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Introductory concept for teaching chirality – symmetry of the asymmetric

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Abstract: Chirality is traditionally a problematic subject for undergraduate students at the beginning of learning organic chemistry, yet it is of great importance in life sciences. If the initial introduction of chirality is conducted carelessly, students will face ambiguity through the rest of the course and education every time they come across chirality-related subjects. Although there are numerous methods for overcoming the problems of visualization of chiral molecules in 3D space, the connection of chirality with molecular changes like vibrations and conformations is usually not explained thoroughly. In this work, chirality is introduced on dynamic (real) systems, because students from the start should perceive molecules in their natural state of constant motion and change. Apart from the proposition of the lecture concept, exercises are also included, that employ free and readily available software.

Keywords: second-year undergraduate; organic chemistry; stereochemistry, pedagogy.

INTRODUCTION

Students often have problems with the perception of chirality in bachelor studies.¹ Because of that, great effort has been put into searching for an efficient method for facilitating students' visualization of chirality in 3D space.² But molecules are dynamic and the inclusion of molecular changes in chirality principles is essential for understanding real systems. We propose a method for the inclusion of molecular changes in chirality lectures, to complement the well-established concept of chirality introduction in undergraduate courses. It relies on the basic knowledge of chemical equilibrium and chemical kinetics, as well as

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molecular motions and bonding, which is usually taught in general chemistry courses.

Traditionally, chirality is introduced firstly on asymmetric tetrahedral C-atoms. We suggest that dynamicity should be taken into account from the start, and the introduction of chirality can be exemplified on the three case studies, describing tetrahedral C-atoms at the end of the lecture. By this approach, atropisomerism can be an integral part of the lecture, and it is usually taught afterward or in higher courses.

Also, clips of molecular motions are available for better following of the lecture. Exercises that utilize free and readily available software are also provided.

CHIRALITY IN DYNAMIC SYSTEMS

Objects that are non-superposable on their mirror image are said to be chiral.³ Familiarity with mirror reflection from everyday life makes this approach universal for teaching. After this initial introduction of the chirality definition, we propose that students should be familiarized with the fact that enantiomers (E_1 and E_2) in achiral environment have the same standard enthalpy of formation and standard entropy. However, enantiomers don't have exactly the same amount of energy. It is estimated that the difference in energy between enantiomers for typical chiral molecules is in the order of magnitude 10^{-15} kJ/mol.⁴ This is the consequence of the phenomenon called parity violation and is caused by the intrinsically chiral nature of the weak nuclear force. But for all practical purposes, it is precise enough to consider that the system that consists solely of E_1 molecules has the same energy as the system that consists solely of E_2 molecules. Since there are no thermodynamical preferences for one of these states, equilibrium is reached when there is an equal number of enantiomers E_1 and E_2 in the system (derivation of this statement is provided in the Supporting Information):

$$E_1 \rightleftharpoons E_2 \quad (1)$$

$$K = \frac{[E_2]}{[E_1]} = 1 \quad (2)$$

$$\Rightarrow [E_1] = [E_2] \quad (3)$$

where E_1 and E_2 are enantiomers, $[E_1]$ and $[E_2]$ are their concentrations and K is the equilibrium constant for the reaction 1.

In other words, chiral systems thermodynamically tend to racemize. Chiral molecules will racemize if there is a way for that (molecules can undergo only those changes which energy barrier they can overcome). The speed of racemization is never zero. The question of practical importance is how fast is it happening.⁵

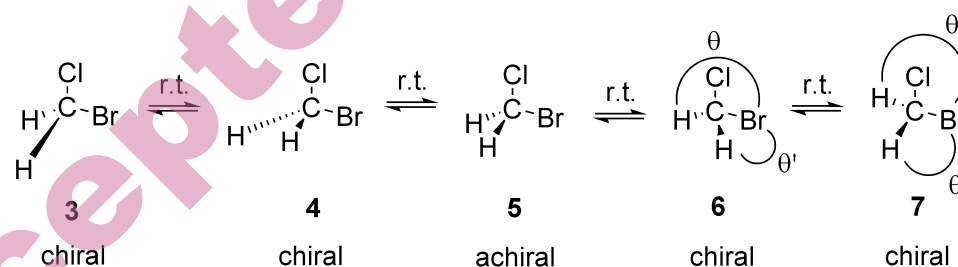
MOLECULAR CHIRALITY

If we want to consider real molecular systems we have to be aware of their real state, since, after all, we want to determine stereochemical properties of a real molecule and not of its model. Standard drawings with dashed lines help us

visualize the molecules and are routinely used in chemistry practice. However, we have to be aware of their limitations.⁶ Atoms in a molecule are not static - bond angles and bond lengths are rapidly changing (literature values for bond lengths and bond angles are average values).⁷ Also, there is another change that molecules undergo – rotation about the C-C bond.⁷ The importance of the awareness of all molecular motions has been emphasized recently, and animations were proposed as a tool for the effective inclusion of these motions in the curriculum.⁸ The impact of molecular changes on chirality properties is analyzed through the following case studies.

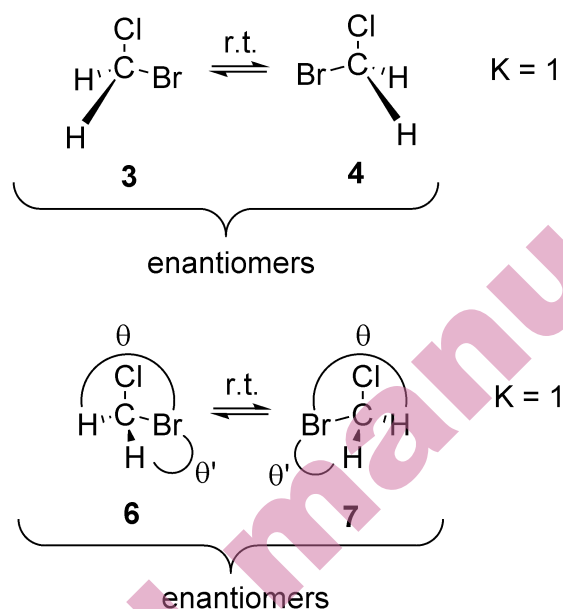
Case study #1

Bromochloromethane is a good example for bond length and bond angle changes because it does not have conformation isomers. Among many structures of bromochloromethane, which are produced by these changes, the ones in which two C-H bonds are not the same length are chiral (Scheme 1, the difference in bond lengths in **3** and **4** is exaggerated for clarity); animation is available at <http://cherry.chem.bg.ac.rs/handle/123456789/5945>. Also, structures that have two different HCCl angles or two different HCB angles (θ and θ' on the Scheme 1) are chiral; animation is available at <http://cherry.chem.bg.ac.rs/handle/123456789/5946>. Simpler – desymmetrization of two hydrogens produces a chiral structure.

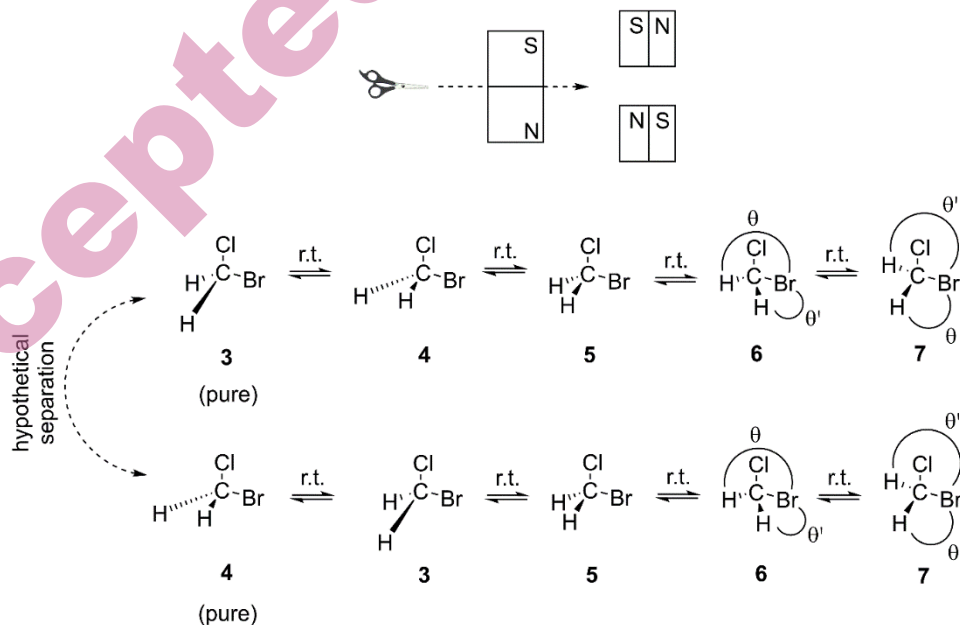


Scheme 1. Macroscopic sample of bromochloromethane contains great number of different molecular structures, which differ in bond angles and bond lengths. All those structures are in dynamic equilibrium. Some of them are chiral.

These “bond length enantiomers” (**3** and **4** on Scheme 1) and “bond angle enantiomers” (**6** and **7** on Scheme 1) are rapidly interconverting and in an achiral environment they are in equilibrium that is a racemic mixture (equation 3). In a system that consists of a great number of bromochloromethane molecules, every chiral structure will have its enantiomer present in the system in the equal amount (Scheme 2).



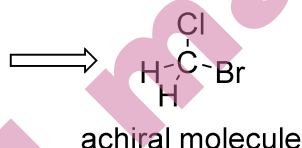
Scheme 2. Every chiral structure of bromochloromethane has its enantiomeric pair present in the system in the equal amount, because the system is in equilibrium.



Scheme 3. Analogy between fast racemization and poles of a magnet. Separation will result in two systems, which are identical as the starting one.

The reason why we don't call this system – a racemic mixture of bond length- and bond-angle enantiomers is because we cannot separate these enantiomers – as it is said, they are rapidly interconverting. If we imagine that we somehow separate one type of chiral molecules from the mixture, the moment we put them to ambient conditions they will equilibrate to a racemic system, identical to the one we have separated them from. This resembles the phenomenon of cutting the north pole of the magnet from the south pole – it results in two magnets with north and south poles (Scheme 3).

Because of that, we call a system consisting of bromochloromethane molecules achiral under ambient conditions, or simpler, we call a bromochloromethane an achiral molecule (Scheme 4).



Scheme 4. Bromochloromethane is considered achiral because it does not exhibit chiral properties in contact with other systems and is not considered a racemic mixture because the separation of its chiral constituents is practically impossible.

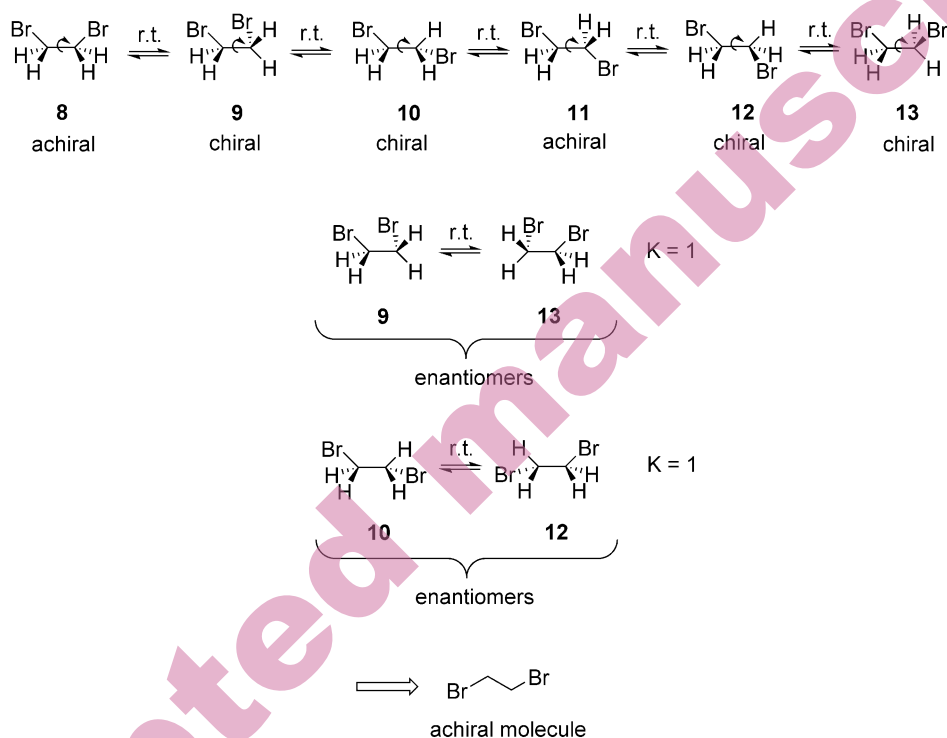
In the following text, changes in bond angles and bond lengths will be neglected for simplicity, but they are always happening.

In Supporting information, there is detailed practice on computational prediction of the IR spectrum of any molecule and generation of vibration animations using readily available free software.

Case study #2

Let's now consider 1,2-dibromoethane. Besides the mentioned bond angle and bond length changes, rotation about the C-C bond also takes place.⁷ The energy required for the full rotation of the C-C bond in this molecule is 42 kJ/mol (10 kcal/mol).⁹ This is relatively a small amount of energy, and is accessible to molecules on ambient conditions. Every conformation is chiral except two (**8** and **11** on Scheme 5). Every chiral conformation can transform into its enantiomer by rotation about the C-C bond - two examples are depicted on the Scheme 5. All conformational enantiomers are equilibrated and the system is achiral (animation is available at <http://cherry.chem.bg.ac.rs/handle/123456789/5947>). The equilibration is rapid at room temperature (if we somehow manage to isolate a chiral conformer, half of the sample will racemize in just 10⁻⁶ s), and consequently, separation of different chiral conformations is impossible. So we call the system

“achiral”, rather than “racemic mixture”, or simpler, we call a 1,2-dibromoethane an achiral molecule.

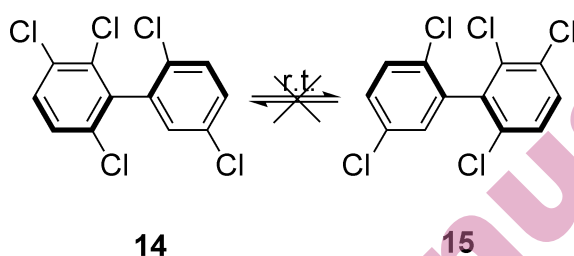


Scheme 5. Conformational changes in the molecules of 1,2-dibromoethane lead to the formation of different chiral structures, which are equilibrated with their enantiomers. Equilibration is fast, so separation of chiral constituents is practically impossible and 1,2-dibromoethane is considered an achiral molecule.

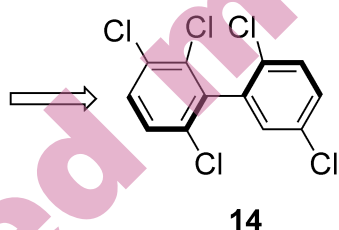
When we think about 1,2-dibromoethane molecules, we think of a large number of molecules that constantly change their bond angles, bond lengths, and conformations but the system as a whole creates an achiral environment because enantiomers are always present in equal amounts.¹⁰

The energy barrier for conformational enantiomer equilibration at room temperature depends on the molecular structure. In some cases, the barrier is high and the rotation about the C-C bond requires a significant amount of time and enantiomers are experimentally isolable on ambient conditions. These systems are considered chiral. For example, compound **14** ((S)-2,2',3,5',6-pentachloro-1,1'-biphenyl) can transform into its enantiomer (**15**) by simple rotation about C-C bond, but the energy barrier for this process is 184 kJ/mol (44 kcal/mol) in this case (animation is available at <http://cherry.chem.bg.ac.rs/handle/123456789/5948>). This amount of energy is too high for the equilibration of **14** and **15** at room

temperature at a significant rate (half of the sample of pure **14** will racemize in 300 billion years, Scheme 6).¹¹



interconversion of conformational
enantiomers is slow

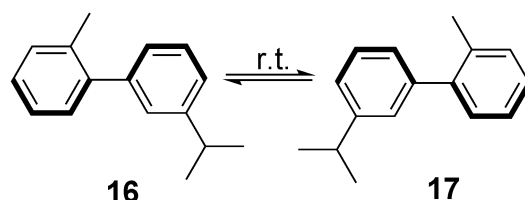


chiral molecule

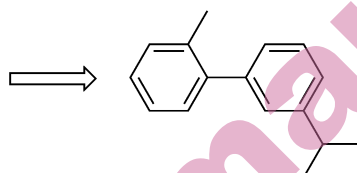
Scheme 6. An example of a compound which chiral conformations are not rapidly interconverting. Separation of its chiral constituents is possible. It is considered chiral.

At higher temperatures, molecules have more energy and equilibration is faster (at 300 °C half the sample of pure compound **14** racemizes in half an hour). But the criterion for calling something “chiral” is based on the practical ability to isolate something at room temperature. Because of that, we consider **14** a chiral compound, in spite of the fact that we can induce its rapid racemization at elevated temperatures. Besides temperature, other factors can accelerate the racemization process. For example solvents, catalysts, acids, bases, etc.

When the interconversion of conformational enantiomers is rapid at room temperature a similar system is considered achiral, analogous to 1,2-dibromoethane. For example, interconversion of **16** and **17** (3'-isopropyl-2-methyl-1,1'-biphenyl) requires 29 kJ/mol (7 kcal/mol) of energy, so these enantiomers are not isolable at ambient conditions (time needed for the racemization of half of the sample of pure **16** on room temperature is in the order of 10^{-9} s) and the compound is considered achiral (Scheme 7, animation is available at <http://cherry.chem.bg.ac.rs/handle/123456789/5949>).¹²



interconversion of conformational enantiomers is rapid



achiral molecule

Scheme 7. An example of a compound which is considered achiral for the same reasons as 1,2-dibromoethane. Fast racemization (conformational equilibration) on ambient conditions makes its chirality unobservable in most experiments.

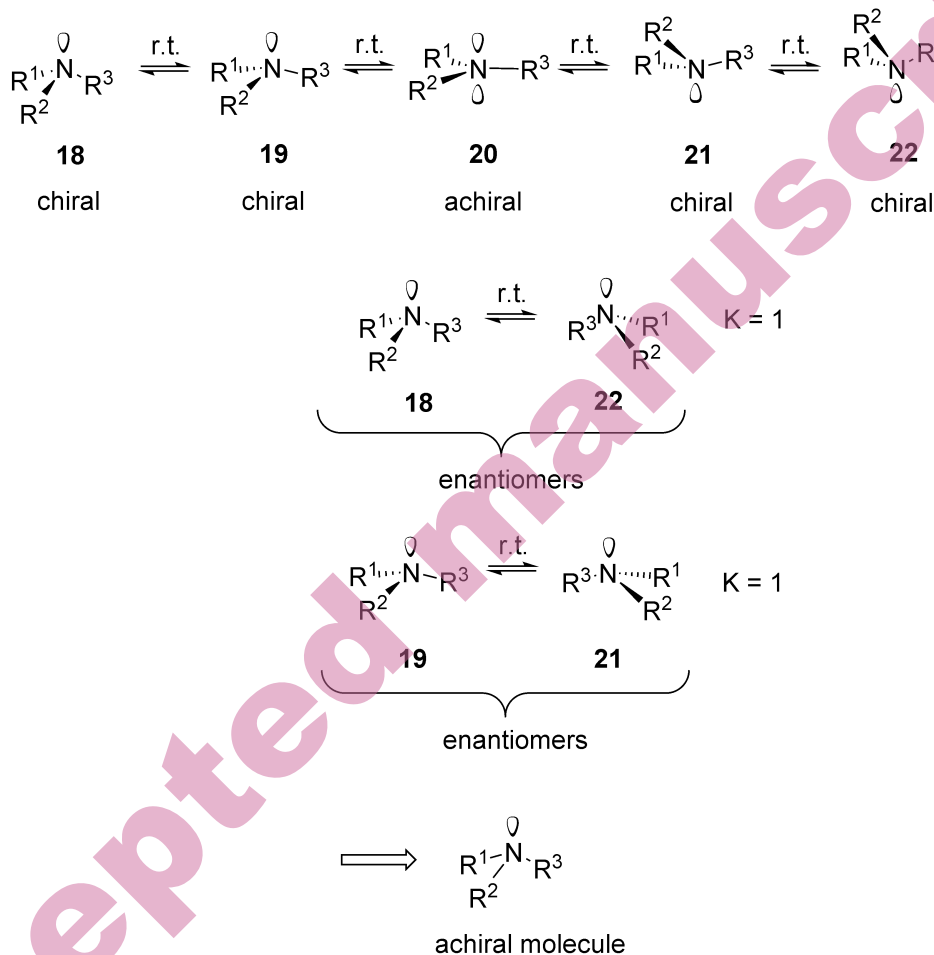
At this point, the introduction of an atropisomerism is consequential from everything mentioned so far, rather than a special case, how it is usually taught.

In Supporting information are provided tasks in which students need to calculate energy barriers of biphenyls and to propose their configurational stability based on the calculations. The procedure is explained in detail using free readily available software.

Schäfer *et al.* pointed out that often achiral substance is dominantly composed of chiral structures (because those chiral structures are the most stable form of that compound).¹³

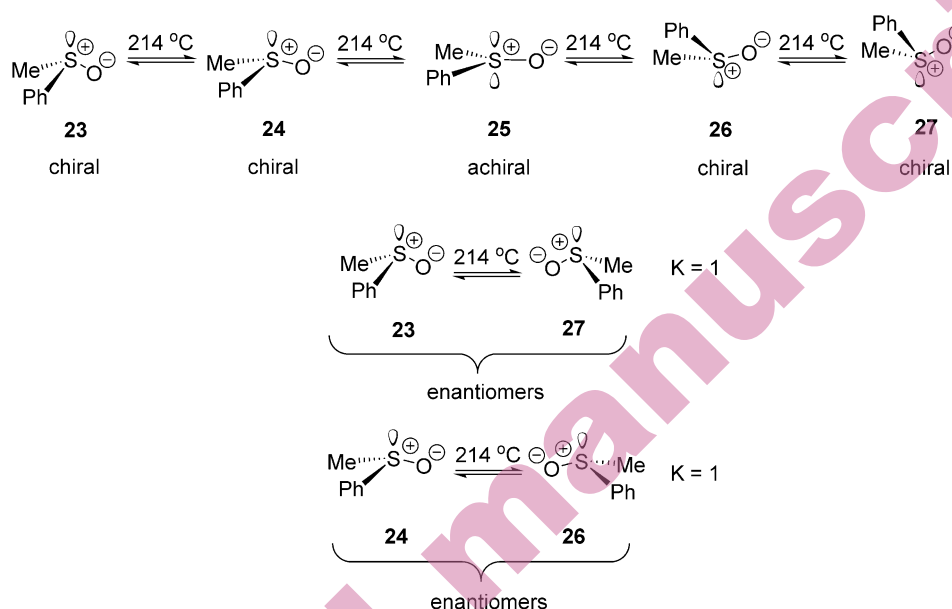
Case study #3

Chiral amines that contain an asymmetrically substituted nitrogen atom can racemize by the mechanism that is called *pyramidal inversion*. For ordinary amines, on average, 29 kJ/mol (7 kcal/mol) is needed for the inversion to take place.¹⁴ So ordinary amines racemize rapidly (half the sample of an ordinary amine racemizes in 10^{-9} s) at room temperature and because of that are not considered chiral (Scheme 8).



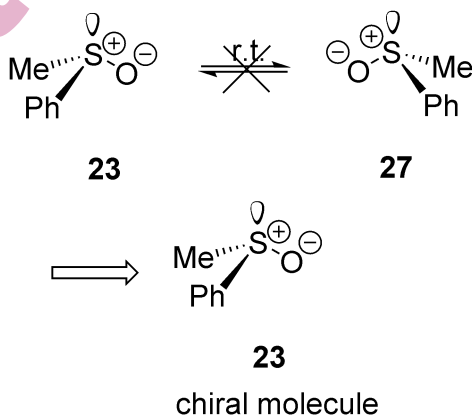
Scheme 8. Although amines racemize by different mechanism, inspection of their chirality follows the same pattern as for the molecules mentioned so far. Fast racemization (equilibration) of chiral structures leads to an achiral system.

For comparison, chiral sulfoxides that contain an asymmetrically substituted sulfur atom are usually configurationally stable at room temperature, but racemize at elevated temperatures.¹⁵ Mechanism for their racemization depends on the structure. Some sulfoxides undergo pyramidal inversion, just like amines. But, the energy required for pyramidal inversion at sulfur is much greater: for example, 171 kJ/mol (41 kcal/mol) for methyl phenyl sulfoxide.¹⁶ This amount of energy is relatively high and racemization on ambient temperature for this molecule takes billions of years (half of the sample racemizes in 2 billion years). But, at 214 °C half of the sample will racemize in just one day (Scheme 9).



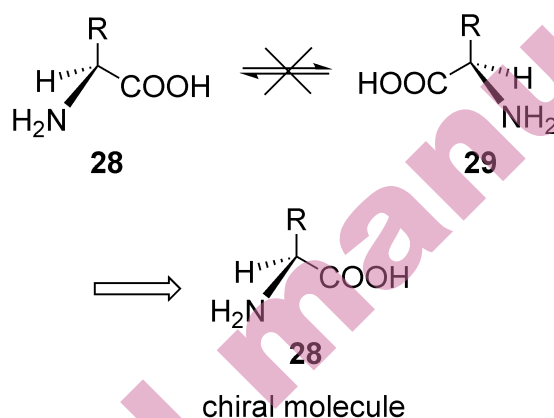
Scheme 9. Pyramidal inversion at sulfur in methyl phenyl sulfoxide requires a high amount of energy. However, at elevated temperatures, it is happening relatively rapidly.

But methyl phenyl sulfoxide is considered chiral, because enantiomers are isolable at ambient conditions (Scheme 10).



Scheme 10. The analogy between Scheme 8 and Scheme 9 is obvious, although sulfoxides are considered chiral because of practical reasons: purification of chemicals in the laboratory is done at room temperature in most cases. At that temperature, sulfoxides are configurationally stable (the rate of racemization is insignificant) and are consequently considered chiral.

Let's analyze α -aminoacids. Enantiomerically pure amino acids, like other molecules, thermodynamically strive for racemization and undergo rapid changes in bond lengths, bond angles, and conformational changes. However, none of these changes can transform L-aminoacid into D-aminoacid (for the bond angles and bond lengths that are possible in organic compounds) (Scheme 11).



Scheme 11. Amino-acids and most other chiral molecules that contain an asymmetrically substituted carbon atom have a stable chirality. That means they will retain their chirality properties in the solutions under usual conditions. Their racemization must proceed through the breakage of the sigma-bond, and that process is slow unless harsh conditions are applied.

To transform a chiral α -amino acid (regardless of the bond length, bond angle, or conformation) into its enantiomer, we would have to break a sigma bond. However, this process is slow under standard conditions. For most purposes, we can approximate that it does not happen at all. But slow racemization of amino acids is important in investigations of life, and is detectable on large time scales or after prolonged heating.¹⁷

It is evident from these examples that theoretical considerations of something that at first seems as fundamental feature of a compound is purely experimental observation of phenomena under a defined set of conditions. The practical use of the word "chiral" can be compared to the use of the word "volatility". We often call compounds volatile or non-volatile, because for practical purposes it is not important whether the substance has a boiling point of 400 °C or 700 °C. In either case, we can isolate it by chromatography and dry it in a vacuum. But also, it is not relevant if the boiling point is 80 °C or 130 °C, we will say it is volatile and that it cannot be chromatographed or dried by usual methods if we want to quantify it. Similarly, while working with a substance, it is of no importance whether the racemization time is 5 years or billion years. The only thing that is usually important is that it will not racemize in a significant amount during the experiment. If that is the case, we call it chiral. Likewise, we will not observe any difference

between the racemization time of 10^{-6} s and 1 s, in most experiments, so we describe the chirality features of those substances with the same attribute – achiral. Specification of actual numbers is important if the experiment is focused on that particular phenomenon, or in the transition cases: for example when the compound has a boiling point of 190 °C, or when half of the sample racemizes in a week at room temperature (which corresponds to the energy barrier of 109 kJ/mol (26 kcal/mol)).

Chemists do not analyze molecular changes and calculate energies for every molecule they work with, to determine its chirality properties, but are rather aware of characteristic structural features that can make a molecule chiral or achiral. Learning those special cases is recommended because students will gain the universal ability to inspect the chirality properties of the largest part of known compounds.¹⁸

SUMMARY OF THEORY

Chirality is a fundamental property of an object. Since racemization is a thermodynamically favorable process, it is most practical not to consider the chirality of a molecule as its inherent property, but rather as a feature of a system that consists of a large number of molecules, under a defined set of conditions. In other words, chirality and associated terminology are based on practical and measurable effects of the system that we consider. Molecular symmetry observed in experiments is actually the averaged structure of non-symmetrical chemical species which constantly change. Detailed discussions on this matter are reported.¹⁹

CONCLUSION

The perception of molecules in a dynamic (natural) state, rather than objects that correspond to drawings on paper is essential in life sciences. This work describes a method for the introduction of chirality that leads students to perceive molecules as dynamic entities and to understand the difference between the fundamental and applied descriptions of the word “chiral”. As further aid for teaching, practice and problems (with solutions) that employ readily available free software are provided.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <http://www.shd.org.rs/index.php/JSCS/article/view/12526>, or from the corresponding author on request.

Author contribution: BK conceived the idea. Conceptualization was performed by BK, VA and IO. Molecular models and animations were created by MZ. BK, MZ, VA and IO participated in discussion, writing, and reviewing.

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ИЗВОД

КОНЦЕПТ ЗА УВОЂЕЊЕ ПОЈМА ХИРАЛНОСТИ – СИМЕРИЈА АСИМЕТРИЈЕ

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Хиралност је педагошки изазовна тема на курсевима органске хемије на основним академским студијама, а изузетно је значајна као феномен јер се јавља практично у свим гранама хемије. Систематично упознавање студената са појмом хиралности је важно због каснијег разумевања сложенијих појава везаних за ову тему. Иако је пријављено мноштво метода које олакшавају визуелизацију тродимензионалних хиралних молекула, молекулске промене као што су вибрације и конформације углавном се не анализирају у контексту хиралности. У овом чланку, хиралност и примена хиралности су објашњене на динамичким (реалним) системима, како би од самог почетка студенти перцепирали молекуле у њиховом природном стању. Осим предлога теоријске наставе на ову тему, предложене су и студентске вежбе на бесплатним и лако доступним софтверима.

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