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Force fields

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Born-Oppenheimer approximation

Assumes that the motion of atomic nuclei and electrons in a molecule can be separated

Difference in mass between nuclei and electrons

Molecular mechanics: Atoms are represented as localized particles carrying a point charge

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Molecular mechanics

Ball and stick model: atoms are the smallest particle and are represented by spheres of a given radius

Component of the energy function:
• Deviations of bonds and angles from their reference values
• Rotation around bonds
• Interaction between non-bonded parts of the systems

Force fields are empirical, there is no "correct" energy function or parameters
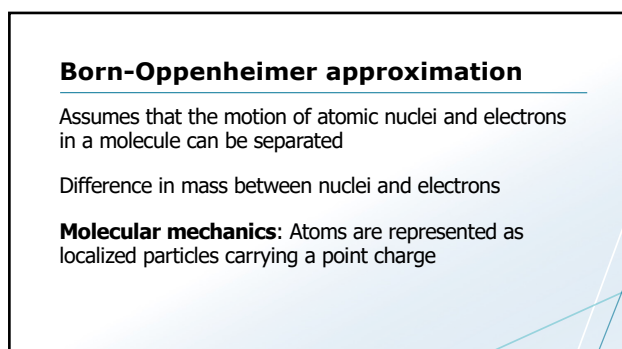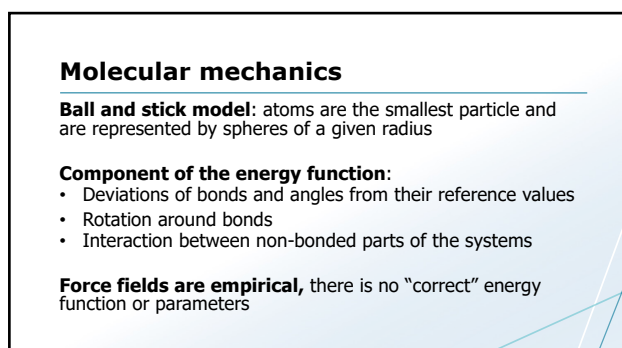
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Molecular mechanics: Equation

$$U_{pot} = \sum_{bonds} \tfrac{1}{2} k_b \cdot \left(r - r_0\right)^2 + \sum_{angles} \tfrac{1}{2} k_\theta \left(\theta - \theta_0\right)^2 +$$

$$\sum_{dihedrals} K_\varphi \cdot \left(1 + \cos\left(n \cdot \varphi - \delta\right)\right) +$$

$$\sum_{\substack{improper \\ dihedrals}} \tfrac{1}{2} k_\xi \left(\xi - \xi_0\right)^2 +$$

$$\sum_{atom\ pairs} \frac{1}{4 \cdot \pi \cdot \varepsilon_0} \frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6}$$

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Atom types

- Atom type is used to define a particular bonding situation, e.g. aliphatic carbon atom in a sp^3 bonding has different properties than a carbon atom found in a His ring
- Need to minimize the of atom types => type specific errors
- Polar atoms (O, N etc) are more influenced by their neighboring atoms => more types

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Atom types

Table 1. List of Atom Types[a]

| atom	type	description
carbon	CT	any sp^3 carbon
	C	any carbonyl sp^2 carbon
	CA	any aromatic sp^2 carbon and (Cε of Arg)
	CM	any sp^2 carbon, double bonded
	CC	sp^2 aromatic in 5-membered ring with one substituent + next to nitrogen (Cγ in His)
	CV	sp^2 aromatic in 5-membered ring next to carbon and lone pair nitrogen (e.g. Cδ in His (δ))
	CW	sp^2 aromatic in 5-membered ring next to carbon and NH (e.g. Cδ in His (ε) and in Trp)
	CR	sp^2 aromatic in 5-membered ring next to two nitrogens (Cγ and Cε in His)
	CB	sp^2 aromatic at junction of 5- and 6-membered rings (Cδ in Trp) and both junction atoms in Ade and Gua
	C*	sp^2 aromatic next to two carbons (e.g. Cγ in Trp)
	CN	sp^2 junction between 5- and 6-membered rings and bonded to CH and NH (Ce in Trp)
	CK	sp^2 carbon in 5-membered aromatic between N and N-R (C8 in purines)
	CQ	sp^2 carbon in 6-membered ring between lone pair nitrogens (e.g. C2 in purines)

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Bond stretching

The contribution to the total energy depends on the deviation from the **reference value r_0**
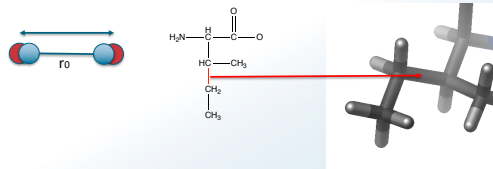
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Bond stretching

- Harmonic potential

$$E_{str}(\Delta R^{AB}) = k_2^{AB}(\Delta R^{AB})^2 + k_3^{AB}(\Delta R^{AB})^3 + k_4^{AB}(\Delta R^{AB})^4 + \dots$$

- Simplest functional form

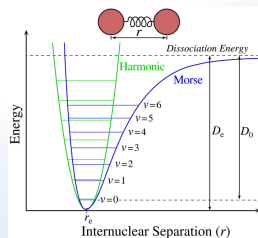- Works well since bonds does not deviate much
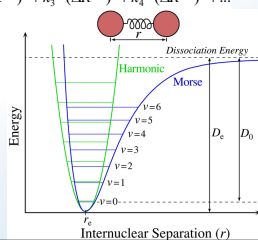
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Bond stretching

- Morse potential:

$$E_{str}(\Delta R^{AB}) = D[1 - e^{\alpha \Delta R}]^2$$
$$\alpha = \sqrt{k/2D}$$

D = Dissociation energy
  - Accurate actual behavior
- Problems
  - computation time
  - poor geometry, slow convergence

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Hands-on: Morse vs harmonic

- Construct the potential energy surface for bond stretching of the following bond:

CT1 – CT1

Harmonic: k=445 kcal/molÅ² r₀=1.54 Å

Morse: D=55.62 kcal/mol α=2 Å⁻²
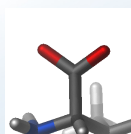
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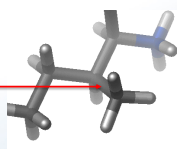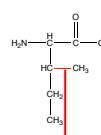## Angle bending

Requires less energy compared to bonds
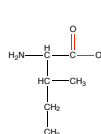
$$E_{bend}(\theta^{ABC} - \theta_0^{ABC}) = k^{ABC}(\theta^{ABC} - \theta_0^{ABC})^2$$
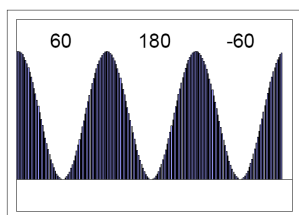
θ_opt

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Torsion

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Torsion

$$E_{tors}(\omega) = \sum_{n=1} V_n \cos(n\omega)$$

- Depending on the situation some of V_n terms are set to 0
  - $n=1$: periodic by 360 degree
  - $n=2$: periodic by 180 degree
  - $n=3$: periodic by 120 degree

  - Ethane : three minima and three maxima
   - $n = 3,6,9, ...$ can have V_n

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Torsions

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Torsion

- Many FFs use only one term for the expansion
- Some FFs use general torsional potential:
  H-C-C-H   H-C-C-C   C-C-C-C
  All three would have the same torsional term
- MM2 is an example of a force field that use several terms for each torsion
- Including more terms requires many parameters to model even small simple molecules

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Torsion

$V(x) = 1.5(1+\cos(3x))+0.5(1+\cos(2x))$
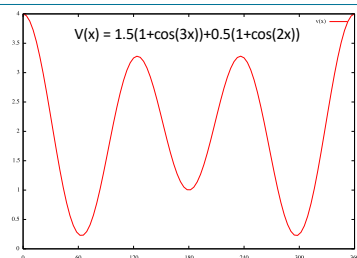
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Torsion

- Most of the variation in structures and relative energies are interplay between torsion and non-bonded potentials
- Always expressed as a cosine series expansion
- Description of complex potential requires several terms

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Improper torsions

- Several chemical systems are planar - e.g. aromatic rings
- Planarity is taken care of by using either improper torsions or out-of-plane bending terms
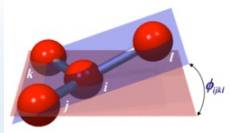 - Improper torsions are between four atoms that are not in a "sequence"

$$U_{imp} = k(1 - \cos 2\varpi)$$
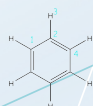
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Improper torsions

- Improper torsions can also be used to keep things at a certain degree out-of-plane
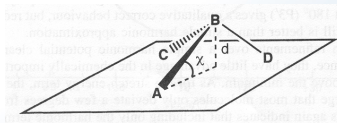- Angle between planes defined by atoms i-j-k and j-k-l

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Improper torsion
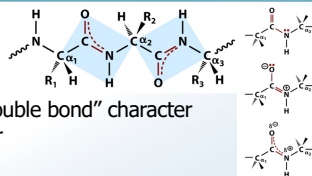
- Harmonic potential

$$U(\chi_B) = k^B(\chi_B)^2$$

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Improper torsions

Peptide bonds have "double bond" character
- Shorter and stiffer than normal
- Different torsion potentials
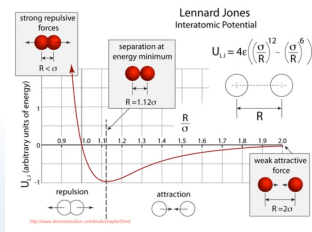- Higher rotation barriers
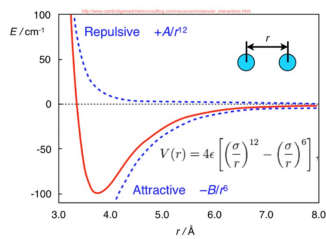
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van der Waals interactions

6-12 Lennard Jones potential

$$E_{LJ}(R) = \varepsilon\left[\left(\frac{R_0}{R}\right)^{12} - 2\left(\frac{R_0}{R}\right)^6\right]$$

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van der Waals interactions

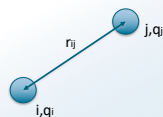$$V(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6\right]$$

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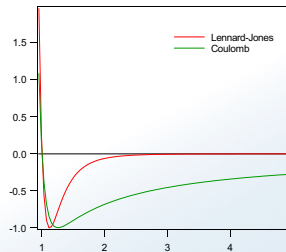## Electrostatic interactions

- Point charge electrostatics:

$$U(elec) = \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

- Coulombic potential
- No dipole induced effects

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Electrostatic interactions
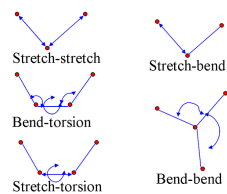

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Hands-on: Maestro

- Build a serine molecule (Use builder and templates)
- Do a rapid torsion scan of the Cα-Cβ bond (Edit =>Rapid torsion scan)
- Plot the potential energy surface
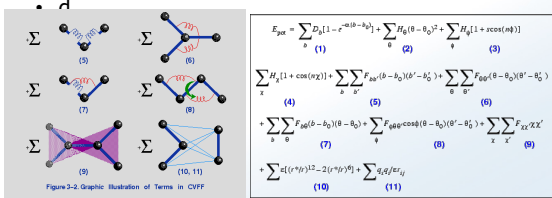- Can you explain the barriers?

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Cross-terms

- coupling between internal coordinates: e.g. stretching of two bonds adjoining an angle

- Main terms to include:

Stretch-stretch   Stretch-bend

Bend-torsion

Stretch-torsion   Bend-bend

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Cross-terms (CVFF)

$$E_{pot} = \sum_b D_b[1 - e^{-\alpha(b-b_0)}] + \sum_\theta H_\theta(\theta - \theta_0)^2 + \sum_\phi H_\phi[1 + s\cos(n\phi)]$$
$$\qquad\qquad\qquad\qquad (1) \qquad\qquad\qquad\quad (2) \qquad\qquad\qquad (3)$$

$$+ \sum_\chi H_\chi[1 + \cos(n\chi)] + \sum_b \sum_{b'} F_{bb'}(b-b_0)(b'-b_0') + \sum_\theta \sum_{\theta'} F_{\theta\theta'}(\theta - \theta_0)(\theta' - \theta_0')$$
$$\qquad\qquad (4) \qquad\qquad\qquad\qquad (5) \qquad\qquad\qquad\qquad\qquad (6)$$

$$+ \sum_b \sum_\theta F_{b\theta}(b-b_0)(\theta - \theta_0) + \sum_\phi F_{\phi\theta\theta'}\cos\phi(\theta - \theta_0)(\theta' - \theta_0') + \sum_\chi \sum_{\chi'} F_{\chi\chi'}\chi\chi'$$
$$\qquad\qquad (7) \qquad\qquad\qquad\qquad (8) \qquad\qquad\qquad\qquad (9)$$

$$+ \sum \epsilon[(r^*/r)^{12} - 2(r^*/r)^6] + \sum q_i q_j / \epsilon r_{ij}$$
$$\qquad\qquad (10) \qquad\qquad\qquad (11)$$

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Class I and II force fields

- Class I: harmonic terms and no cross-terms
- Class II: anharmonic terms and cross-terms
  - Unusual systems (e.g. strain)
  - Vibrational spectra
  - Isolated small molecules and condensed phases

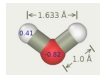30

Water models

Aim: accuracy and efficiency (many water molecule!)

Simple models: SPC, SPC/e, TIP3P, TIP4P, ST2
    Use three to five interaction points
    Fixed geometry

Force fields are usually parameterized with a restricted number of water models

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Water models

	TIP3P	SPC	SPC/E
r_{OH} (Å)	0.9572	1.0	1.0
$\angle HOH$ (°)	104.52	109.47	109.47
$10^3 C_6$ (kJ/mol nm^6)	2.4889	2.6171	2.6171
$10^6 C_{12}$ (kJ/mol nm^{12})	2.4352	2.6331	2.6331
q_O (e)	−0.834	−0.820	−0.8476
q_H (e)	+0.417	+0.410	+0.4238

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Force fields: Summary

$$\vec{F}_i = -\nabla_i U_{pot}$$

potential energy

bonded

nonbonded

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