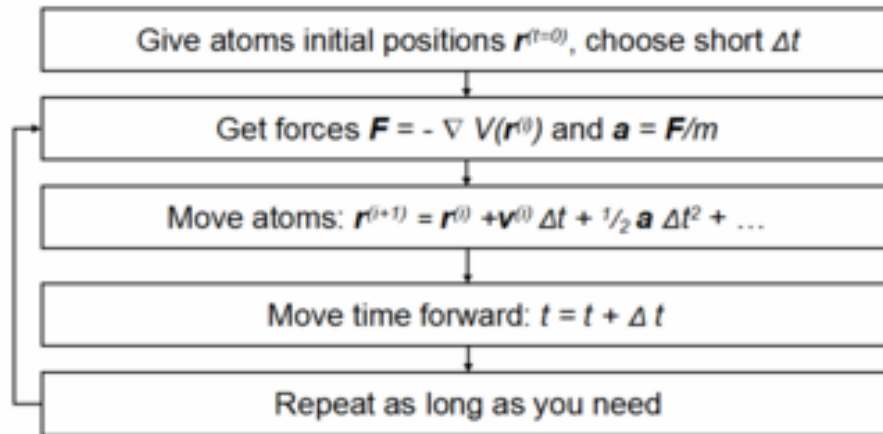
MM/MD (force field) methods: molecular simulations

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: $r^{(i+1)} = r^{(i)} + v^{(i)}\,\Delta t + \frac{1}{2}\mathbf{a}\,\Delta t^2 + \dots$

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
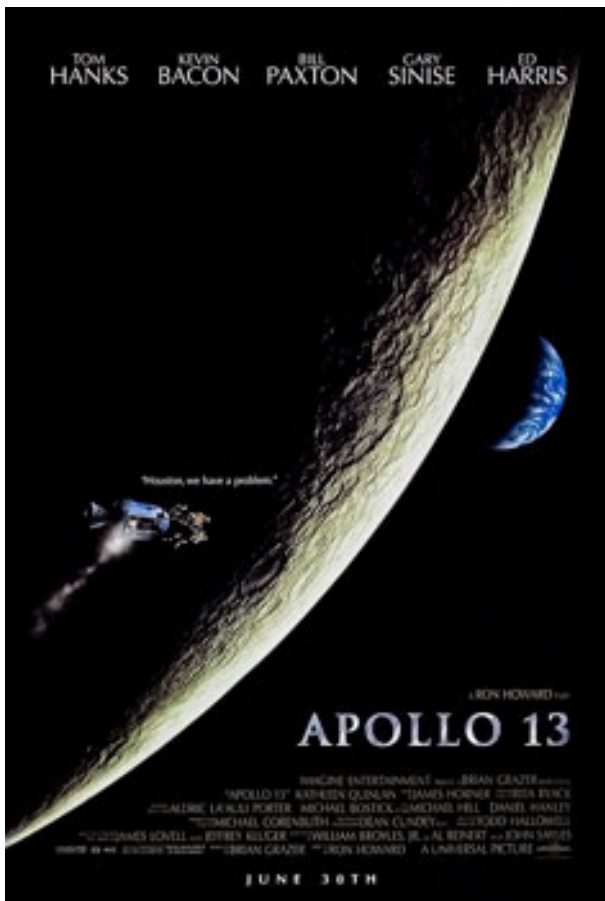
4. Statistical Thermodynamics:

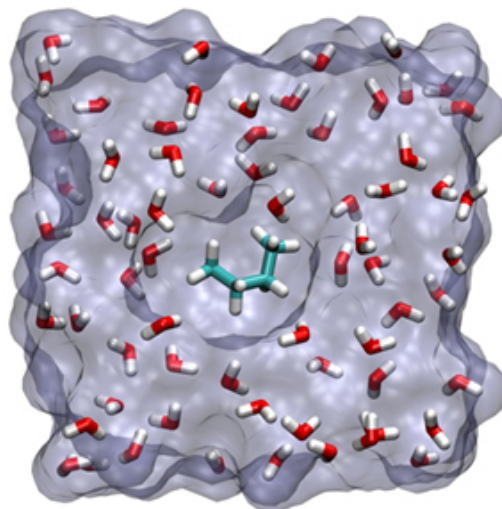*Essential Concepts (Partition Functions, Boltzmann Population, Entropy, Enthalpy, Free Energy)*

5. Solvation Methods: *Polarized Continuum Methods (PCM), Conductor-Like Screening Model (COSMO, COSMO-RS), Explicit Solvation, PBSA/GBSA Methods*
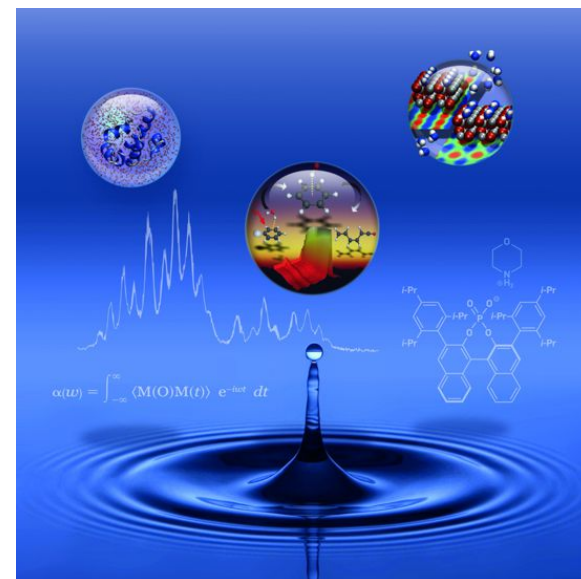
http://mackerell.umaryland.edu/~chris/

Modern Computational Chemistry:

Solvation Energy is (Almost) Everything

Apollo 13 quote:

Power (Energy) is Everything

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.
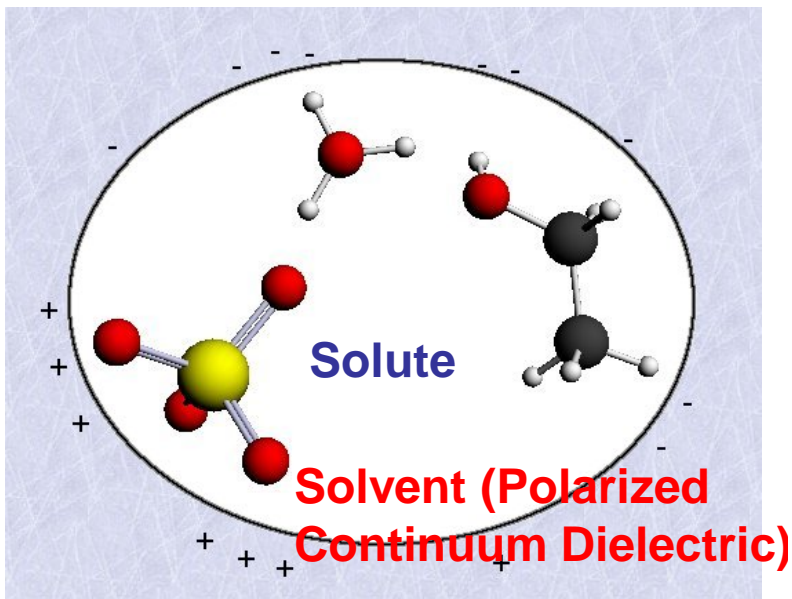
$$\Delta G_{sol} = \boxed{\Delta G_{el}} + G_{rep} + G_{dis} + G_{cav} + \Delta G_{tm} + P\Delta V$$

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

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

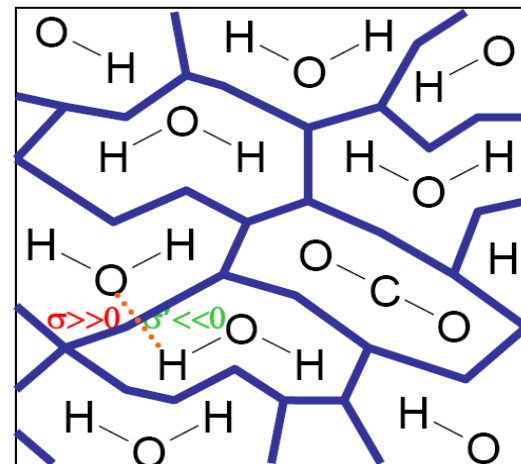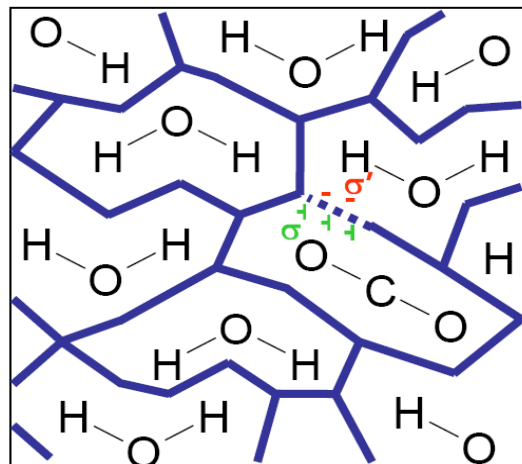$$-\nabla^2 V(\vec{r}) = 4\pi\rho_M(\vec{r}) \quad \text{within } C$$

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

Solute

Solvent (Polarized Continuum Dielectric)

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

$$E_{misfit}(\sigma, \sigma') = a_{eff} \frac{\alpha'}{2}(\sigma + \sigma')^2$$

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

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

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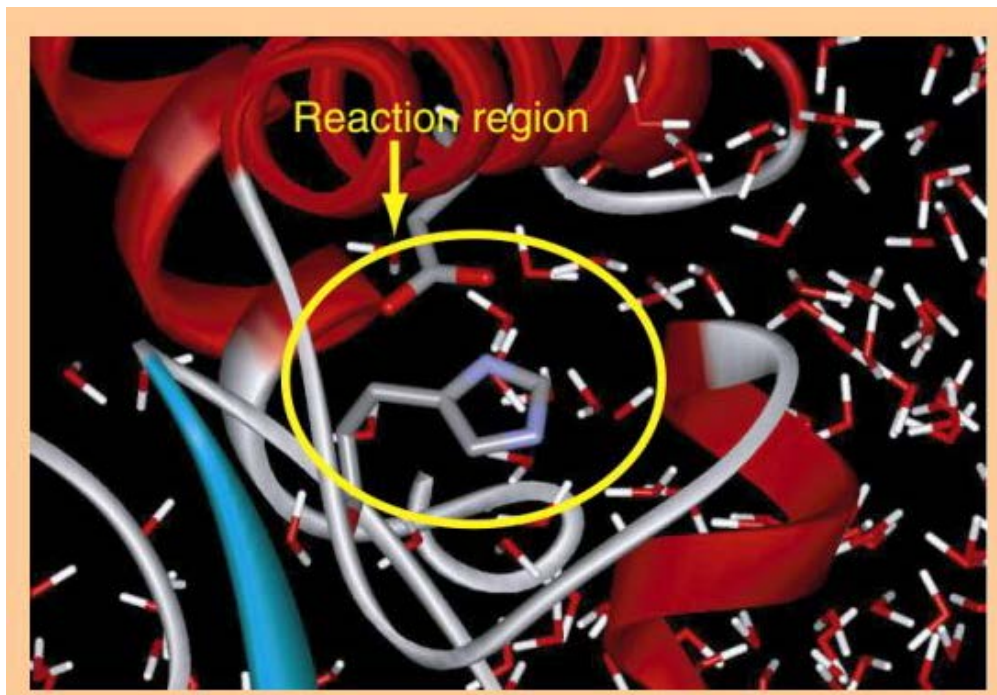
Andreas Klamt, COSMO*logic*

6. QM/MM Methods: *Background, Theory, Applications, and Case Studies (Reaction Mechanisms of Enzymes)*

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:

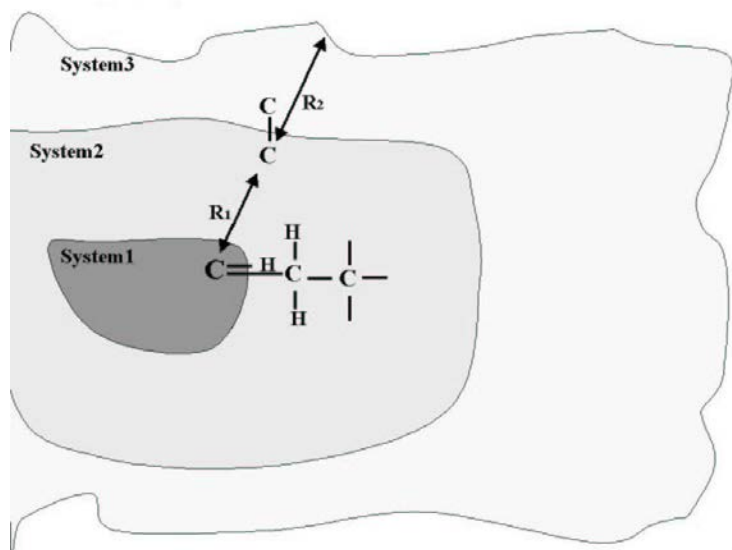1/ Reaction region

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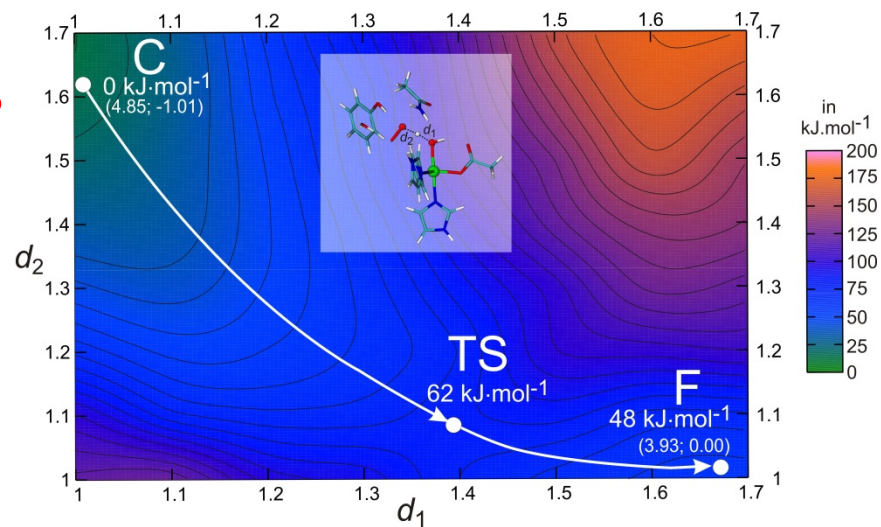
$E(MM,S1)$ … MM energy of S1 with charges of S1 set to zero

U. Ryde and M. H. M. Olsson, *Int. J. Quantum Chem.* **2001**, *81*, 335-347.
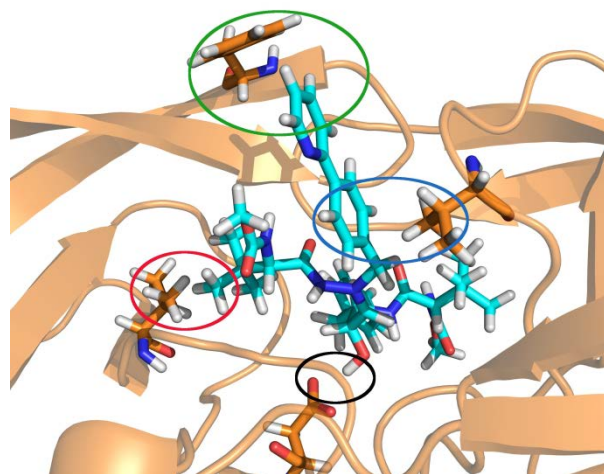
QM/MM: practical applications

Reaction coordinates

QM/MM scoring
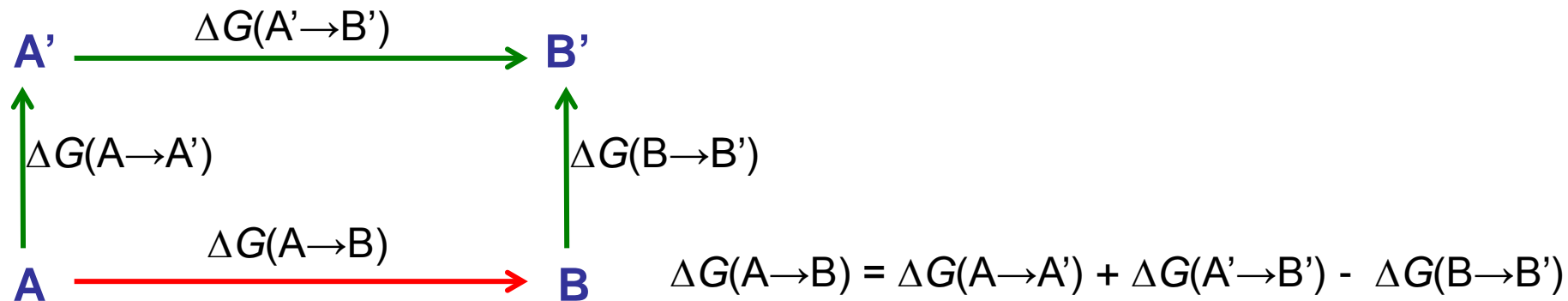(*vide infra* ☺)

e.g. QM/MM-PBSA

7. Thermodynamic Cycles for Computation of a Free–Energy Change in Condensed Phase: *Concepts, Applications (Reduction Potentials and Acidity Constants)*

Thermodynamic Properties

The Concept of Thermodynamic Cycle

A' $\xrightarrow{\Delta G(A' \rightarrow B')}$ B'

$\Delta G(A \rightarrow A')$ $\Delta G(B \rightarrow B')$

$\Delta G(A \rightarrow B)$

A $\xrightarrow{\hspace{3cm}}$ B $\Delta G(A \rightarrow B) = \Delta G(A \rightarrow A') + \Delta G(A' \rightarrow B') - \Delta G(B \rightarrow B')$

Small Molecules and their Physico-Chemical Properties in Solution
(equilibrium constants, acidity constants – pK_a, reduction potentials,
activation energies, …)

$\Delta G(A \rightarrow B) = \Delta G_{solv}(A)$
$\Delta G(B \rightarrow B') = \Delta G_{solv}(B)$
$\Delta G(A' \rightarrow B') = \Delta G_{gp}(A \rightarrow B) = \Delta E_{el}(A \rightarrow B) + \Delta ZPVE(A \rightarrow B) + \Delta[RT\ln(q_{trans}q_{rot}q_{vib})] + \Delta(pV)$

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8. Free Energy Perturbation (Thermodynamic Integration) and PMF Methods: *Concept, Theory, Applications*

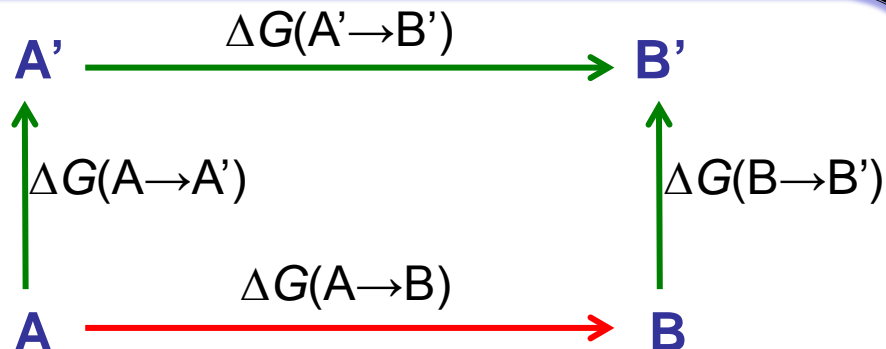# Free Energy Perturbation (Thermodynamic Integration)

$$Z = \int \cdots \int e^{-\beta E(X)} dX$$

$$A(\lambda) = -kT \ln Z(\lambda)$$

$$\Delta A = \int_0^1 \frac{\partial A(\lambda)}{\partial \lambda} d\lambda$$

$$\frac{\partial A(\lambda)}{\partial \lambda} = -kT \left[\frac{\partial \ln Z(\lambda)}{\partial \lambda} \right] = -\frac{kT}{Z(\lambda)} \frac{\partial Z(\lambda)}{\partial \lambda}$$

$$\Delta A = \int_0^1 \left\langle \frac{\partial E(X, \lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

A' — $\Delta G(A' \rightarrow B')$ → B'

$\Delta G(A \rightarrow A')$ $\Delta G(B \rightarrow B')$

$\Delta G(A \rightarrow B)$

A — $\Delta G(A \rightarrow B)$ → B

$\Delta G(A \rightarrow B)$ **known**
$\Delta G(A \rightarrow A')$, $\Delta G(B \rightarrow B')$ calculated via
"alchemical mutations" – parameter λ

9. Transition State Theory: *Eyring Equation (Theory, Applicability and Limitations, Kinetic Isotope Effects, Tunneling Correction), More Advanced Theories (Variational Transition State Theory)*

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

11. Physical Chemistry of Enzyme Catalysis I: *Reaction Rate and Order, Michaelis-Menten Equation, Metals in Enzymology (Stability Constants, Selectivity, Magnetism, Spectroscopy, Redox and Spin-State Activity)*

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
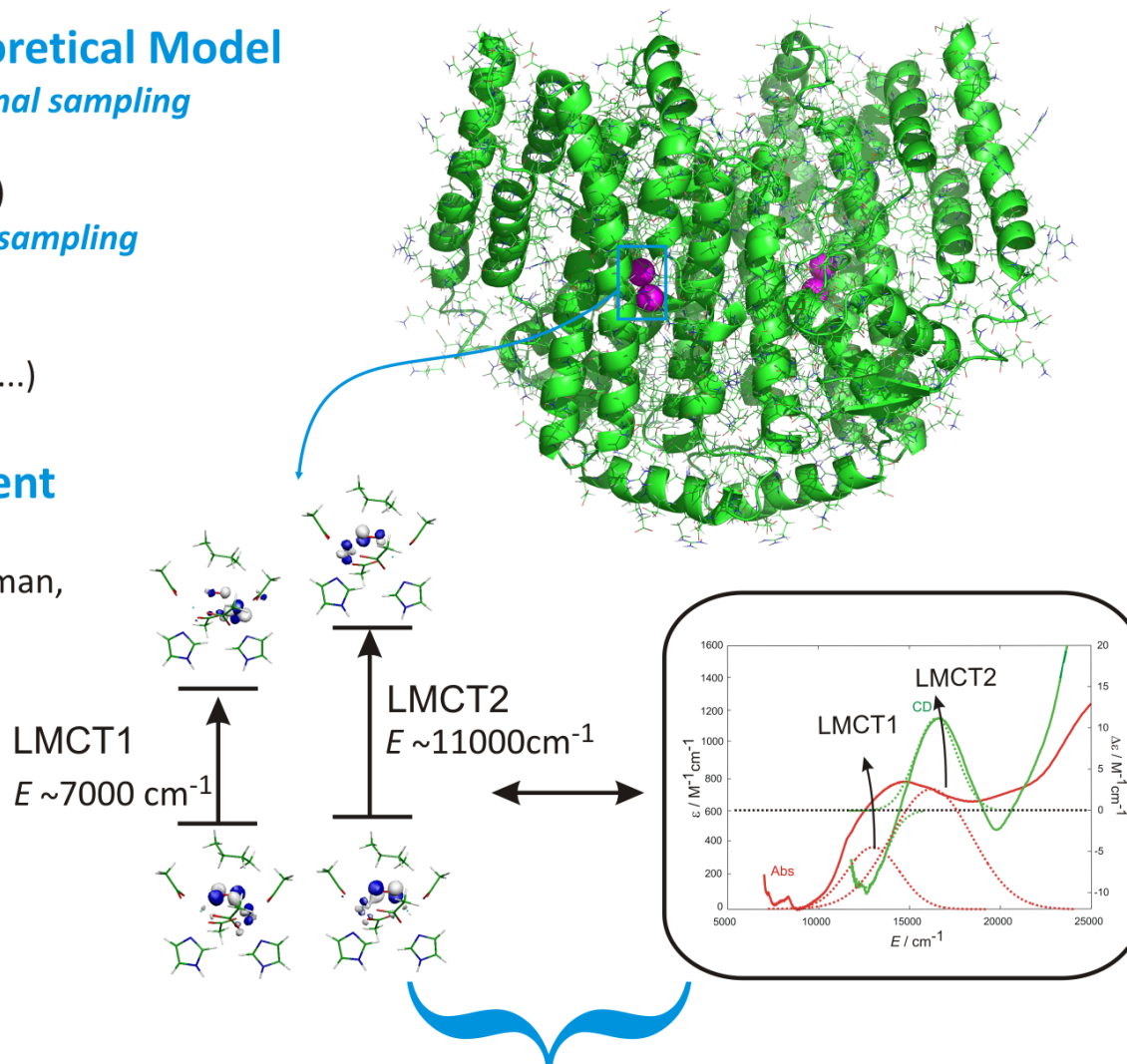rate constants, isotope effect

QM Methods

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

LMCT1
E ~7000 cm^{-1}

LMCT2
E ~11000cm^{-1}

Concepts and Mechanisms

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

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12. Physical Chemistry of Enzyme Catalysis II: *Theoretical Calculations of Reaction Profiles, Electron Transfer Kinetics and Redox Reactions, Marcus Theory, Adiabatic versus Non-adiabatic reaction dynamics (Landau-Zener model and beyond)*

13. Physical Chemistry of Enzyme Catalysis III - Metaloenzymes: *Crystal/Ligand Field Theory, DFT vs. WFT theories (Advantages and Pitfalls), Relativistic Effects (on Reactivity).*

14. Recent Advances in Molecular Modeling. *Outlook and Summary.*

Vocabulary of Theoretical (Computational) 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

Free Energy

Free Energy Perturbation

Homology Modelling

Molecular Mechanics

Molecular Dynamics

Molecular Surface and Volume

Poisson-Boltzman/Surface Area (PBSA)

Protein Structure

QM/MM

Quantitative Structure-Activity Relationship

Quantum Chemical Methods

Semiempirical Methods

Schrodinger Equation

Solvation

Statistical Mechanics

Thermodynamic Integration

Thermodynamics

Trajectory

Wave Function

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