A Set of Hands-On Exercises on Conformational Analysis W

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Undergraduates usually face serious difficulties when viewing and drawing organic molecules *(1–4)*. Conformational analysis is generally the first topic in the organic chemistry curriculum that deals with this crucial question. If students do not tackle this issue early in the course, it is more difficult for them to cope with even more complex subject areas such as chirality. We have devised a set of comprehensive exercises that facilitates the students' understanding of elementary concepts of conformational analysis with the use of a hands-on approach. These exercises also help instructors detect these difficulties early in the course. In addition, it provides illustrations of other topics such as nomenclature, functional groups, and isomerism, and introduces some notions of chirality.

Background

The exercises were designed to complement a series of problems selected from the "Additional Problems" section of Chapter 5: "Alkanes and Cycloalkanes" of Ege's textbook used in the organic chemistry course *(5)*. This course is taken by students with different interests. While most students are pursuing pharmacy, biotechnology, and biochemistry degrees, only a small percentage of the students are chemistry majors. To encourage their interest and thus increase the overall enthusiasm and productivity, we try to add an element of curiosity to our classroom activities. The box exercises described in this article have proven to be highly effective in this sense.

The Box Exercises

The students are divided into four groups of four and each group is given a box labeled "Exercise 1, 2, 3, or 4" that contains the molecular model[1] of a compound and the exercise instructions (Figure 1). Exercises 1 and 3 are about conformational analysis of substituted cyclohexanes while Exercises 2 and 4 use open-chain molecules. The students are instructed to solve the exercises by discussing the possible answers with their group partners. They can also seek advice from the instructor or use the textbook for support. During the class, the instructor supervises each group and checks the answers. Towards the end of class, the students are asked to give a short presentation to explain the exercise to their classmates. In this way, all the students can observe what the others have done.

In Exercise 1, the model compound is 1-isopropyl-1-cyclohexanol (Figure 1). The students are first asked to draw and name the given molecule. Instructors should encourage them to use different kinds of formulas. For instance, the students can draw condensed and carbon-skeleton formulas and also use abbreviations for common groups such as isopropyl or methyl (*i*-Pr and Me, respectively). This simple task

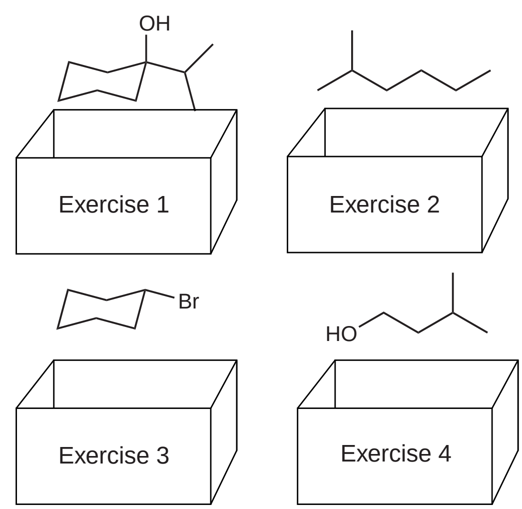

Figure 1. Schematic representation showing the four exercises and the models placed in each box.

is useful to detect very basic mistakes. When students start drawing organic structures they have some doubts as to, for example, whether a stick represents a methyl group or a hydrogen atom. This task helps undergraduate students clear up such ideas.

Students also realize that if they rotate or flip molecules in the plane of the paper either horizontally or vertically, they obtain another representation of the same molecule. After that, students are asked to draw the most stable conformation of 1-isopropyl-1-cyclohexanol and a Newman projection that shows the positions adopted by the substituents. Since undergraduate students usually find it difficult to draw chair conformations, this is also a good opportunity for them to learn how to do it properly *(6–9)*. With the molecular models of the substituted cyclohexane in hand they can actually see that axial substituents are vertically oriented and equatorial groups are parallel to the bonds in the ring. In addition, the use of the molecular models allows the students to flip the ring from one chair to the other chair by passing through the boat conformation and to compare the relative energies of such structures by considering the repulsive steric interactions. They can also appreciate the origin of 1,3-diaxial interactions and thus comprehend the greater stability of cyclohexanes with bulky groups in equatorial positions. Furthermore, the molecular modeling kits assist the students when they first have to draw a Newman projection of a chair, which is a rather complicated assignment for beginners. Instructors should advise students that Newman projections can be drawn looking in either direction along the central bond so four equivalent projections are possible.

Subsequently, the students are asked to build a molecular model of a constitutional isomer and draw and name the resulting compound. This task helps students realize they have to break bonds (i.e., disconnect the molecular modeling pieces) and connect the atoms (i.e., reconnect the pieces) in a different way in order to build different constitutional isomers. The instructor should also emphasize that the actions needed to manually convert molecular model conformers and constitutional isomers are strikingly different. While students only have to gently rotate a single bond in order to interconvert different conformations of the same molecule, they have to energetically break bonds to obtain constitutional isomers. Finally, students are asked to draw another constitutional isomer that has a functional group that differs from the original one. To help the students choose a functional group, they are induced to calculate the number of unsaturations plus rings (SODAR) *(10).* In this way, they appreciate that the ring can be converted to a C–C double bond or to a carbonyl.

In Exercise 2, 2-methylhexane is given as the model compound (Figure 1). As in Exercise 1, students are first asked to draw and name the structure. After that, they are asked how many carbon–carbon bonds can be rotated in the given compound and are instructed to draw the Newman projection and the sawhorse formula of the most and the least stable conformations considering the rotation of the bond between carbon 3 and carbon 4. Finally, the students are asked to build a molecular model identical to the original molecule, using a set of molecular modeling pieces provided in the box. Using one of the models, the students are asked to replace one hydrogen atom of carbon 3 with a bromine atom. Using the other model, students are asked to replace the other hydrogen of carbon 3 by bromine. The students are then asked whether the two resulting molecules are identical. After being induced to superimpose the two models, they conclude that the molecules are different because atoms in carbon 3 do not match exactly. At this point, instructors should remark that both structures have the same molecular formula and the same connectivity and explain that the compounds belong to another class of isomers called stereoisomers. In addition, the concepts of atom equivalence, stereogenic centers, and enantiomers as nonsuperimposable mirror images can be introduced.

Exercises 3 and 4 are essentially the same as Exercises 1 and 2, respectively, using different model compounds (Figure 1). Specific details are provided in the Supplemental Material.[W]

Concluding Remarks

This article describes a set of comprehensive exercises on conformational analysis that exploits a hands-on approach by the use of molecular modeling kits. It provides a review of topics such as nomenclature, functional groups, and isomerism, and introduces some notions of chirality.

We have used these hands-on exercises in our classes for four years. It has been our experience that students like and benefit from incorporating the exercises on typical written problem-based classroom activities. Since this is the first time that most undergraduate students have used molecular modeling kits, they enjoy "playing" with them by rotating bonds, flipping chairs, disconnecting and reconnecting centers, and superimposing atoms. This set of exercises has demonstrated that working with tangible tools such as modeling kits is essential for students to understand what different kinds of formulas represent and how different conformations interconvert. It also helps instructors assess the students' understanding of the concepts. In addition, we believe that cooperative work within the group is an ideal way of developing problem-solving skills as it provides support in a friendly environment that increases students' participation *(11).* Moreover, the final oral presentation of the exercise helps students improve their verbal and oral skills.

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[W]Supplemental Material

Instructions for the students and notes for the instructor are available in this issue of *JCE Online*.

Note

1. We use the flexible molecular model kits, Molecular Visions. Ideally, one model per student should be included in each box.

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