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A Web-based stereochemistry tools to improve students’ ability to draw Newman projections and chair conformations, and R/S assignment

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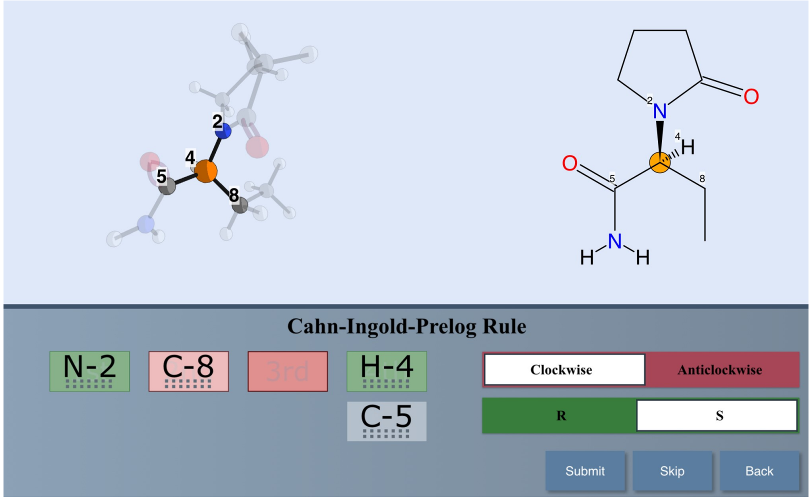
ABSTRACT

A set of web-based stereochemistry tools which help students use virtual 3D models to translate Newman projections, chair conformations and assign *R*/*S* labels to stereocenters from 2D dashed-wedged structures is described. These tools are unique in the way they link 2D dashed-wedged structures to 3D models to help students develop visual/spatial skills. They also provide feedback on the individual parts of a student’s attempt to switch between structural representations and apply the Cahn-Ingold-Prelog rules. The incorporation of these stereochemistry resources into an organic chemistry course led to improvements in students’ ability to draw accurate Newman projections, chair conformations and assign *R* and *S* labels to stereocenters.

GRAPHICAL ABSTRACT



KEYWORDS

Second-Year Undergraduate, Organic Chemistry, Internet/Web-based Learning, Conformational Analysis, Stereochemistry.

INTRODUCTION

Stereochemistry forms a fundamental part of most, if not all, organic chemistry courses. It plays a vital role in our understanding of molecular structure, reactivity, and our ability to synthesize molecules of biological importance.[1]

To master stereochemistry, students have to apply visual/spatial skills to switch between 2D dashed-wedged structures and Newman projections or chair conformations. This is a process known as representational translation.[2,3] Furthermore, visual/spatial skills are also required to be able to assign the *R*/*S* labels using Cahn-Ingold-Prelog (CIP) rules to stereocenters in chiral molecules.[4] It has been documented that students have difficulties performing 3D visualization[5-8] and representational translation.[9-13]

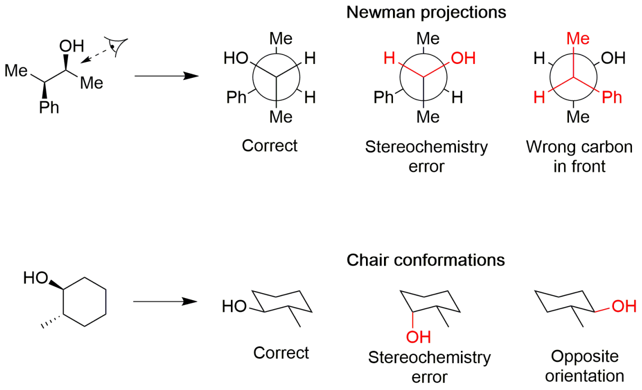


Figure 1: Representational translation from 2D structures to Newman projections and chair conformations, with common student errors.

Recently, we performed some detailed analysis of the types of errors students make when drawing Newman projections from 2D dashed-wedged structures.[14] In summary, we found that students tended to make one or two small errors with the Newman projections they drew. The most common errors were incorrectly drawing the orientation of the three groups around either carbon, thus switching the stereochemistry of the molecule, or having the carbons which should be at the front and rear of the Newman projection the wrong way round (figure 1). When asked to draw 2D dashed-wedged structures from Newman projections, stereochemistry featured as the most common error. When drawing chair conformations, the most common errors were positioning substituents incorrectly in incorrect axial or equatorial positions, which is also switches the stereochemistry. Another common error was changing the orientation of two substituents around the chair from what was given in the 2D structure. When assigning *R* and *S* labels to stereocenters, common students errors included viewing the lowest priority group coming towards the observer, or mixing up if a clockwise or anticlockwise (a synonym for counterclockwise in the UK) rotation is assigned to *R* or *S* (figure 2).

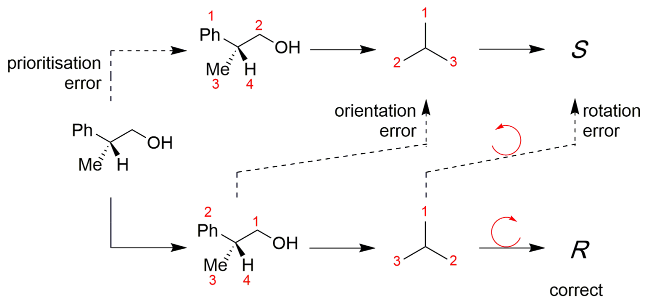


Figure 2: Cahn-Ingold-Prelog process to assign R and S stereocentres, including common errors represented with dashed arrows.

Efforts to support students' ability to visualize molecules in three dimensions to help with mastering stereochemistry goes back many decades.[15-19] Examples can be found in the literature of strategies that can help with *R*/*S* labelling[17, 20-25] and for drawing both Newman projections[12,26-28] and chair conformations.[17,29] The use of technology has also been reported to aid students understanding of stereochemistry concepts[8,29-31] and ability to solve stereochemistry problems.[8,32] The benefits of using technology is that students can work with 3D vitual models, work through problems at their own pace, and receive instant feedback – leading to improvements in students' mastery of stereochemistry. [8, 29-32]

Perhaps the most common advice given to students is to use molecular models to help them perform these types of tasks. Molecular models are thought to aid students by off-loading the cognitive burden of visualizing a molecule in three dimensions, help students develop more complete mental models, and help students relate 3D and 2D representations.[12,27,28] Students who use molecular models to scaffold knowledge are more successful at performing representational translation compared to those who never use a model kit.[28] However, it has also been shown that simply providing a molecular models to students without teaching them how to use it to scaffold the translation is not an effective strategy.[28,33] Students need to be given some guidance of how to use the model kits to perform the required translation.[28] A key finding from the work of Stull was that virtual models are just as effective as a physical models.[28] This indicates that virtual models help to scaffold translations in the same way as physical models.

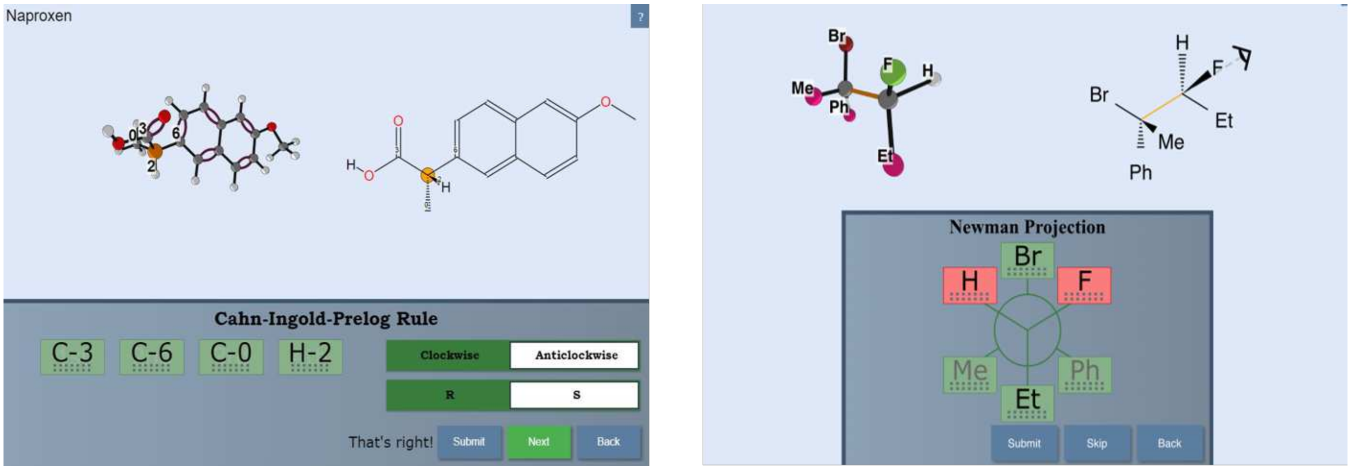
WEB-BASED STEREOCHEMISTRY TOOLS

The aim of this work was to develop resources that students could use to improve their ability to translate 2D dashed-wedged structures to Newman projections and chair conformations, as well as assign *R* and *S* labels to stereocenters correctly. Virtual models were provided and these models were connected to the 2D structures in the problems. We also wanted these resources to break down components of the translation and *R*/*S* assignment of stereocenters so students could identify which part of the process they are making errors with and be able to correct them.

Herein, we describe our work to create a set of open-access, online stereochemistry problems that help students translate between 2D dashed-wedged structures to Newman projections and chair conformations, and assign *R*/*S* labels using CIP rules. These resources break down the components of each type of stereochemistry problem for students to see which parts of the problem they are solving correctly and incorrectly.

GENERAL FEATURES

The desire was to ensure these resources were as accessible to students as possible, which meant being operational on computers, tablets and mobile devices. To achieve this, all resources are web-based and open-access from University of Leeds servers. The Newman projection and CIP tool can be accessed from the same website,[34] while the chair conformation tool is accessed from a different website due to some of its unique features.[35]



That's right!

Figure 3: Partial screenshots of the Cahn-Ingold-Prelog and Newman projection web-based tools. Both resources have computer models linked to the 2D structures and use drag and drop features to answer the problem.

Each tool includes a virtual 3D model and it's corresponding 2D dashed-wedged structure that is linked together. Students can move, rotate and zoom in or out with these structures to view them from different perspectives as they would be able to do with a physical model. The Newman projection and CIP tools have been designed so that when an atom or bond in the 3D structure is selected, the same part of the 2D structure is simultaneously highlighted. In the chair conformation tool, both the 2D and 3D structures are numbered to help develop mapping strategies.[36,37]

Each resource contains problems with different levels of difficulty. Students start with the level that reflects their ability and move to a higher level when they are ready. The lower levels of the Newman projection and CIP tools have 3D models. This is to help with the scaffolding process of using 3D models; but, once students have improved their visual/spatial skills, they can move to the higher levels for which no 3D structure is available. This reflects the need for students to ultimately become able to perform these mental rotations without a 3D model. For both the CIP and chair conformation tools, the complexity of the molecules with which students deal with also increases with the higher levels.

All resources contain a feature highlighting which parts have been answered correctly, in green, or incorrectly in red. If students make errors, they can focus on the aspects that need improving to achieve the correct answer.

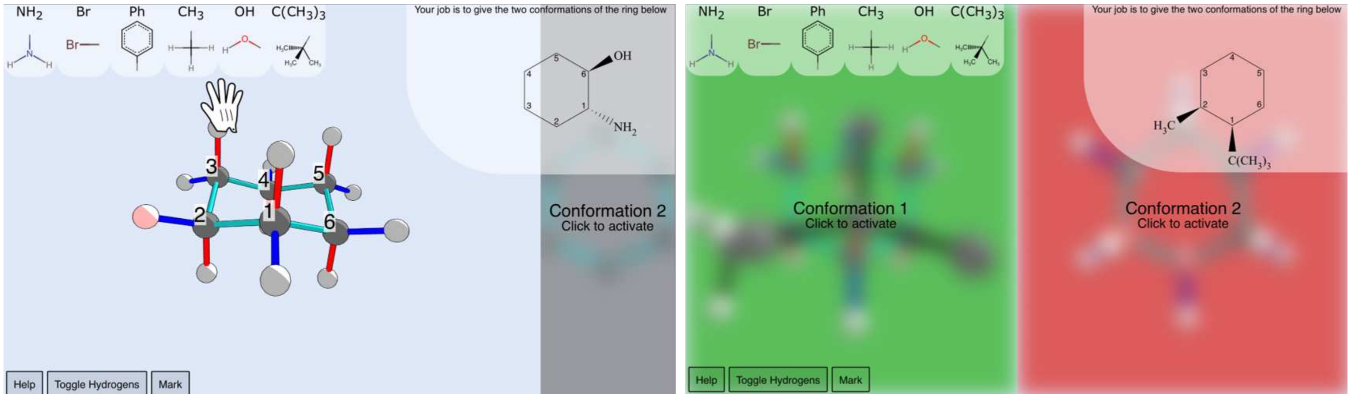
CAHN-INGOLD-PRELOG CIP TOOL

When students select a level in CIP tool, they are given a 2D and 3D structure of the same molecule generated at random. On the Easy level, known drug molecules are used which contain only one stereocenter (figure 3). On the Medium level, natural products and drugs with multiple stereocenters are used. A particular carbon in the molecule is highlighted in orange, which indicates that it is the stereocenter and is the one which needs to be assigned *R* or *S*. The surrounding atoms are also labelled for the prioritization step. Students drag and drop the boxes representing atoms around the stereogenic carbon into the order of their prioritization. They then select the orientation of the highest priority groups to be clockwise or anticlockwise, with the option of using the 3D model to help them do so, and finally select the assignment to be *R* or *S*. Both the rotation and assignment sections have a white box that slides towards the option selected by the student. When the answer is submitted, the correct (green) and incorrect (red) parts of the answer become highlighted. For example, if students make an error with determining the clockwise/anticlockwise direction of the three highest priority groups because they have looked along a C-H bond with the hydrogen at the front, they will see both the clockwise/anticlockwise and *R*/*S* box flash red. The students can then revisit the rules and use the 3D model to observe how the correct orientation is achieved by looking from the correct perspective. Students have the opportunity to correct and resubmit their answers again until they are fully correct.

NEWMAN PROJECTION TOOL

The Newman projection tool helps students translate from 2D dashed-wedged structures to Newman projections or *vice versa*. Students can select which type of translation they wish to perform. For both types of problems, students are given a structure at random with six different substituents around the two respective carbons and an eye indicating the perspective for constructing the correct

Newman projection or 2D structure (figure 3). The accompanying 3D model has the substituents in the same position as the 2D structure. Students can use the 3D model to perform the rotation that occurs when a dashed-wedged structure is rotated to view the same molecule along it's carbon-carbon bond (or *vice versa*), and see how the substituents orientate themselves in this process. Problems requiring a Newman projection from a 2D dashed-wedged structure have a staggered conformation with vacant boxes for the substituents to be placed in. Similarly a 2D dashed-wedged structure with vacant boxes is given in the Newman projection to 2D problems. In both cases, students perform the correct translation by placing the substituents where they think they should be in the Newman projection or 2D structure, respectively. The correct (green) and incorrect (red) parts of the translation are highlighted when students submit their answer. Common errors such as switching the stereochemistry of a carbon will become highlighted; therefore, students can focus on the parts of the translation where they are weaker to improve.


Your job is to give the two conformations of the ring below

Your job is to give the two conformations of the ring below

Figure 4: Partial screenshots of the chair conformation tool before and after an attempt to solve the representational translation.

CHAIR CONFORMATION TOOL

For the chair conformation tool, students translate 2D dashed-wedged structures to chairs by constructing a virtual substituted cyclohexane that matches the 2D structure. To start with, students are given two 3D models of cyclohexane with each carbon in the ring numbered to match the 2D structure (figure 4). The two 3D structures are also ring-flipped conformers. To construct the correct chair models, students are given a menu with five different functional groups. When they drag and drop a functional group over a hydrogen in the 3D model, it will exchange the hydrogen for the functional group. This feature helps students to match the stereochemistry of a functional group in the chair from a 2D structure, and also consider if it should be axial or equatorial. The numbering helps to ensure students can learn how to place substituents around the ring relative to each other. This strategy is known as mapping and has been used successfully in the teaching of curved arrow mechanisms.[37,38] By having two chair conformations, student can learn how substituents change their orientation when the chair flips with the correct stereochemistry and orientation. When students check their answers, each 3D model shows if it is correct (green) or incorrect (red). As with the other tools, students can correct their errors and resubmit their answers. When the students have achieved both correct chairs, they will be given both chair structures in the standard line diagram format. They then select which chair is the more stable to complete the problem.

IMPLEMENTATION OF THE WEB-BASED TOOLS INTO AN ORGANIC CHEMISTRY COURSE

Stereochemistry is taught to Chemistry, Medicinal Chemistry and Natural Science students as part of a 10 credit semester 2 module in year 2. Students are introduced to Cahn-Ingold-Prelog rules, Newman projections and chair conformations as part of the course. The module typically has 150-180 students enrolled each year.

These tools were brought into the teaching of this course for the first time in the 2018/19 academic year. Links to the resources were incorporated into lecture notes as QR codes. The lecturer used these resources to show students how to answer these types of problems. Students were given the opportunity to use them to answer problems in the lectures.

Evaluating the impact of the web-based tools

Anonymous module evaluations are used by the institution for each module. This includes a section where students can comment on what they found positive about the course. 28% of students on the course completed the module evaluation and many students commented that they had found the online resources helpful. This was a useful indication for determining that students found value from using these resources and were engaging with them.

“I really liked the online tools for practice in this particular module and really felt they supported my learning....”

“Online games/activities to support revision are helpful”

“The online tools are really useful and have helped a lot with visualizing and understanding the concepts in the course”

Student engagement with the resources was also determined from the web-usage statistics using Google analytics (figure 5). Throughout the course there was low-level usage of the resource with minor spikes when the resource was introduced in lectures and for the associated tutorial. However, usage increased significantly in the week leading to the final exam. Further analysis of the web-usage statistics confirmed that the majority of users were from the Leeds area which suggests these were students from the University rather than from elsewhere.

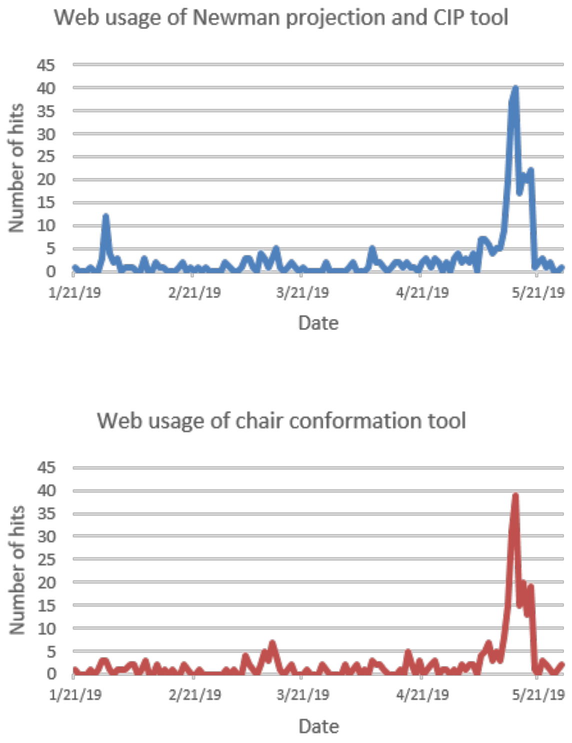


Figure 5: Web-usage of the resources over the duration of the course.

Exam performance on questions that required students to draw a Newman projection or chair conformation, and provide an *R*/*S* assignment were compared before and after the stereochemistry tools were introduced (table 1). Each type of question was worth 5 marks with marks deducted for the types of errors shown in figures 1 and 2. Every type of question showed a significant improvement in the mean percentage score compared to previous years. In comparison, a non-stereochemistry question (Wittig mechanism) showed no significant variation between year groups, indicating the effect was not solely due to the ability of the class.

Student comments and analytics data indicate that some students were engaging with the resources, and the exam performance indicates a possibility that the resources improved students' abilities for solving these types of problems. Further work is required to conclude the exact nature of how these resources aid students.

Table 1. Comparison of Student Exam Performance before and after Implementation of Web-based Stereochemistry Resources

Exam Task	Mean Score, %, by Resource Access			
	Pre-resource			Post-resource
	2016[a]	2017[b]	2018[c]	2019[d]
Draw Newman projection	77	—[e]	79	91
Draw Chair conformation	76	71	—[e]	84
CIP (*R*/*S*) assignment	—[e]	71	67	79
Wittig mechanism (control)	68	74	—[e]	71

[a]*N* = 155. [b]*N* = 165. [c]*N* = 157. [d]*N* = 160. [e]Question not offered

CONCLUSION

In summary, we developed a set of open-access, web-based resources that improve students' abilities to draw Newman projections, chair conformations and for assigning *R*/*S* labels to stereocenters. These resources focused on improving students visual/spatial skills using 3D virtual models which are linked to 2D structures. They also allowed students to see which parts of the representational translation or *R*/*S* assignment are correct or incorrect, thus helping them to focus on the aspects of these processes where they are weaker to order to improve. In the future, further analysis will be conducted to provide a better understanding of how these resources aid student learning.

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Notes

The authors declares no competing financial interest.

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