

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).

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Energetics

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Energetics

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

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

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

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

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

- So what does this energy summation actually mean?

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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)

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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)

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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

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

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Class Exercise

- Compute the fractions of [1R,2R]-2-methylcyclohexanol chair conformations at 5K and at 500K ($k_B=1.381 \times 10^{-23}$ J/K) using the energies you computed in the first exercise.

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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

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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

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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)

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Free Energies

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

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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

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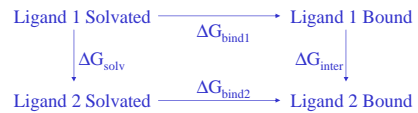
Free Energy Perturbation

- 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 $\Delta G_{\text{bind1}} - \Delta G_{\text{bind2}}$
 - COMPUTATIONALLY INTRACTABLE

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Free Energy Perturbation (cont'd)

- Solution: Free energies are state functions



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

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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

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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

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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

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