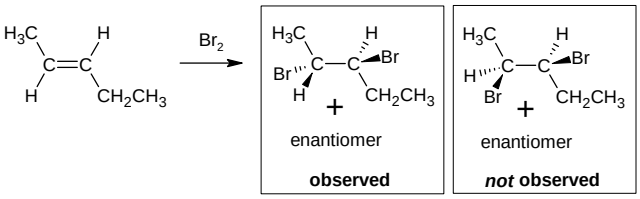
Chapter 7 – Cyclic Compounds. Stereochemistry of Reactions

Introduction

Chapter 7 deals with two topics using tools and concepts developed in earlier chapters. As such, it provides a nice "rest stop" before diving into the new chemical reactions in chapter 8.

The chapter's first topic concerns the structure and conformational preferences of cycloalkanes. Most of the chapter deals with *cyclohexane* and related 6-membered rings. These rings deserve extra scrutiny because they appear more often in biochemical molecules than rings of other sizes.

The second topic deals with the stereochemical outcome of a chemical reaction. Whenever a molecule makes or breaks a bond, we need to ask whether the new bond forms (or the old bond breaks) in a particular *direction*. For example, the addition of Br_2 to 2-pentene could yield four different stereoisomers, but experiments reveal that only two are formed:



The stereochemistry of chemical reactions also has a biological connection. All of the chiral molecules found in biological systems are single enantiomers. Since these molecules must be assembled from other molecules, one must wonder how the stereochemistry of these chemical reactions is controlled.

Checklist

When you have finished studying Chapter 7, you should be able to:

1. Describe the conformational changes, *structural* and *energetic* that cyclohexanes can undergo by
   a. drawing *chair* conformations
   b. identifying *axial* and *equatorial* groups
   c. predicting the conformational preferences of substituted cyclohexanes assuming equilibrium conformer populations
   d. taking into account van der Waals repulsion between substituents and the ring atoms (*1,3-diaxial interactions*)
   e. taking into account van der Waals repulsion between substituents
2. Describe the *cis-trans* stereochemistry of polysubstituted cycloalkanes (not just cyclohexane)
   a. Draw and interpret *planar* and *perspective* (e.g. *chair*) formulas of cycloalkanes
3. Describe the relative energies of isomeric cycloalkanes (including conformers) by referring to:
   a. Torsion strain
   b. Steric (van der Waals) repulsion
   c. Angle strain
4. Identify and name bicyclic alkanes, including *fused*, *bridged*, and *spirocyclic* compounds
   a. Identify *bridgehead* carbons
   b. Identify and name *cis* and *trans* fused rings
   c. Use *bicyclo[l.m.n]alkane* names
5. Apply Bredt's Rule to the stability of bicycloalkene isomers
6. Identify and draw the steroid skeleton
   a. Identify *angular methyl groups*
7. Describe the stereochemical outcomes of familiar[1] chemical reactions
8. Identify transformations that can be described by the following terms (and define what is meant by these terms):
   a. *stereoselective*
   b. *stereospecific*
   c. *retention* and *inversion of configuration*
   d. *backside substitution*
   e. *syn* and *anti* addition

[1] "Familiar" means all functional group transformations covered in chapters 4 and 5. As you read, notice that some transformations occur in particular ways (are *stereoselective* and/or *stereospecific*), while others are not. It will be your job to learn the stereochemical peculiarities of each transformation.

Top 13 Problems for Chapter 7

All of these problems are drawn from the *Additional Problems* located at the end of the chapter 7.

The top 13 for chapter 7 are **36AC, 37A, 38A, 39A, 40(Rxn 1), 50, 54, 55 (draw the mechanism leading to each product), 58, 61, 63, 65, 66**

Supplement

Conformers, Stereoisomers, and Conformational Stereoisomers.

It's still hard for me to accept this, but many years ago, I became an "old school" organic chemist. Word.

What makes me "old school"? Well, lots of things (and more and more things all the time), but the most relevant item here is I think conformers and stereoisomers are different kinds of isomers. If you think back to the "isomer" flowchart that I described in Chapter 6, it went something like this:

Given non-congruent A & B of *identical* composition

- Different connectivity → *constitutional* isomers
- Same connectivity, but interconvert easily → *conformational* isomers
- Same connectivity, but don't interconvert easily → *stereoisomers*
    - Mirror images → enantiomers
    - Otherwise → diastereomers

As you can see, conformational isomers and stereoisomers have something in common: the same connectivity. So, a couple of decades ago, some chemists decided to re-write the flowchart so that conformers were treated as a special type of stereoisomer:

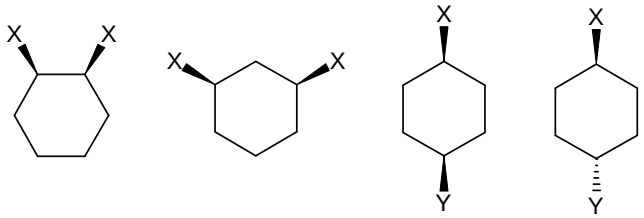
Given non-congruent A & B of *identical* composition

- Different connectivity → *constitutional* isomers
- Same connectivity → *stereoisomers*
    - Mirror images → enantiomers
        - Interconvert easily → enantiomeric *conformers*
    - Otherwise → diastereomers
        - Interconvert easily → diastereomeric *conformers*

I get what they are trying to tell me, I really do, but I'm too "old school" to change. My exam questions will continue to ask whether A & B are identical, constitutional isomers, conformers, or (some type of) stereoisomers. I will never treat conformers as a type of stereoisomer. If A & B interconvert easily, they are "conformers" plain and simple.

Using Planar Structures to Analyze Stereochemistry

This chapter contains many examples of disubstituted cyclohexanes that are achiral. This can come about in several ways:



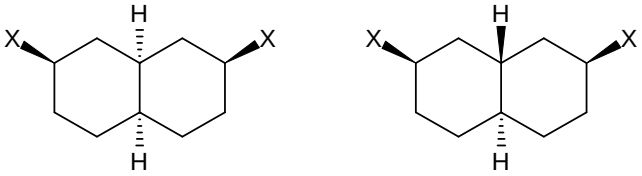
The *cis* and *trans* isomers on the right do not contain asymmetric atoms. The molecules on the left contain asymmetric atoms, but they are both *meso*. As Ch. 7.4D points out, the 1,3-disubstituted isomer exists as a mixture of diastereomeric conformers, one *diaxial* and one *diequatorial*, and both conformers are achiral. The molecule is necessarily achiral. However, the 1,2-disubstituted isomer exists as a mixture of enantiomeric conformers. Both conformers are chiral, but they are always present together in equal amounts and so chemists refer to these molecules as achiral.[2]

The 1,2-disubstituted isomer provides us with a good opportunity for reviewing Pat's rule-of-thumb: if a molecule is achiral in *any reasonable conformation*, regard it as achiral. In this case, the "reasonable" conformation of interest is the so-called "planar structure", the one in which all ring bonds lie in a common plane (see Ch. 7.4C). If the ring was planar, a plane of symmetry would divide the left and right halves of the molecule. The key point here is that, although cyclohexanes never adopt planar structures,

[2] The following statement from Loudon, p. 254 (chapter 6) pertains: *A molecule is said to be achiral when it consists of rapidly equilibrating enantiomeric conformations that cannot be separated on any reasonable time scale.*

we can treat the “planar structure” as a reasonable conformation and use it to analyze stereochemistry.

The stereochemistry of more complicated systems can also be analyzed by taking planar structures as “reasonable” conformations and, if we are careful, we can do this even when the planar structures aren’t actually reasonable! To see this, try making models of the following bicyclic molecules (these are disubstituted *cis*- and *trans*-decalins, respectively).



If you play around with your models (don’t break them!), you’ll see that it is quite impossible to make either molecule adopt a “planar structure”. Despite this, we can rely on the apparent plane of symmetries in the “planar structures” to guess that each is achiral (the symmetry planes include the bridgehead carbon atoms and the hydrogens attached to them).

Use your models to test this conclusion for yourself. You should find that one molecule is rigid and achiral, and you should find that the other molecule exists as a mixture of enantiomeric conformations in which both rings adopt chair shapes.