

Chemistry 137

Molecular Mechanics
PPT modified from Berny
Schlegel, Michigan State U

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Resources

- Grant and Richards, Chapter 3
- Leach, Chapter 3
- Jensen, Chapter 2: 2.1, 2.2 (not .9, .10), 2.3.1, 2.4-2.8
- Cramer, Chapter 2
- Burkert and Allinger, *Molecular Mechanics* (ACS Monograph 177, 1982)
- Bowen and Allinger, *Rev. Comput. Chem.* 2, 81 (1991)

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Empirical Force Fields (FF)

- PES calculated using empirical potentials fitted to experimental and calculated data
- composed of stretch, bend, torsion and non-bonded components

$$E = E_{\text{str}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{non-bond}}$$

- e.g. the stretch component has a term for each bond in the molecule

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FF: transferability

- potential energy curves for individual terms are approximately transferable (e.g. CH stretch in ethane almost the same as in octane)
- terms consist of functional forms and parameters
- parameters chosen to fit structures (in some cases also vibrational spectra, steric energies)

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FF: atom types and parameters

- a force field is comprised of functional forms, parameters and atom types
- each atomic number is divided into atom types, based on bonding and environment (e.g. carbon: sp^3 , sp^2 , sp , aromatic, carbonyl, etc.)
- parameters are assigned based on the atom types involved (e.g. different C-C bond length and force constant for sp^3-sp^3 vs sp^2-sp^2)

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FF: Different examples

- examples: MM2, MM3, Amber, Sybyl, Dreiding, UFF, MMFF, etc.
- differ by the functional forms and parameters
- not mix and match - each developed to be internally self consistent
- some force field use united atoms (i.e. H's condensed into the heavy atoms) to reduce the total number of atoms (but with a reduction in accuracy)

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FF: uses in MD

- molecular mechanics force fields differ from force fields used for vibrational analysis, and analytical potential energy surfaces used for dynamics - these are custom fit for individual systems
- molecular mechanics force fields are designed to be transferable, and can be used for broad classes of molecular systems (but stay within the scope of the original parameterization)

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Bond Stretch Term

- many force fields use just a quadratic term, but the energy is too large for very elongated bonds

$$E_{\text{str}} = \sum k_i (r - r_0)^2$$
- Morse potential is more accurate, but is usually not used because of expense

$$E_{\text{str}} = \sum D_e [1 - \exp(-\beta(r - r_0))]^2$$
- a cubic polynomial has wrong asymptotic form, but a quartic polynomial is a good fit for bond length of interest

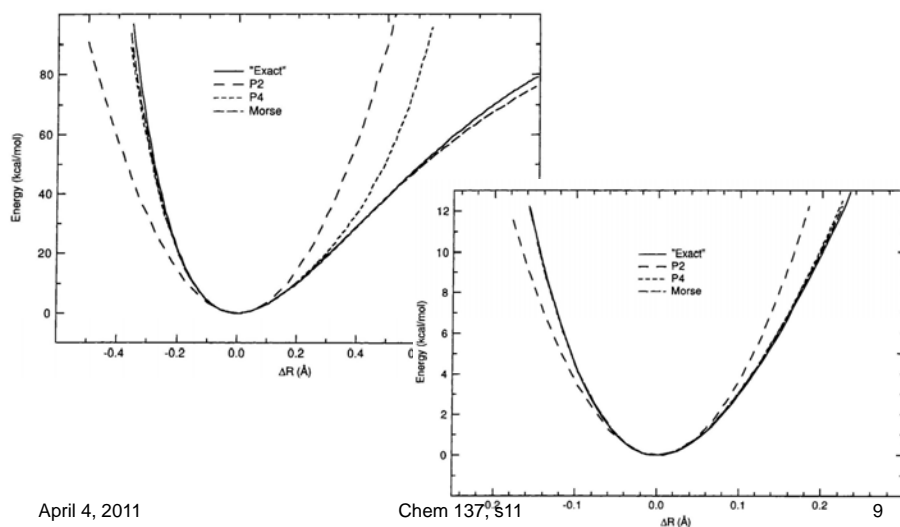
$$E_{\text{str}} = \sum \{ k_i (r - r_0)^2 + k'_i (r - r_0)^3 + k''_i (r - r_0)^4 \}$$
- The reference bond length, r_0 , not the same as the equilibrium bond length, because of non-bonded contributions

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Comparison of Potential Energy Functions for Bond Stretch



Angle Bend Term

- usually a quadratic polynomial is sufficient

$$E_{\text{bend}} = \sum k_i (\theta - \theta_0)^2$$

- for very strained systems (e.g. cyclopropane) a higher polynomial is better

$$E_{\text{bend}} = \sum k_i (\theta - \theta_0)^2 + k'_i (\theta - \theta_0)^3 + k''_i (\theta - \theta_0)^4 + \dots$$

- alternatively, special atom types may be used for very strained atoms

Torsional Term

- most force fields use a single cosine with appropriate barrier multiplicity, n

$$E_{\text{tors}} = \sum V_i \cos[n(\theta - \theta_0)]$$

- some use a sum of cosines for 1-fold (dipole), 2-fold (conjugation) and 3-fold (steric) contributions

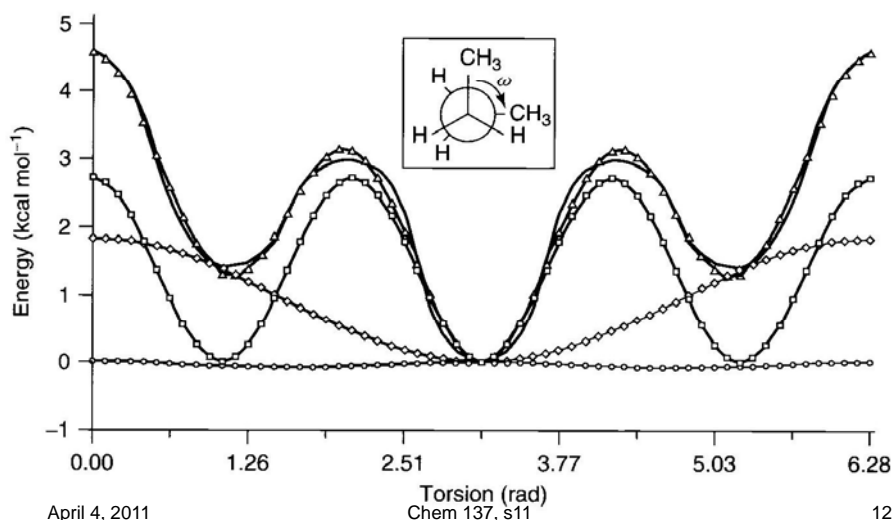
$$E_{\text{tors}} = \sum \{ V_i \cos[(\theta - \theta_0)] + V'_i \cos[2(\theta - \theta_0)] + V''_i \cos[3(\theta - \theta_0)] \}$$

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Torsional potential for n-butane as a sum of 1-fold, 2-fold and 3-fold terms



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Rotational Barrier for Ethane

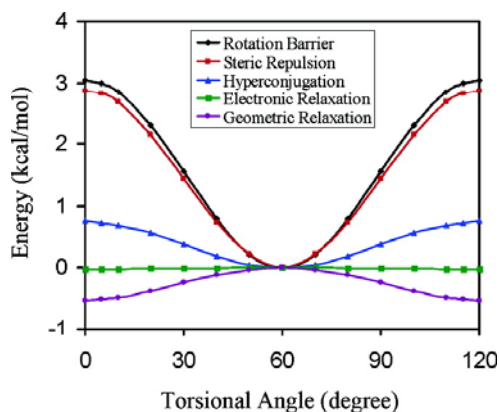
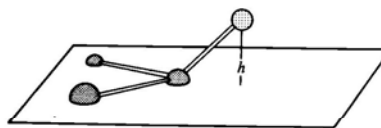
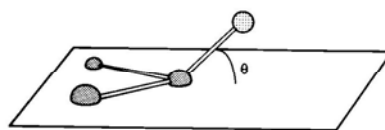


Figure 5 Rotation barrier along with the steric repulsion, hyperconjugation, electronic relaxation, and geometric relaxation energy changes with respect to the torsional angle.

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Out-of-Plane Bending Term

- angle-to-plane or distance-to-plane can be used for the out-of-plane bending coordinate
- improper torsions can also be used for out-of-plane bends
- chirality constraints are required in united atom force fields



Non-Bonded Terms

- van der Waals, electrostatic and hydrogen bonded interactions

$$E_{\text{non-bond}} = E_{\text{vdW}} + E_{\text{es}} + E_{\text{Hbond}}$$

- repulsive part of van der Waals potential
 - due to overlap of electron distributions (Pauli exclusion)
 - rises very steeply (steric repulsion)
- attractive part of van der Waals potential
 - due to London or dispersion forces
 - instantaneous dipole - induce dipole interaction
 - proportional to r^{-6}

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Van der Waals

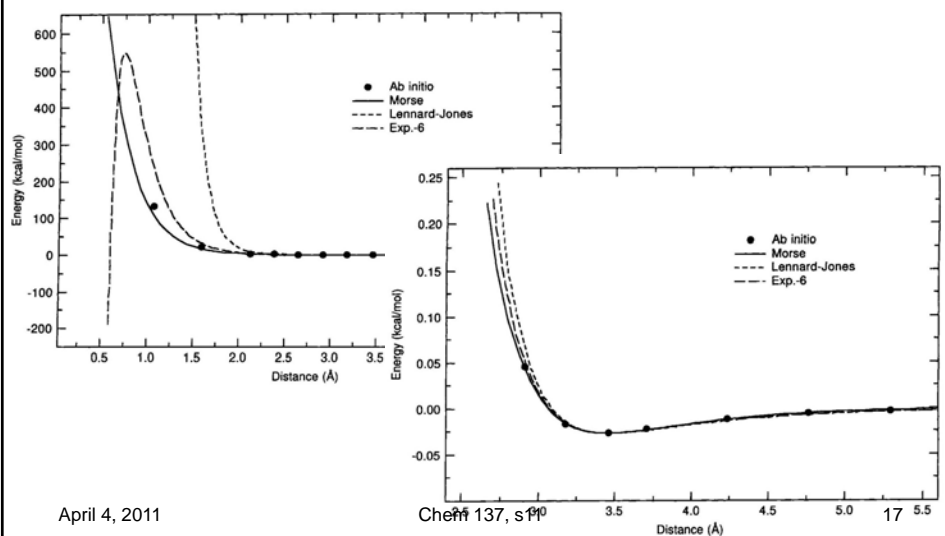
- Lennard-Jones potential
 - $E_{\text{vdW}} = \sum 4 \epsilon_{ij} \left(\left(\sigma_{ij} / r_{ij} \right)^{12} - \left(\sigma_{ij} / r_{ij} \right)^6 \right)$
 - easy to compute, but r^{-12} rises too rapidly
- Buckingham potential
 - $E_{\text{vdW}} = \sum A \exp(-B r_{ij}) - C r_{ij}^{-6}$
 - QM suggests exponential repulsion better, but is harder to compute
- tabulate σ and ϵ for each atom
 - obtain mixed terms as arithmetic and geometric means
 - $\sigma_{AB} = (\sigma_{AA} + \sigma_{BB})/2$; $\epsilon_{AB} = (\epsilon_{AA} \epsilon_{BB})^{1/2}$

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Comparison of Non-Bonded Potential Functions



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Electrostatic Interactions

$$E_{\text{es}} = \sum Q_i Q_j / r_{ij}$$

- atom centered charges can be computed from molecular orbital calculations
- charges can be obtained from population analysis, electrostatic potentials or atomic polar tensors
- however:
 - MO calculations are expensive
 - charges are not uniquely defined
 - charges may vary with conformation

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Electrostatic Interactions

- in addition to atom centered charges, one can also include atom centered multipoles for better fit to electrostatic potentials
- alternatively, one can use off-center charges for better representation of electrostatic potentials around lone pairs
- cheaper (but less accurate) charges can be calculated using the method of electronegativity equalization
- can also include polarization effects – need to compute energy iteratively (expensive and not that much of an improvement)
- can include polarization effects in an average way with distance dependent dielectric constant

$$E_{\text{es}} = \sum Q_i Q_j / D(r_{ij}) r_{ij}$$

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Hydrogen Bonding Interactions

- some force fields add extra term

$$E_{\text{Hbond}} = \sum A r_{ij}^{-12} - C r_{ij}^{-10}$$
 - however, this requires hydrogen bonds to be identified before the calculation is carried out
- other force fields just use a balance between electrostatic and non-bonded terms

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Cross Terms

- more accurate representation of the potential energy surface (e.g. for vibrational frequencies) requires interaction terms between stretch, bend and torsion

- the most important terms are

$$E_{\text{str-str}} = \sum k_{ij} (r_i - r_{i0}) (r_j - r_{j0})$$

$$E_{\text{str-bend}} = \sum k_{ij} (r_i - r_{i0}) (\theta_j - \theta_{j0})$$

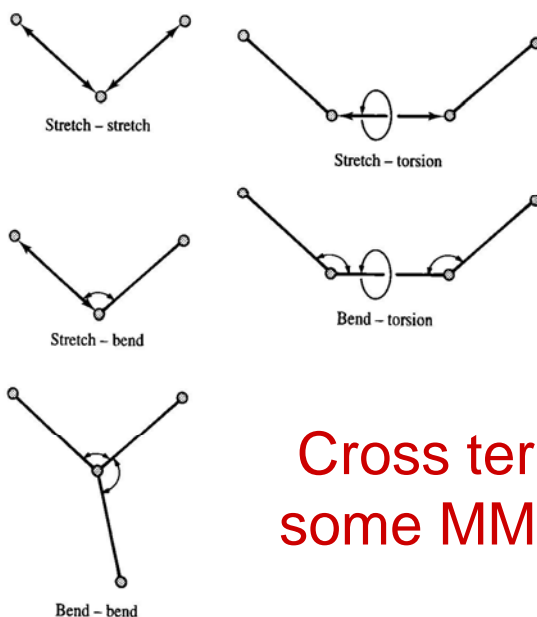
$$E_{\text{bend-bend}} = \sum k_{ij} (\theta_i - \theta_{i0}) (\theta_j - \theta_{j0})$$

$$E_{\text{bend-bend-tors}} = \sum V_{ij} (\theta_i - \theta_{i0}) (\theta_j - \theta_{j0}) \cos[n(\theta_{ij} - \theta_{ij0})]$$

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Cross terms used in
some MM force fields

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Table 2.3 Comparison of functional forms used in common force fields. The torsional energy, E_{tors} , is in all cases given as a Fourier series in the torsional angle

Force Field	Types	E_{str}	E_{bend}	E_{coop}	E_{vdw}	E_{el}	E_{cross}	Molecules
EAS	2	P2	P3	none	Exp.-6	none	none	alkanes
EFF	2	P4	P3	none	Exp.-6	none	ss,bb,bb, st,bb	alkanes
MM2	71	P3	P2+6	P2	Exp.-6	dipole	sb	general
MM3	153	P4	P6	P2	Exp.-6	dipole or charge	sb,bb,st	general (all elements)
MM4	3	P6	P6	imp.	Exp.-6	charge	ss,bb,bb, tt,st,bb,bb	hydrocarbons
CVFF	53	P2 or Morse	P2	P2	6-12	charge	ss,bb,bb, bb	general
CFF 91/93/95	48	P4	P4	P2	6-9	charge	ss,bb,st, sb,bb,bb	general
TRIPOS	31	P2	P2	P2	6-12	charge	none	general
MMFF	99	P4	P3	P2	7-14	charge	sb	general
COSMIC	25	P2	P2	Morse	Morse	charge	none	general
DREIDING	37	P2 or Morse	P2(cos)	P2(cos)	6-12 or Exp.-6	charge	none	general
AMBER	41	P2	P2	imp.	6-12 10-12	charge	none	proteins, nucleic acids, carbohydrates
OPLS	41	P2	P2	imp.	6-12	charge	none	proteins, nucleic acids, carbohydrates
CHARMM	29	P2	P2	imp.	6-12	charge	none	proteins, nucleic acids, carbohydrates
GROMOS		P2	P2	P2(imp.)	6-12	charge	none	proteins, nucleic acids, carbohydrates
ECEPP		fixed	fixed	fixed	6-12 10-12	charge	none	proteins
MOMECC		P2	P2	P2	Exp.-6	none	none	metal coordination
SHAPES		P2	cos($n\theta$)	imp.	6-12	charge	none	metal coordination
ESFF	97	Morse	P2(cos)	P2	6-9	charge	none	all elements
UFF	126	P2 or Morse	cos($n\theta$)	imp.	6-12	charge	none	all elements

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Notation: Pn: Polynomial of order n ; Exp.-6: exponential $+ R^{-6}$; n-m: $R^{-n} + R^{-m}$; fixed: not a variable; imp.: improper torsional angle; ss: stretch-stretch; bb: bend-bend; sb: stretch-bend; st: stretch-torsional; bt: bend-torsional; tt: torsional-torsional; btb: bend-torsional-bend.

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Parameterization

- difficult, computationally intensive, inexact
- fit to structures (and properties) for a training set of molecules
- recent generation of force fields fit to ab initio data at minima and distorted geometries
- trial and error fit, or least squares fit (need to avoid local minima, excessive bias toward some parameters at the expense of others)
- different parameter sets and functional forms can give similar structures and energies but different decomposition into components
- don't mix and match

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Energetics

- steric energy
 - energy relative to an artificial structure with no interactions
 - can be used to compare different conformers of same molecule
- strain energy
 - energy relative to a strainless molecule
 - e.g. all trans hydrocarbons (note: steric energy not necessarily zero)
- very dangerous to decompose energy into components (stretch, bend torsion, non-bonded etc.)
 - different force fields can give similar energies and structures but quite different components
- heat of formation
 - average bond energies added to the strain energy to get approximate atomization energy
 - heat of formation of the molecule = atomization energy of the molecule – heat of formation of the atoms

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Applications

- good geometries and relative energies of conformers of the same molecule (provided that electronic interactions are not important)
- effect of substituents on geometry and strain energy
- well parameterized for organics, less so for inorganics
- specialty force fields available for proteins, DNA, for liquid simulation
- molecular mechanics cannot be used for reactions that break bonds (EVB methods can be used to construct reactive potentials based on molecular mechanics)
- useful for simple organic problems: ring strain in cycloalkanes, conformational analysis, Bredt's rule, etc.
- high end biochemistry problems: docking of substrates into active sites, refining x-ray structures, determining structures from NMR data, free energy simulations

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Summary

- Ground-state potential energy surface is vital input to MD simulation
- Given exactly by finding lowest eigenenergy of electronic problem
- Huge dimensional space for large molecule
- Modeled roughly by force fields, including stretches, bends, torsions, non-bonding, and cross terms
- Speed is always a consideration

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