Exercise

ALL OF

1. Build and save **EACH** chair conformation for the stereoisomers of 2-methylcyclohexanol (the quiz molecule).
2. Minimize each conformation using the same molecular mechanics forcefield.
3. Email me a list of the energies of each conformation (using R/S at positions 1 and 2 to indicate which stereoisomer and axial/equatorial at positions 1 and 2 to indicate which chair conformation an energy corresponds to). Make sure to indicate which molecular mechanics forcefield you used for the exercise.
4. Save your starting and minimized structures onto a disk in case I need to see them. Have it with you on Tuesday (9/14).

Energetics

CHEM8711

Energetics

- Recall that molecular mechanics represents energy as a sum of terms:

$$V=V_{str} + V_{ang} + V_{tor} + V_{nb}$$

- The stretching and angle-bending term are expressed as deviations from a standard value

$$V_{str} = k_s (r - r_0)^2$$

$$V_{ang} = k (\theta - \theta_0)^2$$

- So what does this energy summation actually mean?

Steric Energy

- Most standard molecular mechanics forcefields by default provide a ‘steric’ energy value
  - Steric energy is NOT comparable between forcefields
  - Steric energy is NOT comparable for non-isomeric structures
  - It is useful for comparing conformations, and for comparing isomeric structures (that utilize the same parameters within the forcefield)

Estimating Conformational Populations from Steric Energy

- Statistical mechanics indicates that the number of particles n_i in each energy level is represented by the Boltzmann distribution:

$$\frac{n_i}{N} = \frac{\exp\left(-\frac{\Delta e_i}{k_B T}\right)}{\sum \exp\left(-\frac{\Delta e_i}{k_B T}\right)}$$

- This relation demonstrates that conformational distributions are temperature-dependent (with greater populations of higher-energy conformations at higher temperatures)

Molecular Partition Function

- The molecular partition function (Q, or q) includes all energy states (including degenerate states)
- For the purposes of conformational analysis, vibrational, electronic, nuclear, translational and rotational energy states are ignored

$$Q = \sum \exp\left(-\frac{\Delta e_i}{k_B T}\right)$$

Class Exercise

- Compute the fractions of [1R,2R]-2-methylcyclohexanol chair conformations at 5K and at 500K (k_B=1.381x10^{-23} J/K) using the energies you computed in the first exercise.

Strain Energy

- Steric energies can be converted to strain energies by the subtraction of parameterized values derived from representative ‘strainless’ systems
  - Strain energies can be compared between different molecules
  - Strain energies can NOT be compared between different forcefields

Formation Enthalpy

- ΔH_f can be calculated through the addition of parameterized bond energies to the steric energy
  - Formation enthalpies from different forcefields should be comparable

Internal Energy

$$U = \frac{k_B T^2}{Q}\left(\frac{\partial Q}{\partial T}\right)_V = k_B T^2\left(\frac{\partial \ln Q}{\partial T}\right)_V$$

- Practically $$U = \langle E \rangle = \frac{1}{M}\sum_{i=1}^{M} E_i$$
  - Internal energy is the ensemble average for states examined during a simulation (usually either molecular dynamics or monte carlo)

Free Energies

- Helmholtz
  - experimentally measured under constant temperature and volume (NVT ensemble)
  - A= -k_BT ln Q where Q is the ensemble partition function
- Gibbs
  - experimentally measured under constant temperature and pressure (NPT ensemble)
  - G = -k_BT ln Q + k_BTV (? lnQ/ ? V)

Challenge of Free Energies

- Sampling, sampling, sampling
- Since Q is the ensemble partition function, the accuracy of the free energies determined is based on the ensemble chosen, or sampled
- Often energy differences are sufficient
- Free Energy Difference Methods
  - Free Energy Perturbation
  - Thermodynamic Integration
  - Slow Growth

Free Energy Perturbation

- example: Differences in binding free energies of macromolecular complexes
- System details:
  - each ligand starts out in solvent (ie. water)
  - each ligand transfers to a binding site (ie. protein active site)
  - would like to know $\Delta G_{bind1} - \Delta G_{bind2}$
  - COMPUTATIONALLY INTRACTABLE

Free Energy Perturbation (cont'd)

- Solution: Free energies are state functions

$$\begin{tikzcd}
\text{Ligand 1 Solvated} \arrow[r, "\Delta G_{bind1}"'] \arrow[d, "\Delta G_{solv}"] & \text{Ligand 1 Bound} \arrow[d, "\Delta G_{inter}"'] \\
\text{Ligand 2 Solvated} \arrow[r, "\Delta G_{bind2}"] & \text{Ligand 2 Bound}
\end{tikzcd}$$

- Therefore: $\Delta G_{bind1} + \Delta G_{inter} = \Delta G_{solv} + \Delta G_{bind2}$
- And: $= \Delta G_{bind1} - \Delta G_{bind2} = \Delta G_{solv} - \Delta G_{inter}$
- ΔG_{solv} and ΔG_{inter} are physically meaningless, but computationally tractable

Implementation Issues/Limitations

- Perturbations must be performed with fairly small step sizes to insure smooth transitions and thermodynamic results
- Very large structural changes are not handled well
- Simulation time at each step along the perturbation must be sufficient to reflect free energy changes between the states

Empirical Free Energies

- Free energy computations can be parameterized empirically
- Requires:
  - Multiple systems with known structure and relative free energies
  - A fitted equation that relates features of the structures to their relative free energies
  - Sufficient validation that the equation can be successfully generalized

Reading

- First Edition
  - Re-read 3.16
  - Appendix 5.1
  - Chapter 9 through the end of 9.7
- Second Edition
  - 4.17
  - 6.2
  - Chapter 11 through the end of section 6