

## *“Life through the eyes of a chemist”*

On February 8, 1933, a lecture entitled “Life through the eyes of a chemist” was presented by Professor Albert Szent-Györgyi at an event organized by the Association of Friends of Ferenc József University. The next day’s edition of *Délmagyarország* reported on the lecture, which was followed with great interest. The director of the Medical Chemistry Institute at the time stated, among others, that “there is no relation whatsoever between science and religion because what can be measured is science, and where there is nothing to measure is religion; science, therefore, may be at most a close neighbor of religion.” He said, in addition, that “science investigates depths, it penetrates the tiniest of particles to reveal newer and newer secrets. Biochemistry reached this way the smallest constituent of the human body, the cell, and then the molecules and atoms. Thus, it learned that the amazing machinery we call living body is eighty percent water.” He added, to the great amusement of the audience, that “it is so even if we speak of an honorable gentleman.” His opinion was that “biochemists did not stop at the atom, they entered it, which was a more important event in world history than the Great War.”

The present paper intends to demonstrate through examples how synthetic organic chemistry, a branch of chemistry, helps our everyday life.

## **Organic compounds**

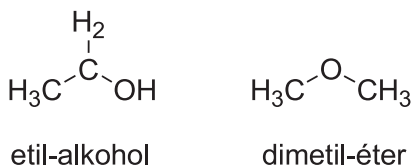
Organic chemistry is the chemistry of carbon compounds. Besides carbon, the molecules of organic compounds typically contain hydrogen, nitrogen, oxygen, sulfur or phosphorus. Their transformations into each other form the basis of the functioning of the living body. Organic chemical reactions were already performed in the antiquity (of course, not knowingly), and these included, for example, the production of wine or vinegar. The Middle Ages were dominated by alchemists and iatrochemists. As is well known, one of the main goals of alchemists was to produce gold. Iatrochemists were interested in medicine, the development of new treatments and medications. Although their efforts failed in many cases, an important recognition of theirs was that chemical substances may also be used for healing.

The experiments with organic chemical reactions were set back by “vitalism,” a theory predominant until the beginning of the 19th century, according

to which it is not possible to produce an organic compound artificially, from an inorganic compound, because it requires “vital force,” something possessed by living organisms only. This theory was disproved in 1828 by the German chemist Friedrich Wöhler, who synthesized, with heating, an organic compound, urea, from ammonium cyanate—which is an inorganic compound. Many questioned this discovery at the time but further experiments clearly confirmed the finding of Wöhler before long. The advance of organic chemistry gathered momentum after this.

What makes organic chemistry special within chemistry is that the carbon atoms that constitute the molecules of organic compounds may form chains of arbitrary length by binding to each other, and these chains may also contain forks → branches. Carbon atoms may form rings as well, in which carbon may also be replaced with another atom (oxygen, nitrogen, sulfur, etc.; a so-called heteroatom). Based on all of this, infinite kinds of organic compounds can be imagined in theory. In any case, the ones known today already number tens of millions.

In chemistry, the phenomenon where certain compounds have the same number and same kinds of elements (they have the same molecular formula) but differ in their structure is called isomerism. The figure shows an isomeric pair that also contains a heteroatom (oxygen)—ethyl alcohol and dimethyl ether, which have the same molecular formula,  $C_2H_6O$ .



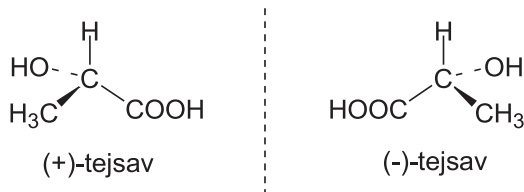
As the number of carbon atoms increases, there is an exponential growth in the number of possible isomers. For example, triacontane, the molecular formula of which is  $C_{30}H_{62}$ , has a theoretical 4,111,846,763 isomers, each of which is a different compound.

## Identities and differences

In the beginning, organic compounds were labeled with so-called “trivial” names. These names could refer to the effect, source, etc. of the compound; e.g., morphine, barbituric acid. With the exponential increase in the number of known compounds came the need for creating a systematic nomenclature

to have a clear link between the structure and the name of the billions of real or yet imaginary compounds. The foundations of the so-called IUPAC (International Union of Pure and Applied Chemistry) nomenclature were laid down as early as 1896, and the rules of the nomenclature are still under constant development today.

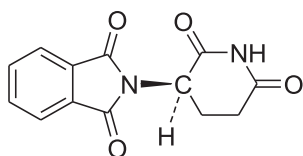
The structure of organic compounds with the same molecular formula may differ in several ways from each other and, based on this, different types of isomerism are distinguished. Out of these, optical isomerism is of marked importance. The carbon atom—because of its electron structure—has a valence of four in most of its compounds and, therefore, up to four different atoms or atomic groups may bind to it. In such case, the four valences of the carbon atom that is situated in the center of an imaginary tetrahedron are pointing at the four vertices of the tetrahedron, where the atoms or atomic groups are located. If these are different, the molecule cannot be superimposed on its mirror image, i.e., the compound has two isomers, which are called enantiomers. The figure shows the structural formulas of the enantiomers of lactic acid (the solid lines, the dashed line and the wedge bind the groups on the plane, behind the plane and in front of the plane of the paper, respectively, to the central carbon atom).



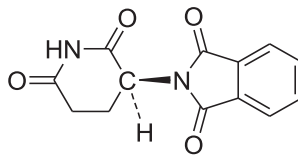
The relationship between the two compounds is like that of the right and the left hand, and therefore—based on the Greek word for “hand”—the phenomenon is called chirality. The label before the name of the compound indicates whether the solution of the given compound rotates the plane of polarized light clockwise or counterclockwise; this is where the term “optical” isomerism originates from. Enantiomers are the same in virtually all of their chemical and physical properties. This fact leads to a difficulty when we wish to separate the two isomers from each other. It is obvious that we should make use of some kind of a difference to achieve separation, but what if there is no difference? Why is it necessary anyway to separate the members of the enantiomeric pair? The main reason for this is that the systems of the living body are also chiral and, because of this, the substances administered into the body may lead to different responses. Thus, for example, if the molecules of an active

drug ingredient form an enantiomeric pair, it may happen that only one of the substances shows the desired effect, whereas the other one is harmful to the body. This phenomenon is similar to the situation when we are try to put the right-handed glove on our left hand. We will have little success; the same as when we are trying to put an unfitting enantiomer in the chiral “pocket” of an enzyme in the body. Why are enzymes chiral? Because their building blocks, the amino acids are mostly also chiral.

The pharmaceutical company Grünenthal put its drug Contergan, which contained thalidomide as the active ingredient, on the market in 1957. During its use, it was found that, out of the enantiomers shown on the figure, only the left one shows the desired sedative, painkilling effect, whereas the other one has a teratogenic effect, i.e., it is harmful to the fetus. In the late ‘50s and early ‘60s, more than 10,000 so-called Contergan babies with limb defects or without limbs were born in 46 countries around the world.



(+)-Thalidomide



(-)-Thalidomide

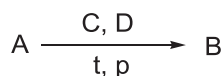
This event raised the attention to the following: if our active drug substance is chiral, the drug should ideally contain the required isomer only, or if the enantiomers cannot be separated in a reasonable way, the effect and destiny in the body of the other enantiomer must be thoroughly investigated. The peculiarity of thalidomide is that even if all of this had been known and the enantiomers had been separated from each other and only the suitable one had been used, it would not have been a solution. This is because in the body, the “good” isomer is able to transform into the “bad” isomer, i.e., it isomerizes, and therefore it would have exerted its harmful effect anyway. Another interesting thing is that thalidomide has recently found its way back into the pharmacological armamentarium because it shows a considerable antitumor effect and—naturally, taking its teratogenic effect into account—it may be used, e.g., in men.

Certain naturally occurring enantiomers differ even in their smell. (+)-carvone smells like caraway, whereas (–)-carvone smells like spearmint. (+)-limonene smells like orange, whereas (–)-limonene has a turpentine-like odor.

Separating enantiomers from each other or the targeted production of one of them is therefore a serious challenge and an important problem to be solved by the organic chemistry of today, and it can be achieved, even if often not easily, by using the principle provided by nature, that is, ensuring a chiral environment.

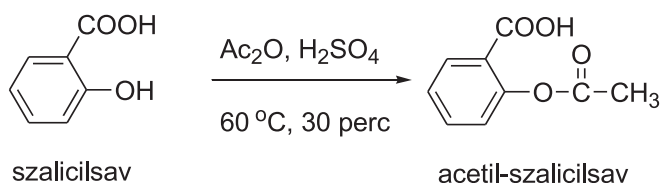
## Equation of organic chemical reactions

Let's see now, in general, how to write the equation of an organic chemical reaction. We start from starting material "A," let's call the product to be produced "B," and an arrow is placed between them, on which the reagents (C, D) and the reaction conditions (t = reaction time, p = pressure, etc.) are usually given.



For a chemical reaction to occur, activation energy is required, which is usually communicated to the system in the form of heat. Instead of heat, we may also use activation by microwaves or light. If a catalyst is used, the activation energy needed for the reaction is lower, and therefore the reaction can occur under milder conditions and faster than without a catalyst. Enzymes are the catalysts of the living body. Reactions in the living body must be catalyzed so that the reactions that ensure the functioning of the body can occur at body temperature, i.e. at 36 to 37 °C in case of the human body.

I will demonstrate through the example of the production of acetylsalicylic acid, the active ingredient of aspirin, how an organic chemical reaction can be performed in the laboratory. “A” in this case is salicylic acid, whereas the resulting product, “B,” is acetylsalicylic acid. Acetic anhydride is used as reagent and sulfuric acid as catalyst.



The following recipe describes the steps of the transformation:

1.4 g (10 mmol) salicylic acid, 2.0 mL acetic anhydride and 3 drops of concentrated sulfuric acid are measured into a 50-mL round-bottom flask.

The mixture is heated over a water bath at 60 °C for 30 minutes, and it is shaken gently every now and then. After this, 20 mL water is added, and the mixture is cooled over an ice bath. The precipitation is filtered, and the raw product is recrystallized from water containing acetic acid.

Now, I wish to demonstrate how close the analogy between such a chemical transformation and one of the most important kitchen activities, cooking, is. If, for example, we wish to make chicken soup, chicken is the starting material (A) and chicken soup is the end result. The required materials are not called reaction partners or reagents here but ingredients. Temperature has an important role here as well. We cook in water, the temperature is therefore 100 °C, and the “reaction time” is about 3 hours. We also have a recipe here, which we may follow to the letter or modify, or we may create a new one, just like when performing reactions.

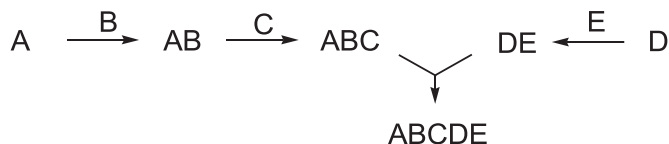
It is worth noticing that the equipment and the methods used in the kitchen and the synthetic organic chemistry laboratory are similar in many aspects. In the kitchen, we cook in pans and pots, whereas in the laboratory, flasks are used for the same purpose. We work in a broad temperature range both here and there, mixing may be necessary in both places, and the magnetic stirrer is the wooden spoon of the laboratory. In the kitchen, water is used as a solvent. Water may also be used for organic reactions but most often, various organic solvents are employed, mainly because most of the organic compounds are insoluble in water. Filtering is needed both here and there. Special gases may be found also in the kitchen, e.g., carbon dioxide or nitrous oxide; usually many types of special gases are used in the laboratory. Reactions requiring pressure may also be performed; in case of the kitchen, in a pressure cooker, whereas in case of the laboratory, in a pressure reactor. To speed up reactions, we may use a microwave oven, and a corresponding equipment can be found in the laboratory. Washing up is required both in the kitchen and the laboratory, and it is usually done manually in both places, but a dishwasher may also be used in either case. Of course, personal protective equipment must be available in both places. There is a considerable difference, however, between the two activities in that we have the opportunity to check the quality by tasting in the kitchen, whereas in the laboratory, we need to use a chemical-analytical method to this end. Another very important difference between the two activities is that in the kitchen, we usually need the end result in the form in which we cooked it, i.e., we need the meal itself. Contrarily, in the laboratory, we need the single substance that we wished to produce (the target compound), and therefore we must extract the desired product from the complex reaction mixture with a certain method after the reaction is

complete. In most cases, organic chemical reactions do not result in a 100% yield, i.e., after a reaction of  $A \rightarrow B$ , unconverted A molecules may remain, or other products may be formed besides B, that is, selectivity issues may occur.

The term “synthesis” is also used in everyday life and it by and large means that from smaller parts, we create a larger one, which is qualitatively different from the sum of the small parts, and which is good or useful for something. In the case of organic chemical syntheses, a new or known organic compound is produced, usually from simple starting materials, with the help of chemical reactions. Syntheses usually consist of several, sometimes many, chemical reactions. Basically two kinds of synthesis strategies can be employed to implement the synthesis: in the case of linear synthesis strategy, we start from the first starting material, and build (in this case) the compound “ABCDE” step by step:



When the convergent synthesis strategy is used, we start with two (or more) pathways, and the smaller assembled units are combined with each other somewhere during the procedure.



Baskets, for example, may be made with the first strategy. During basket weaving, we take the first stave, we add the second one to it, and so forth until the basket is ready. An example for the second strategy may be car manufacturing, where the body of the car is assembled from different parts, in a sequential order. The engine is assembled separately, the piston, the cylinders, the spark plugs, etc. are installed in it, and then the body and the engine are assembled in the appropriate phase.

What can be the purposes of organic chemical syntheses? Several such purposes can be named, e.g.:

- Studying the reactivity of compounds,
- Expanding the application of new organic chemical methods and reactions,
- Producing new compounds to achieve different (physical, chemical or biological) research goals,



- Determining the structure of natural compounds. Organic syntheses were used to confirm the structure of compounds extracted from natural materials mainly in the past. At the time of Albert Szent-Györgyi, before that, and for a few decades even after that, the so-called chemical structure verification provided the means to solve this problem. During the “breakdown,” the compound of unknown structure that had been extracted from a natural material was taken and was subjected to transformations with known effects. As a result of the reactions, smaller compounds with known structure were achieved, and then the structure of the compound of unknown structure was logically presumed based on the structure of these smaller compounds and the reactions conducted. After working out the structure this way, it was still an assumption only, and full certainty was achieved with the so-called total synthesis. It involved taking a commercially available small molecule, performing the synthesis of the target compound starting from it, and comparing the obtained target compound with the one isolated from nature. If the two compounds were identical, the structure gained final verification. Nowadays, it is much easier for synthetic organic chemists to verify a structure because many spectroscopic methods are available to complete this task. The use of these began to spread in the middle of the past century and for the organic chemist, the most important of them is nuclear magnetic resonance (NMR) spectroscopy. It is based on the same principle as the MRI equipment used in clinical practice. The results of spectroscopic measurements give a projection of the structure of the given compound, and if all relevant spectra are available, the same task that could have taken up to ten years a hundred years ago can be completed within a very short time, possibly a few hours.
- Organic chemical syntheses are quite commonly performed also for pharmacochemical purposes. It usually involves the need for producing a large number of compounds and investigating their effects to develop an effective and safe drug in the end. Efforts are not always accompanied by success but sometimes an active ingredient that can be used in a field different from the original is discovered during the research.

Digitoxigenin is an active ingredient improving heart muscle function, which is found, among others, in common foxglove and lily of the valley. Their infusion was used for this purpose in traditional medicine. However, there is a serious problem with the use of this active ingredient; namely, that there is only a small difference between the effective and the lethal dose and, therefore, it is very easy to overdose the drug. Synthetic organic chemists tried to modify



the structure of this compound with the purpose of widening this so-called therapeutic window, but their efforts were not crowned with success. Derivatives of the compound in which the oxygen atom in the ring of the molecules was replaced with nitrogen were also synthesized. Although the resulting abiraterone cannot be used as a cardiac drug, it is an outstanding treatment for benign prostate enlargement.

- Organic syntheses aimed at the production in large amounts of a compound that is scarce in nature but important from some (not only pharmacological) viewpoints are also often developed.

Imperial purple was used to dye the garments of senators and emperors in the antiquity. The dye was extracted from purple dye murex snails, obtaining a mere 1.5 grams of imperial purple by processing about 10,000 snails. The structure of the compound is quite simple, the synthesis of dibromindigo was achieved already in the 1800s. The synthesis of textile dyes that provide a more lasting and better-looking result than imperial purple was also developed. The results are primarily associated with the name of Adolf von Baeyer.

Bombykol is an insect pheromone produced by female silkworm moths. Since mature female silkworm moths have a lifespan of about 3 to 5 days only, and they must mate and lay their eggs during this period, it is important to quickly encounter their male partners. Males can detect very low concentrations of bombykol from a great distance, even from kilometers away. In 1962, 3 mg bombykol was obtained from 31,000 moths, which was sufficient for the verification of its structure. Since the structure of the compound is relatively simple, synthetic chemists were able to achieve its synthesis in the same year. What is the benefit of being able to produce insect pheromones? These compounds may be used in environmentally friendly plant protection, e.g., by placing the attractant in traps. Another method is to contaminate a larger area with it, using very low concentrations but an amount that is enough to prevent the individuals of the opposite sex from meeting each other and, therefore, from mating.

At the time, vitamin C was called hexuronic acid by Albert Szent-Györgyi, who obtained the amount required for his experiments from paprika. This compound can be extracted from other natural sources as well, but it certainly would not be enough to satisfy the vitamin C needs of the world. Its synthesis was developed in the 1940s. The elegant syntheses starting from glucose and consisting of a few steps enable the efficient production of vitamin C.

The last example to be mentioned is the case of taxol. Taxol is found in the bark of the Pacific yew tree, and it was extracted from there in the 1960s. It is excellent for the treatment of certain female cancers. This compound called

taxol is found in very low concentrations in the bark of the yew tree and, on average, the bark of three 100-year-old trees is required for the treatment of a single patient. The yew tree grows quite slowly, lives very long, for several hundreds or even a thousand years, and its wood is very hard, difficult to work on, and extremely durable. To prevent the eradication of the yew tree, synthetic organic chemists tried to perform the total synthesis of this compound. Six or seven research teams managed to do this, and their results were published in the 1990s. The rather complex total syntheses, however, consist of too many reaction steps, and therefore their industry-scale implementation is not economical. At the same time, an active ingredient that is a close structural relative of taxol was extracted from the leaf of the European yew, which is endogenous in Europe and, within it, Hungary, and with its so-called semisynthetic transformation, taxol can be obtained in relatively few steps and efficiently. In 2011, the yew was chosen as the tree of the year. The yew inspired writers and poets as well. It is worth knowing that every part of the yew, except for the aril around the seed, is poisonous, and thus this plant is usually associated with death and passing in the literary examples. An interesting thing is that in the Harry Potter books, the wand of Voldemort is made of yew.

Finally, the opinion of a few Nobel laureates on chemical syntheses:

R. B. Woodward: “There is excitement, adventure and challenge, and there can be great art in organic synthesis.”

R. Hoffmann: “It is the making of such molecules—chemical synthesis—that I want to praise. → I want to praise chemical synthesis, the making of molecules.”

E. J. Corey: “I believe that chemical synthesis will make enormous contributions to human progress in the next century especially when coupled to biology and medicine.”

R. Noyori: “Chemistry has a central role in science, and synthesis has a central role in chemistry.”

The thought of Albert Szent-Györgyi quoted earlier, according to which “science investigates depths, it penetrates the tiniest of particles to reveal newer and newer secrets” is completely true even today. Despite the fact that the researchers of today have, from many aspects, a simpler task than their predecessors, new and new questions arise with the expansion of knowledge, the answers to which will require the results of synthetic organic chemistry—among other disciplines—for a very long time to come.

## References:

- Délmagyarország, February 1933 9.
- Wade, L. G. Jr., Organic Chemistry, 4th ed., Prentice Hall Int., Inc., 1999.
- McMurry, J. Organic Chemistry, 5th ed., Brooks/Cole, 2000.
- Felföldi, K., Wölfling, J., Szerves szintézisek [Organic syntheses], JATEPress, 2011.
- [www.wikipedia.org](http://www.wikipedia.org)