Effective strategies for solving synthesis-type problems in organic chemistry

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BACKGROUND

Synthesis-type problems: an assessment tool used by instructors in organic chemistry education, where students must derive a sequence of chemical reactions that will selectively transform a given starting molecule into a given target molecule.

Desired learning outcomes include:

- Preparing students for real-life synthesis problems, where target molecules may include drugs, advanced materials, and other compounds of interest
- Development of transferable problem-solving skills

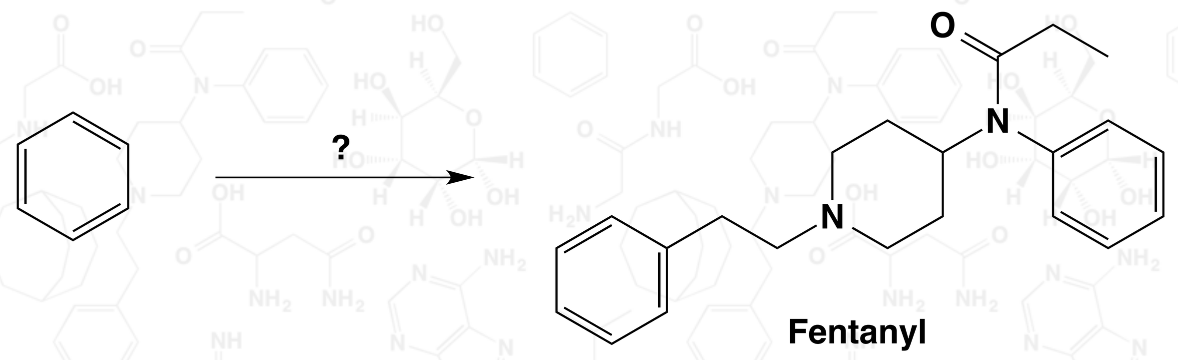


Figure 1. Example of a synthesis problem with a second-year level degree of difficulty. The target molecule is commonly of some real-life significance; in this case it is Fentanyl, a highly potent opioid analgesic.

Findings of previous research:

- Certain approaches to solving synthesis-type problems are more effective than others
- Use of multiple approaches more effective than any single approach
- Identification of several behaviours that students display in their problem solving approaches; suggestions as to how these behaviours may be interrelated

Shortcomings of previous research:

- Use of different behaviours/errors associated with the absence of certain behaviours is not quantified

Therefore, the purpose of this study is to:

- Quantify the behaviours students display when solving synthesis-type problems
- Draw conclusions regarding the importance of certain behaviours, based on how frequently they are used by successful students compared to unsuccessful students.

RESULTS

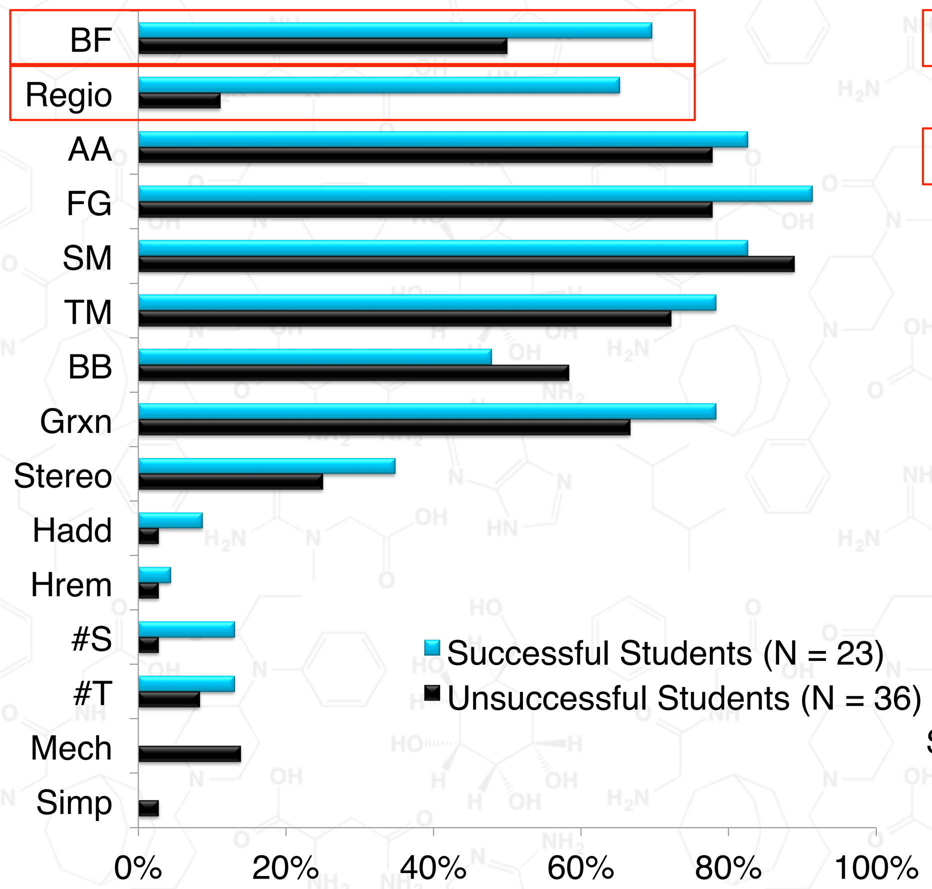


Figure 2. Behaviours correctly employed by CHM2120B (Fall 2013) students on question #11 of midterm exam #2 in a brainstorming/analysis.

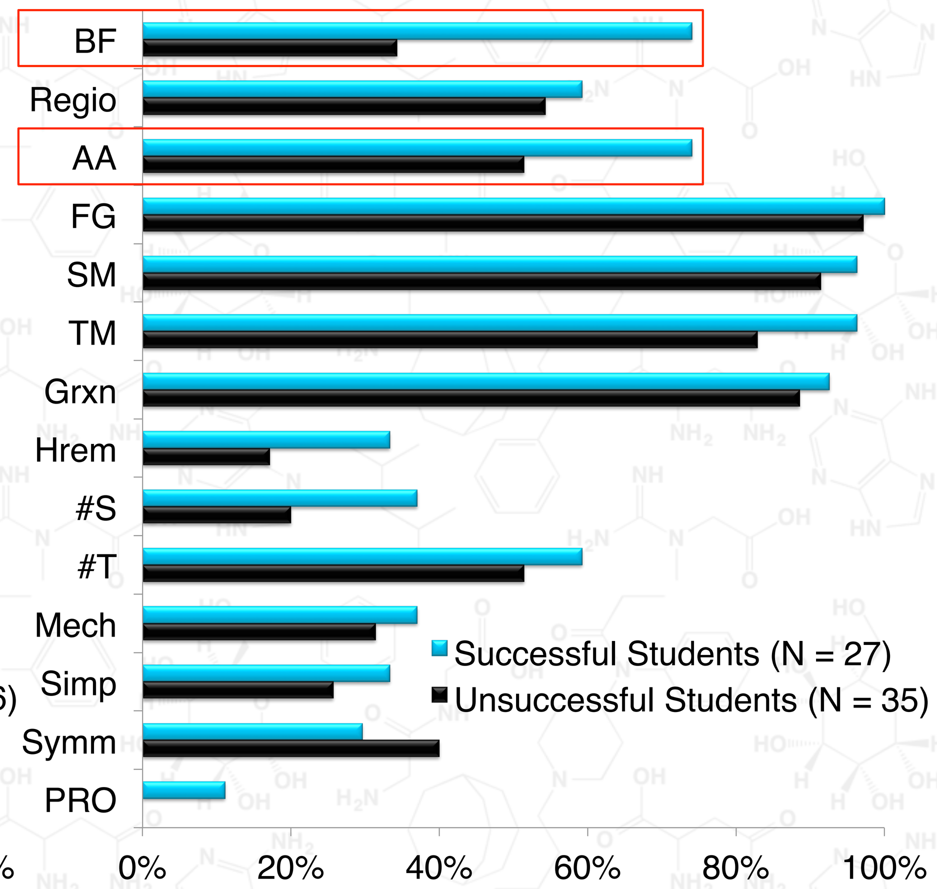


Figure 3. Behaviours correctly employed by CHM2120B (Fall 2013) students on question #17 of the final exam in a brainstorming/analysis.

Key behaviours observed:

1. **Absolute or relative regiochemical considerations noted (Regio)**
   - Midterm exam: 65% of successful students, 11% of unsuccessful students
   - Primary consideration was regioselectivity of a S_N2 reaction in a key reaction step
   - Margin is much smaller on final exam, where the primary consideration was the relationship between functional groups in the target molecule (1,3 diol)
2. **Identified bonds formed (BF)**
   - Midterm exam: 70% of successful students, 50% of unsuccessful students
   - Final exam: 74% of successful students, 34% of unsuccessful students
     - 34% of unsuccessful students did this incorrectly; each of these students highlighted a carbon atom rather than correctly highlighting a carbon-carbon bond (*Figure 6*)
     - Incorrect method was frequently associated with that student breaking the molecule into identical halves, and the use of a "self-aldol" pathway (incorrect)

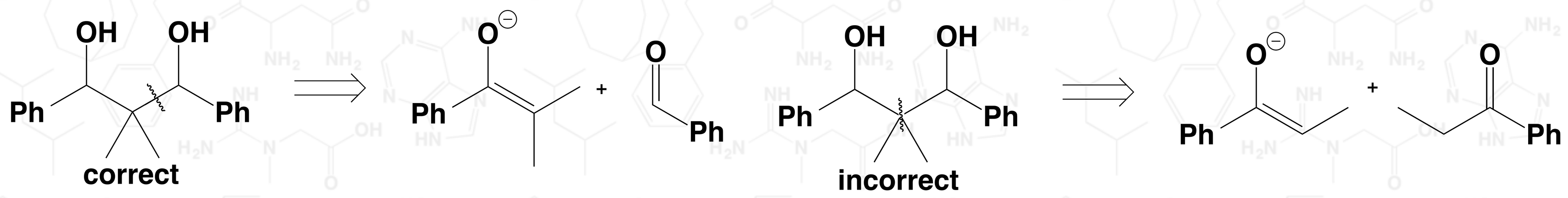


Figure 6. Examples of how bond formation analysis was performed by students on question 17 of the final exam. The correct analysis was commonly associated with pathways that included the enolate and aldehyde shown (correct answer) while the incorrect analysis was commonly with a "self-aldol" pathway (incorrect answer).

3. **Identified atoms added (AA)**
   - Final exam: 74% of successful students, 51% of unsuccessful students

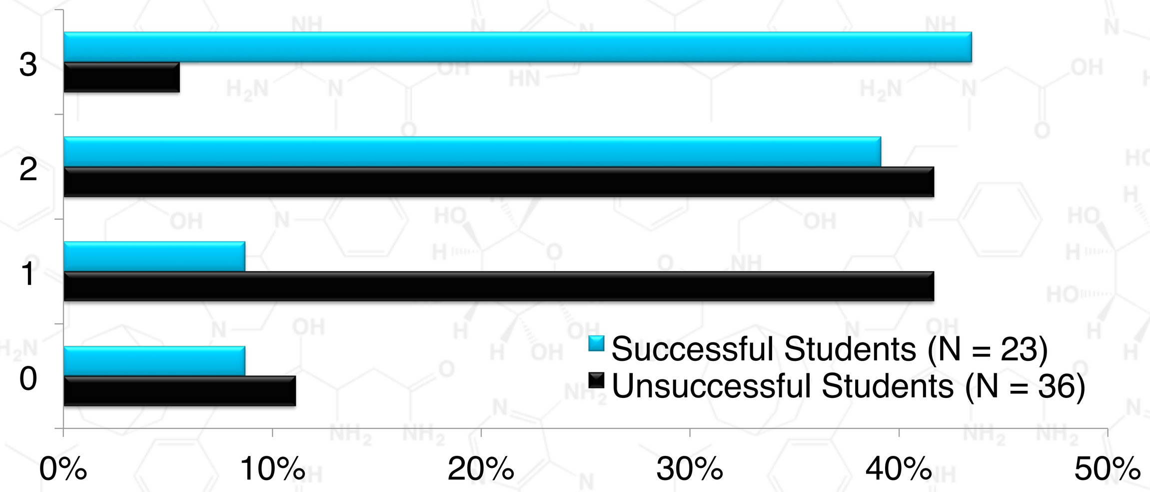


Figure 4. Frequency at which CHM2120B (Fall 2013) students employed either all three, two, one, or none of the key behaviours in their approach to question #11 of midterm exam #2.

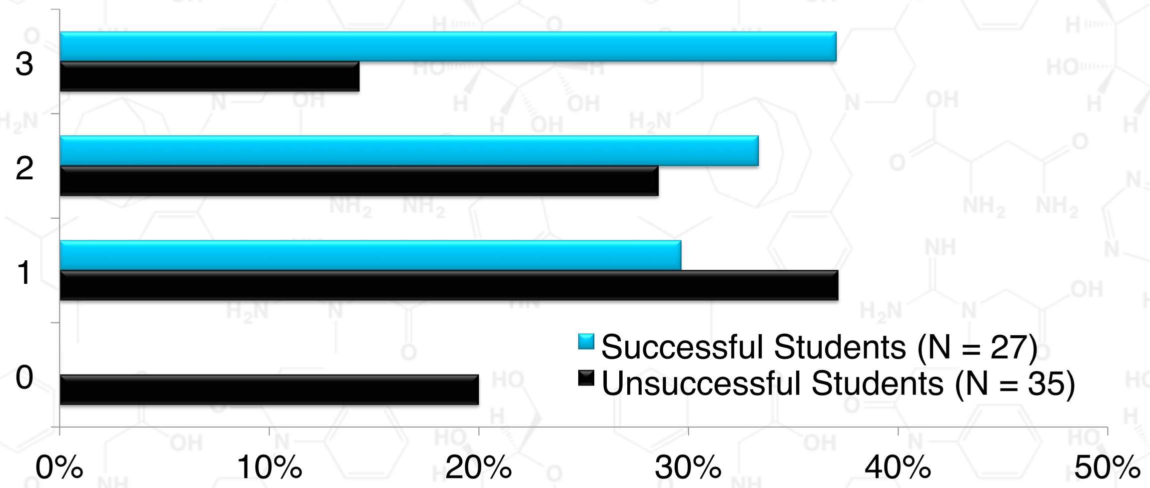


Figure 5. Frequency at which CHM2120B (Fall 2013) students employed either all three, two, one, or none of the key behaviours in their approach to question #17 of the final exam.

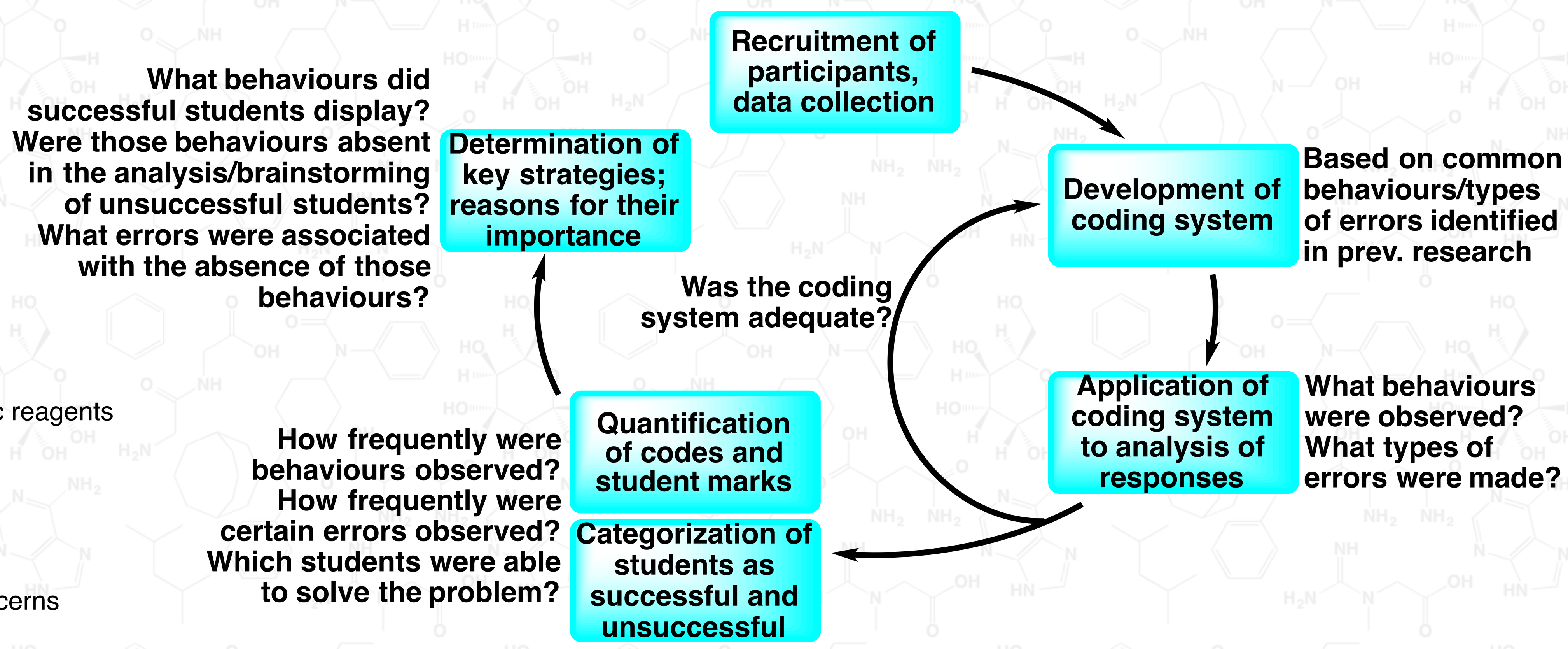
Key behaviours as primary determinants of success:

- Midterm exam: 83% of successful students used at least two of these strategies
  - Only 5% of students who used all three were unsuccessful
- Final exam: All successful students used at least one of these strategies; 70% used at least two
  - 57% of unsuccessful students used either one or none of these strategies

METHODOLOGY AND CODING SYSTEM

- A synthesis-type question was selected from each of the second midterm exam and final exam of CHM2120 (Organic Chemistry II), taught in Fall 2013 at uOttawa by Dr. Alison Flynn – consent was obtained from all participants ($N_{midterm}$ = 59, $N_{final\ exam}$ = 62) – Ethics approval: H08-13-14

Code	Description of behaviour
FG	Identified common functional groups
SM	Rewrote starting material
TM	Rewrote target molecule
#S	Carbon atoms/heteroatoms numbered in starting material
#T	Carbon atoms/heteroatoms numbered in target material
BF	Identified bonds formed
BB	Identified bonds broken
Hadd	Identified hydrogen atoms added
Hrem	Identified hydrogen atoms removed
Regio	Absolute or relative regiochemical considerations noted
Stereo	Absolute or relative stereochemical considerations noted
GRxn	General reaction specified in addition to/instead of specific reagents
Mech	Mechanism drawn (full/part)
Symm	Symmetry elements identified
Simp	Simplification of the molecule drawn (eg. R, Ph)
PRY	Pathway rejected because of anticipated low yield
PRL	Pathway rejected because of length
PRP	Pathway rejected because of practical (ie. laboratory) concerns
PRO	Pathway rejected for another reason



CONCLUSIONS

- **Correct identification of newly formed bonds in the target molecule is a primary determinant of success**
  - This strategy is commonly taught in the context of retrosynthetic analysis; it is emphasized as important for the purpose of determining the optimal synthetic fragments (synthons) from which to assemble a target molecule (Clayden, 2012)
  - Failure to employ this strategy correctly is strongly associated with the use of incorrect synthons
- **Regiochemical analysis is an important behaviour in problem types where a key reaction step must be designed to be regioselective**
  - Identification of regiochemical relationships between functional groups, however, does not appear to have any correlation with higher success rate
- **Correct identification of atoms added to the starting material also has a relatively high correlation with success rates**
- **The use of these behaviours in concert correlates with higher rates of success**
  - This corresponds with previous findings that "successful problem solvers use multiple types of representations when solving problems" (Bowen, 1990)

FUTURE WORK

- Analysis of exams from previous years where in-class learning activities (LAs) were absent from instruction; comparison to years where LAs were present
- Further development of LAs to support student success
- Ongoing: Interviews where students solve synthesis-type problems following a speak-aloud protocol

ACKNOWLEDGEMENTS/CONTACT

- Undergraduate Research Opportunity Program
- Thank you to Dr. Alison Flynn for supervising this project.

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2. Clayden, J.; Greeves, N.; Warren, S. In *Chapter 28: Retrosynthetic Analysis;* Organic Chemistry; Oxford UP: New York, 2012; pp 694-722.