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Introduction

Organic synthesis is a unique area of science because, unlike most other disciplines that study existing matter, it is largely concerned with the creation of new matter – substances that do not exist in nature. Many simple compounds such as nitrobenzene, aniline, ethyl bromide, and others do not exist in nature; they are produced by humans via methods of organic synthesis.

The goal of organic synthesis is to obtain desired compounds from readily available substances via a series of transformations – chemical reactions. For example, naturally occurring benzene can be converted into nitrobenzene via nitration, which is then reduced to aniline, and through further transformations, more complex compounds can be obtained. Thousands of organic reactions are now known; many of them are named after their discoverers, such as the Friedel–Crafts, Claisen, or Wittig reactions.

Research in the field of organic synthesis follows two main directions: the search for new reactions and synthetic methods, and the synthesis of compounds with specific structures, such as natural products and substances with particular functional properties or those used to test scientific hypotheses.

Organic synthesis is deeply interconnected with practical applications, as it is the source of products essential for civilizational and technological progress. The first practical products manufactured by organic synthesis in the late 19th century were dyes. Today, no area of practical activity – construction, transportation, textiles, electronics, agriculture, healthcare, and more – could function without products derived from organic synthesis.

Effective execution of organic synthesis requires deep knowledge as well as the ability to select and identify appropriate pathways and reactions leading from available starting compounds to the desired products. This is a challenging task, as one might think that the vast number of organic reactions used in synthesis processes constitutes encyclopedic knowledge that must be memorized. However, this is not the case – the enormous body of reactions is logically coherent, and understanding and mastering the fundamental laws, rules, and relationships allow one to navigate this material with confidence. Our goal is to present this material in a way that reveals the analogies and connections between the wide variety of organic reactions used in synthesis, as well as the factors determining the course and direction of those reactions.

The fundamental processes of organic synthesis are chemical reactions – the making and breaking of chemical bonds in such a way that the substrate is transformed into the desired product. Therefore, in this introduction, we will analyze the factors that determine the course of chemical reactions.

A set of compounds A (the substrates) can be converted into products B if the transformation proceeds with a negative change in the standard Gibbs free energy, ΔG^0:

$$A \rightleftharpoons B \quad \Delta G^0 = \Delta H^0 - T\Delta S^0 \quad \Delta G^0 < 0,$$

where ΔH^0 is the change in enthalpy, which can be estimated based on the bond enthalpies of the bonds formed and broken during the reaction, and ΔS^0 is the change in entropy, representing the degree of disorder in the system. In general, the equilibrium state depends on the value of ΔG^0 according to the equation:

$$RT \ln K = -\Delta G^0,$$

where K is the equilibrium constant.

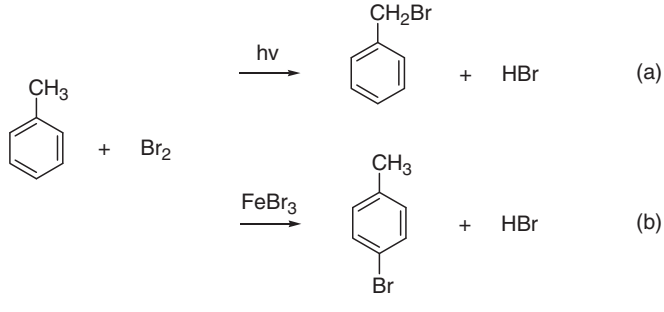
However, this thermodynamic condition for a reaction to proceed in the desired direction informs us only about the possibility of the process and its potential equilibrium position – it does not include the element of time and tells us nothing about the reaction rate.

The question of rates of reactions is addressed by chemical kinetics. Its fundamental concept of the transition state asserts that the transformation A → B proceeds via a transition state $A^{\#}$, and the reaction rate is determined by the free energy of the transition state, $\Delta G^{\#}$:

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}.$$

The free energy of the transition state $\left(\Delta G^{\#}\right)$ determines the height of the energy barrier that must be overcome by a system of molecules for the transformation A → B to proceed. This transformation involves the breaking of chemical bonds in the reactants and the formation of new bonds in the products. While the equilibrium state depends solely on the change in the system's free energy and thus is independent of the pathway by which the transformation proceeds, the height of the energy barrier – and therefore the reaction rate – depends on the sequence and manner of events, i.e., the breaking and forming of chemical bonds. In other words, it depends on the reaction pathway, or reaction mechanism.

A good illustration of these concepts is the reaction of toluene with bromine.



Mixing toluene with bromine at room temperature in the dark does not result in a reaction. The reaction takes place: (a) upon exposure of the reaction mixture to light, or (b) after the addition of a Lewis acid catalyst.

The standard free energy change (ΔG^0) of these two alternative reactions, which lead to different products, is very similar, because the number and type of bonds broken and formed are the same. However, they undoubtedly proceed via different pathways (i.e., via different mechanisms).

The bromination of toluene exemplifies a general situation. A given set of reactants A (in this case, toluene and bromine) can yield many products that meet the condition of a favorable equilibrium state $(\Delta G < 0)$. The possibility of obtaining a specific product depends on the height of the energy barrier along the pathway leading in the desired direction, which is determined by the reaction mechanism. Thus, the feasibility of obtaining a given product from specific reactants is determined by the course of the reaction (in simplified terms, by the mechanism).

The possibility and course of reactions of organic molecules, namely rates and equilibrium constants, are determined by a number of internal and external factors. The **internal factors**, related to the molecular structure, include:

1. Bond energies;
2. Polarity – the presence of bonds between different atoms, which leads to a separation of partial charges within a molecule, for example,

3. Polarizability – the ability of a molecule to distort its electron cloud in response to an external electric field;
4. Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies. Recall that the molecular orbitals occupied by electrons with the highest energy are called HOMO, and the unoccupied molecular orbitals with the lowest energy are called LUMO. Organic molecules typically contain many orbitals, but it is always the HOMO and LUMO that participate in chemical reactions – as they are furthest from the atomic nuclei in the molecule;
5. Spatial arrangement – the mutual positioning of atoms and groups in space – especially groups prone to react (e.g., *cis* and *trans* isomers, *ortho* and *meta* positions in a benzene ring, etc.).

The most important **external factors** are: 1. energy supplied to the system; 2. solvents; 3. catalysts.

1. Energy. The absorption of energy causes a molecule to move to a higher energy level. As it is well known, changes in molecular energy are not continuous but quantized, corresponding to different energy levels. Starting from the lowest, these include:

   - translational levels – movement of molecules through space,
   - rotational levels – rotation around chemical bond,
   - bending (vibrational angular) – changes in bond angles,
   - vibrational levels – stretching of bonds.

Higher energy levels are associated with changes in electron orbital occupancy.

The simplest way to supply energy to a system of molecules is heating. The supplied energy leads to increased population of progressively higher energy levels, beginning with translational levels, and may ultimately lead to the dissociation of bonds with the lowest bond enthalpy. Other energy-supplying methods, such as acoustic energy, high static pressure, or microwaves, are used much less frequently. In all these methods, the energy is supplied non-selectively.

A very important method of supplying energy is irradiating molecules with electromagnetic radiation in the ultraviolet, visible, or, more rarely, infrared range (photochemistry). Radiation can supply energy to a molecule if it is absorbed, which requires the presence of structural elements in the molecule capable of absorbing energy. These structural elements that can absorb visible or UV radiation are called chromophores. When absorption takes place in the visible range, they impart color to organic compounds. The energy provided by UV and visible light is comparable to bond energies and can lead to their dissociation.

2. Solvents. An essential role of the solvent is to enable contact between reagents, which is necessary for the reaction to proceed. In the case of two solid or mutually immiscible liquid substances, molecular contact between reagents is very limited. Dissolving both reactants in a solvent allows free molecular interaction and thus enables the reaction to take place.

When a reaction between molecules is strongly exergonic $\left(\Delta G^0 \ll 0\right)$, the energy released may cause the dissociation of the newly formed molecule. Collisions with solvent molecules help disperse this energy, so the solvent acts as an energy buffer. Specific solvation by the solvent also affects the activity of dissolved substances, which can alter the rate or even direction of the reaction. Therefore, solvents play a crucial role in chemical reactions.

Whether a substance A can dissolve in solvent S is determined by energetic factors. The free energy of the solution must be lower than that of the individual components A and S. This condition is met when the enthalpy of intermolecular interactions between S···A is comparable to that of A···A and S···S. This is expressed by the well-known rule: "like dissolves like."

Entropy also contributes significantly to the gain in free energy during the dissolution process – the solution is a much more disordered system, so the entropy increases during dissolution.

The discussion of interactions between a dissolved substance and a solvent requires a review of the types of forces that govern intermolecular interactions.

a. Dispersion interactions take place between molecules of saturated hydrocarbons and hydrocarbon chains of other organic molecules.
b. Dipole–dipole interactions: Polar molecules have a dipole moment, and as a result of electrostatic interactions, they orient themselves according to Coulomb's law.
c. Dipole–charge interactions: The interaction between polar molecules (dipoles) is particularly strong with particles carrying a full positive or negative charge – ions.

d. Coordinative interactions, which are similar to acid–base interactions. A typical example is the interaction of metal cations with ethers.
e. Hydrogen bonds that occur between acid groups, such as OH, and atoms with a high electron density.

Considering the properties of solvents, they can be divided into several groups:

a. Nonpolar solvents: aliphatic hydrocarbons – hexane, cyclohexane; aromatic – toluene; halogenated compounds – chloroform, methylene chloride, chlorobenzene.
b. Moderately polar, donor solvents: ethers – diethyl ether, tetrahydrofuran, dimethoxyethane, dioxane.
c. Polar aprotic donor solvents: ketones, esters – acetone, ethyl acetate; acetonitrile, dimethylformamide, dimethyl sulfoxide, hexamethylphosphorus triamide, and others, including liquid ammonia.
d. Polar, protic solvents: alcohols – methanol, ethanol; carboxylic acids – formic, acetic; water, etc.

The choice of solvent for carrying out a reaction is a crucial issue, as it can determine the success of the process. The most important criteria for selecting a solvent are: the solvent should not react with the substrates or products; it should not deactivate reagents; it is beneficial if it has an activating effect; it should not cause difficulties in isolating products or removing residues; it should not present a fire, toxicity, or environmental hazard. The regeneration and reuse of the solvent should not pose problems.

3. Catalysts. According to the definition, a catalyst is a substance that participates in a reaction, increasing its rate, but itself is not consumed. In other words, a catalyst speeds up the attainment of chemical equilibrium but does not affect its position. The vast majority of chemical reactions proceed with the involvement of catalysts. Catalytic processes and catalysts can be classified based on many criteria. Undoubtedly, the most common type is acid–base catalysis, for example, under the influence of an acid, an organic molecule transforms into an active form, allowing the desired reaction to proceed, and after the products are formed, the acid is regenerated and can trigger the reaction of another molecule. In recent decades, transition metal catalysis has become widely used: Pd, Pt, Rh, Ru, and others. The vast area of organic reactions catalyzed by transition metals will not be discussed here.

This brief introduction very generally outlines the basic factors determining the course of a reaction. We will now systematically discuss the chemical reactions most significant for organic synthesis. As we stated in the introduction, our goal is to present the vast field of organic synthesis, which includes hundreds of reactions, in such a way that it demonstrates that it is not merely a collection of extensive information, but rather a set that has internal logic. Understanding the basic rules not only allows for navigating this vast material with ease, but also provides the ability to predict and design previously unknown processes.

Classifying this extensive material in a way that highlights the connections between reactions, their similarities and differences, and thus presents the internal logic of the system must naturally be based on mechanistic concepts that explain why and how a given process takes place.

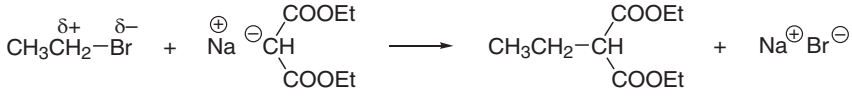
The most extensive and important section of organic synthesis consists of ionic reactions, which can be generally defined as processes in which new bonds are formed by the filling of an empty orbital of one reactant with the electron pair of another reactant, while bond breaking proceeds without the separation of electron pairs.

Ionic reactions will be divided into two main groups: nucleophilic reactions and electrophilic reactions, both of which are quite formally defined. Nucleophilic reactions include those that proceed with the involvement of nucleophilic agents, while electrophilic reactions proceed with the involvement of electrophilic agents. This definition, in turn, requires the definition of nucleophilic and electrophilic agents. Nucleophilic agents are anions or neutral molecules that possess electron pairs in high-lying HOMOs (high-energy HOMO), capable of forming bonds with atoms that have an electron deficiency.

Similarly, electrophilic agents are cations or neutral molecules with an electron deficiency, possessing low-lying LUMOs (low-energy LUMO), coordinatively unsaturated, and capable of accepting an electron pair, which leads to the formation of a new bond.

Nucleophilic agents can react with electrophilic molecules that have electron-deficient fragments, while electrophilic agents can react with molecules that have an excess of electrons.

From these definitions, it is clear that any ionic reaction can be treated as either a nucleophilic or electrophilic reaction, depending on the point of view. Thus, the classification of a reaction as nucleophilic or electrophilic is arbitrary, and the key criterion we have adopted is the relative activity of the reaction partners. For example, in the reaction of alkylation of a malonic ester anion with ethyl bromide



we have no doubt that the active partner is the malonate anion – a nucleophilic agent – so this is a nucleophilic reaction. On the other hand, nitration of benzene

proceeds with the participation of the nitronium ion – a highly active electrophilic agent – so this reaction is classified as electrophilic.

As can be seen, this division is arbitrary, and the classification used is formal. It has been adopted for the ease and efficiency of discussion.

For Further Reading

After reading this book, we strongly recommend becoming acquainted with *Organic Syntheses* (published since 1921, with practically one volume appearing each year; 102 volumes have been published so far). It is a collection of preparative procedures that are either of a general nature or describe the synthesis of organic compounds of particular importance. Each volume contains a dozen or so, more rarely several dozen, procedures. All procedures submitted by the authors are checked by members of the *Organic Syntheses* editorial board. Reading *Organic Syntheses* will allow you to see the reactions used in organic synthesis – usually presented rather dryly in textbooks – from a practical perspective. It seems feasible to go through two volumes a day, which will make it possible to become familiar with the contents of the work in roughly two months without much effort.

Another serial publication important for the organic chemist is *Organic Reactions* (published since 1942, irregularly; 117 volumes have appeared) – "a comprehensive reference work that contains authoritative, critical reviews of many important synthetic methods. In addition to detailed discussions of the mechanism, scope, and limitations of reactions *Organic Reactions* chapters contain exhaustive tables of the varied published examples of the title reactions" (quote from *Organic Reactions* home page). In the list of recommended literature appended after each chapter of this book, we particularly cite reviews from *Organic Reactions*. Although some of them are quite old, they often have not lost their relevance.

The following list of textbooks for further reading is, of course, our arbitrary and by no means complete selection.

1 Jones, M., jr. and Fleming, S. A. (2014). *Organic Chemistry*. Fifth Ed., W. W. Norton & Co.
2 Bruice, P. Y. (2017). *Organic Chemistry*. Eighth Ed., Pearson.
3 Clayden, J., Greeves, N., and Warren, S. (2012). *Organic Chemistry*. Second Ed., Oxford University Press.
4 Carey, F. A. and Sundberg, R. J. (2007). *Advanced Organic Chemistry. Part A: Structure and Mechanisms. Part B: Reactions and Syntheses*. Fifth Ed., Springer.
5 Solomons, T. W. G., Fryhle, C. B., and Snyder, F. A. (2022). *Organic Chemistry*. Thirteenth Ed., Wiley.
6 Wade, L. G. and Simek, J. W. (2020). *Organic Chemistry*. Ninth Ed., Pearson.
7 Klein, D. R. and Starkey, L. S. (2025). *Organic Chemistry*. Fifth Ed., Wiley.
8 Tucker, W. B. (2024). *Organic Chemistry: Structure, Function and Practice*. CRC Press.
9 McMurry, J. (2023). *Organic Chemistry*. Tenth Ed., Open Stax.
10 Smith, M. B. (2025). *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure*. Ninth Ed., Wiley.