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Article

Enhancing Stereochemistry Education through Inquiry-Based Learning and Concrete Molecular Models

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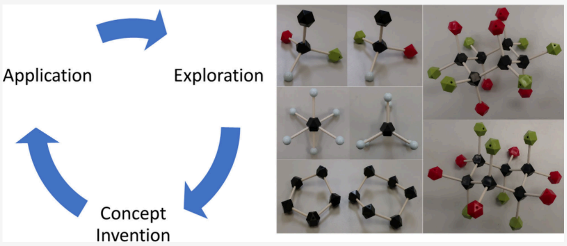
ABSTRACT: Stereochemistry is a vital component of pharmacy education, yet students often find it challenging due to the complex spatial concepts involved. This paper presents an innovative learning activity that combines inquiry-based learning with concrete molecular models to facilitate students' understanding of stereochemistry. The activity was structured around a three-phase learning cycle, including exploration, concept invention, and application and was scaffolded by mini-lectures. Students in small groups constructed and analyzed 3D molecular models of organic compound isomers and formulated definitions and rules for different types of isomerism based on the exploration. Concrete models to visualize molecular structures reduced students' cognitive load and provided kinesthetic and proprioception stimulation. Feedback from participating students indicated positive reception of the activity, highlighting the benefits of using concrete models and small group interactions. This innovative approach has demonstrated the potential of making stereochemistry more engaging and accessible for students.



KEYWORDS: *First-Year Undergraduate, Organic Chemistry, Hands-On Learning, Inquiry-Based, Stereochemistry*

INTRODUCTION

Stereochemistry is a crucial component of pharmacy education, providing the foundation for pharmacists to make informed clinical decisions.[1] One example is warfarin, an anticoagulant with a narrow therapeutic range marketed as a racemic mixture (Figure 1).

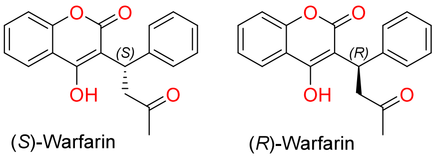


Figure 1. Enantiomers of warfarin. The (S) enantiomer is more active and predominantly metabolized by CYP2C9, whereas the (R) enantiomer is metabolized by multiple CYP enzymes.

The *S*-enantiomer is three to five times more potent than the *R*-enantiomer, and they are metabolized by different enzymes - predominantly CYP2C9 for the *S*-enantiomer and multiple CYP isoforms for the *R*-enantiomer.[2] As a result, pharmacists must pay close attention to any coadministered drugs or food that could potentially induce or inhibit the action of CYP2C9. This knowledge is essential to ensure the safe and effective use of warfarin in patients.

Despite the importance of stereochemistry in pharmacy education, many students find it phobic and challenging.[3] One possible explanation is the taxing demand on spatial cognitive skills, such as spatial visualization and orientation.[4,5] Students must repeatedly navigate between 2D diagrams and 3D structures and mentally rotate those structures.[5] Additionally, they must fluidly transition between different levels of representation (macro, submicro, and symbolic).[6−8] These processes are cognitively taxing and may impose a heavy load on students' working memory, hindering their ability to learn and retain information in their long-term memory.[9−12]

Numerous innovative instructional designs have been reported in the literature to help overcome the obstacles in teaching and learning stereochemistry. These innovations encompass a range of approaches, including gamification through board games[13,14] and escape rooms[15,16] to engage and motivate students. Virtual learning environments[17−21] have also been employed to enhance students' visualization of 3D structures. Mnemonics[22] have proven effective in aiding the interconversion of Fischer projections and pyranose chair forms. Additionally, the use of transparent whiteboards[23] has been shown to improve students' reception of lecture materials. Analogies comparing conformational isomers to apples[24] and cats[25] have been used to facilitate understanding. Furthermore, gesture-based instruction[26] has been utilized to simulate the inversion of chirality centers.

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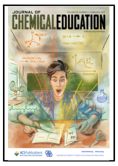

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Despite the abundance of learning activities reported in the literature, stereochemistry is still being taught in a traditional, lecture-based approach where teachers are the primary source of knowledge. In this approach, the teacher presents the definitions of different types of isomerism along with examples and problem sets. The success or failure of this approach is critically dependent on how well the students understand the definitions taught by the teachers. However, because the teacher and the students may not perceive the knowledge the same way, the teacher's conceptual model may not be fully and equally understood by every student due to individual differences and even generation gaps.

To address this issue, the authors of this study designed a series of inquiry-based learning activities. These activities are centered around a three-phase learning cycle: exploration, concept invention, and application.[27−30] For instance, during the exploration phase, students examine the structural characteristics of a pair of isomers. In the concept invention phase, they attempt to formulate a definition of isomerism based on their observations during the exploration phase. In the application phase, they apply the definition to other isomers with additional isomeric features, enabling them to modify and enhance the original definition. Instructor guidance is minimal, allowing each student to construct his or her own conceptual models.

The activity is scaffolded by concrete molecular models to aid spatial visualization and orientation. Manipulating a concrete molecular model by hand is cognitively much easier than rotating a 3D molecule in the mind. Studies have shown that concrete molecular models could help students reduce their cognitive load by substituting internal spatial processes with external real-world actions.[9−11,31,32] As such, the cognitive resources in their working memory can be reserved for mental processes that are germane to learning, for instance, comparing atom connectivity, spatial arrangement of substituents, superimposition, etc.[12]

In addition, via the enactment effect[9,33] and embodied cognition,[26,31] students can receive multiple nonvisual sensory inputs such as touch and proprioception when they are manipulating concrete models, which, in terms, may improve their memory storage and recall.[9]

Mini-lectures covering the Cahn-Ingold-Prelog rules and implications of stereoisomerism in medicinal chemistry are also provided at the appropriate stages of the activity.

To the best of our knowledge, this is the first reported activity emphasizing the use of inquiry-based learning in stereochemistry by prompting students to invent concepts and discover knowledge themselves.

■ IMPLEMENTATION

Materials

Students worked in groups of three to four. Each group of students was provided with a worksheet (Supporting Information SI02 and SI03) and a molecular model kit (Alpha Polyherdron Series, purchased from Maruzen International Co., Ltd.; Figure 2). The kit contents are listed in Table 1.

The activity was conducted in a multidisciplinary laboratory where tables, chairs, whiteboards and televisions were all movable. Therefore, students could sit as a crescent and the instructor, who looked after three to four groups simultaneously. A whiteboard or television was provided to each crescent to aid the instructor's illustration of the use of Cahn-Ingold-Prelog rules and the drawing of Newman projections and cyclohexane chair conformations (Figure 3).

Figure 2. Contents of a model kit. Each group of students was allocated one model kit.

Table 1. Model Kit Contents

item	count	use
14-hedron (black)	50	sp^3 carbon
14-hedron (red)	10	sp^3 oxygen
14-hedron (green)	15	sp^3 heteroatom
sphere (white)	100	hydrogen atom
bond (1.54 Å, straight)	50	single bond
bond (1.33 Å, curve)	12	double bond
bond puller	2	detach bonds from atoms
protractor	2	measure bond angles

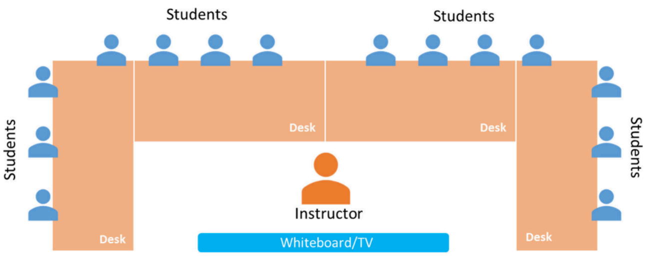


Figure 3. Seating plan for the activity. The students sat around the instructor so that the instructor could reach out to every student easily. A whiteboard or television screen was placed behind the instructor for illustration purposes.

Participants

The activity was conducted for a class of 35 students enrolled in the course BPHM1132 Drug Discovery as part of the Bachelor of Pharmacy program at The University of Hong Kong. Following the activity, an online questionnaire was distributed to gather student feedback and comments, and 31 completed questionnaires were received. This study was reviewed and approved by the university's institutional review board. Informed consent was obtained from the participating students.

Overview of the Learning Activity

The activity was composed of two sessions (Table 2). The first session was focused on stereoisomerism, covering enantiomers,

Table 2. Sessions and Topics

session	part	topics	learning outcome
1	A	constitutional isomers and stereoisomers	define constitutional isomers and stereoisomers
	B	enantiomers	define enantiomers
	C	diastereomers	define diastereomers
		mini-lecture[b]: CIP rules	
	D[a]	CIP rules	use the *R*/*S* designation to redefine enantiomers and diastereomers
	E[a]	meso compounds	define meso compounds
	F[a]	geometric isomers	learn to use the *cis*/*trans* and *E*/*Z* designations
	G[a]	chirality without chirality centers	understand the origin of chirality
mini-lecture[b]: examples of drugs that are stereoisomeric			
2	A	conformations of ethane	Newman projection, eclipsed and staggered conformations, torsional strain
	B	conformations of *n*-butane	gauche- and antistaggered conformations, steric strain
	C	cycloalkanes	molecular formulas of cycloalkanes, similarities of alkenes and cycloalkanes
	D	stability of cycloalkanes	angle strain, nonplanar characteristics when ring size > 3
	E[a]	conformations of cyclohexane	chair and boat conformations, axial and equatorial positions, ring-flip isomerism
	F[a]	1,3-diaxial interaction	stability of ring-flip isomers
	G[a]	polycyclic compounds	spiral, fused, and bridged compounds, *cis*- and *trans*-isomers of decalin

[a] Available in Supporting Information 01. [b] Available in Supporting Information 04.

diastereomers, meso compounds, and stereoconfigurations (*rectus* vs *sinister*, *cis* vs *trans*, *entgegen* vs *zusammen*). Two just-in-time mini-lectures were also included in this session to introduce the Cahn-Ingold-Prelog (CIP) rules and discuss the implications of stereoisomerism in drugs. The second session was focused on conformational isomerism, covering Newman projections, cycloalkanes, conformations, and ring flip of cyclohexane, and polycyclic compounds.

Each session was followed by a few problems for students to practice the knowledge they had constructed in the activity. Instructors could use these problems for a formative assessment.

In this manuscript, the authors focus on the inquiry elements. Readers may refer to the Supporting Information for the remaining components.

Required Prior Knowledge for The Workshop

Before participating in these two sessions, students should have a foundational understanding of the following chemical concepts:

- Carbon valence: The ability of carbon atoms to form four covalent bonds
- Chemical notation conversion: Proficiency in interconverting between structural and skeletal formulas
- Three-dimensional representation: Understanding of wedged and dashed bond notations for depicting molecular geometry

Session 1 Part A

The students were first instructed to build models for isomers **A**, **B** and **C** (Figure 4). At this stage, the students were asked to omit all hydrogen atoms to minimize time and obscurity, except for those on the substituted carbon atoms.

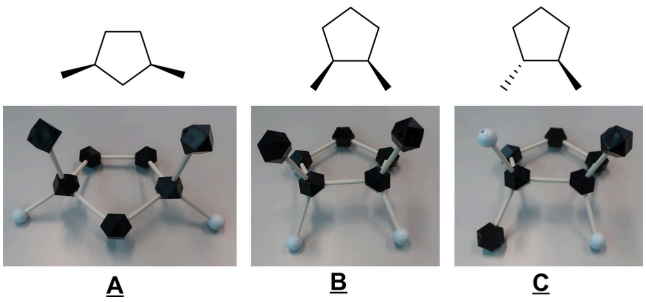


Figure 4. Isomers **A**, **B**, and **C** and their concrete models. Only hydrogen atoms on substituted carbon were installed.

Exploration. The students examined models **A** and **B**. Meanwhile, the instructor remained hands-off from the table to encourage student independence, allowing students to identify the similarities and differences between the two models on their own:

> **A** and **B** have the same molecular formula: C_7H_{14} (this can be determined from the skeletal formulas)
> **A** and **B** are both dimethyl-substituted
> The two methyl groups are separated by one CH_2 in **A** but adjacent to each other in **B**

The instructor waited for the students to identify the three points mentioned above before proceeding. In our experience, students could readily identify the above concepts, drawing upon their prior exposure to these concepts during secondary education. Minimum amount of guidance could be provided to the students if deemed necessary by the instructors or if students did not possess the required prior knowledge, although this was never necessary in the authors' experience.

Concept Invention. The instructor informed the students that **A** and **B** were constitutional isomers and asked them to come up with a definition of constitutional isomerism. It is crucial for the instructor to ensure that the students derive the definition from the models and observations during the exploration phase. This way, the students will be able to develop their own conceptual models for constitutional isomerism. The instructor discouraged any student attempting to search for the answer online.

The model answer is "*two compounds with the same molecular formula but their atoms are connected differently (i.e., different atom connectivity)*".

Application. The instructor asked the students to come up with another constitutional isomer for compound **A**, based on the definition they had created during the invention phase. Examples of responses are presented in Figure 5. Note that whereas **Aa**, **Ac**, and **Ad** are constitutional isomers of **A**, **Ab** is not but identical to **A**. If students propose **Ab**, then instructors may ask the students to assemble models of **A** and **Ab** to address this misconception.

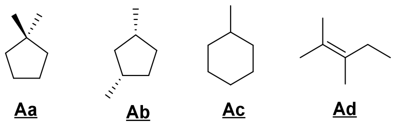


Figure 5. Constitutional isomers of **A** proposed by the students.

Exploration. The students examined the models of **B** and **C**, and they stated the simiarlites and differences.

Concept Invention. The instructor told the students that **B** and **C** were stereoisomers. The students attempted to define stereoisomers based on the observations in the exploration phase. The model answer is "*two compounds with the same molecular formula, same atom connectivity, but different spatial arrangements*". The instructor noted that the students had used laymen terms such as "relative 3D positions of substituents" in place of "spatial arrangements". Consequently, the instructor took this opportunity to educate the students on the correct terminology.

Application. Similar to part A, the students attempted to propose another stereoisomer of **B** based on the definition they had formulated in the invention phase.

Session 1, Part B

This part was intended to guide students to develop knowledge about enantiomerism.

Exploration. The students assembled and examined the models of **D** and **E** (Figure 6). They also attempted to superimpose them with each other and with their mirror images.

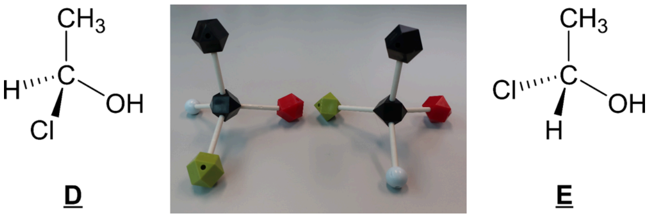


Figure 6. Isomers **D** and **E** and their concrete models. The hydroxyl group is represented by a red atom. Chlorine is presented by a green atom.

Concept Invention. Being told that **D** and **E** were enantiomers, the students attempted to propose a definition for enantiomerism. The correct answer is "*two compounds with the same molecular formula, same atom connectivity, different spatial arrangements, and superimposable with the mirror image of each other*". Additionally, the instructor challenged the students to build a third enantiomer of **D**, which they subsequently found impossible, leading them to the conclusion that enantiomers could occur only in pairs.

Application. See below in part C.

Session 1, Part C

This part was intended to guide students to develop knowledge about diastereomerism.

Exploration (Application of Part B). The students assembled the models of **F**, **G**, and **H** (Figure 7). Using the definition proposed in part B, they identified that **F** and **G** were enantiomers. When they examined **H**, they noted that it was a stereoisomer but not the enantiomer of **F** as its structure is different from that of **G**.

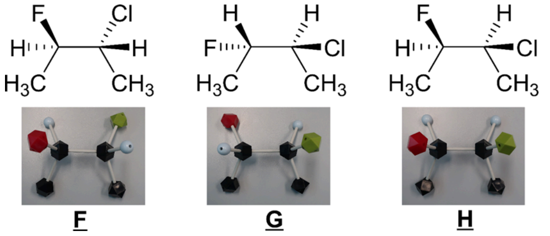


Figure 7. Isomers **F**, **G**, and **H** and their concrete models. Fluorine is represented by a red atom. Chlorine is represented by a green atom.

Concept Invention. The instructor revealed to the students that **H** was a diastereomer of **F**. The students attempted to propose a definition for diastereomers. The correct answer is "*two compounds with the same molecular formula, same atom connectivity, different spatial arrangements, and not superimposable with the mirror image of each other*".

The rest of session 1 (Parts E−G) covered *R*/*S* configurations, meso compounds, geometric isomers, and chiral compounds without chirality centers, respectively. They are summarized in Table 3 and depicted in detail in Supporting Information 01.

Session 2, Parts A

This section focuses on the conformations of aliphatic alkanes. The instructor first introduced Newman projection and dihedral angle but left conformational isomerism, such as eclipse, staggered, anti, and gauche, unmentioned.

Exploration. The students studied the energy diagram of ethane (Figure 8) to identify any patterns. They pointed out the repeating appearance of peaks and troughs separated by 12 kJ/mol.

Concept Invention. Using the molecular model of ethane, the students proposed explanations for the patterns. For instance, the peaks and troughs indicate that ethane exists in two principal "forms" with one form being more energetic than the other. The instructor took the opportunity to educate the students to use the term "conformation". In addition, the instructor also introduced the concepts of eclipsing interactions, torsional strain, and eclipsed and staggered conformations (Figure 9).

Session 2, Parts B

Exploration and Application of Part A. The students assembled the model of *n*-butane (Figure 10) and viewed it alone the C2−C3 bond. With the knowledge acquired in part A, they could see the eclipsed and staggered conformations.

Concept Invention. Through inspection of the model, the students discovered that there were two different eclipsed conformations and two different staggered conformations. Taking this chance, the instructor introduced the terms "anti-staggered" and "gauche-staggered". In addition, the instructor also demonstrated how to draw the Newman projection properly.

Exploration and Application. The students were presented with an energy diagram of *n*-butane (Figure 11). The presence of peaks and troughs on the diagram corroborated the eclipsed and staggered conformations they had identified previously. The instructor guided the students to further realize that one peak was higher than the other, and same for the troughs.

Concept Invention. The students attempted to use the model to explain their observations. Through rotating the C2−C3 bond, they noted that one eclipsed conformation was apparently more "crowded" than the other and the same for the two staggered conformations. The instructor then introduced the concepts of steric strain, Me-Me eclipsing interaction, and Me-Me gauche interaction.

Before proceeding to the next session, the students were asked to apply what they had learned to isopentane (2-

Table 3. Summary of Learning Activities in Session 1

part	exploration	concepts invented/acquired by students	application
A	• models of a pair of constitutional isomers	• definition of constitutional isomers	• suggest other constitutional isomers
	• models of a pair of stereoisomers	• definition of stereoisomers	• suggest other stereoisomers
B	• models of a pair of enantiomers	• definition of enantiomers	• apply the definition on a pair of enantiomers with two chirality centers
C	• models of a pair of diastereomers	• definition of diastereomers	
mini-lecture[b]: Cahn-Ingold-Prelog rules			
D[a]		• redefine enantiomers and diastereomers with the *R*/*S* designation	• predict possible stereoisomers (RRR, SSS, SSR, RRS, ...)
	• count the number of possible stereoisomers	• maximum number of stereoisomers, 2^n (where *n* is the no. of chirality centers)	
E[a]	• models of a meso compound	• definition of meso compounds	
	• assign *R*/*S* to a meso compound		
F[a]	• models of four alkenes	• bond rotation is restricted	
		• limitations of the *cis*/*trans* designations	
	• assign *cis*/*trans* and *E*/*Z* to an alkene	• the *cis*/*trans* and *E*/*Z* designations are not synonymic	
	• models of two allenyl isomers	• chiral molecules may not always possess chirality centers	
mini-lectures[b]: stereochemistry in drugs			

[a] Available in Supporting Information 01. [b] Available in Supporting Information 04.

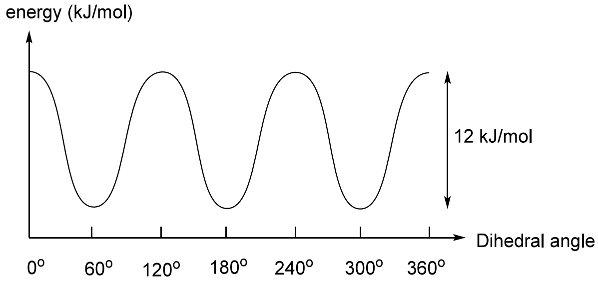
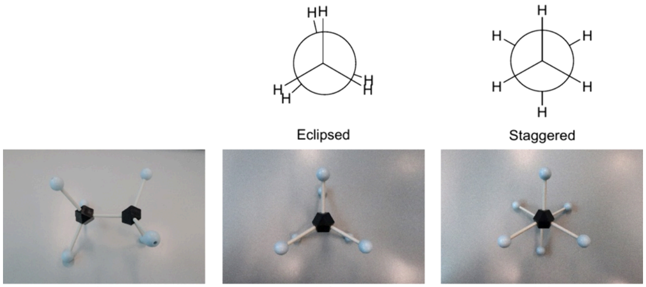


Figure 8. Energy diagram of ethane. The peaks and troughs indicated two principal conformations: eclipsed (peak) and staggered (trough).



(A) (B) (C)

Figure 9. Models and conformations of ethane. (A) Saw-horse projection, (B) eclipsed Newman projection, and (C) staggered Newman projection.

methylbutane), including drawing the Newman projections of its conformers and predicting their relative stability.

Session 2, Parts C

In part C, the focus was shifted to cycloalkanes.

Exploration. The students examined the expanded structures and molecular formulas of four cycloalkanes (Figure 12).

Concept Invention. The students generalized the formula of cycloalkanes as C_nH_{2n}. By comparing that with aliphatic alkanes (C_nH_{2n+2}) and aliphatic alkenes (C_nH_{2n}), they discovered that cycloalkanes and alphatic alkenes shared the sample general formula.

The instructor further elaborated on the similarities between cycloalkanes and alkenes, for instance, the limited or restricted bond rotation and the possibility of geometric isomerism.

Session 2, Parts D

Exploration. The students calculated the internal angles of five different polygons: triangle (60°), square (90°), pentagon (108°), hexagon (120°), and heptagon (129°). The instructor introduced the concept of angle strain and asked the students to predict the relative stability of cycloalkanes (ring sizes 3 to 7) based on their internal angles (Table 4).

The instructor then presented the students with a chart of the strain energy of cycloalkanes (Figure 13). The students observed that their predictions were overall correct for smaller rings (up to nine carbons) but were surprised to find that cyclohexane was more stable than cyclopentane.

Concept Invention. The students attempted to explain the discrepancy with concrete models (hydrogen atoms were excluded in this stage). They were also suggested to use the protractor in the model kits to measure the bond angles. They began to realize:

i. Cyclopropane and cyclobutane were highly strained
ii. Cyclopentane and cyclohexane were not flat but puckered
iii. The bond angles of cyclopentane and cyclohexane were very close to 109.5°; both were almost free of angle strain
iv. Cyclopentane contained a small amount of torsional strain
v. Cyclohexane was free of torsional strain

For i, cyclopropane was not accessible with the Maruzen model because the plastics bonds were not bendable. Cyclobutane was barely accessible and had a high chance of breaking the bonds. The instructor allowed the students to experience the strong angle strain in small rings firsthand.

For ii, the butterfly geometry of cyclobutane was not discussed, as it was not covered in the course syllabus.

To arrive at parts iv and v, the students were instructed to assemble all missing hydrogen atoms to cyclopentane and cyclohexane and view along every C−C bond. The instructor

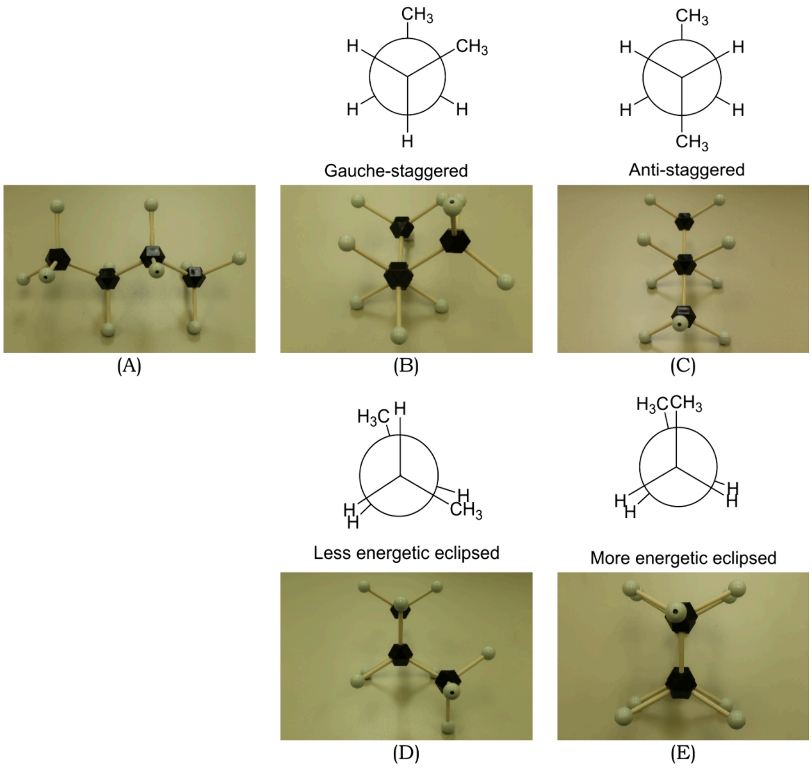


Figure 10. Models and conformations of *n*-butane. Newman projections of (B) gauche-staggered, (C) antistaggered, (D) less strained eclipsed, and (E) more strained eclipsed.

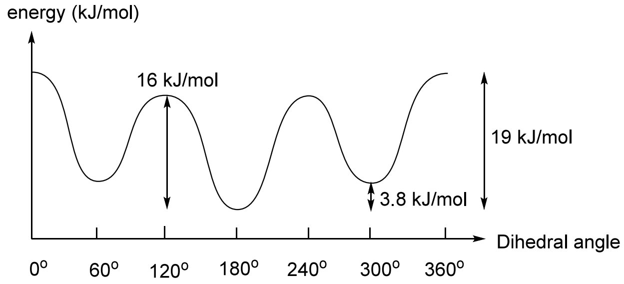


Figure 11. Energy diagram of *n*-butane. The higher peak represented an eclipsed conformation with a Me−Me eclipsed interaction. The lower peak represented eclipsed conformation with Me−H eclipsed interaction. The lower trough represented antistaggered conformation. The higher trough represented gauche-staggered conformation.

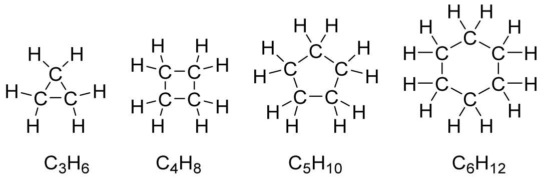


Figure 12. Expanded structures and molecular formulas of cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

also ensured that the models were in envelope and chair shapes, respectively.

The students continued to explore and discover other characteristics of cycloalkanes, including chair and boat conformations, 1,3-diaxial interactions, and polycyclic compounds (spiral, fused, and bridged). A detailed description is available in Table 5 and Supporting Information 01.

Table 4. Predicted Ring Stability Based on Internal Angles

ring size	deviation from 109.5°	predicted stability
three	49.5°	lowest
four	19.5°	low
five	1.5°	highest
six	−10.5°	moderate
seven	−19.5°	low

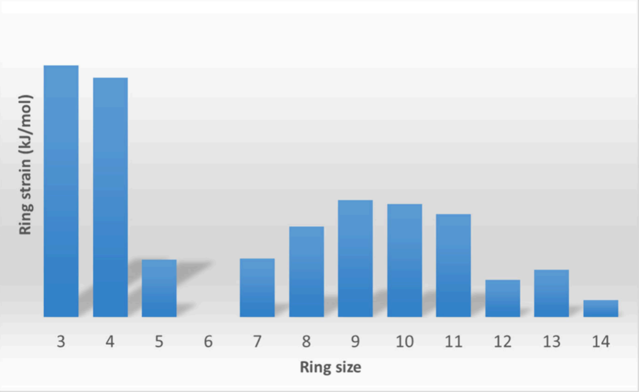


Figure 13. A chart showing the ring strain values of cycloalkanes.[34]

■ RESULTS AND DISCUSSION

Questionnaire

The questionnaire comprised nine questions that gathered the students' feedback on their perception of the learning activity and their experience using the concrete molecular models. The results were overwhelmingly positive, with an average of 52% and 46% of the respondents indicating agreement and strong

Table 5. Summary of Learning Activities in Session 2

part	exploration	concepts invented/acquired by students	application
A	• model, Newman projections, and energy diagram of ethane	• two principal conformations of ethane (staggered and eclipsed) with different stability	• study the conformers of *n*-butane (see part B)
B	• model, Newman projections, and energy diagram of *n*-butane	• four conformations of *n*-butane (antistaggered, gauche staggered, and two eclipsed conformations)	• study the conformers of 2-methylbutane
C	• molecular formulas of cycloalkanes	• cycloalkanes and alkenes share the same molecular formulas • similarities between cycloalkanes and alkenes (restricted/limited bond rotation and geometric isomerism)	
D	• calculate internal angles of five polygons, and predict relative stability for different ring sizes • actual energy diagram of different ring sizes • models of cycloalkanes	• cycloalkanes with ring size ≥ 4 are puckered • cyclohexane (chair) is the most stable with bond angle = 109.5°, and free of torsional strain	
E[a]	• relative positions of the 12 hydrogen atoms on cyclohexane (chair) • structure of cyclohexane before and after ring-flip	• axial and equatorial positions • swapping of axial and equatorial substituents during ring-flip	• study the conformations of methylcyclohexane (see part F)
F[a]	• model of methylcyclohexa-ne	• 1,3-diaxial interaction • a conformation is more favorable when the largest group is placed equatorial	• study the conformations of 1-(*tert*-butyl)-4-methylcyclohexane
G[a]	• models of decalin isomers	• shapes and structural rigidity of *cis*-/*trans*-decalin	

[a] Available in Supporting Information 01.

Table 6. Results of the Questionnaire Survey

	(*n* = 31)				
question	strongly disagree (%)	disagree (%)	neutral (%)	agree (%)	strongly agree (%)
1. I found the learning activity interesting	0	0	0	58	42
2. The learning activity could help me understand the concepts	0	0	0	52	48
3. The learning activity could motivate me to learn	0	0	3	58	39
4. The learning activity could encourage my participation	0	0	0	55	45
5. I prefer this type of learning activity over conventional didactic lectures	0	0	0	52	48
6. There should be more learning activities of a similar format in the pharmacy program	0	0	6	42	52
7. The model could help me understand the concepts	0	0	3	55	42
8. The model could help me visualize the 3D nature of organic molecules	0	0	0	42	58
9. The model is easy to use	0	0	13	52	35

agreement, respectively, across all nine questions. Overall, the students agreed that this learning activity could help them understand abstract concepts in stereochemistry (Table 6, Question 2). They found it interesting and motivating (Table 6, questions 1 and 3–4) and expressed a preference for this type of learning activity over traditional lecture-based approaches (Table 6, Question 5). They also agreed that the pharmacy program should incorporate more of this type of activity (Table 6, Question 6).

The students also appreciated the usefulness of the molecular models in visualizing 3D structures of organic molecules and grasping abstract concepts (Table 6, Questions 7–8). They also found the models easy to use, although 13% expressed neutrality on this aspect (Table 6, Question 9). The instructors did not observe any students experiencing difficulty in assembling the models, but some students reported using similar concrete models in secondary schools. Thus, it was surmised that the neutrality expressed by some students may have been due to a lack of pre-exposure to the models.

Comments from the Students. The questionnaire also included a section for open-ended comments from the students. Of the 31 respondents, 17 provided feedback on what aspects of the activity they found most useful or valuable. Thirteen of these students mentioned building molecular models, with five recognizing the helpfulness of models in visualizing molecular structures. Additionally, four students appreciated the benefits of a small group size for facilitating engagement and interaction with the instructor. When asked how the activity could be improved, seven students gave relevant responses, with three recommending a slower pace or dividing the activity into more subsessions to allow for more breaks. Two students suggested the involvement of more instructors to facilitate smaller-group learning. One student recommended the inclusion of triple bonds. Since there is no stereochemistry aspect for alkynes, the authors surmised that the student might have simply found building a triple bond model with three curved bonds fascinating. Nevertheless, the model kits used in this implementation contained plenty of curved bonds and 14-hedron atoms. Instructors may allow students to build and explore other interesting structural features during breaks. Finally, one student requested that every student be provided with a model kit. Although this request was feasible, it might discourage student cooperation and communication.

Assignment

The students were given an assignment consisting of 12 questions as a formative assessment—five questions related to stereoisomerism and seven related to conformational isomerism (Table 7). These questions are available in Supporting Information 02 (Page 13) and 03 (Page 13).

Table 7. Student Performance in the Assignment

question	theme	average score[a,b]
1	assigning stereoconfigurations (*R*, *S*, *E* and *Z*)	87%
2	drawing enantiomers and diastereomers, determing isomeric relationships	52%
3	identifying meso compounds	94%
4	drawing chirality centers	89%
5	stating relationships between different stereoisomers	98%
6	conversion: dash-and-wedge to Newman projection	94%
7	conversion: Newman projection to dash-and-wedge	78%
8	determing stability of rotational conformers	100%
9	conversion: dash-and-wedge to chair	94%
10	conversion: chair to dash-and-wedge	83%
11	determing stability of chair conformers	83%
12	clinical application: testosterone and digoxin	97%
	average	88%

[a] Full marks are adjusted to 100% for easy comparison. [b] Calculated from nine assignments submitted by nine groups of students.

The average score was 88%, indicating a good overall comprehension of the material. Of note is Question 2, which required the students to draw all possible stereoisomers of *cis*-1,2-dimethyl-cyclohexane and indicate their isomeric relationships. While two groups scored full marks by correctly drawing and labeling the isomers (Figure 14A), five groups missed points for not specifying all of the isomeric relationships despite drawing the isomers correctly (Figure 14B). Two groups received zero marks—one for failing to indicate all isomeric relationships (Figure 14C) and the other for submitting an irrational response (Figure 14D). The author concluded that the students did demonstrate a solid understanding of the concept, since they were able to draw the stereoisomers correctly (as seen in Figure 14B and C). Lower scores were a result of misinterpreting the question (Figure 14B) or simply making careless mistakes (Figure 14C).

Examination

The course's final examination consisted of 40 four-option multiple choice questions concerning topics of organic chemistry and eight written questions concerning pharmacology, medicinal chemistry, and immunology. Six multiple choice questions were related to stereochemistry (Table 8). On average, 87% of the candidates selected the correct asnwers. This is comparable to the average score (88%) of the assignment.

Table 8. Student Performance in the Final Examination

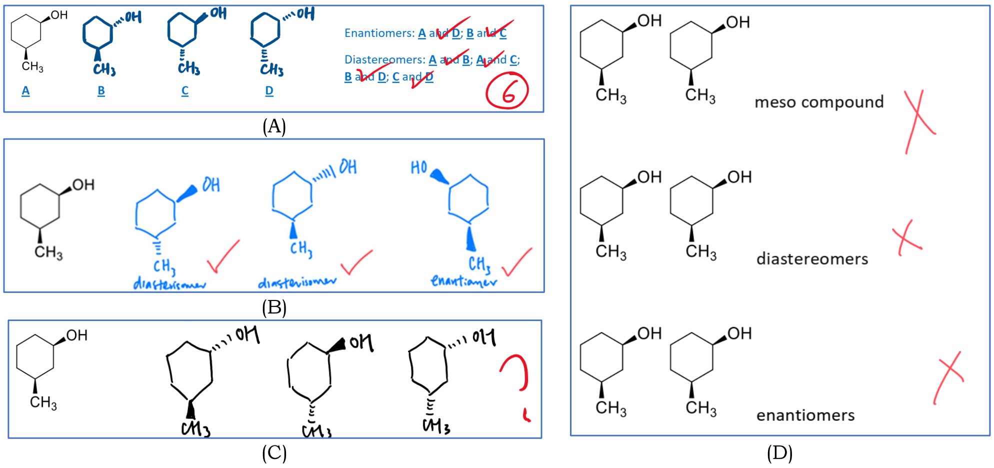
question	theme	right answer (% of candidate[a])
1	determining isomeric relationship—diastereoisomerism	73%
2	determining isomeric relationship—constitutional isomerism	82%
3	assigning configuration—*R*/*S* designations	91%
4	Newman projection—stability of conformational isomers	94%
5	Newman projection—stability of conformational isomers	97%
6	chair conformation—conversion between chair and 2D drawing	82%
	average	87%

[a] Total number of candidate = 33.

Suggestions for Instructors to Facilitate the Activity

The process of concept invention lies at the center of inquiry-based learning. Students must discover the knowledge themselves. Therefore, it is important for instructors to take a step back and avoid rushing to provide the correct answers too quickly. This requires more time and patience than traditional lecturing, and instructors should be prepared for this. In addition, instructors should allow sufficient time for students to assemble concrete models, as this provides valuable kinesthetic and proprioception stimulation. It is recommend to allocate at least three h for each session to allow ample time for these activities.

Instructors should also check whether the students' models are assembled correctly. A wrong model could lead to confusion or even to alternative concepts. This is especially crucial for parts involving stereoisomerism as swapping any two substituents will completely invert the configuration of a stereoisomer.



(A) (B) (C) (D)

Figure 14. Selected examples of student answers to question 2. (A) Full mark. (B) Isomers are drawn correctly but some isomeric relationships are missing. (C) Isomers are drawn correctly but the isomeric relationships are missing. (D) Irrational answer.

When exploring models of cycloalkanes, especially cyclopropane and cyclobutane, students may accidentally break a plastic bond and leave a piece of remnant in the atom, rendering both the bond and the atom unusable. However, instructors should not penalize the students for this mistake, as it is unintentional and more a result of the design and material of the model. Additionally, this provides students with an opportunity to experience immense ring strain in three- and four-membered ring systems through hands-on learning. Instead, instructors can inform them of this possibility at the beginning and ensure them that they will not be penalized for any broken parts. Instructors should also encourage students to hand in any broken parts for replacement.

CONCLUSION

Stereochemistry, often viewed as a repelling and challenging topic, can be approached in a more engaging and accessible manner. This paper has presented a learning activity that effectively combined the use of concrete models and inquiry-based methods to enhance students' understanding of stereochemistry. By using concrete models, students could better comprehend complex spatial concepts. Additionally, the inquiry-based approach encouraged students to actively define different types of stereoisomers and explore the fascinating characteristics of conformational isomers. The survey results indicated that this activity was well-received, as the students appreciated using concrete models and the opportunity for more personalized interactions with the instructor in small group settings. This innovative approach has demonstrated that stereochemistry can be captivating and enjoyable for students.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.4c00829.

Session 1 (Parts D to G) and session 2 (Parts E to G) (PDF)
Worksheet for session 1 (PDF)
Worksheet for session 2 (PDF)
Mini-lecture for session 1 (PDF)
Questionnaire (PDF)
Questionnaire results (PDF)

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Notes

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