

Calculation of Relative Energies of Conformers and Stereoisomers and Equilibrium Ratios of Products using Molecular Mechanics

Molecular mechanics uses a *force field* to calculate the steric energy of the molecule and then adjusts the conformation of the molecule to minimize the steric energy. A force field is set of parameters for the bond lengths, angles, torsional parameters, electrostatic properties, van der Waals interactions, etc.

$$E_{\text{steric}} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{tors}} + E_{\text{vdW}} + E_{\text{electrostat}} + E_{\text{solv}}$$

$$F = k (r - r_0)$$

$$E_{\text{stretch}} = (1/2) k_{\text{str}} (r - r_0)^2$$

$$E_{\text{bend}} = (1/2) k_{\text{bend}} (\theta - \theta_0)^2$$

$$E_{\text{tors}} = (1/2) V_1 (1 + \cos \omega) + (1/2) V_2 (1 + \cos 2\omega) + (1/2) V_3 (1 + \cos 3\omega)$$

$$E_{\text{vdW}} = \epsilon [(r_0/r)^{12} - 2 (r_0/r)^6]$$

$$E_{\text{electrostat}} = q_1 q_2 / D r$$

Popular force fields include MM2, MM3, and MMFF. The MM2 force field was developed in the 1970's to fit relative energies of stereoisomers and conformers simple molecules such as butane, cyclohexane, and their derivatives. It is good for organic compounds containing common functional groups such as ketones, ethers, aromatic compounds etc. The MM3 force field is a more sophisticated version of the force field with more complex potential functions. In MacroModel, these force fields are implemented as MM2* and MM3*, which are equivalent to MM2 and MM3.

The Merck Molecular Force Field (MMFF) was developed in the 1990's to incorporate quantum mechanical calculations of parameters for a variety of functional groups. It is probably the most general all-purpose force field in use today. In MacroModel, the Merck Molecular Force Field is implemented in two versions: MMFF and MMFFs. The MMFFs version duplicates the experimentally observed planar conformation of amide groups, while the MMFF version duplicates the very slight degree of pyramidalization observed in quantum mechanical calculations.

The MMFF (and MMFFs) force field is a good general-purpose force field for most molecular mechanics calculations.

The conformation generated by molecular mechanics is a *local minimum*. A local minimum is a conformation at the bottom of an energy well (i.e., a conformer). It is not necessarily the lowest energy conformer (i.e., the global minimum). If you start near gauche butane, you will generate gauche butane as a local minimum; if you start near anti butane, you will generate anti butane as a local minimum that is also the global minimum. If you start with a boatlike conformation of cyclohexane, you will end up with a twist-boat conformer; if you start with a chairlike conformation of cyclohexane, you will end up with a chair conformer.

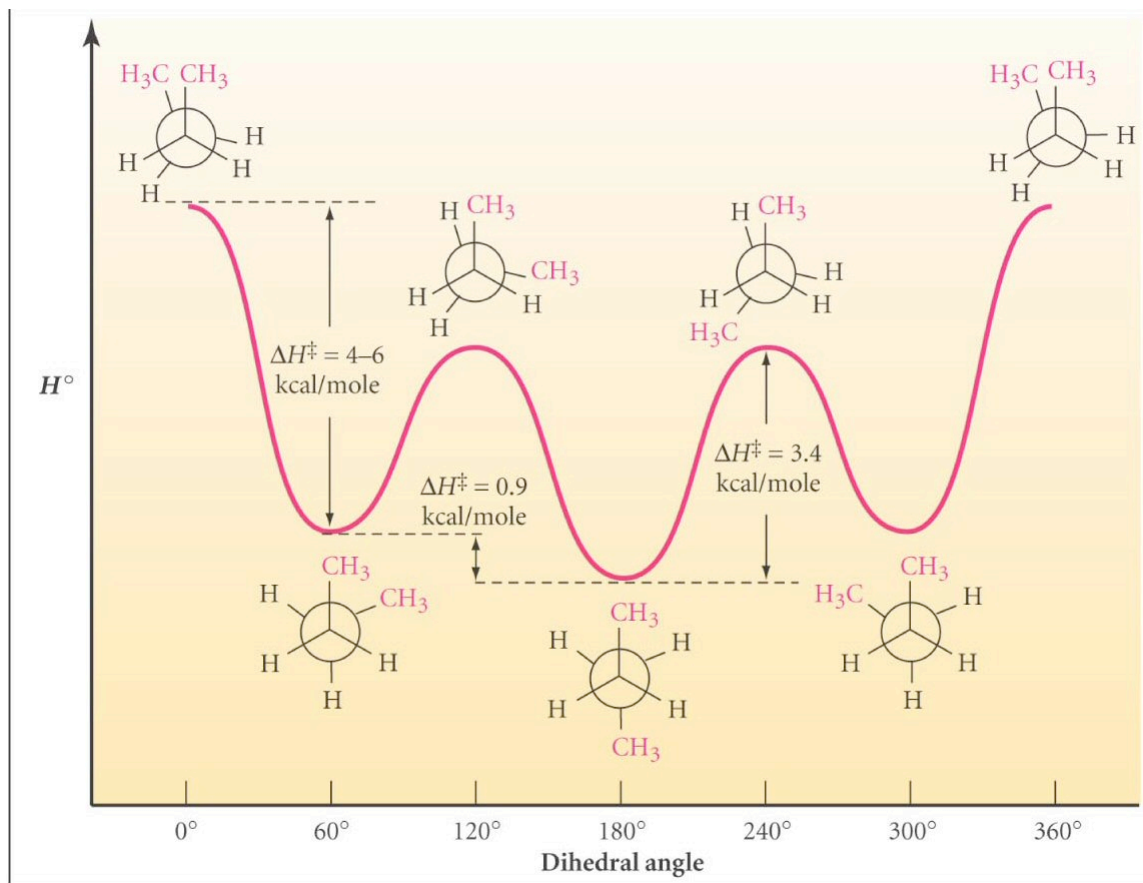


Image from: <http://chemistry.umeche.maine.edu/CHY251/Butane.html>

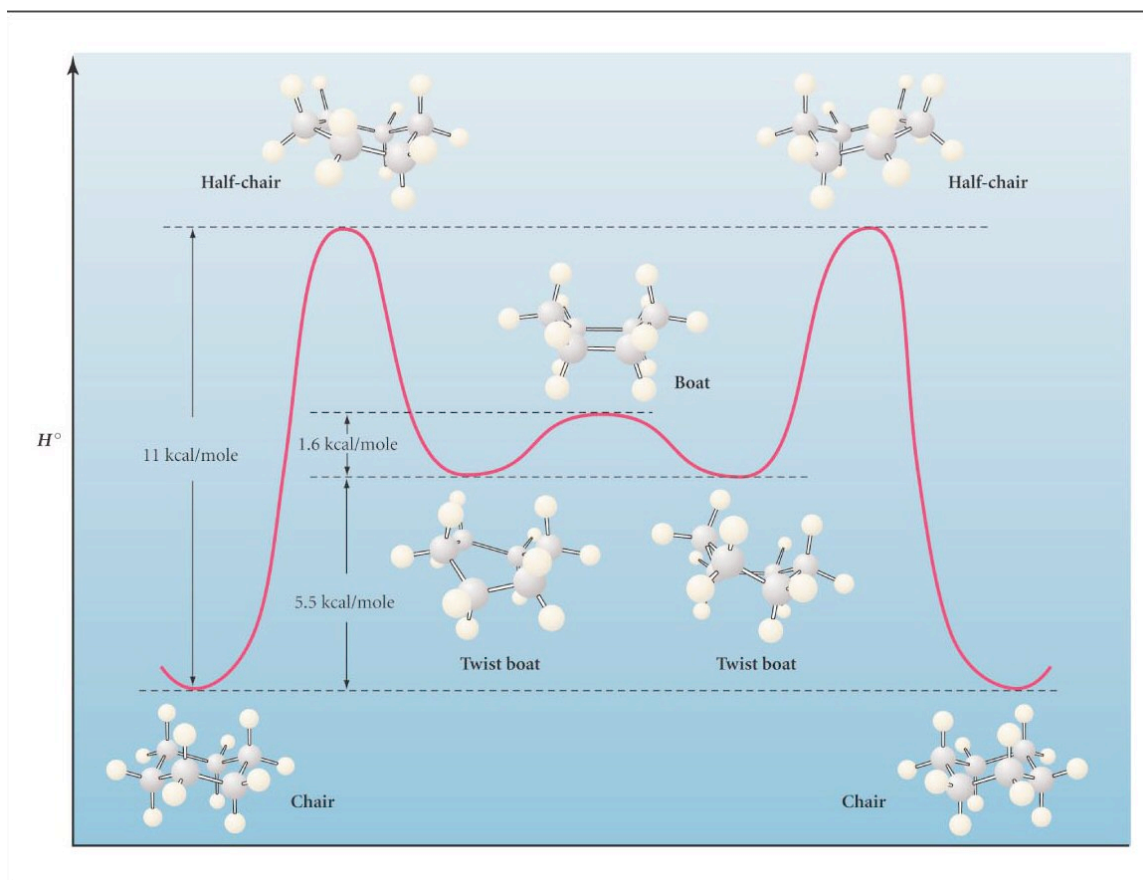
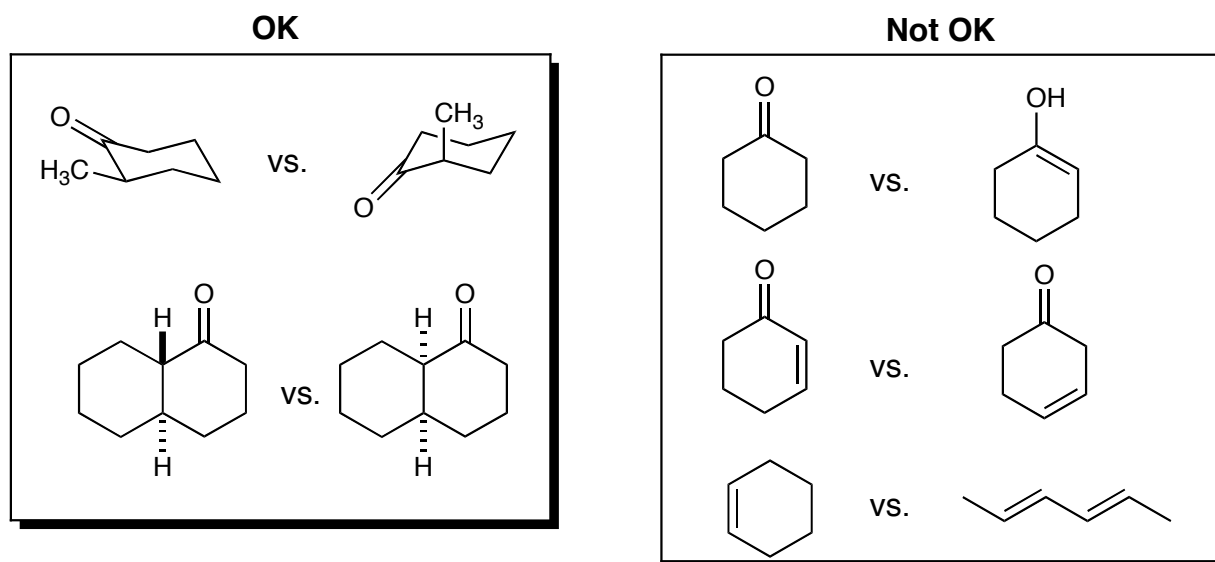
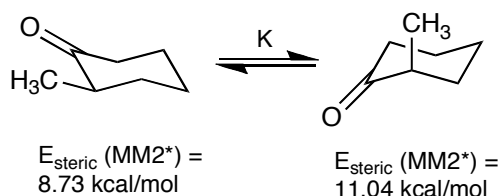


Image from: <http://chemistry.umeche.maine.edu/CHY251/Cyclohexane.html>

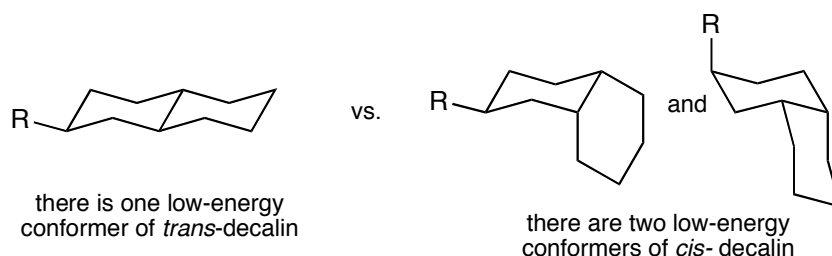
Molecular mechanics is well suited for calculation the relative energies (steric energies) of different conformers or stereoisomers. It is not generally suitable for calculating the relative energies of tautomers, double-bond isomers, or other constitutional isomers. The steric energies calculated by molecular mechanics are not generally meaningful numbers. The *energy difference* between two conformers or stereoisomers is meaningful and corresponds to a *difference in enthalpy* (ΔH).



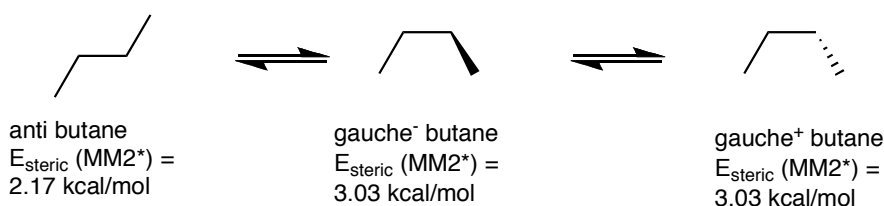
Under certain circumstances, we can use this energy difference to calculate the position of the equilibrium between two (or more) conformers or stereoisomers. Specifically, we can do this *if the entropies of the two conformers or stereoisomers* are roughly the same. In this case, their enthalpies are approximately equal to their free energies. The following examples illustrate this idea.



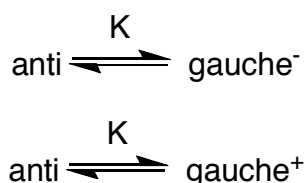
Entropy becomes a consideration in when comparing two isomers in which one or both of the isomers have more than one low-energy conformer. For example trans decalin has one low energy conformer, but cis decalin has two. Entropy is also a consideration when symmetry leads to degeneracy of one conformer (e.g., the enantiomeric conformations of gauche butane).



Entropic differences of this sort can be addressed by considering each conformer separately. For example, consider the equilibrium between anti and gauche butane. The entropy of gauche butane is not the same as that of anti butane because there are two (enantiomeric) gauche conformers. If we consider each of the conformers separately, then we can address this problem.



Let's calculate the percentage of butane in the gauche conformer at 295 deg. This sounds a little confusing at first, but can be done if we consider *two* equilibria:

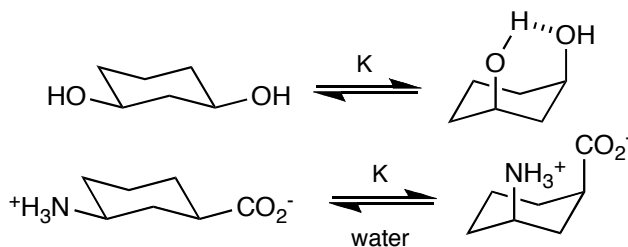


For each equilibrium, $K = e^{-0.86/(0.001987)(295)} = 0.23$

The ratio anti : gauche⁻ : gauche⁺ is 1.0 : 0.23 : 0.23

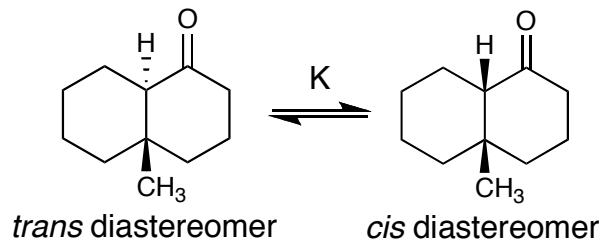
Thus, the percentage of gauche butane is $(0.23 + 0.23)/(1.0 + 0.23 + 0.23) \times 100\% = 31.5\%$

The assumption that we can neglect the difference between enthalpy and entropy is not always valid (e.g., where internal hydrogen bonding or ring formation occurs, or where there are differences in solvation of the different conformers or isomers.) In such circumstances, the equilibrium constant cannot be accurately calculated by considering steric energies of each conformer. In such circumstances, equilibrium constants are better calculated by molecular dynamics (MD) calculations or other methods of calculating free energy. We will discuss these methods later in the course.

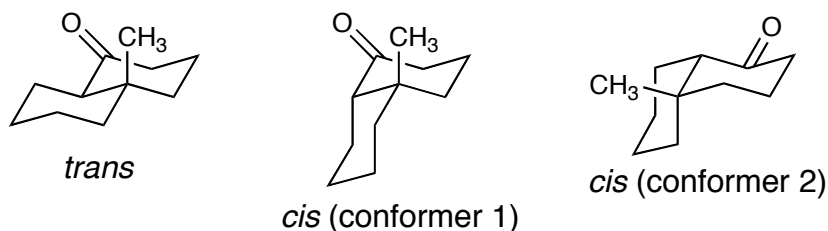


Exercise

This exercise uses the ideas we have just discussed to calculate the equilibrium ratio of two stereoisomers of a ketone. The *trans* and *cis* diastereoisomers of 1-decalones can be equilibrated with base. We will use molecular mechanics energy calculations to calculate the percentage of the *cis* stereoisomer present at equilibrium.



To do this, we will calculate the relative energies of steric energies of the *trans* diastereomer and the two low-energy conformers of the *cis* diastereomer.



- a. Generate model a model of the *trans* diastereomer. Build the model using the Maestro 3D builder.
- b. Use MacroModel to generate a minimum energy structure for the *trans* diastereomer:
 1. Select MacroModel/Minimization under the Applications menu.
 2. Select MMFF under Force Field.
 3. Select None under Solvent.
 4. Under the Mini tab, enter a large number (for example 3000) for Maximum Iterations.
 5. Select Start and give the Job the Name "trans".
- c. Clear the workspace with the Clear tool on the Workspace Toolbar or the Clear command under the Workspace menu. Build a model of conformer 1 of the *cis* diastereomer. Use MacroModel to generate a minimum energy structure, naming the Job "cis-conf1".
- d. Clear the workspace with the Clear tool on the Workspace Toolbar or the Clear command under the Workspace menu. Build a model of conformer 2 of the *cis* diastereomer. Use MacroModel to generate a minimum energy structure, naming the Job "cis-conf2".

A. Check the Project Table and copy the *relative* energies (enthalpies) of the *trans* diastereomer and the two conformers of the *cis* diastereomer. Note that the values are listed in kJ/mol

trans diastereomer: _____ kJ/mol

cis diastereomer conformer 1: _____ kJ/mol

cis diastereomer conformer 2: _____ kJ/mol

B. Which conformer of the *cis* diastereomer is more stable? _____

By how many kJ/mol? _____

C. Which diastereomer is more stable? _____

By how many kJ/mol? _____

D. Calculate the percentage of the *cis* diastereomer at equilibrium at 298 K. (Note that $R = 0.008314$ kJ/mol K and that 4.184 kJ = 1 kcal.)

percentage *cis* diastereomer at equilibrium: _____

Hint: You may think of the *trans* diastereomer as being in equilibrium with each of the *cis* conformers, just as we did on page 4, where the anti conformer of butane was treated as being in separate equilibria with the gauche⁺ conformer of butane and the gauche⁻ conformer of butane. The percentage of the *cis* diastereomer at equilibrium is then calculated as the net amount of the two conformers.