

## Chapter 4 Mechanism and Rate of Reactions

### Contents

#### 4.1 Types of organic reactions

- (a) Classification based on the relation between reactants and products
  - (1) Substitution
  - (2) Addition
  - (3) Elimination
  - (4) Rearrangement
- (b) Classification by the mode of cleavage/formation of bonds
- (c) Nucleophilic reactions and electrophilic reactions
- (d) Mechanism of nucleophilic substitution
  - (1) Cleavage of the C-Br bond followed by the formation of the C-O bond.
  - (2) Simultaneous bond cleavage and bond formation
  - (3) Formation of the C-O bond followed by cleavage of the C-Br bond
- (e) Reaction coordinate--energy diagram
  - (1) The path *via* a reaction intermediate
  - (2) The path *via* a transition state

#### 4.2 Unimolecular reactions and bimolecular reactions

#### 4.3 Reaction intermediates

- (a) Carbon radical
- (b) Carbocation
- (c) Carbanion

#### 4.4 Structure of reactants and the reaction mechanism

- (a) Nucleophilic substitution of primary alkyl halides
- (b) Nucleophilic substitution of tertiary alkyl halides
- (c) Does a nucleophilic substitution occur without fail?
- (d) Radical substitution

Problems

Answers

So far you have learned mostly on the structure and property of individual molecules.

Though such knowledge is essential in studying organic chemistry, it will contribute for you to learn the path and result of the reaction between two or more than two compounds.

When chemists plan to synthesize some compound, they first draw a chemical equation from the starting material to the target molecule, and cause to react some reactants. They want to understand how the reaction goes and how fast the reaction will be regardless the reaction is successful or not. This is the study of mechanism and rate of reactions. In this chapter, the basic knowledge on reaction mechanism will chiefly be discussed, but an essential background of rate of reaction will be covered.

## 4.1 Types of organic reactions

### (a) Classification based on the relation between reactants and products

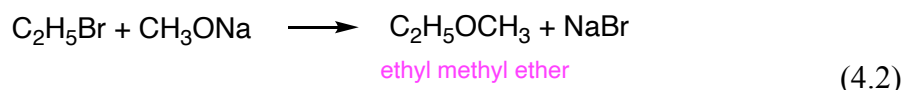
Since there are a variety of organic reactions, it is convenient to classify them based on the relation between the structures of reactants and products. You can say this is a formal classification of organic reactions. After formally classifying reactions, usually you will proceed to further classification based on the reaction mechanism. Organic reactions are in general classified formally into four types (1)-(4).

#### (1) Substitution

A **substitution reaction** is defined as a reaction in which a part of reactant A is replaced by another reactant B or by its part. Typical examples are photochlorination of methane  $\text{CH}_4$



and the reaction between ethyl bromide and sodium methoxide.



In most organic reactions, one of the reactants is an organic compound, and the other is an inorganic compound or a relatively small organic compound. The former is often called a **substrate**, and the latter a **reagent**. In the case of Eq. 4.2, either sodium methoxide as a whole, or methoxide ion  $\text{CH}_3\text{O}^-$ , which is the actual reagent to participate in the reaction, may be called the reagent.

In Eq. 4.1, a hydrogen atom of the substrate molecule, methane, is replaced by a chlorine atom, a part of chlorine molecule. The product, methyl chloride  $\text{CH}_3\text{Cl}$  derived from the substrate, and the other product, hydrogen chloride,  $\text{HCl}$ , is formed from the rest of the substrate and the reagent.

#### **Exercise 4.1** Analyzing a substitution reaction

Analyze the reaction given in Eq. 4.2 in a similar manner as that for Eq. 4.1.

#### **Answer**

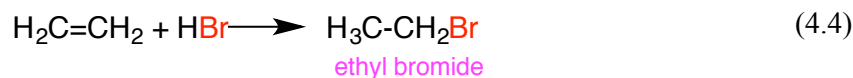
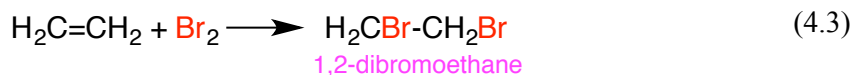
Two reactants have much the same size. If we assume ethyl bromide as a substrate, bromine atom of the substrate is replaced by the methoxide ion of the reagent sodium methoxide. The products are ethyl methyl ether derived from the substrate, and sodium bromide, which is formed from the rest of the substrate and the reagent.

#### (2) Addition

An **addition reaction** takes place for a substrate with unsaturated bond(s). The unsaturated bond will open and the reagent split into two parts will add to two terminals of the opened unsaturated bond. The reaction proceeds as below.



A typical example is an addition of bromine  $\text{Br}_2$  or hydrogen bromide  $\text{HBr}$  to ethylene  $\text{CH}_2=\text{CH}_2$ .



In these cases compounds with unsaturated bonds are called the substrate, and the molecule to be added is called the reagent.

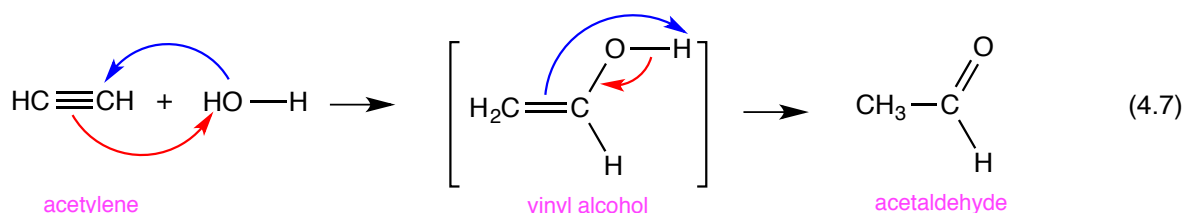
### (3) Elimination

An **elimination reaction** is formally a reverse reaction of an addition reaction. Elimination of hydrogen bromide from ethyl bromide, or elimination of water from ethanol is typical examples. Many of these reactions will take place only under the presence of some catalysts.



### (4) Rearrangement

Generally a **rearrangement reaction** is a complex process, and it is difficult to find a simple example. A frequently quoted example is the formation of acetaldehyde by the addition of water to acetylene. In Eq. 4.7, the symbol  $\curvearrowright$ , so called “curry arrow” indicates a shift of electron pair. If the electron pair is a bonding electron pair, the shift of an atom will accompany.



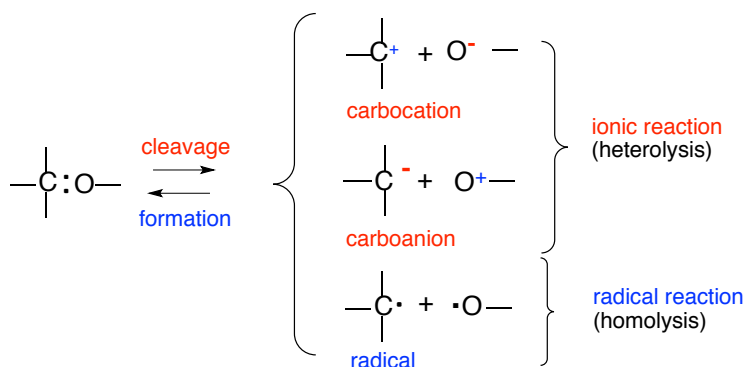
A simple addition of water to acetylene will yield vinyl alcohol. The result is the formation of acetaldehyde rather than that of vinyl alcohol. This result can be explained as below. Vinyl alcohol was once formed, and then the proton moved from oxygen to carbon. In a word, a rearrangement took place. This process is a typical example of isomerization, so-called **keto-enol tautomerism**, which you will learn later (Ch. 11.5(c)).

In this regard, this reaction is not a typical example of “rearrangement”. This reaction may be classified as “isomerization”.

### (b) Classification by the mode of cleavage/formation of bonds

Another method of classification of reactions is based on the mode of cleavage/formation of bonds. All chemical reactions must accompany cleavage of existing bonds and formation of new bonds. Though there should be a variety of the mode of cleavage/formation of bonds, a cleavage/formation of single bond between a carbon atom and an oxygen atom will firstly be

discussed for the sake of simplicity (Figure 4.1).



**Figure 4.1** Pattern of bond cleavage and bond formation

The difference in the modes of bond cleavage is based on how the two electrons forming the cleaved bond are allocated between two atoms. The difference in the modes of bond formation is based on how the two electrons forming the new bond are supplied by two atoms. If two electrons are allocated to one atom during cleavage, an ionic species (cation or anion) will necessarily be formed.

In Figure 4.1, if two electrons are allocated to the oxygen atom, the carbon atom will become electron deficient **carbocation**, and if two electrons are allocated to the carbon atom, the carbon will become electron rich **carbanion**. In both cases, an ionic species will be formed and such reactions are referred to as **ionic reactions**, or alternatively, **heterolysis** in the sense that the electrons are unequally allocated.

When two electrons are allocated equally to two atoms, a carbon radical and an oxygen radical, which have an unpaired electron, are formed. This type of reaction is named as **radical reactions**, or alternatively, **homolysis**, in the sense that the electrons are equally allocated.

You will learn about carbocation, carbanion, and carbon radical more in detail in Ch. 4.3.

### (c) Nucleophilic reactions and electrophilic reactions

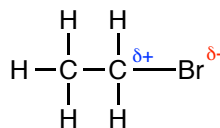
The next step of classification of reactions is to differentiate two modes of ionic reactions. This differentiation is made by distinguishing the roles of the carbon atom (of the substrate) and the oxygen atom or the reagent during the bond formation.

Ionic reactions between a carbocation and an anion from the reagent are named as **nucleophilic reactions**. This naming indicates that the key of the reaction is the attack of the reagent to positively charged carbocation, which is compared to the positively charged nucleus of an atom. The reagent which attacks to positive charge, *e.g.*,  $\text{CH}_3\text{ONa}$  in Eq. 4.2, is named as a **nucleophile** or a **nucleophilic reagent**.

Ionic reactions in which a carbanion and the positive charge of the reagent are involved are called an **electrophilic reaction**. Since a negatively charged carbanion is electron rich, the key of the reaction is the attack to the “electron”. The reagent to attack the negative charge (the oxygen cation in Figure.4.1) is named an **electrophile** or an **electrophilic reagent**.

In practice, not all reactions necessarily involve the cleavage of the bond to form positive and negative charges. In some reactions, the cleavage of the bond does not occur, and instead, the polarization of the bond to form partial positive and negative charges takes place. These reactions are also classified as ionic reactions, and depending on the direction of polarization, are further classified as nucleophilic and electrophilic reactions.

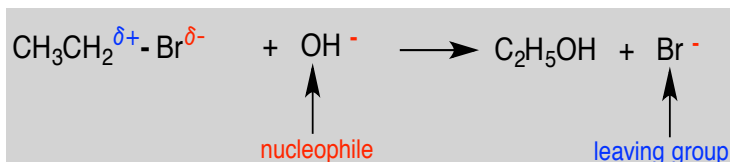
In the case of Eq. 4.2, sodium methoxide is electrically dissociated into  $\text{CH}_3\text{O}^-$  and  $\text{Na}^+$ , the substrate ethyl bromide does not electrically dissociate into ethyl cation  $\text{C}_2\text{H}_5^+$  and bromide ion  $\text{Br}^-$ . However, because of large electronegativity of bromine, the C-Br bond is polarized as shown below.



This reaction is a nucleophilic substitution in which the positively charged (in part) carbon center is attacked by a nucleophile.

In nucleophilic substitutions, such chemical species as bromide ion  $\text{Br}^-$  which is repelled from the substrate by the nucleophile are called a **leaving group**.

**Point:** Nucleophilic substitution



#### (d) Mechanism of nucleophilic substitution

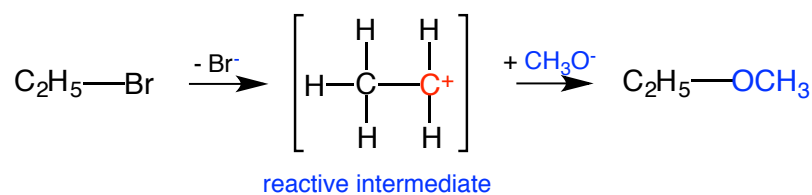
The course of the reaction in Eq. 4.2 is understood as the attack of the nucleophilic reagent  $\text{CH}_3\text{O}^-$  on the carbon center with a partial positive charge  $\delta^+$ . You cannot say, however, that the whole reaction mechanism is fully clarified because one important point, the relation between the time of bond formation by the attack of  $\text{CH}_3\text{O}^-$  on the carbon atom, and the time of bond cleavage by the leave of bromine from the carbon atom as  $\text{Br}^-$ , is not clear. There are three possibilities as for the timing of bond cleavage (of C-Br bond) and bond formation (of C-O bond); *i.e.*

- (1) bond cleavage and then bond formation
- (2) bond cleavage and bond formation proceed simultaneously
- (3) bond formation and then bond cleavage.

Each possibility will be discussed in detail.

#### (1) Cleavage of the C-Br bond followed by the formation of the C-O bond

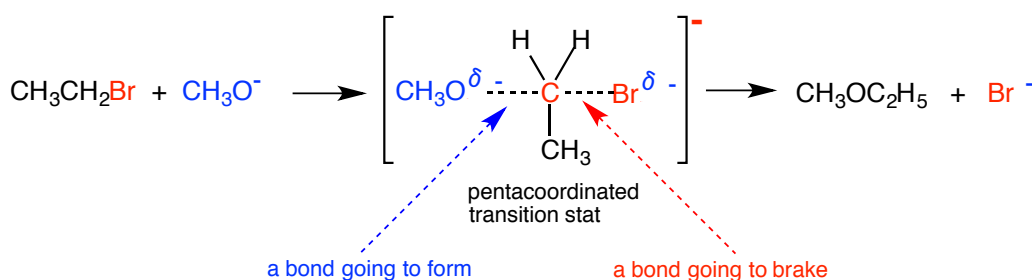
If the bromine atom leaves from the carbon atom as  $\text{Br}^-$ , there remains a carbocation ( $\text{C}_2\text{H}_5^+$ ). Carbocations are unstable, and are difficult to isolate under the standard condition. However, it has been established by many researches that such chemical species are generated during the reactions. These are named **reaction intermediates** (Figure 4.2).



**Figure 4.2** A path accompanied by the formation of a reaction intermediate

## (2) Simultaneous bond cleavage and bond formation

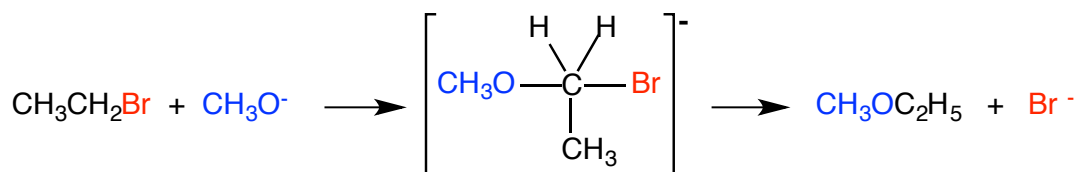
If the two processes proceed simultaneously, generation of a pentacoordinate species must be assumed in which the central carbon atom is bonded with three atoms or groups of atoms by normal covalent bonds, and in addition, it has a semi-cleaved bond with the leaving group, and a semi-formed bond with the nucleophile. These semi-cleaved or semi-formed bonds are weaker, and their length is also longer than the normal bonds. Such a pentacoordinate structure does, however, suffer from some strain since the carbon atom is primarily tetravalent, and it is necessarily crowded. Hence such cannot exist even in a very short time, and is named a **transition state**. In the transition state, the negative charge is shared by the leaving group and the nucleophile (Figure 4.3).



**Figure 4.3** A path *via* a transition state.

## (3) Formation of the C-O bond followed by cleavage of the C-Br bond

For this path, a pentavalent carbon atom, to which five atoms or group of atoms are covalently bonded (Figure 4.4) should be involved. Such a structure is hardly possible in view of the electron configuration and valence of carbon atoms. Hence we do not discuss this path.



**Figure 4.4** A path accompanied by a pentavalent carbon species.  
The negative charge will spread over the whole molecule.

We have to find out whether the reaction proceeds *via* path (1) or path (2). It is impossible to decide this from the product since the two paths will give the same product. The answer is to be obtained from the analysis of the rate of reactions. It will be better for you to learn a bit of the rate of reactions.

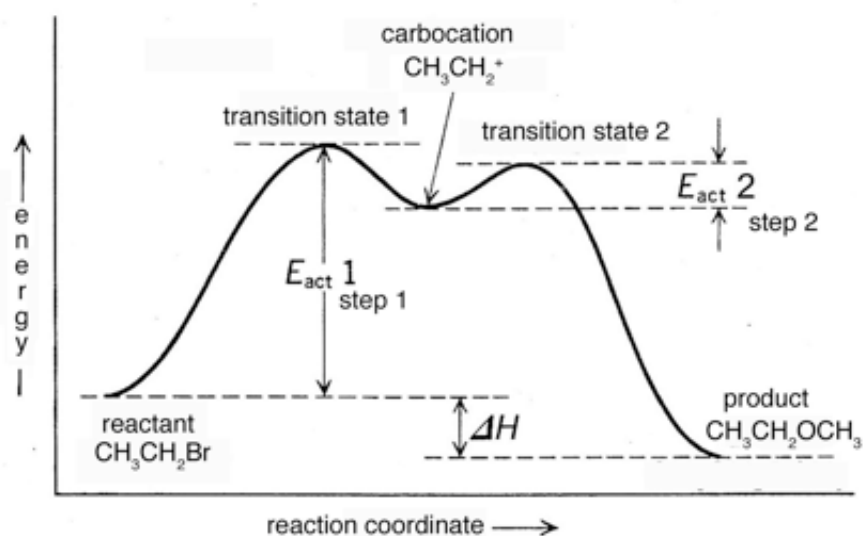
## (e) Reaction coordinate–energy diagram

### (1) The path *via* a reaction intermediate

One method to analyze the path of a reaction is to examine the change of the energy of the reaction system (including all compounds involved in the reaction) that takes place during the progress of the reaction. In practice, a **reaction coordinate**-energy diagram is prepared in which the progress of the reaction is plotted along the horizontal axis, and the energy of the reaction system are plotted along the vertical axis.

As an example, a reaction coordinate-energy diagram for the reaction in Figure 4.2 which involves the formation of a reaction intermediate (carbocation) (Figure 4.5). If the energy of reactants is higher than that of the products, the reaction is exothermic, and if the reverse is the case, the reaction is endothermic. In any case, the energy of the reaction intermediate is much higher than that of reactants or products. Nevertheless, a reaction intermediate has a certain length of life, and the energy at this stage is necessarily minimum (local minimum but not global minimum).

There is a transition state between the reactant and the intermediate, and between the intermediate and the product, respectively. The energy of each transition state is slightly higher than that of the reaction intermediate.

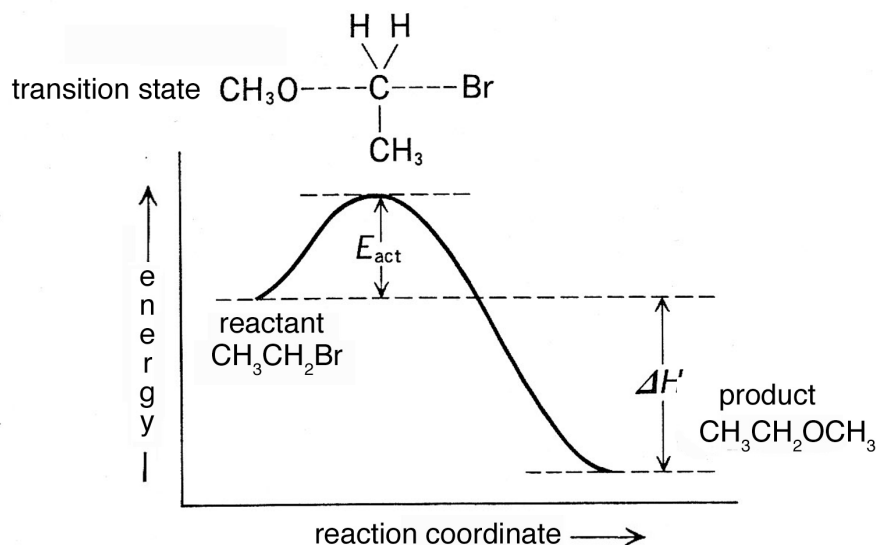


**Figure 4.5** A reaction coordinate-energy diagram for the reaction involving formation of a reaction intermediate.  $E_{\text{act}}$ ; activation energy;  $\Delta H$ ; heat of reaction.

As is clear from Figure 4.5, a reaction in which formation of a reaction intermediate is involved can be regarded as a two-step reaction. The 1<sup>st</sup> step corresponds to the process from the initiation of the reaction to the formation of the reaction intermediate, and the 2<sup>nd</sup> step to the process from the intermediate to the products. The activation energy of the total reaction is that of the 1<sup>st</sup> step from the reactants to the transition state 1 since the activation energy of the 2<sup>nd</sup> step is extremely small.

## (2) The path *via* a transition state

In this case the reaction proceeds as a one-step reaction, and the energy of the system will be maximum (global maximum) at the transition state. The activation energy of the total reaction corresponds to the energy difference between the reactants and the transition state (Figure 4.6).



**Figure 4.6** A reaction coordinate-energy diagram for the reaction involving formation of a transition state.  $E_{\text{act}}$ ; activation energy;  $\Delta H'$ ; heat of reaction.

## 4.2 Unimolecular reactions and bimolecular reactions

The rate of reaction, or **reaction velocity**, is defined as the rate of decrease of the reactants, or the rate of increase of products. Here again, we use Eq. 4.2 as an example, and examine the rate of this reaction in each of two paths.

In the case of the path (1) *via* a reaction intermediate, it seems that the rate of reaction is proportional solely to the concentration of the reactant. Such a reaction is named a **unimolecular reaction**, and its rate equation is expressed as below.

$$v = -k[\text{C}_2\text{H}_5\text{Br}] \quad (4.8)$$

where  $v$  is the rate of reaction and  $k$  a proportional constant called a **rate constant** (a negative sign indicates the decrease of reactants).

In the case of the path (2) *via* a transition state, the rate equation is proportional both to the concentrations of the reactant and the reagent since the reaction is initiated by the collision of the reactant and the reagent. The rate equation is given as below.

$$v = -k[\text{C}_2\text{H}_5\text{Br}][\text{CH}_3\text{ONa}]$$

$$\text{or } v = -k[\text{C}_2\text{H}_5\text{Br}][\text{CH}_3\text{O}^-] \quad (4.9)$$

Such a reaction is named a **bimolecular reaction**.

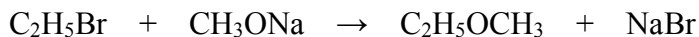
As you learned in the previous section, the path (1) is composed of two steps, and the activation energy for the 2<sup>nd</sup> step is much lower than that for the 1<sup>st</sup> step. Hence, it is the rate of the 1<sup>st</sup> step which determines the rate of the whole reaction. The step that determines the rate of multistep reaction is named the **rate-determining step**.

To summarize, nucleophilic substitution can be subdivided into unimolecular reaction



(abbreviated as  $S_N1$ ) and bimolecular reaction (abbreviated as  $S_N2$ ) depending on the mechanism of the reaction. It is now established that almost all nucleophilic substitutions proceed either *via*  $S_N1$  or  $S_N2$ .

**Point:** Nucleophilic substitution

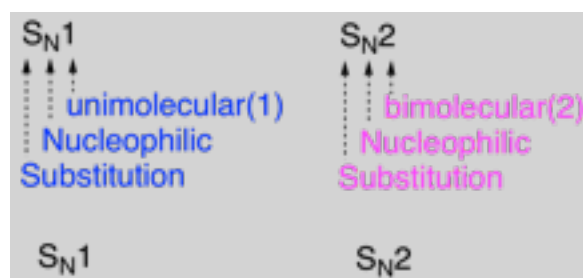


Rate constant of **unimolecular reaction**

$$v = -k[C_2H_5Br]$$

Rate constant of **bimolecular reaction**

$$v = -k [C_2H_5Br][CH_3ONa] \quad \text{or} \quad v = -k [C_2H_5Br][CH_3O^-]$$



Now your understanding on the reaction mechanism was deepened. However, the problem still remains because you cannot determine whether the reaction proceeds *via*  $S_N1$  or  $S_N2$  by studying the products. To solve this problem, the stereochemistry of the reaction, that is, the stereochemistry of reactants, intermediates and products, should be determined. Details of the stereochemistry of reactions will be treated in Ch. 8 and after.

### 4.3 Reaction intermediates

Besides carbocations, there are several other unstable chemical species which are formed during the reaction. Representative examples will be introduced below.

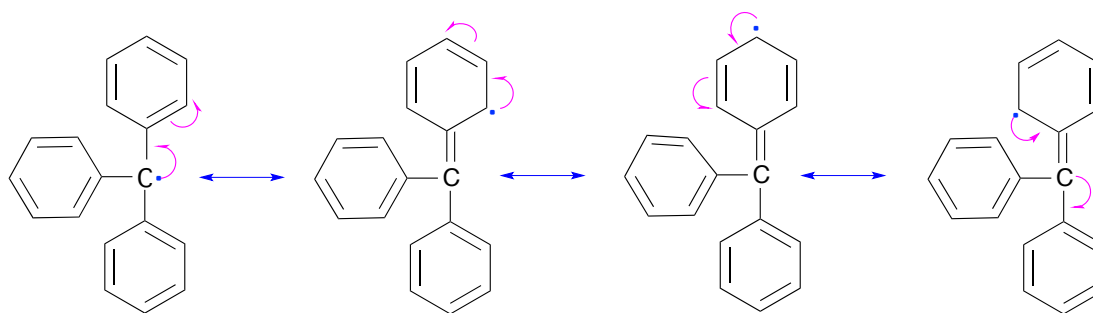
#### (a) Carbon radicals

Radicals are chemical species carrying an unpaired electron, in other words, carrying odd number of valence electrons, and are generated when a chemical bond evenly cleaved (homolysis). Homolysis of C-H bond of methane yields methyl radical  $CH_3\cdot$  and hydrogen atom. Hydrogen atom is a chemical species with odd number of valence electron. Methyl radical is the simplest carbon radical.

Almost all radicals are highly reactive, and these react with other radicals or with neutral molecules *via* a radical mechanism. In order to give some stability to the radical (a carbon atom), it is necessary to delocalize the unpaired electron on carbon so that resonance structures can be drawn. The idea is much the same with the discussion made for carboxylic acids and phenols.

Triphenylmethyl radical, one of the first radical extensively investigated, has many resonance

formulas (Figure 4.7). The unpaired electron exists not only on the methyl carbon atom, but also delocalizes to *ortho* and *para* positions of benzene rings.



**Figure 4.7** Resonance formulas of triphenylmethyl radical

**Exercise 4.2** Resonance formulas of triphenylmethyl radical

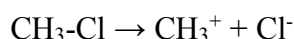
Triphenylmethyl radical has resonance formulas other than those given in Figure. 4.7. Draw all other resonance formulas.

**Answer**

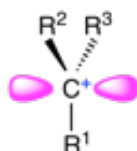
In Figure. 4.7, resonance structures in which only one of the benzene rings is involved in the resonance. It is possible to draw three resonance structures for each of the remaining two benzene rings. Hence ten resonance structures are possible for triphenylmethyl radical.

**(b) Carbocation**

Trivalent carbon chemical species with positive charge are named as **carbocations**. If chloride anion leaves from methyl chloride, a methane derivative obtained from methane by substituting a hydrogen atom with electronegative chlorine, the simplest carbocation, methyl cation is formed.



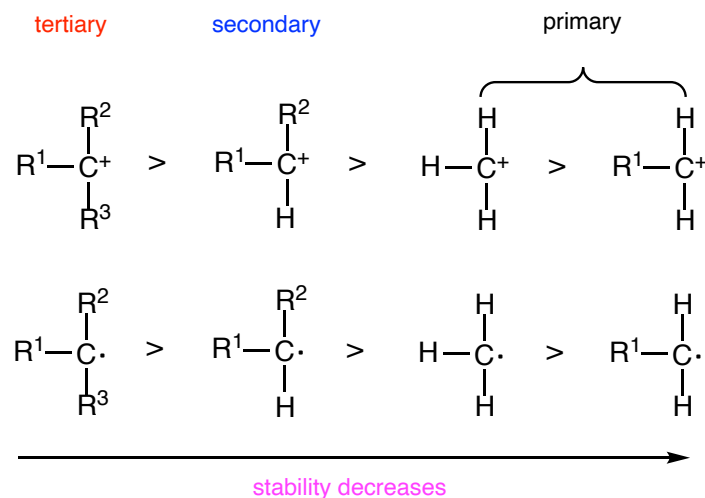
Sometimes carbocations are referred to as **carbenium ion**, but in this book the term carbocation will be used. The positively charged carbon atom of carbocation is  $sp^2$  hybridized, and three atoms or group of atoms lie in one plane, and the empty p orbital is perpendicular to this plane.



Though a methyl radical is very unstable, its stability will increase as an alkyl group R or aryl group Ar replaces the hydrogen atoms. A **primary radical** with one alkyl group is more stable than methyl radical, and a **secondary radical** substituted by two alkyl groups are more stable than the primary radical (Figure 4.8). A **tertiary radical** with three alkyl groups is even more stable.

One reason for this increasing stability is the electron donating property of alkyl group. A methyl group has a mild electron donating property and stabilizes the positively charged carbon center with

it. The other is the steric effect. Because of alkyl groups, the approach of other reagents to the carbon center will be inhibited to retard the reaction. This type of phenomena is named as **steric protection**.



**Figure 4.8** Decreasing order of stability of carbocations and carbon radicals

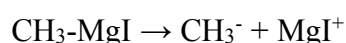
**Point:** Decreasing order of stability of carbocations and carbon radicals

The larger the number of alkyl groups, the more stable.



### (c) Carbanion (carboanion)

Negatively charged, trivalent carbon species are referred to as carbanions. Such methane derivatives substituted by an electropositive atom are the source of carbanions. For instance, methylmagnesium iodide  $\text{CH}_3\text{MgI}$ , an organometallic compound, will yield the simplest carbanion, methyl anion, if  $\text{MgI}^+$  is removed from it



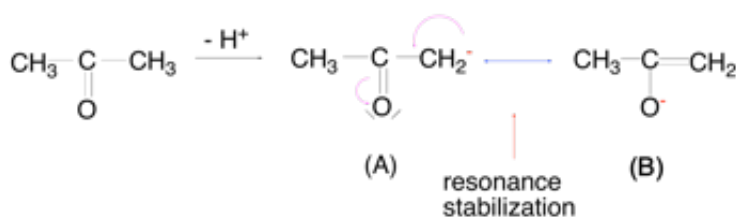
Negatively charged carbon atom of carbanions is  $\text{sp}^3$  hybridized, and substituted by three hydrogen atoms or groups of atoms with occupied lone pair.



Carbanions are also unstable species, and delocalization of negative charge is essential to attain a certain amount of stabilization. A typical example is the stabilization of carbanions adjacent to a carbonyl group. The details will be discussed in Ch.11.

When acetone reacts with a strong base, a hydrogen atom is drawn out as a proton, and a carbanion (A) is formed. Because this negative charge is conjugated with the carbonyl group, a more stable enolate anion (B) is formed by electron transfer. The reactivity of carbon atoms adjacent to a

carbonyl group is due to this resonance between carbanion and enolate anion.



#### Exercise 4.3 Relative stability of unstable species

Point out the more stable one from the following pairs. Explain your reasoning.

- (a)  $\text{CH}_3\text{CH}_2\text{CH}_2^+$  and  $\text{CH}_3\text{CH}^+\text{CH}_3$   
 (b)  $\text{CH}_3\text{CH}_2^-$  and  $\text{CH}_3\text{COCH}^-\text{COCH}_3$   
 (c)  $(\text{C}_6\text{H}_5)_3\text{C}^+$  and  $(\text{CH}_3)_3\text{C}^+$

#### Answer

- (a)  $\text{CH}_3\text{CH}^+\text{CH}_3$ , the left cation is primary, but the right one is secondary.  
 (b)  $\text{CH}_3\text{COCH}^-\text{COCH}_3$ , A resonance formula, in which the charge on carbon is delocalized to oxygen, can be drawn.  
 (c)  $(\text{C}_6\text{H}_5)_3\text{C}^+$ , there exists stabilization due to resonance.

### 4.4 Structure of reactants and reaction mechanism

#### (a) Nucleophilic substitution of primary alkyl halides

Let us return to the reaction depicted in Eq. 4.2. Experiments showed that the rate equation of this reaction is:

$$v = -k[\text{C}_2\text{H}_5\text{Br}][\text{CH}_3\text{ONa}]$$

Thus, the reaction is  $\text{S}_{\text{N}}2$ . The question remains, however, why this reaction is  $\text{S}_{\text{N}}2$ , but not  $\text{S}_{\text{N}}1$ ?

This question can be solved by deciding which path will be more favorable. According to the reaction coordinate-energy diagrams, Figure 4.5 and Figure 4.6, the system must surmount a high energy mountain (a reaction intermediate or a transition state). Then, which mountain, one for  $\text{S}_{\text{N}}1$  and the other for  $\text{S}_{\text{N}}2$ , is lower?

Suppose the reaction proceeds *via*  $\text{S}_{\text{N}}1$ . The reaction intermediate is a primary carbocation, a very unstable one. This is the largest condition which makes  $\text{S}_{\text{N}}1$  unfavorable.

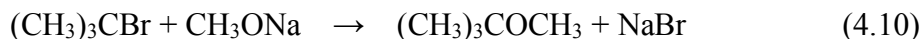
Suppose the reaction proceeds *via*  $\text{S}_{\text{N}}2$ . Since the central carbon atom is primary, the steric congestion of its pentacoordinate transition state is not too much. Furthermore, semi-cleaved C-Br bond and semi-forming C-O bond are both longer than the corresponding normal bonds.

As Figure 4.3 indicates, it is likely that the methoxide ion will attack the carbon atom from the rear side of the bromine atom to avoid the steric congestion and electrostatic repulsion. This will reduce the jamming of the transition state.

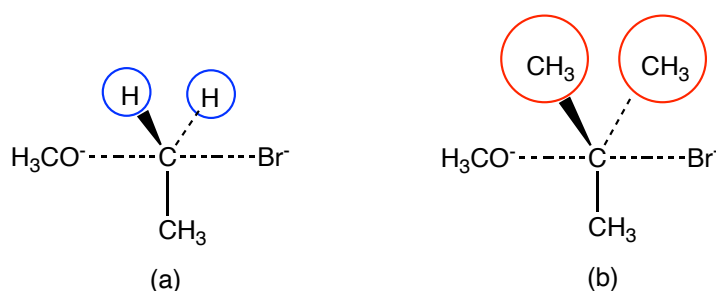
Thus, it is quite understandable that the reaction of Eq. 4.2 proceeds *via*  $\text{S}_{\text{N}}2$ . This discussion can be extended to other nucleophilic reactions of primary compounds under a basic condition (see Ch. 9).

**(b) Nucleophilic substitution of tertiary alkyl halides**

What type of compounds will react *via*  $S_N2$ ? The answer can be obtained from the above discussion. Of the carbocations which are the reaction intermediate of  $S_N1$  reactions, a tertiary carbocation is more stable than a primary one. It is likely that the nucleophilic substitution of tertiary alkyl halides proceeds *via*  $S_N1$ . Eq. 4.10 is a good example.



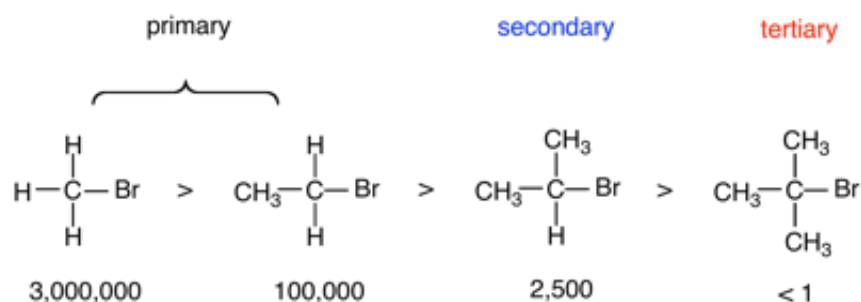
If this reaction proceeds *via*  $S_N2$ , the transition state will be the one in Figure 4.9(b). This structure is even more sterically congested as compared with that of a primary alkyl bromide shown in Figure 4.9(a). If the nucleophilic substitution of tertiary alkyl halide proceeds *via*  $S_N1$ , the intermediate is a relatively stable tertiary carbocation  $(\text{CH}_3)_3\text{C}^+$ , making this path favorable.



**Figure 4.9**  $S_N2$  transition states of primary alkyl halides (a) and tertiary alkyl halides (b).

The property of secondary alkyl halides is in between that of primary halides and that of tertiary halides. As for the stability of carbocations, secondary halides are not particularly favorable, and as for the steric congestion of reactive intermediates, they are not particularly favorable. For this reason, the path of reaction for secondary halides is a kind of mixtures. The ratio of  $S_N1$  to  $S_N2$  is case by case, and is not one-sided as is the case for primary or tertiary halides.

The relative reactivity of  $S_N2$  under basic condition can be summarized as Figure 4.10. The rate of reaction for tertiary alkyl halides is only one in three million of that of ethyl bromide which has the smallest steric inhibition.

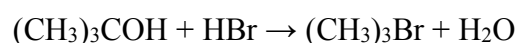


**Figure 4.10** Relative reactivity of  $S_N2$

As you will learn in Ch. 9, the nucleophilic substitution competes with the elimination and its ratio is again case-by-case. In this chapter you learn only nucleophilic substitution.

**Point:** S<sub>N</sub>1 or S<sub>N</sub>2?**S<sub>N</sub>1:** Stability of carbocation intermediatesubstrate is primary → S<sub>N</sub>2substrate is **tertiary** → S<sub>N</sub>1**S<sub>N</sub>2:** Steric congestion of pentacoordinate transition statesubstrate is primary → S<sub>N</sub>2 (not overcrowded)substrate is **tertiary** → S<sub>N</sub>1 (overcrowded)substrate is **secondary** → S<sub>N</sub>1 and S<sub>N</sub>2 (in parallel)**Exercise 4.4** S<sub>N</sub>1, S<sub>N</sub>2 and rate of reaction

Assume the reaction proceeds *via* nucleophilic substitution in which OH group is substituted by Br. How is the rate of reaction affected when the reaction condition is changed.



- (a) The concentration of HBr is doubled.  
 (b) The concentration of HBr is made half, and the concentration of (CH<sub>3</sub>)<sub>3</sub>COH is doubled.

**Answer**

Since the substrate is a tertiary compound, the reaction is likely to proceed *via* S<sub>N</sub>1. Then the concentration of HBr does not affect the rate of reaction, but that of the substrate does.

- (a) no change, (b) the rate is doubled.

**(c) Does a nucleophilic substitution occur without fail?**

In the reactions so far discussed, *i.e.*, the reaction between alkyl halides and a methoxide ion, nucleophilic substitutions take place though the mechanism may be different. There arises one question: does a nucleophilic substitution occur without fail at the carbon center substituted by electron withdrawing substituent?

There are many nucleophiles which in principle can repel electronegative atoms bonded to the central carbon atom as a leaving group (Table 4.1). Those with stronger nucleophilic power are mostly negative ions. Neutral species such as water, alcohols and ammonia, with a lone pair(s) on nitrogen or oxygen, also act as weak nucleophiles. Some negative ions can be leaving groups as well as nucleophiles.

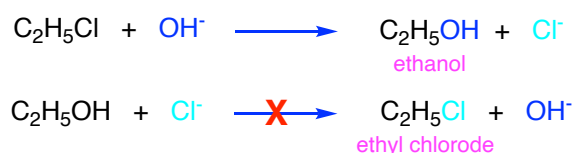
**Table 4.1** Important nucleophiles (only attacking parts are shown)

nucleophile*	chemical formula	product*	name of product
cyanide	CN <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> CN	propionitrile
acetate	CH <sub>3</sub> COO <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> OCOCH <sub>3</sub>	ethyl acetate
hydroxide	OH <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> OH	ethanol
methoxide	CH <sub>3</sub> O <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> OCH <sub>3</sub>	methyl ethyl ether
ethoxide	C <sub>2</sub> H <sub>5</sub> O <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> OC <sub>2</sub> H <sub>5</sub>	diethyl ether
chloride	Cl <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> Cl	ethyl chloride
bromide	Br <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> Br**	ethyl bromide
iodide	I <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> I	ethyl iodide
ammonia	NH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> NH <sub>3</sub> Br	ethylammonium bromide

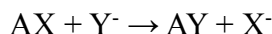
\*A reaction between ethyl bromide (as a reactant) and each nucleophile is assumed.

\*\* The reactant and product are identical.

The two reactions below are formally very similar but there is a difference. The first reaction takes place easily, but the second one is difficult to occur.





The reason is that hydroxide ion is stronger than chloride ion as a nucleophile (Table 4.2). In general, whether a reaction



takes place depends on the relative strength of X<sup>-</sup> and Y<sup>-</sup> as a nucleophile.

Furthermore, whether the leaving group can leave easily or not also affect the path and rate of the reactions (Table 4.2). The easiness of release of the leaving group is parallel with the stability as a negative ion, but not necessarily with the order of strength as nucleophiles.

**Table 4.2** Strength of nucleophiles and easiness of leaving of leaving groups

$\text{CN}^- > \text{I}^- > \text{OH}^- \rightleftharpoons \text{CH}_3\text{O}^- \rightleftharpoons \text{C}_2\text{H}_5\text{O}^- > \text{Br}^- > \text{C}_6\text{H}_5\text{O}^- > \text{Cl}^- > \text{CH}_3\text{COO}^- > \text{RSO}_3^-$

decreasing order of strength as a nucleophile
$\text{I}^- > \text{Br}^- > \text{Cl}^- \gg \text{F}^- > \text{CH}_3\text{COO}^- > \text{OH}^- > \text{CH}_3\text{O}^- > \text{H}_2\text{N}^-$

decreasing order of stability as an anion and easiness of leaving as a leaving group

**Exercise 4.5** Reactivity of  $S_N2$ 

Arrange the following compounds in the decreasing order of reactivity in  $S_N2$  reaction.

**Answer**

The reactivity in  $S_N2$  reaction is higher when the easiness of release of the leaving group is larger.

**(d) Radical substitution**

Following the previous sections treating ionic substitution, you will learn in this section an outline of radical substitution.

The photoreaction shown in Eq. 4.1 proceeds *via* a somewhat complicated path. By photoirradiation, a chlorine molecule is cleaved into two chlorine atoms  $\text{Cl}\cdot$



The 1<sup>st</sup> step in which a radical is formed is called the **initiation** of a series of reactions. The chlorine atom thus formed attacks methane to induce a homolytic cleavage of C-H bond, and methyl radical  $\text{CH}_3\cdot$  and hydrogen chloride are formed.

If a radical reacts with a neutral molecule, a new radical and a new neutral molecule are formed and so on. Such a repetition is characteristic of radical reactions and this process is called **propagation**.



Almost all carbon radicals are highly reactive, and the methyl radical reacts with chlorine molecule to form methyl chloride and chlorine atom.



This stage is also the propagation stage (propagation 2). If the chlorine atom generated in propagation 2 will return to propagation 1, the reaction will be repeated one after another. This sequence is named a **chain reaction**.

A radical may react, not only with neutral molecules but also with other radicals though the possibility is low. In this case a neutral molecule is formed from two radicals to terminate the chain reaction. This step is named as the **termination** of radical reactions.





It is a general characteristic of radical reactions that three distinct steps can be defined.

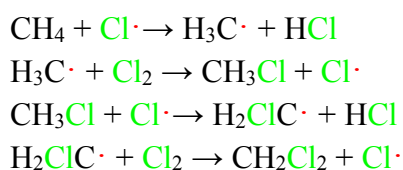
**Point:** Three steps of radical reactions

Initiation: cleavage of a neutral molecule  $\rightarrow$  generation of radicals

Propagation: neutral molecule 1 + radical 1  $\rightarrow$  neutral molecule 2 + radical 2

Termination: radical + radical  $\rightarrow$  neutral molecule

In practice, photochlorination of methane yields not only methyl chloride, but also methylene chloride  $\text{CH}_2\text{Cl}_2$ , chloroform  $\text{CHCl}_3$  and carbon tetrachloride  $\text{CCl}_4$ . It is reasonable if we assume that methyl chloride once formed changes into methylene chloride in an identical mechanism, and this is further chlorinated to chloroform and then to carbon tetrachloride. The exhaustive chlorination will give carbon tetrachloride.



The same process forms  $\text{CHCl}_3$  and  $\text{CCl}_4$ .

**Problems****4.1**

Classify following reactions based on the classification given in Ch. 4.1. Some cases may be considered as two step reactions.

- (a)  $\text{C}_6\text{H}_5\text{SO}_3\text{H} + \text{OH}^- \rightarrow \text{C}_6\text{H}_5\text{OH} + \text{SO}_3\text{H}^-$   
 (b)  $\text{CH}_3\text{CH}_2\text{CH}_2\text{S}^+(\text{CH}_3)_2 + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{N}^+\text{H}_2\text{CH}_3 + (\text{CH}_3)_2\text{S}$   
 (c)  $\text{CH}_3\text{CH}_2\text{CH}_2\text{S}^+(\text{CH}_3)_2 + \text{OH}^- \rightarrow \text{CH}_3\text{CH}=\text{CH}_2 + (\text{CH}_3)_2\text{S} + \text{H}_2\text{O}$   
 (d)  $\text{CH}_3\text{CH}=\text{CH}_2 + \text{Cl}_2 \rightarrow \text{CH}_3\text{CHClCH}_2\text{Cl}$   
 (e)  $(\text{CH}_3)_2\text{C}(\text{OH})\text{C}(\text{OH})\text{C}(\text{CH}_3)_2 \rightarrow (\text{CH}_3)_3\text{CCOOCH}_3 + \text{H}_2\text{O}$   
 (f)  $\text{CH}_3\text{CH}=\text{CHBr} + \text{OH}^- \rightarrow \text{CH}_3\text{C}\equiv\text{CH} + \text{H}_2\text{O} + \text{Br}^-$

**4.2**

Explain the mechanism of the following reactions, and point out the chemical species which plays an important role in each reaction.

- (a)  $\text{CH}_3\text{CH}_2\text{Br} + \text{CH}_3\text{Na} \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_3 + \text{NaBr}$   
 (b)  $\text{CH}_3\text{COOH} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{COOC}_2\text{H}_5 + \text{H}_2\text{O}$

**4.3**

When *t*-butyl chloride  $(\text{CH}_3)_3\text{CCl}$  reacts with acetic acid, *t*-butyl acetate  $\text{CH}_3\text{COO}(\text{CH}_3)_3$  is formed.

- (1) Draw the structure of the reaction intermediate.  
 (2) Will the rate of reaction be increased if sodium acetate is added to the reaction mixture?

**4.4**

Point out the more stable one out of each pair of unstable species. Give your explanation.

- (a)  $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{C}^+\text{H}$  and  $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}^+\text{H}_2$   
 (b)  $\text{C}_6\text{H}_5\text{CHC}^+\text{H}_2$  and  $\text{C}_6\text{H}_5\text{C}^+\text{HCH}_3$   
 (c)  $\text{CH}_3\text{C}^+\text{HCH}_2\text{CH}_3$  and  $\text{CH}_3\text{COC}^+\text{HCH}_3$   
 (d)  $\text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}^+$  and  $(\text{CH}_3)_3\text{C}^+$

**4.5**

Explain the effects caused by each of the following factors in  $\text{S}_{\text{N}}1$  and  $\text{S}_{\text{N}}2$ .

- (a) structure of substrates  
 (b) nucleophiles  
 (c) leaving groups

**Answers****4.1**

(a) substitution (b) substitution (c) elimination (d) addition (e) elimination + rearrangement (a series of reaction from the reactant pinacol to the product pinacolone (or pinacolin) is called pinacolin rearrangement) (f) elimination

**4.2**

(a) nucleophilic substitution (Williamson's ether synthesis);  $\text{C}_2\text{H}_5\text{Br}$  (substrate),  $\text{CH}_3\text{ONa}$  (nucleophile;  $\text{CH}_3\text{O}^-$  is the attacking species),  $\text{Br}^-$  (leaving group)

(b) nucleophilic substitution (esterification);  $\text{CH}_3\text{COOH}$  (substrate),  $\text{C}_2\text{H}_5\text{ONa}$  (nucleophile;  $\text{C}_2\text{H}_5\text{O}^-$  is the attacking species),  $\text{OH}^-$  (leaving group)

**4.3**

(1) It can be assumed that the 1st step of the reaction is  $(\text{CH}_3)_3\text{CCl} \rightarrow (\text{CH}_3)_3\text{C}^+ + \text{Cl}^-$  and the 2nd step is  $(\text{CH}_3)_3\text{C}^+ + \text{CH}_3\text{COO}^-$ , the reaction intermediate is *t*-butyl cation  $(\text{CH}_3)_3\text{C}^+$ .

(2) By adding sodium acetate, the concentration of acetate ion  $\text{CH}_3\text{COO}^-$  will be increased. However, the rate-determining step is the 1<sup>st</sup> one, and acetate ion does not affect the rate of reaction.

**4.4**

The underlined species is more stable.

(a)  $\text{CH}_3\text{CH}_2(\text{CH}_3)\underline{\text{C}^+\text{H}}$  is secondary and  $\text{CH}_3\text{CH}_2\text{CH}_2\underline{\text{C}^+\text{H}_2}$  is primary.

(b)  $\text{C}_6\text{H}_5\text{CH}_2\underline{\text{C}^+\text{H}_2}$  is primary and  $\underline{\text{C}_6\text{H}_5\text{C}^+\text{HCH}_3}$  is secondary.

(c)  $\text{CH}_3\underline{\text{C}^+\text{HCH}_2\text{CH}_3}$  is devoid of stabilization by resonance but  $\underline{\text{CH}_3\text{COC}^+\text{HCH}_3}$  can form an enolate anion.

(d)  $\text{C}_6\text{H}_5(\text{CH}_3)_2\underline{\text{C}^+}$  is stabilized by the conjugation with benzene rings but  $(\text{CH}_3)_3\underline{\text{C}^+}$  is devoid of such stabilization.

**4.5**

See Ch. 4.4.