Molecular Mechanics

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Palacky University, Olomouc 01/2017

Outline

1. Molecular Mechanics (MM)
2. Quantum Mechanics (QM)
3. Solvent Representation

Molecular Mechanics (MM)

Simplified theoretical description of molecules based on classical mechanics (= “dead-man potential”)

Hooke’s law (died 1703) – spring stiffness

Coulomb’s law (d. 1806) - electrostatics

Force-fields – CHARMM, AMBER, GROMOS, CVFF, MMFF, …..

$$E_{MM} = E_{bond} + E_{nonbond}$$

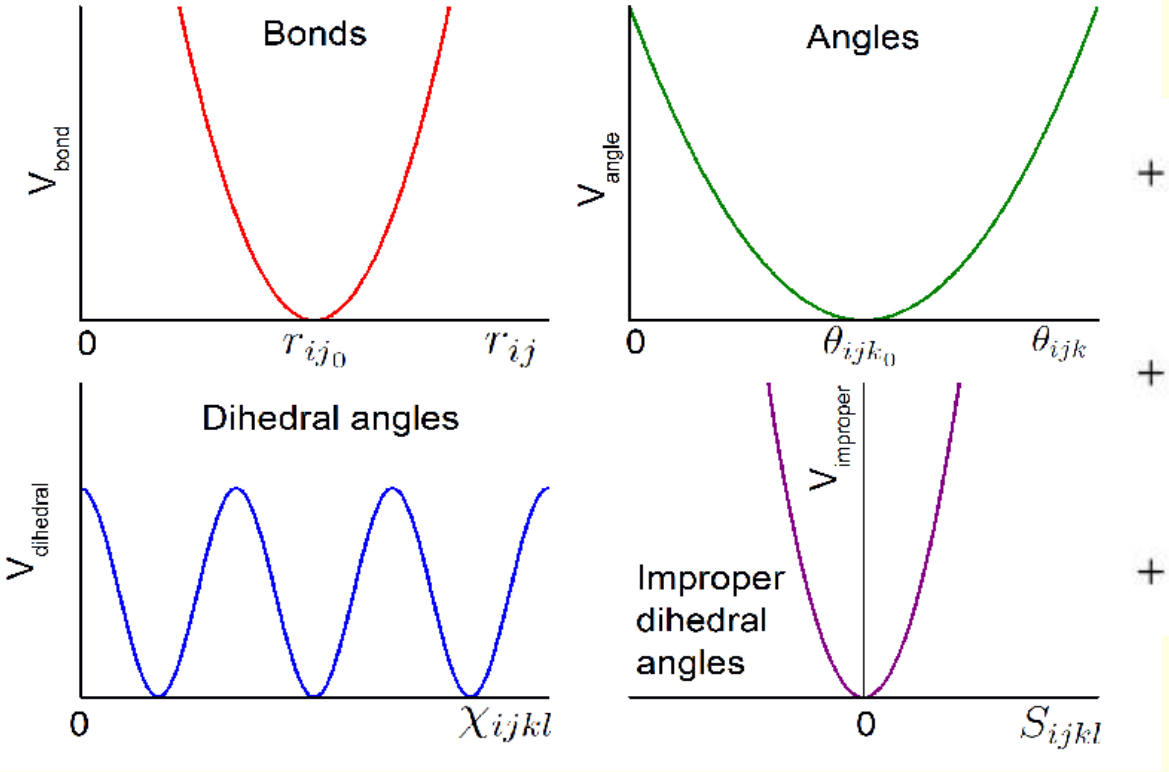
Nobel Prize in Chemistry, 2013 (Karplus, Warshel, Levitt)

MM - Bonded Terms

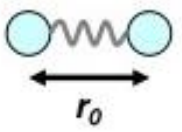
Atom = mass

Molecule = atoms connected by springs

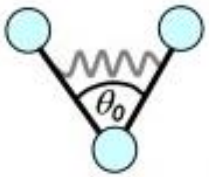
$$E_{bonded} = E_{bond} + E_{angle} + E_{dihed} + E_{improper}$$



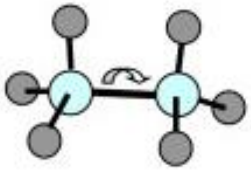
$$+ \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2$$



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



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



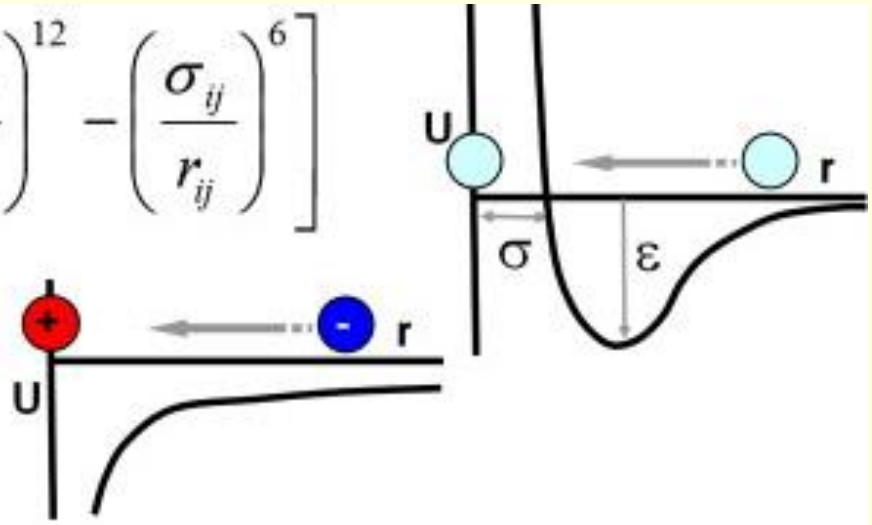
MM - Nonbonded Terms

Electrostatic: Coulomb

van der Waals: Dispersion

$$E_{nonbond} = E_{Coulomb} + E_{vdW}$$

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



Molecular Dynamics

- simulating molecular movements

- solving Newton's equations of motion for nuclei in MM (electrons as parameters)

$$-dE/dx = \mathbf{F} = \mathbf{m * a} = m * dv/dt = m * (dx/dt)/dt$$

Trajectory – x (coordinate frames)
Velocity - v (t)

Quantum Mechanics (QM)

mathematical description of particle-wave duality of electrons
Time-independent Schrődinger equation: $\mathbf{\hat{H}\psi = E\psi}$
$\hat{H}$ –Hamilton operator
ψ - Wave function
E – energy

Heisenberg's uncertainty principle
Position, x, and momentum, p of a particle cannot be determined precisely

Probability distributions

Quantum Chemistry

Application of QM to chemistry

Wave model of atom: positively charged nucleus surrounded by clouds of electrons in **atomic orbitals**

Quantum numbers
Pauli Exclusion Principle – two electrons in one orbital differ by their spin
Hund's Rules – determine the ground state of an atom
Aufbau Principle – order by which electrons occupy orbitals

Atomic Orbitals: linear combinations → Molecular Orbitals
- Basis sets

Basis Sets

Set of functions → representations of molecular orbitals (MO-LCAO)
Slater - Gaussian

- Minimal basis set (one function per orbital)
- Polarization functions
- Diffuse functions

- STO-3G, 3-21G, 6-31G*, 6-311+G**, SVP, aug-cc-pVTZ

Ab initio QM methods (”from first principles)

Approximations for molecules of >3 atoms

Born-Oppenheimer approximation: separates movement of nuclei and electrons

Hartree-Fock – electronic effects as mean field, H-bond described, not dispersion (electron correlation)

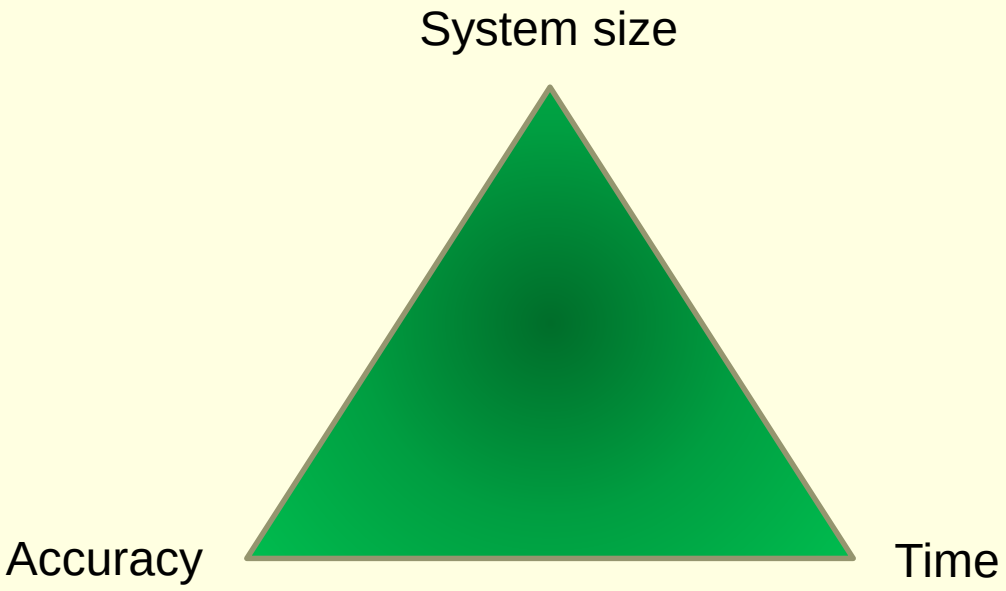
Møler-Plesset perturbation theory (MP2, MP3, ….)

CCSD(T) – coupled-cluster, singles doubles triples

Scaling – HF (N^4), MP2 (N^5), CCSD(T) (N^6)

Quantum Chemistry

Covalent Reactions – electron rearrangements
Noncovalent Interactions
- proton/charge transfer
- sigma-hole bonding
- metals
- ligands (no parametrization)



Density Functional Theory (DFT)

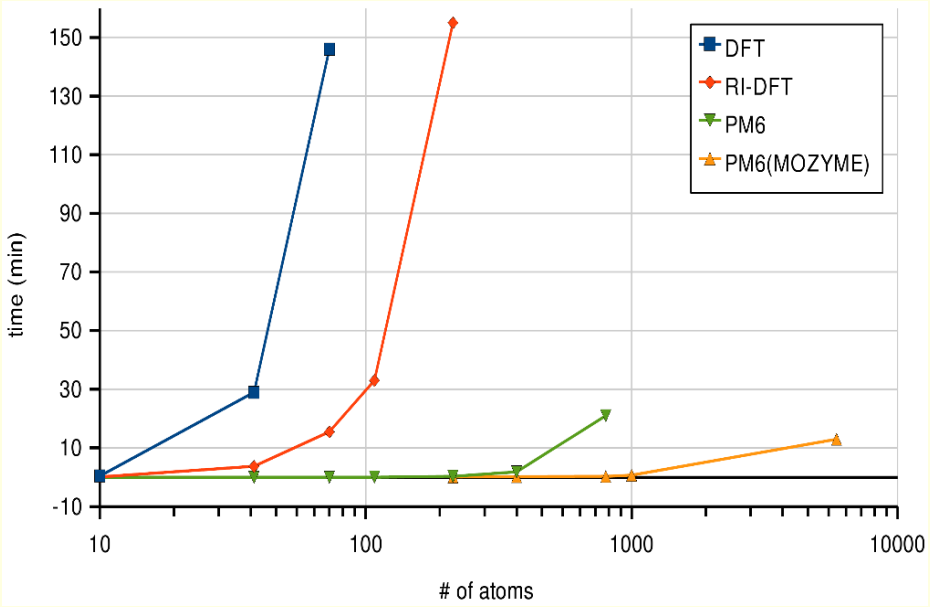
Alternative (non-ψ) description
Electron Density
Partial description of dispersion

Exchange-correlation Functionals: B3LYP, PBE, BP86, M06

Missing Dispersion - Empirical

Semiempirical QM

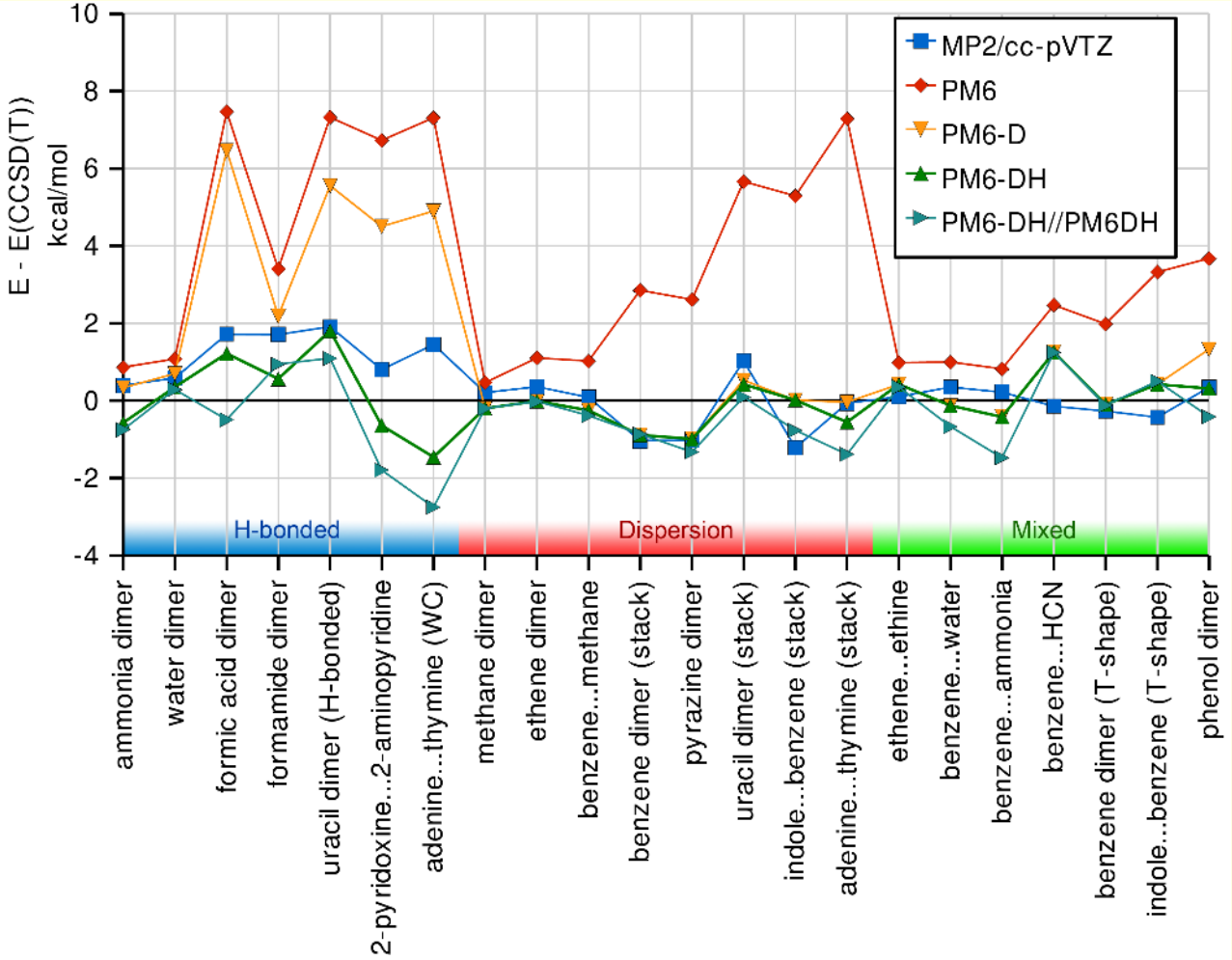
Integrals – parameters
Simplified HF, no dispersion
AM1, PM6 - MOPAC
SCC-DF-TB
Linear scaling (N): MOZYME
Underestimate H-bonds, repulsion subminimal basis, only valence orbitals, core-core



Stewart J, MOPAC2012.

Corrected Semiempirical QM

D3H4X – reliable: corrections for H-bonding, D-dispersion, X-bonding



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Řezáč, Hobza, *Chem. Phys.Lett.* **2011**, 506, 286

Řezáč, Hobza, *J. Chem. Theory Comput.* **2012**, 8, 141

Parametrization

Model systems

Consistent Datasets CCSD(T)/CBS
H-bonding, dispersion, stacking (S22, S66)
Nonequilibrium geometries (S22x5, S66x8)
X-bonding (X40)
Large dispersion (L7)

Solvent Representation

Explicit

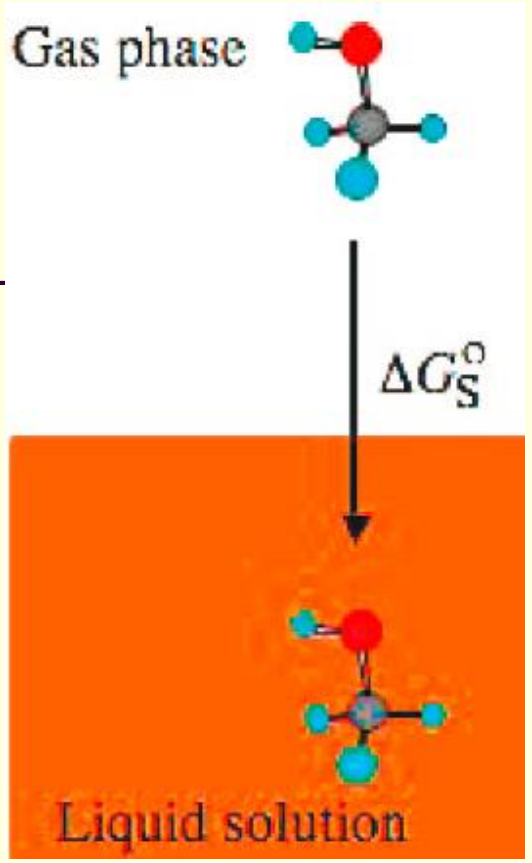
- MM: TIP3P, SPC,….TIP5P, SPC/E
- QM: H_3O^+, OH^-

Implicit = Continuum

- MM: generalized Born, Poisson-Boltzmann
- QM: PCM, COSMO, SMD

Solvation Free Energy

$$\Delta G_S^o(A) = \lim_{[A]_{sol} \to 0} \left\{ -RT \ln \frac{[A]_{sol}}{[A]_{gas}}\bigg|_{eq} \right\}$$



Implicit = Continuum

- Damping of electrostatic interactions

Explicit

- specific H-bonds

Conclusions

1. Molecular Mechanics (MM)
2. Quantum Mechanics (QM)
3. Solvent Representations