JOURNAL OF CHEMICAL EDUCATION

Communication

pubs.acs.org/jchemeduc

A Biochemistry Question-Guided Derivation of a Potential Mechanism for HbA1c Formation in Diabetes Mellitus Leading to a Data-Driven Clinical Diagnosis

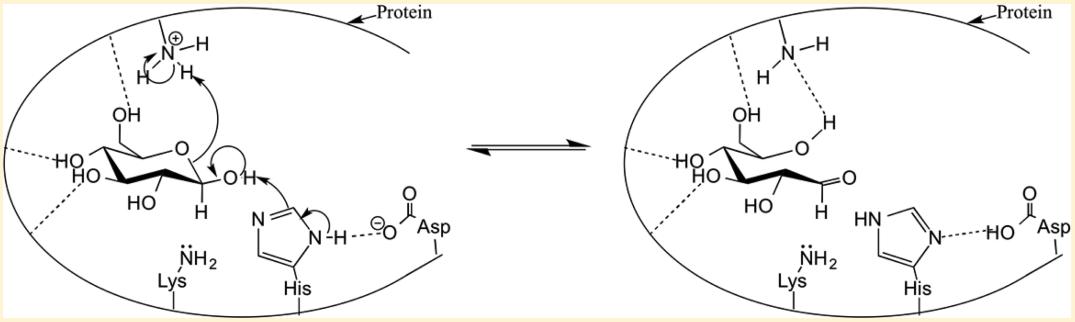
Bomina Park,[†] Robert W. Holman,[*,†] Tyler Slade,[‡] Margaret Murdock,[†] Kenneth J. Rodnick,[‡] and Arthur L. M. Swislocki[§,∥]

Departments of [†]Chemistry and [‡]Biological Sciences, Idaho State University, Pocatello, Idaho 83209, United States

[§]Divisions and Endocrinology and Metabolism, Department of Internal Medicine, University of California Davis School of Medicine, Sacramento, California 95817, United States

[∥]Veterans Affairs Northern California Health Care System, Martinez, California 94553, United States

Supporting Information



ABSTRACT: A unique homework exercise with a related clinical case study has been designed as a tool for teaching applied biochemistry. Within the framework of the homework exercise, students derive a mechanism for the covalent attachment of glucose to hemoglobin. This process is critical to understand both nonenzymatic glycation and the molecular basis of diabetes mellitus. The homework exercise teaches first-principles using a data-driven, question-guided approach. The accompanying case study contextualizes the principles derived by students into a tangible clinical application. In the case study, students interpret analytical chemistry data from a clinical setting for a diabetic patient and must make conclusions on the best control and treatment for the patient. To make the proper clinical assessment, students must understand the mechanistic principles regarding nonenzymatic glycation of proteins that they learned in the homework exercise. Overall, the homework exercise and the case study tether together principles from organic chemistry (electrophiles/nucleophiles, Brønsted−Lowry acid−base theory, thermodynamics, blood glucose concentration, and cation exchange column chromatography) with those from biochemistry (covalent and noncovalent interactions, lock and key vs induced fit paradigms, and organic chemistry mechanisms for nonenzymatic formation of hemoglobin HbA1c and carbamylated hemoglobin, CHb) into a practical and tangible medical application.

KEYWORDS: *Biochemistry, Organic Chemistry, Inquiry-Based/Discovery Learning, Problem Solving/Decision Making, Upper-Division Undergraduate, Bioorganic Chemistry, Applications of Chemistry, Noncovalent Interactions*

INTRODUCTION

A novel homework exercise and related clinical case study have been designed as tools for teaching applied biochemistry. While the homework exercise teaches first-principles using a data-driven, question-guided approach,[1−3] the accompanying case study contextualizes the principles derived by students into a tangible clinical application utilizing analytical chemistry. In the early portion of the homework exercise, students derive principles from data to understand glucose mutarotation and how it applies to the nonenzymatic glycation process. As students proceed through the question-guided homework set, they derive an arrow-pushing mechanism for the covalent attachment of glucose to human hemoglobin (HbA), which is central to the nonenzymatic glycation process that is operative in diabetes mellitus. The intent is to equip students to see and appreciate the connection between chemistry principles and biological applications to human health. To make this connection more concrete, a clinical case study has also been developed, which includes laboratory measurements at several time points within the medical history of a patient. The

Received: July 9, 2015
Revised: January 14, 2016

DOI: 10.1021/acs.jchemed.5b00554
J. Chem. Educ. XXXX, XXX, XXX−XXX

chemical principles that students developed in the directed homework set are applied to explain discordance between the laboratory measurements for the patient and reference data for normal and diabetic patients. Students ultimately learn that decisions about patient condition and treatment should not be based on one particular variable, but it is necessary to look at other complications and factors. Furthermore, the case study shows students that understanding organic chemistry mechanisms and principles can help clinicians solve complicated medical problems.

PEDAGOGICAL APPROACH TO HOMEWORK EXERCISE AND CASE STUDY

Classic pedagogical presentations focus on textbook narratives and results, but not actual experiments or data. In an effort to enhance student problem-solving skills, question-guided approaches[1−3] have been applied in homework exercises whereby data interpretation leads to deriving principles. Specifically, these previous exercises enabled students to derive principles either from data using a question-driven laboratory experiment (QDLE) approach[2] or using a question-guided, data-driven lecture (QGDDL) approach.[3] These approaches led students to interpret data in order to solve problems, and to develop higher-order reasoning skills. Students also saw the process by which principles are generated and new principles extend from existing ones. A modified QGDDL approach is utilized in the current homework exercise. The current case study, which is also question-driven, provides students an opportunity to apply previously derived principles to explain the discordance of clinically relevant measurements for a patient versus reference data. This principle-first-then-data justification and real-world application not only are a time-efficient method of content delivery, but also provide students with unique problem-solving opportunities using basic concepts in organic chemistry and biochemistry.

GENERAL UNIQUENESS OF EXERCISE/CASE STUDY

Only two homework exercises that use a data-driven approach have been published, both from our group.[2,4] Each of these homework exercises were designed for students in organic chemistry, with one completely unrelated to this work.[2] The other[4] centered on the mechanism of glucose mutarotation in solution but did not extend to biochemistry nor did it have a clinical application. To date, there have been three case studies published in this *Journal* that are designed for biochemistry students.[5−7] However, a data-driven approach was not utilized in these case studies. There have been two published articles involving glycated proteins.[8,9] One was an experiment to separate glycated HbA proteins from one another,[8] and the second was a discussion of the glycation process in HbA and did not include an exercise or experiment.[9] Neither of these articles discussed the binding of glucose or the events that are required for a protein to become glycated. Although there was an experiment to study the binding of oxygen to hemoglobin,[10] to our knowledge, there have been no experiments or exercises published that involve the substrate−protein interaction of glucose with HbA. Finally, no published exercise, case study, or experiment involves a mechanistic assessment of protein glycation or incorporates clinical diagnosis.

CONCEPTS INCORPORATED INTO THE EXERCISE/CASE STUDY

Review principles applied within the composite of the homework exercise/case study include the following:

(1) Blood glucose concentration and measurements of HbA1c
(2) Brønsted−Lowry acid−base theory
(3) Cation-exchange column chromatography
(4) Covalent and noncovalent interactions
(5) Electrophiles and nucleophiles
(6) Lock and key vs induced fit paradigms
(7) Nonenzymatic formation of HbAlc and CHb
(8) Protein and carbohydrate interactions
(9) Thermodynamics

Each of these nine concepts are addressed within the homework exercise and/or case study and utilized by the students to answer the provided questions. Hyperlinks for most of these concepts are incorporated within the homework exercise/case study so that students can review the general concepts.

IMPLEMENTATION

Upon the basis of student feedback and assessment, the homework exercise and case study can be implemented successfully as a take-home assignment during a biochemistry preview near the end of a two-semester organic chemistry sequence or at the beginning of a biochemistry course. As an alternative, the homework exercise and the case study can be implemented within a dry-lab in either organic chemistry or biochemistry. Further, the homework exercise and the case study can be given separately from one another (though the homework exercise clearly facilitates the case study). The two together can be completed within a 3 h time period,

OVERVIEW OF HOMEWORK EXERCISE

The homework exercise (Supporting Information) opens with a brief treatment on nonenzymatic protein glycation and how it is manifested in diabetes mellitus. A question-driven approach follows where students derive principles by answering questions posed and from the interpretation of provided data. The questions posited and the data provided are formulated to build upon one another and, thus, to emphasize a student's acquired knowledge of each preceding concept. Within the framework of the exercise, students derive an arrow-pushing mechanism for the initial process that leads to covalent bonding of glucose to HbA. This process is critical to understand nonenzymatic glycation.

OVERVIEW OF THE CASE STUDY

A general overview of nonenzymatic glycation from an organic chemistry perspective, the significance of glycemic control, and methods for the diagnosis and management of diabetes are initially addressed. Students are then provided with reference analytical data and, finally, with clinical laboratory measurements for a patient with complicating issues. A narrative of the patient's medical history is addressed, and guided questions with new data are provided. Students must integrate all of the data within the patient's medical history and utilize their mechanistic understanding of nonenzymatic glycation to answer questions that build upon one other with the goal being a student-derived diagnosis for the patient. To arrive at

DOI: 10.1021/acs.jchemed.5b00554
J. Chem. Educ. XXXX, XXX, XXX−XXX

Table 1. Summary of Student Time for Completion of Homework Exercise/Case Study with Student Performance Indicated for Four Different Student Groups

Student Category Class	Average Time To Complete Homework Exercise (min)	Average Time To Complete Case Study (min)	Average Score % Homework Exercise	Average Score and Case Study
Organic Chemistry I	90	110	86	78
Organic Chemistry I and II	90	100	93	85
Organic Chemistry and Biochemistry	80	90	94	91
Upper Class Special Topics	68	65	95	98

the proper diagnosis for the patient, the student must recognize that the initial methods associated with the assays were not sufficient to draw a conclusion. In view of the organic and analytical chemistry principles learned within the homework exercise/case study, through a question-driven data-interpretation approach, the students utilize an alternative assay and then can make a diagnosis for the patient. From this, students realize that their organic and analytical chemistry skills can relate to solving health-related problems.

STUDENT PERFORMANCE/FEEDBACK

The composite homework exercise/case study was given as a take-home assignment that was open book and open note to students in four categories:

(1) Students in week 12 of an Organic Chemistry I course
(2) Students with a full year (two semesters) of Organic Chemistry completed
(3) Students with a full year of Organic Chemistry and currently in Biochemistry I
(4) Students who were in an advanced special topics bioorganic course having completed both a year of Organic Chemistry and Biochemistry.

Table 1 summarizes the performance of these four student groups with data regarding time for completion included.

For those students in week 12 of an Organic Chemistry I course, 99% of the comments received (77 of 78 comments) were positive. The most represented comments regarding the homework exercise were "an enjoyable and good learning tool", and "liked that the answers for certain questions were embodied in follow-up questions aiding in understanding." The most common comments associated with the case study were "the homework exercise/case study felt like I was doing research and inspired me to want to do research" and "liked the application to biochemistry, real-world, and/or the medical field." Those students who had completed a full year of Organic Chemistry uniformly appreciated the concrete connection between organic chemistry and biochemistry stating that the homework exercise/case study made them look forward to taking biochemistry. The biochemistry students most represented comment was that they enjoyed the opportunity to take what they learned in biochemistry and organic chemistry and see it manifest in a real-world application within a health-related field. All four groups of students gave exceedingly positive testimony that the homework exercise/case study tested their knowledge base, expanded their knowledge base, and enhanced their ability to see the connectedness between organic principles and real-world clinical biochemistry. This is, in our view, testimony that the homework exercise/case study is effective and of value to the students.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00554.

Case study in final form suitable for distribution to students (PDF, DOCX)
An instructor's guide for the case study with the complete answers (PDF, DOCX)
The homework exercise ready for student distribution (PDF, DOCX)
An instructor's guide with the complete answers for the entire homework exercise (PDF, DOCX)

AUTHOR INFORMATION

Corresponding Author

*E-mail: holmrobe@isu.edu.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Teixeira, J. M.; Byers, J.; Perez, M.; Holman, R. W. The Question-Driven Laboratory Exercise: A New Pedagogy Applied to a Green Modification of Grignard Reagent Formation and Reaction. *J. Chem. Educ.* **2010**, *87* (7), 714−716.
(2) Davis, T.; Bryant, P.; Holman, R. W. Interrelating Conjugation, Aromaticity, and the Acid-Base Chemistry of Aromatics via a Computational Question-Driven Exercise. *Chem. Educ.* **2013**, *18*, 33−34.
(3) Teixeira, J. M.; Holman, R. W. The Question-Guided Data-Driven Lecture: A New Approach Applied to the Presentation of the Principles Associated with SN2, SN1, E1, and E2 Reactions. *Chem. Educator* **2011**, *16*, 79−81.
(4) Murdock, M.; Holman, R. W.; Slade, T.; Clark, S. L. D.; Rodnick, K. J. An Introductory Organic Chemistry Review Homework Exercise: Deriving Potential Mechanisms for Glucose Ring Opening in Mutarotation. *J. Chem. Educ.* **2014**, *91* (12), 2146−2147.
(5) Cornely, K.; Bennett, N. Thalidomide Makes a Comeback: A Case Discussion Exercise That Integrates Biochemistry and Organic Chemistry. *J. Chem. Educ.* **2001**, *78* (6), 759−761.
(6) Dewprashad, B. ConfChem Conference on Case-Based Studies in Chemical Education: Case Study Teaching in the Community College. *J. Chem. Educ.* **2013**, *90* (2), 262−263.
(7) Cornely, K. The Use of Case Studies in an Undergraduate Biochemistry Course. *J. Chem. Educ.* **1998**, *75* (4), 475−478.
(8) Jackman, L. E. Separation of glycohemoglobins by ion exchange chromatography: An undergraduate biochemistry laboratory experiment. *J. Chem. Educ.* **1981**, *58* (1), 77−78.
(9) Kerber, R. C. The A1c Blood Test: An Illustration of Principles from General and Organic Chemistry. *J. Chem. Educ.* **2007**, *84* (9), 1541−1545.
(10) Hanson, R. W. Further experiments with hemoglobin. *J. Chem. Educ.* **1981**, *58* (1), 75−76.

DOI: 10.1021/acs.jchemed.5b00554
J. Chem. Educ. XXXX, XXX, XXX−XXX