chapter 1

Retrosynthesis, Stereochemistry, and Conformations

1.1. INTRODUCTION

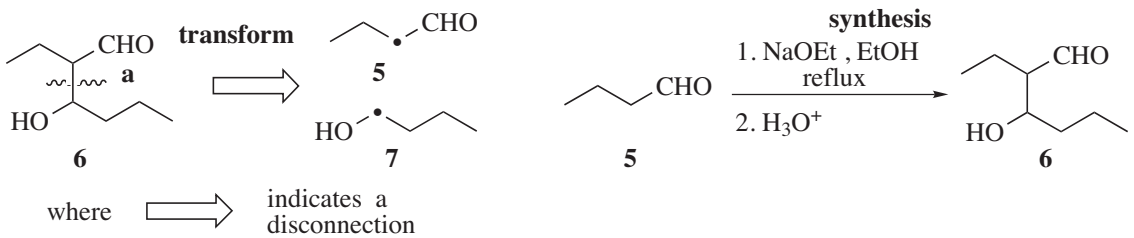
Where does one begin a book that will introduce and discuss hundreds of chemical reactions? To synthesize a complex organic molecule many reactions must be used, and the strategy used for that synthesis must consider not only the type of reaction but also the mechanism of that reaction. We begin with a brief introduction to synthetic planning. A full discussion of strategies for total synthesis will be introduced in chapter 10, but surveying the fundamental approach can help one understand how reactions are categorized.

The total synthesis of complex natural products usually demands a thorough knowledge of reactions that form carbon-carbon bonds as well as those that change one functional group into another. Examination of many syntheses of both large and small molecules, reveals that building up a carbon skeleton by carbon-carbon bond forming reactions is rarely done successfully unless all aspects of chemical reactivity, functional group interactions, conformations, and stereochemistry are well understood. The largest number of actual chemical reactions that appear in a synthesis do not make carbon-carbon bonds but rather manipulate functional groups.

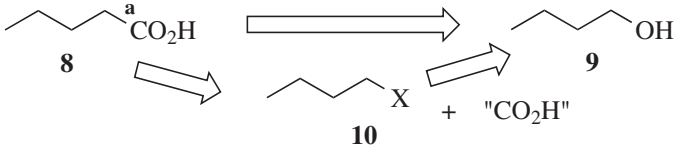
1 **2** **3** **4**

Changing one functional group into another is defined as a **functional group interchange** (FGI). Simple examples are the loss of H and Br from 2-bromo-2-methylpentane (**1**) to form 2-methyl-2-pentene (**2**), or oxidizing the alcohol unit in 2-pentanol (**3**) to the carbonyl unit in 2-pentanone (**4**). Contrast these reactions with a reaction that brings reactive fragments together to form a new bond between two carbon atoms, such as the condensation of two molecules of butanal (**5**) under basic conditions to give **6**, which is known as the **aldol condensation**. The aldol condensation forms a carbon-carbon bond but before such a reaction can occur one usually must incorporate or change key functional groups. This observation is an important reason that more functional group exchange reactions are typically required, relative to carbon-carbon bond forming reactions. Several different functional groups may also be structural units of the molecule being synthesized.

Nowadays, the relationship of two molecules in a synthesis is commonly shown using a device known as a **transform**, defined by Corey and co-workers[1] as: "the exact reverse of a synthetic reaction to a target structure". The **target structure** is the final molecule one is attempting to prepare. The synthetic transformation that converts butanal (**5**) to hydroxy-aldehyde **6** via the **aldol condensation** (see sec. 9.4.A) is an example. The transform for this synthetic step is, therefore, **6** ⇒ **5**. Inspection of **6** and **5** reveals that mentally breaking the highlighted bond (bond ***a***) in **6** (represented by the squiggly line) leads to disconnect fragments **5** and **7** and in this process bond *a* is said to be **disconnected**. An elementary disconnection approach quickly becomes an integral part of how one thinks about molecules. The focus here, however, is on how to put molecules together. How does the disconnection approach assist us in this endeavor? Understanding why bond *a* is important comes from a thorough knowledge of the chemical properties of compound **6**. When we disconnect bond *a*, we eventually want to make that bond by a chemical reaction. To understand the molecular characteristics of **6** that led us to disconnect bond *a*, we must understand the chemical reactions required to form that bond.

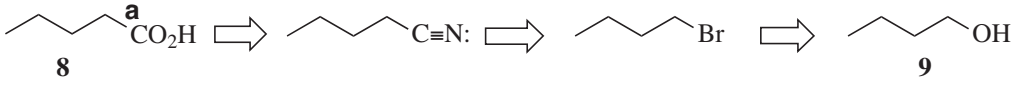


Pentanoic acid (**8**) is a simple target that illustrates the approach. Disconnection of the carbon-carbon bond marked *a* leads to 1-butanol (**9**) as the precursor (the starting material). Analysis of the targeted carboxylic acid as well as the product alcohol shows a change in oxidation state, and a one-carbon extension of the carbon chain. Of the four carbon-carbon bonds in target **8**, bond *a* must be used to attach the carbonyl to the starting material **9**. Disconnection of bond *a* leads to the simplified structure **10** and the CO_2H (carboxyl) fragment, which is not a real molecule. These two structures are termed **disconnect products** but **10** contains an unspecified X group, that must be a reactive functional group and could be hydroxyl (as in **9**). In addition, the carboxyl fragment shown does not exist and a **synthetic equivalent** of the disconnect product that is a real molecule must be found. In other words, to complete any reaction a real molecule or reagent must be used who reaction generates the disconnect fragment directly. Alternatively, a surrogate can be used to give a product that can be converted to the fragment. For example, in the disconnection C–NH_2 to C and NH_2, ammonia reacts with an alkyl halide to give an amine, but there are problems with over-alkylation. The NH_3 is the direct equivalent



1. Corey, E.J.; Cheng, X. *The Logic of Chemical Synthesis*, Wiley-Interscience, NY, ***1989***.

of NH_2. To overcome such problems, the phthalimide anion reacts with an alkyl halide to give the phthalimide, and subsequent reaction with hydrazine liberates the amine. Phthalimide is a surrogate for NH_2, used to circumvent problems with the ammonia reaction. In the case of **8**, we require a COOH surrogate, since COOH is not a real molecule. It is known that carbon dioxide (CO_2) reacts with Grignard reagents (**10**, where X = MgBr) to give a carboxylic acid after hydrolysis of the resulting carboxylate salt in a second step. Therefore, the disconnection shown is a viable process since we know a chemical reaction to make that bond. Working backward in this manner is termed **retrosynthetic analysis** or **retrosynthesis**, defined by Corey as "a problem-solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simple materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis".[2]



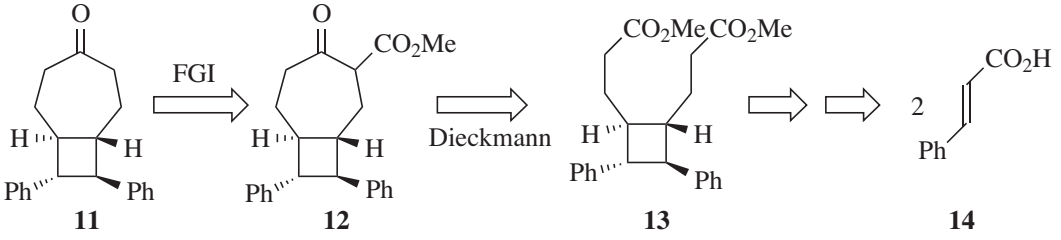
8 **9**

Based on our retrosynthetic analysis, one solution to this synthetic problem is to use the reaction of cyanide ion with primary halides via second order nucleophilic substitution (S_N2, see sec. 2.6.A), to generate a nitrile. The cyano unit is readily hydrolyzed to an acid. Is there an alternative? The answer is yes via a Grignard reaction with carbon dioxide (sec. 8.4.C.iv), but this strategy requires that alcohol **9** be converted to an alkyl halide and then to the corresponding Grignard reagent. Subsequent reaction with carbon dioxide and hydrolysis will give **8**. Formation of an alkyl halide from an alcohol is a functional group interchange (FGI) reaction (see sec. 2.8.A), as is conversion of the halide to a nitrile and the nitrile to an acid. The retrosynthesis effectively describes the reactions necessary for the real synthesis starting from **8**, but reagents must be added to complete the synthesis. Determining the key bond for disconnection in the target led to the conclusion that the synthesis required a carbon-carbon bond forming reaction as well as FGI reactions. Thinking about the synthesis and disconnections led us to analyze and understand the reactions that must be used.

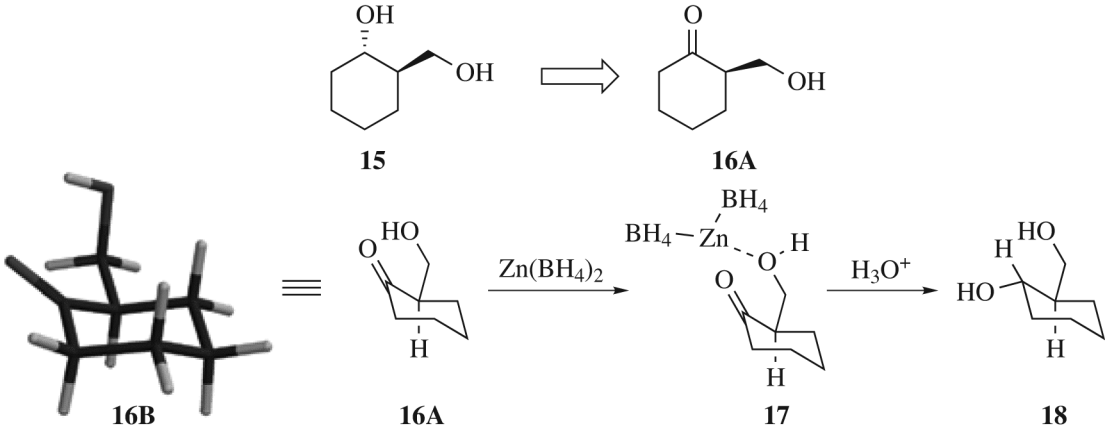
It is important to point out that rarely does one take a retrosynthetic analysis and use the exact reverse track with simple reagents to synthesize the target. For mono-functional molecules this approach often works, but for molecules with multiple functionality, particularly complex natural products, the idea of doing a retrosynthetic analysis and simply providing reagents to convert the starting material to the target is very naïve. There are usually steps that simply do not work using available reagents or those suggested by literature precedent, and the reactions may give poor yields or the wrong stereochemistry. There are unanticipated interactions of functional groups and unexpected requirements for protecting groups. In short, the approach shown here is a beginning, intended to get you to think about how to pull molecules apart, what reactions may be appropriate to put them together again, and to think about strategies

2. Reference 1, p 6.

for synthesis. These ideas are elaborated in chapter 10. When we ask how **8** is prepared from **9**, we are forced to examine how many reactions that form carbon-carbon bonds we actually know how to use, as well as those reactions that prepare and interchange functional groups. In other words, it forces us to review our understanding of Organic chemistry. Other important concepts in Organic chemistry must be brought to bear, including stereochemistry and conformational theory.



The importance of stereochemistry is illustrated by the disconnection sequence **11** ⇒ **12** ⇒ **13** ⇒ **14**, described by Corey.[3] The second transform involves a **Dieckmann condensation reaction** (see sec. 9.4.B.ii), and several steps are required to prepare **13** from 14. Focus attention on the stereochemical relationship of the various groups and of the ring juncture. It is insufficient to consider methods that simply make a bond, because we must be able to form the bond with control of the relative and absolute stereochemistry.



Another important analysis of organic reactions can be found in the transform **15** ⇒ **16A**. Why does this transform lead to the relative stereochemistry (trans) shown in **15**? The proper spatial relationship of the functional groups in the target must be known prior to making the choice for a chemical reaction. This relationship can be difficult to see using the two-dimensional (2D) structures shown. A different model of the molecule such as a 3D-model will usually

3. Reference 1, p 13.

give a better understanding of stereochemical and conformational relationships. In this case, representation **16B** (produced by the computer program Spartan06™)[4] provides much more detail than **16A**, and shows that the hydroxyl group is positioned on one side of the carbonyl. If a chelating metal such as zinc is used with the reducing step (zinc borohydride, see sec. 4.4.B), coordination with the hydroxyl (**17**) may deliver hydride primarily from the same face as the CH_2OH unit, leading to the observed trans stereochemistry in **18**. In this example, the **conformation** (3D shape) of the molecule provides a model that helps us understand the stereochemical outcome of the reaction.

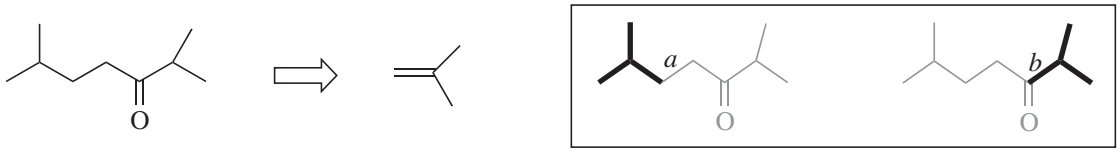
Three important factors will be reviewed in this chapter: (*1*) disconnection and retrosynthesis, (*2*) stereochemistry, (*3*) conformational analysis. This review will not to formally introduce synthesis (synthetic theory will be presented in chapter 10),[5] but focus attention on concepts that help us understand reactions.

1.2. THE DISCONNECTION PROTOCOL

When retrosynthetic theory is introduced, it is easy to become embroiled in making the "correct" disconnection rather than focusing on the chemical reactions and concepts required to form the disconnected bond in the synthesis. In reality, the disconnection is dictated by the ability to form the bond in the context of stereochemistry and selectivity, not the other way around. The synthesis of organic molecules dates to the nineteenth century, but the work of Perkin, Robinson and others in the early twentieth century demonstrated the importance of synthetic planning.[1] In the 1940s and 1950s, Woodward, Robinson, Eschenmoser, Stork and others clearly showed how molecules could be synthesized in a logical and elegant manner. In the 1960s, Corey identified the rationale behind his syntheses, and such logical synthetic plans (termed retrosynthetic analyses) are now a common feature of the synthetic literature.[2] The disconnection approach is used to teach synthesis, and Warren has several books that describe this approach in great detail.[6] Several different strategies for the synthesis of organic molecules are available (see chapter 10) and all are useful. When these strategies are applied to a first synthesis in an introductory course, the most critical issue raised after a disconnection is what to do with the disconnect products. All disconnection approaches assign priorities to bonds in a molecule and disconnect those bonds with the highest priorities, as with Corey's

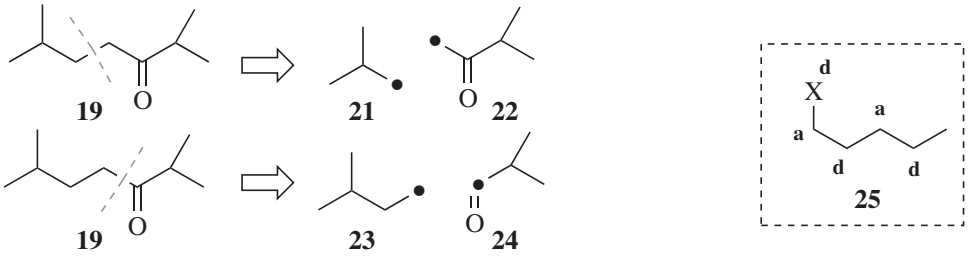
4. Spartan™ is a trademark of Wavefunction Inc., Irvine, CA, Spartan'06.
5. (a) Corey, E.J.; Wipke, W.T. *Science*, ***1969***, *166*, 178; (b) Corey, E.J.; Long, A.K.; Rubinstein, S.D. *Ibid* ***1985***, *228*, 408; (c) Corey, E.J.; Howe, W.J.; Pensak, D.A. *J. Am. Chem. Soc.* ***1974***, *96*, 7724; (d) Corey, E.J. Quart. Rev. Chem. Soc. ***1971***, *25*, 455; (e) Corey, E.J.; Wipke, W.T.; Cramer III, R.D.; Howe, W.J. *J. Am. Chem. Soc.* ***1972***, *94*, 421; (f) Corey, E.J.; Jorgensen, W.L. Ibid ***1976***, *98*, 189.
6. (a) Warren, S. *Organic Synthesis: The Disconnection Approach*, John Wiley, Chichester ***1982***; (b) Warren S. *Workbook for Organic Synthesis: The Disconnection Approach*, John Wiley, Chichester ***1982***; (c) Warren, S. *Designing Organic Synthesis: A Programmed Introduction to the Synthon Approach*, Wiley, Chichester ***1978***. Also see (d) Wyatt, P.; Warren, *S. Organic Synthesis, Strategy and Control*, Wiley, New Jersey, ***2007***.

strategic bond analysis (see sec. 10.5).[1,5] Smith described a simple method where the priorities are based only on the relative ability to chemically form the bond broken in the disconnection,[7] based on known reactions.



19A **20** **19B** **19C**

In a typical introductory Organic chemistry course, there are two fundamental types of synthesis problems. In the first, both the starting material and the target are specified. In the second, only the final target is given and the synthetic chemist must deduce the starting material. This latter case usually poses a more difficult problem. We can illustrate the fundamentals of a retrosynthetic analysis with the first type of problem, and will delay discussion of the second type until Chapter 10. In the disconnection **19** ⇒ **20**, 2-butene is the designated starting material, which means that the target (**19**) is to be synthesized from 2-methylpropene (**20**). The four carbons of **20** must be "located" in **19** since this will define the carbon atoms that must be disconnected for the synthesis. The presence of two methyl groups in **20** limits the possibilities, and there are two different locations where the four carbons in isobutene may be found (see **19B** and **19C**). If we choose the pattern shown in **19B**, this dictates that bond *a* must be disconnected. If we choose the pattern in **19C**, then bond *b* must be disconnected. Disconnection of bond *a* in **19B** leads to two fragments (disconnect products), **21** and **22**. Similarly, disconnection of bond *b* in **19C** leads to disconnect products **23** and **24**. Both disconnections must be considered, but structures **21-24** are not real molecules so we cannot evaluate the relative merit of each disconnection using these fragments. Real molecules and real reactions are required. Therefore, two assumptions will be made: (*1*) The key carbon-carbon bonds will be formed by a small subset of reactions and (*2*) the bonds will be made by reactions involving polarized or ionic intermediates.

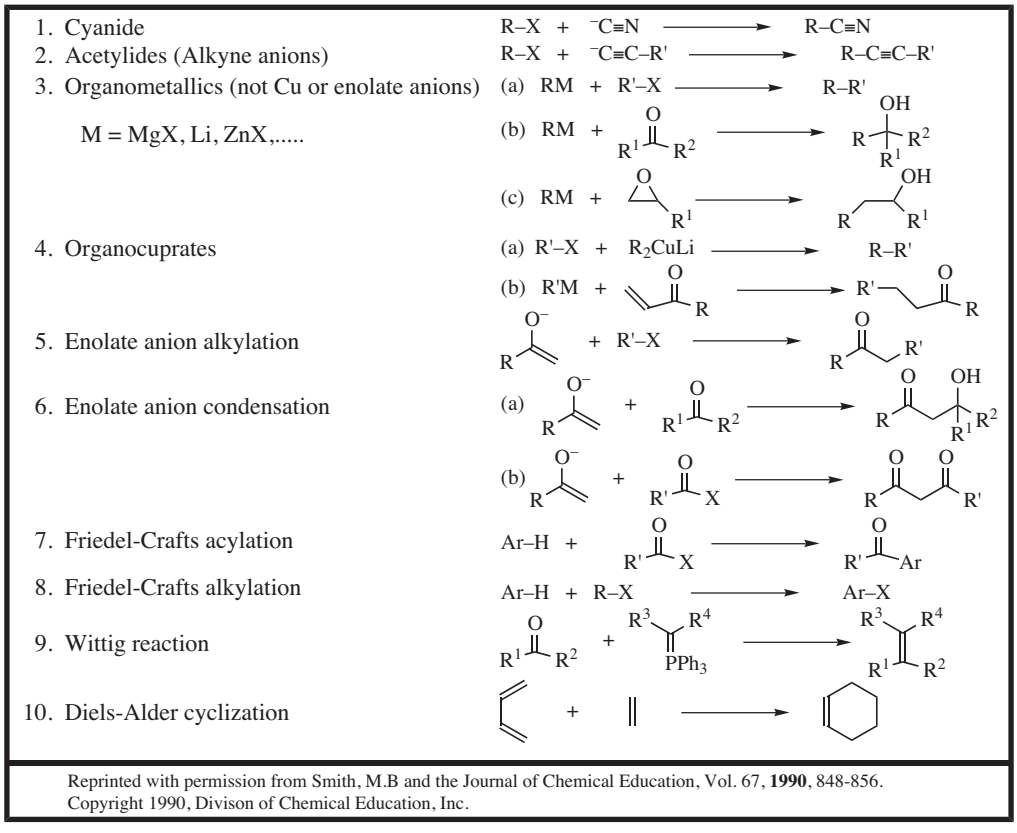


The first assumption is based on the carbon-carbon bond-forming reactions shown in Table 1.1,[7] which are usually presented in a typical sophomore Organic chemistry course. The second

7. Smith, M.B. *J. Chem. Educ.* ***1990***, 67, 848.

assumption is based on the observation that all reactions in the table except entry 10 (the **Diels-Alder reaction**, see sec. 11.4.A) involve highly polarized or ionic intermediates. With this assumption in hand, it is reasonable to assume that the disconnections generated from **19** will lead to ionic or polarized intermediates, and we can form the carbon-carbon bonds with one of the reactions found in Table 1.1. These assumptions allow us to convert each disconnect product (**21-24**) into a polarized fragment.

Table 1.1. Carbon-Carbon Bond-Forming Reactions

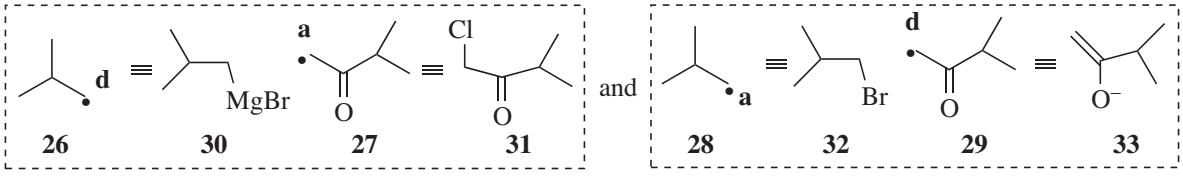


The concept of nucleophilic and electrophilic atoms in ionic and polarized intermediates is well known. Polarized bond notation such as $C^{\delta+}$–$Br^{\delta-}$ and $C^{\delta-}$–$Li^{\delta+}$ is commonly used in describing the reactivity of such bonds. The polarizability of various atoms and molecules is also reflected in hard and soft acid and base (HSAB) theory (see sec. 2.4).[8] Seebach used structure **25** to formalize a bond polarization model.[9] The sites marked ***d*** in **25** represent *donor* sites or *nucleophilic* atoms. The sites marked ***a*** are *acceptor* sites and correspond to

8. Ho, T-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, ***1971***, pp 1-3 and 27-34.
9. Seebach, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 239.

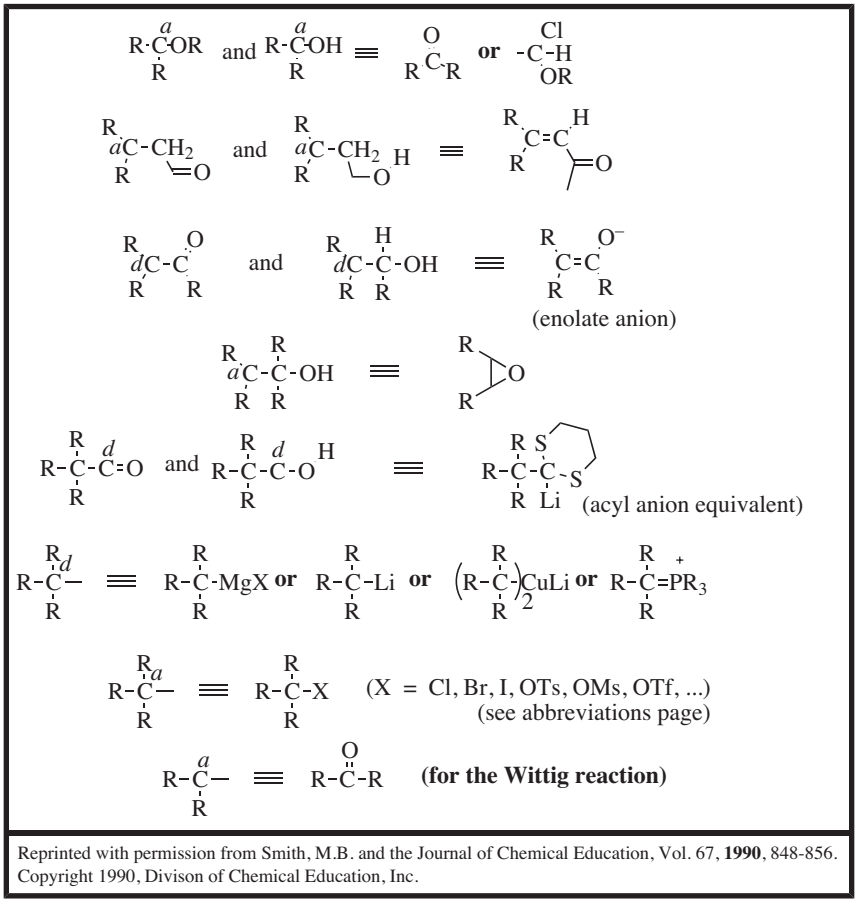
electrophilic atoms. Bond polarization induced by the heteroatom extends down the carbon chain, due to the usual inductive effects that are a combination of through-space and through-bond effects.[10] The electrophilic carbon adjacent to X (C1 for example) is designated C^a (an acceptor atom) since proximity to the δ– electronegative atom (X) induces the opposite polarity. Similarly, C2 is a donor atom (C^d), but less polarized than X (this carbon is further away from the electrons that induce the bond polarization), and C3 is a weak acceptor atom. As a practical matter, the effect is negligible beyond C4 and will be ignored.

If this protocol is applied to disconnect fragments **21** → **24**, either carbon at the point of disconnection can be assigned as a donor (d) or an acceptor (a) giving four different possibilities. Disconnect products **21** and **22**, for example, become **26** or **27** and **28** or **29**, respectively. Fragments **26** → **29** are not real molecules, and another step is required before the best donor-acceptor pair can be chosen. Each fragment must be correlated with a synthetic equivalent. Table 1.2[7] provides a list of common synthetic equivalents, leading to the definition of **synthetic equivalent** as a molecular fragment that is equivalent to a real molecule by virtue of its chemical reactivity.[11] A C^d site on an unfunctionalized carbon, for example, is equivalent to the $C^{\delta-}$ of a Grignard reagent (see sec. 8.4) and a C^a site on an unfunctionalized carbon is equivalent to the electrophilic carbon on an alkyl halide. Each synthetic equivalent in Table 1.2 is based on an ionic or highly polarized nucleophilic substitution or nucleophilic acyl addition reaction. Using Table 1.2, fragment **26** is the equivalent of a Grignard reagent, **30** (an organocuprate such as $[Me_2CHCH_2]_2CuLi$ can also be used as in sec. 8.7.A). The equivalent of its partner (fragment **27**) is α-chloroketone **31**. Similarly, the synthetic equivalent of **28** is bromide, **32** (another halide can be used) and the equivalent of **29** is an enolate anion, **33** (see sec. 9.2, 9.3). In the actual synthesis, **30** will react with **31** and **32** will react with **33**, and both reactions will produce **19**. Bromide **32** is derived from the 2-methylpropene starting material, but the functional group must be modified. To accomplish this, the chemical relationship between the C-C-Br and C=C must be known. In other words, what reagents are required to transform an alkyl a halide into an alkene, and vice-versa. Figure 1.1[7] provides a functional group reaction diagram to interconvert one functional group into another by known chemical pathways. Since

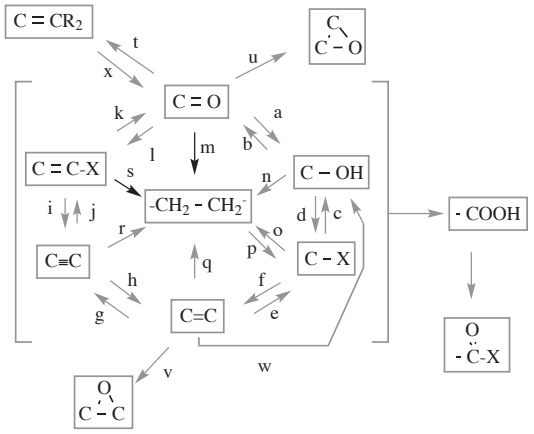


10. (a) Baker, F.W.; Parish, R.C.; Stock, L.M. *J. Am. Chem. Soc.* ***1967***, *89*, 5677; (b) Golden, R.; Stock, L.M. *Ibid* ***1966***, *88*, 5928; (c) Holtz, H.D.; Stock, L.M. *Ibid* ***1964***, *86*, 5188; (d) Branch, G.E.K.; Calvin, M. *The Theory of Organic Chemistry*, Prentice-Hall: New York, ***1941***, chapter 6; (e) Ehrenson, S. *Progr. Phys. Org. Chem.* ***1964***, *2*, 195; (f) Roberts, J.D.; Carboni, C.A. *J. Am. Chem. Soc.* ***1955***, *77*, 5554; (g) Clark, J.; Perrin, D.D. *Quart. Rev. Chem. Soc.* ***1964***, *18*, 295.
11. See Reference 1, p 30.

Table 1.2. Common Synthetic Equivalents for Disconnect Products



an alkene and a halide are chemically related by the reactions indicated, either could be used in the disconnect product since one can easily be converted to the other at the appropriate time. Similar analysis of disconnect fragments **23** and **24** may lead to different reactive fragments, giving a different synthesis.

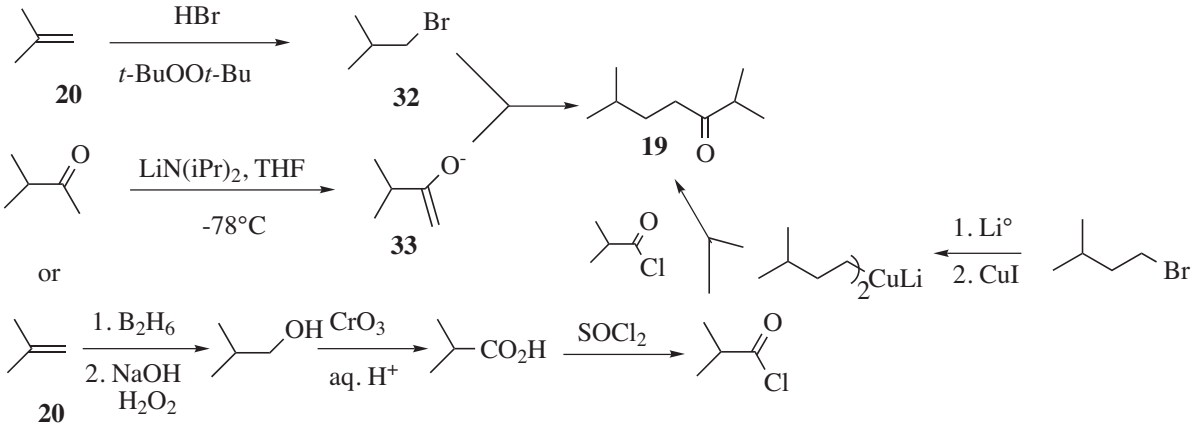


a. $LiAlH_4$ or $NaBH_4$ or H_2/cat
b. CrO_3
c. $NaOH/H_2O$ or i. PPh_3, RCO_2^-, $MeO_2C\text{-}N{=}N\text{-}CO_2Me$ (the Mitsunobu reaction)
d. PCl_5, $SOCl_2$ (X = Cl); PBr_3 (X = Br); i. NaH ii. ii. ^-OH iii. H_3O^+ RX (X = OR); i. PBr_3 or RSO_2Cl ii. K-phthalimide; hydrolysis or NaN_3; H_2/cat. (X = NH_2)
e. HX
f. $NaOH/H_2O$ or RO^-/ROH
g. i. Br_2 ii. $NaNH_2$
h. H_2/cat or $Na/NH_3/EtOH$
i. $NaNH_2/NH_3$
j. HX
k. H_3O^+
l. PCl_5
m. N_2H_4/KOH or Zn(Hg)/HCl
n. i. RSO_2Cl ii. $LiAlH_4$ (only one carbon reacts)
o. $LiAlH_4$ or H_2/cat.
p. X_2/hν or heat
q. H_2/cat
r. 2 H_2/cat
s. excess H_2/cat.
t. $Ph_3P{=}CR_2$
u. $Me_2S^+—CH_2^-$
v. RCO_3H
w. i. B_2H_6 ii. $NaOH/H_2O_2$ or i. $Hg(OAc)_2$ ii. $NaBH_4$
x. i. O_3 ii. Me_2S or H_2O_2

Figure. 1.1. Functional Group Exchange Reaction Wheel. A Visual Reminder of the Interconvertibility of Functional Groups.

In most undergraduate Organic chemistry textbooks, the functional group approach to introducing chemistry means that groups with related chemical properties may be presented in different semesters. Although alkenes and carbonyl both react as a base in the presence of an acid, these groups are presented at different places and at different times during a typical course. The approach can make the relationship of one functional group to another difficult to see. Figure 1.1[7] provides a visual reminder of these relationships, which are often essential for completion of a total synthesis. In the context of this chapter, it illustrates chemical relationships that can be used to understand functional group interchange reactions. In the example at hand, the relationship between a bromide and an alkene is apparent from the table (C-C-Br ⇒ C=C). It is also possible to write a functional group exchange based on the alkene as C=C ⇒ C-C-Br.

It is important to emphasize that Figure 1.1 is *not* intended as a device to memorize specific reactions, but rather to introduce the idea of using various functional groups in a synthesis by recognizing their synthetic relationships. Synthetic sequences for *both* disconnections *a* and *b* are shown. The best route is probably involves conversion of **20** to 1-bromomethyl-propane and reaction with enolate **33** (see sec. 9.2, 9.3.A), which is derived from 3-methyl-2-butanone. This synthesis is considered to be better than the second one shown (based on disconnection *b*) since it involves simpler reagents and is shorter (fewer chemical steps). The synthetic chemist must decide which is best, however, based upon his or her own experience and goals. The best route is a subjective judgment, although it usually makes more sense to follow a short and simple route rather than a long and complex one.



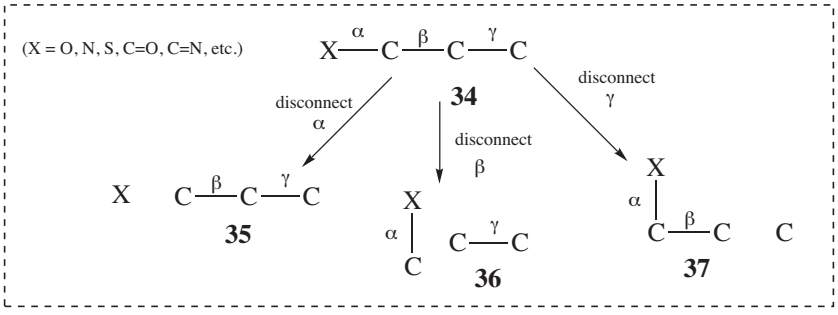
1.3. BOND PROXIMITY AND IMPLICATIONS FOR CHEMICAL REACTIONS

How is the synthetic analysis just presented related to a study of chemical reactions? In all of these disconnections, we converted the disconnect products to actual compounds so we could predict which chemical reactions might work. In all cases, the disconnected bonds were either the one directly attached to the functional group (C-X) or the one next to it (C-C-X). We can use these observations to understand what reaction types are important for making C-C bonds.

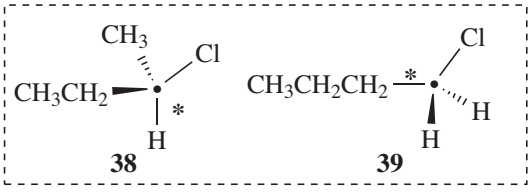
When a functional group (X) is attached to a carbon atom, the bond polarity is important to about the third bond, as indicated in **25**. If we make the *assumption* that most reactions involve highly polarized species, then the three bonds just mentioned become very important. The three important bonds are the C-X bond (called the α bond), the adjacent one (the β bond), and the γ bond, as seen in **34**. If we disconnect the α bond, the synthetic step to form that bond requires direct attack of an X group (where X is an heteroatom) on a suitably functionalized carbon. This process is illustrated by **35**, where a nucleophilic X group attacks the electrophilic

carbon. A simple example is the reaction of azide ion (N_3^-) with 1-iodopropane to give 1-azidopropane. If we disconnect the β bond, we obtain **36**, where the natural bond polarization suggests a reaction in which a nucleophilic carbon species attacks the electropositive carbon of the C-X unit. If we assume the functional group is C=O, addition of a Grignard reagent to an aldehyde fits this description. Finally, disconnection of bond γ leads to **37** (also see Chapter 10), and conjugate addition of an organocuprate to a α,β-unsaturated ketone fits this type of disconnection (where X is C=O).

The point of this section is to show how disconnection of molecules that contain polarized functional groups c an be based on natural bond polarization characteristics. This analysis is based on a variety of common reactions, which is important not only for planning a synthesis but for understanding how chemical reactions work. This general theme will be elaborated in many chapters to follow.



1.4. STEREOCHEMISTRY



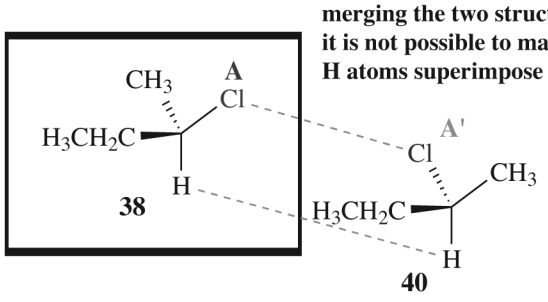
The concept of chirality and absolute configuration is introduced early in undergraduate Organic chemistry courses. For that reason, this section is intended as a review and it is assumed the reader has some familiarity with the concepts. This section will discuss stereoisomers, particularly enantiomers and diastereomers. We will begin with chlorides **38** and **39**, which have the same empirical formula but are clearly different molecules. They are isomers: two or more molecules that have the same empirical formula. They are different molecules! The term isomer does not adequately characterize the relationship between **38** and **39**, since they are of the same chemical type. The term used to define the relationship between **39** and **38** is **regioisomer**: two or more molecules with the same empirical formula, but with a different attachment of the atoms (*different connectivity*).

Another type of isomerism occurs when two molecules have the same empirical formula and also have the same conductivity of atoms but are different molecules. They differ only in the

relative spatial positions of the atoms, and are called **stereoisomers**.[12] The following sections will discuss different types of stereoisomers and their characteristic properties.

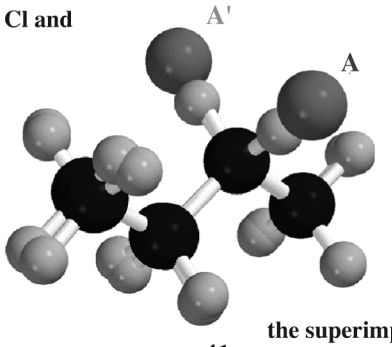
1.4.A. Absolute Configuration in Chiral Nonracemic Molecules

When an atom is bound to four different atoms or groups in a tetrahedral arrangement, that atom is said to be **stereogenic** or chiral. The second carbon (C*) in 2-chlorobutane (**38**) is a stereogenic center. The C* in **39** is not stereogenic, since that carbon has two identical atoms (H) attached to it. Why is identification of C* in **38** as a stereogenic center important? The answer appears when the mirror image of **38** is drawn (see **40**), and the Cl of **38** is reflected into the Cl in **40**. In addition, hydrogen reflects to hydrogen, methyl to methyl, and ethyl to ethyl, but



merging the two structures shows that it is not possible to make the Cl and H atoms superimpose

comparing the two enantiomers shows that Et reflects to Et, C to C, and Me to Me but Cl does not reflect to Cl and H does not reflect to H



41

the superimposed mirror images

this process leads to two different molecules. 2-Chlorobutanes **38** and **40** are ***not superimposable*** by any rotation of bonds, or positioning of the molecules, and they are ***different molecules.*** More precisely, the molecules have no symmetry (they are asymmetric)[13] as can be seen in **41**, which is an attempt to superimpose **38** and **40**. It is clear that while the Me and Et groups superimpose in **41**, the Cl and H atoms do not. Confirm this for yourself with any manual or electronic model, by making both enantiomers and trying to make all groups superimpose. They do not! 2-Chlorobutanes **38** and **40** are different molecules, but they are clearly isomers, and they are closely related since they are mirror images. They are not regioisomers because the connectivity of atoms is the same. These two molecules are **stereoisomers** (molecules that differ in their spatial arrangement of atoms but have the same point of attachment).[12] 2-Chlorobutanes **38** and **40** are further distinguished as a special type of stereoisomer called **enantiomers**, that is, stereoisomers that are nonsuperimposable mirror images. If a structure

12. For a general discussion of stereoisomers, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of OrganicCompounds,* Wiley-Interscience, New York, ***1994***, pp 49-70.
13. For a general discussion of symmetry, symmetry operators and their importance in organic chemistry, see Ref. 12, pp 71-99.

and its mirror image are superimposable by rotation or any motion other than bond making and breaking, then they are identical (a single molecule and not enantiomers; **39** is an example). Make a model of **39** and its mirror image and demonstrate that they are superimposable. When molecules contain more than one stereogenic center, diastereomers (a new type of stereoisomer) will be present, but this will be discussed in sec. 1.4.B.

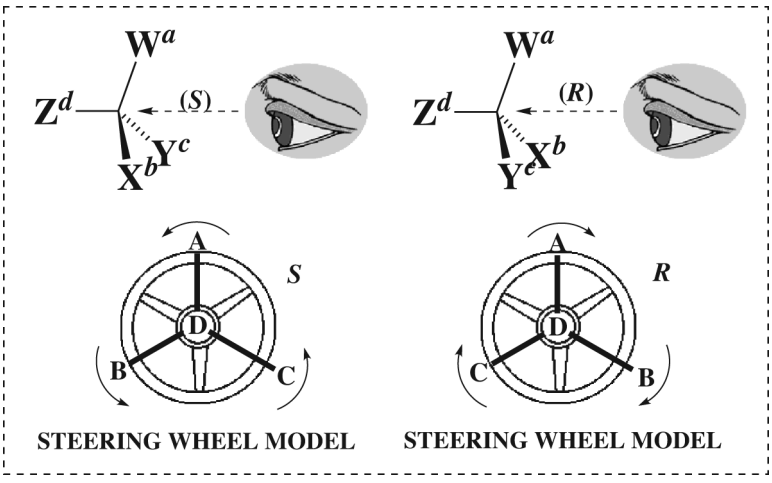
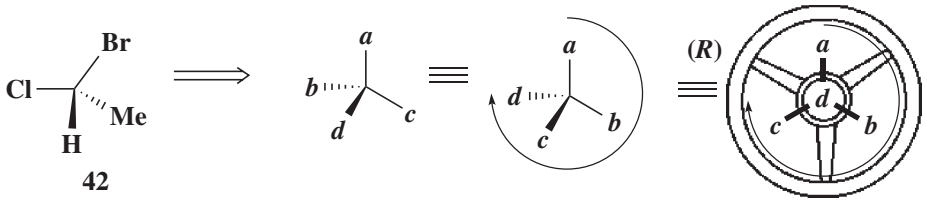


Figure 1.2. The Steering-Wheel Model. In Part, Rreprinted with permission from Cahn, R.S. and the Journal of Chemical Eductation, Vol. 41, **1964**, 116-125. Copyright 1964, Divison of Chemical Education, Inc.

Since 2-chlorobutanes **38** and **40** are different molecules, each must have a unique identifier that allows one enantiomer to be distinguished from the other. The method used is the (*R*/*S*) system, which employs a set of priority rules developed by Cahn, Ingold, and Prelog.[14] In this system, each atom attached to the stereogenic center is assigned a priority (***a*** to ***d***, where *a* is the highest priority atom and *d* is the lowest priority atom). Using the **steering wheel model** (see Figure 1.2) the viewer positions the molecule in such a way that one can sight down the C*-Z^d bond, *with Z^d projected away from the viewer*, as shown. An imaginary line *a*→*b*→*c* is drawn and inspected to see if that line of rotation around the wheel follows a clockwise (right) or a counterclockwise (left) path. If the *a*→*b*→*c* sequence is clockwise the enantiomer is assigned the (*R)* configuration. Conversely, if it is counterclockwise, the enantiomer is assigned the (*S*) configuration. When applying this model, the molecule *must* be rotated so that *d* is Z^d prior to sighting down the C*-Z^d bond. Several different molecular representations are shown below, along with the correct orientation for determining the (*R/S*) configuration.

14. (a) Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* ***1982****, 21*, 567; (b) Cahn, R.S. *J. Chem. Educ.* ***1964****, 41*, 116 (see p 508); (c) Cahn, R.S.; Ingold, C.; Prelog, V. *Angew. Chem. Int. Ed.* ***1966****, 5,* 385; (d) Cahn, R.S.; Ingold, C.K. J. *Chem. Soc. (London)* ***1951,*** 612; (e) Cahn, R.S.; Ingold, C.K.; Prelog, V. *Experientia* ***1956,*** *12*, 81.



42

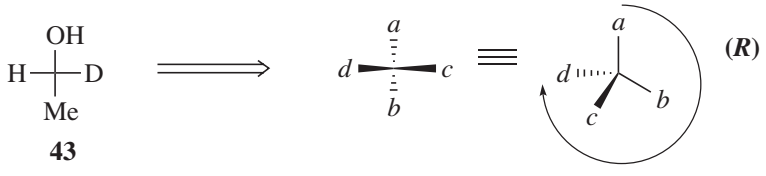
Determining the relative priority (*a* to *d*) is accomplished by a series of rules just mentioned, the so-called **Cahn-Ingold-Prelog (or CIP) selection rules**.[14,15,16]

1. **Atoms with a higher atomic number precede atoms of lower atomic number**

   O > N > C > H

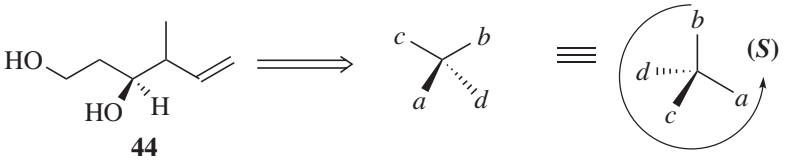
2. **Isotopes with a higher mass number precede isotopes of lower mass number**

   This rule applies to isotopes such as tritium, deuterium and protium ($^3H > ^2H > ^1H$). These two rules are illustrated first by 1-bromo-1-chloroethane (**42**), where Br > Cl > Me > H and the *a*→*b*→*c* rotation is clockwise, giving an (*R*) configuration. Similarly, in 1-deuterioethanol (**43**) the priority is O > C > D > H and the *a*→*b*→*c* sequence is also clockwise for an (*R*) configuration. Note the use of a **Fischer projection** for **43**, where the horizontal lines project out of the paper towards you, and the vertical line projects behind the paper. Fischer projections are not used as much nowadays.



43

   A problem arises when two of the atoms (not the groups) attached to C* are the same. In 4-methylhex-5-en-1,3-diol (**44**), the priorities of the atoms attached to C* are O > C ≈ C > H. Rules 1 and 2 do not allow us to distinguish the two carbon atoms. A new rule is required to solve this problem.



44

15. Reference 12, pp 101-112.
16. IUPAC Commission on Nomenclature of Organic Chemistry *Pure Appl. Chem.* ***1974, 45***, 13.

3. **When the highest priority atoms are identical, compare the number of priority atoms at the first point of difference to distinguish them.**

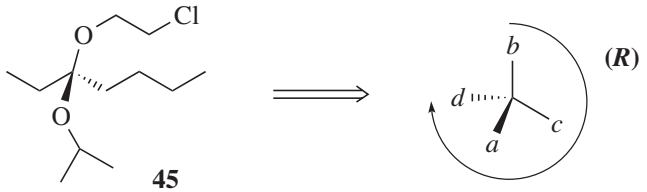
Generic priorities by this rule are:

$$C^{CCC} > C^{CCH} > C^{CHH} > C^{HHH}$$

and

$$C^{OOO} > C^{OOC} > C^{OCC} > C^{CCC}$$

Examination of **44** reveals that the two carbon atoms attached to C* are C^{CHH} and C^{CCH}. The secondary carbon has a higher priority than the primary carbon. The absolute configuration of **44** is (*S*). Another example is the ketal, **45**. The priority analysis is [C*-O-C^{CHH} = *b*], [C*-O-C^{CCH} = *a*] and [C*-C^{CHH}-C^{HHH} = *d*], [C*-C^{CHH}-C^{CHH} = *c*] so the absolute configuration of **45** is (*R*).

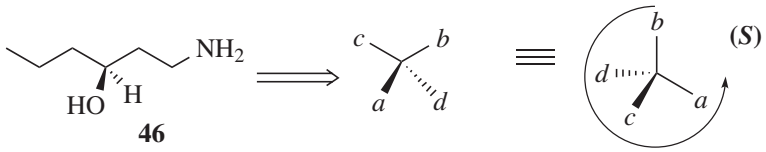


45

There is another problem in example **45**. As one proceeds down the carbon chain, the ethyl (C^{CHH}) and butyl (C^{CHH}) groups have the same atoms attached directly to C*, and are therefore considered to have identical priorities (no point of difference). To determine the priority, follow the chain to the next carbon of the ethyl and the butyl where there is a point of difference (C^{HHH} versus C^{CHH}). Similarly, the oxygen chains show no point of difference with oxygen attached to C* in both cases (O^{CHH}), but a point of difference was reached at the carbon attached to each oxygen atoms (O-C^{CHH} versus O-C^{CCH}), and this analysis can be formalized as a general rule.

4. **When the first point of difference contains two or more identical atoms, proceed atom by atom down the highest priority chain to the next point of difference and apply rules 1, 2 or 3 to determine the priority.**

One must proceed down a chain to find a point of difference in 3-hydroxy-1-aminohexane (**46**), which shows the following priority for atoms attached to C*: O (*a*) > C ~ C > H (*d*). Comparing the two chains gives [C*-C^{CHH}-C^{NHH} = *b*] and [C*-C^{CHH}-CH^{CHH} = *c*].



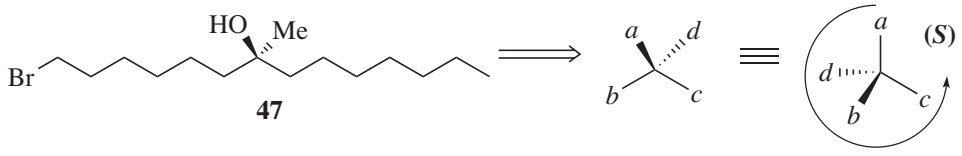
46

It is necessary to go to the second atom to find a point of difference that will distinguish these groups, and **46** has an (*S*) configuration. Similarly, 1-bromo-7-methyl-7-tetradecanol (**47**) shows the hydroxyl O and the methyl group to be (*a*) and (*d*), respectively, but to determine (*b*) and (*c*) requires analysis to the sixth carbon in each chain. This priority establishes the (*S*) configuration.

$$O(a) > C \approx C \approx C \qquad C^{*}\text{-}C^{HHH} = (d)$$

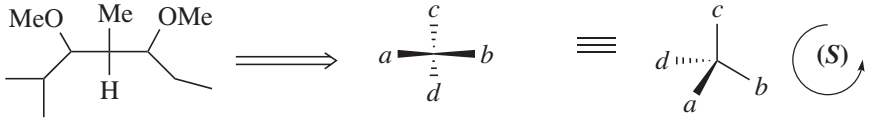
$$C^{*}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{BrHH} = (b)$$

$$C^{*}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH}\text{-}C^{CHH} = (c)$$



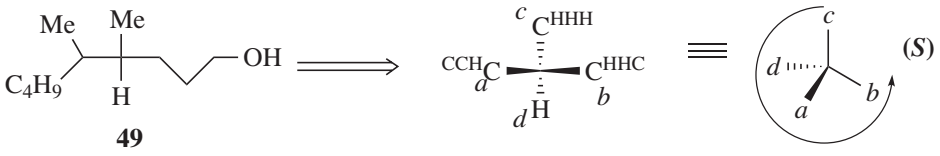
47

In **48**, the methyl and hydrogen are assigned the priorities (*c*) and (*d*). To determine the *a* and *b* priorities we must focus on the two arms that contain OCH. The highest priority chain is along C-O-C (the oxygen chain), but both groups are $O^{C}\text{-}C^{HHH}$. They are identical and we cannot use them to establish the priority. In such a case, the lower priority carbon chain must be used (in this case, the isopropyl and ethyl groups rather than the methoxy groups), giving $C^{*}\text{-}C^{OCH}\text{-}C^{CCH}$ for (*a*) and $C^{*}\text{-}C^{OCH}\text{-}C^{CCH}$ for (*b*) and the molecule has the (*S*) configuration.



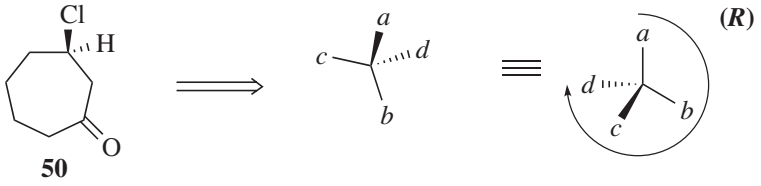
48

A common misconception for rules 3 and 4 arises from an incorrect interpretation of rules 1 and 2. In **49**, methyl and hydrogen are the (*c*) and (*d*) groups. An analysis by rule 3 predicts $C^{CCH} > C^{CHH}$. In the C^{CHH} chain ($-CH_2CH_2CH_2OH$), however, there is an oxygen. The $CH(Me)CH_2CH_2CH_2CH_3$ (C^{CCH}) chain does not contain a heteroatom. *The rules dictate that the priority be determined at the first point of difference, not the second.* The presence of the oxygen is, therefore, irrelevant and the C^{CCH} chain will



49

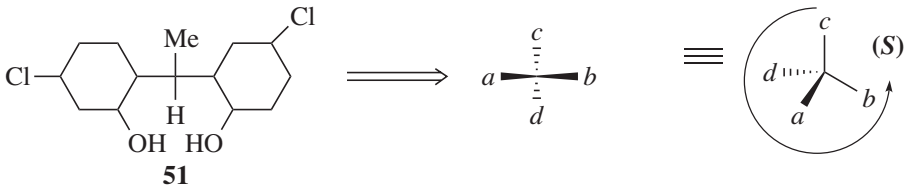
have priority over the C^{CHH} chain. The absolute configuration of **49** is (*S*). Cyclic compounds are treated by the same rules, but each arm of the ring is viewed as a different group and then compared atom-by-atom. 3-Chlorocycloheptanone (**50**), for example, has Cl(*a*) > C ≈ C > H(*d*). The carbonyl chain is $C^*\text{-}C^{CHH}\text{-}C^{OO^\circ C}$ (*b*), in contrast with the carbon arm, $C^*\text{-}C^{CHH}\text{-}C^{CHH}$ (*c*). The configuration is (*R*).



50

In **51**, the methyl and hydrogen are again (*c*) and (*d*), but the rings pose a problem, one arm of the ring points to chlorine and one to hydroxyl. Since the secondary hydroxy carbon is closest to C*, the bottom arm of each ring is followed rather than the top arm. By this route, the left ring is highest priority:

($C^*\text{-}C^{CCH}\text{-}C^{COH}\text{-}C^{CHH}\text{-}C^{ClCH}$ vs. $C^*\text{-}C^{CCH}\text{-}C^{COH}\text{-}C^{CHH}\text{-}C^{CHH}$), and the absolute configuration is (*S*).



51

Cycloheptanone (**50)** contained a carbonyl, and the analysis treated that carbon as C^{OOC}. Where did the second oxygen come from? Multiply bonded atoms such as this are found in alkenes, alkynes, carbonyls, and nitriles, and they require yet another rule.

5. **If an atom is attached to another by a multiple bond (double or triple) both atoms are considered to be duplicated. The duplicated atom (X°) is considered to have a valence of zero and has a lower priority than a real atom (X), if that is the only point of difference.**

This rule will convert the following common functional groups into their phantom counterparts for consideration in the priority scheme.

$C^*\text{-}CH{=}CH_2 \equiv C^*\text{-}C^{HCC^\circ}\text{-}C^{C^\circ HH}$ $C^*\text{-}C(=O)\text{-}C \equiv C^*\text{-}C^{OO^\circ C}\text{-}{}^{OCC^\circ\bullet\bullet}$

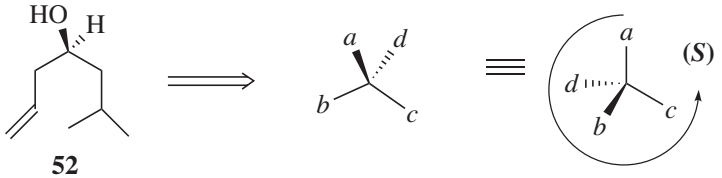
$C^*\text{-}C{\equiv}C\text{-}Me \equiv C^*\text{-}C^{CC^\circ C^\circ}\text{-}C^{CC^\circ C^\circ}\text{-}C^{HHH}$ $C^*\text{-}CO_2H \equiv C^*\text{-}C^{OO^\circ O}\text{-}O^{CC^\circ\bullet\bullet}$

$C^*\text{-}C{\equiv}N \equiv C^*\text{-}C^{NN^\circ N^\circ}\text{-}N^{CC^\circ C^\circ}$

Generally, both X° and X are simply treated as real atoms. If the only choice is between a duplicated atom X° and a real atom (X), however, the duplicated atom has a lower priority (in this case, all other rules have failed to establish the priorities). With the *tert*-butyl fragment, for example, proceeding down the chain to the first point of difference leads to *tert*-butyl with a lower priority than the alkynyl fragment:

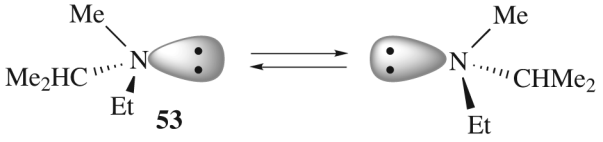
$C^*\text{-}C{\equiv}C\text{-}Me$ vs. $C^*\text{-}CMe_3$ $C^*\text{-}C^{CC^\circ C}\text{-}C^{CC^\circ C} > C^*\text{-}C^{CCC}\text{-}C^{HHH}$

The C and C° are taken as equal in this analysis and rule 4 determines the priority. We compare $C^{CC^\circ C}$ with C^{HHH}, giving the alkyl fragment a higher priority. Another example of this rule is the analysis of 6-methyl-hept-1-en-4-ol (**52**), which shows O(*a*) > C ≈ C > H(*d*). The alkenyl arm is $C^*\text{-}C^{CHH}\text{-}C^{CHC^\circ}$ and the alkyl arm is $C^*\text{-}C^{CHH}\text{-}C^{CCH}$. In this case the rules are unable to distinguish the priority of these two fragments. One proceeds to the next atom ($C^{C^\circ HH}$), which is compared with C^{HHH} (=CH_2 vs. CH_3). The former atom is higher in priority and becomes group (*b*). The absolute configuration of **52** is (*S*).



52

The International Union of Pure and Applied Chemistry (IUPAC) Commission assembled a list of common substituents, sorted by increasing order of sequence rule preference (number 76, iodo, is the highest priority and number 1, hydrogen, is the lowest priority in that table).[16] With this table two or more substituents can be evaluated in order to determine their relative priority using the CIP selection rules.[17] Higher numbers have a higher priority. Iodo (76) has a higher priority than bromo (75) and hydrogen (1) has the lowest priority. Similarly, allyl (10) has a higher priority than propyl (4), acetylenyl (21, C≡CH) has a higher priority than *tert*-butyl (19), and hydroxyl (57) has a higher priority than amino (43).



53

17. Cahn, R.S. *J. Chem. Educ.* ***1964****, 41,* 116.

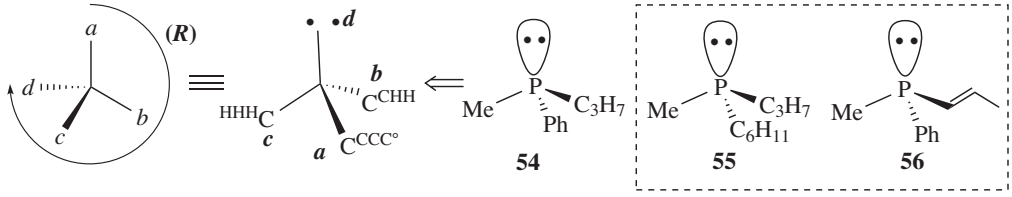
In principle, a nitrogen atom can be stereogenic if there are three different alkyl groups on nitrogen (the fourth group is the lone pair of electrons on nitrogen). The nitrogen may be a stereogenic center, but rapid inversion at nitrogen leads to the mirror image (see **53**) being present at the same time. Because of this facile racemization such compounds are not optically active unless this **fluxional inversion** can be inhibited. Approximately 2 x 10^{11} inversions occur each second for ammonia.[18] The energy barrier for this inversion is somewhat higher in amines (see Table 1.3)[20] due the presence of alkyl groups on nitrogen that are bulkier than the hydrogens in ammonia. Nonetheless, alkyl amines undergo rapid inversion.[19] The magnitude of the energy barrier to inversion in amines is determined by the inter-group bond angle (α, C1-N-C2), and the corresponding bending force constant.[20] Table 1.3[20] shows values of the parameter (α) for ammonia, trimethylamine, phosphine, and trimethylphosphine, along with an estimate for the energy barrier to inversion. Older estimates of these energy barriers are also included.[21] The inversion at nitrogen in alkyl amines cannot be stopped at the reaction temperatures usually employed in organic chemical reactions. When inversion is impossible due to structural features of a molecule such as those found in bicyclic and polycyclic amines, the nitrogen is stereogenic and enantiomers are observed.

Table 1.3. Energy Barrier to Inversion of Amines and Phosphines

Compound	α	$E_{inversion}$ (kcal mol^{-1})	$E_{inversion}$ (kJ mol^{-1})
NH_3	106.77°	5.58[a]	23.2[a]
		11[b]	46.0[b]
PH_3	93.3°	27[a]	112.9[a]
		47[b]	196.5[b]
NMe_3	109.0°	7.46[a]	31.2[a]
		15[b]	62.7[b]
PMe_3	100°	20.4[a]	85.3[a]
		57[b]	283.3[b]

[a] Reference 20 [b] Reference 21

18. Smith, M.B.; March, J. *March's Advanced Organic Chemistry, 6th ed.*, Wiley, New York, ***2007***, pp 142-144.
19. (a) Mislow, K. *Pure Appl. Chem.* ***1968****, 25*, 549; (b) Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970****, 9, 400*; (c) Lambert, J.B. *Top. Stereochem.* ***1971****, 6*, 19.
20. Koeppl, G.W.; Sagatys, D.S.; Krishnamurthy, G.S.; Miller, S.I. *J. Am. Chem. Soc.* ***1967****, 89,* 3396.
21. Kincaid, J.F.; Henriques, Jr., F.C. *J. Am. Chem. Soc.* ***1940****, 62*, 1474.



The energy barrier for inversion is low for second row elements (C, O, N), and rapid inversion occurs. With elements in the third row (such as P and S), however, inversion is slow at ambient temperature and those molecules may exist as enantiomers. Methylphenylphosphine (**54**) is configurationally stable at 25°C, although it rapidly inverts at 130°C.[22b] At 130°C, this barrier was measured to be 30.7 kcal mol^{-1} (128.4 kJ mol^{-1}),[22a] for a rate of inversion of 3.34 x 10^5 s^{-1}.[22] At 130°C, phosphine **55** showed a rate of inversion of 0.043 x 10^5 s^{-1} and the rate for **56** was 1.44 x 10^5 s^{-1} [E_a = 32.2 kcal mol^{-1} (134.6 kJ mol^{-1})].[23]

If a nitrogen atom is a stereogenic center, it must be assigned a configuration by the CIP selection rules. An example is the bridgehead nitrogen in (–)-castoramine (**57**),[24] which is incapable of inversion at nitrogen because of its rigid bicyclic structure.[25] Castoramine is also drawn such that the *trans*-orientation of the electron pair is indicated, which is preferred to the *cis*- orientation by ≈ 2.4 kcal mol^{-1} (10.0 kJ mol^{-1}).[25] This barrier effectively locks the molecule into the trans conformation. In this case, the electron pair must be considered a group but the first five rules do not allow it to be assigned a priority. A sixth rule is necessary.

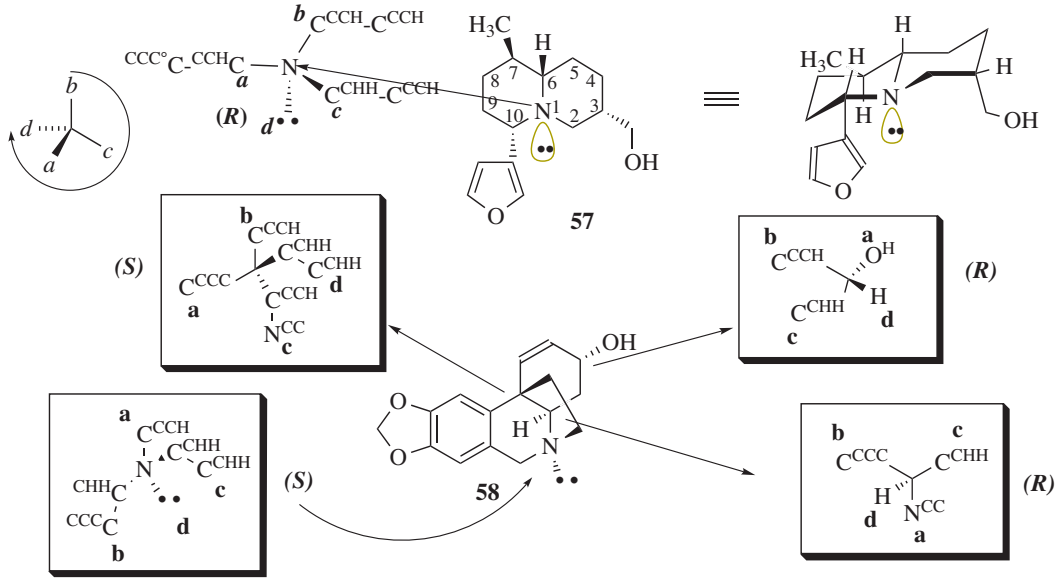
6. Lone electron pairs receive an atomic number of zero and are assigned the lowest priority. The duplicated C, O and N atoms from rule 5 have a higher priority rather than an electron pair.

For (–) castoramine (**57**), rule 6 sets the priority such that the stereogenic nitrogen center is (*R*). Just as a nitrogen atom can be stereogenic, a phosphorus atom in a phosphine such as **54** can be considered chiral at temperatures up to about 130°C, as noted in Table 1.3. The lone pair electrons have the lowest priority by rule 6, and the absolute configuration is (*R*).

The six rules for determining the priority of groups on stereogenic centers can be applied to any molecule. Natural products are particularly interesting, since they are

22. (a) Horner, L.; Winkler, H.; Rapp, A.; Mentrup, A.; Hoffmann, H.; Beck, P. *Tetrahedron Lett.* ***1961***, 161; (b) Horner, L.; Winkler, H. *Ibid* ***1964***, 461.
23. Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 3090.
24. LaLonde, R.T.; Muhammad, N.; Wong, C.F.; Sturiale, E.R. *J. Org. Chem,* ***1980****, 45*, 3664.
25. (a) Aaron H.S.; Ferguson, C.P *Tetrahedron Lett.* ***1968****,* 6191; (b) Aaron H.S. *Chem. Ind. (London)* ***1965****,* 1338.

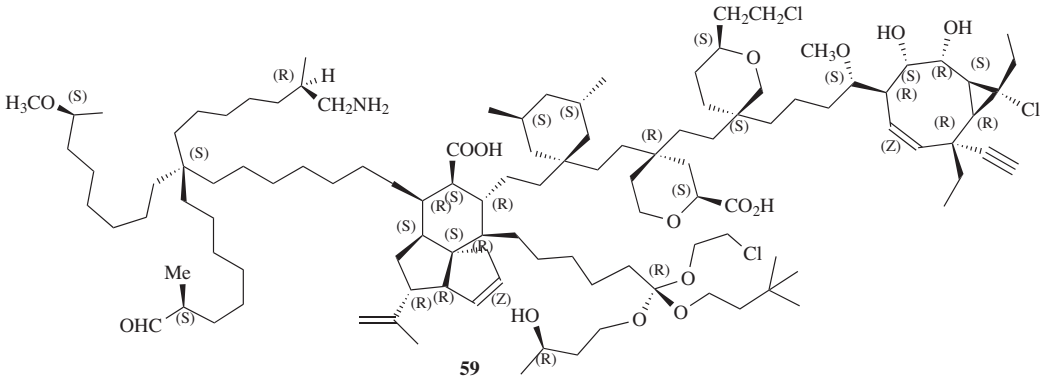
the targets of many synthetic endeavors. As noted above, the absolute and relative configuration of such molecules must be known if they become synthetic targets, and this must be factored into the retrosynthetic plan. The *Amaryllidaceae* alkaloid crinine (**58**) has four stereogenic centers, including the ring-fused nitrogen atom. The absolute stereochemistry for each stereogenic center, as the molecule is drawn, is indicated where



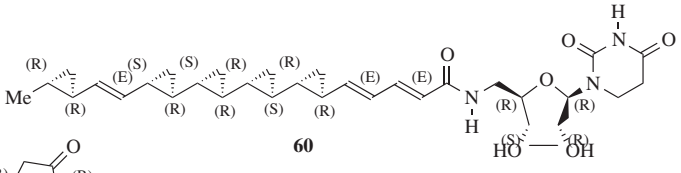
each is treated as if it were an individual and isolated atom. In other words, focus on the carbon bearing the OH group, treat it as an individual tetrahedral carbon with four attached groups (independent of the fact they are all part of one molecule) and then assign priorities. Once done, that carbon atom is determined to have an absolute configuration of (*R*). This fundamental approach is used for all the stereogenic centers, and it can be applied to any molecule, regardless of the complexity. In some cases assigning priorities can be tedious and occasionally confusing, but there are rules to cover all contingencies.

The rules given above allow (*R*) or (*S*) configuration to be assigned for relatively simple molecules, and both **57** and **58** are included as a relatively simple molecule, but application to complex molecules can be problematic. Compound **59**, for example, is non-trivial, and assigning all stereogenic centers by this manual method is at best time consuming, at worst difficult and prone to error. Modern computational methods, with algorithms to asses the absolute configuration, make such assignments rapid and rather easy. One simply draws the structure with the correct stereochemical relationships in the model, and the program makes the correct assignment. Indeed, the computer-generated assignments are shown in **59**. Draw structures **60** and **61**, and assign the

absolute configuration using Spartan, and compare with the results that are given. Try it using the rules just discussed as well! Compound **60** is the oligocyclopropane FR-900848,[26] and **61** is the macrolide toxin pectenotoxin 2.[27] A similar analysis of the absolute configuration is shown for all stereogenic centers in ciguatoxin, **62**.[28]



59



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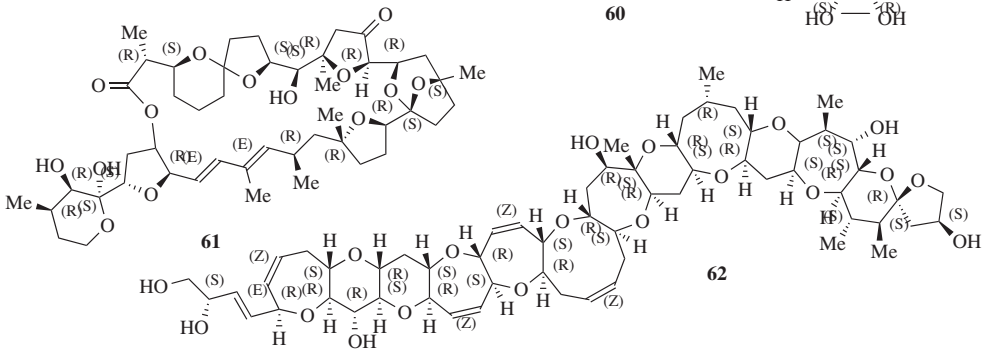


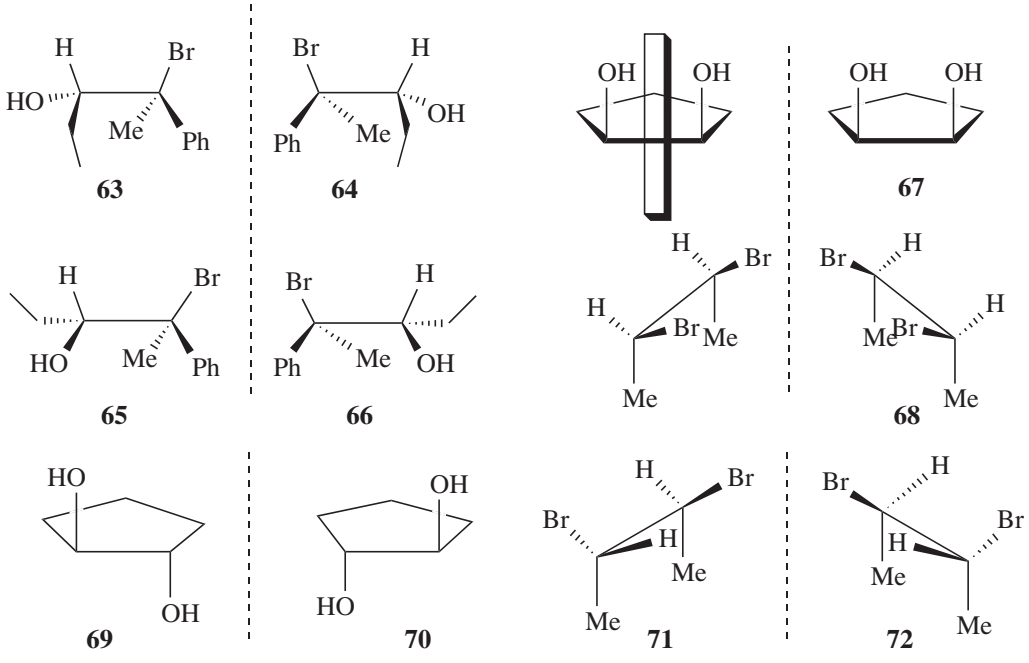
61

62

26. Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* ***1990****, 43,* 748.
27. (a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, G. K.; Matsumoto, J. *Tetrahedron* ***1985****, 41,* 1019; (b) Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* ***1986****, 50*, 2693; (c) Sasaki, K.; Wright, J.L.C.; Yasumoto, T. *J. Org. Chem.* ***1998****, 63*, 2475; (d) Suzuki, T.; Beuzenberg, V.; Mackenzie, L.; Quilliam, M.A. J. *Chromatogr. A* ***2003****, 992,* 141; (e) Miles, C.O.; Wilkins, A.L.; Samdal, I.A.; Sandvik, M.; Petersen, D.; Quilliam, M.A.; Naustvoll, L.J.; Rundberget, T.; Torgesen, T.; Hovgaard, P.; Jensen, D.J.; Cooney, J.M. *Chem. Res. Toxicol.* ***2004****, 17,* 1423; (f) Halim, R.; Brimble, M.A.; Merten, J. *Org. Lett.* ***2005****, 7*, 265.
28. (a) Scheuer, P.J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. *Science* ***1967****, 155*, 1267; (b) Murata, M.; Legurand, A.M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* ***1990****, 112*, 4380; (c) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* ***1997****, 119*, 11325; (d) Hamajima, A.; Isobe, M. *Org. Lett.* ***2006****, 8*, 1205.

1.4.B. Diastereomers

When there is more than one stereogenic center, the maximum number of possible stereoisomers is predicted by the **2^n rule** (for *n* stereogenic centers there is a maximum of **2^n** stereoisomers). Therefore, two stereogenic centers in a molecule such as **63** lead to four possible stereoisomers with the configurations C1(*R*)-C2(*R*), C1(*S*)-C2(*S*), C1(*R*)-C2(*S*) and C1(*S*)-C_2(*R*). Bromohydrin **63** has the configuration (*SS*), and its enantiomeric mirror image (**64**) is (*RR*). Similarly, the (RS) compound (**65**) and its mirror image (**66**) with the (*SR*) configuration are enantiomers. Comparison of **63** and **65** shows they are also stereoisomers, but they are *not* mirror images *nor* are they superimposable. This type of stereoisomer is given the name **diastereomer**: stereoisomers with two or more stereogenic centers that are not superimposable and not mirror images. By this definition, **64** and **66** are also diastereomers, as are **64** and **65** or **63** and **66**.



There are cases when a plane of symmetry bisects a diastereomer, as in *cis*-1,2-cyclopentanediol (**67**) and (2*R*,3*S*)-dibromobutane **68**. The mirror image of (2*R*,3*S*)-dibromobutane is (2*S*,3*R*)-dibromobutane, the same compound. In effect, one half of the molecule is the mirror image of the other half as a result of the symmetry in the molecule, which leads to *fewer* stereoisomers than the maximum predicted by the **2^n** rule. Structures **67** and **68** are superimposable upon their mirror images so *they are not enantiomers but are the same compound* and are called **meso compounds**. The cis-diol **67** is a meso compound but its diastereomer, the trans-diol, exists as enantiomers **69** and **70**. There are a total of three stereoisomers: isomers **67** and **69** or **67** and **70** are diastereomers, **69** and **70** are enantiomers and **67** is a meso compound. Similarly, **67** is a meso compound, but **71** [(2*S*,3*S*)-dibromobutane] and **72** [(2*R*,3*R*)-dibromobutane]

are enantiomers giving the three stereoisomers. Note that changing the configuration of one stereogenic center (2*R* → 2*S*) cannot be done by rotation but only by making and breaking bonds. Dibromides **68** and **71** are diastereomers, as are **68** and **72**.

In chapters to come we will see that many different types of organic reactions produce diastereomers. These diastereomeric pairs show rotation about the carbon-carbon bond (see sec. 1.5.A), which precludes the configurational rigidity necessary for using the cis- and trans-isomer designations. Separate nomenclature systems have been developed based on the relationship of the groups on the stereogenic centers. One system for distinguishing diastereomers labels them threo- and erythro. Unfortunately, there is more than one definition for threo- and erythro. Winstein and co-workers gave the following definition of these diastereomers: in a compound with two asymmetric carbons that has two common ligands and a third that differs, the isomers that would be meso if the third ligand were identical are erythro diastereomers.[29] An alternative definition is: if two asymmetric carbons have only one ligand in common, then the other four ligands are paired in the same commonsense way and isomers that would have equal pairs eclipsed in any conformation are erythro.[30] Eliel, Mislow and their co-workers[31] defined erythro and threo in terms of Fischer projections. The aldol products (see sec. 9.4.A) **73** and **74**, and the ester-aldehyde condensation products **75** and **76**[32] are shown with the erythro and threo notation.

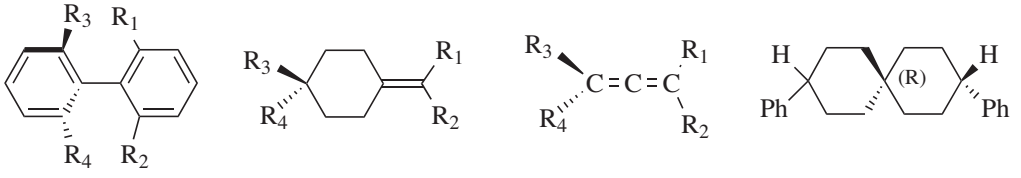
To alleviate the confusion of the various uses and perceptions of the erythro/threo notation,[33] Masamune proposed the terms syn and anti to describe the relative stereochemistry of diastereomers.[34] In this notation, adjacent groups on the same side of an extended (zigzag) structure are syn, and those on opposite sides are anti. This model is illustrated with **77-79**.[34,35] An extended structure is used as the basis of the model.

> The clearest way to show differences is to use the absolute configuration (*R*) or (*S*) nomenclature for each stereogenic center in both enantiomers or in enantiomerically pure diastereomers. Throughout this book, the correct configuration will be cited or the syn- and anti- terminology will be used.

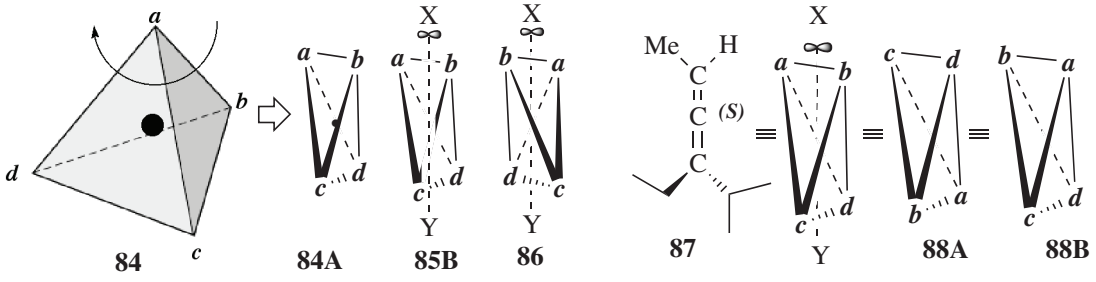
29. Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* ***1939****, 61,* 1576, 2845.
30. (a) Lucas H.J.; Schlatter, M.J.; Jones, R.C. *J. Am. Chem. Soc.* ***1941****, 63*, 22; (b) Cram, D.J. *Ibid* ***1952****, 74*, 2149; (c) Curtin, D.Y.; Kellom, D.B. *Ibid* ***1953****, 75*, 6011; (d) House, H.O. *Ibid* ***1955****, 77,* 5083.
31. (a) Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, ***1994***; (b) Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, ***1962***; (c) Mislow, K. *Introduction to Stereochemistry,* W.A. Benjamin, New York, ***1965***.
32. Meyers, A.I.; Reider, P.J. *J. Am. Chem. Soc.* ***1979****, 101*, 2501.
33. Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982****, 21,* 654.
34. Masamune, S.; Ali, Sk.A.; Snitman, D.L.; Garvey, D.S. *Angew. Chem. Int. Ed.* ***1980****, 19*, 557.
35. Heathcock, C.H. in *Asymmetric Synthesis, Vol. 3*, Morrison, J.D. (Ed.), Academic Press, New York, ***1984***.

1.4.C. Chiral Molecules without a Stereogenic Center (Molecules Containing a Chiral Axis)

A few classes of organic molecules have a chiral axis although they do *not* have a stereogenic center.[36] The mirror image of such a molecule is not superimposable, *which means it is possible to have enantiomers without the presence of a stereogenic center*. Four important classes of compounds that exhibit this property are biaryls such as **80**, alkylidene cyclohexanes (**81**), substituted allenes such as **82** and substituted spiranes such as 3,9-diphenylspiro[5.5]tridecane (**83**).[17,36] Chiral biaryls are important chiral catalysts and are used in many reactions



(see sec. 4.8.A, 4.9.G, and sec. 11.9). Obviously, it is important to determine the absolute configuration of both the chiral reactants and the asymmetric products resulting from their use. Allenes are common partners in pericyclic reactions (see secs. 11.4, 11.10 and 11.11) and they are chiral partners in some of these reactions. Alkylidene cyclohexanes are produced by phosphorus ylids upon reaction with cyclohexanone derivatives (see sec. 8.8.A) and the potential for creating asymmetric products is a key consideration in planning a synthesis of such compounds. However, no chiral atom is present and the CIP rules just described do not directly apply.

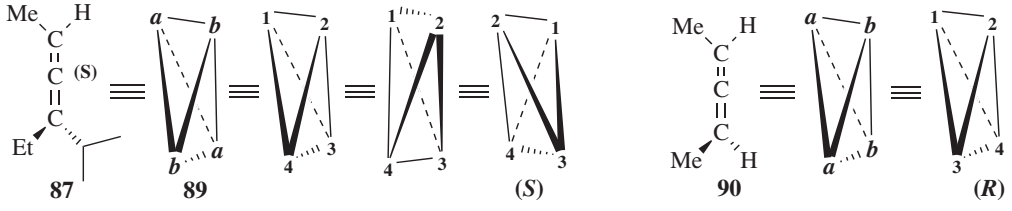


Chiral molecules that have no stereogenic center are evaluated by recognizing the presence of an extended tetrahedron (**85A**).[37] A normal tetrahedral atom is shown by **84**, and if the bond lengths for atoms $a \rightarrow d$ were distorted to give an extended tetrahedron **85A** would be obtained. Rather than a chiral atom, **85A** contains a **chiral axis**, which can be used to assign priorities (see X---Y in **85B**). This model requires that **85B** not be interconvertible with its mirror image

36. For a general discussion of this concept and molecules that exhibit this property, see Reference 12, pp 1119-1190.
37. Reference 12, pp 1119-1122.

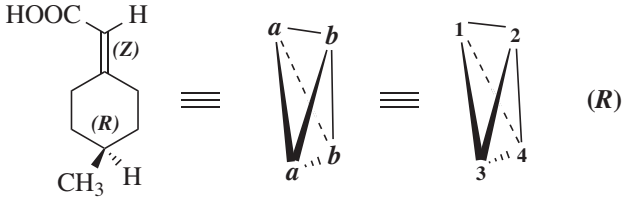
86 (i.e., rotation about the chiral axis X---Y must not interconvert **85** and **86**).

Allene **87** has a chiral axis since there are four different groups at each corner of the extended tetrahedron. These groups can be assigned priorities $a \rightarrow d$ (**88A**) by the usual rules, and a first glance suggests **88B** (obtained by rotating **88A** so the $a \rightarrow b \rightarrow c$ sequence is in front and the *d*-atom is to the rear) as the structure to be used for determining the absolute configuration. This is ***incorrect***. There is nothing here to suggest the appropriate angle from which to view the extended tetrahedron. There is no C*-C^{d} axis from which to view the molecule. The CIP rules were modified to accommodate an extended tetrahedron.[17] (*1*) The top edge of the extended tetrahedron is prioritized *a,b* and the bottom edge of the extended tetrahedron is also prioritized *a,b*. (*2*) Near groups precede far groups when viewed from the top of the extended tetrahedron. With these rules, **87** is converted to **89** where the top *a,b* pair is associated with 1,2 ($a = 1$, $b = 2$). Similarly, the bottom *a,b* pair is assigned 3,4 ($a = 3$, $b = 4$) since top has priority over bottom. The model is rotated to put (4) to the rear and follows the order $1 \rightarrow 2 \rightarrow 3$ that gives a counterclockwise pathway and an (*S*) configuration. This new model can also be used with allene **90**, where only two different groups are present. The methyl-hydrogen priorities are shown in **86** and converted to the $1 \rightarrow 4$ priority scheme, which places (4) to the rear, giving an (*R*) configuration.[17] Molecules such as this can also be evaluated *a priori* using the **Lowe-Brewster rules**.[38] Eliel et al.[39] point out that the configuration of allenes and alkylidenecycloalkanes can be predicted by these rules in most case, but the model fails for many spirans.



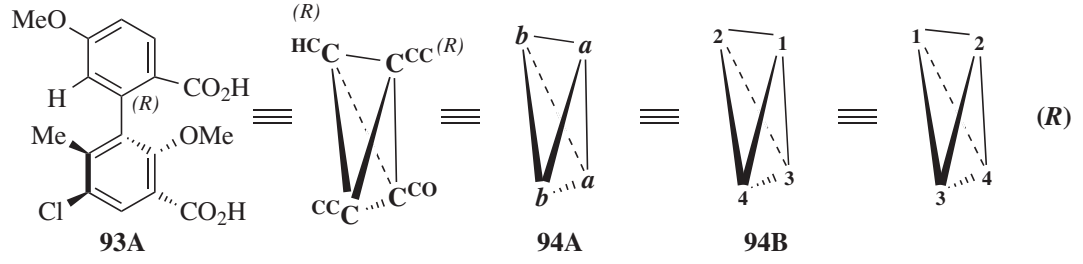
Chiral axes occur for cyclic molecules containing an exocyclic alkylidene moiety such as **91**, which has two different groups at C4 of the cyclohexyl system and two different groups attached to the π bond. The $C^{OOO} > H$ priority for CO_2H and H on the alkene is straightforward, and this constitutes the top of the extended tetrahedron. The cyclohexyl arms are in the plane of the π bond, but the methyl and hydrogen at C4 of the cyclohexane ring are in a different plane that constitutes the bottom of the extended tetrahedron. Since the methyl carbon has priority over the hydrogen the extended tetrahedron is **92A**, which leads to **92B** and the (*R*) configuration.[17]

38. (a) Lowe, G. *Chem. Commun.* ***1965,*** 411; (b) Brewster, J.H. *Top. Stereochem.* ***1967,*** *2*, 1; (c) Reference 12, pp 1129-1132.
39. Reference 12, p 1091.

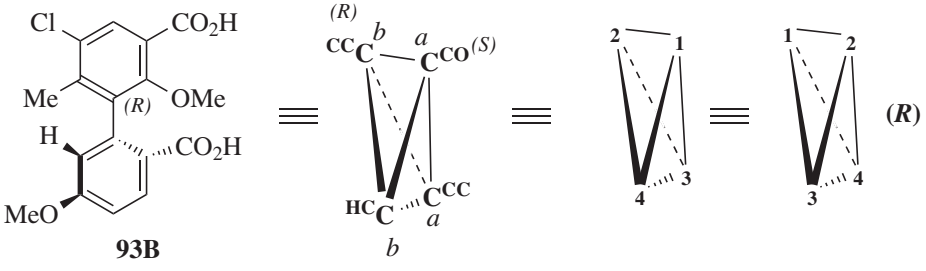


91 **92A** **92B**

Biaryls such as **93A** can be analyzed with the extended tetrahedron model. The top aromatic ring is prioritized as *a,b* for the 2,6 substituents, as is the bottom ring (see **94A**). The near-far rule leads to **94B** and an (*R*) configuration.[19] A reasonable question asks which aryl ring is on top and which is on the bottom of the extended tetrahedron. Do the rules accommodate these two orientations? Structure **93B** is identical to **93A** except the former has been rotated by 180°. Analysis of both structures leads to an (*R*) configuration. Prioritizing top and bottom *separately* accounts for rotating the molecule in this manner, but the top must be assigned ***before*** prioritizing the molecule and must ***not*** be changed after the process has begun. An example of a fused aromatic system used in synthesis is the reducing agent BINAL-H (an abbreviation for **95**, see sec. 4.8.A.).[40] The extended tetrahedron reveals an (*R*)-. Note that binding the aluminum atom into a ring, as shown in **95**, effectively locks the aromatic rings into a single configuration and does not allow racemization unless the C-C-C-C-Al-O- ring is disrupted.

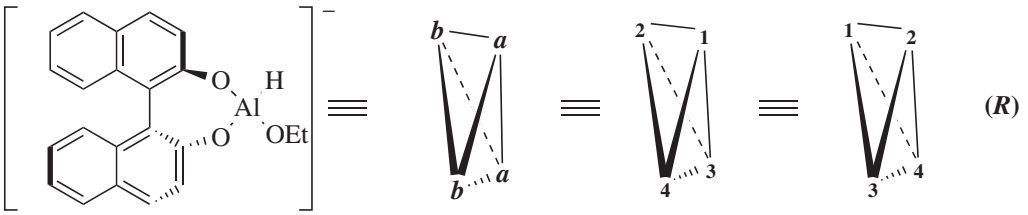


93A **94A** **94B**



93B

40. (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* ***1984****, 106,* 6709; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *Ibid* ***1984****, 106*, 6717.



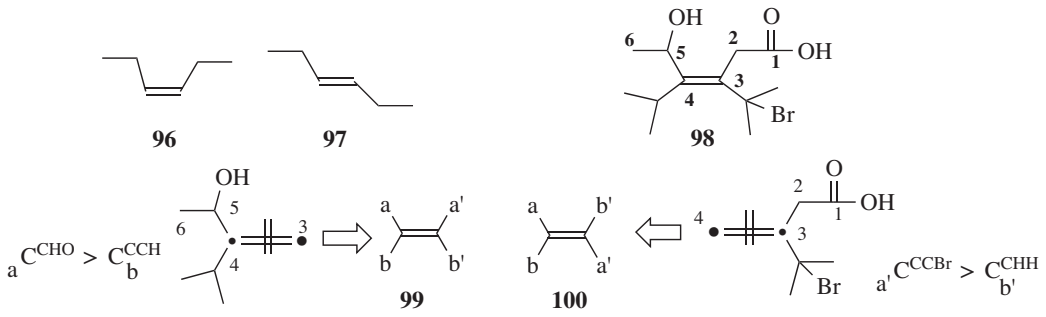
95

1.4.D. (*E*/*Z*) Isomers

Alkenes can exist as stereoisomers. If asked to draw the structure of 3-hexene, two different molecules can be drawn (**96** and **97**). They are not superimposable, nor are they mirror images. Rotation is not possible around the C=C moiety, so the ethyl groups and the hydrogens have different spatial relationships. Those groups cannot be interconverted by rotation. Although no stereogenic center is present, **96** and **97** are stereoisomers and are formally considered to be diastereomers. In this particular case, the C=C unit has identical groups (ethyl) attached and the ethyl groups can be identified as being on the same side of the C=C or on opposite sides. When an alkene contains identical groups and those groups are on the same side, it is called a cis-alkene. When the two identical groups are on opposite sides, it is called a trans-alkene. Alkene **96** is *cis*-3-hexene and **97** is *trans*-3-hexene. These terms are part of the nomenclature as shown.

The terms cis and trans are applied in a straightforward manner for simple alkenes such as *cis*- and *trans*-3-hexene or *cis*- and *trans*-1,2-dibromoethene. For 3-(1-bromo-1-methyl-ethyl)-5-hydroxy-4-(1-methylethyl)-hex-3-enoic acid (**98**), however, the cis-trans nomenclature does not apply. Which of the groups are used to determine sidedness? A more general nomenclature system is required, the (*E*/*Z*) system.[17,41] The CIP selection rules are used for this system, to assign priorities to each carbon of the double bond. In **99**, *a* and *a*' have the higher priorities and *b* and *b*' have the lower. Since *a* and *a*' are on the same side of the double bond, they are given the designation (*Z*) (from zusammen = together). Similarly, *a* and *a*' are on opposite sides in **100** and this arrangement is given the designation (*E*) (from entgegen = opposite). With this system, the hydroxyl-bearing carbon of C4 in **98** is assigned the highest priority (C^{CHO} vs. C^{CCH} for the isopropyl carbon). Analysis of C3 shows the bromine-bearing carbon to be the highest priority (C^{CCBr} vs. C^{CHH}). This is analogous to **100**, and the name of **98** is (*E*)-(1-bromo-1-methylethyl)- 5-hydroxy-4-(1-methylethyl)-hex-3-enoic acid. This nomenclature is generally applicable to all alkenes that do not have identical groups on one of the alkenyl carbons. 3-Hexene **96** is (*Z*)-3-hexene and **97** is (*E*)-3-hexene. The (*E*/*Z*) system will be used extensively throughout this book, but the cis/trans designations will be used for simple molecules and to describe relative stereochemistry. For example, the carbonyl group and the hydroxyl-bearing moiety in **98** are cis to each other.

41. Reference 12, pp 541-543.



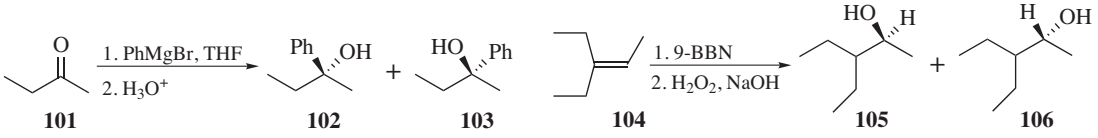
1.4.E. Prochiral Centers

There are molecules that do not possess a stereogenic center but generate a product with a stereogenic center after a chemical reaction. In terms of planning a reaction, it is important that we try to predict whether the product will have an (*R*)- or an (*S*)-configuration. To make this prediction, we must know from which face of the molecule the reagent will approach during the reaction. If it approaches from one face the (*R*)-enantiomer is generated; if it approaches from the opposite face the product is the (*S*)-enantiomer.

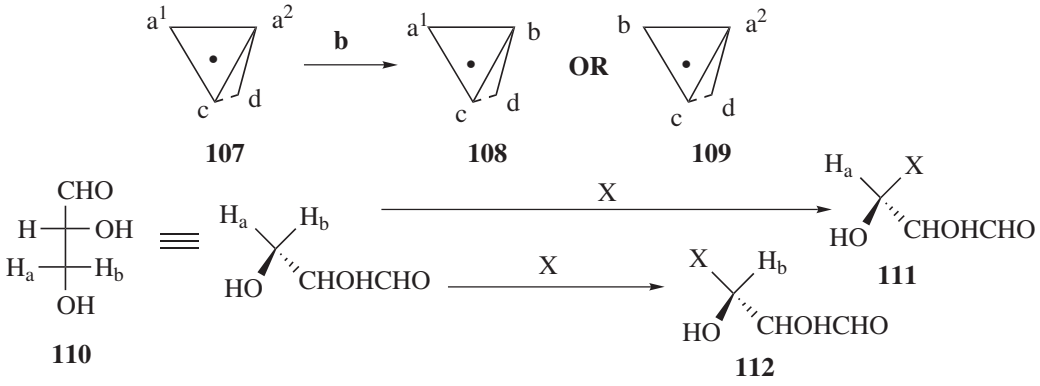
It is obvious that ketone **101** (2-butanone), and alkene **104** do not contain a stereogenic center. If **101** reacts with a Grignard reagent such as phenylmagnesium bromide (PhMgBr), however, the product is a racemic alcohol with enantiomers **102** and **103** (see sec. 8.4.C). Reaction of alkene **104** with a borane such as 9-BBN (9-borabicyclo[3.3.1]nonane) followed by oxidation gives a racemic alcohol, that is, enantiomers **105** and **106** (see sec. 5.4.A). In both cases, the reaction has produced a product that contains a stereogenic carbon. The ketone and alkene are described as **prochiral**,[42] and a working definition of **prochirality** was provided by Hanson:[43] "If a chiral assembly is obtained when a point ligand in a finite non-chiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral". A ligand is simply a group attached to the prochiral atom (*a, b, c, d*). A point ligand for a prochiral center has two characteristics: "(*1*) any two point ligands may be identical or non-identical, and (*2*) two point ligands may not occupy the same position in space."[43] Addition of a point ligand to a prochiral center creates a new chiral center.[43] If the ligands are assigned a priority *a-b-c-d* by the CIP selection rules, configurations for each face of the prochiral center can be obtained. This rule is illustrated by conversion of the prochiral atom in **107** to either **108** or **109**. In this example, **109** represents a (*S*) chiral center and is formed by replacement of a^1 with *b*. Similarly, replacing a^2 generates a (*R*) chiral center **108**. The a^1 and a^2 atoms are described by the terms ***pro-S*** and ***pro-R***, respectively. A *pro-R* center is a point ligand in a prochiral molecule whose replacement leads to an (*R*) center. Analogously, a *pro-S* center is a point ligand in a prochiral molecule whose replacement leads to an (*S*) center. In **107**, ligand a^2 is

42. Reference 12, pp 465-488.
43. Hanson, K.R. *J. Am. Chem. Soc.* ***1966****, 88,* 2731.

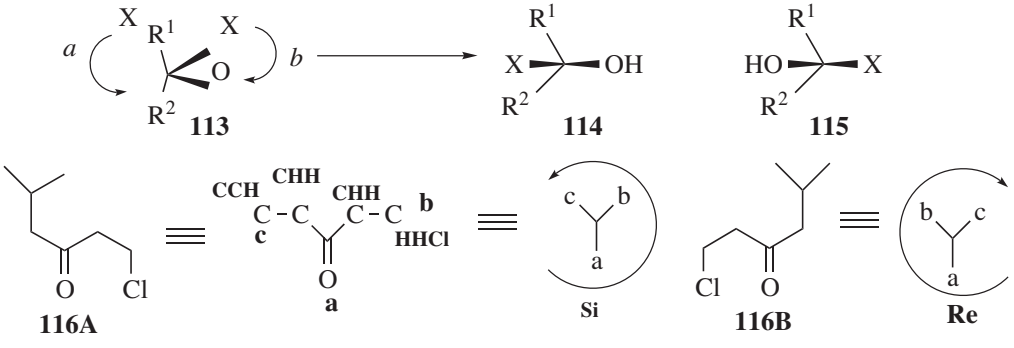
pro-R and a^1 is *pro-S*, and an example is D-glyceraldehyde **110**. The methylene group adjacent to the chiral center is prochiral, and replacement of H_b with a group X gives a (*S*) center in **111** (assuming X has a priority of *c* with H = *d*). Replacement of H_a gives a (*R*) center (in **112**) and that hydrogen is *pro-R*.



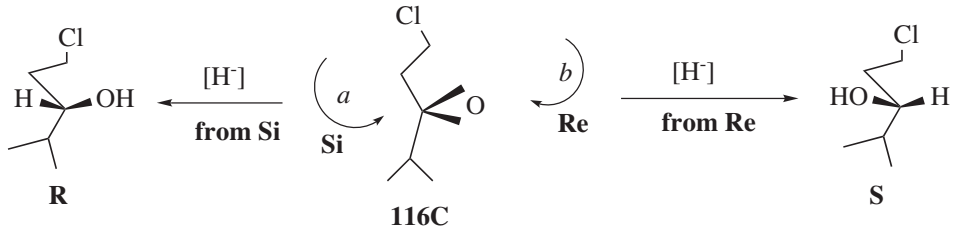
Hanson[43] described rules that accommodate most situations observed with prochiral centers. The reader is referred to this work for specific examples that do not yield to a simple analysis. The intent of this section is to familiarize the reader with nomenclature and the uses of *pro-R* and *pro-S* sites in reactions.



As noted above, synthetically important prochiral centers are the carbonyl of an unsymmetrical ketone or aldehyde and the double bond of an alkene. These functional groups do not contain a *pro-R* or *pro-S* group but it is clear that delivery of a fourth point ligand from one face or the other will lead to an (*R*) or (*S*) stereogenic center, as in conversion of **113** to **114** and/or **115**. If the carbonyl group is oriented as in ketone **116A**, priorities can be

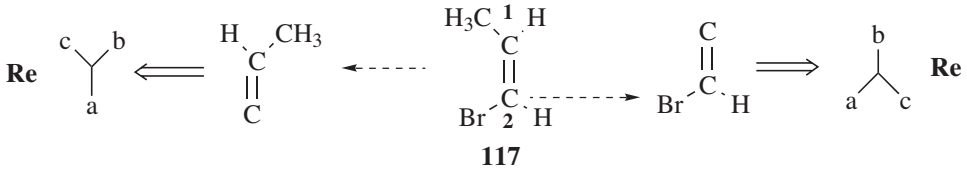


assigned to the three atoms connected to the prochiral atom based on the CIP rules. For **116A**, the $a \rightarrow b \rightarrow c$ priority is counterclockwise and is analogous to (*S*). It is not really an (*S*) configuration, of course, since it is not a stereogenic center but this (*S*) sequence is termed *si*, from the Latin *sinister*.[43] When the incoming group approaches the π-bond from this face (with the orientation shown in **116A**) it is called the ***si*** face. If the molecule is given the opposite orientation, as in **116B**, the priority sequence $a \rightarrow b \rightarrow c$ is clockwise or (*R*) and this face is termed



re, from the Latin *rectus*. That face is the ***re*** face.[43] In this example, face ***a*** (see **116C**) is the *si* face and face ***b*** is the *re* face. Attack of hydride (see secs. 4.2.B, 4.7) from face ***a*** (the *si* face) leads to the (*R*) alcohol and attack from face ***b*** (the *re* face) leads to the (*S*) alcohol. The configuration of the final product depends on the priority of the new group added to the prochiral center.

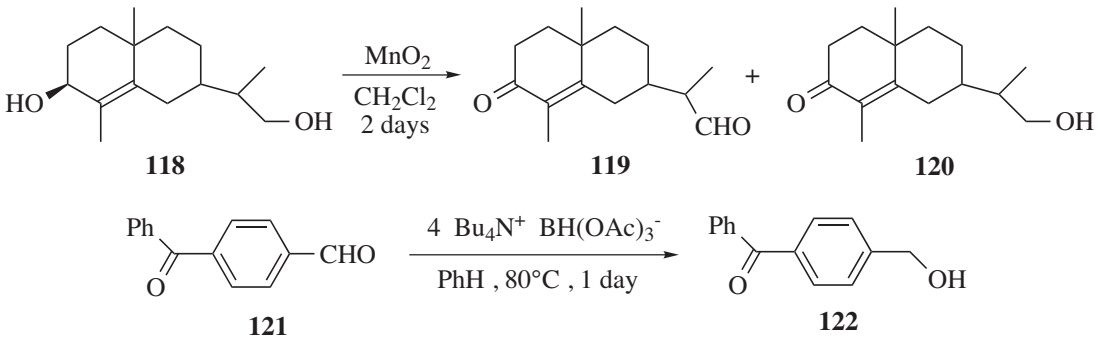
Similar terminology can be applied to alkenes, as with (*Z*)-1-bromo-1-propene (**117**). In this case, there are two prochiral centers to be considered (C1 and C2 of the C=C bond), and *re* or *si* is assigned to each carbon. For **117**, the top faces of both C1 and C2 are *re* (*re*-*re*) and the bottom faces are *si* (*si*-*si*)



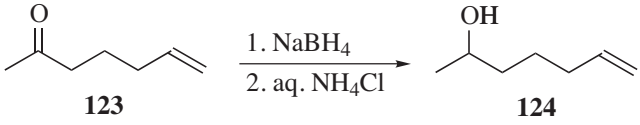
1.4.F. Definitions of Selectivity

In the preceding sections various types of molecules were classified as regioisomers or stereoisomers (further categorized as diastereomers and enantiomers). When there are two different functional groups in a molecule, a given reagent may react preferentially with one rather than the other. Such a reaction is sometimes termed **chemoselective**. Oxidation of **118** with manganese dioxide (MnO_2, see sec. 3.2.F.iii) gave a 50% yield of **119** and 25% of **120**.[44] Manganese dioxide showed a preference for oxidation of the secondary allylic alcohol at the

44. Hlubucek, J.R.; Hora, J.; Russell, S.W.; Toube, T.P.; Weedon, B.C.L. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 848.

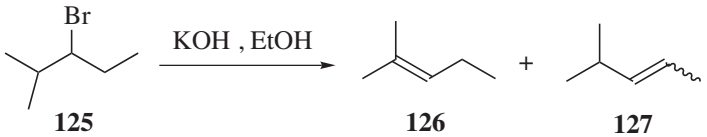


expense of the primary alcohol. The reagent selected one over the other, which leads to the term **chemoselective** (of two or more reactive functional groups, one reacted preferentially to give the major product in the mixture). When both products are formed but one is formed in greater proportions the term selective applies. Contrast this reaction with Gribble's reduction of ketoaldehyde **121** with tetrabutylammonium triacetoxyborohydride [Bu_4N^+ $BH(OAc)_3^-$, where Ac = acetate and Bu = butyl, see sec. 4.5.A], to give **122** in 88%.[45] If the result had been different, and the aldehyde carbonyl was reduced and a portion of the ketone carbonyl was also reduced, the reaction would be chemoselective rather than chemospecific. If there had been 100% reduction of the aldehyde but 0% of the ketone, the reaction would be termed **chemospecific**. Trost defined these terms: "of two or more reactive functional groups, only one reacts (specific), or one predominates (selective)". Reduction of alkenyl ketone **123** gave alcohol **124** and only the carbonyl reacts with sodium borohydride ($NaBH_4$). Since 0% of the alkene reacted, the reaction is chemospecific.

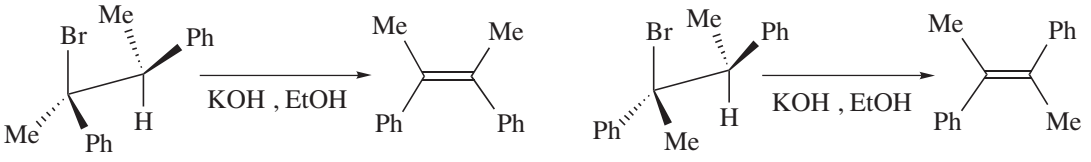


As noted above, the use of the terms selective and specific for giving a preponderance of a given product or only that product, respectively, can be applied for all reactions involving stereochemistry. If a reaction can produce two or more regioisomers, it is regioselective or regiospecific. The second order (E2) elimination (see sec. 2.9.A) of the racemic bromide **125** gave a mixture of **126** and **127** with **126** being the major product, so the reaction is regioselective. Elimination of the enantiopure (*S,S*)-diastereomer (**128**), however, gave *only* the (*Z*)-alkene **129** with none of the (*E*)-isomer and none of the alkene formed by removal the β-hydrogen on the methyl. The reaction is regiospecific and also stereospecific. This result was confirmed by reaction of the (*R,S*)-diastereomer **130** under E2 conditions, which gave only **131**. If **128** and **130** gave an unequal mixture of **129** and **131** the reaction would be stereoselective. One product is formed, so the reaction is stereospecific.

45. Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* ***1983****, 24,* 4287.



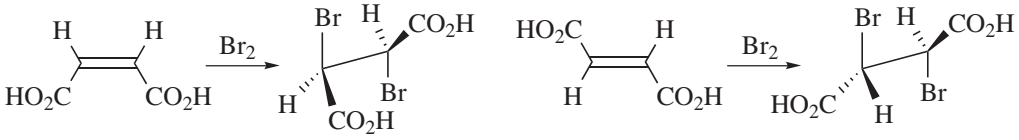
125 **126** **127**



128 **129** **130** **131**

Similar terminology is applied to formation of diastereomers. March and Smith[46] gave the example of maleic acid (**132**) and fumaric acid (**134**) and their reactions with bromine. On addition of bromine to **132**, a racemic mixture of **133** was formed. Addition to **134** gave only *meso*-**135**. In both cases the reaction was diastereospecific. If **132** gave predominantly **133** with only a trace of the diastereomer (**135**), the reaction would be diastereoselective rather than diastereospecific.

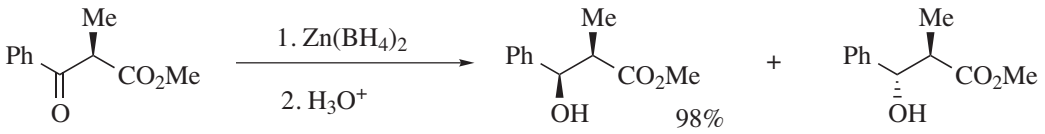
The term stereoselectivity is applied to reaction products. If a reaction produces at least one substance that is not a stereoisomer of the major product, that reaction cannot be stereospecific but at most stereoselective.[47] If stereoisomeric starting materials react to give a single stereoisomeric product, the reaction is **stereospecific**, but if



132 **133** **134** **135**

another stereoisomer is also produced (giving a mixture of products) the reaction is **stereoselective**. These terms apply to all types of stereoisomers, including enantiomers (**enantioselective** and **enantiospecific**), diastereomers (**diastereoselective** and **diastereospecific**) and regioisomers (**regioselective** and **regiospecific**). Reduction of keto ester **136** with zinc borohydride [$Zn(BH_4)_2$, see sec. 4.4.B and 4.7.B] gave 98% reduction with a >99:1 preference for **137** over **138**. The reaction produced two diastereomers, and it is **diastereoselective**.[47] Since traces of **138** are produced, the reduction cannot be diastereospecific.

46. Reference 18, pp 1002.
47. Oishi, T. in *New Synthetic Methodology and Functionally Interesting Compounds*, Yoshida, Z. (Ed.), Kodansha/Elsevier (Tokyo/Amsterdam), ***1986***, pp 81-98.



136 **137** **138**

The final definition concerns formation of enantiomers, and the terms enantioselective and enantiospecific are used. If a reaction produces an unequal mixture of enantiomers it is enantioselective. If it generates only one enantiomer of two possibilities it is **enantiospecific**. The baker's yeast reduction (see sec. 4.10.F) of **139** gave **140** with >99% ee (S).[48] (Here **% ee** means percent of **enantiomeric excess**.) A 0% ee means a 50:50 mixture (racemic mixture), 50% ee means a 75:25 mixture and 90% ee means a 95:5 mixture. The predominance of the (*S*) enantiomer makes this reaction highly enantioselective.

139 **140**

The selectivity terms introduced in this section will be used throughout the book for reactions that generate stereoisomers. In addition to % ee, % de (diastereomeric excess, defined in the same way as ee but for diastereomers), or % dr (diastereomeric ratio) will be used throughout.

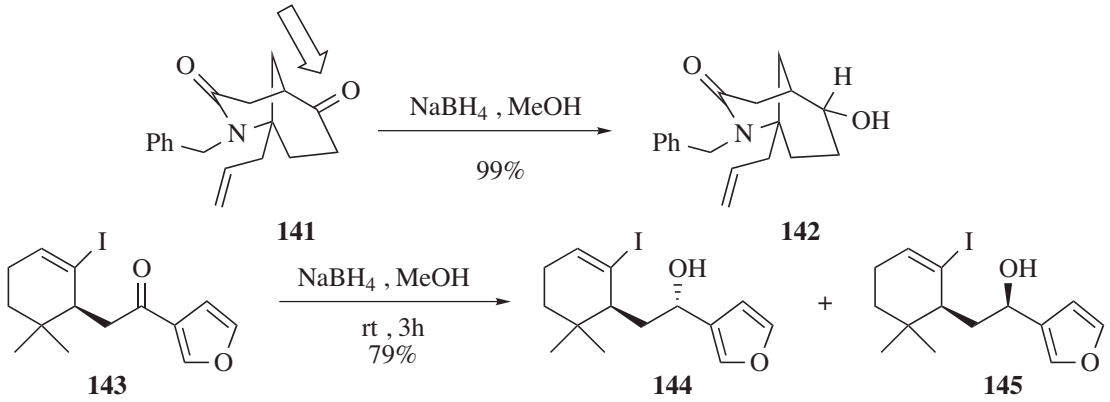
1.5. CONFORMATIONS

Organic molecules can largely be categorized as having tetrahedral, trigonal or digonal (linear) geometry around each sp^3, sp^2, or sp hybridized carbon atom, respectively. When organic molecules absorb energy from the environment they can partially dissipate excess energy by molecular vibrations, including rotation or twisting about all carbon-carbon single bonds. Generally, the more energy absorbed, the more facile will be the rotation. The three dimensional nature of carbon compounds, and rotation around carbon-carbon bonds leads to different spatial orientations of molecules called **rotamers**. Different rotamers are not different structures, but different orientations of the same molecule. Analysis of the spatial relationships of the groups can give information about the interactions of the groups as they rotate around the carbon-carbon bond. Based on these ideas, the shape that a molecule assumes is determined by understanding the rotamer population for all bonds, which leads to the overall shape (conformation) of the molecule. This shape is generally taken as the lowest energy **conformation** of that molecule.. Most molecules have more than one conformation, but one or at least a small subset will constitute the low energy conformation(s). This information is

48. Bolte, J.; Gourcy, J.-G.; Veschambre, H. *Tetrahedron Lett.* ***1986,*** *27*, 565.

used to determine how reagents will approach the molecule, and even the stereochemistry of certain reactions.

When we draw the structure of an acyclic molecule we usually draw the lowest energy rotamer, so we draw it with a regular shape rather than as an amorphous shape. For cyclic and polycyclic molecules the various interactions of the groups will lead to at least one and often several energy minima that are drawn to represent the shape of that molecule. In chemical reactions, the shape of the molecule will influence the way an incoming reagent interacts with it and this can have a significant effect on both reactivity and stereochemical induction, especially with the more rigid cyclic and polycyclic molecules. This section will discuss the fundamental conformational preferences of simple acyclic and cyclic molecules. These principles will be applied throughout the book for discussions of chemoselectivity and stereoselectivity.



An example of the link between conformation and stereochemistry is illustrated with bicyclic ketone **141**, which assumes a rigid structure so that a simple drawing is sufficient to conclude that one face is more encumbered than the other. It is, therefore, possible to anticipate the direction of hydride attack (see sec. 4.4.A) to be from the more open face of the molecule, from the direction of the arrow in **141** as it is drawn to give equatorial alcohol **142** as the only isomer isolated in 99% yield. This reaction was take from the total synthesis of the microbial immunosuppresive agent FR901483, by Weinreb and co-workers.[49] Acyclic molecules are problematic, however, since they do not assume a rigid conformation. They are quite flexible and all but the simplest molecules may exist in a variety of different shapes or conformations. Indeed, the shape of such molecules depends on the torsional angles involving the various single bonds. Generally, it is not possible to say which carbonyl face is likely to be the less crowded in a flexible ketone, and what the stereochemistry of a reaction product will be. The second example using ketone **143** is far more typical, where there are several possible conformations. Each has a different three-dimensional structure with different hindered or exposed regions. When **143**, taken from Jan and Liu's synthesis of (+)-ricciocarpin A, was

49. Kropf, J.E.; Meigh, I.C.; Bebbington, M.W.P.; Weinreb, S.M. *J. Org. Chem.* ***2006****, 71*, 2046.

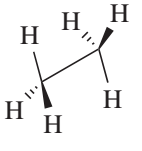
reduced with $NaBH_4$ (sec. 4.4.A), a 1:1.7 mixture of diastereomeric alcohols **144** and **145** was formed.[50] Even this relatively simple molecule shows enough conformational flexibility that a mixture of diastereomers is formed. In sec. 4.7.B, the Cram model and the Felkin-Ahn model will be discussed in order to predict selectivity in acyclic systems. However, both models assume that one key conformation is present in order to make the prediction. Identification of the "relevant" conformer or set of conformers is a necessary first step to anticipate product selectivity, and a conformational analysis is required.

1.5.A. Conformations of Acyclic Molecules

1.5.A.1. Conformations of Simple Alkanes

Different conformers result from rotation about single bonds and also from restricted rotations in rings. The number of different conformers depends on the number of single bonds and on the number and size of the flexible rings. A simple rule of thumb is that each single bond multiplies the number of possible conformers by three. Thus, a molecule with one single bond has three conformers, a molecule with two single bonds has nine conformers, and so forth. It is more difficult to elaborate conformers for flexible rings. Three-membered rings are conformationally rigid and four and (for the most part) five-membered rings can be considered to be rigid. Six-membered rings comprising sp^3 centers typically exhibit two "chair" conformers, although higher-energy "twist-boat" conformers are also possible. Seven-membered and larger rings generally posses an even grater number of conformers. In the final analysis, even a reasonably sized organic molecule can exhibit hundreds to thousands of possible conformations. Thus, identifying the relevant shape cannot be accomplished by simply looking at a single drawing or by simple manipulation of a model.

This section will introduce and illustrate computer-based conformational analysis tools. Properly used, these tools can furnish reliable predictions as to what shapes flexible molecules adopt and, in so doing provide insight into how they are likely to react. We start by introducing important conformational preferences established for organic molecules with only a single degree of conformational freedom. Our treatment relies heavily on data from quantum chemical calculations. This allows more detailed analysis than would otherwise be possible.



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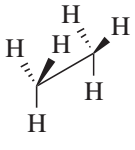

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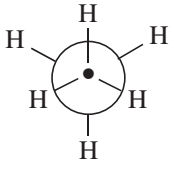

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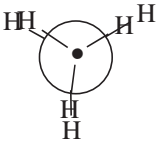


149

50. Jan, N.-W.; Liu, H.-J. *Org. Lett.* ***2006****, 8,* 151.

Ethane is a simple example of an acyclic molecule capable of rotation about two carbon atoms. If one could freeze this motion at different positions, the result would be different rotamers. Inspection of rotamer **146** and its **Newman projection** (the dot and circle model used in **148**)[8] reveals that the C–H bonds and the hydrogen atoms attached to each carbon are as far removed from each other as possible. Rotamer **147** (its Newman projection is **149**) sharply contrasts with **146**, since the C–H bonds and the hydrogen atoms attached to each carbon are as close together as possible. The traditional view is that non-bonded interaction between the two eclipsing hydrogens atoms and the electronic repulsion of the C-H bonds destabilizes this rotamer, making it higher in energy. Indeed, a review categorizes the destabilizing interactions as Pauli exchange steric repulsion, hyperconjugation, and relaxation energy changes.[51] In addition, skeletal relaxation effects play a role.[51] An analysis of ethane shows that the energy depends on the angle of torsion about the carbon-carbon bond. Complete (360°) rotation about the C–C bond (see Fig. 1.3) leads to three identical staggered structures (**146A**) that are energy minima and three identical eclipsed structures (**148A**) that are energy maxima. The difference in energy between the staggered and eclipsed structures is referred to as the barrier to rotation. At ~12 kJ/mol,[52] it is small enough that bond rotation will be very fast at normal temperatures.[53] This means that any measured properties for ethane actually represent an average of properties of the three (identical) conformers. The three (identical) eclipsed structures **148A** do not contribute to the properties of ethane because they do not exist in the sense of contributing to the population.

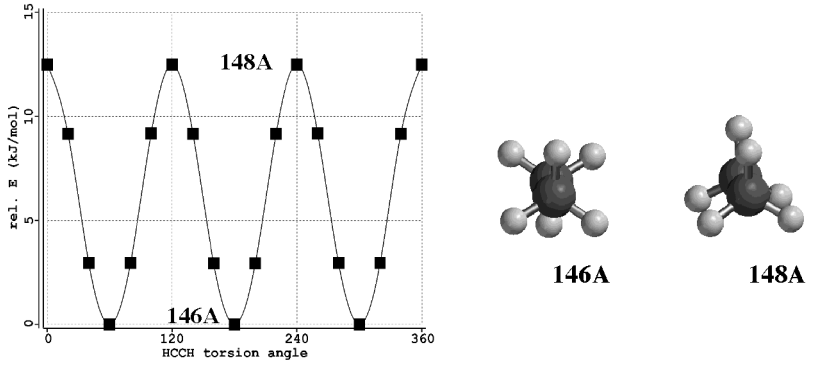
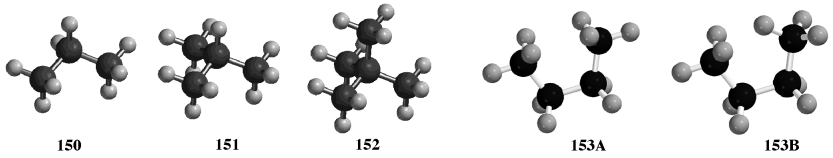


Figure 1.3. Energy barrier for ethane over a rotation of 360°

Propane (**150**), with two identical carbon-carbon bonds, gives rise to nine identical energy minima and nine identical energy maxima. As with ethane, only the minima contribute to the

51. Goodman, L.; Pophristic, V.; Weinhold, F. *Acc. Chem. Res.* ***1999****, 32*, 983.
52. Measured at 2.9 kcal mol^{-1} (12.1 kJ mol^{-1}):. (a) Gunstone, F.D. *Guidebook to Stereochemistry*, Longman, London, ***1975***, p 56; (b) Reference 12, p 599; (c) Reference 29b, p 125 (d) Kagan, H. *Organic Stereochemistry*, Halsted Press/Wiley, New York, ***1979***, p 50; (e) Hine, J. *Physical Organic Chemistry, 2nd Ed.,* McGraw-Hill, New York, ***1962***, p 36.
53. The relative energies of conformers will be expressed in units of kJ mol^{-1}.

properties of the molecule. 2-Methylpropane (**151**) has three identical C–C bonds that give rise to 27 identical sets of energy minima and maxima, and 2,2-dimethylpropane (**152**) has four identical C–C bonds that give rise to 81 identical sets of energy minima and maxima. *Energy plots for all four molecules are identical, except for different rotational barriers.*



Butane has a new structural feature that must be addressed. The C1-C2 and the C3-C4 bonds are identical in terms of their substitution pattern, but the C2–C3 bond is different with each carbon having one methyl and two hydrogen atoms: H_3C—CH_2-CH_2—CH_3 versus H_3C-CH_2—CH_2-CH_3 (see **153A**). Rotation can occur about both C1–C2 and C3–C4, as seen by comparing **153A** and **153B**. Rotation of the central carbon-carbon bond in *n*-butane leads to three energy minima and three energy maxima, as indicated in Fig. 1.4. Two of the minima

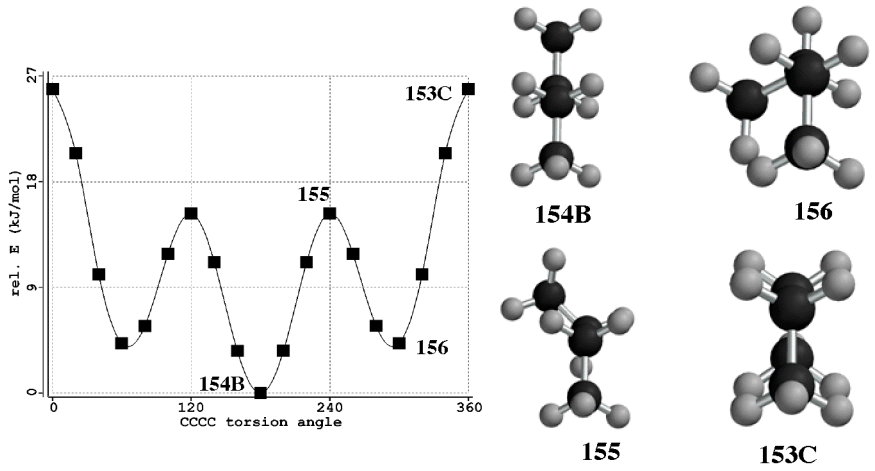


Figure 1.4. Energy barrier for butane over a rotation of 360°

minima (so-called *gauche* conformers) are identical, while the third minimum (the so-called *anti* conformer) is different. Likewise, two of the energy maxima (connecting *gauche* and *anti* minima) are the same, while the third maximum (connecting the two *gauche* minima) is different. The magnitude of the barriers connecting *anti* and *gauche* conformers depends on the direction of rotation (*anti* to *gauche* or *gauche* to *anti*), the difference being the same as the energy difference between *anti* and *gauche n*-butane conformers. The maximum barrier to rotation is estimated to be 4.5-4.9 kcal mol^{-1} (19-21 kJ mol^{-1}),[54] which represents the methyl-

54. (a) Reference 52c; (b) Reference 52a, p 57; (c) Reference 12, p 602; (d) Reference 31b, p 126.

methyl interaction. The other energy barrier represents each Me-H eclipsing interaction and is estimated to be 3.6 kcal mol^{-1} (15 kJ mol^{-1}).[55] The energy estimated for each ***gauche*** conformation is 0.96 kcal mol^{-1} (4 kJ mol^{-1}),[52b] an indication that the methyl groups are close but do not eclipse.

It is possible to categorize butane as a dimethyl substituted ethane. Energy profiles for rotation about the central carbon-carbon bond for a molecule such as 1,2-dichloroethane other disubstituted ethanes are qualitatively similar, in that each shows two *gauche* minima and one *anti* minimum (see Fig. 1.5). The relative energies of *gauche* and *anti* conformers and rotation barriers depend on the substituents. *Anti* conformers are usually preferred over *gauche* arrangements, for example, for 1,2-dichloroethane and for 1-chloropropane (**A** and **B** in Fig. 1.5, respectively). One reason for this preference is a desire to minimize unfavorable non-bonded contacts between the substituents. Another factor in some cases is electrostatics, the desire to align bond dipoles as to minimize the total dipole moment, for example, to align the $^{\delta+}$C-F$^{\delta-}$ bond dipoles in difluoroethane such that they subtract rather than add.

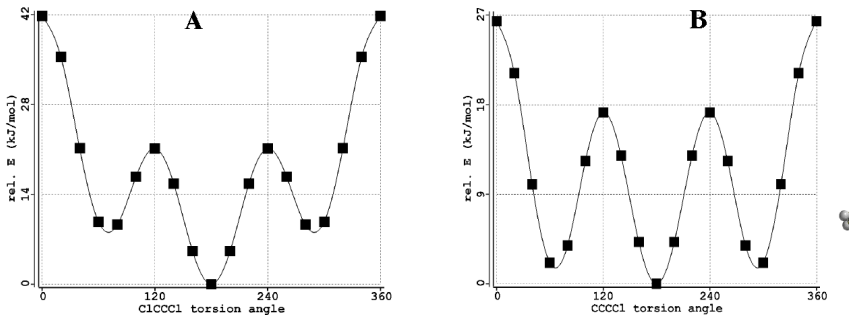


Figure 1.5. Energy barrier for substituted ethanes over a rotation of 360°

1.5.A.2. The Boltzmann Distribution: Average Properties of Flexible Molecules

To obtain the properties of any sample of *n*-butane, it is necessary to average the properties of the *anti* and *gauche* conformers. More generally, to find the average value of a property (**A**) of a flexible molecule, it is necessary to sum over all possible different conformers, taking into account the value of the property for that conformer (**a**) as well as both the number of times that the conformer appears (**n**) and its Boltzmann weight (**W**).

$$\mathbf{A} = \sum \mathbf{a}_i \, \mathbf{n}_i \, \mathbf{W}_i$$

The Boltzmann weight depends on the energy of the conformer relative to the energy of the lowest energy conformer ($\Delta\mathbf{E}$), and on the temperature (**T**): $\mathbf{W_i} = \exp(-\Delta E_i/kT)/\sum\exp(-\Delta E_i/kT)$ where k is the Boltzmann constant. An energy difference of 4 kJ mol^{-1} leads to a Boltzmann

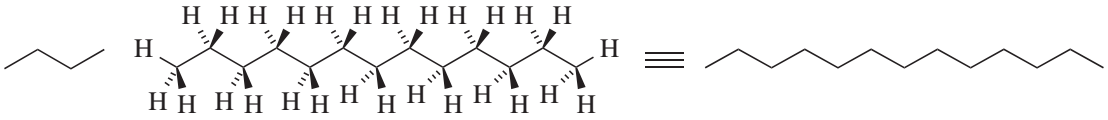
55. (a) Reference 52a, p 57; (b) Reference 52c, pp 48-53.

weight of ~0.1 (10%) at room temperature, an energy difference of 1.9 kcal mol^{-1} (8 kJ mol^{-1}) to a weight of ~0.05 (5%), and a difference of 12 kJ mol^{-1} to a weight of ~0.01 (1%). Only rarely will more a few of the possible conformers have Boltzmann weights in excess of 1% and contribute significantly to the equilibrium. For molecules like ethane and propane where all conformers are the same, the average is independent of temperature. For *n*-butane, where the *anti* and the two equivalent *gauche* conformers contribute, the average depends on temperature. At very low temperatures, the average will be dominated by the lowest energy (*anti*) conformer, but it will limit to an equal weighting of both conformers as the temperature increases.

Note that measurements of some quantities, such as the NMR spectrum, yield averages over possible conformations while others such as the IR spectrum provide information about individual conformers. In the latter case, low Boltzmann weights will almost always preclude actually "seeing" any but the few lowest-energy conformers. Whether a particular measurement yields an average or discrete quantities depends on the time scale of the underlying physical process. Relaxation of magnetic spin (the basis of NMR) is typically slower than conformational equilibrium at normal temperatures, while molecular vibration (the basis of infrared spectroscopy) is much faster. The time scale of the experimental measurement must be established before interpreting the result.

Energy barriers for various molecules are quantified in terms of enthalpy (H°), and calculation of the energy of a given rotamer allows an estimate the relative population of that rotamer (see Boltzmann distribution above). The relative energy of the conformations can be correlated with the relative percentage of each rotamer. An enthalpy difference of 1 kcal mol^{-1} (4.186 kJ mol^{-1}) between the *anti* rotamer and the next most populous rotamer corresponds to the presence of about 72% of the anti-isomer at room temperature.[56] For butane, **154** is the all-anti conformation. The zigzag or extended look to conformation **154** is typically drawn to represent straight-chain alkanes. *n*-Tridecane (**157**), for example, is drawn as the all anti conformation, the extended conformation. Virtually all acyclic hydrocarbon chains are *assumed* to exist primarily in this conformation. This assumption is, of course, incorrect and conformer **157** probably does not exist to a significant extent in a real distribution. The previous discussion establishes that if butane exists in several conformations, the more flexible tridecane will exist in many more and we can use a Boltzmann distribution to estimate the contribution of different conformations. When drawing molecules, we usually draw straight-chain alkanes or alkyl fragments in this fully extended form. In reality, the conformational picture is much more complex and it is unlikely that molecules really look this way. This is a convention that is useful for drawing, but not for an analysis of chemical properties.

56. (a) Reference 31b, pp 131-133.



154 **157**

1.5.A.3. Heteroatom Substituents

Thus far, discussion has concerned rotation about carbon-carbon bonds. The same principles apply to rotation about carbon-heteroatom bonds, particularly carbon-nitrogen and carbon-oxygen bonds. Consider methylamine and methanol. Different examples are methylamine and methanol. The nitrogen in organic amines is sp^3 hybridized. Three of the hybrids form single bonds to other atoms while the fourth hybrid is thought of as a non-bonded pair of electrons (a lone pair). Similarly, the oxygen in alcohols or ethers is sp^3 hybridized. In both cases, two of the hybrids are employed to bond to other atoms, leaving two lone pairs. This implies that both sp^3 nitrogen and oxygen centers are roughly tetrahedral, consistent with the fact that nitrogen centers in amines are pyramidal and oxygen centers in alcohols and ethers are bent. Energy plots for methylamine (**A**) and methanol (**B**) are similar to that for ethane as seen in Fig. 1.6. All show three identical sets of energy minima and maxima. Rotational barriers are somewhat smaller than that in ethane: ~8 kJ mol^{-1} in methylamine and ~4 kJ mol^{-1} in methanol.

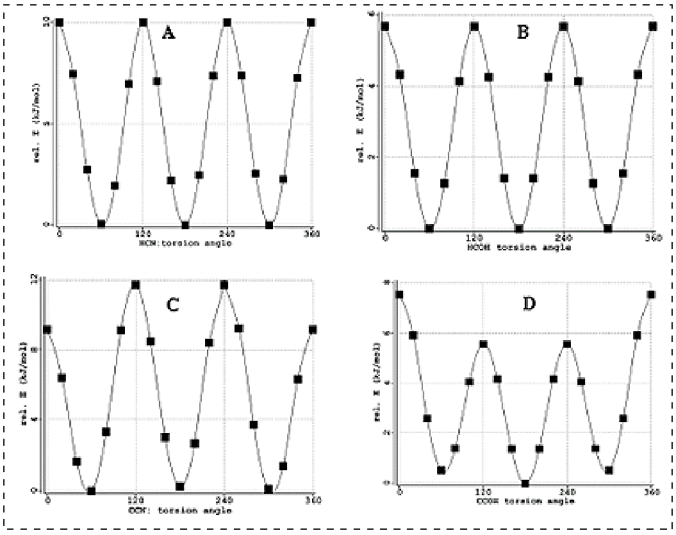
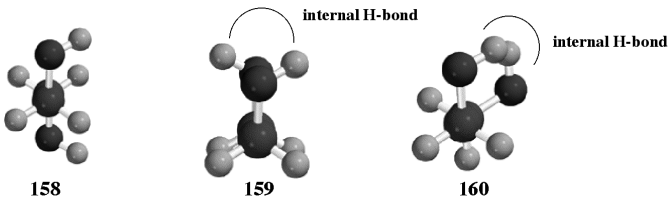


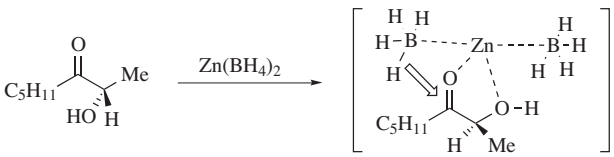
Figure 1.6. Energy barrier for substituted amines, alcohols, and ethers over a rotation of 360°

Substitution of a hydrogen on nitrogen in methylamine to give a secondary amine or on oxygen in methanol to give an ether, does not change the fundamental nature of the energy curves seen for the parent compounds, although it does change the details (energy barriers). On the other

hand, substitution on carbon in both methylamine (to give ethylamine) and methanol (to give ethanol) leads to energy curves which, like that for *n*-butane, show two different minima (**C** for ethylamine in Fig. 1.6 and **D** for ethanol). Note that *anti-gauche* energy differences for both molecules are very small.



Groups capable of hydrogen bonding provide a stabilizing interaction that can compensate for the destabilizing interaction expected by steric repulsion. One can draw both an anti conformation (**158**) and a *syn*-conformation (**159**) for 1,2-ethanediol (ethylene glycol), and the hydroxyl group is capable of hydrogen bonding. Rotating the molecule to the *gauche* conformation **160** relieves the eclipsing interaction but maintains the hydrogen bonding, making **160** the expected low-energy conformation *if no hydrogen-bonding solvent is present*. If the solvent is unable to hydrogen bond with ethylene glycol, the molecule will hydrogen bond with itself as shown. If the solvent can hydrogen bond, intermolecular hydrogen bonding will compete with intramolecular hydrogen bonding, and intermolecular hydrogen bonding will win on the basis of statistics (entropy).



161 **162**

Another way to stabilize an eclipsed or *gauche* conformation is to coordinate a heteroatom substituent with a metal ion (chelation). Oishi and co-worker's reduction of **161** with zinc borohydride proceeds via a chelated species, **162**.[57] Chelation of zinc to the hydroxyl and carbonyl groups effectively immobilizes the reactive components into a single conformation in the transition state required for reaction, as shown in **162**. This fixed conformation sets the position of the methyl and hydrogen at the α-carbon, which leads to facial bias, and the hydride is delivered from the less hindered face over the hydrogen in **162** (see secs. 4.4.B and 4.7.B). Since transition metal salts usually behave as Lewis acids, the presence of a heteroatom that functions as a Lewis base (O, S, N, or P, see sec. 2.3) will lead to chelation. The most favored acyclic conformation is usually a *gauche* or analogous rotamer.

1.5.A.4. Heteroatom-Heteroatom Bonds

Many molecules have heteroatom-heteroatom bonds, such as N-N in hydrazines or O-O in peroxides. The energy profile for hydrazine (**163** in Fig. 1.7) is quite different from those of previous systems, containing two identical minima corresponding to arrangements in which the nitrogen lone pairs are perpendicular, and two different maxima. The higher maximum is ~44 kJ mol^{-1} above the minima and corresponds to an arrangement in which both NH bonds eclipse

57. Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* ***1983****, 26*, 2653.

and the two lone pairs eclipse. The other maximum is only 13 kJ mol^{-1} above the minima and is very broad. It corresponds to a range of conformers centered around a structure in which the two lone pairs are *anti* to each other. Unfavorable lone pair-lone pair interactions are much larger than bond-bond or bond-lone-pair interactions even if the lone pairs point away from each other. The best way to minimize them is to keep the lone pairs perpendicular. Note that the preference due to lone pair interactions is much larger than preferences previously noted due to bond-bond and bond-lone pair interactions. Hydrogen peroxide provides another example of the consequences of interaction of lone pairs. The curve (**164** in Fig. 1.7) shows a pair of identical minima with torsional angles around 120° and 240°. The curve shows two different maxima. The higher is ~40 kJ mol^{-1} above the minima and corresponds to a *syn* conformer (HOOH angle = 0°), while the lower is ~5 kJ mol^{-1} above the minima and corresponds to an *anti* conformer (HOOH angle = 180°). In summary, hydrazine and hydrogen peroxide, like ethane, methylamine and methanol, are both described in terms of a single structure.

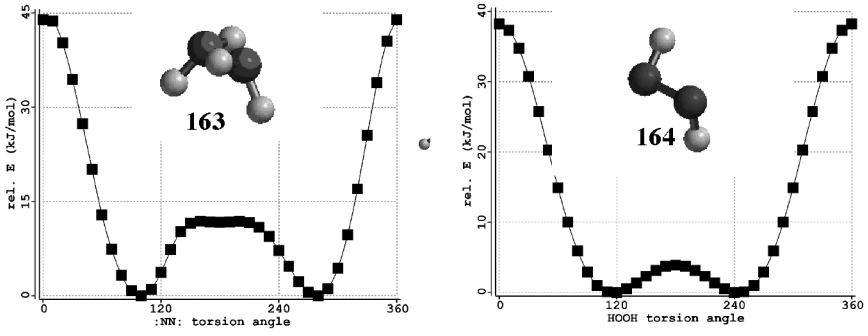


Figure 1.7. Energy barrier for substituted amines, alcohols, and ethers over a rotation of 360°

1.5.A.5. Bonds Connecting sp^3 and sp^2 Hybrids: Propene and 1-Butene

The planar sp^2 carbon atoms in alkenes are relatively easy to distinguish, but what effect does the C=C unit have on the adjacent sp^3–sp^2 bond? A plot of energy versus the C=C-C-H torsional angle in propene (**A** in Fig. 1.8) shows three identical minima and three identical maxima, just like that for ethane. Even the rotation barrier is similar (~8 kJ mol^{-1} in propene versus ~12 kJ mol^{-1} in ethane). However, the methyl group in propene sees a different environment than the methyl group in ethane. If it staggers the vinylic C-H bond, then it must eclipse the C=C unit and vice versa. The minima in propene correspond to arrangements in which one of the methyl C-H bonds eclipse the carbon-carbon double bond but two methyl carbons stagger the alkene C-H bond. The plot for the central carbon-carbon single bond in 1-butene (**B** in Fig. 1.8) closely resembles the corresponding curve for *n*-butane. It shows three minima, two that are identical corresponding to arrangements in which a (methylene) C-H bond eclipses the carbon-carbon double bond, and the third only ~3 kJ mol^{-1} higher in energy in which the C–C

single bond eclipses the double bond. There is a general rule that single bonds eclipse double bonds.

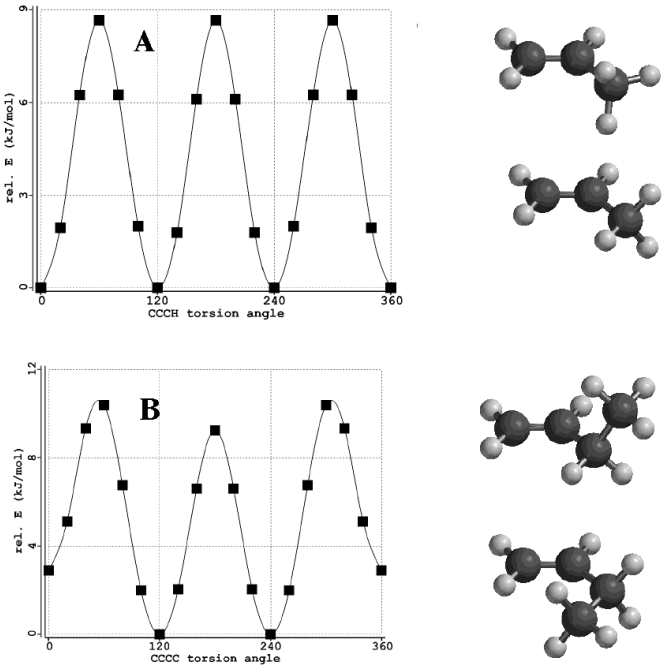
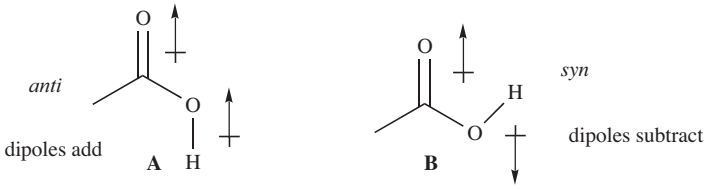


Figure 1.8. Rotation of propene and butene about 360°



Much larger conformational preferences involving single and double bonds can occur. The most conspicuous are the C-O bonds in carboxylic acids and carboxylic acid esters, between sp^2 (carbonyl group) and sp^3 (oxygen) centers. Energy curves for CO bond rotation in acetic acid and in methyl acetate (**A** and **B**, respectively, in Fig. 1.9) both show two minima corresponding to *syn* (O=CCH and O=CCC = 0°) and *anti* (O=CCH and O=CCC = 180°) arrangements, and a pair of identical maxima in between. The *syn* conformer is preferred by nearly 60 kJ mol^{-1} for both molecules. In both conformers, C=O and O-H (O-Me) bonds eclipse but the C=O and C–O bond dipoles subtract in the *syn*-confomer and they add in the *anti*-conformer (see **A** and **B**).

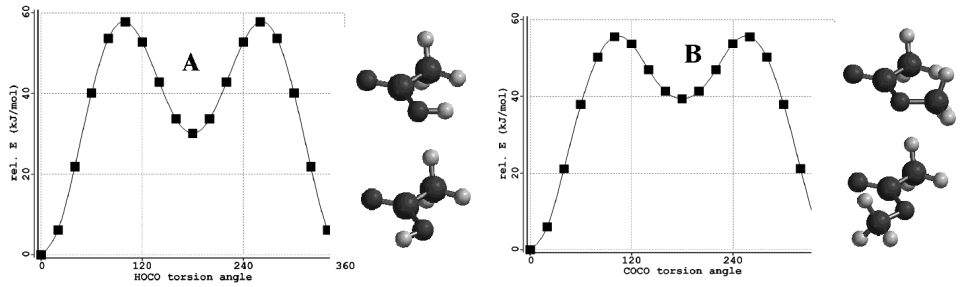


Figure 1.9. Rotation of propene and butene about 360°

1.5.A.6. Bonds Connecting sp^2 Hybrids: 1,3-Butadiene and Styrene

A final case is presented that focuses on the carbon-carbon single bond connecting two sp^2 hybridized atoms, such as those found in conjugated dienes or styrene derivatives. The conventional wisdom is that the two double bonds need to be coplanar in order to maximize "conjugation". While *trans* planar 1,3-butadiene is an energy minimum, the corresponding *cis* planar conformer is not (see **A** in Fig. 1.10). There is an energy minimum nearby (CCCC torsion angle ~40°) that is ~12 kJ mol^{-1} higher than a cis form (an energy maximum), and ~12 kJ mol^{-1} higher in energy than the *trans* form. The energy barrier to rotation about C_2-C_3 has been shown to be 5 kcal mol^{-1} (21 kJ mol^{-1}).[58] The two rotamers mentioned arise by rotation about the C_2-C_3 single bond: **165** with the two π bonds cis- to each other and **166** with the π-bonds trans. Rotamer **165** is called the s-cis conformation, and **166** is the s-trans-conformation. When the diene is substituted, (*E,E*)-, (*Z,E*)- and (*E,Z*)- dienes are possible. The s-cis conformation of (*Z,Z*)-3,5-hexadiene (**167**) is even less favorable than the s-trans conformation (**168)**, when compared with 1,3-butadiene. In **167**, the Me-Me interaction is quite apparent, and although the s-trans conformer (**168**) has two methyl-hydrogen interactions, it is lower in energy than the Me-Me interaction in **167**.

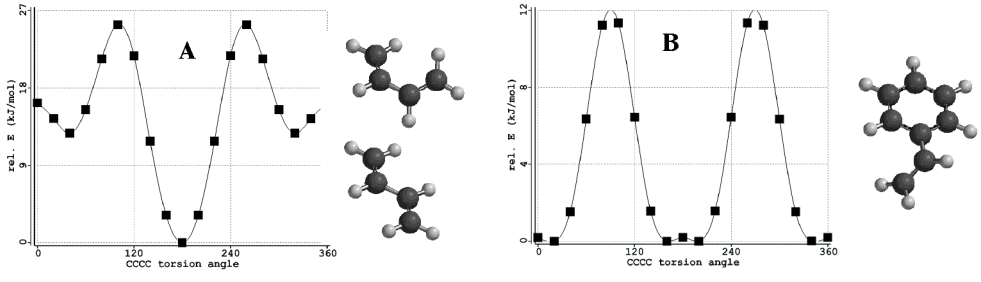
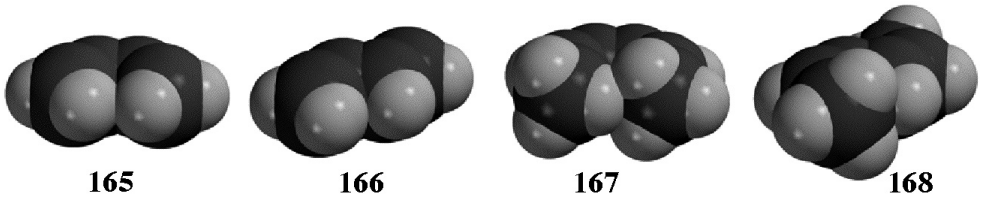


Figure 1.10. Rotation of propene and butene about 360°

58. Reference 52c, p 54.

Similar expectations apply to styrene (see **B** in Fig. 1.10) where there is only one unique conformer. Here the vinyl and phenyl groups are nearly coplanar and the energy barrier through planar styrene is tiny. With the advent of coupling reactions such as the Heck reaction (sec. 12.7.A), such compounds have gained greater importance.



165 **166** **167** **168**

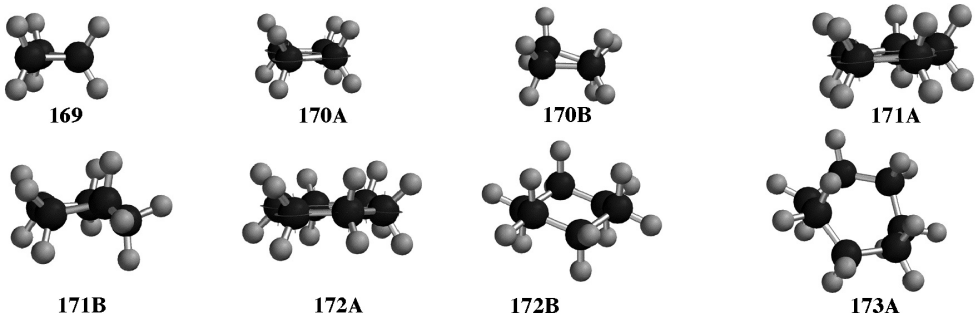
1.5.B. Conformations of Cyclic Molecules

Steric and electronic interactions influence the rotation about bonds within acyclic molecules, leading to a relatively small population of low-energy rotamers. The cyclic nature of these molecules imposes additional energy barriers to conformational mobility relative to acyclic molecules. Although the C–C bonds in cyclic compounds are not capable of complete rotation, they undergo what is known as pseudorotation, largely by twisting and bending around the various carbon-carbon bonds in the ring. Depending on the flexibility of the ring, which is related to the size of the ring, many conformations are possible. As with acyclic compounds, there are usually a small number of low energy conformation that dominate the population.

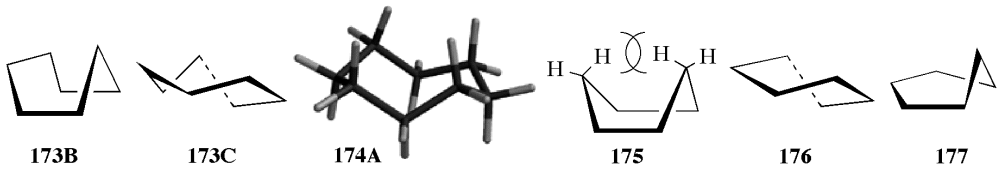
An important difference that is observed in cyclic molecules is deformation of the bond angles from 109°28' as the molecule attempts to rotate around the C-C bonds, which can be severe when the ring is small. Cyclopropane, for example, has a C-C-C bond angle of ~ 60° (see **169**) which induces great strain in the molecule. This type of strain is called **Baeyer** or **angle strain**, formally defined as the increase in energy of cyclic compounds that arises from the deformation of the optimum valence angle of 109°28' for sp^3 carbon or 120° for sp^2 carbon. The higher ground state energy for cyclopropane is the result of such strain. Formation of three-membered rings is common, but the higher ground state energy is important in the reactions of cyclopropane as well as those that form cyclopropanes.[58] Deformation of the σ bonds leads to significant p character (the hybridization is $Csp^{2\cdot3}$), and many ring-opening reactions of cyclopropane mimic the chemistry of alkenes. The increased p-character is reflected in the diminished electron density of the C–C bonds in cyclopropane, which is slightly displaced from linearity between the nuclei.[59] The four-carbon cyclic compound is cyclobutane (see **170**) with bond angles of ~90°, and in planar cyclopentane (**171A**) with bond angles of ~108°. Cyclobutane has significant Baeyer strain, less than in cyclopropane but more than in cyclopentane.

59. (a) Bernett, W.A. *J. Chem. Educ.* ***1967****, 44*, 17; (b) de Meijere, A. *Angew. Chem. Int. Ed.* ***1979****, 18,* 809; (c) Reference 12, pp 676-678; (d) Reference 31b, pp 204-306 and 124-179.

Cyclopropane (**169**), planar cyclobutane (**170A**) and planar cyclopentane (**171A**) exhibit a second major type of strain, which is the same as that seen in acyclic molecules. All C-H bonds in these planar molecules are eclipsed, with severe nonbonded interactions of the eclipsed hydrogens and electronic repulsion of the eclipsed bonds. This type of strain is called **Pitzer** or **bond opposition strain** and is defined as the increase in energy for a compound arising when adjacent bonds are eclipsed, bringing the attached atoms into close spatial proximity. Cyclic molecules generally do not exist in the planar form due to the Pitzer strain. Although rotation of 360° about the C-C bonds is not possible, twisting and bending is possible via partial rotation (pseudorotation) to minimize Pitzer strain.[59] One or two low-energy conformations are usually drawn to represent the entire molecule, although as the ring becomes larger and the flexibility increases more low energy conformations are possible. For cyclobutane, a bent or puckered conformation (**170B**) is taken as the low energy conformation,[60] which minimizes Baeyer strain relative to the planar form (**170A**).[61] For cyclopentane, the bent conformation assumes an envelope shape as in **171B**.[61] Although Baeyer strain is increased in the envelope conformation (**171B**) relative to the planar form (**171A**),[62] the decrease in Pitzer strain more than compensates and **171B** is the low-energy conformation of cyclopentane. Analysis of planar cyclohexane (**172A**) reveals extensive Pitzer strain and the bond angles would be 120°, introducing Baeyer strain. Pseudorotation leads to the familiar chair conformation (**172B**) as the low energy conformation. Chair cyclohexane has virtually no Baeyer strain with bond angles of 109°28'. Cycloheptane has similar bond angles[63] but is more flexible, and there are several low energy conformations, although only **173A** is shown. Cycloheptane also has a boatform (**173B**) that is very close in energy to a chair form **173A**.[64] The lowest energy form of cycloheptane, however, is the twist-chair conformation, **173C**.[65]



60. (a) Reference 12, p 676; (b) Reference 31b, p 248.
61. (a) Dunitz, J.D.; Schomaker, V. *J. Chem. Phys.* ***1952****, 20,* 1703; (b) Rathjens, Jr., G.W.; Freeman, N.K.; Gwinn, W.D.; Pitzer, K.S. *J. Am. Chem. Soc.* ***1953****, 75*, 5634.
62. Kilpatrick, J.E.; Pitzer, K.S.; Spitzer, R. *J. Am. Chem. Soc.* ***1947****, 69*, 2483.
63. (a) Reference 12, pp 686-689; (b) Reference 29b, p 252.
64. Allinger, N.L. *J. Am. Chem. Soc.* ***1959****, 81,* 5727.
65. Wiberg, K.B. *J. Org. Chem.* ***2003****, 68,* 9322.



As mentioned, cyclohexane is known to favor a "chair" structure in which all six carbons are equivalent but the hydrogens divide into two sets of six *equatorial* hydrogens and six *axial* hydrogens, marked in **178**. However, the fact that only one proton resonance is seen in its room temperature NMR spectrum suggests a rapid conformation change in which *equatorial* and *axial* hydrogens exchange. An energy profile for the process (Fig.1.11) shows the two identical chair structures as the starting and ending points, respectively, marked **178** and **179**. There is a boat conformation (**175**), as well as two identical higher-energy "twist-boat" minima (**176**). In **175**, there is a cross ring (**transannular**) interaction of the 1,4-hydrogens (referred to as flagpole hydrogens). The curve contains three energy maxima. Two are identical "half chairs" (**177**) and connect the chair a twist boat forms, while the boat (**175**) connects the two twist-boat forms.

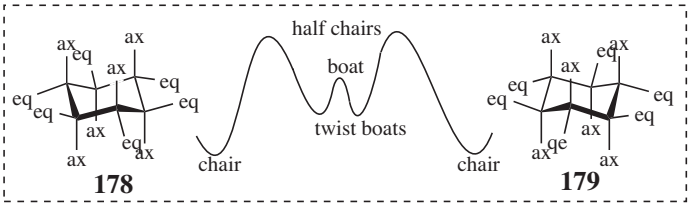
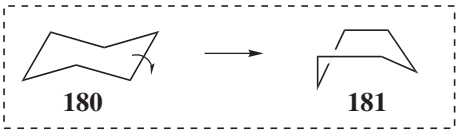


Figure. 1.11. Conformational mobility of cyclohexane.



Chair cyclohexane is ~28 kJ mol^{-1} lower in energy than the twist-boat (or just twist) conformation, suggesting that the latter will have little influence on the properties of cyclohexane. It is not possible to attach a simple label to the geometrical coordinate in Fig. 1.11 responsible for this process. However, interconversion of chair cyclohexane into the twist-boat form can be viewed as a restricted rotation about one of the ring bonds (see **180** to **181**). Correspondingly, the interconversion of the twist-boat intermediate into the other chair form can be viewed as rotation about the opposite ring bond.

The molecular conformations induced by relief of Baeyer strain and Pitzer strain are reflected in the energy required for intramolecular cyclization reactions to form each ring. As two reactive ends of the acyclic fragment come together, the strain inherent to the ring product becomes important (see sec. 6.6.B.i). In other words, the acyclic precursor assumes the conformation of the ring that is being formed in the transition state of the reaction. Strain in this transition state is important for the formation of the cyclic product. Figure 1.12(a) shows the relative

reactivity for formation of lactones from ω-hydroxy acids of ring size C3 to C17.[66] There is a reactivity maximum at C5 and reactivity minima at C3 and C8.[66] Figure 1.12(b) shows the enthalpy (ΔH) of several cyclic alkanes, with a minimum at C6 and a maximum at C9.[67] There are two other important features of Figure 1.12 (b). Rings of C8-C13 members are significantly higher in energy than the small rings (C3 → C7) or the large rings (≥ C14). These medium size rings are extremely difficult to form using intramolecular cyclization.[66] The other feature of Figure 1.12(b) is the higher energy required to form rings with an odd number of atoms when compared to the energy required to form rings with an even number of atoms. Compare cyclohexane and cycloheptane to see the difference. Cycloheptane has an odd carbon that is not easily accommodated by the low-energy chair (all *gauche*) form, and its presence leads to an increase in Pitzer strain.[67,66] Similar effects are seen for all odd carbon rings.

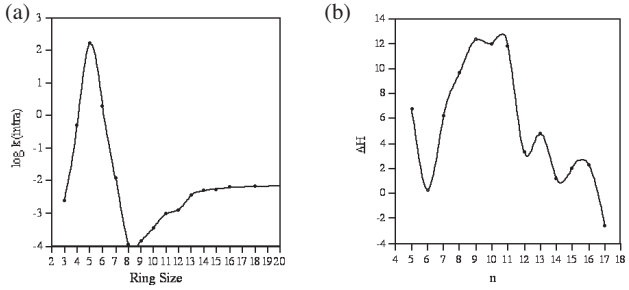
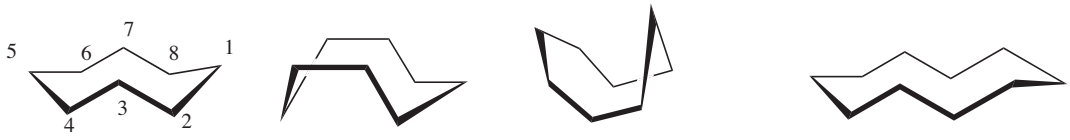


Figure 1.12. (a) Reactivity Profile for Lactone Formation. (b) Enthalpy of Cycloalkanes [CnH2n]. [Reprinted with permission from Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95. Copyright © 1981 American Chemical Society.]

As the ring size increases to eight members and higher, increased flexibility leads to an increasing number of lower energy conformations. Indeed, an inspection of cyclooctane reveals there are several conformations, including **174B** (crown), **174C** (boat-chair), a boat-boat conformation (**174D**)[68,64] as well as twist-boat-chair and twist chair-chair conformations.[69] These latter conformations are higher in energy than the crown (**174B**).[70] Wiberg used calculations to show that the boat-chair is the lowest energy conformer, with the twist boat-chair, twist chair-chair and the crown as the next higher energy conformations.[64] The boat-boat conformation is relatively high in energy.[64] A crown conformation is observed for cyclodecane, **182A**,[67b,71]

66. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* ***1981,*** *14*, 95. Also see Ref. 12, p 680.
67. Also see (a) Dunitz, J.D.; Prelog, V.P *Angew. Chem.* ***1960,*** *72*, 896; (b) Prelog, V. in *Perspectives in Organic Chemistry*, Todd, A.R. (Ed.), Interscience, New York, ***1956***, p 96.
68. Bellis, H.E.; Slowinski, E.J. *Spectrochim. Acta* ***1959,*** *15*, 1103;
69. Pauncz, R.; Ginsburg, D. *Tetrahedron* ***1960,*** *9*, 40.
70. (a) Reference 12, pp 765-766; (b) Reference 31b, p 253; (c) Allinger, N.L.; Hu, S. *J. Am. Chem. Soc.* ***1961,*** *83,* 1664.
71. Prelog, V. J. Chem. Soc. 1950, 420.



174B **174C** **174D** **182A**

which conforms to the same extended chair conformation found in diamond (see Fig. 1.13). Crown-cyclodecane[64] fits on this diamond lattice[68] and it is usually taken as an important low energy conformation. The odd-membered ring in cyclononane shows a twist, also found in cycloheptane when compared to chair cyclohexane[60] and a slight increase in Pitzer strain. As seen in Figure 1.5, the twist in crown-like cyclononane makes it unable to superimpose on the diamond lattice. Even large rings such as cyclooctadecane can show this chair-like or crown-like conformation in a low energy form.

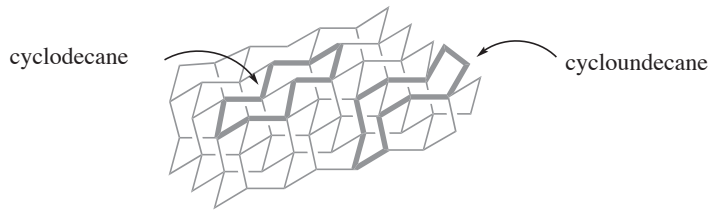
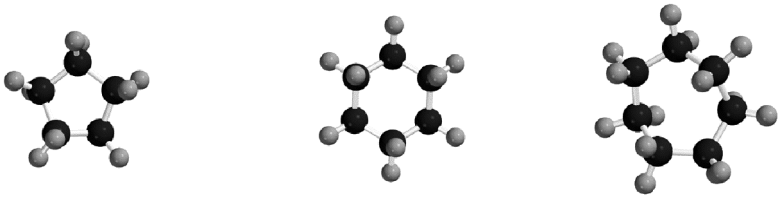


Figure 1.13. Cyclodecane and Cycloundecane on a Diamond Lattice.

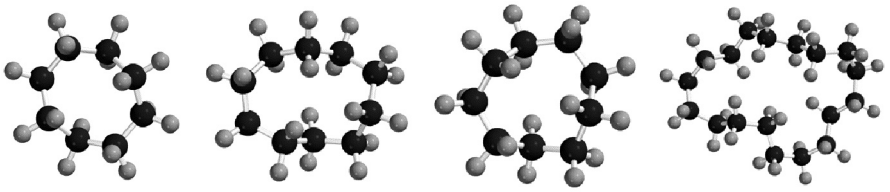
Another type of strain that is found in large ring compounds must be introduced To better see this interaction, models of cyclopentane-cyclooctadecane are shown looking down on the top of each ring, exposing a cavity in the center of each ring. If the conformation of a ring brings atoms in close proximity, *within the cavity of the ring*, this is known as a **transannular interaction**.[66] Hydrogen atoms do not intrude into the internal cavities of envelope cyclopentane (**171C**) or chair cyclohexane (see **172C**), so there are no transannular interactions. In cycloheptane (see **173D**), two of the hydrogen atoms can move into positions that are slightly within the cavity,



171C **172C** **173D**

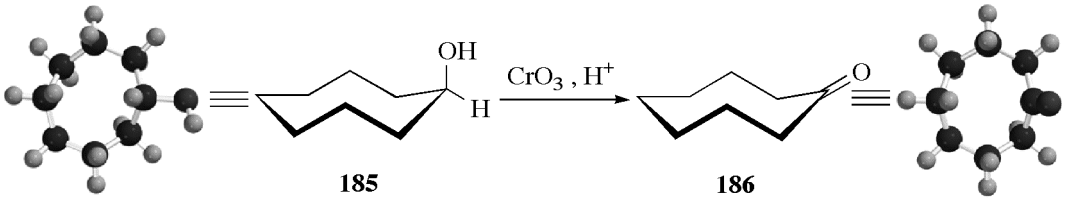
contributing to modest transannular strain and partially accounting for the higher energy of cycloheptane. In crown-cyclooctane (**174E**), pseudorotation moves hydrogen atoms that are on opposite sides of the ring into the cavity, contributing to a significant transannular interaction, and a significant increase in the inherent energy for that ring. There is also significant transannular

strain in cyclononane (**183**) and crown-cyclodecane (**182B**). As the ring size increases, the cavity becomes larger, and the net energy decreases after reaching a maximum at cyclodecane. Although the potential for a transannular interaction is quite high in cyclooctadecane (**184**), the large cavity and increased flexibility allow the transannular hydrogens to sweep past each other upon pseudorotation. The cavity inside the ring is large enough to accommodate these atoms without generating a large energy gradient.



174D **182B** **183** **184**

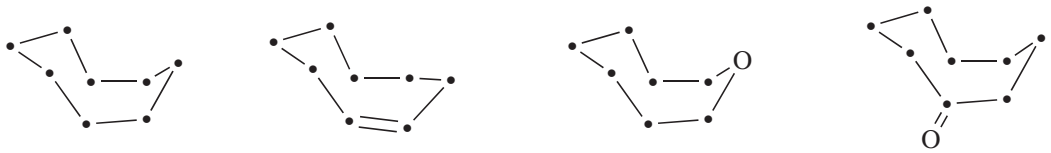
As shown above, the higher energy of medium size rings results from unfavorable dihedral angles.[71] This type of strain has been termed ***I-strain*** (internal strain).[72] Formally, *I strain* involves the change in strain when going from a tetrahedral to a trigonal carbon or vice versa (as in changing an alcohol to a ketone). For medium-size rings, tetrahedral bond angles bring the transannular substituents into close proximity. Conversion to a trigonal planar carbon relieves this interaction somewhat and lowers the energy of the system.[73] An example is the oxidation of cyclooctanol (**185**) to cyclooctanone (**186**, see sec. 3.2.A). The reverse process (the reduction, see secs. 4.2.B, 4.8.C, 4.9.B: **186 ® 185**) is more difficult due to the increased *I* strain as well as increased transannular strain in the alcohol.[74]



185 **186**

The presence of a heteroatom, a C=C unit, or a carbonyl influences the conformation of medium-size rings, but the changes are often subtle. The calculated low-energy conformation of cyclooctane (**187**) is compared with those of *cis*-cyclooctene (**188**), the ether oxocane (**189**) and cyclooctanone (**190**). Although **188** is somewhat flattened, the conformations of the other three eight-membered rings are rather similar.[75]

72. (a) Brown, H.C.; Fletcher, R.S.; Johannesen, R.B. *J. Am. Chem. Soc.* ***1951***, *73*, 212; (b) Brown, H.C.; Borkowski, M. *Ibid* ***1952***, *74*, 1894.
73. Prelog, V. *Bull. Chim. Soc. Fr.* ***1960***, 1433.
74. Reference 31b, pp 266-269.
75. Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4586.



187 **188** **189** **190**

Estimating the conformations of large ring compounds (macrocycles) is more complicated, and more difficult than with compounds discussed in the section 1.4. Since this class of compounds includes macrolide antibiotics,[76a] important commercial products such as muscone and also crown ethers,[76b] there is a great deal of interest in macrocycles.[76] Both the chemical and physical properties of macrocycles depend on the conformations of the large ring.[77] An analysis of conformations of small and medium ring compounds was reported that used an analysis of the sign of torsional angles,[78] and when combined with the use of dihedral maps.[79] Weiler[80] produced a **polar map analysis** of macrocycles that yielded conformational information. This method has also been applied to the conformational analysis of macrocyclic ethers.[81] Another way to represent this conformation is based on Dale's numerical system describing the number of bonds found between corner atoms.[82c] Dale's system is sometimes called **wedge notation**.[83] Unfortunately, calculations can be difficult, and the method does not seem to be widely used. The system is based on the idea that even-membered rings can exist in four quadrangular (four-cornered system) conformations (see **191**). (*1*) All four sides contain an odd number of bonds (*a*-*d* = odd). (*2*) Two adjacent sides are odd with the others even (*ab* odd, *cd* even; or *bc* odd, *ad* even). (*3*) Two adjacent sides are odd with the others even (*ac* odd, *bd* even; or bd odd, ac even). (*4*) All sides contain an even number of bonds ($a \rightarrow d$ = even). For odd membered rings, the best conformation arises when there are three (a triangular system) or five corners (a quinguangular system). When there are three corners all three sets can be odd, or two can be even with one odd and one side must have one or more convex faces. For five corners, all can be odd, two adjacent or next to adjacent can be even with the other three odd, or one can be odd and four even, so there must be one or more concave faces.

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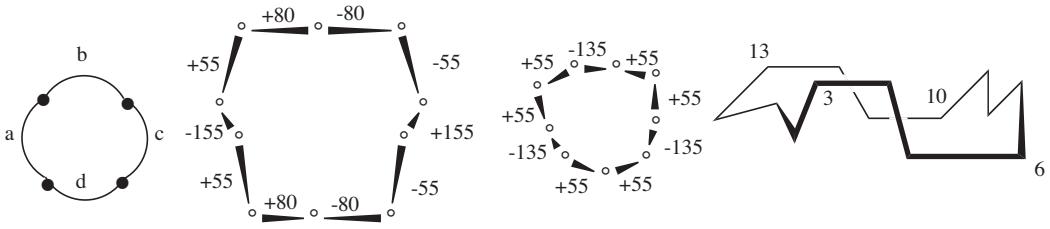
76. (a) Paterson, I.; Mansuri, M.M. *Tetrahedron* ***1985***, *41*, 3568; (b) Hayward, R.C. Chem. Soc. Rev. 1983, 12, 285; (c) Still, W.C.; Galynker, I. *Tetrahedron* ***1981***, *37*, 3981 and references cited therein.
77. (a) Dale, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 1000; (b) Idem *Top Stereochem.* ***1976***, *9*, 199; (c) Idem *Acta Chem. Scand.* ***1973***, *27*, 1115.
78. (a) Bucourt, R. *Top Stereochem.* ***1974***, *8*, 159; (b) DeClerq, P.J. *Tetrahedron* ***1984***, *40*, 3729; (c) Idem *Ibid* ***1981***, *37*, 4277; (d) Toromanoff, E. *Ibid* ***1980***, *36*, 2809.
79. Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* ***1978***, *100*, 6733.
80. (a) Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* ***1987***, *64*, 568; (b) Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* ***1988***, *110*, 7858.
81. Clyne, D.S.; Weiler, L. *Tetrahedron* ***2000***, *56*, 1281.
82. (a) Dale, J. *Acta Chem. Scand.* ***1973***, *27*, 1115, 1130; (b) Dale, J. *Acta Chem. Scand.* ***1973***, *27*, 1149; (c) Björnstad, S.L.; Borgen, G.; Dale, J.; Gaupset, G. *Acta Chem. Scand. Ser. B* ***1975***, *B29*, 320.
83. Reference 12, pp 763-764, 766-769.



191 **192** **193** **194**

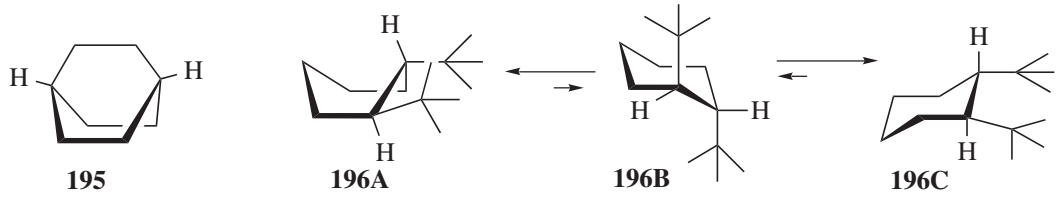
The actual notation is illustrated for the diamond form of cyclodecane, **192** (see Fig. 1.13). The dihedral angles were measured from a Dreiding Model™ (this can also be done with appropriate computer software), and the corners determined for a given conformation. For **192**, those angles for the four corners are +55/+80 and -55/-80. This method takes the number of bonds on each side, starting with the short side and gives the lowest possible combination of numbers. For **192**, there are 2, 3, 2 and 3 bonds, respectively, and this is [2323]-decane. Nonane has an odd number of atoms, and has three corners. Conformation **193** represents nonane and it has three corners with angles determined to be +55/+55, leading to the notation [333]nonane. For cyclotetradecane, the lowest energy conformation is **194**, the [3434] conformation. When substituents are attached to large rings, they tend to occupy only exterior positions to minimize the large transannular interactions.[84] A fully substituted atom of a macrocycle will usually occupy a corner position since this is the only position where it does not cause severe transannular strain.[82] For both substituted and unsubstituted macrocycles, the conformation of the ring will impose restraints on the torsional angles available to each unit of carbons (four carbons define a torsional angle). The use of polar maps of torsional angles may be of value for determining the conformation of many macrocyclic compounds. Fourteen-membered 3-keto lactones, for example, have been synthesized and their conformations analyzed using this technique.[85] This ability to predict conformational bias is important to the stereochemical outcome of chemical reactions involving macrocyclic rings.

1.5.C. Estimating Conformational Populations

The preceding discussion focused on a low-energy conformation of several ring compounds, but in fact there may be several conformations for each ring that lie close together in energy. To obtain a complete picture several conformations of equal, close, or higher energy must be considered. The conformational mobility of cyclohexane includes, for example, the two low-energy chair conformations, six degenerate twist-boat conformations, and six degenerate

84. Dale, J. *Stereochemistry and Conformational Analysis*, Verlag-Chemie, New York, ***1978***.
85. Neeland, E.G.; Ounsworth, J.P.; Sims, R.J.; Weiler, L. *J. Org. Chem.* ***1994, 59***, 7383.

boat conformations.[86,87] If all the energies for the various conformations are known, it should be possible to estimate the percent of each. Since the chair conformation usually constitutes the majority of this conformer population, a typical assumption is usually be made to ignore the other conformations for an initial estimation. Building cyclohexane using Spartan and minimizing the structure will generate a chair cyclohexane. Eliel et al.[88] estimated that the energy difference between the boat and chair forms is about 4 kcal mol^{-1} (16 kJ mol^{-1}), which means "only one molecule in a thousand will be in the boat form" at 298 K (25°C). Note that the boat form exists in certain bridged cyclohexane molecules such as bicyclo[2.2.2]-octane (**195**) which is all boat, or it may be forced on the ring by bulky substituents (e.g., *trans*-1,2-di-*tert*-butylcyclohexane) which contains about 12% of the boat **196A**.[88,89]



195 **196A** **196B** **196C**

The discussions of cyclohexane given above have made it clear that the chair conformations are lower in energy. The boat and two chair conformations are shown for **196** (trans-1,2-di-*tert*-butylcyclohexane). It is clear that there are significant steric interactions in the boat (**191A**) because the two *tert*-butyl groups are in close proximity, whereas in the diaxial chair (**196B**) those groups are on opposite sides of the ring. Interestingly, the interaction of the *tert*-butyl groups is somewhat relieved in the twist-boat conformation, which exists alongside the more stable **196A**,[88] but the structures shown indicate that **196C** (the *tert*-butyl groups are both equatorial) is lower in energy than **196B** (the *tert*-butyl groups are both axial). Why is **196B** higher in energy than **196C**, and why is the low energy form the boat conformation **196A** or the twist-boat conformation mentioned? The answer reveals two major sources of strain in chair cyclohexanes, which have both axial and equatorial bonds (see **178** and **179**). In cyclohexane, this interaction of the axial hydrogen atoms on either side of the ring is minimal because hydrogen atoms are relatively small as seen in the space filling model **172D**. Replacing the hydrogen atoms in the axial positions with substituents leads to competition for the space above and below the ring, giving rise to a transannular interaction (***A* strain**, or ***$A^{1,3}$*-strain**, a **1,3-diaxial interaction**, see Fig. 1.14). When one hydrogen is replaced with a methyl group (methylcyclohexane, **197**), the interaction between methyl and hydrogen is

86. (a) Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd Ed.,* Harper and Row, New York, ***1987***, p 141; (b) Squillacote, M.; Sheriden, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc. **1975**, 97,* 3244; (c) Hirsch, J.A. *Concepts in Theoretical Organic Chemistry*, Allyn and Bacon, Boston, ***1974***, pp 249-252.
87. Barton, D.H.R. *Experientia **1950**, 6*, 316.
88. van de Graaf, B.; Baas, J.M.A.; Wepster, B.M. *Recueil Trav. Chim. Pays-Bas **1978**, 97,* 286.
89. Allinger, N.L.; Freiberg, L.A. *J. Am. Chem. Soc. **1960**, 82,* 2393.

greater, making the transannular interaction much higher in energy relative to the hydrogen-hydrogen interaction of cyclohexane. ***This is $A^{1,3}$ strain.*** In 1,3-dimethylcyclohexane (**198**) and in 1,3,5-trimethylcyclohexane (**199**) $A^{1,3}$-strain increases significantly as the steric interactions increase. This $A^{1,3}$-strain destabilizes the conformations with the axial substituents, shifting the equilibrium to the lower energy chair form that has the substituents in the equatorial position. Returning to **196B**, it is clear that each axial *tert*-butyl group will interact with the two axial hydrogen atoms on its side of the ring, leading to significant $A^{1,3}$-strain) estimated to be about 12 kcal mol^{-1} (50.2 kJ mol^{-1}) or 6 kcal/*tert*-butyl group.[90] There is no question that the equilibrium for the two chair conformations will shift to favor the chair with the two *tert*-butyl groups in the equatorial position, effectively eliminating the $A^{1,3}$-strain.

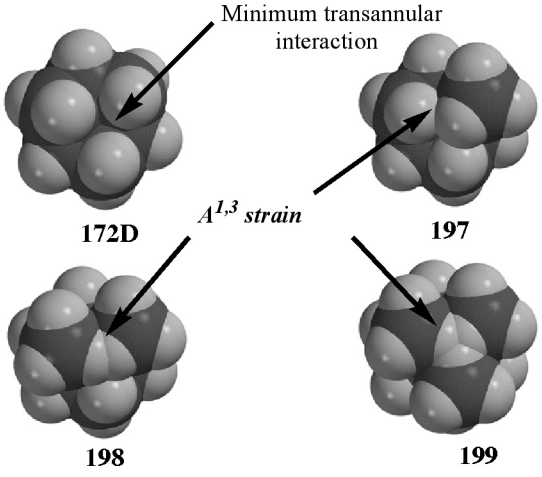


Figure 1.14. $A^{1,3}$ Strain in Cyclohexane, Methylcyclohexanes.

Closer inspection of **196C** reveals that $A^{1,3}$-strain has been eliminated but the 1,2-diequatorial *tert*-butyl groups are in close proximity, producing a new type of strain called ***G* strain**. The energy of the interaction (the ***G* value**)[91] is 2.5 kcal mol^{-1} (10.47 kJ mol^{-1}), per *tert*-butyl group (see Fig. 1.15). This type of steric interaction is analogous to the interactions found in the *gauche* butane conformation, and is often referred to as a *gauche* interaction. If we take cyclohexane as a model the trans-diequatorial hydrogens in **172**E show little interaction, but replacing them with methyl (see *trans*-1,2-dimethylcyclohexane, **200**) causes significant *G*-strain. When the two *tert*-butyl groups in **196** are trans-diequatorial (see **196C**), the interaction is very large and destabilizes that conformation. If both chair conformations have high energy interactions, the molecule will distort to minimizes these interaction, and **196** exists largely in either the boat or the twist-boat.

90. Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955,*** *77*, 5562.
91. Corey, E.J.; Feiner, N.F. *J. Org. Chem.* ***1980,*** *45,* 765.

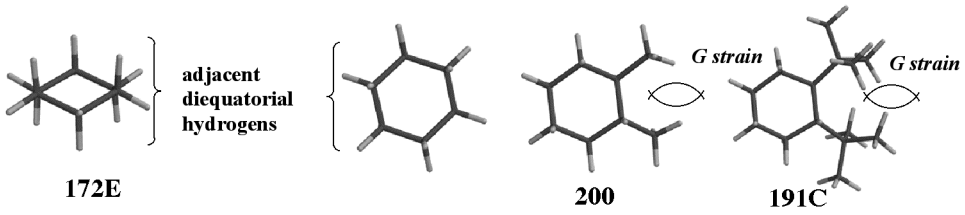
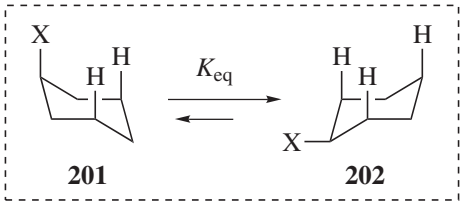


Figure 1.15. *G* Strain in 1,2-Dimethylcyclohexane and 1,2-Di-*tert*-butylcyclohexane.

Why are these physical chemistry concepts being discussed in a reactions-synthesis book? It will be apparent throughout this book that the conformation of a molecule has a critical effect on the reactivity and stereochemistry of many reactions. Strain energies that influence the conformation of a molecule can be quantified in some cases, and the percentage of each conformation can be calculated. With such information we can make more reasonable predictions of reactivity and stereochemistry. The following protocols are presented in an attempt to reinforce the idea that conformational analysis is a critical part of synthetic analysis, and to introduce the most basic approaches to conformational analysis.

We will focus on cyclohexane derivatives to illustrate the fundamental idea. When a reagent approaches a cyclohexane ring, the conformation of the ring will influence how the reagent interacts with any functional group on that ring. The populations of the two chair conformations can influence the relative rate and the stereochemical outcome of a given reaction. The relative populations of both chair conformations in cyclohexane derivatives can be predicted with some accuracy by calculating the *A* and/or *G* values. For a monosubstituted cyclohexane, two chair forms are possible (**201** and **202**) and they are in a dynamic equilibrium. If X ≠ H, the diaxial steric interaction (*A* strain) in **201** will be larger than in **202** and a higher percentage of **202** is expected. This non-bonded interaction can be measured in terms of *F*°, the conformational free energy.[92] Since there are two conformations of differing energies, this difference is represented by ($\Delta F°$),[86a] and it is possible to relate this energy term to the free energy of the system by: $\Delta G° = \Delta H° - T\Delta S°$. For a given temperature, the entropy term will be small relative to $\Delta F°$ (taken to be $\Delta H°$ hereafter) and a second assumption can be made, that $\Delta S° = 0$, leading to $\Delta G° \approx \Delta H°$.



The $\Delta S°$ term is not zero, but is usually measured in calories (J) and the $\Delta H°$ term in kilocalories (KJ), so ignoring $\Delta S°$ will introduce only a small error into the calculation. Lowry and

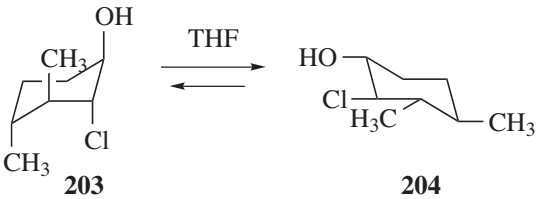
92. (a) Eliel, E.L. *J. Chem. Educ.* ***1960****, 37*, 126; (b) Reference 12, pp 694-698; (c) Reference 31b, pp 234-239; (d) Reference 86a, pp 138-140; (e) Hammett, L.P. *J. Am. Chem. Soc.* ***1937****, 59*, 96; (f) Hammett, L.P. *Physical Organic Chemistry, 2nd Ed.,* McGraw-Hill, New York, ***1970***, p 347ff; (g) Jaffé, H.H. *Chem. Rev.* ***1953****, 53,* 191; (h) Hansch, C.; Leo, A.J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, ***1979***; (i) Reference 12, p 654.

Richardson's[93] list of $\Delta H°$ and $S°_{298}$ values for a variety of specific bonds demonstrates this difference. In the C- Me bond, for example, $\Delta H°$ is -10.08 kcal mol^{-1} (42.2 kJ mol^{-1}) and $S°_{298}$ is 30.4 cal mol^{-1} (127.2 J mol^{-1}). Similarly, $\Delta H°$ for cyclopropane is listed as 27.6 kcal mol^{-1} (115.5 kJ mol^{-1}) and $S°_{298}$ is 32.1 cal mol^{-1} (134.3 J mol^{-1}).[93]

The $\Delta H°$ term is related to $\Delta G°$, the free energy, which is related to the equilibrium constant by the expression: $\Delta G° = -2.303$ RT log K_{eq}. The conformational equilibrium between **201** and **202** is represented by K_{eq}, which can be calculated from the percentage of the two conformers: K_{eq} = % 202 / % 201, where % **201** + % **202** = 100%. Note that a general discussion of the Curtin-Hammett principle[92c-f] (product composition is related to the relative concentrations of the conformers)[92i] may be of value in any discussion of this equilibrium reaction.

For this process to work, some estimation of $F°$ (hereafter called $H°$) must be made. In connection with the development of the interactive synthesis computer program *L*ogic and *H*euristics *A*pplied to *S*ynthetic *A*nalysis (LHASA, sec. 10.4.B),[1,5] Corey developed a protocol for determining the conformational energies of cyclohexane derivatives,[91] and assembled a list of H values for various substituent interactions in Table 1.4.[91] This table is related to a similar one, first assembled by Hirsch and co-workers.[94,95] The energy for a given conformation is taken to be the sums of all monoaxial interactions (A values), any 1,2-diequatorial interactions (G values) and any multiple diaxial interactions (defined by Corey as U values[86] and found in the two structures labeled). Simple doubling or tripling of the appropriate A value did not give correct results in this latter case and more accurate U-values were required. Note that the A and U values are identical in many cases. They usually differ if the substituent contains unsaturation.

The protocol for calculating the percentage of each conformation is illustrated by the two chair conformations of 2-chloro-3,4-dimethylcyclohexanol, **203** and **204**. Using Table 1.4, the pertinent interactions are U_{OR}, the two U_{CH_2R} and U_{Cl} in **203** and the two G_{CH_2R}, G_{OR} and G_{Cl} in **204**.

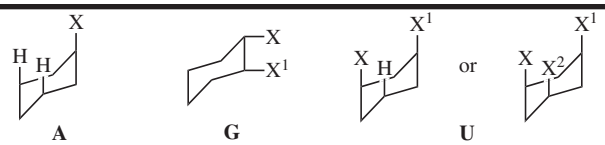


203 **204**

$$\Delta H° = H_{product} - H_{reactant} = H_{\mathbf{204}} - H_{\mathbf{203}} = (G_{CH_2R} + G_{Cl} + G_{CH_2R} + G_{OR}) - (U_{OR} + U_{CH_2R} + U_{CH_2R} + U_{Cl}) = (0.4 + 0.5 + 0.4 + 0.2) - (0.8 + 1.8 + 1.8 + 0.4) = (1.5) - (4.8) = -\mathbf{3.3}\text{ kcal mol}^{-1}\text{ (-13.8 kJ mol}^{-1}\text{)}.$$

93. Reference 86a, pp 164-165.
94. Hirsch, J.A. in *Topics in Stereochemistry, Vol. 1,* Allinger, N.L.; Eliel, E.L. (Eds.), Wiley-Interscience, New York, ***1967***, pp 199-222.
95. (a) Reference 31b, pp 236-237; (b) Barrett, J.W.; Linstead, R.P. *J. Chem. Soc.* ***1936***, 611. For a list of energy values for several functional groups, see Reference 12, pp 696-697.

Table 1.4. Corey's A, G, and U Values for Calculating Conformational Energies of Cyclohexane Derivatives.



A **G** **U**

Group	*A* (kcal mol^{-1})[a]	*G* (kcal mol^{-1})[a]	*U* (kcal mol^{-1})[a]
H	0	0	0
F	0.2 (0.84)	0	0
Cl	0.4 (1.67)	0.5 (2.09)	0.4 (1.67)
Br	0.4 (1.67)	0.8 (3.35)	0.4 (1.67)
I	0.4 (1.67)	1.0 (4.19)	0.4 (1.67)
PR_3	1.6 (6.7)	1.6 (6.7)	1.6 (6.7)
SR	0.8 (3.35)	0.5 (2.09)	0.8 (3.35)
S(O)R	1.9 (7.95)	2.7 (11.30)	1.9 (7.95)
$S(O_2)R$	2.5 (10.47)	3.5 (14.65)	2.5 (10.47)
OR	0.8 (3.35)	0.2 (0.84)	0.8 (3.35)
NH_3^+	2.0 (8.37)	0.5 (2.09)	2.0 (8.37)
NR_3^+	2.1 (8.79)	0.5 (2.09)	2.1 (8.79)
NHR	1.3 (5.44)	0.3 (1.26)	1.3 (5.44)
N=	0.5 (2.09)	0.1 (0.42)	0.5 (2.09)
N≡	0.2 (0.84)	0.1 (0.42)	1.2 (5.02)
NO_2	1.1 (4.61)	0.3 (1.26)	0.5 (2.09)
C≡	0.2 (0.84)	0	1.2 (5.02)
aryl	3.0 (12.56)	1.2 (5.02)	0.5 (2.09)
CO_2^-	2.0 (8.37)	0.5 (2.09)	2.0 (8.37)
CHO	0.8 (3.35)	0.3 (1.26)	0.8 (3.35)
C=	1.3 (5.44)	0.2 (0.84)	0.9 (3.77)
CR_3	6.0 (25.11)	2.5 (10.47)	6.0 (25.11)
CHR_2	2.1 (8.79)	0.8 (3.35)	2.1 (8.79)
CH_2R	1.8 (7.54)	0.4 91.67)	1.8 (7.54)

[a] The value in parentheses is the energy in kJ mol^{-1}

If $\Delta H° \approx \Delta G°$, then *assume* $\Delta G° = -3.3 = -2.303\ RT \log K_{eq}$. At 25°C, $-2.303\ RT = -1.364$. Therefore,

$$\Delta G° = -3.3 = -1.364 \log K_{eq} \text{ sp } \log K_{eq} = -3.3/-1.364 = 2.42$$
$$\text{and } K_{eq} = 10^{2.42} = 262.6.$$

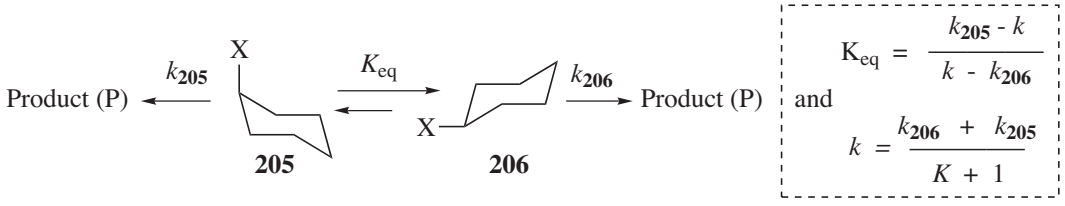
Since %**203** + %**204** = 100%, where **204** = 1 - **203**, then K_{eq} = 204/203 = 1-204/203 and K_{eq} (**203**) = 1 - **203**);

so, 262.6 (**203**) = 1 - (**203**), and 262.6 (**203**) + (**203**) = 1 or 262.6 + 1 (**203**) = 1, which leads to

(**203**) (263.6) = 1 and (**203**) = 1263.6 = 0.0038

Therefore, there is 0.38% of **203** and 99.62% of **204**. *Remember that two major assumptions were made for this calculation*: (*1*) all conformations except **203** and **204** were ignored, and (*2*) $\Delta S°$ was assumed to be zero.

As first shown by Barton,[87] the relative percentage of a given conformation directly influences the rate of a reaction. As summarized by Eliel,[92a] the equilibrium between **205** and **206** is given by the equilibrium constant (*K*), and the rate of conversion of each conformation to product is given by k_{205} and k_{206}, as developed by Winstein and Eliel.[92a] The overall rate will be Rate = k [*C*], where k is the observed specific rate and [*C*] is the stoichiometric concentration of the cyclohexane.[92a] Rate = k_{205} [**205**] + k_{206} [**206**] for this system, and the value k is related to the equilibrium constant as shown in the following:



As mentioned above, the percentage of a given conformation is an essential factor in determining the rate and viability of a given reaction and these calculations allow the synthetic chemist to estimate conformational populations. Just as the minor chair conformation influences the rate, so other conformations (boat, twist-boat, etc.) can also exert an influence, depending on their relative populations.

MOLECULAR MODELING: Conformers of Cyclohexane

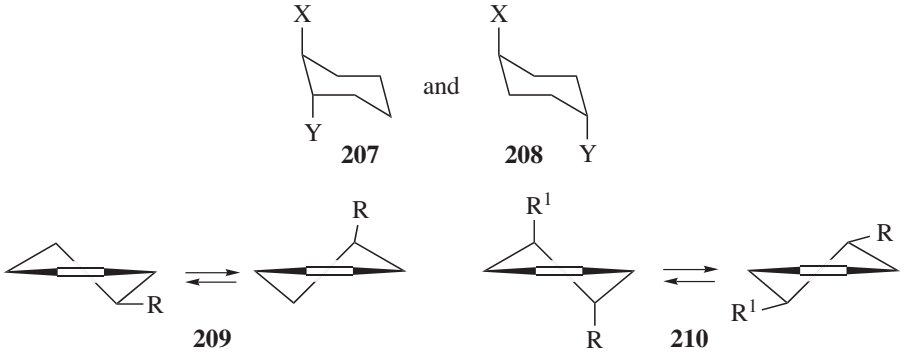
It is well known that cyclohexane adopts a chair conformation. Actually, the molecule exists in both chair and twist-boat conformers. The chair structure is the lower-energy conformer (quantum chemical calculations suggest that the twist-boat conformer is ~30 kJ/mol higher in energy), and the two interconvert via a low-energy half-chair transition state. The large energy difference and the small barrier to interconversion mean that detecting (let alone isolating) twist-boat cyclohexane is nearly impossible. Quantum chemical calculations show that a temperature in excess of 1500 K would be needed to achieve 10% of an equilibrium mixture of these conformers.

Interconversion of equivalent chair conformers of cyclohexane may be thought of as proceeding in two stages that "mirror" each other. The first is interconversion of one chair conformer to the twist-boat conformer via a half-chair transition state, and the second is interconversion of the twist-boat conformer to the second chair conformer via a second (equivalent) half-chair transition state. A plot of the energy profile for the process appears on screen. You can step through the individual structures that make up the sequence or "animate" it using the **Step** and **Play** keys, respectively at the bottom left of the screen.

MOLECULAR MODELING: Conformers of Cyclohexane, con't

Substitution should change the relative energies of chair and twist-boat conformers of cyclohexane. First, build and obtain energies for both chair and twist-boat conformers of cyclohexane. For each in turn, *click* on > to the right of the tab(s) at the top of the screen and select ***Continue***. The chair structure can be taken from the **Rings** menu. Build the twist-boat conformer by joining the ends of a chain of sp^3 carbons into a distorted boat-like structure. Next, build both chair and twist-boat conformers for the *cis* isomers of 1-2-dimethylcyclohexane, 1,2-di-*tert*-butylcyclohexane and 1-2-diphenylcyclohexane and obtain energies for each. Use the same sequence of operations (*click* on > and select ***Continue***) as before in order to keep the text on screen. Is the chair-twist-boat energy difference for any of these disubstituted molecules significantly less than that for cyclohexane itself?

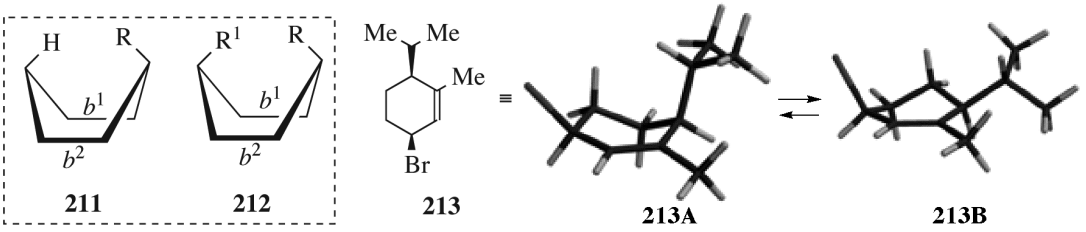
In addition to the values in Table 1.4 used for calculations of substituted cyclohexane derivatives,[85] Corey developed formulas for several other cyclic molecules. Incorporation of two halogens with a 1,2- or 1,4-diaxial relationship on a cyclohexane ring led to a higher proportion of the diaxial conformer[96] due to the more favorable electrostatic interactions of the lone pair electrons.[97] Corey's models in this case were **207** and **208**, and the equation used to calculate the conformational energy is E = 1/2 (A_X + A_y). Introduction of a π-bond or a heteroatom in the cyclohexane ring changes the energy relationships, since the presence of a π bond flattened the ring. The usual *U* and G values were used for monosubstituted or disubstituted derivatives such as **209** or **210**, respectively. A carbonyl or an aldehyde unit led to a diminished value for *A*, and a spirocyclic or fused ring structure also diminished *A*. Introduction of an oxygen in the ring (to form a pyran) led to a diminished value for *A*.



Corey and co-workers[91] also developed parameters to evaluate boat conformations, which are often important contributors to the conformational population of cyclohexane derivatives (see above). The energies for boat conformations with one or more substituents in the flagpole

96. Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971****, 3,* 139.
97. Wood, G.; Woo, E.P.; Miskow, M.H. *Can. J. Chem.* ***1969****, 47*, 429.

positions use a new term (*b*): E = ($b^1 + b^2$) A^R for **211**, and E = ($b^1 + b^2$) ($U^R + U^{R'}$) for **212**), derived from the bowsprit-flagpole interactions (R-H in **211** or R^1-R in **212**). Introduction of a π bond, a cyclopropane or a cyclobutane ring flattens the boat, leading to increased destabilization. Fused five-membered rings and larger fused rings do not flatten the ring of interest.



These structural types emphasize that the presence of π bonds and heteroatoms will influence the overall conformation. "Flattening" of a ring is often an important structural feature of natural products and other attractive synthetic targets. The π bond in a cyclohexene moiety flattens the ring in **213A** and its other low-energy conformer, **213B**. These are actually half-chair conformations analogous to **177**.[98] The isopropyl group (*i*-Pr) is less stable in the pseudo-axial position and more stable in the pseudo-equatorial position.[99] The *i*-Pr↔Br interaction is largely alleviated in **213B**. This effect is compatible with **213B** as the major conformation and higher relative energy for **213A**.

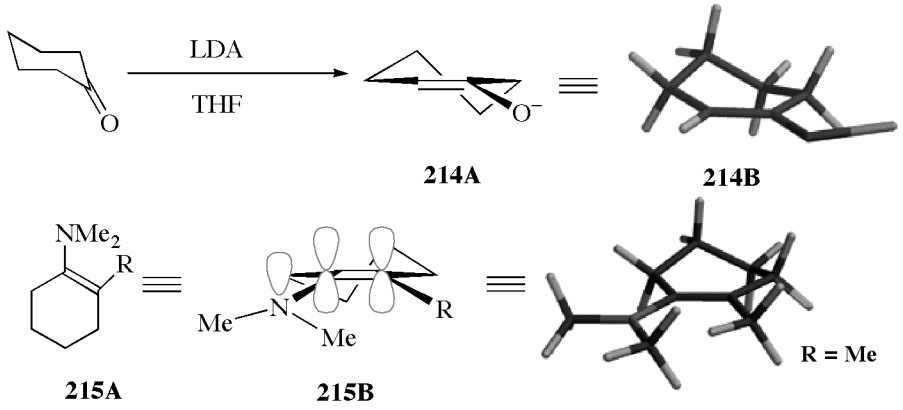
MOLECULAR MODELING: *Axial*/*Equatorial* Preferences in Disubstituted Cyclohexanes

It is well known that substituents on cyclohexane generally (but not always) prefer to be *equatorial*. Where there are two different substituents and only one can be *equatorial*, for example, in a *cis*-1,4-disubstituted cyclohexane, the substituents will "compete" for the favored position. Build the conformer of cis-1-bromo-4-*tert*-butylcyclohexane with the Br *axial* and the *tert*-butyl group *equatorial* and obtain its energy. Next, *click* on > to the right of the tab at the top of the screen and select ***Continue*** to bring up a fresh builder palette. Build the conformer in which the Br is *equatorial* and the *tert*-butyl group is *axial* and determine its energy. Which substituent, bromine or *tert*-butyl, "wins" the competition and assumes the *equatorial* position? Is the higher energy conformer likely to be observed in a room-temperature equilibrium distribution? Hint: a 95:5 ratio of major to minor conformers corresponds to an energy difference of around 8 kJ/mol.

A similar competition exists for disubstituted cyclohexenes, for example for cis-3-bromo-6-*tert*-butyl-1-cyclohexene. Obtain energies for the two possible conformers (bromine *axial* and *tert*-butyl *equatorial* and *vice versa*). Which substituent, bromine or *tert*-butyl, assumes the *equatorial* position? Is the difference in energy between the conformers, smaller, larger or about the same as for *cis*-1-bromo-4-*tert*-butylcyclohexane? If smaller or larger, examine the geometries of the two cyclohexane conformers and two cyclohexene conformers to provide an explanation.

98. (a) Böeseken, J.; de Rijck van der Gracht, W.J.F. *Rec. Trav. Chim.* ***1937, 56***, 1203; (b) Reference 31b, p 239.
99. (a) Reference 31b, p 240; (b) Dauben, W.G.; Pitzer, K.S. in *Conformational Analysis in Steric Effects in Organic Chemistry*, Newman, M.S. (Ed.), Wiley, New York, **1956**, pp 38-39.

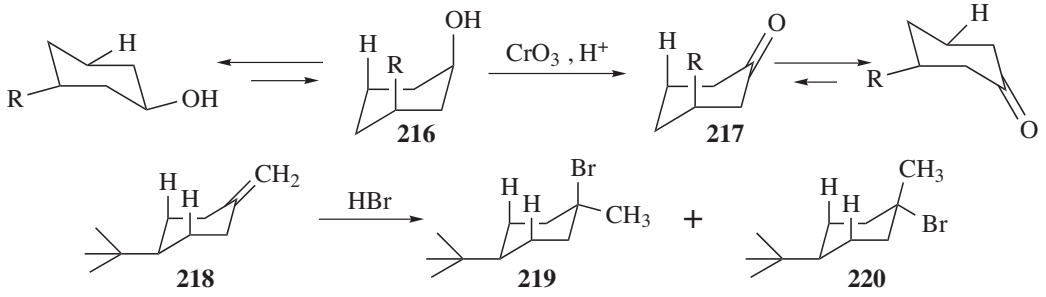
Similar conformational effects arise in other functionalized systems, including reactive intermediates. Conversion of cyclohexanone to its enolate anion (**214A**, see sec. 9.2) flattens the ring (see **214B**), and leads to a cyclohexene-like conformation. Note the conformational similarity of **214A** to cyclohexene derivative **213A**. The dimethylamino enamine (see sec. 9.6) of cyclohexanone (**215A**) also shows this half-chair conformation (see **215B**). In these cases, the lone pair electrons (on oxygen in **214** and on nitrogen in **215**) overlap with the π bond.



When compared to chair cyclohexane, the presence of the trigonal planar carbonyl in cyclohexanone removes the 1,3-diaxial hydrogen atom interactions and, as seen in the models for Corey's calculations, partially flattens the ring. The conversion of alcohol **216** to ketone **217** illustrates this point. Although **216** is an equilibrating mixture with an axial or equatorial hydroxyl group, upon oxidation to the ketone the flattening effect of the carbonyl is easy to see. Energetically, the R↔OH interaction (*U* value) in **216** is removed upon oxidation to **217**. In the ketone, the carbonyl effectively eclipses the α-equatorial hydrogens, further lowering the conformational energy.[100] Ketone **217** exists as an equilibrating conformational mixture favoring the R group in an equatorial position.

Exocyclic methylene compounds such as **218** will exhibit the same flattening effect observed with the carbonyl group. An interesting effect is seen in the conversion of **218** to **219** or **220**, where *A* strain is increased in the products, relative to the methylene group. Further, the greater *A* strain of methyl (1.8 kcal mol^{-1} in Table 1.4) versus 0.4 kcal mol^{-1} for Br (7.5 and 1.7 kJ mol^{-1} respectively) suggests that **219** may predominate after addition of HBr to the alkene (see sec. 2.10.A). This analysis ignores the relative trajectories of approach of the reagents (see sec. 6.6.A) and other steric interactions, however.

100. (a) Allinger, N.L.; Blatter, H.M. *J. Am. Chem. Soc.* ***1961****, 83*, 994; (b) Allinger, N.L.; Freiberg, L.A. *Ibid* ***1962****, 84,* 2201.



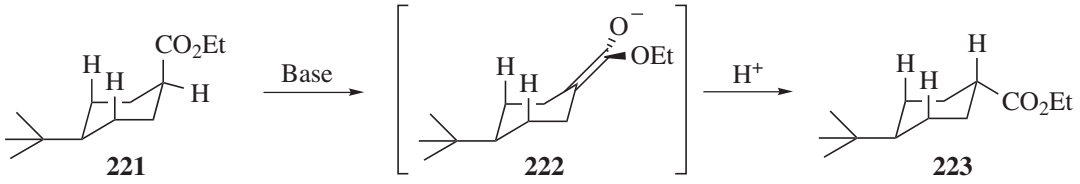
MOLECULAR MODELING: Electrophilic Bromination of Methylenecyclohexane

Electrophilic bromination of 4-*tert*-butylmethylenecyclohexane can lead to either **219** or **220**. The mechanism presumably involves addition of "H^+" to the external methylene carbon, follow by attack of Br^- on the resulting carbocation. Examine a LUMO map for the intermediate carbocation. This colors an electron density surface depicting the overall molecular size and shape with the value of the lowest-unoccupied molecular orbital. By convention, regions on the surface where the LUMO is concentrated are colored "blue" while those where it is absent are colored "red". Bromide would be expected to add where the LUMO is most concentrated. Is there a clear preference for addition to one face of the carbocation over the other? If there is, which product would be favored, **219** or **220**?

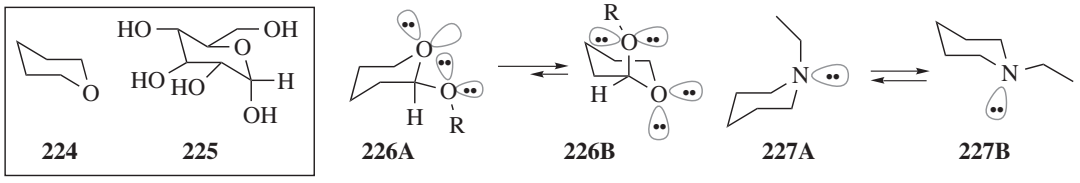
In addition to the endocyclic double bond usually found in an enolate anion such as **214**, enolate anions can be formed that have an exocyclic double bond (also see sec. 9.5.D). Relief of strain will presumably assist formation of the enolate anion, and may influence the final stereochemistry of groups in the product when the enolate anion reacts with an a suitable reagent (see sec. 9.3.A, 9.4).[101] This effect can also be seen in the equilibration of the cis-ester **221** to the trans-ester **223** via the planar enolate (**221**).[98] This equilibration (accomplished by treating **221** with a base followed by a proton source) favors **223** due to reduction of the *A* strain of the axial carboethoxy group in [A_{COOR} = 1.20 kcal mol^{-1} (4.99 kJ mol^{-1})].

Six-membered rings containing oxygen (pyran derivatives based on **224**) are an integral part of carbohydrates such as α-D-glucopyranose (**225**). Less substituted pyrans show similar effects. The presence of the α-alkoxy group in **229** leads to a significant effect also seen in α-alkoxy pyrans, the **anomeric effect**.[102] An alkyl group on cyclohexane or pyran usually prefers the equatorial position due to increased *A* strain. When an alkoxy group is attached to pyran, however, it prefers the axial position. This effect is probably due to dipolar interactions of the oxygen lone pairs (see **226A** and **226B**).[103] The anomeric effect is evident in glucose, where α-D-glucopyranose (**225**) accounts for a significant portion of the conformational equilibrium.

101. Reference 52a, p 67.
102. (a) Lemieux, R.U. *Pure Appl. Chem.* ***1971****, 27,* 527; (b) Angyal, S.J. *Angew. Chem. Int. Ed.* ***1969****, 8*, 157; (c) Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, New York, ***1983***.
103. David, S.; Eisenstein, O.; Salem, L.; Hehre, W.J.; Hoffmann, R. *J. Am. Chem. Soc.* ***1973****, 95*, 3806.

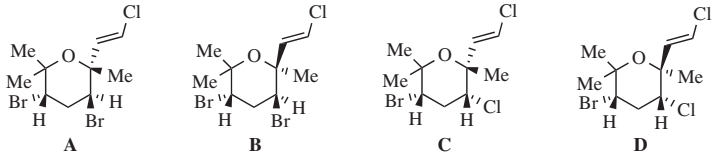


The influence of substituents on conformational stability is also evident in amines such as *N*-ethyl piperidine. The chair conformation can be drawn with the ethyl group axial (N lone pair equatorial in **227A**) or equatorial (N lone pair axial as in **227B**). The greater *A* value for ethyl than for the lone pair suggests a predominance of **227B** in this equilibrium mixture. This preference for the larger group being in an equatorial position is analogous to the effects seen in pyrans and cyclohexanes.



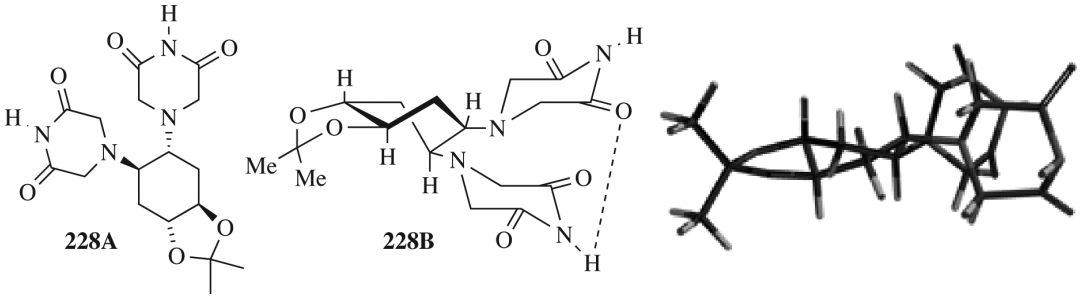
MOLECULAR MODELING: Conformational Mobility of Tetrahydropyran Rings

Compounds **A**-**D** were isolated from *Aplysia kurodai* by Kakisawa and co-workers (*J. Org. Chem.* ***1987****, 52,* 4597-4600). Proton NMR was used to assign the structures of **C** and **D**, but led to ambiguous results for **A** and **B**. (An X-ray crystal structure was required to verify the structure of **B**, which was then used to elucidate the structure of **A**). The authors interpreted the NMR results to indicate that **A** and **B** are conformationally mobile whereas **C** and **D** are rigid.

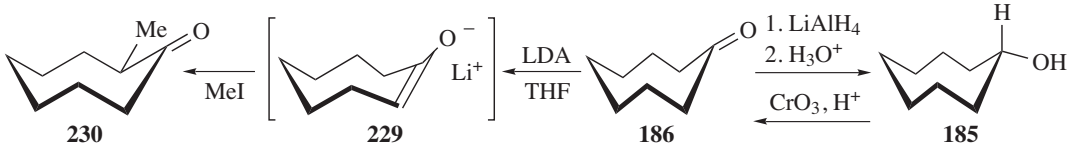


While rotation about single bonds is normally too rapid to be "frozen out" in an NMR experiment, chair-chair interconversion in cyclohexane (and presumably tetrahydropyran) derivatives is much slower and can be stopped at low temperatures. One after the other, build and obtain the energy for the two different chair conformers or either **A** or **B** (or both) and of **C** or **D** (or both). Note that you need to consider the possible conformations about the bond connecting the ring to the vinyl group, choosing the lowest energy for each. Hint: Try the vinyl group "up" and the vinyl group "down" to begin, determine the energy of each and then try one or two other vinyl conformations. For the second and following calculations, *click* on > to the right of the tab at the top of the screen and select ***Continue*** to bring up a fresh builder palette. Are the energies of the two chairs for **A** (or **B**) similar or significantly different? Are the energies of the two chairs for **C** (or **D**) similar or significantly different? If (**A** (or **B**) and **C** (or **D**) exhibit different behavior, suggest why. Are your results in line with the conclusion from the NMR experiments, that A and B are conformationally mobile while C and D are not?

The presence of bulky substituents, or substituents capable of chelation or hydrogen bonding can alter conformational populations,[104,105] as first seen with ethylene glycol. In **228A**, there are two effects that influence the conformation.[106] Bulky substituents lead to large *A* and *G* strain in both chair conformations. In addition, internal hydrogen bonding of the glutarimide moieties helps stabilize the twist-boat conformation shown in **228B**, which is the lowest energy conformation of this molecule. The 3D model shows the twist in the cyclohexane moiety as well as the proximity of the two diketopiperazine units. The twist-boat conformation is also observed in the absence of internal hydrogen bonding. As confirmed by X-ray crystallography, *cis,trans,trans*-1,2,4,4-tetraisopropylcyclohexane exists as a twist-boat.[107]



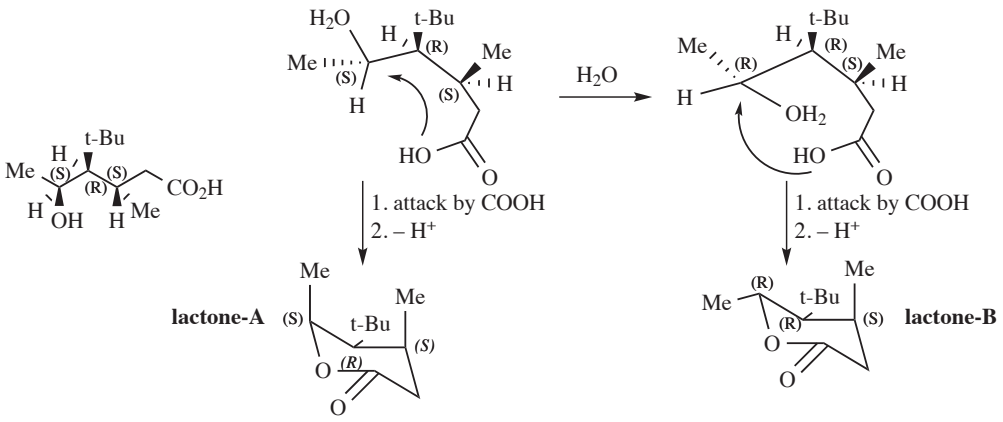
As mentioned in an earlier example, the reduction of cyclooctanone (**186**) shows how conformations can influence reactivity. Treatment of **186** with lithium aluminum hydride ($LiAlH_4$, see sec. 4.2.B) generates the alcohol (**185**). The alcohol will have greater transannular strain than the ketone. The reduction may be somewhat sluggish relative to similar reduction of cyclohexanone. The oxidation, however, converts **185** to **186** using chromium trioxide (see sec. 3.2.A) and leads to diminished strain as the newly introduced carbonyl flattens the ring slightly. As the product is somewhat more stable than the starting material, the oxidation is more facile. Similarly, formation of the enolate (**186** → **229**) with lithium diisopropylamide (LDA, see sec. 9.2.B) should be facile due to relief of transannular strain for formation of the planar enolate moiety. A subsequent alkylation step (**229** → **230**, see sec. 9.3.A) may be sluggish, however, since the methyl group in **230** may introduce a bit more strain in the product (remember there are several other low energy conformations for the eight-membered ring) than in the original unsubstituted cyclooctanone (**186**).



104. Reference 18, p 200.
105. (a) Stolow, R.D. *J. Am. Chem. Soc.* ***1961,*** *83*, 2592; (b) Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *Ibid* ***1964,*** *86*, 2165.
106. Witiak, D.T.; Wei, Y. *J. Org. Chem.* ***1991,*** *56*, 5408.
107. Columbus, I.; Cohen, S.; Biali, S.E. *J. Am. Chem. Soc.* ***1994,*** *116,* 10306.

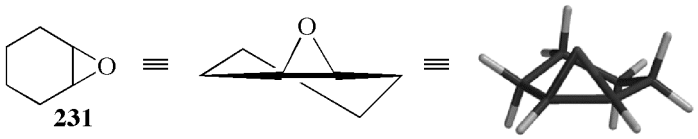
MOLECULAR MODELING: Thermodynamic Control of Product Distributions

Where reactions have very low energy transition states, thermodynamics is likely to control product distribution. Reactions that involve protonation followed by deprotonation are good examples. In the gas phase and in non-interacting solvents, both protonation and deprotonation occur with little or no barrier, meaning that final product distributions are dictated only by relative product energies. In the presence of aqueous acid, the hydroxy acid shown below does not give rise to its lactone (lactone A) but rather to lactone B. This reaction occurs via protonation of the hydroxyl unit of the acid, followed by displacement of the hydronium ion by the carboxyl unit. The carbon in lactone B proximal to the lactone oxygen atom has undergone epimerization from (*S*) to (*R*). This transformation requires that the initially formed oxonium ion is displaced by water, with inversion, to form a new oxonium ion, and subsequent reaction with the carboxyl group leads to lactone-B. Why should the epimerization reaction be preferred to direct lactone formation?



Assuming that the reaction is under thermodynamic control, the lactone that is formed will be the more stable lactone, irrespective of how it was formed. Build lactone-A and obtain its energy. *Click* on > to the right of the tab at the top of the screen and select ***Continue*** to bring up a fresh builder palette. Build lactone-B and obtain the energy. Which lactone is lower in energy? Suggest a reason for this preference. Does the information you have obtained suggest a reason for the observation that epimerization followed by formation of-B occurs preferentially to direct formation of lactone-A? Elaborate.

1.5.D. Conformations in Polycyclic Molecules

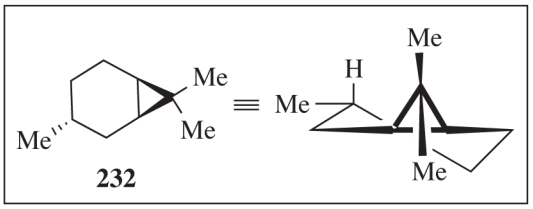


231

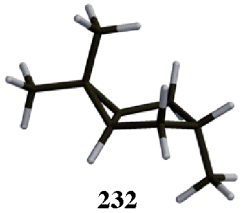
The conformational constraints in monocyclic molecules are magnified in bi-, tri-, and polycyclic molecules. A simple case is cyclohexene oxide (**231**) where the planar three-membered ring flattens the ring. Similar effects are seen in cyclohexene, and also occur when cyclopropane is

fused to a ring. Bicyclo[3.1.0]hexanes also show this flattening effect. An example is carane (**232**), which exists primarily in the conformation shown (note that the geminal dimethyl groups are perpendicular to the plane of the cyclopropane ring). The cis-isomer (**233**) is expected to show a significant Me-Me interaction, which is not present in the trans-isomer, **232** (carane).

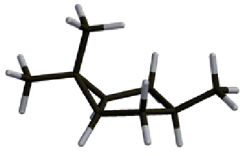
The conformational constraints peculiar to [m.n.0]alkanes (n ≠ 1) can be illustrated by comparing the cis- and trans- isomers of bicyclo[3.3.0]octane (**234**), hydrindane (**235**), as well as **236** (decalin). Each five- and six-membered ring tends to assume an envelope conformation or a chair conformation respectively in their lowest energy form. *cis*-Bicyclo[3.3.0]octane (**237**) shows a bent conformation with the two envelope shapes relieving some of the cross ring interactions.[108,92] *trans*-Bicyclo[3.3.0]octane (**238**) shows a more extended or open structure, and there is some distortion of the five-membered ring. Compound **238** is ~ 6 kcal mol^{-1} (25.1 kJ mol^{-1}) higher in energy than **237**.[109] Both cis- and trans- isomers are easily prepared, however.[110]



232



232



233

Hydrindanes have the five-membered ring in the envelope conformation with the six-membered ring in a chair. The *cis*-indane (**239**) shows a 1,3-diaxial interaction with substituents, and there is a *gauche*-like interaction. In the trans-isomer (**240**), the 1,3-diaxial interaction is diminished, and the extended conformation in **240** is slightly lower in energy (about 1 kcal mol^{-1} or 4.19 kJ mol^{-1}) than **239**.[111] Similar analysis of *cis*-decalin (**241**) and *trans*-decalin (**242**) leads to the same bent and extended forms, with both six-membered rings in a chair conformation.[112] In **241**, one ring can assume more of a boat like structure in some conformations. There is a 1,3-diaxial interaction in substituted **241**, and the overall energy of **241** is lower due to decreased nonbonded interactions.[113] Eliel describes the conformations of several other bicyclic and polycyclic compounds.[114]

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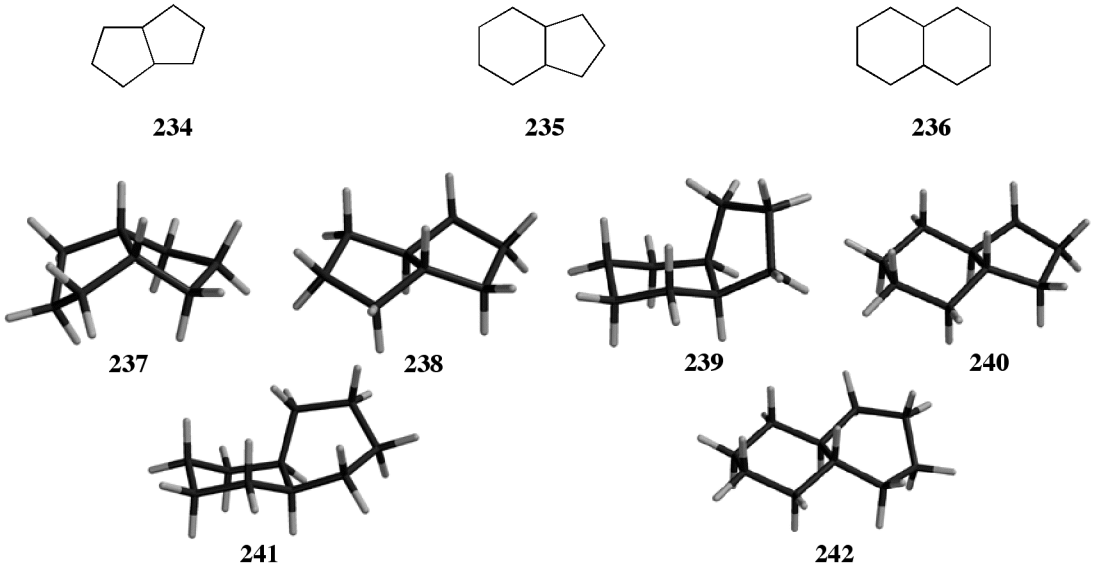
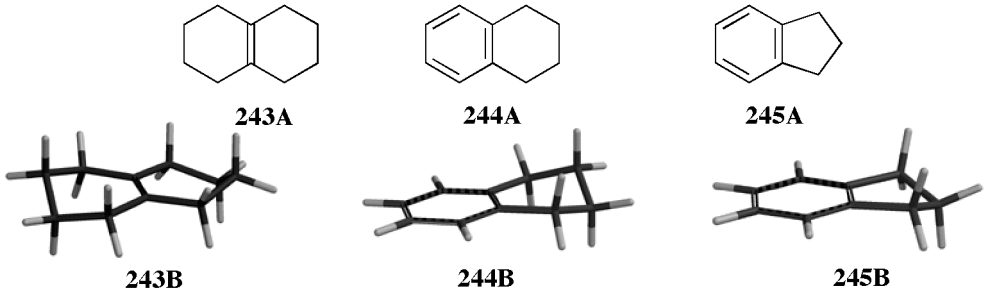
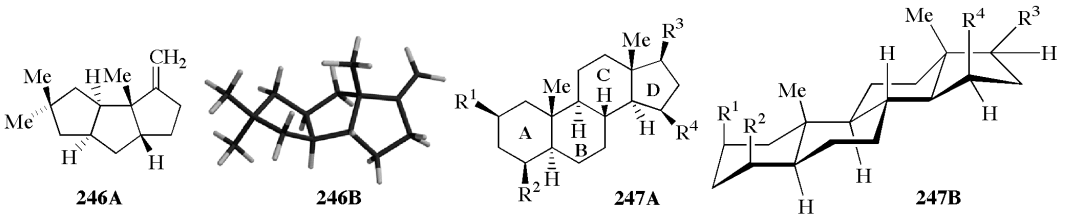
108. See reference 12, p 776.
109. (a) Reference 12, pp 774-775; (b) Reference 31b, p 274.
110. Owen, L.N.; Peto, A.G. *J. Chem. Soc, **1955,*** 2383.
111. (a) Reference 12, pp 776-779; (b) Reference 31b,p275; (c) Browne, C.C.; Rossini, F.D. *J. Phys. Chem. **1960**, 64,* 927.
112. Turner, R.B. *J. Am. Chem. Soc. **1954**, 74*, 2118.
113. (a) Reference 31b, p 279; (b) Hückel, W. *Annalen, **1925**, 441,* 1; (c) Hückel, W.; Friedrich, H. *Ibid **1926**, 451,* 132.
114. Reference 12, pp 780-793.



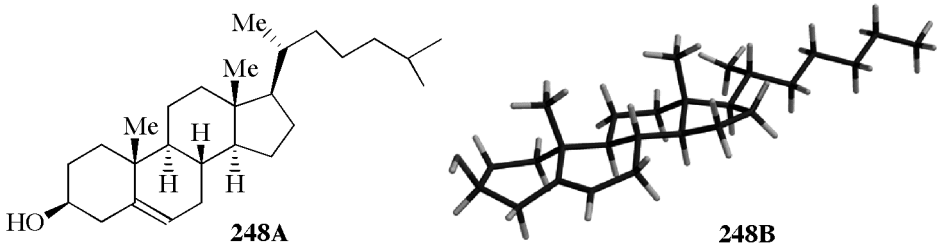
Incorporation of a π bond from an alkene or aryl moiety into a bicyclic system leads to significant flattening of the ring. Examples are **243A** (9-decalene) and the benzene-containing derivatives tetrahydronaphthalene (**244A**) and 1*H*-dihydroindene (**245A**). The planar alkene moiety in **243A** (see **243B**) forces the four allylic carbons to be coplanar and each ring more or less behaves as if it were cyclohexene. The planar benzene ring in **244A** (see **244B**) imposes similar conformational constraints, and the carbons of the nonaromatic ring assume a conformation similar to cyclohexene. In **245A** (see **245B**), the nonplanar cyclopentane ring behaves more or less like cyclopentene. The presence of three or more fused rings is rather common in nature. The natural product hirsutene (**246A**)[115] also shows the conformational bias imposed by three fused five-membered rings (see model **246B**).



115. For leading references relating to the structure and synthesis of this molecule, see (a) Hua, D.H.; Venkataraman, S.; Ostrander, R.A.; Sinai, G.-Z.; McCann, P.J.; Coulter, M.J.; Xu, M.R. *J. Org. Chem.* ***1988****, 53,* 507; (b) Curran, D.P.; Raciewicz, D.M. *Tetrahedron* ***1985****, 41*, 3943.



A last example of this phenomenon is seen in the steroid nucleus (**247A**). Each of the cyclohexane moieties will exist in a chair conformation and the cyclopentane will be in an envelope conformation, as seen in **247B**. If a carbonyl or alkene moiety is included, the six-membered ring will be flattened and its conformation will be very similar to that of cyclohexanone or cyclohexene. As seen in conformational drawing **247B**, each trans-fused cyclohexane ring resembles *trans*-decalin and the four fused rings impart great conformational rigidity to the molecule. Only the terminal cyclohexyl and cyclopentyl rings have some mobility. The interaction R^1-R^2-Me of the cyclohexane ring is important, as are the R^3-Me and R-R^4 interaction of the cyclopentane ring. Examples of the conformational variations in steroids are seen by examination of cholesterol (**248A**) and β-estradiol (**249A**).[116] When the A ring is aromatic, as in estradiol (**249**), the A/B ring system is flattened, inducing significant distortion in the C ring as well (see **249B** relative to **248B**). Changes in conformation for polycyclic systems can often be predicted using the simple five- and six-ring models discussed above.



It is reasonable to assume that the simple concepts introduced for monocyclic rings such as cyclopentane, cyclohexane, cyclohexene, and cyclohexanone can be applied with little change to complex molecules containing those units. Throughout this book the analysis of simple rings will be used to understand the conformational bias and reactivity of larger and more difficult synthetic targets.

116. Fieser, L.F.; Fieser, M. *Steroids,* Van Nostrand Reinhold, New York, ***1959***.

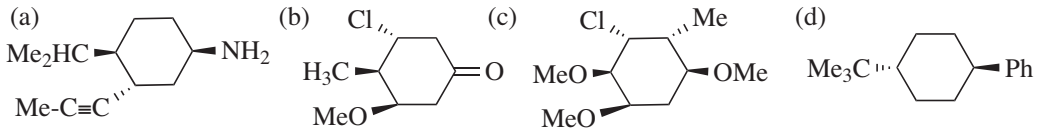
1.6. CONCLUSION

This chapter has reviewed the most fundamental concepts of stereochemistry and conformational analysis, with some applications to more complex problems. For students who have had a good undergraduate Organic chemistry course, it is intended as a review since these concepts are integral to the understanding of organic reactions. The concept of disconnection and retrosynthetic analysis is a prelude to a discussion of synthetic strategies in Chapter 10. The disconnection method and pertinent transforms will, however, be presented in virtually every chapter as new reactions are introduced.

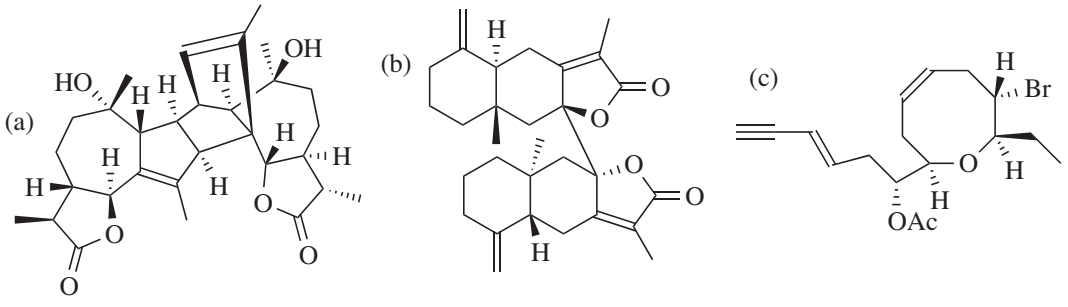
The introduction to organic reactions will be continued in the functional group exchange reactions in Chapter 2, which will review the reactions introduced in a typical first Organic chemistry course. Some of the concepts will be expanded and updated to include more synthetically useful reactions. Oxidation and reduction will be presented in separate chapters to focus attention on the vast number of reactions that fall under these categories.

HOMEWORK

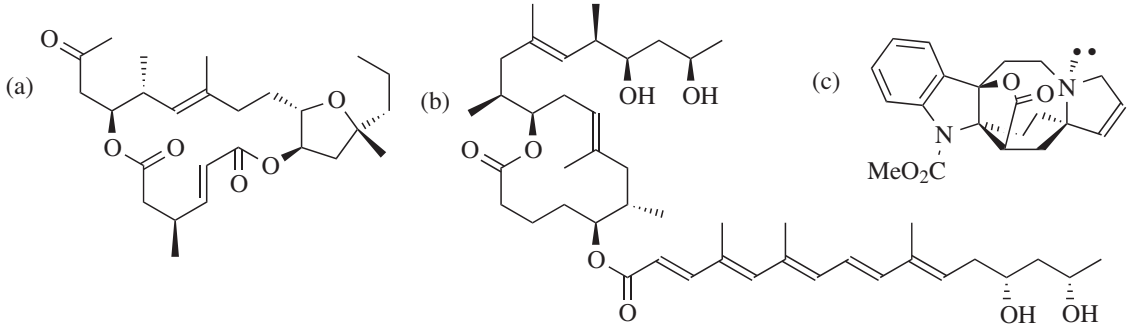
1. For each of the following molecules calculate the percentage for both chair conformations using the values in Table 1.4. Calculate using the temperatures 150°C for (a), 35°C for (c) and 25°C for (b) and (c).



2. Determine the absolute configuration (*R* or *S*) for every stereogenic center in the following molecules:

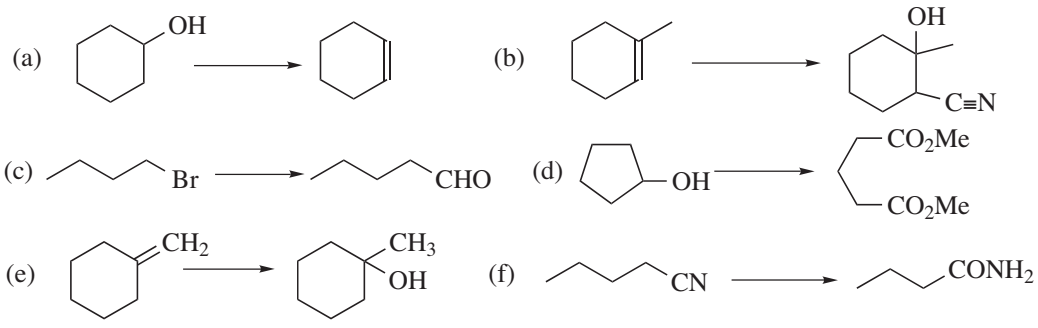


3. Determine the absolute configuration for every stereogenic center in the following molecules:



4. For disconnect fragments **23** and **24** in Section 1.2, convert each to a real molecule using synthetic equivalents in Table 1.2. Briefly discuss the retrosynthetic and synthetic sequences and show the complete retrosynthetic analysis based on this disconnection.

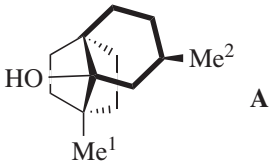
5. Using the reaction wheel (Fig. 1.1) give reasonable syntheses, including reagents and all intermediates (no mechanisms).



6. Use the *Compendium of Organic Synthetic Methods* (Vol. 11) to give three *different* reactions (with literature references and reactions) for each of the following:

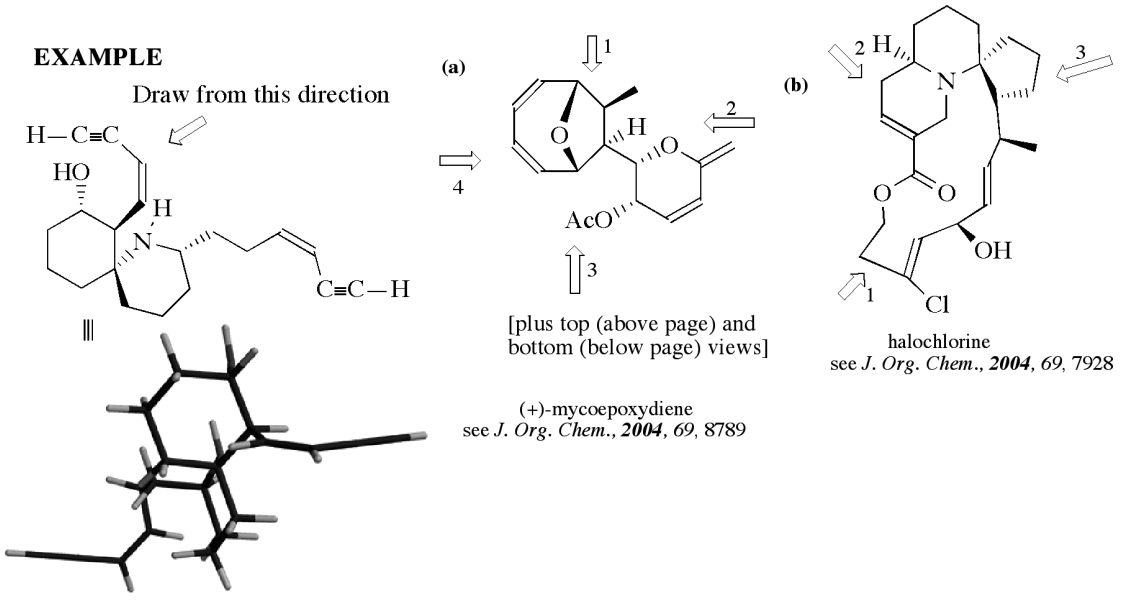
   (a) acids from nitriles
   (b) aldehydes from nitriles
   (c) amides from halides
   (d) amines from nitriles
   (e) ethers from halides
   (f) halides from amines
   (g) ketones from olefins
   (h) alkenes from aldehydes

7. Draw molecule **A** in what should be the low-energy conformation. Briefly discuss the conformation for the highlighted rings in molecule A. Also discuss the conformational preference (axial or equatorial) for all both methyl groups as well as the hydroxyl.

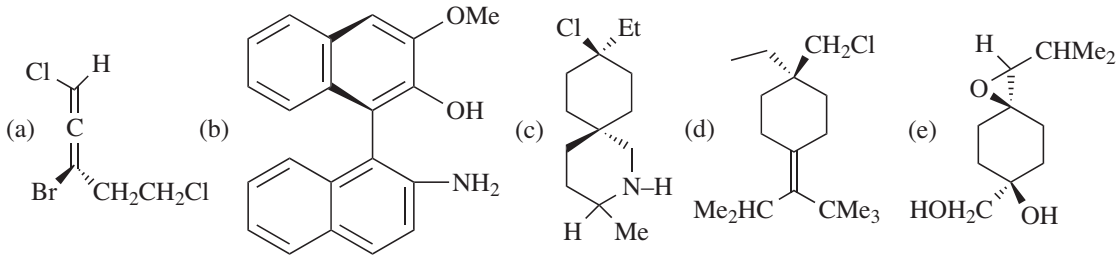


A

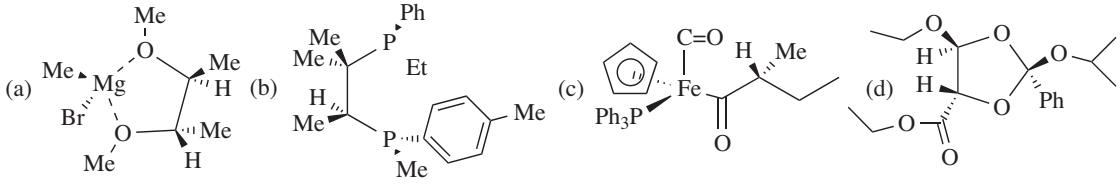
8. Use a 3D computer drawing program, draw molecules (a) and (b) in 3D form, from the indicated perspective (see the example below).



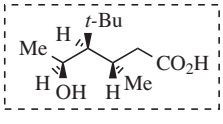
9. Determine the absolute configuration (R or S) for each chiral axis in the following molecules:



10. Determine the absolute configuration for each chiral center in the following molecules.:

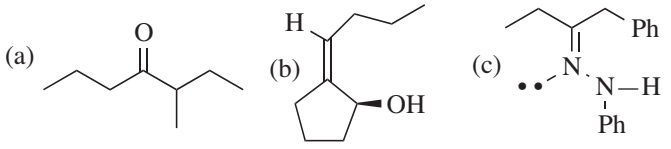


11. The conversion of the hydroxy-acid shown to the right, to the corresponding lactone, is rather slow. When pushed under aqueous acid conditions, epimerization at the carbon bearing the hydroxyl can occur. Draw the lactone and explain the observations noted in this question.

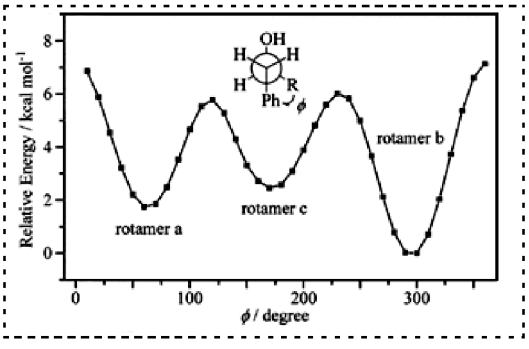


12. Explain why *cis*-1,3-cyclohexanediol exists mainly in the diaxial conformation in aqueous ethanol solution, when by Corey's ΔG calculations (see Table 1.4), the diequatorial conformation should be lower in energy.

13. Determine the correct *re/si* label for each prochiral atom in the following molecules.

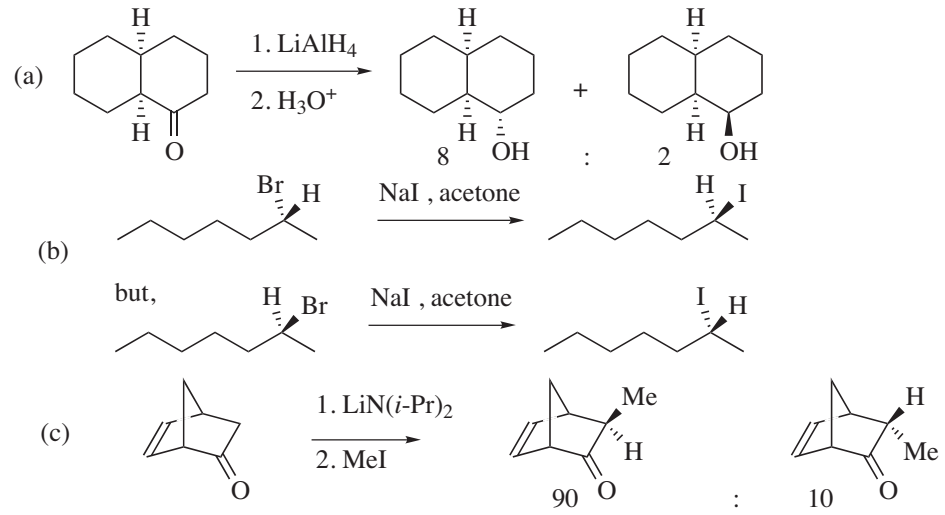


14. Draw the three most significant anti-rotamers of 1-phenyl-1-ethanol (R = Me in the accompanying diagram), and correlate them with the rotamers marked a-c on the energy curve.



15. (a) Draw the (2*S*, 3*R*,4*R*) and the (2*S*, 3*S*, 4*S*) derivative of molecule **A**. (b) Draw both the erythro/threo and the syn/anti forms of molecule **B**.

16. Classify each of the following reactions as stereospecific/stereoselective and/or regiospecific/regioselective.



17. Explain why the ground state energy of cyclodecane is higher than that of cyclooctadecane. Why is cyclopentadecane higher in energy than cyclohexadecane?

18. Draw the boat conformation of *cis-,trans-,trans*-1,2,3,4-tetraisopropylcyclohexane.