Cycloalkanes

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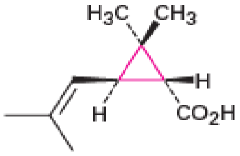
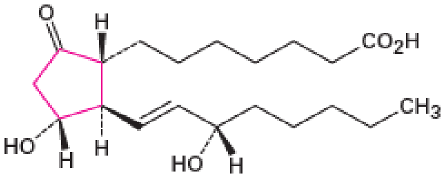
Cyclic molecules are encountered in most pharmaceuticals and in all classes of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids, it's important to understand the behaviors of cyclic structures.

Although we've only discussed open-chain compounds up to now, most organic compounds contain *rings* of carbon atoms. Chrysanthemic acid, for instance, whose esters occur naturally as the active insecticidal constituents of chrysanthemum flowers, contains a three-membered (cyclopropane) ring.



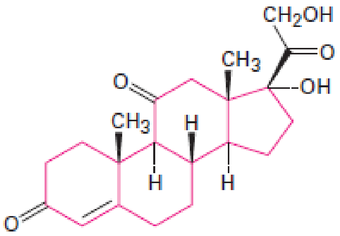
Chrysanthemic acid

Prostaglandins, potent hormones that control an extraordinary variety of physiological functions in humans, contain a five-membered (cyclopentane) ring.



Prostaglandin E_1

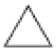
Steroids, such as cortisone, contain four rings joined together 3 six membered (cyclohexane) and 1 five-membered.

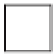


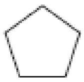
Cortisone

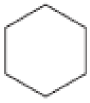
Naming Cycloalkanes

Saturated cyclic hydrocarbons are called **cycloalkanes**, or **alicyclic** compounds (**aliphatic cyclic**). Because cycloalkanes consist of rings of -CH_2- units, they have the general formula $(CH_2)_n$, or C_nH_{2n}, and can be represented by polygons in skeletal drawings.


Cyclopropane


Cyclobutane


Cyclopentane

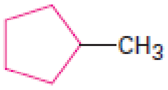

Cyclohexane

Substituted cycloalkanes are named by rules similar to those we saw in the previous chapter for open-chain alkanes. For most compounds, there are only two steps.

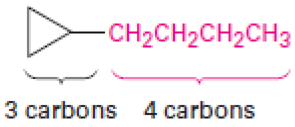
Step 1

Find the parent.

Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent is greater than the number in the ring, the compound is named as a cycloalkyl-substituted alkane. For example:



Methylcyclopentane

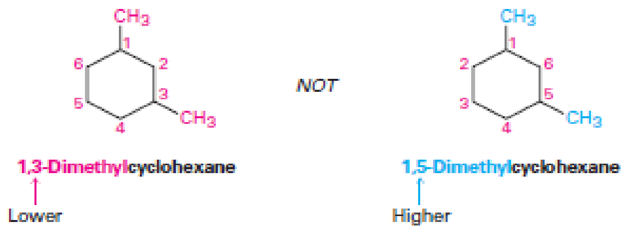


1-Cyclopropylbutane

Step 2

Number the substituents, and write the name.

For an alkyl- or halo-substituted cycloalkane, choose a point of attachment as carbon 1 and number the substituents on the ring so that the *second* substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found.



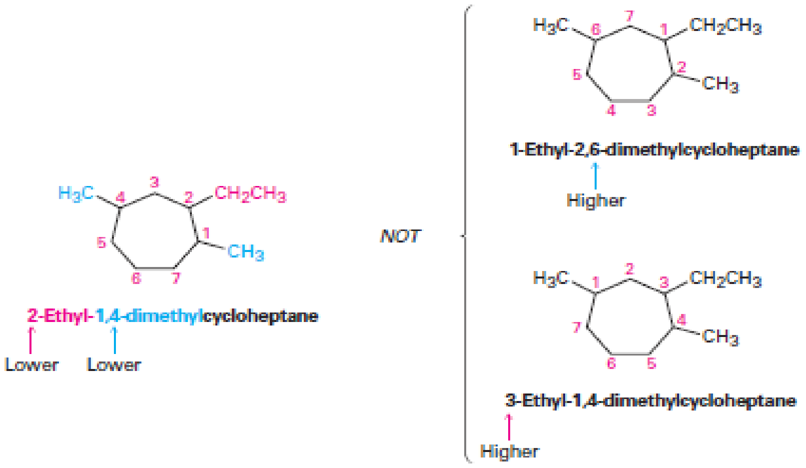
1,3-Dimethylcyclohexane

Lower

NOT

1,5-Dimethylcyclohexane

Higher



2-Ethyl-1,4-dimethylcycloheptane

Lower Lower

NOT

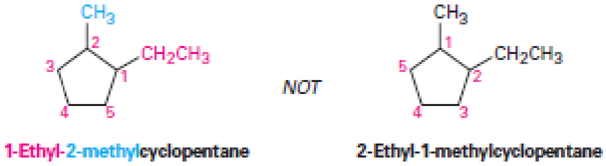
1-Ethyl-2,6-dimethylcycloheptane

Higher

3-Ethyl-1,4-dimethylcycloheptane

Higher

(a) When two or more different alkyl groups are present that could potentially take the same numbers, number them by alphabetical priority, ignoring numerical prefixes such as di- and tri-.



1-Ethyl-2-methylcyclopentane

NOT

2-Ethyl-1-methylcyclopentane

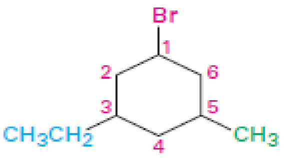
(b) If halogens are present, treat them just like alkyl groups.

1-Bromo-2-methylcyclobutane

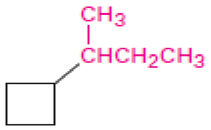
NOT

2-Bromo-1-methylcyclobutan

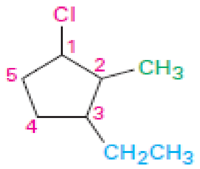
Some additional examples follow:



1-Bromo-3-ethyl-5-methyl-
cyclohexane



(1-Methylpropyl)cyclobutane
or *sec*-butylcyclobutane



1-Chloro-3-ethyl-2-methyl-
cyclopentane

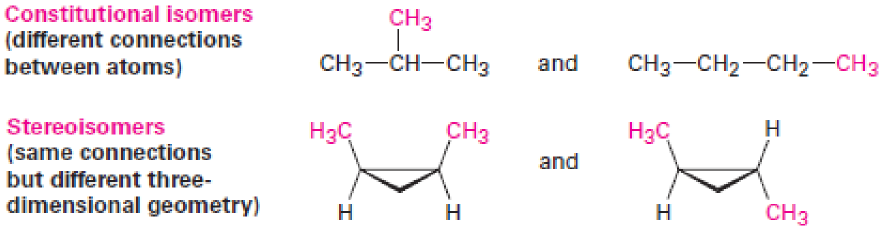
Cis–Trans Isomerism in Cycloalkanes

Because of their cyclic structures, cycloalkanes have two faces when viewed edge-on, a “top” face and a “bottom” face. As a result, isomerism is possible in substituted cycloalkanes. For example, there are two different 1,2-dimethylcyclopropane isomers, one with the two methyl groups on the same face of the ring and one with the methyl groups on opposite faces **(Figure 4-2)**. Both isomers are stable compounds, and neither can be converted into the other without breaking and reforming chemical bonds.

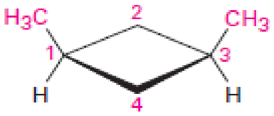
cis-1,2-Dimethylcyclopropane *trans*-1,2-Dimethylcyclopropane

Figure 4-2 There are two different 1,2-dimethylcyclopropane isomers, one with the methyl groups on the same face of the ring (cis) and the other with the methyl groups on opposite faces of the ring (trans). The two isomers do not interconvert.

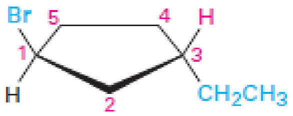
Unlike the constitutional isomers butane and isobutane, which have their atoms connected in a different order, the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, with atoms connected in the same order but differing in three-dimensional orientation, are called stereochemical isomers, or **stereoisomers**. More generally, the term **stereochemistry** is used to refer to the three-dimensional aspects of chemical structure and reactivity.



The 1,2-dimethylcyclopropanes are members of a subclass of stereoisomers called **cis–trans isomers**. The prefixes *cis*- (Latin “on the same side”) and *trans*- (Latin “across”) are used to distinguish between them. Cis–trans isomerism is a common occurrence in substituted cycloalkanes and in many cyclic biological molecules.



cis-1,3-Dimethylcyclobutane

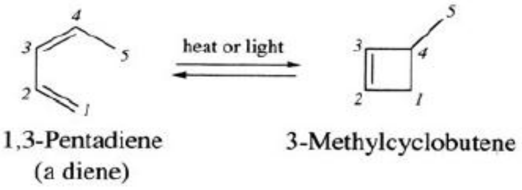


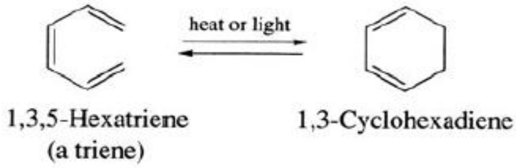
trans-1-Bromo-3-ethylcyclopentane

Synthesis of Cycloalkanes

Intramolecular Cyclization

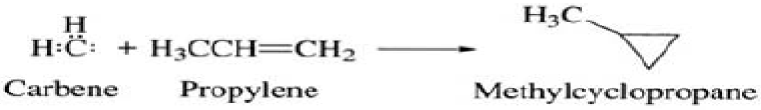
This technique applies to many open-chain compounds. Pertinent here is the intramolecular cyclization of polyenes (an **electrocyclic reaction**).



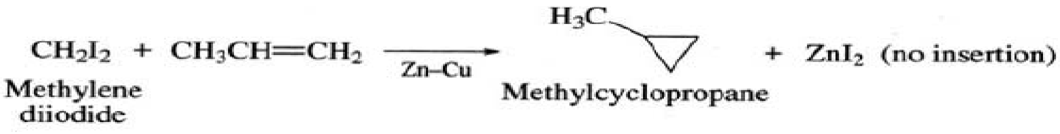


Intermolecular Cyclization

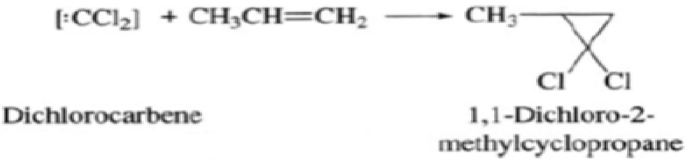
In this method, two or occasionally more, open-chain compounds are merged into a ring. Examples are the common syntheses of cyclopropanes by the addition of carbene (CH_2) or substituted carbenes to alkenes



Methylene can be transferred directly from the reagent mixture, CH_2I_2 + Zn-Cu alloy, to the alkene without being generated as an intermediate (**Simmons–Smith reaction**).



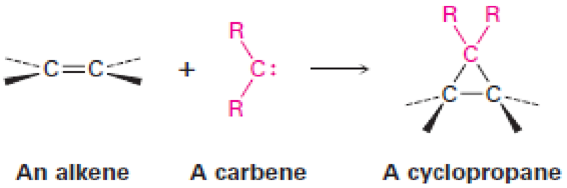
The carbene $:CCl_2$ generated from chloroform, $CHCl_3$, and KOH in the presence of alkenes gives substituted cyclopropanes.



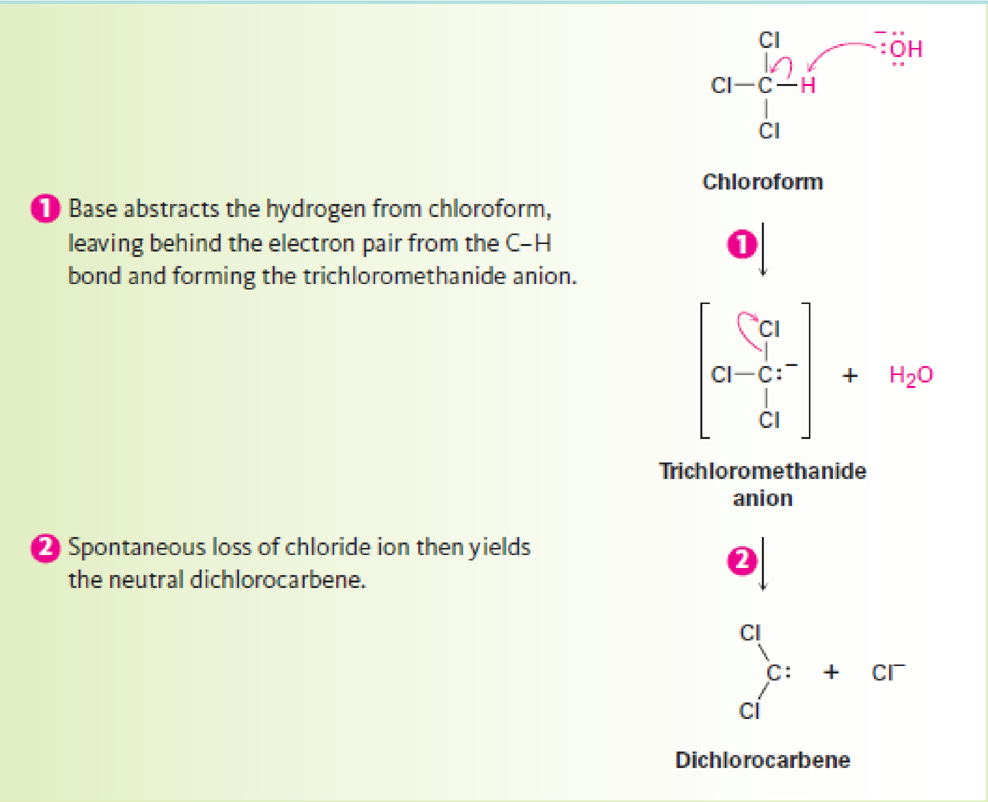
Addition of Carbenes to Alkenes: Cyclopropane Synthesis

Yet another kind of alkene addition is the reaction with a ***carbene*** to yield a cyclopropane. A **carbene, R_2C:** is a neutral molecule containing a divalent carbon with only six electrons in its valence shell. It is therefore highly reactive and generated only as a reaction intermediate, rather than as an isolable molecule.

Because they're electron-deficient, carbenes behave as electrophiles and react with nucleophilic **C=C** bonds. The reaction occurs in a single step without intermediates.



One of the simplest methods for generating a substituted carbene is by treatment of chloroform, $CHCl_3$, with a strong base such as KOH. As shown in **Figure 8-8**, the loss of a proton from $CHCl_3$ gives trichloromethanide anion, - **:**CCl_3, which spontaneously expels a Cl- ion to yield dichlorocarbene, **:**CCl_2.

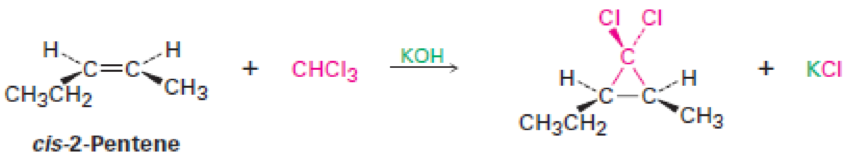


① Base abstracts the hydrogen from chloroform, leaving behind the electron pair from the C–H bond and forming the trichloromethanide anion.

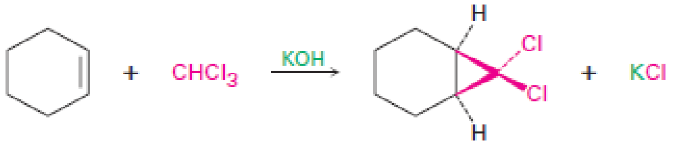
② Spontaneous loss of chloride ion then yields the neutral dichlorocarbene.

Figure 8-8 Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base. Deprotonation of $CHCl_3$ gives the trichloromethanide anion, - :CCl_3, which spontaneously expels a Cl- ion.

If dichlorocarbene is generated in the presence of an alkene, addition to the double bond occurs and dichlorocyclo propane is formed. As the reaction of dichlorocarbene with *cis*-2-pentene demonstrates, the addition is **stereospecific**, meaning that only a single stereoisomer is formed as product. Starting from a cis alkene, for instance, only cis-disubstituted cyclopropane is produced; starting from a trans alkene, only trans-disubstituted cyclopropane is produced.



cis-2-Pentene



Cyclohexene

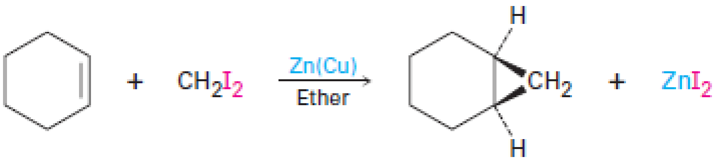
The best method for preparing non halogenated cyclopropanes is by a process called the **Simmons–Smith reaction**. First investigated at the DuPont company, this reaction does not involve a free carbene. Rather, it utilizes a *carbenoid*—a metal-complexed reagent with carbene-like reactivity. When diiodomethane is treated with a specially prepared zinc–copper mix, (iodomethyl) zinc iodide, ICH_2ZnI, is formed. In the presence of an alkene, ICH_2ZnI transfers a CH_2 group to the double bond to yield cyclopropane.

For example, cyclohexene reacts cleanly and with good yield to give the corresponding cyclopropane. Although we won't discuss the mechanistic details, carbene addition to an alkene is one of a general class of reactions called *cycloadditions*,

$$CH_2I_2 + Zn(Cu) \longrightarrow ICH_2{-}ZnI \quad [\text{":}CH_2\text{"}]$$

Diiodomethane

(Iodomethyl)zinc iodide
(a carbenoid)

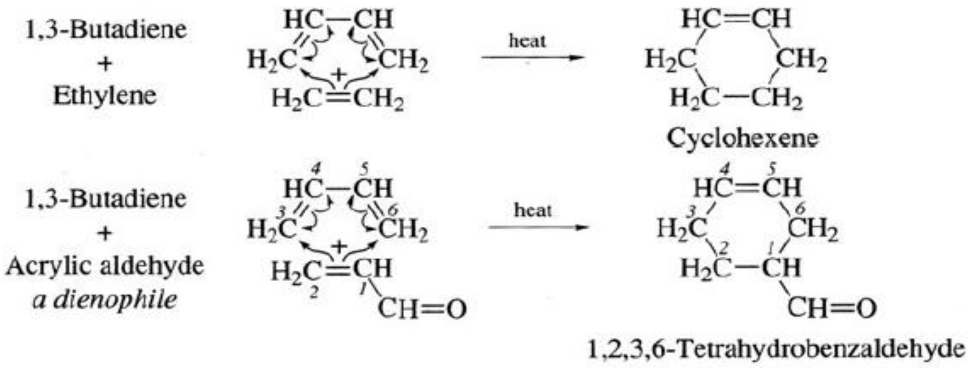


Cyclohexene

Bicyclo[4.1.0]heptane
(92%)

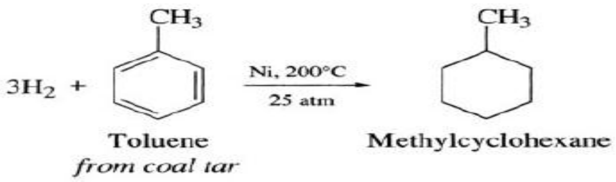
Cycloaddition Reactions of Alkenes (The Diels-Alder reaction [2+4]).

A conjugated diene and an alkene form a cyclohexene. Reactive alkenes (dienophiles) have electron-attracting groups on their unsaturated C's.



Hydrogenation of benzene rings

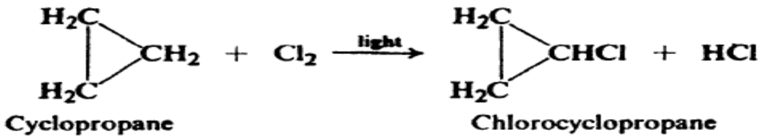
Cyclohexanes may be formed by hydrogenating compounds with benzene rings, many of which are isolated from coal, as illustrated with toluene:

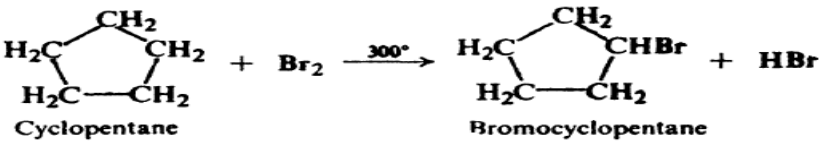


Reactions of Cycloalkanes

Free-radical substitution

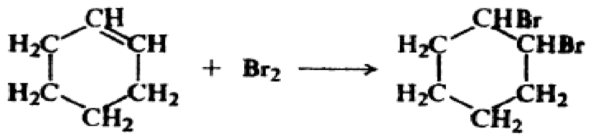
Alicyclic hydrocarbons undergo the same reactions as their open-chain analogs. Cycloalkanes undergo chiefly free-radical substitution for example:



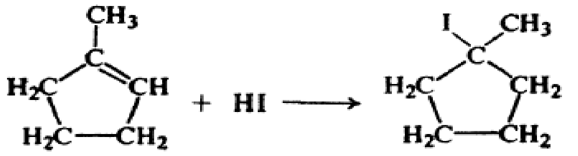


Addition reactions

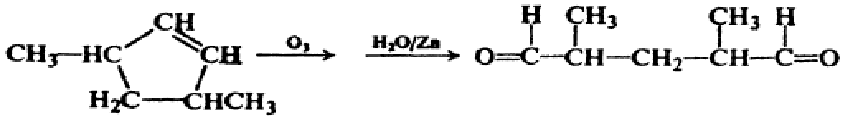
Cycloalkenes undergo chiefly addition reactions, both electrophillic and free radical; like other alkenes, they can also undergo cleavage and allylic substitution for example:



Cyclohexene 1,2-Dibromocyclohexane



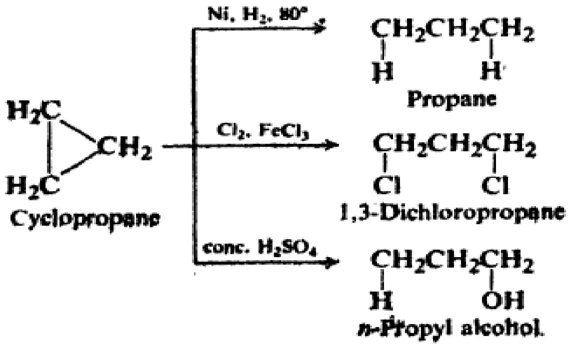
1-Methylcyclopentene 1-Iodo-1-methylcyclopentane



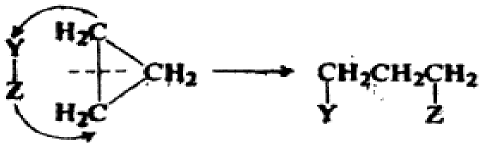
3,5-Dimethylcyclopentene A dialdehyde

Reactions of Small Rings. (Cyclopropane and cyclobutane)

Besides the free-radical substitution reactions that are characteristic of cycloalkanes and of alkanes in general, cyclopropane and cyclobutane undergo certain addition reactions. These addition reactions destroy the cyclopropane and cyclobutane ring systems, and yield open-chain products for example:



In each of these reactions a carbon-carbon bond is broken, and the two atoms of the reagent appear at the ends of the propane chain:



Addition of HBr to 1,1-dimethylcyclopropane resemble Markovnikov addition. The proton of HBr is attacked by an electron pair of a bent cyclopropane sigma bond to form a carbocation that adds Br$^-$ to give a 1,3-Markovnikov-addition product.