Methodologies for Retrosynthesis

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Introduction

The workshop setting at the University of Rochester is designed to provide an environment in which students can practice their problem solving skills necessary for success in organic chemistry. Some of the metacognitively more difficult problems that students will run across are retrosynthetic analyses. A recent study by Grove, et al., showed that drawing mechanistic arrows is not particularly helpful to students in their problem solving processes.

However, in our experience as workshop leaders we have seen that drawing out mechanistic arrows is helpful. This not only helps students to visualize the mechanism, but it also enables the students to metacognitively evaluate their problem solving process. Additionally, other problem solving strategies such as carbon numbering and labeling are useful skills to master. For example, numbering and labeling carbons aids in the process of determining where new bond connections are made, especially in light of the fact that many students seem to lose or add carbons somewhere in their mechanistic analyses.

Thus, despite the current literature, we hypothesize that when students show their thought process by labeling/numbering carbons and drawing mechanistic arrows, they will show a marked improvement compared to when they did not perform this retrosynthetic analysis.

Methods
Students were tested under two conditions. In week one, students were given a complex molecule, a product of a Robinson annulation, and were prompted to give the starting materials for the molecule through retrosynthetic analysis. In week two, students were given a different molecule of comparable complexity and were given the same prompt, with the addition of requiring students to count all carbons and show arrow-pushing mechanisms throughout their entire retrosynthetic analysis. This experiment was performed with a sample size of approximately 20 students.

![Robinson annulation products](image)

**Figure 1.** Robinson annulation products presented to students for Quiz 1 (left) and Quiz 2 (right).

**Data**

An initial analysis of the data yielded no significant differences between Quiz 1 and Quiz 2; 44% and 41% answered correctly respectively. Upon further investigation, approximately 25% of the students who took Quiz 2 did not number/label their carbons and did not show any mechanistic arrows in their retrosynthetic analysis. As a result, their responses were not included in the adjusted calculation for Quiz 2. It may be important to note that none of the aforementioned students answered correctly.
Using the adjusted calculation for Quiz 2, it was seen that there was a 12% increase from Quiz 1.

Analysis

Upon first comparison between Quiz 1, in which students were not directed to label their carbons or show arrow-pushing for their retrosynthesis, and Quiz 2, in which students were directed to perform this analysis, it appears as if there is no significant difference between the two conditions – 44% of the students answered correctly for Quiz 1, whereas 41% of the students answered correctly for Quiz 2. However, the results of Quiz 2 were further examined and it was found that of the 22 students sampled, 6 failed to follow the directions for Quiz 2. As these students did not follow the directions for Quiz 2, their results were eliminated from our data. This now changed our results to 56%
students answered Quiz 2 correctly when they counted carbons and showed arrow-pushing for their retrosynthetic analysis, which is a significant improvement of 12% more students answering the retrosynthesis correctly. These results may suggest that enhanced analysis for the retrosynthesis of complex molecules, such that it forces one to think through their problem solving process step-by-step on paper, aids students in correctly answering these types of problems.

Additionally, it may be noteworthy that of the 6 students who did not follow the prompt for Quiz 2, none answered the problem correctly. This may be due to the fact that students were making disconnections in their retrosyntheses, yet did not draw the products of this disconnection correctly (i.e. wrong number of carbons or the wrong carbon connectivity), or made a disconnection by an unfavorable route. This unfavorable reaction would most likely have been identified when a student would have been unable to draw an arrow-pushing mechanism that explains their disconnection. Additionally, this result gives credence to our earlier hypothesis that a visualized, step-by-step retrosynthetic analysis on paper is superior.

**Conclusion**

Based on the 12% increase in students correctly answering retrosynthesis problems when prompted to count carbons and show arrow-pushing mechanisms to explain their analysis, it is likely that this advanced analysis leads to better student performance in retrosynthetic problems. However, our results differ from those found in the literature, specifically those of Grove, Cooper, and Rush, who found no significant enhancement of student performance in organic chemistry problems when arrow-pushing
was shown by the student. Interestingly, in Grove, Cooper, and Rush’s study, almost 60% of students did not draw arrow-pushing in answering organic chemistry problems, even when prompted to. While we experienced similar difficulty in having our students show their arrow-pushing (25% failed to do so), it is nowhere near the magnitude experienced by Grove, Cooper, and Rush, especially considering their large sample size. This failure of students to draw arrow-pushing may be reflective of a deeper process at work, in that a student’s perception of how useful arrow-pushing is influences its effectiveness in helping that student answer a problem correctly.

The organic chemistry curriculum at the University of Rochester is unique in its peer-led workshop program, which allows students to solve organic chemistry problems in a format that is much more collaborative than recitations, which is common for organic chemistry curriculums at many other universities. In these workshops, it is possible to build upon important concepts, such as the importance of arrow-pushing, that are assumed, and not emphasized in lecture or a recitation. Therefore, since workshops strongly stressed arrow-pushing, it is likely our students were much more appreciative of its usefulness, and this positive view may have influenced our students to use arrow-pushing in their retrosynthesis. However, at the large university where Grove, Cooper, and Rush performed their study, it is unlikely that students have a similar peer-led workshop program. They may not have been taught the usefulness of arrow-pushing in lecture, and may not hold the same positive view of arrow-pushing shared by organic chemistry students at UR. Since the students in Grove, Cooper, and Rush’s study may have held a negative or neutral view of arrow-pushing, this perception may have actually decreased its usefulness in solving problems, such as through a self-fulfilling prophecy.
that believing arrow-pushing is not useful in organic chemistry actually decreases its usefulness.

This negative perception may explain why such a high percentage of students in Grove, Cooper, and Rush’s study chose not to use arrow-pushing to solve the problems, compared to the much lower percentage of students in our study that held positive views of arrow-pushing. It may also explain that even when students did use arrow-pushing, their metacognitive belief that arrow-pushing is not useful came to fruition and did not give any advantage in problem solving. This could have created no significant difference in the percentage of students who correctly answered problems when they used arrow-pushing compared to when they did not use arrow-pushing.

While no examples can be found in the literature, it is likely that a similar paradigm holds for carbon counting in that if a student perceives counting carbons to be useful in retrosynthetic analysis, then that student will be more likely to use this methodology, and will also gain more success in employing it.

Another possible reason for the disparity of our results from those of the literature is our small sample size of approximately 20 students, compared to an entire, large class of organic chemistry students tested by Grove, Cooper, and Rush. Given the varied abilities of our students, our small sample size may not be indicative of organic chemistry students in general.

These conclusions are highly applicable to the workshop setting. If a student’s perception of arrow-pushing and carbon counting directly influences their usefulness, it is vital for workshop leaders to stress their importance early and often in workshop. Since these skills can not be practiced often in lecture, workshop leaders must help their
students develop these tools and create a positive view of arrow-pushing and carbon counting, thus enhancing their utility for organic chemistry students.

References
