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FUNDAMENTALS OF BIOORGANIC CHEMISTRY

TEXTBOOK FOR MEDICAL STUDENTS

С.Э. ЗУРАБЯН

ОСНОВЫ БИООРГАНИЧЕСКОЙ ХИМИИ

УЧЕБНИК

Chapter 4
A BRIEF SURVEY OF ORGANIC REACTIONS

Millions of organic compounds undergo millions of chemical transformations and, at first sight, organic chemistry could be considered a mere collection of infinite numbers of disconnected facts. There are only a few general concepts that can be applied to most chemical reactions. In fact modern organic chemistry is a very logical subject, therefore the best way to learn it consists in understanding concepts but not in memorization of numerous facts.

This chapter is concerned with fundamental types of organic reactions, classification of reactants, and general description of the reactions.

4.1. TYPES OF ORGANIC REACTIONS

While studying organic chemical reactions two aspects should be taken into account: what types of reactions exist and how a reaction proceeds. First it is more reasonable to look at the types of reactions. Organic reactions can be grouped into several types according to the overall result. They are:
- addition reactions;
- elimination reactions;
- substitution reactions;
- rearrangements (or isomerization reactions);
- oxidation and reduction reactions;
- acid-base interactions.

The latter reactions will be discussed in detail in Chapter 6. Other types of reactions listed above will be briefly characterized.

Addition reactions are those in which two substances react to form a single compound. In this case no atom is removed from both reactants. It can be generalized as follows:

$$A \ + \ B \longrightarrow AB$$

An example of this reaction is the addition of a halogen to an alkene:

$$CH_2{=}CH_2 + Br{-}Br \longrightarrow BrCH_2{-}CH_2Br$$
$$\text{ethylene} \qquad\qquad\qquad \text{1,2-dibromoethane}$$

Elimination reactions are, to some extent, the reverse of addition reactions. The parts of a molecule are removed from adjacent atoms of the reactant to give two products:

$$AB \longrightarrow A \ + \ B$$

One product is an unsaturated compound and the other is usually a small inorganic molecule such as hydrogen, water, ammonia, and so on. The reaction is exemplified in dehydration (elimination of a water molecule) from an alcohol under appropriate conditions:

$$\underset{\text{1-propanol}}{CH_3-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH} \xrightarrow{H_2SO_4,\ heat} \underset{\text{propene}}{CH_3\diagdown \diagup H \atop C=C \atop H\diagup \diagdown H} + HOH$$
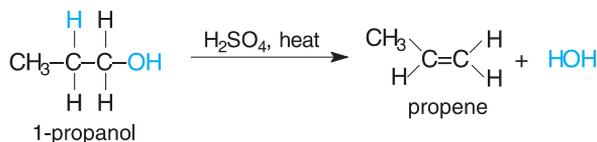
Substitution reactions occur when a group of atoms of one reactant replaces a group of atoms of another reactant. In other words, two reactants exchange their parts to give two new products:

$$A-B \ + \ C-D \longrightarrow A-C \ + \ B-D$$

These reactions are among the most common and most useful ones in organic chemistry. An example of such a reaction is demonstrated by the action of an aqueous alkali on a haloalkane to give an alcohol:

$$\underset{\text{propyl bromide}}{CH_3CH_2CH_2Br} \ + \ NaOH \longrightarrow \underset{\text{propyl alcohol}}{CH_3CH_2CH_2OH} \ + \ NaBr$$

Rearrangements consist in reorganization of chemical bonds and atoms in a reacting molecule on retention of the molecular formula, i. e. in formation of an isomeric product.

This process often accompanies reactions of other types, but rearrangements in «pure form» are known as well, for example, on heating of aromatic allyl ethers:

$$\underset{\text{allyll phenyl ether}}{\text{⬡}-OCH_2CH=CH_2} \xrightarrow{200\ °C} \underset{\text{2-allylphenol}}{\text{⬡}\genfrac{}{}{0pt}{}{-OH}{-CH_2CH=CH_2}}$$
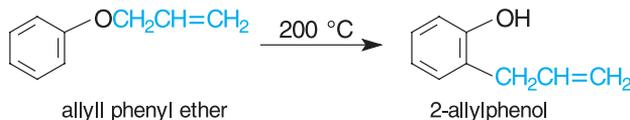
Oxidation and **reduction reactions** are defined in organic chemistry in a different manner as compared with definitions in inorganic chemistry.

Remember that in inorganic chemistry oxidation is defined as the loss of electrons, and reduction is defined as the gain of electrons. In organic reactions it is not easy to estimate whether electrons are removed from an atom or added to it. The notion of an oxidation number (or oxidation state) is necessary only for writing balanced equations.

Oxidation of an organic molecule usually corresponds to increasing its oxygen content or decreasing its hydrogen content. Conversely, reduction of the organic molecule is classified as decreasing the oxygen content of the molecule or increasing its hydrogen content. The symbols **[O]** and **[H]** are often used to indicate oxidation and reduction processes, respectively. Oxidation-reduction reactions can be represented as follows:

$$\underset{\text{hydrocarbon}}{R-CH_3} \underset{[H]}{\overset{[O]}{\rightleftarrows}} \underset{\text{alcohol}}{R-CH_2OH} \underset{[H]}{\overset{[O]}{\rightleftarrows}} \underset{\text{aldehyde}}{R-CH=O} \underset{[H]}{\overset{[O]}{\rightleftarrows}} \underset{\text{carboxylic acid}}{R-C\genfrac{}{}{0pt}{}{\diagup O}{\diagdown OH}}$$

Increase of carbon oxidation state ⟹
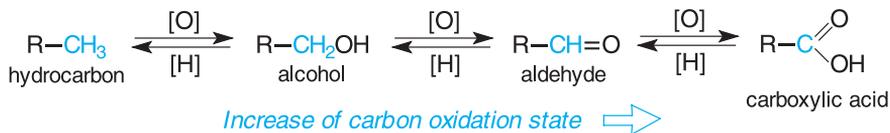
Problem 4.1. Classify the following reactions according to the types discussed before:

(a) $(CH_3)_3COH + HCl \longrightarrow (CH_3)_3CCl + H_2O$

(b) $CH_2=CH_2 + H_2 \longrightarrow CH_3CH_3$

(c) ⬡ $\longrightarrow$ ⬡ $+ 3H_2$

(d) $C_6H_5CH=O + O_2 \longrightarrow C_6H_5COOH$

(e) $CH_3CH=O + H_2 \longrightarrow CH_3CH_2OH$
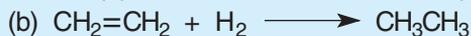
4.2. REACTION MECHANISMS

Chemical equations express the overall result of chemical transformation. They show the structures of reactants and products, but they tell us nothing how the reactants are turned to the products. Now we are interested in how the reaction takes place, i. e. its *reaction mechanism*.

📖 A reaction mechanism is a step-by-step description of all changes in reacting compounds that occur at the molecular level, as the reactants become products.

The mechanism describes which bonds are broken and which bonds are formed and in what order. It takes into account energy changes on the pathway from the reactants to the products including relative stability of intermediates formed in the reaction. The complete mechanism must also account for the relative rates of the steps and stereochemical result of the reaction.

4.2.1. Radical and Polar Processes

All reactions of organic compounds involve the breaking and making of covalent bonds. Generally speaking, there are two ways in which a covalent bond can break in a hypothetical molecule A**:**B. In the first one, the bond breaks in an electronically symmetrical way so that one electron is retained with each fragment:

Homolytic process   A**:**B $\longrightarrow$ A˙ + B˙
free radicals

Such bond splitting leads to the neutral species A˙ and B˙ that have an unpaired electron in one of its orbitals and are called *free radicals*, or often simply radicals. This type of bond breaking is known as *homolysis* (from the Greek *homo* – the same, and *lysis* – cleavage), or *homolytic* process.

It should be noted that we use a half-headed curved arrow (like a «fishhook») to show the movement of only one electron, whereas we use an ordinary curved arrow to show the movement of an electron pair. The tail of the arrow indicates the position of the electrons prior to the reaction, and the head of the arrow shows their location after the reaction.

Remember, we have already used curved arrows to describe *p* electron shifting for representation of a mesomeric or inductive effect. To avoid confusion, the electron movement in the bond breaking and bond making are shown here and later in the text with *coloured* arrows. Black arrows will be used for representation of electronic effects.

The amount of energy required for the homolytic cleavage of a covalent bond is called the *bond dissociation energy*, or simply the bond energy. The same amount of energy is released when the radicals A˙ and B˙ combine to form the product A–B. Appendix 1 lists some data for bond dissociation energies.

Another type of bond breaking called *heterolysis* or heterolytic process results in formation of charged fragments or ions (for example, a cation A^+ and an anion B^-) as it is shown below. This is a consequence of electronically unsymmetrical splitting in which both bonding electrons remain with one fragment, leaving the other fragment with an empty orbital:

$$\text{Heterolytic process}\quad A:B \longrightarrow A^+ + :B^-$$
$$\text{cation}\quad\text{anion}$$

Similarly, there are two ways in which a covalent bond can form: a *homogenic* way when each reactant donates only one electron to the new bond, or a *heterogenic* way when both bonding electrons are donated to the new bond by one reactant.

With the foregoing considerations, the overwhelming majority of organic chemical transformations may be classified as *radical reactions* and *polar reactions*. The former involve symmetrical bond breaking and bond making with participation of a free radical reactant and intermediates. The latter involve unsymmetrical bond breaking and bond making with participation of species with an even number of valence electrons. Both types of the reactions will be exemplified here only schematically.

Radical reactions. A free radical X˙ can take away a part from a molecule A–B, for example, a species A˙ yielding a product A–X and leaving behind a new radical B˙. The net result of the reaction is radical substitution:

$$A:B + X˙ \longrightarrow A:X + B˙$$

These reactions are typical for nonpolar organic compounds, e. g. alkanes, subjected to reagents that bear free radicals under appropriate conditions (Sec. 4.2.2). Chlorination of methane demonstrates this:

$$CH_4 + Cl_2 \xrightarrow[-HCl]{UV} CH_3Cl \xrightarrow[-HCl]{Cl_2} CH_2Cl_2 \longrightarrow etc.$$
$$\text{methane}\qquad\qquad\text{chloro-}\qquad\qquad\text{dichloro-}$$
$$\text{methane}\qquad\qquad\text{methane}$$
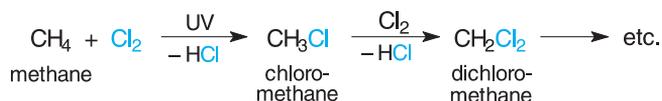
Polar reactions. These reactions occur as a result of attractive forces between positive and negative charges (full or partial) on both reactants. Despite the fact that most organic substrates are electrically neutral, certain bonds within a molecule are polar. It will be recalled that bond polarity is a consequence of the difference in atom's electronegativity.

The term *substrate* originates from biochemical terminology and means a compound that is exposed to a *reagent* (the latter is an enzyme in biochemical reactions).

Polar reagents of different types can react with organic substrates. Examples of substitution reactions are represented below where both substrates A–B and polar reagents XY differ from each other in reactions (1) and (2):

POLAR SUBSTITUTION REACTIONS

$$A:B \ + \ X^+Y^- \longrightarrow A{-}X \ + \ B^+Y^- \qquad (1)$$

$$A:B \ + \ X^+Y^- \longrightarrow A{-}Y \ + \ X^+B^- \qquad (2)$$

Polar reactions are of very common occurrence in organic chemistry. No example will be given here because most organic reactions, especially those discussed in this book, belong to this type.

4.2.2. Types of Reagents

We saw in the preceding section that two types of reagents take part in a polar reaction, namely the electron-poor reagent X^+ in reaction (1) or the electron-rich reagent Y^- in reaction (2). The former has an electron-poor site and seeks electrons in the substrate. The latter has an electron-rich site and can form a bond by donating a pair of electrons to an electron-poor site in the substrate. Polar reagents are classified on this basis as either *electrophiles* or *nucleophiles* (literally, electron-loving or nucleus-loving, respectively).

📖 An electrophile is an electron-poor reagent; a nucleophile, by contrast, is an electron-rich reagent.

These two types of reagents are illustrated in the addition reaction of ethylene and in the substitution reaction of ethyl bromide (detailed mechanisms of these reactions will be considered in further chapters).

$$CH_2{=}CH_2 \ + \ \underset{\text{electrophile}}{H^+Cl^-} \longrightarrow CH_3{-}CH_2Cl$$

$$\underset{\text{nucleophile}}{CH_3CH_2{\overset{\delta+}{\rightarrow}}\overset{\delta-}{Br} \ + \ Na^+OH^-} \longrightarrow CH_3CH_2{-}OH \ + \ Na^+Br^-$$
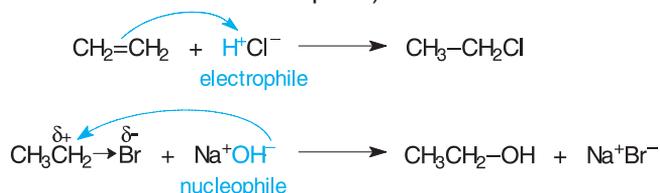
Electrophiles are often positively charged. Typical electrophiles are a proton, halonium ions (Cl^+ and Br^+), carbocations, or neutral molecules such as sulfur trioxide, SO_3, or compounds of the general formula R–X, where X is an electron-withdrawing group.

Nucleophiles are often, though not always, negatively charged. The most widely known nucleophiles are a hydroxide ion, alkoxide ions (RO^-), thiolate ions (RS^-), halide ions, a hydride ion (H^-), carbanions (particles with negatively charged carbon), and many neutral compounds such as water, alcohols, thiols, ammonia, and amines. Both electrophilic and nucleophilic reagents will be further considered in more details.

Free radicals. These neutral species contain an atom with an unpaired electron in its outer shell; they are usually highly reactive for this reason. Halogen radicals such as $Cl^{\bullet}$ and $Br^{\bullet}$ are of great importance in organic chemistry, particularly in some industrial processes. They can be produced from halogens on heating or by ultra-

violet radiation. The process represents homolytic cleavage of relatively weak bond in halogen molecules:

$$:\!\overset{..}{\underset{..}{Cl}}\!:\overset{..}{\underset{..}{Cl}}\!: \xrightarrow{\text{UV or heat}} 2 \; :\!\overset{..}{\underset{..}{Cl}}\!\cdot$$
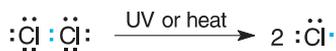
A compound that possesses unpaired electrons in an outer shell is ordinary molecular oxygen. On the basis of paramagnetic properties and the interatomic distance (121 pm) which is much shorter than the length of a single bond O–O (148 pm), the O_2 molecule can be described as a biradical $:\!\overset{.}{O}\!=\!\overset{.}{O}\!:$ in a ground state. As it is well known, oxygen is responsible for many oxidation reactions both *in vitro*, including industrial processes, and in living systems.

Thus, taking into consideration a type of reaction and the nature of reagents we can classify addition reactions as electrophilic, nucleophilic, and radical ones. Mechanisms of these reactions are designated by the symbols A_E, A_N, and A_R, respectively. Substitution reactions can be classified in a similar way as electrophilic, nucleophilic, and radical ones, using the symbols S_E, S_N, and S_R, respectively.

All these reactions are studied in this book. General principles will be demonstrated first with simple examples and then transferred to objects of biological importance.

> **Problem 4.2.** Classify reactions (1) and (2) represented in Sec. 4.2.1 according to their mechanisms.

4.3. ENERGETICS OF CHEMICAL REACTIONS

Subject matters presented in this section are usually discussed in a course of General Chemistry. A cursory introduction to the question will be made here only for understanding a reaction mechanism.

4.3.1. Activation Energy and Reaction Energy Diagram

In order to react, reactant particles must collide with each other. Not all collisions between them are effective, however. A chemical reaction takes place when some conditions are provided for redistribution of the electron density of the colliding molecules. To form products, the molecules must have enough energy and the right orientation so that the breaking and making of the bonds can occur. The course of the reaction can be characterized by three consecutive states:

REACTANTS $\longrightarrow$ ACTIVATED COMPLEX $\longrightarrow$ PRODUCTS

initial state   transition state   final state

For a generalized one-step reaction between two gaseous compounds A_2 and B_2, the *transition state* corresponds to the formation of an activated complex $A_2\!\cdots\!B_2$. In this complex, the bonds A–A and B–B break simultaneously with the formation of new A–B bonds:

$$\begin{matrix} A\!-\!A \\ + \\ B\!-\!B \end{matrix} \longrightarrow \begin{matrix} A\!-\!-\!-\!A \\ \vdots \quad \vdots \\ B\!-\!-\!-\!B \end{matrix} \longrightarrow \begin{matrix} A \quad A \\ | \;+\; | \\ B \quad B \end{matrix}$$

reactants   transition state   products
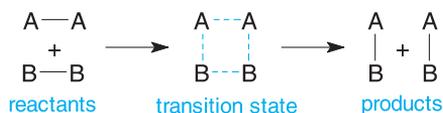
The activated complex exists for a very short time (less that 10^{-10} sec) and cannot be isolated, of course. Then it decomposes to form either a product A–B or the initial compounds A_2 and B_2. The energy required for the formation of the activated complex is a barrier to reaction. It is called the *activation energy*, E_a, and it determines how rapidly the reaction occurs. The greater is the activation energy, the slower is the reaction, and *vice versa*[1].

Most organic reactions have activation energies in the range of 170–650 kJ/mol. Reactions with activation energies less than 80 kJ/mol occur spontaneously at room temperature or below, whereas many reactions require heating to provide the energy necessary for the reactants to overcome the activation barrier. Some reactions, including highly exothermic ones, are either retarded or do not take place at all because of high-energy barriers. It is well known that wood, paper, petrol, and other inflammables can be oxidized and burn in air. But they do not ignite spontaneously under normal conditions because the reaction requires a considerable activation energy.

The energy changes occurring in the course of a reaction is usually depicted in the form of a *reaction energy diagram* (Fig. 4.1). The progress of the reaction from the beginning (left) to the end (right) is plotted against the X-axis that is called the reaction coordinate. The potential energy of the system is plotted against the ordinate.
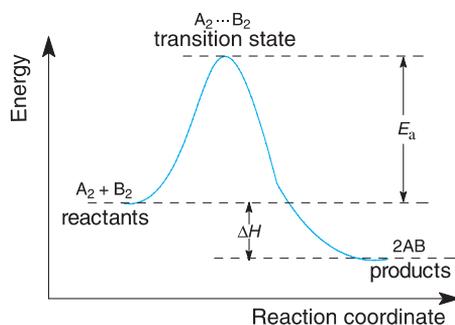
Figure 4.1. Reaction energy diagram
for the one-step $A_2 + B_2 = 2AB$ reaction

The energy spent on activating the reactants is later, partly or wholly, liberated during the formation of the reaction products. If the amount of energy liberated during the decomposition of the activated complex is greater than the activation energy, heat is given off in the reaction. Such a reaction is *exothermic*, as it is shown in Fig. 4.1. In other words, the products are lower in energy than the reactants, i. e. the difference in enthalpy between products and reactants is negative ($\Delta H < 0$). Otherwise, when heat is absorbed ($\Delta H > 0$), the reaction is *endothermic*.

4.3.2. Catalysis

One of the common methods of accelerating reactions is catalysis. A catalyst is a substance that increases the reaction rate by participating in an intermediate chemical interaction with reactants and is recovered unchanged after the reaction. The course of the overall reaction is altered in the presence of a catalyst and the rate of the reaction is altered as well. Rate increasing is associated with lower activation energy of a new pathway, which is usually multi-step in catalyzed reactions.

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[1] This resembles the situation of a traveller who climbs over a mountain pass. The traveller needs a lot of energy to overcome a high pass and will reach a top slowly. If the pass is low, the traveller needs less energy and will surmount the barrier quickly.

Let us consider a reaction between compounds A and B that forms, through an activated complex A···B, a product AB (the black curve in Figure 4.2). If its activation energy is high, the reaction if any proceeds at a very slow rate. Let us now assume that a catalyst C reacts readily with A to form an intermediate compound AC (the coloured curve in Figure 4.2):

$$A \ + \ C \ \longrightarrow \ A \cdots C \ \longrightarrow \ A \!-\! C$$

<div align="center">activated   intermediate
complex 1</div>
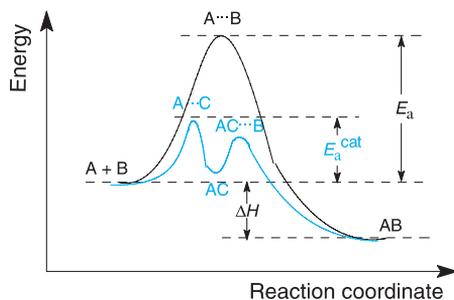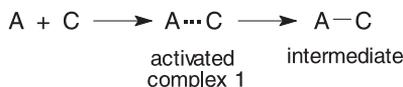
Figure 4.2. Reaction energy diagram
for a noncatalyzed reaction (the black curve)
and for a catalyzed reaction (the coloured curve)

The catalyzed route has the lower activation energy, E_a^{cat}, than the original, noncatalyzed path. The compound AC reacts then readily with the reactant B (for the same reasons) to form the product AB and a recovered catalyst C:

$$A \!-\! C \ + \ B \ \longrightarrow \ A \!-\! C \cdots B \ \longrightarrow \ AB \ + \ C$$

<div align="center">activated   product
complex 2</div>
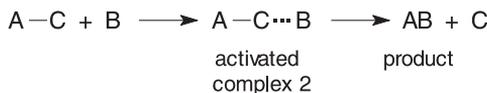
It should be noted that the activation energy for the reverse reaction is lowered exactly by the same amount as for the forward reaction. Thus the catalyst speeds up the *two* reactions and has no effect on chemical equilibrium. It only accelerates the attainment of equilibrium in the system. On the other hand, the value of ΔH does not change when the catalyst is used as it is shown in Figure 4.3. Only the reaction mechanism and the activation energy change.

Catalytic reactions are most varied in organic chemistry. As we will see later, a proton and a hydroxide ion have a great effect on the rate and direction of chemical reactions. The catalytic effect appears in many reactions in an indirect form. These are the reactions in solution where a solvent activates the reactants by means of polarization or ionization.

There is no doubt that the most important catalysts are *enzymes*, organic molecules responsible for catalyzing a broad spectrum of reactions in living systems. Biochemistry is a science which studies biological processes. The application of chemical principles and an understanding of molecular structures have been important in advances made in biochemistry.

Additional Problems

4.3.   Classify the following reactions according to the types discussed in Section 4.1:

(a) $CH_3CH(OH)CH_3 \xrightarrow{\text{catalyst}} CH_3CH=CH_2 + H_2O$;

(b) $CH_2=CHCH_3 + HBr \longrightarrow CH_3CHBrCH_3$;

(c) $+ 3H_2 \longrightarrow$;

(d) $CH_3CH=O + H_2 \longrightarrow CH_3CH_2OH$;

(e) $CH_3CH_2COOH \xrightarrow{[H]} CH_3CH_2CH_2OH$.
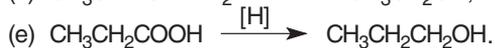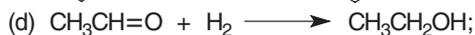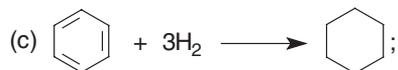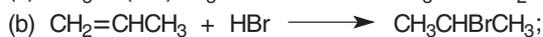
4.4.   Which of the following species would you expect to belong to electrophiles and which to nucleophiles, *if any*: (a) methane; (b) carbon dioxide; (c) water; (d) a phenoxide ion, $C_6H_5O^-$; (e) a hydronium ion, H_3O^+?