

## Chapter 9 Alkyl Halides and Aryl Halides

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#### 9.4 Reactions of aryl halides

- (a) Nucleophilic substitution
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Problems

Answers

Organohalogen compounds, in which halogen atoms are substituted on carbon atoms of organic compounds, scarcely exist as such in nature, and many of them are synthetic materials. These are relatively easily synthesized in quantity. Because of their high reactivity, they are widely used in laboratories and industries.

Among halogenated aliphatic compounds, especially alkyl halides of low molecular weight play an important role as organic solvents. These exhibit solubility to many organic compounds higher than corresponding hydrocarbons. Aryl halides, in which halogen atoms are bonded directly to the benzene ring are also very useful materials.

When the kind of halogen atoms are changed in organohalogen compounds, their properties are accordingly varied. This fact provides good materials for theoretical study.

Many kinds of organohalogen compounds are produced in industrial scale, and are used as agricultural chemicals, solvents, and for other purposes. Recently, however, there arises a major problem with their residual, stability, and toxicity. Today, there is a tendency to put restrictions on use of many of them.

## 9.1 Properties and nomenclature of organohalogen compounds

### (a) Alkyl halides

#### (1) Types and names of alkyl halides

Organic compounds containing halogens are roughly classified into two groups: one in which halogen atoms are directly bonded to carbon atoms, and the other, acid halides in which the OH group in the carboxy group is replaced by a halogen atom. The latter will be treated in Chapter 12, carboxylic acids and their derivatives.

Organohalogen compounds are roughly classified into two groups: one, alkyl halides or haloalkanes, in which hydrogen atoms of alkanes are replaced with halogen atoms, and the other, aryl halides or haloarenes, in which hydrogen atoms of arenes are replaced with halogen atoms. In addition, there are halogenated alkenes and alkynes.

**Point:** Classification of organohalogen compounds  
 Aliphatic halogenated compounds: alkyl halides, *etc.*  
 Aromatic halogenated compounds: aryl halides, *etc.*

If hydrogen atoms of alkanes are substituted by chlorine, bromine, or iodine atoms, their melting and boiling points increase in this order. The melting and boiling points of the fluorinated compound change very little. The density of alkyl halides increases due to the introduced halogen atoms.

The volatility of alkyl fluorides is high and their surface tension is small. Alkyl fluorides with a small number of fluorine atoms (including those which contain chlorine in addition to fluorine) are called “flon”, and once widely used as coolants, cleaning solvents, and propellants. It has been pointed out that these compounds are responsible for the destruction of the ozone layer, and now the use of some flons are regulated. Some of chlorinated alkanes are also under regulation.

#### (2) Nomenclature of alkyl halides

Generally, alkyl halides are named based on both the substitutive nomenclature and radicofunctional nomenclature. Common names are already introduced.

haloalkane, haloarene (substitutive nomenclature)

alkyl halide, aryl halide (radicofunctional nomenclature)

In substitutive nomenclature, “halogen” is to be used exclusively as a prefix. Mixed use of two methods of nomenclatures should be avoided.

[Example]  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$

1-chloropropane (substitutive)

propyl chloride (radicofunctional)

propane chloride (error; mixed use)

[Example]  $\text{CH}_3\text{CHClCH}_3$

2-chloropropane (substitutive)

isopropyl chloride (radicofunctional)

[Example]  $\text{BrCH}_2\text{CH}_2\text{Br}$

1,2-dibromoethane (substitutive)

ethylene dibromide (radicofunctional)

ethane dibromide (error; mixed use)

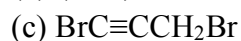
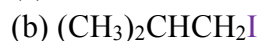
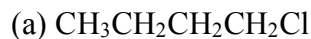
[Example]  $\text{CH}_2=\text{CHCl}$

chloroethylene (substitutive)  
vinyl chloride (radicofunctional)

**Exercise 9.1** Naming of alkyl halides

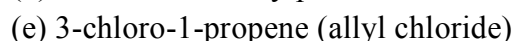
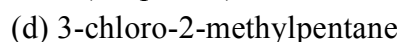
(1)

Name the following compounds.

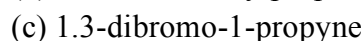
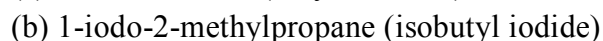


(2)

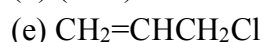
Draw the (simplified) structures of the following compounds.

**Answer**

(1)



(2)



In Table 9.1, examples of alkyl halides (haloalkanes) are listed.

**Table 9.1** Representative alkyl halides

name*	structural formula	melting point (°C)	boiling point (°C)
methyl chloride (chloromethane)	$\text{CH}_3\text{Cl}$	-97.72	-23.76
methyl bromide (bromomethane)	$\text{CH}_3\text{Br}$	-93.66	3.56
methyl iodide (iodomethane)	$\text{CH}_3\text{I}$	-66.45	42.8
methylene chloride (dichloromethane)	$\text{CH}_2\text{Cl}_2$	-96.8	40.21
chloroform** (trichloromethane)	$\text{CHCl}_3$	-63.5	61.2
carbon tetrachloride** (tetrachloromethane)	$\text{CCl}_4$	-28.6	76.74
ethylidene dichloride (1,1-dichloroethane)	$\text{CH}_3\text{CHCl}_2$	-96.7	57.3
1,2-dichloroethane	$\text{ClCH}_2\text{CH}_2\text{Cl}$	-35.3	83.38
vinyl chloride (1-chloroethylene)	$\text{CH}_2=\text{CHCl}$	-150.7	-13.70
vinylidene chloride (1,1-dichloroethylene)	$\text{CH}_2=\text{CCl}_2$	-122.1	31.7
benzyl chloride (chloromethyl)benzene***	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	-39.2	179.3-179.4

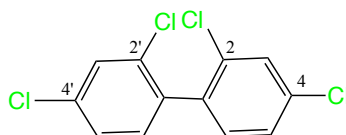
\* radicofunctional name (substitutive name) \*\* common name \*\*\* IUPAC name

**(b) Aryl halides**

**(1) Types and names of aryl halides**

Aryl halides are very useful compounds as such, and are used as the starting materials for other aromatic compounds. The problem is their stability, and hence their residual components are problematic if these are used in industry in quantity.

Polychlorobiphenyl (PCB), obtained by chlorination of biphenyl, is a mixture of compounds containing three or four chlorine atoms. These had been used widely because these are relatively cheap, stable to heat, and have excellent electric property. Their use was prohibited because of their strong toxicity and their bad influence on the environment.



One example of PCB; 2,2',4,4'-tetrachlorobiphenyl

**(2) Nomenclature of aryl halides**

Aryl halides are generally named by the substitutive method and halogens are used as prefix.

[Example]  $C_6H_5Br$

bromobenzene (substitutive)

phenyl bromide (radicofunctional; seldom used)

Occasionally some aryl halides are named by radicofunctional method by combining some group (such as aryl, benzyl, etc) with chloride, bromide, *etc.*

[Example]  $C_6H_5CH_2Cl$

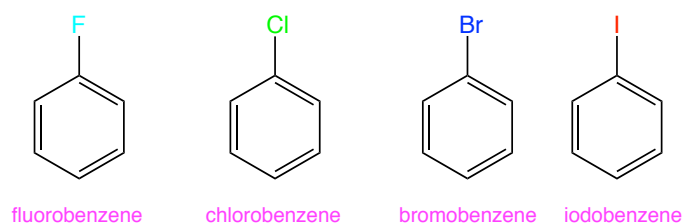
chlorophenylmethane (substitutive)

benzyl chloride (radicofunctional; commonly used)

In Table 9.2, examples of aryl halides are listed.

**Table 9.2** Some aryl halides

name	structural formula	melting point (°C)	boiling point (°C)
fluorobenzene	$C_6H_5F$	-41.9	82.7
chlorobenzene	$C_6H_5Cl$	-45	132
bromobenzene	$C_6H_5Br$	-30.6	156.15
iodobenzene	$C_6H_5I$	-31.33	188.45
1,2-dichlorobenzene ( <i>o</i> -dichlorobenzene)	$1,2-C_6H_4Cl_2$	-17.03	180.48
1,3-dichlorobenzene ( <i>m</i> -dichlorobenzene)	$1,3-C_6H_4Cl_2$	-24.76	173.00
1,4-dichlorobenzene ( <i>p</i> -dichlorobenzene)	$1,4-C_6H_4Cl_2$	53.5	174.12



## 9.2 Structure of organic halides

Because halogens are monovalent, there arises little change in the structures of organic compounds when hydrogen atom(s) in them are substituted by halogen atom(s). A fluorine atom is slightly larger than a hydrogen atom, while the size of a chlorine atom is much the same with a methyl group. A bromine atom and an iodine atom are considerably larger than a chlorine atom.

The repulsion with adjacent hydrogen atoms is not as large as that expected from the van der Waals radii because the carbon-halogen bond length is large. In Table 9.3 van der Waals radii of halogen atoms and the carbon-halogen (C-X) bond lengths are summarized. A large difference is observed between fluorine and the other halogen atoms.

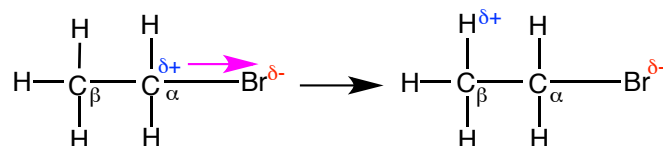
1,2-dichloroethane and other 1,2-dihaloethanes have antiperiplanar conformations (see Table 5.4). In addition to the steric hindrance, an electric repulsion between two halogen atoms plays a role.

**Table 9.3** Van der Waals radii and C-X bond lengths of halogens

halogen	van der Waals radius (nm)	C-X bond length (nm)
F	0.147	0.1323
Cl	0.175	0.1767
Br	0.185	0.1935
I	0.198	0.215

## 9.3 Reaction of alkyl halides

The most significant feature of chemical properties of organohalogen compounds is the polarization of C-halogen bonds due to the large electronegativities of halogens. In ethyl bromide, for instance, the carbon atom to which the bromine atom is bonded ( $\alpha$ -carbon) and the hydrogen atom which is bonded to the adjacent carbon ( $\beta$ -carbon) bear partial positive charge by the effect of bromine atom. As a result, alkyl halides perform elimination in addition to substitution.



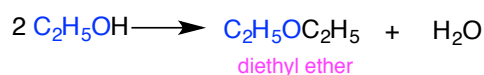
### (a) Nucleophilic substitution

The nucleophilic substitution is the most important reaction of alkyl halides and this aspect is already discussed in detail in connection with reaction mechanism in Ch. 4. A few examples of nucleophilic substitution will be introduced.

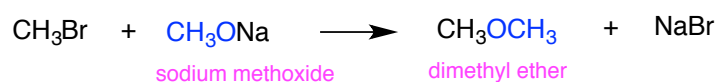
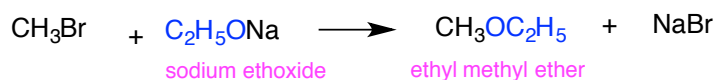
#### (1) Williamson's ether synthesis

The well-known ether synthesis, that is, heating an alcohol with concentrated sulfuric acid

can provide only symmetric ethers such as diethyl ether.



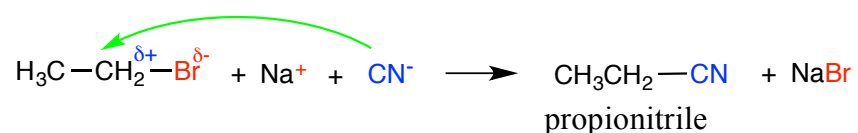
To the contrary, Williamson's ether synthesis, invented by Alexander William Williamson (1824-1904), the reaction between alkyl halides and alkoxides (such as methoxide or ethoxide) can provide asymmetric ethers. By changing the combination of starting compounds, any type of ethers can be synthesized.



## (2) Reaction with cyanides

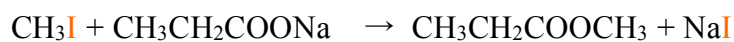
The nucleophilic reaction between alkyl halides and cyanide ions produce nitriles which have one more carbon atom than the starting halides. Nitriles are hydrolyzed to carboxylic acids *via* amides (Ch. 12).

This nucleophilic substitution is important as one of the methods to add carbon atoms to organic compounds. In practice, halides and sodium cyanide or potassium cyanide are reacted as shown below.



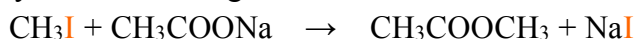
## (3) Esterification

Esters are generally synthesized by the reaction between carboxylic acids and alcohols. However, there are other methods of ester synthesis. One example is the reaction between halides and the salts of carboxylic acids.

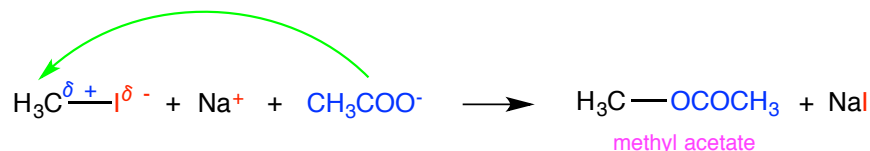


**Exercise 9.2** Analysis of nucleophilic substitution

Analyze the following reaction in a similar manner as the previous example.

**Answer**

The crucial point is that the nucleophilic reagent of this reaction is “carboxylate ion”.

**(b) Stereochemistry of nucleophilic substitution**

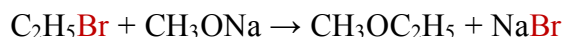
In Ch. 4, the reaction mechanism of the nucleophilic substitution was discussed in detail. The important aspect of stereochemistry of the reaction was not, however, treated.

When the carbon atom of the reaction center is asymmetric, its chirality may be temporarily lost in the intermediate or in the transition state as is suggested from the reaction mechanism discussed in Ch 4.1.

Now we will discuss the stereochemistry of Williamson’s ether synthesis. Firstly, we will consider the case where no asymmetric carbon atom is involved.

**(1) Stereochemistry of S<sub>N</sub>1 reactions**

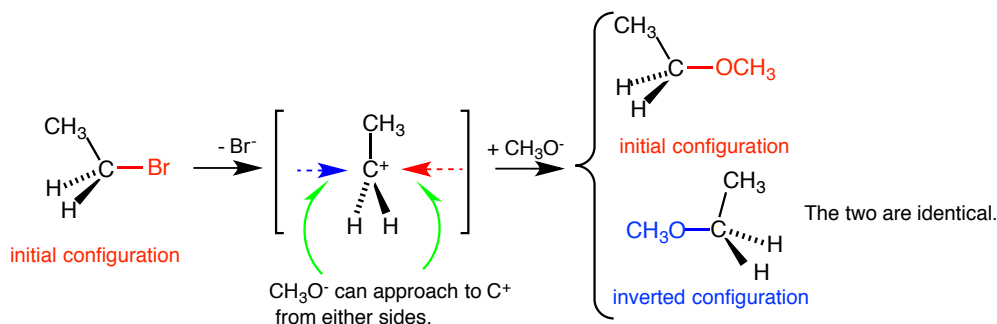
We will examine the process of the reaction between ethyl bromide and sodium methoxide



in a three-dimensional manner.

If the reaction proceeds *via* S<sub>N</sub>1, bromide ion leaves first, and a tri-coordinate and sp<sup>2</sup> hybridized carbocation intermediate is formed (Figure 9.1). Methoxide ion, the nucleophile, will approach to the carbocation from the right side or from the left side with equal probability. As a result, the product will be a mixture of equal amount of the one with the configuration of the starting molecule and the other with the inverted configuration of the starting molecule.

In this case, however, the one with the original configuration and the other with inverted configuration are identical. Hence only one product will be obtained.

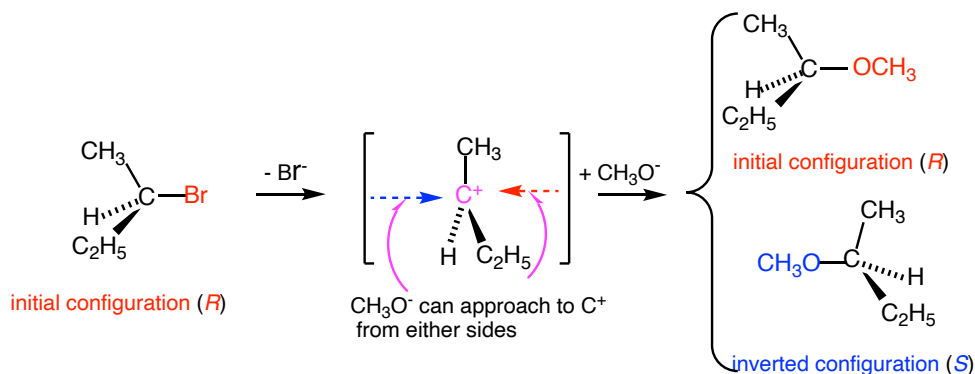


**Figure 9.1** Stereochemistry of S<sub>N</sub>1 reaction of ethyl bromide

What will happen if the reactant is *s*-butyl bromide (2-bromobutane; in this example

*R*-configuration) which has an asymmetric carbon atom? The nucleophilic reagent approaches to the generated carbocation from both sides with equal probability (Figure 9.2).

The product, 2-methoxybutane, is a 1:1 racemic mixture of the one with the original configuration and the other with inverted configuration. Thus,  $S_N1$  reaction of optically active (*R*)-*s*-butyl bromide yields the product, an optically inactive racemic mixture of 2-methoxybutane. If the starting molecule is optically active, and the product is a racemic mixture, you can say that the reaction proceeded via  $S_N1$ .

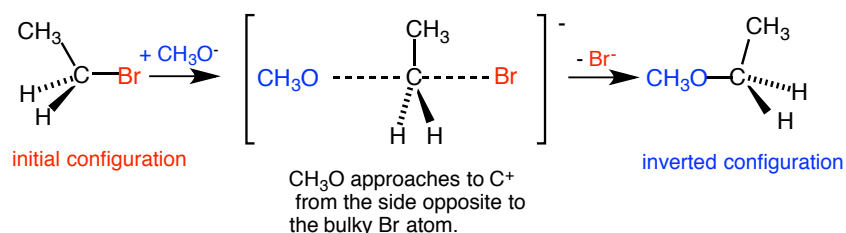


**Figure 9.2** Stereochemistry of  $S_N1$  reaction of *s*-butyl bromide

## (2) Stereochemistry of $S_N2$ reactions

Suppose the reaction between ethyl bromide and sodium methoxide proceeds *via*  $S_N2$ . First, methoxide ion will approach to the carbon atom from the opposite side of bromine to form penta-coordinated transition state (Figure 9.3). Then, the bromine atom is removed as a bromide ion. During this process, the hybridization state of the carbon atom returns to  $sp^3$ , the position of bromine atom and that of methoxide ion is exchanged. Hence the configuration of the product is inverted (**inversion**).

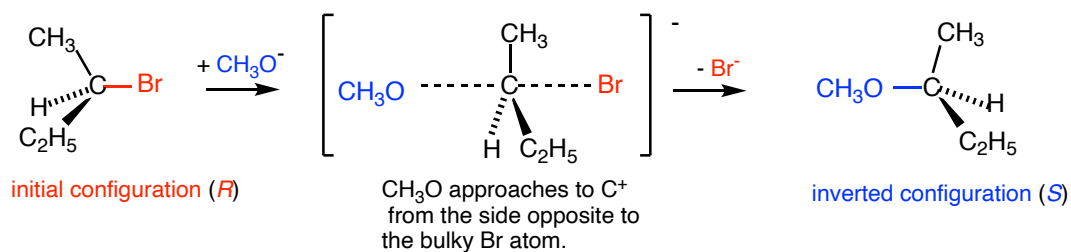
The product, ethyl methyl ether has no asymmetric carbon atom and optically inactive. This means that the inversion is not proved in this case.



**Figure 9.3** Stereochemistry of  $S_N2$  reaction of ethyl bromide

What will happen if the reactant is (*R*)-*s*-butyl bromide (2-bromobutane) which has an asymmetric carbon atom? First, methoxide ion will approach to the carbon atom from the opposite side of bromine to form penta-coordinated transition state (Figure 9.4). Then, the bromide ion is removed and the inversion of configuration takes place. The result is different from the case of ethyl bromide since in this case both the reactant and the product are optically active, and the inversion can be proved from the change of specific rotation.





**Figure 9.4** Stereochemistry of S<sub>N</sub>2 reaction of *s*-butyl bromide

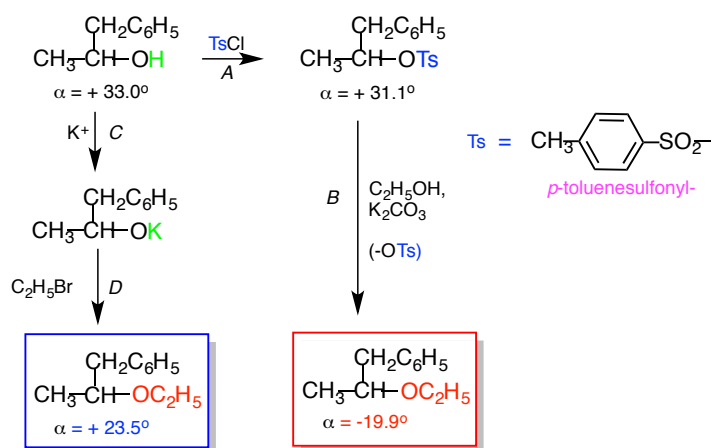
In practice, if the specific rotations of (*R*)- and (*S*)-*s*-butyl bromide and (*R*)- and (*S*)-2-methoxybutane are known, the stereochemical process of the reaction can be traced by measuring the specific rotation. In fact, the stereochemistry of S<sub>N</sub>1 and S<sub>N</sub>2 reactions has been proved by many experiments involving measurements of specific rotation.

You must notice that there is no relation between the configuration and the sign of specific rotation, as was mentioned before (Ch. 8.2(a)). Even if (*R*)-reactant is inverted to become (*S*)-product, sometimes the sign does not change (the value itself may, however, change).

### (3) Example of inversion

An example which proves the inversion does in fact take place by measuring the specific rotation. The starting compound is optically active 1-phenyl-2-propanol, and its dextrorotatory, *i.e.*, (+)-isomer. Figure 9.5 shows the course of the reaction.

The ethyl ether of 1-phenyl-2-propanol is synthesized *via* two different procedures. The absolute value of specific rotation of the product *via* reactions A and B, and that of the product *via* reactions C and D are relatively close. The signs are, however, opposite, indicating that the two are enantiomers each other. This means that an inversion in fact takes place at one of the reactions A, B, C, and D. What happens in each reaction is summarized below.



**Figure 9.5** Nucleophilic substitution of optically active 1-phenyl-2-propanol ( $\alpha = [\alpha]_D$ )

Reaction A: bond cleaved; O-H. bond formed O-S

Reaction B: bond cleaved; C-O. bond formed C-O

Formation of an ether by the reaction between acid chloride and ethanol

Reaction C: bond cleaved; O-H. bond formed O-K

Formation of an alkoxide by the reaction between acid bromide and ethanol

Reaction D: bond cleaved; O-K. bond formed O-C (Williamson's ether synthesis).

Notice that the asymmetric carbon atom is not the reaction center.)

Except reaction *B*, no reaction takes place at the asymmetric carbon atom. Hence, if an inversion takes place, this should occur in reaction *B*.

In this way, the fact that an inversion really takes place and that the reaction *B* proceeds via  $S_N2$  is experimentally proved.

**Point:** Stereochemistry of nucleophilic substitution ( $S_N$ )

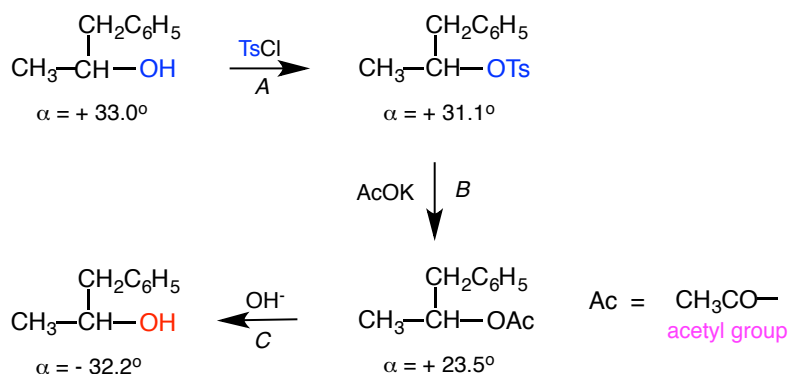
$S_N1$  is related to racemization

$S_N2$  is related to inversion

These relations can only be proved by experiments with the one enantiomer of optically active pair.

**Exercise 9.3** Experimental proof of inversion

Following the method of Figure 9.5, analyze each step of the reaction below. Guess the conclusion which can be obtained from the measurements of specific rotation.



**Answer**

The reactant and the product are both 1-phenyl-2-propanol. The magnitude of their specific rotation is much the same but the sign is different. This indicates that at some stage an inversion occurred. What happens in the reactant in each reaction is summarized below.

Reaction *A*: bond cleaved; O-H. bond formed O-S (the same with Figure 9.5)

Reaction *B*: bond cleaved; C-O. bond formed C-O.

Nucleophilic substitution between an ester and acetoxide ion  $\text{AcO}^-$

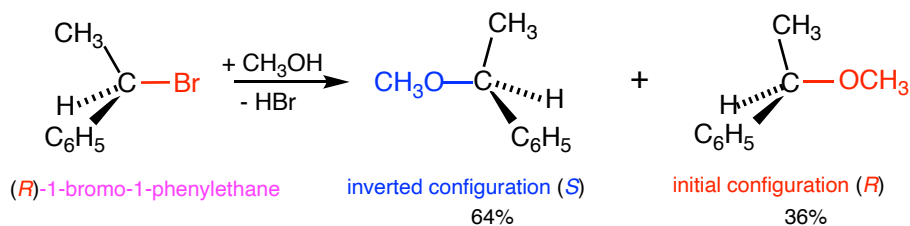
Reaction *C*: bond cleaved; O-C. bond formed O-H

(Hydrolysis of an ester)

The bond cleavage or bond formation at the asymmetric carbon atom takes place only in reaction *B*. It can be concluded that the inversion takes place in this reaction.

**(4) Simultaneous progress of  $S_N1$  and  $S_N2$**

This problem was already discussed in Ch. 4.4. This can be proved by using optically active reactants. Simultaneous progress of  $S_N1$  and  $S_N2$  tends to occur when the reactant is a secondly compound (Figure 9.6). Experiments, that is, incomplete racemization or incomplete inversion, prove this fact.



**Figure 9.6** An example of simultaneous progress of  $S_N1$  and  $S_N2$

**Exercise 9.4** Simultaneous progress of  $S_N1$  and  $S_N2$

Estimate the proportion of inversion ( $S_N2$ ) to racemization ( $S_N1$ ) based on the distribution of stereochemistry of the products of the reaction depicted in Figure 9.6.

**Answer**

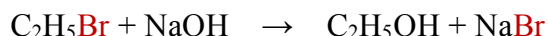
Make the ratio of inversion as  $x$ . By inversion,  $x$  of (*S*) isomer will be formed while by racemization each  $(1 - x)/2$  of (*S*) isomer and (*R*) isomer will be formed

For (*S*)  $x + (1 - x)/2 = 0.64$ . For (*R*),  $(1 - x)/2 = 0.36$ . Then  $x = 0.28$ . Racemization is 28 %.

**(c) Elimination**

**(1) Driving force of elimination**

So far, we do not consider the possibility of simultaneous progress of two reactions. Though  $S_N1$  and  $S_N2$  do progress simultaneously, these are expressed by the same reaction formula. In this sense these two reactions may be regarded as the same reaction. In the world of organic chemistry, rather frequently, two, or more than two reactions progress simultaneously. For example, the reaction between ethyl bromide and sodium hydroxide proceeds via  $S_N2$  mechanism because the halide is a primary compound devoid of steric hindrance.



Generally, however, in the substitution in which a halide ion is replaced by a hydroxide ion, an elimination in which a hydrogen halide is removed accompanies.



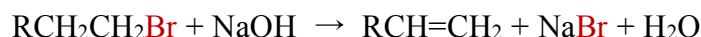
The driving force of this reaction is also the polarization of C-halogen bond due to the large electronegativity of the halogen.

In Ch. 9.3, it was shown that the hydrogen atom  $H_\beta$  bonded to  $C_\beta$  bears some positive charge because positively charged  $C_\alpha$  draws electron from neighboring atoms including  $C_\beta$ . The nucleophile, hydroxide ion in this case, attacks  $H_\beta$  rather than  $C_\alpha$ , and withdraws  $H^+$  from ethyl bromide (to form  $H_2O$ ) competitively. By the following processes, hydrogen bromide is eliminated from ethyl bromide to form ethylene.

**(2) Unimolecular elimination (E1)**

If the rate of elimination reaction is determined, and examined the dependency of the concentration of the reactant, it is possible to differentiate the unimolecular reaction and the

bimolecular reaction. The situation is the same with substitution reactions. For the reaction



the rate equation will be one out of the two.

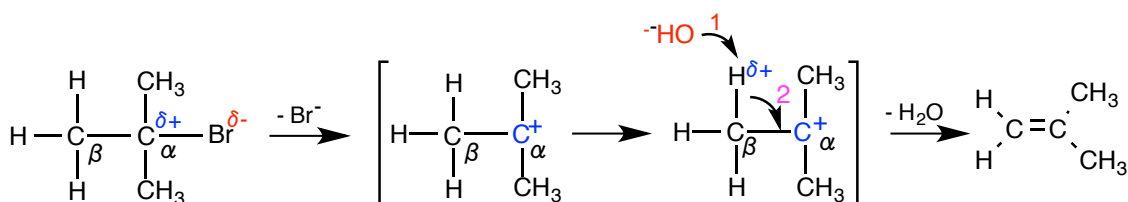
$$v = k[\text{RCH}_2\text{CH}_2\text{Br}] \quad (\text{unimolecular reaction, E1})$$

$$v = k[\text{RCH}_2\text{CH}_2\text{Br}][\text{OH}^-] \quad (\text{bimolecular reaction, E2})$$

Each type of the reaction is designated as E1 or E2 (E stands for elimination).

Following the example of  $\text{S}_{\text{N}}1$ , the rate-determining step of E1 should be the removal of bromide ion from alkyl bromide (*i.e.*, formation of carbocation). In this case also tertiary alkyl halide is more reactive for E1 than primary halide. The process up to this stage is the same if the reaction proceeds via  $\text{S}_{\text{N}}1$  mechanism. If the electrophilic part of nucleophile (*i.e.*, hydroxide ion) will attack  $\text{C}_{\alpha}$ , the mechanism will be  $\text{S}_{\text{N}}1$ . If, however, the hydroxide ion attacks  $\text{H}_{\alpha}$  to pull it up as a proton, a double bond is formed between  $\text{C}_{\alpha}$  and  $\text{C}_{\beta}$ . Thus, the elimination E1 is complete.

The flow of the elimination with *t*-butyl bromide as the reactant is shown in Figure 9.7. Three stages of the reaction should clearly be recognized.



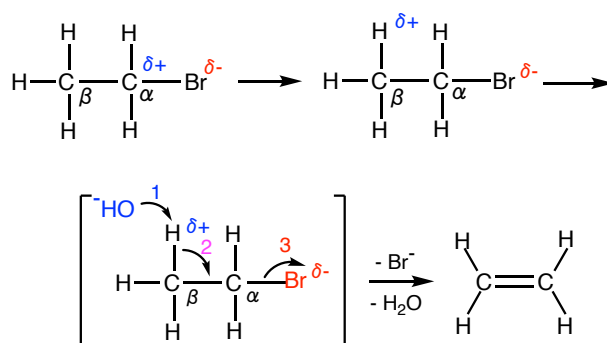
**Figure 9.7** Unimolecular elimination (E1) of *t*-butyl bromide

**Point:** The three stages of unimolecular elimination (E1)

- (1) Elimination of bromide ion and formation of carbocation
  - (2) Pulling out of  $\text{H}_{\alpha}$  by a base (arrow 1 in Figure 9.7)
  - (3) Removal of hydrogen (as water). The shared electron pair of  $\text{C}-\text{H}$  bond is used to form a double bond (arrow 2 in Figure 9.7).
- (2) and (3) occur simultaneously.

### (3) Bimolecular elimination (E2)

Bimolecular eliminations (E2) tend to occur, as is the case with nucleophilic substitution, when the reactants are primary alkyl halides. Figure 9.8 shows the flow of the reaction. Three stages of the reaction should clearly be recognized.



**Figure 9.8** Bimolecular elimination of ethyl bromide

**Point:** The three stages of bimolecular elimination (E2)

(1) Pulling out of  $H\alpha^+$  by a base (arrow 1 in Figure 9.8)

(2) The shared electron pair of C-H bond moved to form a double bond (arrow 2 in Figure 9.8)

(3) Elimination of bromide ion (arrow 3 in Figure 9.8). The shared electron pair of C-Br bond turns into unshared electron pair of bromide ion.

(1), (2), and (3) occur simultaneously.

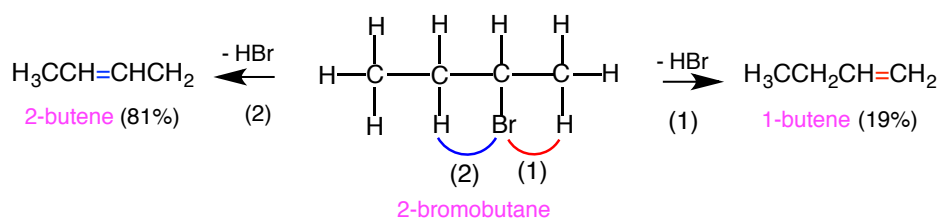
#### (4) Orientation of elimination

Suppose a hydrogen halide is added to an alkene with differently substituted two carbon atoms. The structure of the products may be different depending on the carbon atom firstly attacked by the hydrogen atom. Which one is in fact obtained is the orientation of addition (see Ch. 6.3).

Orientation is also relevant to elimination. If there are two or more than two carbon atoms adjacent to the carbon atom bonded to the halogen atom to be removed and possess removable hydrogen(s), the problem of orientation arises.

An example is given below. When hydrogen bromide is eliminated from 2-bromobutane, two processes (1) and (2) are possible depending on which hydrogen is removed. The products will be either 1-butene or 2-butene depending on the processes (1) or (2) (Figure 9.9). According to the experiment, the main product is 2-butene by the process (2).

Russian chemist Aleksander Mikhaylovich Zeitssev (1841-1910) summarized the experimental results into an empirical rule, that is, **Zeitssev rule**.



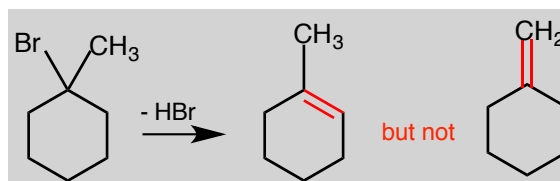
**Figure 9.9** Orientation of elimination

**Point:** Zeitssev rule

When hydrogen halides are eliminated from alkyl halides, the more substituted alkenes will be formed.

**Exercise 9.5** Zaitsev rule

Draw the structure of the main product when 1-bromo-1-methylcyclohexane is reacted with a strong base (*e.g.*, KOH).

**Answer****(5) Competition between substitution and elimination**

When organohalogen compounds react with nucleophiles, four types of reactions may take place depending on the structure of reactants and the reaction condition. Whether reaction conditions are acidic (*e.g.*, in concentrated hydrochloric acid), or basic (*e.g.*, nucleophiles are  $\text{OH}^-$ ,  $\text{OCH}_3^-$  or  $\text{OC}_2\text{H}_5^-$ ) are very important. In Figure 9.10, a few examples are summarized. In both acidic conditions and basic conditions,  $\text{S}_{\text{N}}1$  and  $\text{E}1$  do not take place when the substrates are primary. In basic conditions,  $\text{E}2$  occur rather easily when the substrates are secondary or tertiary.

**Table 9.4** Competition between substitution and elimination

structure of reactant	condition	$\text{S}_{\text{N}}1$	$\text{S}_{\text{N}}2$	$\text{E}1$	$\text{E}2$
$\text{RCH}_2\text{X}$ (primary)	acidic	X	O	X	X
	basic	X	O	X	$\Delta$
$\text{RR}'\text{CHX}$ (secondary)	acidic	$\Delta$	$\Delta$	X	$\Delta$
	basic	$\Delta$	$\Delta$	X	O
$\text{RR}'\text{R}''\text{CX}$ (tertiary)	acidic	O	X	O	X
	basic	X	X	O	O

X: hard to occur

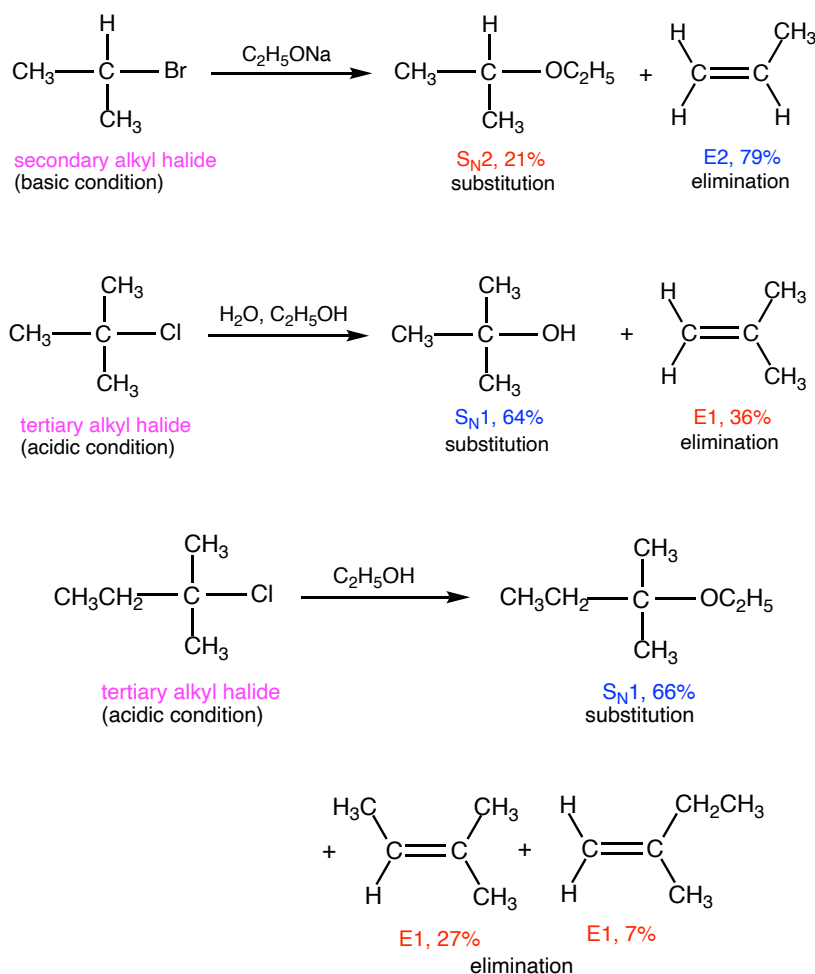
$\Delta$ : may occur depending on the reaction condition

O: easy to occur

acidic condition; *e.g.* in conc. hydrochloric acid

neutral condition, *e.g.* in water or alcohol

basic condition; such nucleophiles as  $\text{OH}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{C}_2\text{H}_5\text{O}^-$



**Figure 9.10** Competition between substitution and elimination

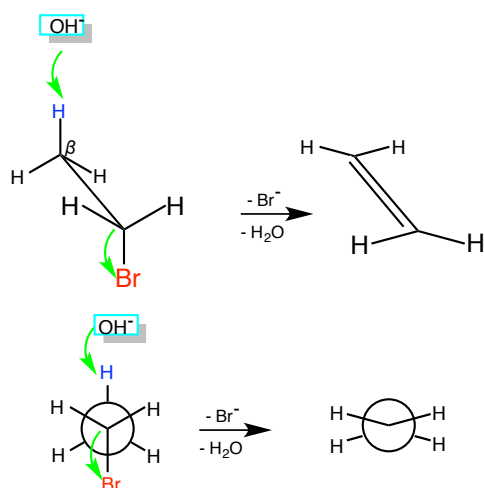
When reactants are primary,  $\text{S}_{\text{N}}2$  are main reactions, but  $\text{E}2$  are also possible.

When reactants are secondary, there are competition between substitution ( $\text{S}_{\text{N}}1$  or  $\text{S}_{\text{N}}2$ ) and elimination ( $\text{E}1$ ). Judging from the amount of the products, elimination is more important.

When reactants are tertiary, there are competition between substitution ( $\text{S}_{\text{N}}1$ ) and elimination ( $\text{E}1$ ) in acidic conditions. These points are summarized in Table 9.4. This is a mere guideline, and cases different from this table may take place depending on the structures and properties of reactants or reagents, or on reaction condition.

#### (d) Stereochemistry of elimination

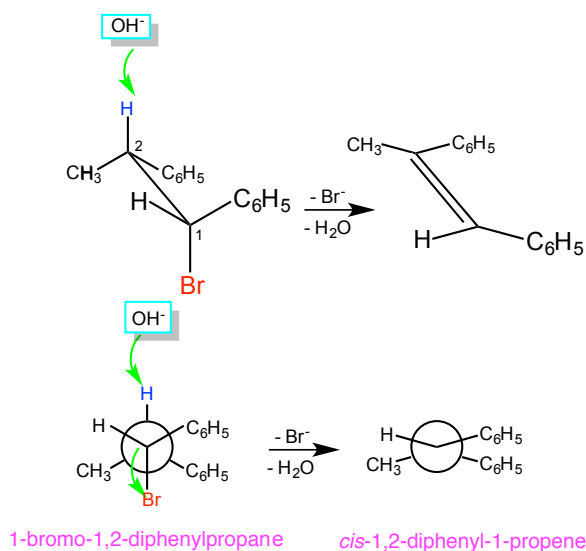
In the case of nucleophilic substitution, the nucleophile approaches to the carbon atom from the back side of the leaving group. This is to avoid the steric hindrance which is unavoidably involved. This should be the case with elimination, and when the hydroxide ion approaches to  $\text{H}_{\beta}$ , it chooses the hydrogen atom which is furthest to bromine atom, that is, *trans* hydrogen. In other words, the leaving hydrogen atom and bromine atom are *trans* each other. Hence elimination of this type is named ***trans* elimination**, or *anti* elimination. In Figure 9.11, *trans* elimination of ethyl bromide is illustrated by two ways, the perspective view and Newman projection.



**Figure 9.11** The stereochemistry of the *trans* elimination of ethyl bromide

The situation is very close to the case of *trans* addition of bromine or hydrogen bromide to alkenes. Similarly, it is impossible to confirm that this reaction does take place according to this pathway. In Figure 9.11, even if a hydrogen which is not *trans* to the bromine atom is eliminated, the product is also ethylene. This is because the reactant, and hence the product is much too simple.

If a little more complex reactant is employed, the product *via trans* elimination and the product *via* another route will be different. In Figure 9.12, both C<sup>1</sup> and C<sup>2</sup> of 1-bromo-1,2-diphenylpropane are asymmetric carbon atoms. Hence, if the leaving bromine atom and hydrogen atom take *trans* position, the positions of remaining atoms and groups of atoms are fixed, and *cis*-1,2-diphenyl-1-propene is necessarily formed.



**Figure 9.12** The stereochemistry of *trans* elimination of 1-bromo-1,2-diphenylpropane



- (1) Determine the configuration of 1-bromo-1,2-diphenylpropane given in Figure 9.12 in terms of (*R*, *S*) convention.
- (2) Draw the process, like Figure 9.11, of the *trans* elimination of hydrogen bromide from 1-bromo-1,2-diphenylpropane which has the reverse configuration at C<sup>2</sup>.

### Answer

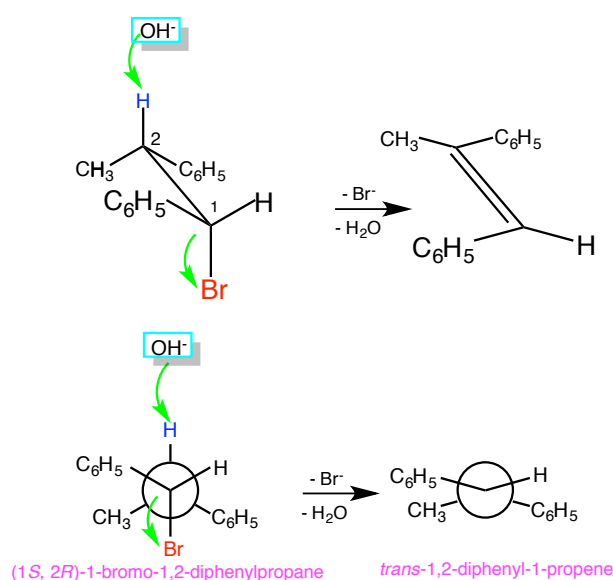
(1) The priority is as follows.

C<sup>1</sup>: Br > C<sub>6</sub>H<sub>5</sub> > the half of the molecule > H (*R* configuration)

C<sup>2</sup>: the half of the molecule > C<sub>6</sub>H<sub>5</sub> > CH<sub>3</sub> > H (*S* configuration)

The configuration is (1*R*, 2*S*)

(2) The *trans* elimination of (1*S*, 2*R*)-1-bromo-1,2-diphenylpropane is explained by Figure 9.13. The product is *trans*-1,2-diphenyl-1-propene.

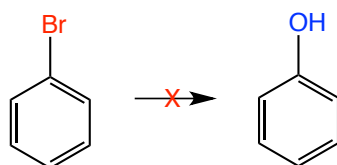
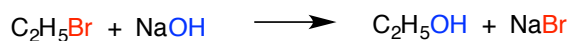


**Figure 9.13** *trans*-elimination of (1*S*, 2*R*)-1-bromo-1,2-diphenylpropane

## 9.4 Reactions of aryl halides

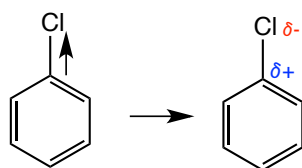
### (a) Nucleophilic substitution

Will nucleophilic substitution, most popular for alkyl halides, also take place for aryl halides? Differences in the reactivity of aromatic and aliphatic compounds also exist among organohalogen compounds. Under the condition in which ethyl bromide reacts with sodium hydroxide to form ethanol, bromobenzene does not react with sodium hydroxide to form phenol.

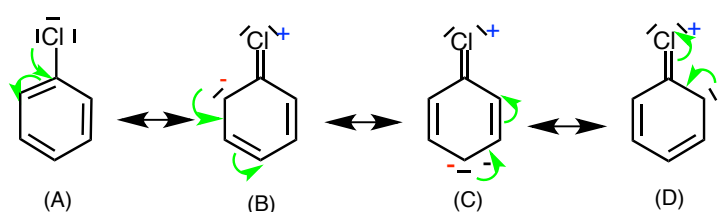


The difference of reactivity of alkyl halides and that of aryl halides is due to the presence of aromatic ring. Because of the large electronegativity of halogens the C-X bond is polarized and

the carbon atom to which the halogen atom is bonded bears a partial positive charge (*I* effect). The situation is much the same with alkyl halides.



The unshared electron pair of halogen atom flows into the benzene ring (delocalization), and the ring as a whole (including the carbon atom to which the halogen atom is bonded) bears partial negative charge (*R* effect). Hence, the situation is different from alkyl halides (Figure 9.14). For this reason nucleophilic substitution reactions do not easily occur for aryl halides.



**Figure 9.14** Resonance structure of chlorobenzene

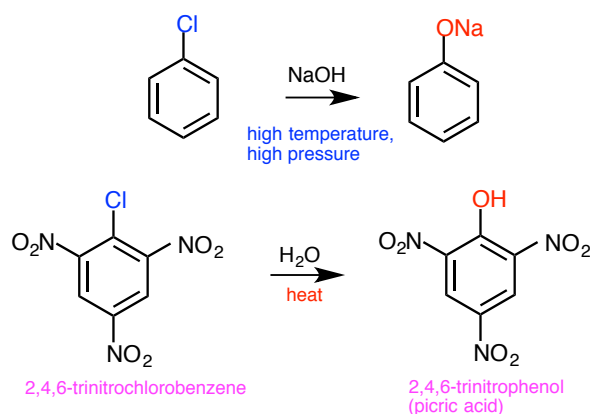
When two or more than two strong electron withdrawing groups (such as  $\text{NO}_2$  group) are introduced into the benzene ring, electrophilic substitution also occur with aryl halides. Under high pressure-high temperature condition, the reaction between aryl halides and sodium hydroxide affords phenol via phenoxides. This reaction is employed for industrial purpose (Figure 9.15).

2,4,6-trinitrochlorobenzene turns into 2,4,6-trinitrophenol (picric acid) when water is added and warmed.

## Electrophilic substitution

### (1) Halogens as substituents

Typical reactions of aromatic halides are aromatic electrophilic substitution. When compared with aromatic electrophilic substitution of benzene, as is the case with toluene (Ch. 7.3(b)), the following two points are to be discussed.



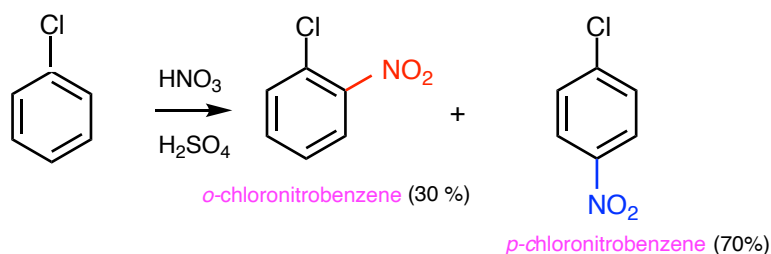
**Figure 9.15** Nucleophilic substitution of chlorobenzenes

- (i) Are aryl halides more reactive than benzene?  
 (ii) In which position will the second substituent be introduced?

The answer to question (i) may be obtained from the result of toluene. Halogens have  $+R$  and  $-I$  effects to benzene. If the latter is superior, the electron density of benzene ring is as a whole increased, aryl halides are more susceptible to electrophilic substitution.

Since nitration of chlorobenzene requires a little more severe reaction condition as compared with that of benzene, the reactivity of aryl halides is lower than that of benzene. Since the effect of decreasing electron density due to the electron withdrawing effect of halogens, the reactivity is decreased. Such substituents like halogens are called inactive substituents.

The answer to question (ii) is more easily predictable. When resonance effect is in action, the electron density of  $o$ - and  $p$ -positions are increased (but not for  $m$ -position), it is expected that the second substituent selectively enters into  $o$ - and  $p$ -positions. As the experimental results indicate (Figure 9.16), the prediction is confirmed.



**Figure 9.16** Nitration of chlorobenzene

**Point:** Substituent effect of aromatic electrophilic substitution

Go in and out of electrons occur at  $o$ - or  $p$ -position.

If the substituents are electron-donating, electron density increases.

If the substituents are electron-withdrawing, electron density decreases.

$I$ -effect: Depends on the type on substituents. The effect is larger if the substituents are closer.

$R$ -effect: Effective only at  $o$ - or  $p$ -position. No direct effect at  $m$ -position.

The **decreasing** order of electron density

Electron donating substituents: *ortho*, *para* > *meta*

Electron withdrawing substituents: *meta* > *ortho*, *para* (no increase at *meta*)

## (2) Electronic effect and steric effect

In case of nitration of chlorobenzene, suppose the reactivity of  $o$ - and  $p$ -positions are completely equal. Statistically  $o$ -isomer is expected to be formed twice as much as that of  $p$ -isomer. The reverse is, however, the case.

The reason is that  $o$ -position suffers from the steric hindrance by chlorine atom, and as a result,  $\text{NO}_2^+$  is difficult to approach to the ortho sites.

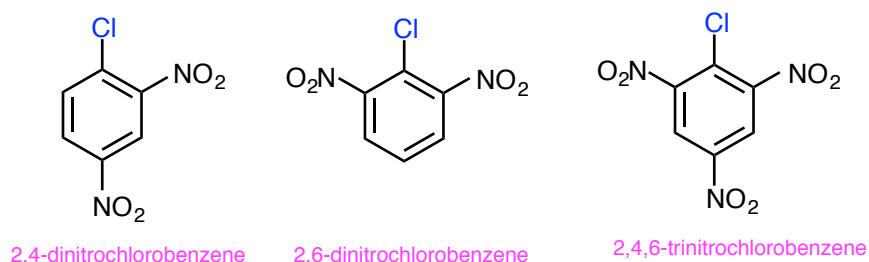
When organic reactions are discussed, not only electronic effect ( $R$ -effect and  $I$ -effect) but also steric effect is to be considered simultaneously.

**Exercise 9.7** Nitration of chlorobenzene

If nitration of chlorobenzene is carried out at higher temperature, it is anticipated that two or more than two nitro groups will be introduced to benzene ring. Predict the structures of the products.

### Answer

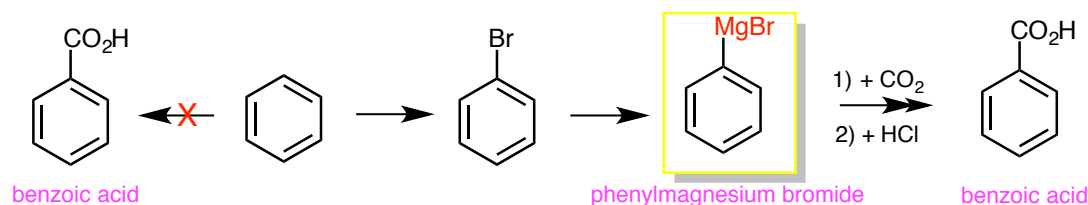
Since chlorine atom is an *o,p*-directing group, much the same result will be expected as that of toluene.



### (3) Grignard reagent

Aryl halides, such as chlorobenzene or bromobenzene, are readily obtainable from benzene, and these can be a good starting material of a variety of organic compounds.

When bromobenzene is reacted with magnesium (as powder or flake) in diethyl ether, phenylmagnesium bromide, in which magnesium atom inserts between carbon atom and bromine atom, is obtained (Figure 9.17).



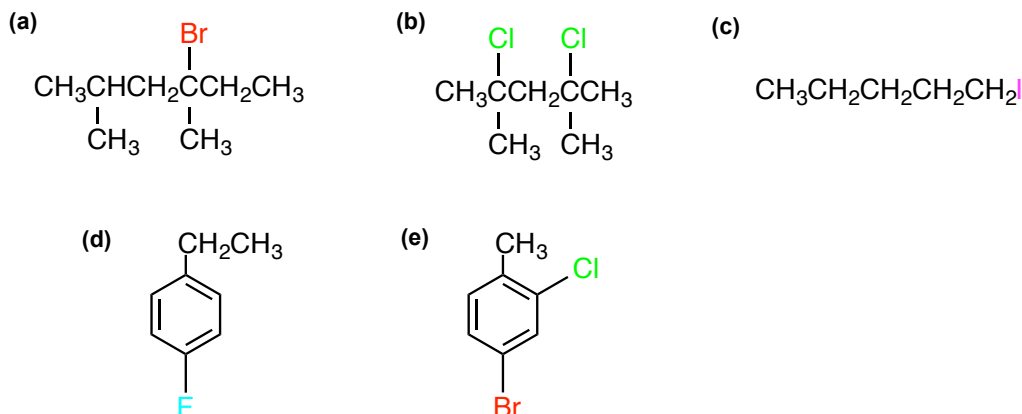
**Figure 9.17** An example of Grignard reaction

Phenylmagnesium bromide is a kind of organometallic compounds in which carbon-metal bonds are incorporated. This type of organometallic compounds is named Grignard reagent after the name of the inventor, François Auguste Victor Grignard (1871-1935). Reactions in which Grignard reagents are participating are named **Grignard reactions**, and these are widely used in organic synthesis (details are given in Ch. 11.4 (h)).

In the above example, Grignard reagent and carbon dioxide reacts to give benzoic acid by the hydrolysis of the product. It is very difficult to introduce directly a carboxy group into a benzene ring except rather special cases such as Kolbe-Schmitt reaction (Ch. 10.3). Thus, this method is now accepted as the standard procedure to obtain aromatic carboxylic acid.

**Problems****9.1**

Give names to the following compounds.

**9.2**

Draw the structural formulas of the following compounds.

- 2,3-dichloro-4-methylhexane
- 2-chloro-3-iodoheptane
- chlorocyclohexane
- 1-bromo-3,5-dimethylbenzene
- 2-fluoronaphthalene

**9.3**

Complete the following equations.

- $(\text{CH}_3)_2\text{CHI} + \text{KCN} \rightarrow ?$
- $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{ONa} \rightarrow ?$
- $\text{CH}_3\text{COONa} + \text{CH}_3\text{CH}_2\text{I} \rightarrow ?$

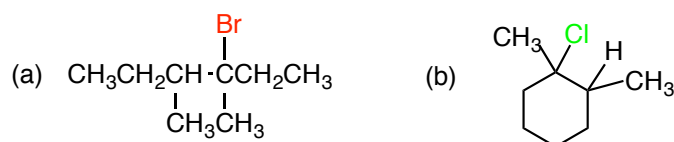
**9.4**

Draw the perceptive view of the following reaction intermediates or transition states. If possible, explain the hybridization states of carbon atoms.

- $(\text{CH}_3)_3\text{C}^+$
- $(\text{CH}_3)_3\text{C}^-$
- Transition state of the reaction  $\text{CH}_3\text{CH}_2\text{Br} + \text{KOH} \rightarrow \text{CH}_3\text{CH}_2\text{OH} + \text{KBr}$

**9.5**

When each of the following compounds is heated with KOH in ethanol, alkenes are formed.



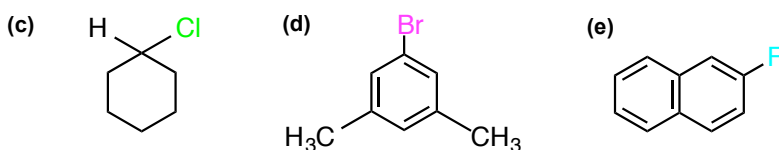
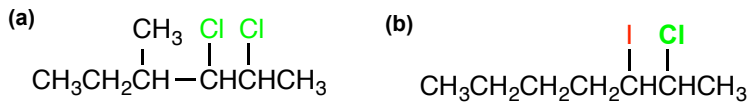
- Give names to each compound.
- Draw the structural formulas of all alkenes which may possibly be formed.
- Indicate the alkene that is formed in the largest amount. Explain the reason why.

**Answers**

## 9.1

- (a) 3-bromo-3,5-dimethylhexane
- (b) 2,4-dichloro-2,4-dimethylpentane
- (c) 1-iodopentane (pentyl iodide)
- (d) *p*-ethylfluorobenzene
- (e) 4-bromo-2-chlorotoluene

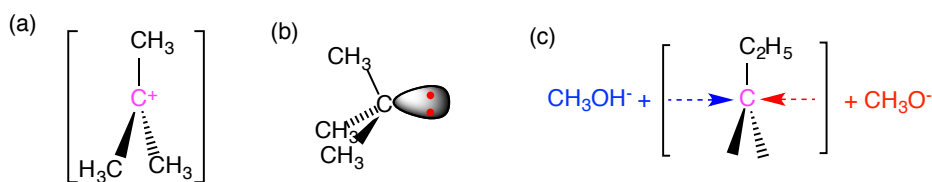
## 9.2



## 9.3

- (a)  $(\text{CH}_3)_2\text{CHI} + \text{KCN} \rightarrow (\text{CH}_3)_2\text{CHCN} + \text{KI}$
- (b)  $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{ONa} \rightarrow (\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3 + \text{NaCl}$
- (c)  $\text{CH}_3\text{COONa} + \text{CH}_3\text{CH}_2\text{I} \rightarrow \text{CH}_3\text{COOCH}_2\text{CH}_3 + \text{NaI}$

## 9.4

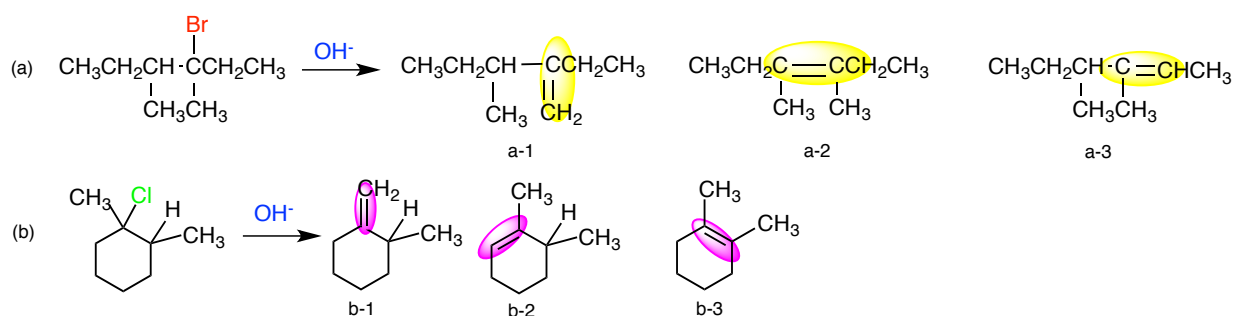


## 9.5

(1)

- (a) 3-bromo-3,5-dimethylhexane
- (b) 1-chloro-1,2-dimethylcyclohexane

(2)



(3)

(a-2) and (b-3). Both do not have hydrogen atoms directly bonded to the double bonds.