

Chapter 2 - Molecular Mechanics

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2.1 History and Fundamental Assumptions

$$U(r) = U(r_{eq}) + \frac{dU}{dr} \Big|_{r=r_{eq}} (r - r_{eq}) + \frac{1}{2!} \frac{d^2U}{dr^2} \Big|_{r=r_{eq}}$$

$$(r - r_{eq})^2 + \frac{1}{3!} \frac{d^3U}{dr^3} \Big|_{r=r_{eq}} (r - r_{eq})^3 + \dots$$

Taylor expansion about r_{eq}

$$r_{eq} = r_0$$

U = potential energy

Simplify (make first two values = 0)

$$U(r_{AB}) = \frac{1}{2} K_{AB} (r_{AB} - r_{AB,eq})^2$$

$$K = \frac{d^2U}{dr^2}$$

K is the force constant for a spring

Hooke's Law For a Spring

* Force constants and equilibrium bond lengths may vary from one pair of atoms to another

Conclusion: molecular enthalpies could be determined as a sum of bond enthalpies

2.2. Potential Energy Functional Forms

2.2.1. Bond Stretching

problem:

The equation for $U(r_{AB})$ becomes ∞ when the bond length increases too much



solution:
$$U(r_{AB}) = \frac{1}{2} [k_{AB} + k_{AB}^3 (r_{AB} - r_{AB,eq})] \\ (r_{AB} - r_{AB,eq})^2$$

new problem: the ~~cubic~~ cubic force constant is negative; the equation diverges to negative ∞ w/ increasing bond length



new solution:

*
$$U(r_{AB}) = \frac{1}{2} [k_{AB} + k_{AB}^3 (r_{AB} - r_{AB,eq}) + k_{AB}^4 (r_{AB} - r_{AB,eq})^2]$$

includes the quartic term; ~~quadratic~~ quartic functional forms are used in the general organic force field, MM3

Another Solution

*
$$U(r_{AB}) = D_{AB} [1 - e^{-\alpha_{AB}(r_{AB} - r_{AB,eq})}]^2$$

✓ dissociation energy of the bond

Morse potential (computationally less efficient)

$$k_{AB} = 2\alpha_{AB}^2 D_{AB}$$

2.2.2. Valence ~~Angle~~ Angle Bending

Typical Force Field Function for angle strain:

$$U(\theta_{ABC}) = \frac{1}{2} [K_{ABC} + k^3_{ABC} (\theta_{ABC} - \theta_{ABC,eq}) + k^4_{ABC} (\theta_{ABC} - \theta_{ABC,eq})^2 + \dots]$$

θ = valence angle b/w bonds AB and BC

bond = vector connecting two atoms

force constants are subscripted ABC to emphasize that they are dependent on three atoms

Problems w/ the equation

- No power expansion having the form of this equation will show the appropriate chemical behavior as the bond θ becomes linear, i.e.

at $\theta = \pi$

- It is possible to have multiple equilibrium values

- There is another kind of angle bending, "out-of-plane" bending

2.2.3 Torsions \rightarrow periodic

Torsional angle = dihedral angle

$$\pi \leq \omega \leq \pi \quad (-180^\circ \leq \omega \leq 180^\circ)$$

$$U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABC'D}} V_{j, ABCD} [1 + (-1)^{j+1}]$$



torsional potential energy

potential energy

function = expansion of
periodic functions

$\{j\}_{ABC'D}$ = four atoms
connected in
sequence

$\{j\}$ = set of
periodicities

the values of the
signed term
amplitudes V_j

Ψ = phase
angle

Notes

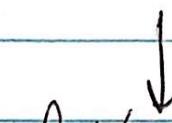
- The $\frac{1}{2}$ on the r.h.s is included so that the term amplitude V_j is equal to the maximum the particular term can contribute to ~~U~~ U .

- The factor of $(-1)^{j+1}$ is included so that the function in brackets within the sum is zero for all j when $\omega = \pi$, if the phase angles Ψ are all set to ϕ

2.2.4 Van der Waals Interactions

* When there are no dissipative forces, the relationship b/w force F in a given coordinate direction g and potential energy U is:

$$F_g = -\frac{\partial U}{\partial g}$$



Let's complicate this!

$$U(r_{AB}) = \frac{a_{AB}}{r_{AB}^{12}} - \frac{b_{AB}}{r_{AB}^6}$$

$a + b =$
specific
constants
to atoms
 A and
 B

simplest
functional forms
that tends to
be used in
force fields
to represent
the combination
of the dispersion
and repulsion
energies

"Lennard-Jones potential"

$$r_{AB} = \sqrt{(x_A - x_B)^2 + (y_A - y_B)^2 + (z_A - z_B)^2}$$

$$\text{minimum of potential} = r_{AB}^* = 2^{1/6} a_{AB}$$

Lennard-Jones + Morse Potential and
+ 'Hill' Potential:

$$U(r_{AB}) = \epsilon_{AB} \left[\frac{6}{\beta_{AB}-6} \exp\left(\beta_{AB} \frac{1-r_{AB}}{r_{AB}^*}\right) - \frac{\beta_{AB}}{\beta_{AB}-6} \left(\frac{r_{AB}^*}{r_{AB}} \right)^6 \right]$$

β is a new parameter

$-r^*$ = bond length at the minimum

- the constants a and b are replaced by
the constants ϵ and β

2.2.5 Electro Static Interactions

$$U_{AB} = M^{(A)} \cdot V^{(B)} \rightarrow U = \sum_{A} \sum_{B} M^{(A)} V^{(B)}$$

$A, B =$ two molecules interacting at a large distance

$M^{(A)}$ is an ordered vector of the multipole moments of A (i.e. charge (zenith moments), x, y, z components of the dipole moment, the nine components of the quadrupole moment)

$V^{(B)}$ = similarly ordered row vector of the electrical potentials deriving from the multipole moments of B.

$$2 \rightarrow U_{AB} = \frac{q_A q_B}{\epsilon_{AB} r_{AB}}$$

interaction energy

assign each van der waals atom a partial charge

$$3 \rightarrow U_{AB/CD} = \frac{\mu_{AB} \mu_{CD}}{\epsilon_{AB/CD} r_{AB/CD}^3} (\cos \chi_{AB/CD} - 3 \cos \chi_{AB} \cos \chi_{CD})$$

$\mu =$ dipole moment
(bond moment vectors magnitude)

$U =$ Interaction energy b/w bonds AB and CD

extra: ~~$U(r_{XH}) = \frac{a' x_H}{r_{XH}^{12}} - \frac{b' x_H}{r_{XH}^{10}}$~~

$x =$ heteroatom to which H is not bound

2.2.6 Cross Terms and Additional Non-Bonded Terms

→ we can expand the full molecular potential energy in a multi-dimensional Taylor expansion, which is a generalization of the one-dimensional case

$$U(q) = U(q_{eq}) + \sum_{i=1}^{3N-6} (q_i - q_{i,eq}) \frac{\partial U}{\partial q_i} \Big|_{q=q_{eq}}$$

q = molecular geometry vector of $3N-6$ internal coordinates and the exp

A more "complete" force field:

$$U(r_{AB}, \theta_{ABC}) = \frac{1}{2} K_{AB,ABC} (r_{AB} - r_{AB,eq}) (\theta_{ABC} - \theta_{ABC,eq})$$

$K_{AB,BC}$ = mixed partial derivative from Taylor expansion

~~stretch~~ stretch-stretch term bend-coupling terms

* stretch torsion coupling can be useful in systems where eclipsing interactions lead to high degrees of strain. The coupling has the form:

$$U(r_{BC}, \omega_{ABCD}) = \frac{1}{2} K_{BC,ABCD} (r_{BC} - r_{BC,eq}) [1 + \cos(j\omega + \psi)]$$

j = periodicity of the torsional term

ψ = phase angle

2.2.7 Parameterization Strategies

Observables Occurrences

$$Z = \left[\sum_i \sum_j \frac{(Calc_{i,j} - expt_{i,j})^2}{\omega_i^2} \right]^{1/2}$$

\downarrow
 ω = weighting factor

penalty function = a function that provides a measure of how much deviation there is between our predicted values and our experimental values

∇_{goal} = select force-field parameters that minimize the penalty function

Z is evaluated using optimized geometries for all molecules

Observables = bond lengths, bond angles, torsion angles, heats of formation, neutral molecular dipole moments, etc.

\sqrt{Z} is dimensionless

Problem: chemist faces an undetermined optimization of parameter values in analyzing the force field

$$\sigma_{AB} = \sigma_A + \sigma_B$$

$$\epsilon_{AB} = (\epsilon_A \epsilon_B)^{1/2}$$

Solution: making certain parameters that depend on more than one atom themselves functions of single-atom specific parameters

2.3. Force-Field Energies and Thermodynamics

* We have not yet established any kind of connection b/w the force-field energy and any kind of thermodynamic quantity



Key Points

* The strain energies for two different molecules cannot be meaningfully compared unless the zero of energy is identical

A typical force-field energy calculation will report any or all of:

- (i) a strain energy = energetic consequence of the deviation of the internal molecular coordinates from their equilibrium values
- (ii) a force-field energy = the sum of the strain energy + non-bonded interaction energies
- (iii) heat of formation = sum of force-field energy and the reference heats of formation for the constituent atom types

* For some atom types, thermodynamic data may be lacking to assign a reference heat of formation.
When a molecule contains one or more of these atom types, the force field cannot compute a molecular heat of formation, and energetic comparisons are necessarily limited to conformers, or other isomers that can be formed w/o any change in atom types.

2.4. Geometry Optimization

* One of the key motivations in early force-field design was the development of an energy functional that would permit facile optimization of molecular geometries

→ One priority in force field development is to adopt reasonably simple functional forms so as to facilitate geometry optimization.

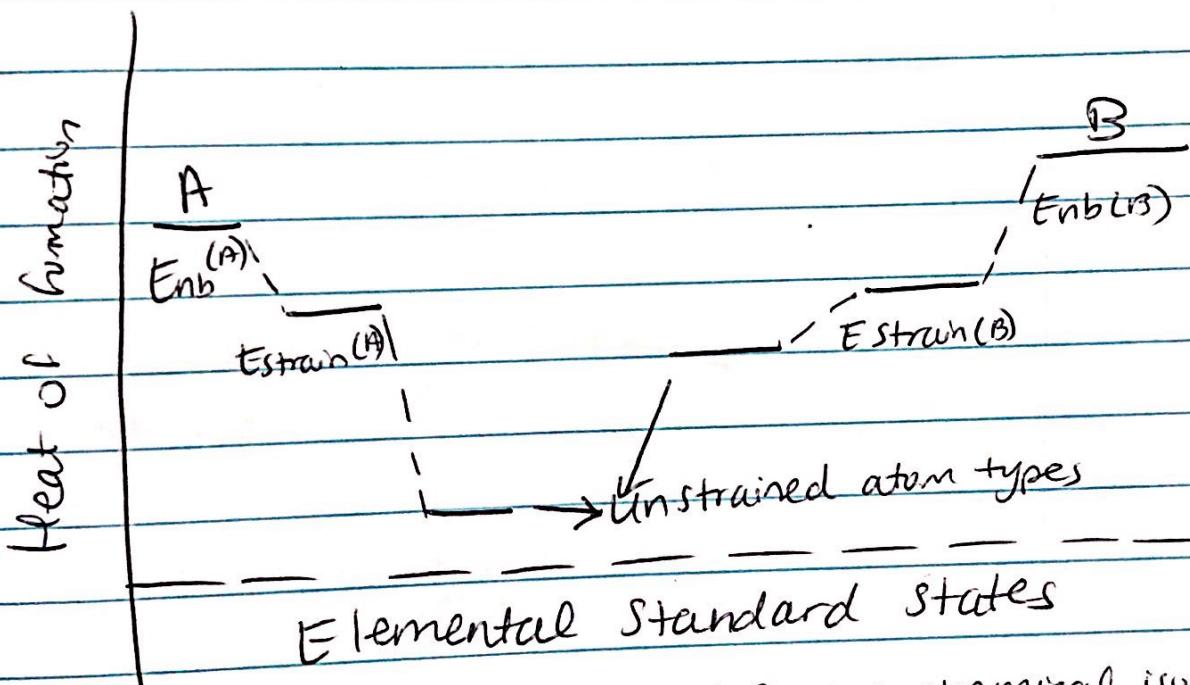


Figure 2.8. Molecules A and B are chemical isomers, but are composed of different atomic types. Thus, the sums of the heats of formation of their respective unstrained atom types, which serve as their zeroes of force field energy, are different. To each zero, strain energy and non-bonded energy (the sum of which are force-field energy) are added to determine heat of formation. In this example, note that A is predicted to have a lower heat of formation than B even though it has a substantially larger strain energy (and force field energy); this difference is more than offset by the difference in the reference zeroes

~~2.4.1~~ Optimization Algorithms

Problem: How does one find a minimum in an arbitrary function of many variables?

Newton-Raphson procedure!

$$U(g^{(k+1)}) = U(g^{(k)}) + (g^{(k+1)} - g^{(k)})^T g^{(k)} + \frac{1}{2} (g^{(k+1)} - g^{(k)})^T H^{(k)} (g^{(k+1)} - g^{(k)})$$

\downarrow \downarrow

$g^{(k)}$ = reference point $g^{(k)}$ = gradient vector
 for the
 reference
 point

$$H_{ij}^{(k)} = \frac{\partial^2 U}{\partial g_i \partial g_j} \Big|_{g=g^{(k)}}$$

\Rightarrow rewriting force field
energy in matrix notation

$$g^{(k+1)} = g^{(k)} - (H^{(k)})^{-1} g^{(k)}$$

This equation provides a prescription for the location of stationary points.

→ Steps

- ① Start from an arbitrary structure having coordinates $g^{(k)}$
- ② Compute gradient vector g and Hessian matrix H
- ③ Select a new geometry $g^{(k+1)}$

2.4.2 Optimization Aspects Specific to Force Fields

- Force fields present several specific issues with respect to practical geometry optimization that merit discussion. Most of these issues revolve around the scaling behavior that the speed of a force-field calculation exhibits with respect to increasing system size.

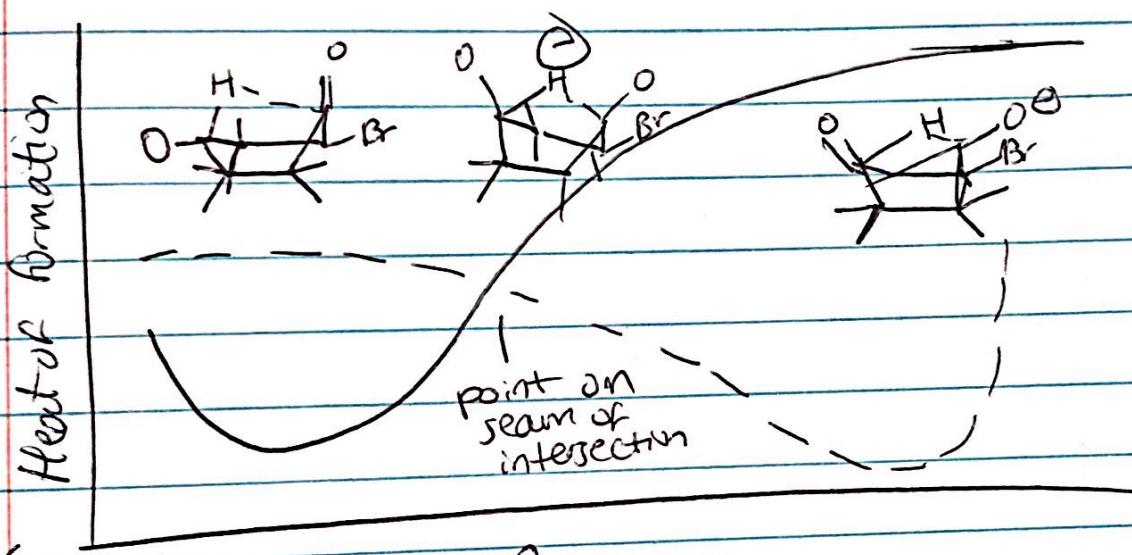


Figure 2.9. ${}^9\text{H}$

↓
Slice through two intersecting enthalpy 'surfaces' along an arbitrary coordinate describing the location of a transferring H atom. The solid curve corresponds to bond stretching of the solid bond from reactant to the H atom being transferred. The dashed curve corresponds analogously to the dashed bond. At the point of intersection, the structure has the same energy irrespective of which bonding scheme is chosen.

↓
A possible TS structure is one whose molecular geometry is computed to have the same energy irrespective of whether the atomic connectivity is that of the reactant or that of the product

2.5 Menagerie of Modern Force Fields

2.5.1 Available Force Fields

Nomenclature of force fields:

①

↓
add last two digits of the year of the most recent
change to the force field

e.g. MM3(92) → MM3(96)

↓
characterized by inter alia different hydrogen
bonding parameters

e.g. CFF → consistent force field

e.g. MMFF → Merck molecular force field

identified by trailing year numbers

② certain existing force fields have been used as
~~selected~~ starting points for development by
new teams of researchers.

e.g. MM2 MM3
↓ ↓
MM2* MM3*

uses a non-directional 10-12 potential for hydrogen
bonding in place of an MM3
Buckingham potential

* = the use of point
charges to evaluate
the electrostatics &
instead of bond dipoles +
a different formalism
for handling conjugated
systems.

③ Some force fields are named after their
software packages

↳ e.g.: AMBER

Conclusion: papers now need to list all force
field parameters as supplementary
material due to the ambiguous naming

2.5.2 Validation

-The process of testing the utility of a force field for molecules other than those over which it was parameterized is known as 'validation'!



Pick the force field that has previously been shown to be most effective for the most closely related problem one can find

→ When experimental data is not available, recourse to well-converged quantum mechanical calculations for a few examples is a possibility, assuming the computational data is not prohibitive.

→ QM values would then take the place of experimental data

★ A last point that should be raised with regard to validation is that any comparison between theory and experiment must proceed in a consistent theory.

→ Finally, any experimental measurement carries with it some error, and obviously a comparison b/w theory and experiment should ~~be~~, ~~and~~ never be expected to do better than the experimental error.

This is applicable to ~~for~~ comparisons b/w experiment and QM theories as well.

Assuming experimental data is available, it is best to do a survey of several force fields to gauge their reliability.