JOURNAL OF CHEMICAL EDUCATION

pubs.acs.org/jchemeduc Article

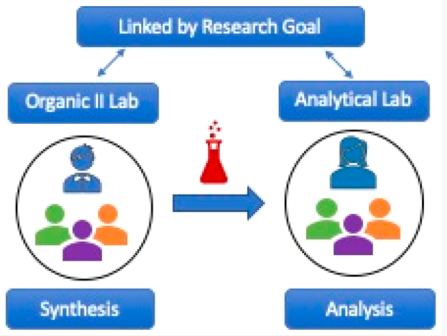
Design and Implementation of an Organic to Analytical CURE Sequence

William E. Allen, Kathryn N. Hosbein, Anthony M. Kennedy, Brandon Whiting, and Joi P. Walker*

Cite This: J. Chem. Educ. 2021, 98, 2199–2208 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: This paper describes the design and implementation of a course-based undergraduate research experience (CURE) sequence in chemistry that links a lower-division, organic chemistry course to an upper-division, analytical chemistry course. The focus of student research is on blood preservation using trehalose derivatives in order to mimic the tardigrade, a microscopic extremophile, which produces sugar molecules to survive desiccation and freezing. Students created a library of modified sugar molecules in the organic CURE and then evaluated the behavior of those molecules within membranes in the analytical CURE. The CURE sequence has been run with three student cohorts which were selected to match the demographics of all students in the course. This article details the student selection process, the course design, the faculty implementation, and revisions. Fidelity of the CURE is demonstrated with survey results. We also describe adaptation of the research courses to accommodate the COVID-19 restrictions.



KEYWORDS: *Analytical Chemistry, Organic Chemistry, Laboratory Instruction, Undergraduate Research, Second-Year Undergraduate, Upper-Division Undergraduate, Curriculum*

INTRODUCTION

Participation in undergraduate research has been identified as a high-impact practice which can lead to increased persistence in science,[1−3] improved science process skills,[4,5] and increased entry into graduate school.[6] The apprenticeship model, in which students conduct independent research projects in an individual faculty member's laboratory, is a well-established approach to providing undergraduate research experiences. However, this model is limited by an individual faculty member's laboratory program, laboratory space, and instructional commitments. Embedding research within the curriculum through course-based undergraduate research experiences (CUREs) is a recognized strategy for increasing access to research.[7,8] Students entering college may not know that research exists, and if they know that research would be beneficial, they may not know how to apply or have the confidence to approach a faculty member. This is particularly true of groups that are traditionally marginalized in science.[8] When students enroll in a course that includes research as part of the curriculum, they can engage in research without applying or being selected. In this way, CUREs can greatly increase both access and equity in research opportunities for undergraduates.[8] Nationally, science faculty members have been experimenting with such an approach, creating CUREs across the scientific disciplines. Tested models are available, and there is a growing body of literature on the efficacy of this approach, for both students and faculty.[9,10]

The Freshman Research Initiative (FRI) has implemented CUREs across multiple disciplines.[11] Investigation of the long-term effects of students in the FRI program found that students who participated in three semesters were significantly more likely than their non-FRI peers to earn a STEM degree and had a 94% probability of graduating within 6 years. The effect, however, was moderated by the number of semesters students participated in the FRI courses. FRI students that only completed 1 or 2 semesters had a predicted probability of graduating in 6 years, equivalent to non-FRI students.[12] A chemistry-focused example of broad implementation of the course-based research concept is the Center for Authentic Science Practice in Education (CASPiE).[13,14] CASPiE studies showed several benefits for students, including an increase in students' connections between science and everyday life, increased critical thinking skills, and increased engagement for women and underrepresented groups.[9,15] Research supporting chemistry-focused CUREs at the introductory and upper-division levels has seen a rise in publications indicating the communities' interest in this high-impact instructional practice.[16−19] An example of a cross-disciplinary research

Received: February 9, 2021
Revised: May 12, 2021
Published: June 16, 2021

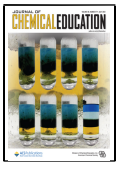


Table 1. Alignment with CURE Elements

Course Element	Organic Chemistry II Laboratory	Quantitative Analysis Laboratory
Scientific practices	Synthesis design and execution, Mass Spec, HPLC and NMR analysis of compounds	Lipid Preparation, differential scanning calorimetry, fluorescence, UV-absorption and infrared spectroscopy
Discovery	Synthesis of new compounds; adaptation of literature-based procedure required.	Interpretation of instrumental analysis
Relevance	The overarching problem that the linked CURE addresses, "How do we preserve blood for more than 42 days?", is currently being researched in the wider bioanalytical field.	
Collaboration	Students work in teams of 3−4 and considered results between teams.	Students work in teams of 3 and focused on a specific instrumental analysis.
Iteration	Teams made changes to methods and repeated syntheses.	Teams made changes to methods and repeated analyses.

project that involved students in an analytical chemistry laboratory course and students in an environmental toxicology course answering a research question that could not be fully answered by chemistry or environmental science alone was recently published, indicating an expansion of the CURE concept beyond a single course.[16]

The institution in this study, a primarily undergraduate institution (PUI), has a 6-year graduation rate of 59.0% for STEM majors and 66.8% for non-STEM majors. Given research suggesting that participation in undergraduate research over multiple semesters may increase STEM graduation rates, we have developed a 2-semester CURE sequence that bridges a lower-division organic chemistry laboratory with an upper-division analytical laboratory. The concept of this CURE sequence, i.e., a multicourse research project, was supported by research indicating a greater impact as students engage in multiple semesters of research and the need to remove barriers to research that exist for many students.[12] Within the CURE sequence, a collaborative research project focused on developing a blood preservative presented an opportunity to meet this objective. The research team consisted of an organic chemist who was working on synthesis of the target molecules and an analytical chemist conducting analysis on the ability of the molecules to displace water in the phospholipid membrane. The research project designed for the CURE sequence involved undergraduate students in research-based laboratory courses in organic chemistry and bioanalytical/biophysical chemistry, each lasting a single semester. The overarching research question for the CURE sequence, "How do we preserve blood for more than 42 days?", is currently being researched in the wider bioanalytical field.[20−22] The students were not expecting to directly answer this question, but their work contributed to the process in a fundamental way through the synthesis of analysis of potential blood preservatives.

METHODOLOGY

Collaborative Research Project

Organisms with naturally high concentrations of trehalose in their tissues tend to thrive in unusually harsh environments: extreme cold, the driest deserts, even the vacuum of space. The preservative character of trehalose is believed to arise from its ability to lodge within cell membranes and displace water molecules. By varying the linker length between trehalose and the anchor, we hypothesized that the depth of membrane penetration could be controlled, perhaps leading to preservatives that would be effective at the low concentrations suitable for clinical use with human red blood cells. Many studies have specifically focused on understanding the manner by which trehalose stabilizes the phospholipid interactions suggesting that it may penetrate the lipid and reside close to the polar headgroups of the membrane, replacing water, and subsequently hydrogen bonding to the phospholipid molecules, giving rise to a mechanism termed the "water replacement" hypothesis.[23−26]

Preliminary data comparing sucrose and its structural analogue sucralose strongly supports this hypothesis and shows that sucralose, the slightly more hydrophobic sugar, interacts with membranes in a very different manner than sucrose. This disaccharide displays unusual properties when interacting with fully hydrated model membranes of the lipid dipalmitoylphosphatidylcholine, and data indicates that sucralose induces interdigitation coupled with dehydration of the bilayer at the membrane water interface accompanied by increased spacing of the lipid headgroups.[27] A detailed study of those interactions will help researchers understand the impact of small hydrophobic changes on disaccharides and the subsequent effect on their behavior with biomembranes. The study of these modified sugar molecules should lead to insights for the development of new cell preservatives which may prove particularly useful for cryopreservation of blood. To address this research problem within the CURE sequence, students in organic chemistry created a library of substituted trehalose molecules to produce molecules with a wide range of hydrophilic and lipophilic properties which were subsequently studied in the analytical laboratory course. Both courses were designed to align with the five components of a CURE (scientific practices, discovery, relevance, collaboration, and iteration) that have been previously recommended.[27] Table 1 presents the alignment of elements of each CURE with these five recommended components.

CURE Facilities and Structure

In order to allow the organic reactions to reflux for extended periods of time, it was necessary to have a dedicated research space for the CUREs. The department identified an underutilized laboratory that could be set up as an enhanced teaching lab dedicated to research-based courses. The facility had six workstations that accommodated up to four students each with the necessary glassware for conducting the research. There was a center bench for instrumentation and a bench along the back wall where two rotary evaporators and a lyophilizer were set up. The instrumentation included a high-performance liquid chromatograph, fluorimeter, infrared spectrometer, UV−vis spectrometer, and differential scanning calorimeter.

Participants

The CURE sequence followed the recommended curriculum structure with Organic II Laboratory in the Spring and Quantitative Analysis in the Fall. This study was approved by

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

the East Carolina University Internal Review Board (16002076), and consent was obtained from all participants.

The participants for the first cohort of the CURE sequence were recruited from a pool of students from the Organic I lecture course. All students were given an informational flyer, with a box to indicate interest in the CURE (yes or no) and to provide identifying information. The CURE participants were selected from the "yes" group using matched sampling based on three parameters: major, gender (male/female), and underrepresented minority (URM) status. We recognize that gender is not a binary construct and therefore those who identify with other genders not listed as options defined by the registrar at the university have been left out of this study. URM status in this study was defined as Black, Hispanic, Native American, Alaska Natives, or two or more races.[28] Near the end of the spring semester, the analytical professor presented the research continuation in analytical chemistry. The analytical laboratory courses had a capacity of 12 students. Seven students from the organic CURE elected to continue the research sequence. The additional 5 participants were recruited from the Organic II lecture courses. All students enrolled in Organic II were given an informational flyer with a portion to indicate interest in the CURE (yes or no) and to provide identifying information. The 5 new CURE participants were selected using matched statistical sampling, based on major, gender, and URM status.

The participants for the second and third cohort were recruited from a pool of students from the Organic I lecture course. For both cohorts, an informational flyer was again provided, but rather than a simple "yes/no" students were provided a survey link with a short application designed to solicit information on student interest in the research. Applicants were asked to provide 50-word response to two questions: (1) What are your career goals? and (2) Why are you interested in the CURE? The same three parameters were used in selecting applicants; however, a preference was given to sophomore chemistry and biochemistry majors in order to ensure a sufficient applicant pool for the analytical CURE, a majors-only course.

We used a χ^2 analysis to compare all of the students recruited with those that applied. In addition, we compared those that were recruited with those that participated in the CURE. The comparisons were conducted on the basis of gender, URM status, major (STEM vs non-STEM), and GPA.

Organic CURE Design and Implementation

The Organic Chemistry Laboratory II course was offered as a corequisite for the lecture course. The organic CURE was designed to meet the learning outcomes for the Organic Chemistry Laboratory II course but in a research-focused environment based on relevant and meaningful exposure to instrumentation for research purposes (see SI for sample syllabus). Published synthetic procedures were adapted by students.[29] Student performance was evaluated using laboratory notebook checks, a formal paper, and a presentation. Table 2 outlines the course assignments and grading. The formal lab report was written in three sections: introduction, methods, and results and discussion. In an attempt to simulate collaborative writing in research, each section had a primary or lead author who collaborated with a second group member, the secondary or coauthor.

Cohort 1 was divided into groups of four students each. Target molecules for the groups differed by the number of intervening $-CH_2-$ groups in the linker (e.g., zero, one, three, five, or nine) which attached to an aromatic anchor (pyrene) to trehalose via an ester or amide bond (Figure 1). Groups typically chose to further subdivide into pairs, with each pair pursuing different routes to the desired products. Groups were responsible for all aspects of the synthesis, purification, and characterization of new molecules. Thus, all participants in the organic CURE gained experience in reaction design, extraction, TLC and HPLC, mass spectrometry (MS), and proton NMR. The success of the research conducted by each group was assessed on the basis of the completed synthesis of their target compound. The CURE lab was open access with times coordinated with the graduate teaching assistant. Students voluntarily came into lab for 1−4 additional hours each week to work up reactions, run HPLC, or work on their notebook.

Table 2. Organic CURE Graded Assignments

Assignment	Percentage
Notebook check (2)	22%
Formal lab report	
Lead author	22%
Coauthor	22%
Poster and presentation	22%
Lab practical exam	12%

Cohort 2 consisted of two course sections of 18 students each in which students worked in groups of 3. The course met twice weekly on consecutive days for 1.5 h each. Working from a common fluorescent platform (diphenylacetylene), each team chose a water-solubilizing "headgroup" and one or more membrane-anchoring "tails", based on their reading and discussion of relevant literature references (Figure 2). Construction of the preservatives introduced classic reactions like nucleophilic substitution of alkyl halides (S_N2) and Fischer esterification of carboxylic acids, in addition to more modern Pd(0)-catalyzed carbon−carbon bond formations. By meeting on two consecutive days, the need for students to have access to the lab was virtually eliminated. In addition, the time in lab was more productive. The groups were successful in synthesizing the backbone structure, which was a significant accomplishment. The final step, adding the trehalose, was not carried out due to time constraints and confusion on the part of some students, further described below.

Cohort 3 also consisted of two course sections of 18 students each in which students worked in groups of 3. The course met twice weekly on consecutive days for 1.5 h each. The synthesis shown in Figure 3 allowed for variation in chain length of both the glycoside and the imide. The "click" reaction to join the two precursors was expected to give a better yield using acetonitrile as the solvent, but groups were given the option to avoid using toxic CH_3CN if they wished. Finally, there were two possible methods for reduction of the $-NO_2$ group at the southern end of the imide, which were to be tested with a mock compound to inform the group choice.

Analytical CURE Design and Implementation

The analytical CURE was designed to meet the learning outcomes for a traditional analytical laboratory course through bioanalytical/biophysical chemistry research. Students were expected to spend 1 h in lab the day before their scheduled course time to prepare unilamellar liposomes by extrusion. The liposome preparation required 90 min the day before so that the biomembranes could rest overnight in a refrigerator, which leads to more consistent data. The course was organized

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

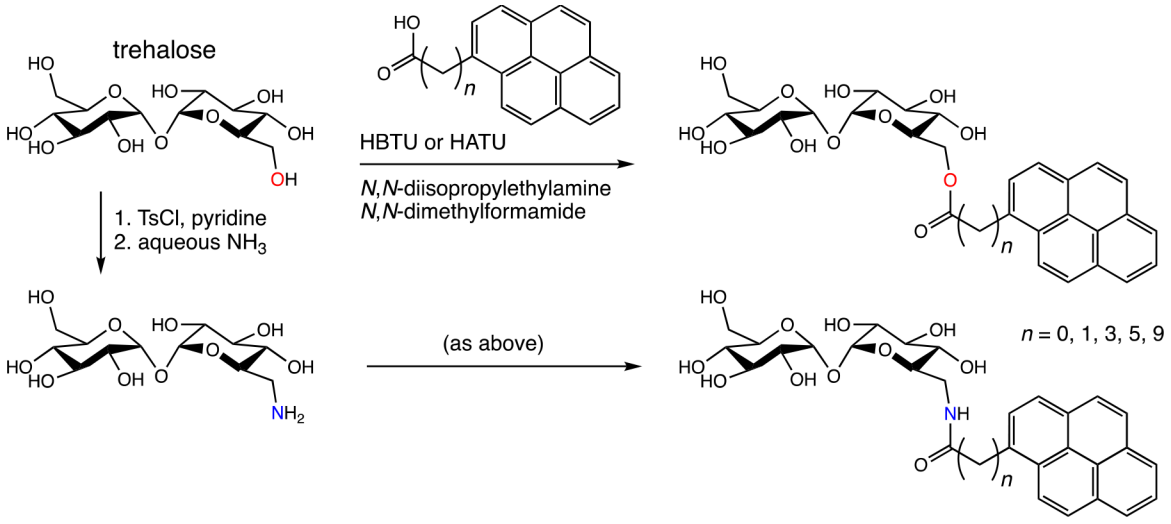


Figure 1. Cohort 1 synthesis.

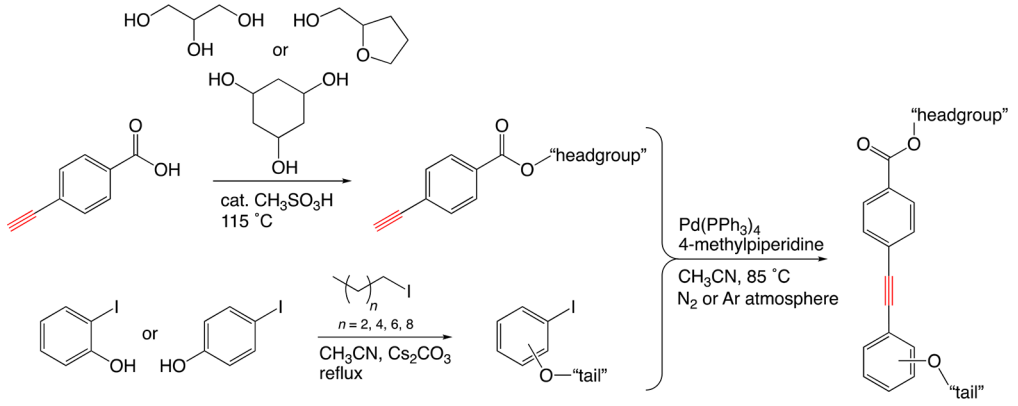


Figure 2. Cohort 2 synthesis.

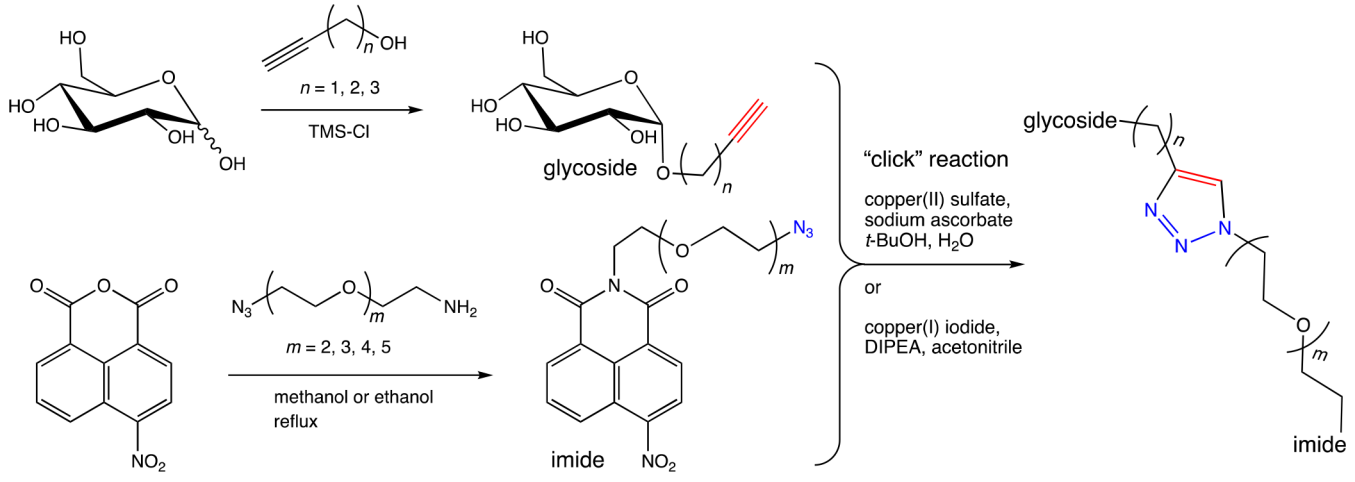


Figure 3. Cohort 3 synthesis.

around completion of four research modules that are described in Figure 4.

It was anticipated that each group would use a sugar compound prepared the previous semester in the organic CURE. Stock sugars (e.g., maltose, trehalose, sucrose, and sucralose) were available for groups that did not complete the synthesis molecules with sufficient yield to utilize in further experimentation. Table 3 outlines the course assignments and grading. The analytical course is designated as writing intensive (WI), and the CURE followed the established writing protocol by having individual students write each section of their own report in stages over the semester. A draft of each section was reviewed by the instructor, revised, and submitted for grading. The complete draft report undergoes blind peer review prior to

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

Module 1: Thermodynamic Characterization with Calorimetry: The impact of varying concentrations of sugars on liposome vesicles on liposome fatty acid chain organization and headgroup mobility can be determined using differential scanning calorimetry (DSC). Changes in the main phase transition temperature, measured using DSC, at varying substituted sugar concentrations can indicate stabilization or destabilization of one liposome phase.

Module 2: UV-Vis Absorbance Spectrophotometry: The impact of varying concentrations of sugars on liposome vesicles containing merocyanine-540 (MC540) can be observed by monitoring changes in the absorbance spectra. The optical probe MC540 is highly sensitive to lipid packing and it can provide details about changes in packing efficiency induced by additional molecules introduced to the system. These changes can be monitored above and below the transition temperature.

Module 3: Fluorescence Emission Spectrophotometry: The impact of varying concentrations of sugars on liposome vesicles containing merocyanine-540 (MC540) or laurdan can be observed by monitoring changes in the emission spectra. The optical probe MC540 is highly sensitive to lipid packing and it can provide details about changes in packing efficiency induced by additional molecules introduced to the system, whereas laurdan provides information related to the polarity near the probe. These changes can be monitored above and below the transition temperature.

Module 4: Infrared Characterization of Transitions and Hydrogen Bonding: Infrared spectroscopy may be used to follow changes in vibrational modes within the probe molecule and the lipid molecule by recording spectra at various temperatures above and below the main phase transition while at the same time varying concentrations of the probe molecule. Changes in the lipophilic region can be monitored by examining the methylene carbon hydrogen stretching region whereas potential hydrogen bonding and reorientation or disruption of headgroup packing can be followed by monitoring changes in the phosphate region.

Figure 4. Research Modules for the analytical CURE.

Table 3. Analytical CURE Graded Assignments

Assignment	Percentage
Notebook check (weekly)	24%
Research Paper Draft Sections	
Abstract	4%
Introduction	4%
Experimental	4%
Results and discussion	4%
Conclusions	4%
Peer review	10%
Final lab report	10%
Data and figure quality	16%
Presentation	20%

submission of a final report. This model for scientific writing was embedded in the analytical course 10 years ago, so the process is not unique to the CURE.

Survey Data

The Classroom Undergraduate Research Experience (CURE) survey[30] and the Laboratory Course Assessment Survey (LCAS)[31] were used in this study. It is important to stipulate that survey results are based on student self-reporting and should be interpreted with awareness of the potential bias students may have in completing survey questions.[32] The CURE survey and LCAS have been shown to provide valid and reliable data, but due to the small sample size in this study validity and reliability evidence in this specific context was not possible.[5,17,19,31]

The CURE survey was administered to cohort 1 via Qualtrics during the first and last 2 weeks of the semester in the organic CURE. The LCAS was administered to students enrolled in cohorts 1 and 2 of the analytical CURE during the last 2 weeks of the semester. It is possible for longer surveys to result in a higher percentage of nonresponse rates which can impact the overall validity of survey assessment.[32] The CURE survey is longer (46 items) in comparison to the LCAS (17 items). The decision to use the CURE survey for the organic course and the LCAS for the analytical course was based on the number of students in each of the CUREs to avoid survey fatigue.

Three sets of items were pulled from the CURE surveys for analysis: perceived learning gains of course elements, perceived gains in course benefits, and overall evaluation of the course. Learning gains (25 items) were measured on the postsurvey with a response scale ranging from "No gain or very small gain" to "Very large gain". Course benefits (21 items) and overall evaluation (4 items) were measured on the postsurvey and were on a response scale ranging from "No gain or very small gain" to "Very large gain" on a Likert scale, respectively.

The LCAS had 17 items and used a Likert scale to measure students' perceptions of three design features of laboratory courses: (1) collaboration (6 items), (2) discovery and relevance (5 items), and (3) iteration (6 items). The LCAS was designed to measure design features that make CUREs distinctive as learning experiences, based on input from experts in undergraduate research and a thorough review of research on these experiences.

RESULTS AND DISCUSSION

Participants

Student demographic information on the CURE applicants, participants, and recruitment pool is presented in the Supporting Information with the corresponding χ^2 tests. These results indicated that the CURE students were representative of the eligible student population with respect to binary gender (female/male) and URM status for all three cohorts. This was important as equal access to research was a central goal of the project. In cohort 1, 53.7% of the students enrolled in organic chemistry indicated an interest in the CURE, and there was not a significant difference between the student population and the CURE students for major or GPA. The GPA information was not considered in the CURE selection process, yet there was a significant difference in the GPA of the applicants for all three cohorts when compared to nonapplicants. Introducing the more detailed applications in cohorts 2 and 3 reduced the applicant pool to 39.5% and 38.2%, respectively. Introducing an application can be a barrier to research, and this reduced applicant pool suggests increased

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

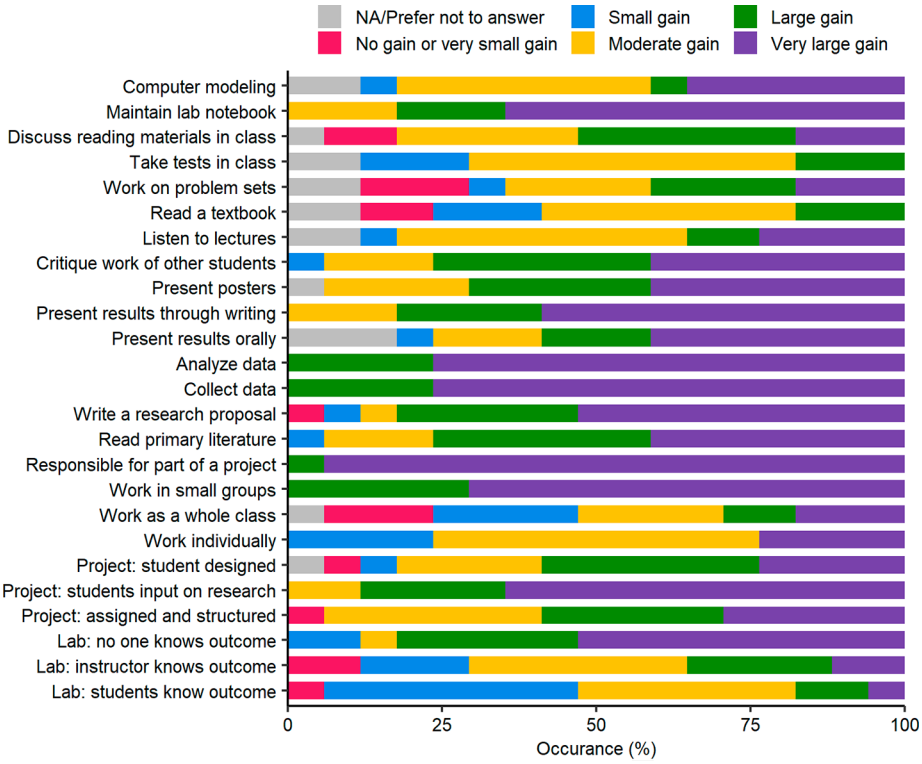


Figure 5. Perceived learning gains of course elements.

self-selection by students. Comparison of the applicant vs nonapplicants for cohort 2 showed that significantly more STEM majors and high-GPA students applied for the CURE; this trend continued with cohort 3 for GPA, but not for STEM majors. There was also a significant difference with respect to major and GPA for the CURE students compared to the student population for cohorts 2 and 3. The preferential selection of chemistry majors and the self-selection of the applicants were responsible for this difference.

The preferential sampling in combination with the increase in CURE participants, 36 rather than 24, resulted in 21 applicants for cohort 2 of the analytical CURE. The 12 participants were selected using matched statistical sampling, based on gender, URM status, and major. In anticipation of continued applicants sufficient to fill two sections of the analytical CURE, a second section was created for Fall 2020. We had 24 students express interest and enroll in the analytical CURE sections; however, with the uncertainty of online courses due to COVID-19, 10 students withdrew, 5 from each section, from the analytical CUREs. We report on cohort 3 for the analytical CURE described (N = 7); the second CURE section was a pilot study that is still in development.

Organic CURE

As judged by mass spectrometry, all six groups in cohort 1 were initially successful in covalently attaching an aromatic anchor (pyrene) to trehalose via an ester bond. Yields for this "single-step" approach to the targets were low (<30%), which was attributed to the poor nucleophilicity of the trehalose −OH units. Four student teams subsequently modified trehalose with more-nucleophilic $-NH_2$ groups but were unable to couple the saccharides to pyrene before the semester concluded. For the ester products, even with the lipophilic anchor present, participants found that the compounds retained much of the water solubility of trehalose itself. This made their isolation by extraction challenging, further lowering the yields. Unfortunately, the light sensitivity of pyrene, which is essential to its desirable fluorescent properties, also appeared to render the anchored trehalose molecules prone to degradation. Most did not persist long enough to be purified by HPLC.

Cohort 2 participants were more successful in isolating and characterizing stable final compounds. We attributed this to the revised course format of meeting twice per week on consecutive days. This allowed the teams to run reactions overnight and work them up immediately upon completion, minimizing the likelihood of compound degradation while providing the cohort with a more consistent sense of forward progress. On the basis of NMR, all groups created a fluorescent diarylacetylene backbone featuring a simple headgroup which was to serve as a model of trehalose. Teams ran out of time before they could repeat the syntheses with trehalose itself. In at least one case, a team misunderstood the role of the model headgroup, thinking it was the actual sugar. This resulted in apparently inexplicable solubility issues for the analytical CURE. An unexpected finding of the diarylacetylene synthesis was that the presence of a long-chain ether group at the ortho position led to restricted rotation about the central alkyne. This was revealed by the appearance of two sets of peaks in the proton NMR spectrum, which the student researchers immediately recognized as odd because prior TLC analysis of the compound had shown a single spot. The students synthesized these seemingly conflicting results to correctly conclude that the single compound must exist as two rotational isomers.

All groups in cohort 3 had isolated the glycoside and the naphthalimide and were beginning to complete the "click" reaction and to practice the reduction reaction with mock compounds by week 8 of the course (just before the spring

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

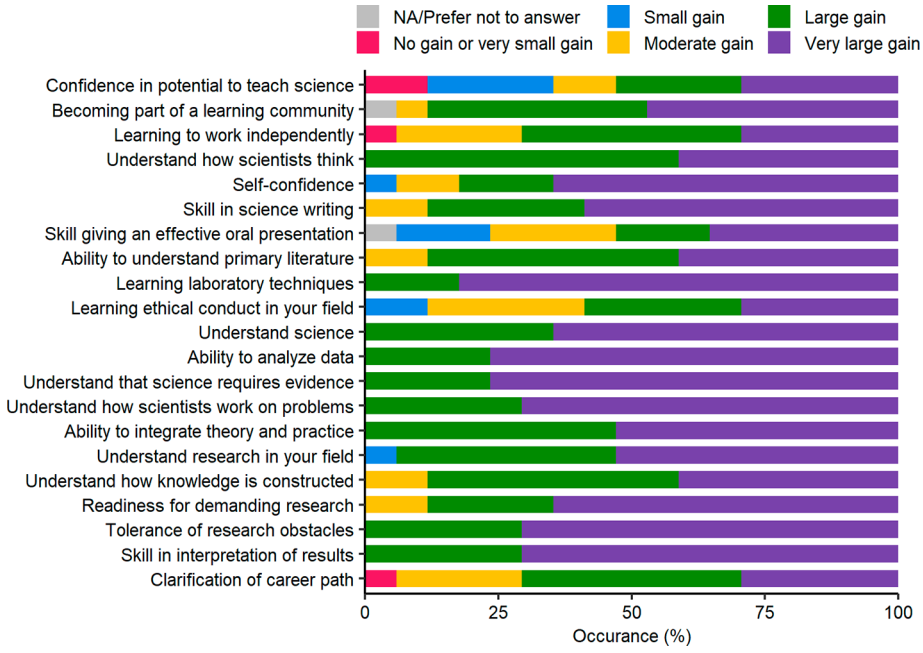


Figure 6. Perceived gains in course benefits.

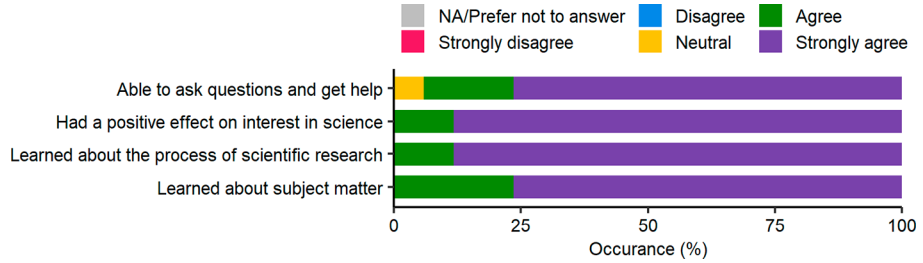


Figure 7. Overall evaluation of the course.

break week). The students did not return to campus due to the pandemic; however, this was a significant amount of synthesis for the groups to have completed. Implementation of a 20 min group discussion made a tremendous difference in group dynamics and productivity. Each week, the first lab meeting began with a review of the previous week's accomplishments, generating an outline for next steps that resulted in a clear plan of where to go next. Graduate teaching assistants (GTAs) observed that the group meeting was helping scientific language development and use which is something we will investigate in future studies. Each group shared one notebook with rotating responsibility for upkeep. This allowed more time for lab work, as only one person from the group was tasked with maintaining the notebook during a given lab meeting. Students were able to maintain continuity and complete their lab report, and group presentations took place via a web conference.

In hindsight, some organic synthesis targets were too ambitious given the requirements of the analytical CURE. The primary need of the analytical lab was water solubility, which was found to be poor for teams that chose lengthy linkers and/or tails. Additional issues arose from low purities and quantities of the synthetic compounds, which were limited, in part, by access to the CURE lab's single HPLC instrument. The organic researcher (W.E.A.) routinely has more undergraduate than graduate researchers. Teaching the CUREs has prompted him to focus on the design of projects that are accessible to undergraduate researchers. The graduate student's research (W.E.A.'s lab) benefitted significantly from the broad spectrum of work completed in the CURE, which saved months of work by an individual.

CURE Survey

Figure 5 presents the student responses to the perceived learning gains of course elements. Design features of the CURE, such as *a lab or project where no one knows the outcome* and *a project in which students have some input into the research process* showed large to very large gains by more than 75% of the respondents. Other course elements, such as, *become responsible for a part of the project*, *collect data*, and *analyze data*, showed large to very large gains by 100% of the CURE students. These results indicate that students perceived the elements of research to be present in the course and, in addition, perceived learning gains related to the course elements defined for a CURE (Table 1).

Figure 6 presents the student responses to the course benefit items. Almost all of the items had 75−100% large to very large perceived gains reported by the CURE students. Areas where gains were weak to moderate are interesting in terms of elements that might be added to the CURE sequence, such as *learning ethical conduct in your field*. Other elements, such as *learning to work independently* and *take tests in class*, were explicitly removed from the course, so the students' reporting small to moderate gains is not surprising. One area of note is

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

Table 4. LCAS Results for the Analytical CURE Cohorts 1 and 2 (N = 24) Compared to Literature Values

		Analytical CURE		Cruz et al., 2020		Corwin et al., 2015	
	Range of Scores	Mean	SD	Mean	SD	Mean	SD
Collaboration	6−24	22.04	2.44	17.25	4.09	21.11	3.20
Discovery	5−30	24.25	5.32	22.08	4.74	24.35	4.04
Iteration	6−36	29.00	5.12	25.87	6.18	28.71	4.15
Overall score	17−90	75.29	8.12	65.19	12.22	75.10	8.67

the no gain to moderate gain response on *skill in how to give an effective oral presentation*. The presentations were the last day of class, and many of the students had completed the survey prior to giving their presentations. The presentations were overall excellent and demonstrated an exceptional command of organic chemistry with phrases such as "we had to use a different solvent for the extraction to reduce loss of product" or the explanation of erroneous peaks in the NMR spectrum as being "due to an unexpected side product".

Similar results were reported in a study that utilized CURE survey data for comparing the students in a physical chemistry CURE (N = 22) to a national data set of students. The authors report statistically significant differences for CURE students in three course benefit items, *tolerance for obstacles*, *readiness for research*, and *skill inscience writing*.[17] We see large to very large gains for over 75% of the responses in these three areas as well.

Finally, Figure 7 presents the overall course evaluation items, where all four have 75−100% agree to strongly agree responses. This level of response certainly supports the concept of course-based research experiences and specifically the embedding of research into the curricular structure.

Analytical CURE

The groups in cohort 1 working with maltose and trehalose incorporated merocyanine 540 into their lipid membranes for fluorescence and absorption experiments. By the end of the semester, it was clear that the interactions students were observing were highly complex and difficult to explain. Nevertheless, several groups spent time looking for insight in the published literature and were able to hypothesize reasonable explanations based on the interaction of the compound with the liposome. In addition, difficulty dissolving modified sugars and obtaining suitable data was a problem. The students worked as well as could be expected in trying to overcome the difficulties, and in the end, each group obtained enough meaningful data for a group presentation and a final course paper. The plan was for groups to rotate through the four course modules (Figure 4: differential scanning calorimetry, fluorescence, UV−vis absorption, and infrared spectroscopy); however, it was clear early in the semester that this plan was overly ambitious, and students spent the semester focused on one or two of the techniques while also being briefly exposed to the other techniques. This change was dictated by the students themselves who worked to pull everything possible out of the data which was then used in designing follow-up experiments.

Cohort 2 ran into the same issues with solubility which were further complicated by a general unwillingness of the group to prepare the liposomes early. Preparing the liposomes during the lab time meant less time on the instrumentation, and the liposomes were not ideal since the biomembranes could not rest overnight in a refrigerator, which leads to more consistent data. This was frustrating to the faculty researcher but prompted us to adjust the course schedule in the future to explicitly include the 1 h biomembrane preparation and not rely on students to come into the lab on their own time.

Cohort 3 was directly impacted by the COVID-19 restrictions. The Fall 2020 semester start date was moved two weeks earlier in August with a goal of in-person classes. The university was forced to close two weeks later. There was an exception to the "online only" for undergraduate researchers, which we made sure included CUREs. Before the semester began, 5 students had withdrawn from the CURE. When asked, the remaining 7 agreed to continue the CURE with in-lab research. Working in two pairs and a group of three, individual students alternated preparing the biomembranes or conducting analyses. This system meant no more than one group member was in the lab on a given day. This system eliminated groups working directly together; the students had to communicate with each other explicitly and provide details of their work, so that the team could move forward. The faculty researcher shifted the project away from using the organic CURE products, to analysis on the 4 sugars, maltose, sucrose, sucralose, and trehalose. The goal was that each team would work on a single sugar, share data, and draw conclusions about the interactions with the membranes. Using calorimetry, it was determined that sucrose had little to no interaction, so this sugar was not studied further. The students then conducted UV−vis and fluorescence experiments on the remaining sugars. This work replicated research conducted in the faculty researcher's laboratory with concentration variations. The data collected in the CURE conflicted with previous data but was of such high quality that this has prompted further investigation. As we continue this CURE sequence, we will develop a system to establish yield, purity, and solubility of the compounds following completion of the organic CURE to facilitate planning for the analytical CURE.

LCAS

The subscores from the LCAS in this study were compared to those reported in the literature.[18,31] Table 4 summarizes the LCAS scores from the analytical CUREs and two published studies.

The LCAS was designed and its data validated by Corwin and colleagues (2015).[31] From their study, it was found that the LCAS succeeded in differentiating between CUREs and traditional laboratory courses, specifically around the CURE elements of discovery, relevance, and iteration. Their results indicated that the LCAS was useful for characterizing and comparing laboratory courses along with being able to determine the relative importance of the three CURE design features.[31] There is good agreement of the scores for the analytical CURE in this study with the LCAS scores by Corwin et al. which indicates that the analytical CURE design was consistent with published work. The second comparison is to results reported by Cruz and colleagues (2020).[18] In their study, a CURE model with specific objectives relating to synthetic chemistry was integrated into the latter half of a

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208

traditional organic laboratory course. After the students had participated in a number of scripted experiments to become familiar with basic synthetic chemistry techniques, they then participated in the limited research portion of the laboratory course. The LCAS mean scores from the analytical CURE in this study were higher than those from Cruz et al. which was to be expected when comparing a single module to implementation of a two-semester sequence. This conclusion was anecdotal as there was no statistical analysis done between the comparison LCAS scores. What can be reflected though is that LCAS scores were closely representative of each other, supporting our claim that students within the CURE sequence had experiences similar to those in other CUREs.

Lessons Learned

Participant Selection. An application process, such as those included in cohorts 2 and 3, imposes a potential barrier to non-STEM majors. In bringing research from a lower-level course to an upper-level course, there is a need to have enough chemistry majors in the lower-level CURE to continue into the upper-level CURE.

Course Structure/Schedule. The organic CURE was improved by splitting the 3 hour lab time over two consecutive days, allowing time in the first lab meeting of each week for reflection and planning, and a shared notebook between the group members with rotating responsibility. The need for liposome preparation prior to the actual lab meeting was found to best be designated each week to a specific student.

Synthesis Authentication. For purity, yield, and solubility, sufficient yield of the trehalose compounds was rarely achieved in the organic CURE, such that the synthesis needs to be simplified. Alternatively, multiple teams could prepare the same compound and combine products. A key distinction between organic chemistry and analytical chemistry is the need for high-purity compounds and reasonable water solubility.

Team Science. Adding the weekly meeting to the CURE was found to have multiple benefits which are now being studied through a team science lens. Interviews with the faculty suggest that there was improved group communication, better use of laboratory time, and increased research productivity.

Research Designation. When the university moved to online learning, research courses were allowed to continuing meeting in-person. The CUREs were designated as research courses, which allowed regional students and those in off-campus housing to continue their research courses.

LIMITATIONS AND IMPLICATIONS

The results are limited by the number of students enrolled in the CURE sections. While the CURE survey and LCAS have been shown to provide valid and reliable data in other samples,[5,17,19,31] with the small sample size, validity and reliability evidence of the CURE survey and LCAS data in this specific context was not possible. While this implies caution, it is important to note that the CURE survey has been used nationally in a wide range of educational contexts, and the results in this research are aligned with other CUREs. Although we made a significant effort to remove barriers to participation in research, the students did self-select into applicant pool which does limit the generalizability of the survey results.

CUREs provide a path for more undergraduate students to engage in authentic research. Over three years, this project has provided research experiences to 96 organic students and 36 analytical students. It is important to recall that the CURE students were selected on the basis of reported gender, major, and URM status from a large pool of applicants in an effort to provide research experience to students with diverse backgrounds and academic potential. While the students in the CURE did self-select, common barriers to participation in research were mitigated.[33,34]

CUREs are typically limited to a single-semester experience, whereas independent research experiences may evolve over multiple academic semesters or even years. Previous research suggests that the greatest benefit is seen with at least three semesters of research experience.[12] Research collaboration between faculty provides opportunities to develop multidisciplinary research experiences that students could access in multiple courses as they progress in their program of study. A multicourse CURE which allows student to continue the research project within their course of study provides the opportunity for more students to have the extended experience of this high-impact practice.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.1c00129.

Organic CURE sample syllabus (PDF)
Analytical CURE sample syllabus (PDF)
Demographics of students (PDF, DOCX)

AUTHOR INFORMATION

Corresponding Author

Joi P. Walker − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858, United States;* orcid.org/0000-0001-7783-4706; Email: walkerjoi15@ecu.edu

Authors

William E. Allen − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858, United States;* orcid.org/0000-0003-0650-9441

Kathryn N. Hosbein − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858, United States;* orcid.org/0000-0001-6771-3660

Anthony M. Kennedy − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858, United States*

Brandon Whiting − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jchemed.1c00129

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by a grant from the National Science Foundation (EHR DUE: 1712141). We thank all the students that participated in the CURE experience; their willingness to try something new has allowed us to implement CUREs throughout the chemistry curriculum and the university.

REFERENCES

(1) Nagda, B. A.; Gregerman, S. R.; Jonides, J.; von Hippel, W.; Lerner, J. S. Undergraduate Student-Faculty Research Partnerships Affect Student Retention. *Rev. High. Educ.* **1998**, *22* (1), 55−72.

(2) Hurtado, S.; Eagan, M. K.; Cabrera, N. L.; Lin, M. H.; Park, J.; Lopez, M. Training Future Scientists: Predicting First-Year Minority Student Participation in Health Science Research. *Res. High. Educ.* **2008**, *49* (2), 126−152.

(3) Barlow, A. E. L.; Villarejo, M. Making a Difference for Minorities: Evaluation of an Educational Enrichment Program. *J. Res. Sci. Teach.* **2004**, *41* (9), 861−881.

(4) Kardash, C. M. Evaluation of Undergraduate Research Experience: Perceptions of Undergraduate Interns and Their Faculty Mentors. *J. Educ. Psychol.* **2000**, *92* (1), 191−201.

(5) Lopatto, D. Survey of Undergraduate Research Experiences (SURE): First Findings. *Cell Biol. Educ.* **2004**, *3* (4), 270−277.

(6) Hathaway, R. S.; Nagda, B. A.; Gregerman, S. R. The Relationship of Undergraduate Research Participation to Graduate and Professional Education Pursuit: An Empirical Study. *J. Coll. Stud. Dev.* **2002**, *43* (5), 614−631.

(7) National Research Council. *Discipline-Based Education Research: Understanding and Improving Learning in Undergraduate Science and Engineering. A Report Prepared by the Committee on the Status, Contributions, and Future Directions of Discipline-Based Education Research Board on Science Education, Division of Behavioral and Social Sciences and Education*; Singer, S. R., Nielsen, N. R., Schweingruber, H. A., Series Eds.; National Academies Press: Washington, DC, 2012.

(8) Bangera, G.; Brownell, S. E. Course-Based Undergraduate Research Experiences Can Make Scientific Research More Inclusive. *CBE-Life Sci. Educ.* **2014**, *13* (4), 602−606.

(9) Linn, M. C.; Palmer, E.; Baranger, A.; Gerard, E.; Stone, E. Undergraduate Research Experiences: Impacts and Opportunities. *Science* **2015**, *347* (6222), 1261757.

(10) Committee for Convocation on Integrating Discovery-Based Research into the Undergraduate Curriculum; Division on Earth and Life Studies; Division of Behavioral and Social Sciences and Education; National Academies of Sciences, Engineering, and Medicine. *Integrating Discovery-Based Research into the Undergraduate Curriculum: Report of a Convocation*; National Academies Press: Washington, D.C., 2015.

(11) Freshman Research Initiative. https://cns.utexas.edu/fri (accessed Oct 30, 2016).

(12) Rodenbusch, S. E.; Hernandez, P. R.; Simmons, S. L.; Dolan, E. L. Early Engagement in Course-Based Research Increases Graduation Rates and Completion of Science, Engineering, and Mathematics Degrees. *Life Sci. Educ.* **2016**, *15* (2), ar20.

(13) Szteinberg, G. A. Long-Term Effects of Course-Embedded Undergraduate Research: The CASPiE Longitudinal Study. Unpublished Dissertation, Purdue University, Indiana, 2012.

(14) Szteinberg, G. A.; Weaver, G. C. Participants' Reflections Two and Three Years after an Introductory Chemistry Course-Embedded Research Experience. *Chem. Educ. Res. Pract.* **2013**, *14* (1), 23−35.

(15) Chase, A. M.; Clancy, H. A.; Lachance, R. P.; Mathison, B. M.; Chiu, M. M.; Weaver, G. C. Improving Critical Thinking via Authenticity: The CASPiE Research Experience in a Military Academy Chemistry Course. *Chem. Educ. Res. Pract.* **2017**, *18* (1), 55−63.

(16) Lau, J. K.; Paterniti, M.; Stefaniak, K. R. Crossing Floors: Developing an Interdisciplinary CURE between an Environmental Toxicology Course and an Analytical Chemistry Course. *J. Chem. Educ.* **2019**, *96* (11), 2432−2440.

(17) Williams, L. C.; Reddish, M. J. Integrating Primary Research into the Teaching Lab: Benefits and Impacts of a One-Semester CURE for Physical Chemistry. *J. Chem. Educ.* **2018**, *95* (6), 928−938.

(18) Cruz, C. L.; Holmberg-Douglas, N.; Onuska, N. P. R.; McManus, J. B.; MacKenzie, I. A.; Hutson, B. L.; Eskew, N. A.; Nicewicz, D. A. Development of a Large-Enrollment Course-Based Research Experience in an Undergraduate Organic Chemistry Laboratory: Structure−Function Relationships in Pyrylium Photoredox Catalysts. *J. Chem. Educ.* **2020**, *97* (6), 1572−1578.

(19) Pagano, J. K.; Jaworski, L.; Lopatto, D.; Waterman, R. An Inorganic Chemistry Laboratory Course as Research. *J. Chem. Educ.* **2018**, *95* (9), 1520−1525.

(20) Walmagh, M.; Zhao, R.; Desmet, T. Trehalose Analogues: Latest Insights in Properties and Biocatalytic Production. *Int. J. Mol. Sci.* **2015**, *16* (12), 13729−13745.

(21) Reid, T. J.; LaRussa, V. F.; Esteban, G.; Clear, M.; Davies, L.; Shea, S.; Gorogias, M. Cooling and Freezing Damage Platelet Membrane Integrity. *Cryobiology* **1999**, *38* (3), 209−224.

(22) Diez-Silva, M.; Dao, M.; Han, J.; Lim, C.-T.; Suresh, S. Shape and Biomechanical Characteristics of Human Red Blood Cells in Health and Disease. *MRS Bull.* **2010**, *35* (5), 382−388.

(23) Crowe, J. H.; Crowe, L. M.; Chapman, D. Preservation of Membranes in Anhydrobiotic Organisms: The Role of Trehalose. *Science* **1984**, *223* (4637), 701−703.

(24) Crowe, L. M.; Crowe, J. H. Solution Effects on the Thermotropic Phase Transition of Unilamellar Liposomes. *Biochim. Biophys. Acta, Biomembr.* **1991**, *1064* (2), 267−274.

(25) Golovina, E. A.; Golovin, A.; Hoekstra, F. A.; Faller, R. Water Replacement Hypothesis in Atomic Details: Effect of Trehalose on the Structure of Single Dehydrated POPC Bilayers. *Langmuir* **2010**, *26* (13), 11118−11126.

(26) Pennington, E. R.; Day, C.; Parker, J. M.; Barker, M.; Kennedy, A. Thermodynamics of Interaction between Carbohydrates and Unilamellar Dipalmitoyl Phosphatidylcholine Membranes: Evidence of Dehydration and Interdigitation. *J. Therm. Anal. Calorim.* **2016**, *123* (3), 2611−2617.

(27) Auchincloss, L. C.; Laursen, S. L.; Branchaw, J. L.; Eagan, K.; Graham, M.; Hanauer, D. I.; Lawrie, G.; McLinn, C. M.; Pelaez, N.; Rowland, S.; Towns, M.; Trautmann, N. M.; Varma-Nelson, P.; Weston, T. J.; Dolan, E. L. Assessment of Course-Based Undergraduate Research Experiences: A Meeting Report. *Cell Biol. Educ.* **2014**, *13* (1), 29−40.

(28) Women, Minorities, and Persons with Disabilities in Science and Engineering. NSF—National Science Foundation, 2019. https://ncses.nsf.gov/pubs/nsf19304/digest (accessed Feb 1, 2021).

(29) Grasso, G. I.; Gentile, S.; Giuffrida, M. L.; Satriano, C.; Sgarlata, C.; Sgarzi, M.; Tomaselli, G.; Arena, G.; Prodi, L. Ratiometric Fluorescence Sensing and Cellular Imaging of Cu2+ by a New Water Soluble Trehalose-Naphthalimide Based Chemosensor. *RSC Adv.* **2013**, *3* (46), 24288.

(30) CURE Survey. Grinnell College. https://www.grinnell.edu/academics/areas/psychology/assessments/cure-survey (accessed Apr 29, 2017).

(31) Corwin, L. A.; Runyon, C.; Robinson, A.; Dolan, E. L. The Laboratory Course Assessment Survey: A Tool to Measure Three Dimensions of Research-Course Design. *Cell Biol. Educ.* **2015**, *14* (4), ar37−ar37.

(32) Porter, S. R.; Whitcomb, M. E.; Weitzer, W. H. Multiple Surveys of Students and Survey Fatigue. *New Dir. Institutional Res.* **2004**, *2004* (121), 63−73.

(33) Woodin, T.; Smith, D.; Allen, D. Transforming Undergraduate Biology Education for All Students: An Action Plan for the Twenty-First Century. *CBE Life Sci. Educ.* **2009**, *8* (4), 271−273.

(34) Wei, C. A.; Woodin, T. Undergraduate Research Experiences in Biology: Alternatives to the Apprenticeship Model. *CBE-Life Sci. Educ.* **2011**, *10* (2), 123−131.

https://doi.org/10.1021/acs.jchemed.1c00129
J. Chem. Educ. 2021, 98, 2199−2208