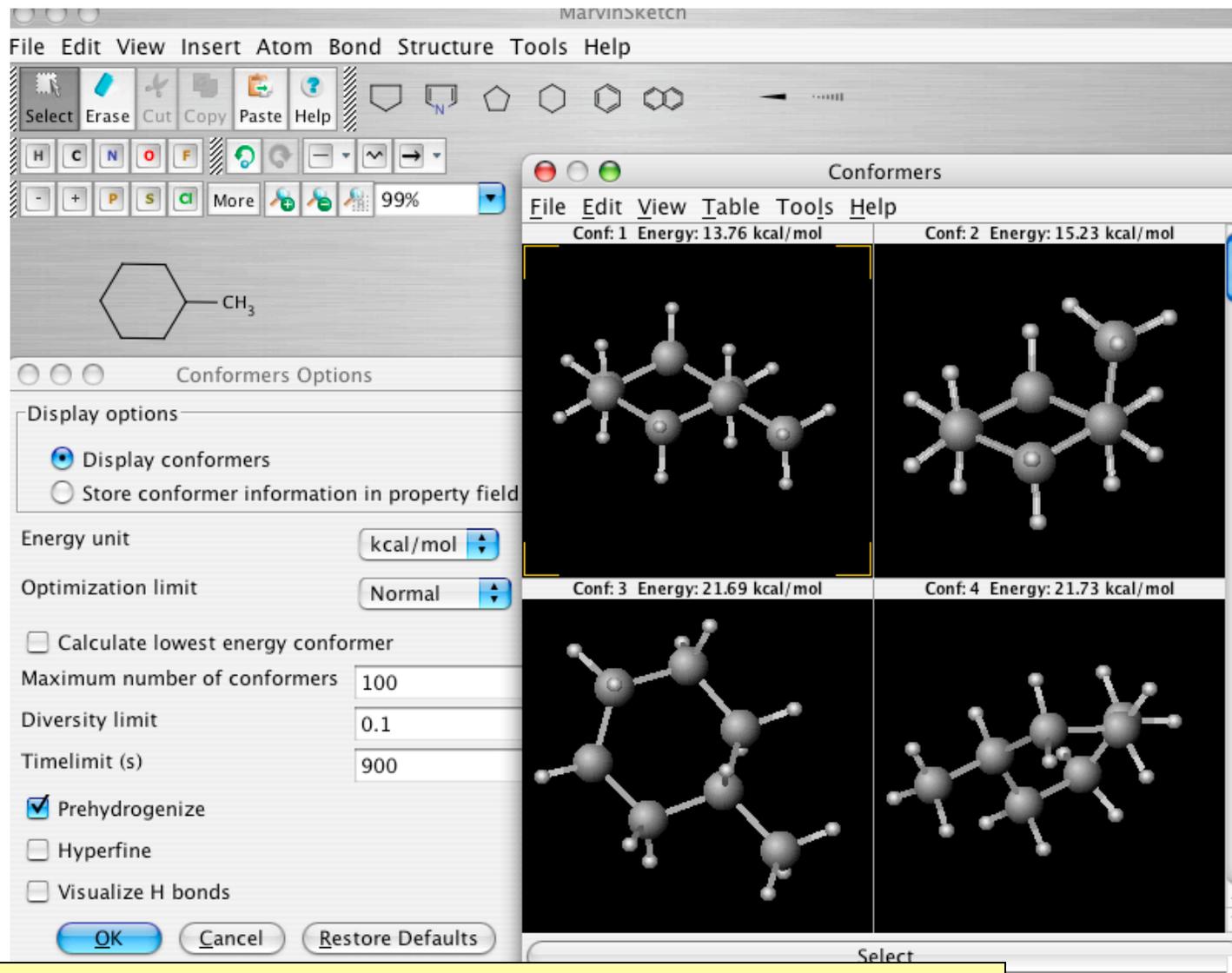


Making Sense of Complexity

The addition of the methyl substituent sends the conformational calculator in MarvinSketch into a state of frustration. MarvinSketch tries to generate all of the conformations that have low-lying energy. The calculation is eventually successful, but will require patience on your part (how much patience will depend on the speed of your computer; also note that a timelimit is placed on the calculation).

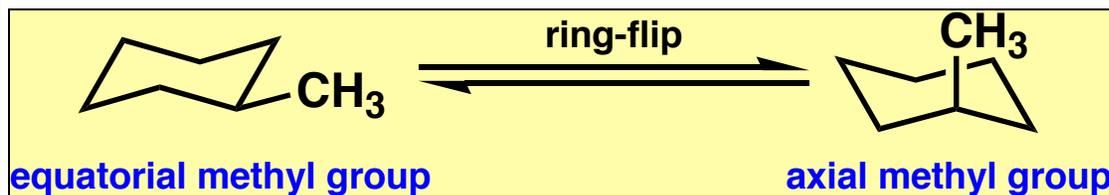


At least 30 different conformations can be found. It isn't important that you analyze all of the conformations. Note that the two lowest conformations have the methyl group in the equatorial and axial positions. The other conformations are variations of the twisted and boat forms that we previously discussed. **The most important point is for you to realize that as the complexity of the molecule increases, the number of conformations quickly becomes overwhelming. If we are to make sense of the diverse structural complexity presented by chemistry, we must be well grounded in the parent compound (cyclohexane).**

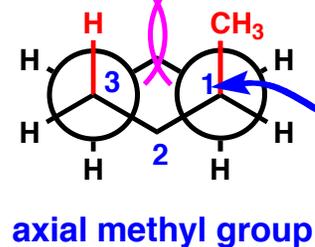
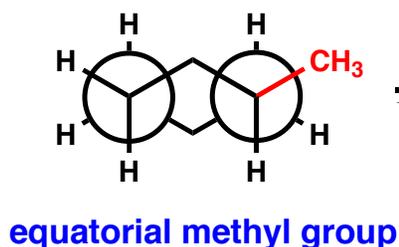


Methylcyclohexane Experiences Sterically Unfavorable 1,3-Diaxial Interactions

Monosubstituted cyclohexanes have a single substituent that replaces one of the hydrogen atoms on the ring. The action of ring flipping transposes a hydrogen atom and a substituent from equatorial to axial positions.



Due to steric interactions, one ring-flipped form may be more favorable than the other. In general, substituents prefer to occupy equatorial positions to avoid sterically unfavorable 1,3-diaxial interactions.

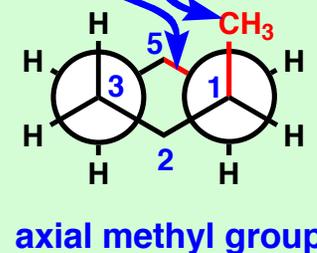
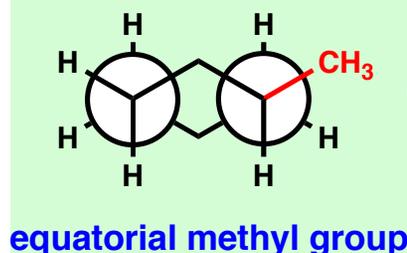


this symbol is used to indicate that the van der Waals spheres overlap and thus experience a steric clash

the unfavorable interaction is called a 1,3-diaxial interaction since it's between the axial methyl group on ring atom 1 and the axial hydrogen atom on ring atom 3

Reasoning by analogy with butane's conformation, a "gauche butane" interaction is found between the substituent on one carbon and a non-hydrogen atom on an adjacent carbon. There are two gauche butane interactions in axial methylcyclohexane. Each gauche butane contributes 0.9 kcal/mol of instability, meaning the axial methyl is roughly 1.8 kcal/mol less stable than the equatorial.

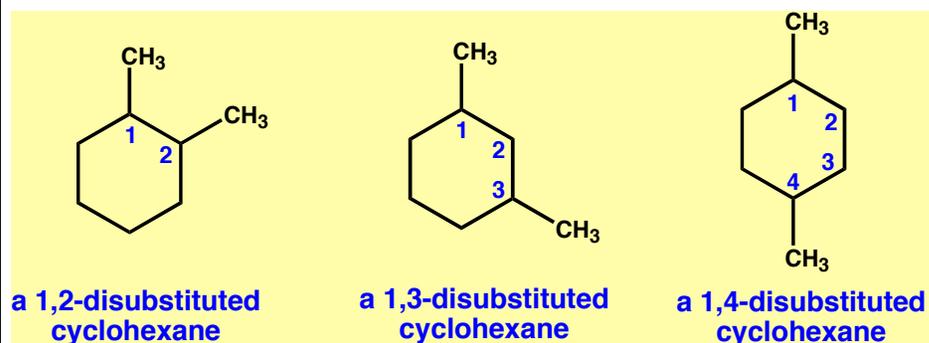
Estimating the energy



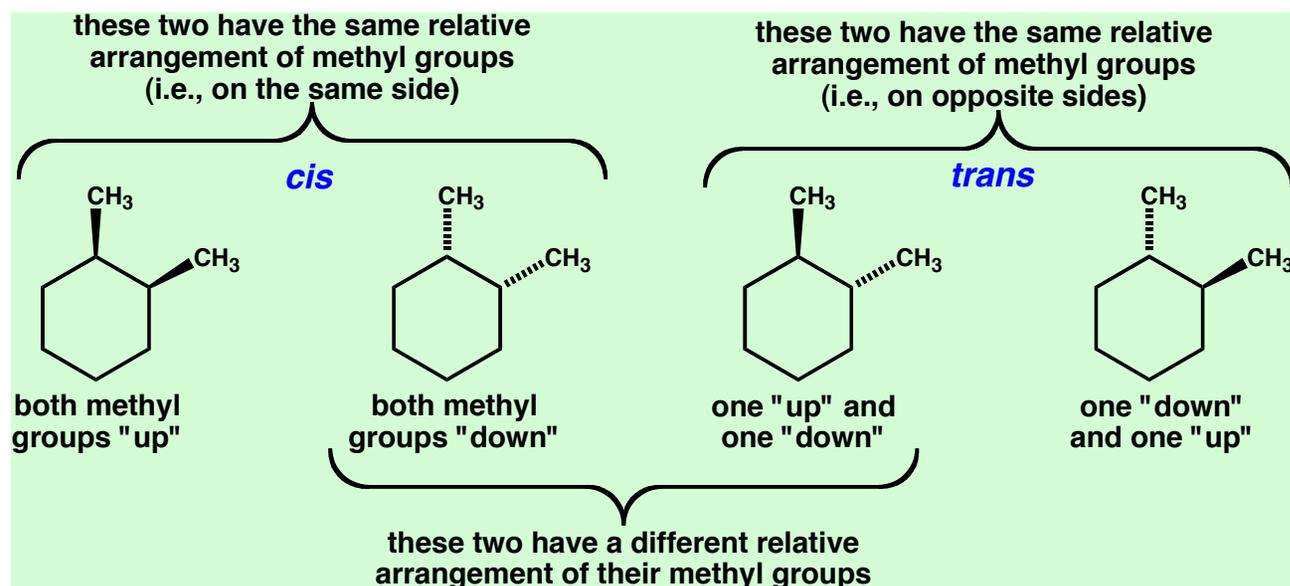
a gauche butane interaction between -CH₃ and ring atom 5

Disubstituted Cyclohexanes - Relative Stereochemistry

Complexity continues to grow as the number of substituents increases. Disubstituted cyclohexanes differing by their ring connectivity are shown. These are **constitutional isomers**, meaning they have the same molecular formula but differ according to their pattern of bonding connectivity. For each of these structures, there are two additional levels of complexity that must be considered: (1) the relative spatial relationship (stereochemistry) of the substituents and (2) conformations of each unique structure.

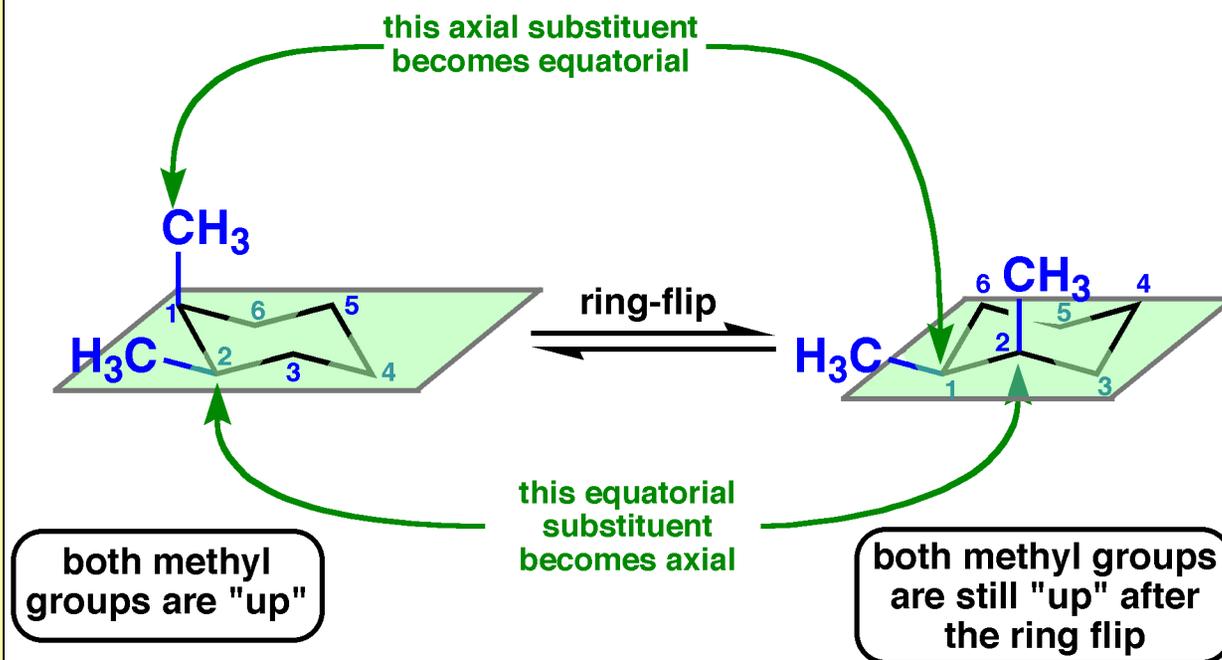
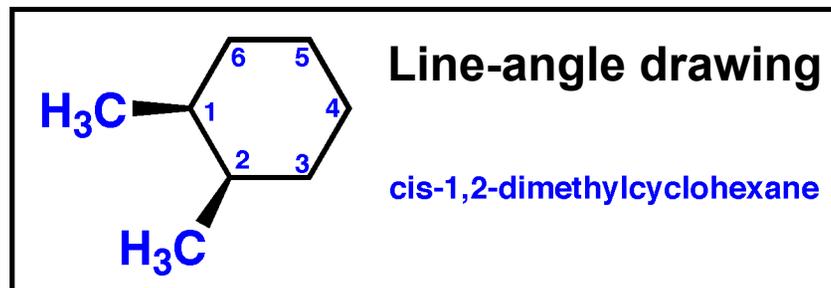


Consider the possible *relative* arrangements of the methyl groups. The word “relative” is important. Relative simply means how one methyl group exists in relation to the other. For each of the disubstituted cyclohexanes, there are two different relative arrangements. Look at 1,2-disubstituted cyclohexane. One relative arrangement is for both groups to be pointed in the same direction (e.g., both “up” or both “down”). We call these the *cis* isomers (*cis* is a Latin word meaning “on the same side”). Another possibility is that one methyl could be up and the other could be down. We call these the *trans* isomers (*trans* is a Latin word meaning “on opposite sides”).

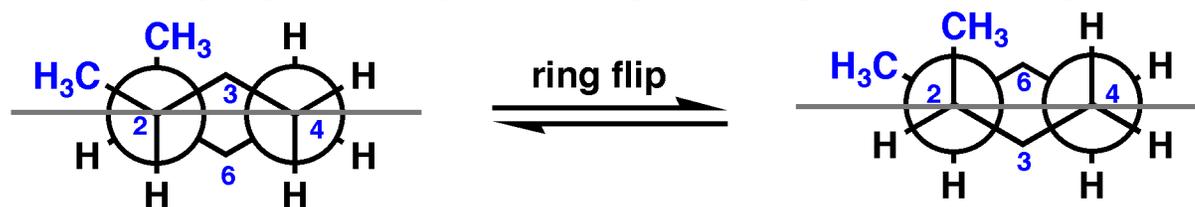


Conformations of Cis-1,2-Dimethylcyclohexane

Line-angle drawings are 2D projections of structures that have 3D form. When we transform these structures into 3D we will see their conformations. So, how do line-angle drawings relate to their 3D structures? First, let's understand what we mean by "up" and "down". These words refer to the relative position of the methyl groups as they are oriented with respect to the plane that slices through the chair. The diagram illustrates that, relative to the plane, the orientation of the methyl group on carbon atom 1 is unchanged by the process of ring flipping. The same is true of the methyl group on carbon atom 2. Thus, even though the axial methyl becomes equatorial, and vice versa, they do not change the direction with respect to the ring plane, nor their relative *cis* arrangement. The Newman projection clearly shows that the methyl groups do not change their orientation upon ring flipping. The gray line slicing through the Newman projection is helpful to see which substituents are "up" and which are "down".

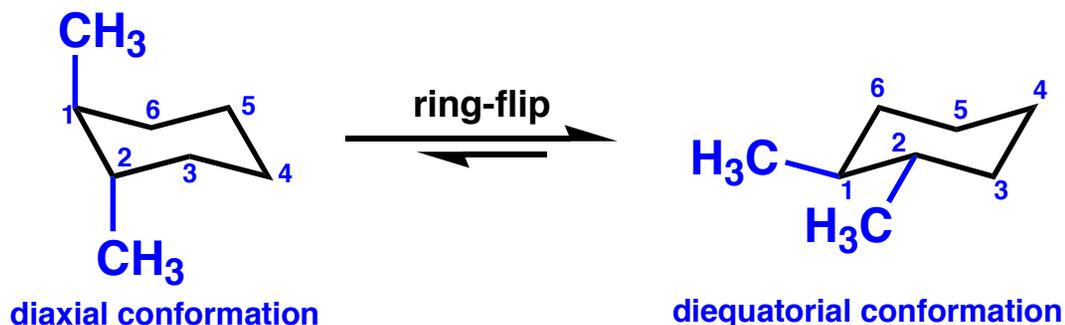
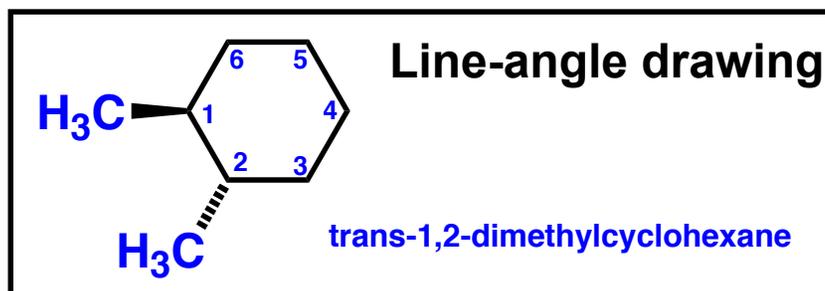


Newman projections (line-of-sight along atoms 3 & 6)

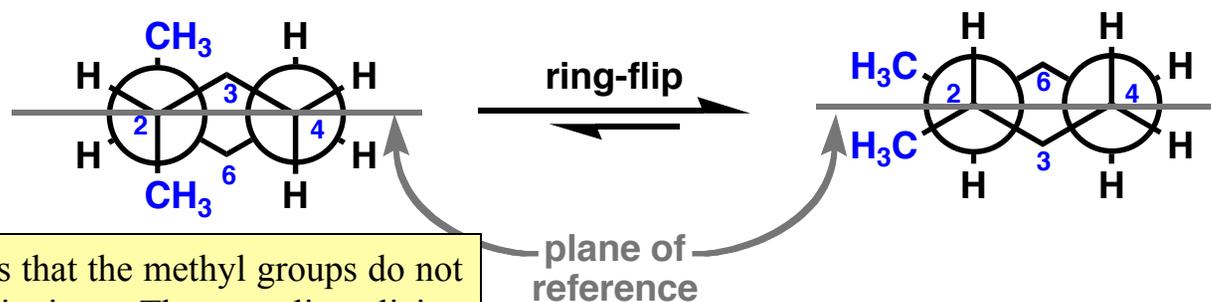


Conformations of Trans-1,2-Dimethylcyclohexane

In the case of cis-1,2-dimethylcyclohexane above, we saw that the ring flipping does not result in a new conformation. Both conformations had one equatorial and one axial methyl group. The situation is different for the trans case. In one conformation, both methyl groups are axial. After ring flipping, both are equatorial. The relative arrangement remains unchanged (one methyl group is “up” and the other is “down” in both conformations). However, the **diequatorial** conformation is more stable than the **diaxial** conformation (notice that the equilibrium arrows are written to favor the diequatorial conformation).



Newman projections (line-of-sight along atoms 3 & 6)



The Newman projection clearly shows that the methyl groups do not change their orientation upon ring flipping. The gray line slicing through the Newman project is helpful to see which substituents are “up” and which are “down”.

By counting the number of gauche butane interactions you can estimate how much more stable the diequatorial conformation is relative to the diaxial.