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Creating 3-Dimensional Molecular Models to Help Students Visualize Stereoselective Reaction Pathways

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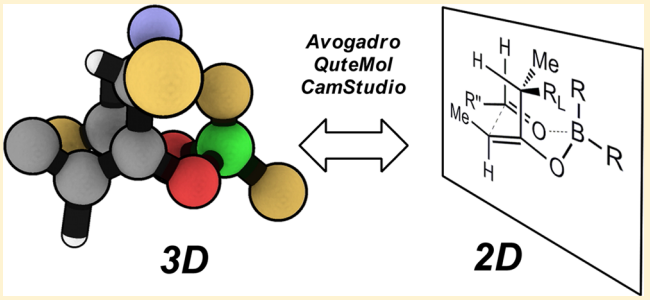
Supporting Information

ABSTRACT: An approach to the creation of learning materials that aid the visualization of stereoselective reaction pathways is presented. Molecular editing software can be used to create models of various transition-state geometries. These 3-dimensional models can be manipulated, using suitable visualization software, to select relevant viewpoints. By using an overlay annotation tool, line-diagrams can be drawn directly over these 3-dimensional representations. This may help students to make representational translations between the 3-dimensional structures (transition states, etc.) and the 2-dimensional diagrams typically used to depict these objects.



KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Multimedia-Based Learning, Stereochemistry*

INTRODUCTION

For some students, stereochemistry can be a particularly challenging aspect of their organic chemistry education.[1] There is often significant variation in students' "spatial-awareness"[2] and their ability to visualize and mentally manipulate 3-dimensional structures. In particular, students sometimes find it difficult to make the cognitive connection between a 3-dimensional object, for instance a transition-state geometry or conformational structure, and the necessarily 2-dimensional diagrams typically used to depict it. Educationally, this might be seen as a "threshold" concept[3] as students often make significant progress once a certain level of understanding has been reached but progressing past this level is hard.

Molecular models, either real or virtual, are an extremely useful tool in aiding students' understanding of stereochemical concepts.[4] The approach outlined here uses a series of molecular editing and visualization tools to create learning materials aimed at supplementing these activities.

EXAMPLE OF COURSE MATERIAL

As an illustrative example of a challenging stereoselective reaction pathway, a particular slide from one of our third year optional B.Sc. courses, *Diastereoselectivity in Natural Product Synthesis*, is shown in Figure 1. This shows a conformational line-diagram of the proposed "Zimmerman-Traxler" transition state[5] for a boron-mediated aldol coupling of an α-chiral ethyl ketone with an aldehyde via the *E*-enolate. The rationale for this transition state is based on (1) adoption of a "chair" conformation for the 6-membered transition state; (2) adoption of an enolate conformation which minimizes $A_{1,3}$ strain between the *E*-methyl group and the substituent on the α-carbon, thus placing the smallest of the α-substituents (hydrogen) in the plane of the enolate double bond; and (3) the approach by the aldehyde toward the least hindered "face" of the enolate, i.e., closer to the methyl group rather than the large alkyl group R_L; in other words, R_L is on the "outside" of the transition state in a sterically less demanding position.[6]

There are several aspects of this example that highlight various areas of difficulty students have with visualization. First, although some students have the ability to form a 3-dimensional mental representation of the transition state from the conformational diagram used to depict it, others find this quite difficult. Perhaps more difficult is the "mental" rotation of the viewpoint required to go from the conformational diagram of the immediate product to the "standard" line diagram, even when the required viewpoint and the bonds that are "in the plane of the paper" in the new viewpoint are indicated. Finally, flipping the final product either horizontally or vertically can also present difficulty.

APPROACH TO VISUALIZATION

By using 3-dimensional models with a combination of screen-casting and "virtual-transparency" applications, it is possible to clearly demonstrate the relationships between starting materials, transition-state geometries, and products (and their 3- and 2-dimensional depictions) in a straightforward manner.

A combination of real (e.g., Molymod) and virtual molecular models were used. Real models have the obvious advantage that

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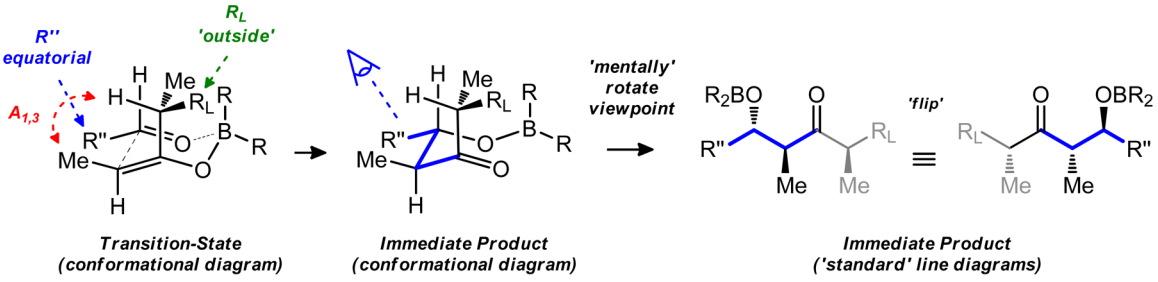

Figure 1. Course notes slide for the aldol reaction of *E*-boron-enolates of α-chiral ketones via a Zimmerman−Traxler-type transition state. The immediate product is drawn in the same conformation as that of the transition state. The bonds highlighted in blue in the immediate product conformational diagram indicate which bonds will be "in the plane of the paper" of the "standard" line diagram on the right. The required viewpoint for this is indicated with the eye symbol. The stereochemical configuration in the "greyed out" section of the product line diagrams is already known from the starting materials.

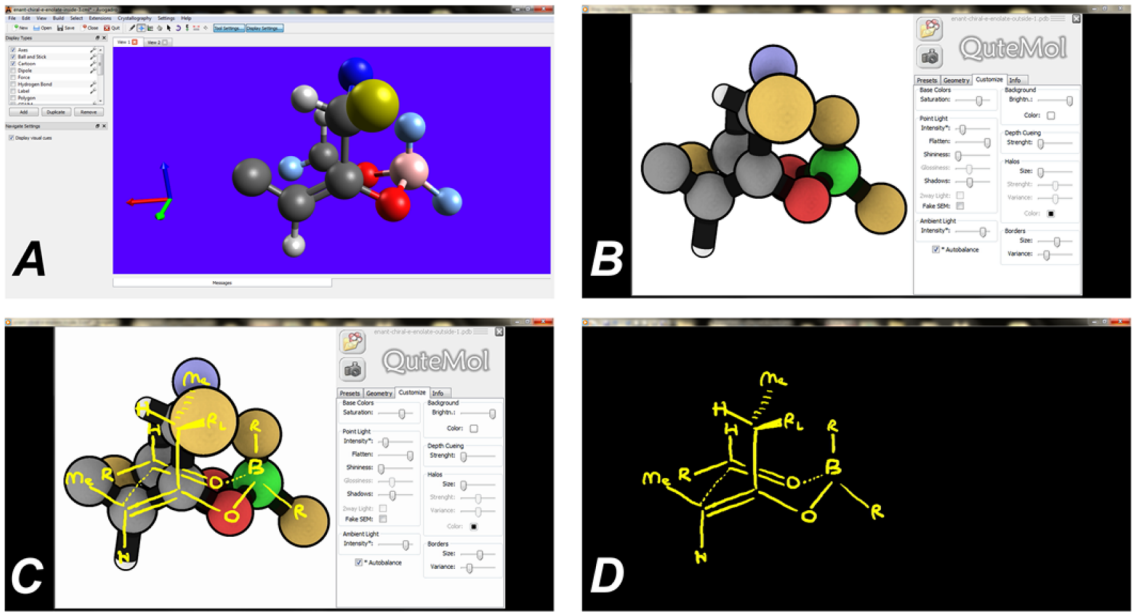

Figure 2. Workflow for stereochemical visualization. (A) Transition-state geometry created in Avogadro. (B) QuteMol used for manipulation and visualization in lectures or screencasts. (C) EpicPen or Annotate!Pro can be used to draw an overlay line-diagram on the structure in QuteMol. (D) The line diagram can be temporarily isolated by opening a blank window over QuteMol.

students can physically interact with them and actually see them in 3-dimensions. An advantage of using virtual models is that bond lengths, bond angles, and valencies are not restricted in any way. In addition, virtual models are essentially free, assuming free access to a computer, and take no time to reconstruct, thus allowing students to easily swap between several models.

For the virtual models, the freely available and open-source Avogadro[7] software package was used for their creation. Importantly, Avogadro allows the user to build 3-dimensional molecules from scratch and also permits the arbitrary placement and movement of different atoms, regardless of bond length or bond angles. Individual atoms or groups of atoms can be selected and dragged into the desired positions. As such, it is reasonably straightforward to construct any particular arrangement required. In addition, certain structural motifs, for instance the chair conformation of a 6-membered ring, can also be reached very easily using the built-in energy minimization routines. These can then serve as a convenient starting point for other structures, e.g., Zimmerman−Traxler transition states. Another important feature of Avogadro is the ability to select any bond and rotate around the dihedral angle arbitrarily. This is very useful when creating Felkin−Anh-type or antiperiplanar transition states. In general, for a particular reaction, Avogadro was used to create a 3-dimensional model of the proposed transition state as well as the corresponding 3-dimensional model of the product, where the atoms were arranged with the same geometry as the transition state. To facilitate clear visualization, elements other than those actually present were substituted in to represent various groups based on their size and color. The structures of the transition state and product geometries only differed significantly in the arrangement of bonds whereas the atoms remained more-or-less in the same position (see Supporting Information for examples of .pdb files of structures created in Avogadro).

In addition to being extremely useful for building and editing 3-dimensional structures, Avogadro is also able to display the structures with reasonable clarity. However, for structural display, the QuteMol[8] package, which is also freely available and open-source, was preferred. QuteMol enables high-quality real-time manipulation and rendering of chemical structures. Its settings are highly configurable, and a wide variety of molecular display types are available, including ball-and-stick types closely resembling the Molymod structures. It also has some built-in

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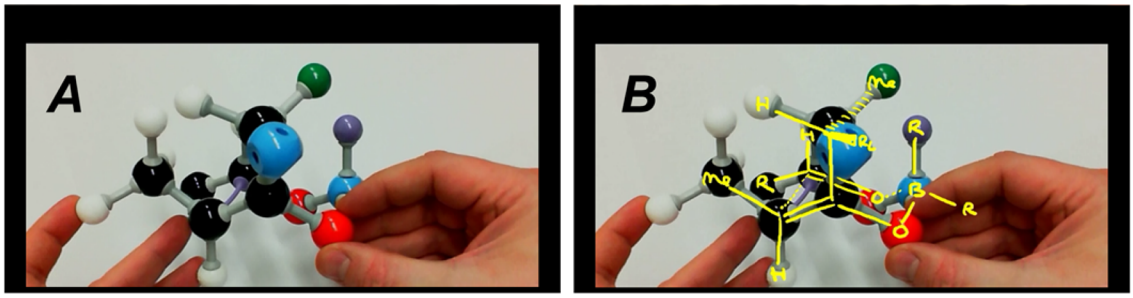

Figure 3. Use of physical models (Molymod). (A) Transition-state structure made with the Molymod system that is manipulated using a webcam to make a video. (B) Video played and paused to show a particular viewpoint. EpicPen or Annotate!Pro can be used to draw an overlay of the line-diagram. CamStudio can be used to capture screen/voice to make an instructional video.

settings that serve as convenient start points for further adjustment. One limitation of QuteMol is that it represents all bonds as single bonds. This obviously needs to be explained when these models are being used. Also, bonds seem to be constructed in QuteMol according to the distance between atoms in the .pdb representation, so occasionally atoms need to be moved slightly further apart (in Avogadro) to avoid having bonds being inadvertently inserted between atoms simply because they are too close to each other. Despite these minor issues, the increased clarity and visual appeal of QuteMol made it the preferred display method. The settings used (see Supporting Information for details) allowed bold "cartoonish" ball-and-stick structures to be displayed. Importantly, QuteMol is able to draw borders around structural features, making it easier to see which atoms/bonds are in front of other atoms/bonds.

To make connections between various views of the 3-dimensional structures and their 2-dimensional depictions, for example standard molecular line drawings, it was desirable to be able to draw line diagrams directly on top of the corresponding 3-dimensional structure, and then to show only the line drawing itself. This required a "virtual transparency" application. For this purpose, transparency tools, such as EpicPen[9] or Annotate!Pro,[10] can be used. This creates a transparent drawing canvas on top of the entire desktop. The pen settings (e.g., color, thickness) are configurable, and the drawings can easily be turned on or off or even erased. A pen input tablet was used to draw these line diagrams (Wacom Bamboo).

A typical workflow is shown in Figure 2. Structures created in Avogadro are opened in QuteMol, where they can be manipulated to show different viewpoints. The annotation tool, e.g., EpicPen or Annotate!Pro, is then used to draw line-diagrams over the various 3-dimensional views. The 3-dimensional view can then be temporarily removed simply by bringing any clear window to the front of the display, leaving the line diagram on its own. The line diagram can then be erased and the molecule manipulated to show another viewpoint onto which a new line diagram can be drawn. In this way, the instructor can demonstrate the link between the various viewpoints of a particular 3-dimensional representation and the corresponding 2-dimensional line diagrams. In addition to use in lectures, instructional videos can easily be created using screen-casting software alongside this approach. CamStudio,[11] a free and open-source screencasting application, was used for this purpose (several videos outlining the approach are provided in the Supporting Information). By making the 3-dimensional structure files for transition-state geometries available to download on our intranet, students are also able to investigate them in their own time.

In addition to using virtual 3-dimensional models, real models (e.g., Molymod) can also be used with this approach (Figure 3), thereby supplementing the students' own use of physical models. To a certain extent, the use of real models with this approach is more difficult in that the molecules need to be held in place by hand. This means that the overlay drawing cannot be done at the same time and necessitates the recording of a video of the manipulation first, then creating a new one with the annotation added. This could be alleviated if some clamping mechanism was used to hold the model steady while the overlaid line diagram was being drawn.

CONCLUSIONS

Both anecdotal evidence and student feedback strongly suggest that these learning materials have been extremely beneficial to our undergraduates, especially those who previously tended to struggle with the visualization and mental manipulation of 3-dimensional conformational structures. Particular areas of the course where this approach has been used include Zimmerman−Traxler transition states (e.g., stereoselective aldol reactions), stereoselective reductions (e.g., Evans−Saksena, Prasad), and Diels−Alder cycloadditions. These are all currently taught in the third year of our undergraduate degrees in both the B.Sc. and MChem-integrated Masters courses. However, the approach should also find use in many other areas of organic chemistry, particularly those involving stereochemistry or conformational analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00250.

Structure files of the Zimmerman−Traxler transition state and product (use Avogradro to open) (aldol immediate product geometry) (CML)
Structure files of the Zimmerman−Traxler transition state and product (use QuteMol to open) (aldol immediate product geometry) (PDB)
Structure files of the Zimmerman−Traxler transition state and product (use Avogradro to open) (aldol transition state geometry) (CML)
Structure files of the Zimmerman−Traxler transition state and product (use QuteMol to open) (aldol transition state geometry) (PDB)
Video demonstrating the approach (molymod immediate aldol product geometry) (AVI)

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Video demonstrating the approach (molymod 'linear' aldol product geometry) (AVI)
Video demonstrating the approach (molymod aldol transition state geometry) (AVI)
Video demonstrating the approach (qutemol aldol product geometries) (AVI)
Video demonstrating the approach (qutemol 'flipping' of aldol product geometries) (AVI)
Video demonstrating the approach (qutemol aldol transition state geometry) (AVI)
Video demonstrating the approach (qutemol aldol transition state allylic conformation) (AVI)

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Notes

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