

Electrochemical Quantification of Acetaminophen: An Engaging Cyclic Voltammetry Laboratory for the Quantitative Analysis Course

Nathan T. Hart, Weldon C. Lane, and Linda de la Garza*



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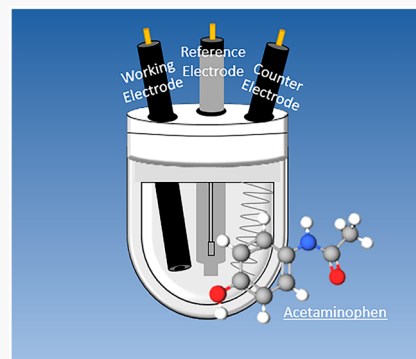
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Supporting Information

ABSTRACT: An engaging, simple, and cost-effective laboratory experiment has been implemented at our institution to teach undergraduate chemistry students about cyclic voltammetry and electrochemistry in general. This experiment involves the application of cyclic voltammetry to analyze a sample of acetaminophen (APAP) with the objective of determining the mass of APAP in a tablet of over-the-counter medication. During five semesters, students working in groups of typically four students each, carried out the experiment as part of their coursework in the laboratory. Seven out of ten groups reported results containing the expected value of 500 mg APAP per tablet in their calculated 95% confidence intervals. Students completed a 10-question quiz at the beginning of the semester and a similar one at the end of the semester. The scores of pre- and postcourse evaluations, which include 10 questions on basic general chemistry quantitative concepts, had an average percent change of 99.2% after, from a 50.7% average percent change before, laboratory implementation. The growth in normalized learning gains in classes performing this experiment also increased by 10.8%.

KEYWORDS: Second Year Undergraduate, Analytical Chemistry, Laboratory Instruction, Problem Solving, Electrochemistry



INTRODUCTION

Electrochemistry is an important topic in undergraduate chemistry programs,^{1,2} but students may find the subject difficult and subsequently lose interest in it. The laboratory portion of the quantitative analysis course often includes experiments such as redox and conductometric titrations, and it could include the electrochemical analysis of several substances, including natural³ and pharmaceutical compounds such as ascorbic acid,⁴ iron supplements,⁵ and acetaminophen (APAP).^{6,7} The quantification of APAP has been explored in undergraduate laboratories by several techniques such as colorimetry,⁸ spectrophotometry,^{9–11} and in complex samples by ¹H NMR¹² and liquid chromatography.^{13,14} Measuring APAP content in over-the-counter medications is important due to how frequently it is used as an analgesic and antipyretic drug, and given the APAP toxicity, since at higher dosages becomes hepatotoxic and genotoxic, the correct concentration of APAP in the medication is of paramount importance.^{15–17} The relevance of this analysis is also highlighted by the recent reports on the development of specific and stable electrodes for the electrochemical sensing of APAP with possible applications in pharmaceutical quality control.^{18,19}

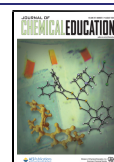
To increase student engagement in the quantitative analysis laboratory, we have decided to implement a laboratory experiment tailored to the interests of our specific student body. With many of our undergraduate chemistry students interested in attending pharmacy school, we believe that analyzing a well-known over-the-counter medication is a way

to introduce students to electrochemistry topics which would be interesting and relevant to their career goals.^{20,21} This laboratory experiment introduces students to electrochemistry topics and the cyclic voltammetry (CV) technique^{22,23} with the quantitative analysis of a sample of an over-the-counter medication.^{24,25} Previous reports of APAP quantification using CV have been suggested for advanced undergraduate courses such as instrumental analysis, and have not been related to student learning gains.^{6,7} Herein, we report a laboratory experiment concerning the quantification of APAP using CV, which has been tested by undergraduate students throughout several sections of the second-year quantitative analysis course yielding accurate results. Furthermore, given that laboratory experiences are extremely important for the learning process of chemistry topics, the impact of the implementation of this laboratory in student's learning gains was evaluated.^{26–28} Basic concepts covered in the experiment are oxidation, reduction, and types of electrodes (indicator and reference electrodes). In addition, students learn CV applications in quantitative analysis, as this technique allows the experimenter to directly quantify substances which

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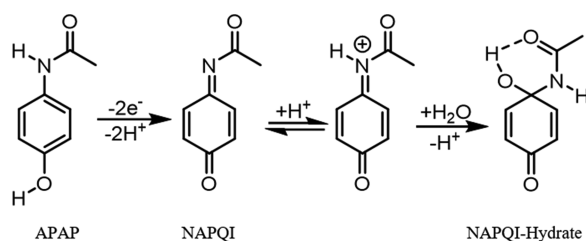
undergo oxidation, reduction, or both. In this experiment, students determine the anodic peak current (i_p) from a voltammogram and use it along with a calibration curve to determine the mass of APAP contained in a single tablet of medication.

The Randles-Sevcik equation²⁹ (1) directly relates the concentration of the solution to the peak current which is produced as a result of analysis by CV:

$$i_p = (2.69 \times 10^5) n^{3/2} A D^{1/2} \nu^{1/2} C \quad (1)$$

where i_p is peak current (amperes), A is area (cm^2), D is the diffusion constant (cm^2/sec), ν is scan rate (V/sec), n is the number of electrons transferred, and C is concentration (mol/mL). This equation only applies to reversible systems in which oxidation and reduction are both possible. At low pH, the oxidation of APAP to *N*-acetyl-*p*-quinoneimine (NAPQI) rapidly yields the hydrated NAPQI form (NAPQI-Hydrate) as shown in Scheme 1.^{6,30} Thus, the oxidized compound is

Scheme 1. Oxidation Mechanism of APAP



rapidly removed, and no reverse peak is observed. This is known as an EC mechanism, where the redox system is perturbed by a following chemical reaction, which in the case of APAP, prevents the presence of the oxidized form and thus the appearance of the corresponding cathodic current.³¹

For the two-electron oxidation of APAP, the i_p is still directly proportional to the concentration the solution, and the i_p data from the sample voltammogram can be used to determine the mass of APAP per tablet.

The student's learning objectives for the laboratory are the following:

- identify working, auxiliary, and reference electrodes
- assemble a three-electrode electrochemical cell
- run a cyclic voltammetry experiment
- identify oxidation and reduction processes
- read a voltammogram and use data in calculations
- perform a percent by weight calculation

Additionally, students include in their reports a discussion comparing their results to the expected mass content of APAP in the tablet and include possible factors affecting their data.

With many undergraduate chemistry students interested in pharmacy and medical school, the analysis of an over-the-counter medication is an interesting and relatable way to introduce students to electrochemistry and to keep them engaged in the quantitative analysis course. In addition, due to the relative ease of conducting a CV experiment, an experiment with a low chance of user error is ideal for undergraduate students as well as novice students in performing electrochemical experiments. For our classes, there was an increased student engagement in the course, resulting in improved learning outcomes as demonstrated with the pre- and postevaluation's scores for classes before and after laboratory

implementation. Students completed a 10 question quiz on general chemistry quantitative concepts at the beginning of the semester and a similar one at the end of the semester. Pre- and postscores of these quizzes showed higher percent change (+99.2% change) for the five semesters that included this laboratory, than for two semesters prior (+50.7% change) to its implementation in the course. The normalized gain scores are often used as metric for changes in student performance; they are calculated as the difference between post- and pretest divided by the difference between the maximum value and the pretest score.^{32,33} In our evaluations, the normalized gain scores yielded a 0.366 average value after laboratory implementation versus 0.259 average value before implementation. These positive changes indicate that the analysis of an over-the-counter medication is an effective laboratory experience to introduce electrochemical techniques in the quantitative analysis course while contributing to an encouraging impact in the student's overall learning gains.

SETTING

This study was conducted at Valdosta State University (VSU), a regional comprehensive institution of the University System of Georgia which currently serves about 11,000 students in the southeastern United States. The data reported involves students enrolled in the quantitative analysis course offered by the VSU Chemistry Department. The class meets weekly for the laboratory (3 h); students work individually for the first 6 weeks of the course in a series of analyses with acid–base titrations and gravimetric analysis. After that, laboratories are completed in groups of usually four students, including a conductometric titration, spectroscopy, and liquid chromatography experiments, and now a CV experiment. Students submit individual laboratory reports in an online notebook system including an introduction, procedure, observations, results, and conclusions.

EXPERIMENT

Equipment and Operating Specifications

A BASi Epsilon potentiostat and C3 Cell stand (with accompanying BASi software) are used to carry out the CV measurements in a glass cell vial (MF-1208, BASi). The working electrode is a 3.00 mm diameter glassy carbon electrode (MF-2012, BASi). The auxiliary electrode is a platinum wire, and voltages are measured against an Ag/AgCl (3 M NaCl) reference electrode. Nitrogen is continuously bubbled into the solution when the cell is not in use in order to prevent oxygen from entering the solution. The scan settings are initial potential, 0 V; switching potential, 1 V; ending potential, 0 V; scan rate, 40 mV/s.

Chemicals

Citric acid (CAS 77-92-9, Alfa Aesar Citric Acid, 99+%) and Na_2HPO_4 (CAS 7558-79-4, Fisher Scientific, 100%) and distilled water are used to prepare the McIlvaine⁶ buffer solution at $\text{pH } 2.42 \pm 0.05$. Samples analyzed for acetaminophen content were Tylenol Extra Strength tablets (500 mg) purchased from a local retail establishment. The calibration curve was obtained from standard solutions prepared with 4-acetamidophenol (CAS 103-90-2, Acros Organics, 98%) in the buffer solution at $\text{pH } 2.42$. Ferrocenemethanol (CAS 1273-86-5, Alfa Aesar, hydroxymethylferrocene, 97%) was used as reference.

Procedure

In the second-half portion of our course, students work in groups in laboratory rotations. Since two other laboratories include the building of calibration curves, the calibration curve data are provided to students in this experiment. The experiment and calculations can be carried out in one 3-h laboratory session by a group of four students, but several groups could be accommodated given the rapid sample analysis time and setup. The student group prepares the electrodes and materials needed to assemble the three-electrode electrochemical cell and makes 100 mL of buffer solution ($\text{pH } 2.42 \pm 0.5$). The buffer solution is then placed in the electrochemical cell, and a CV run is done as the "blank." After running the "blank" solution, 0.025–0.030 g of crushed tablet sample are dissolved in 50 mL of buffer solution, and another CV run is completed and labeled as a "sample" run. The voltammogram shows an oxidation peak (irreversible) at around 0.80 V vs Ag/AgCl. Two more sample runs may be performed, cleaning the working electrode before each run. A small amount of ferrocenemethanol is added to the sample solution and a CV run is done and saved as "sample + FcM". The "sample + FcM" run shows new peaks assigned to the ferrocenemethanol/ferrocenium couple, with reversible CV behavior and a midpoint potential of 0.22 V. The APAP oxidation peak appeared again at around 0.80 V. The resulting I_{pa} for the "sample run" is recorded and applied to the calibration curve to determine the concentration of APAP in the solution in mg/mL, and the statistical information is obtained using the LINEST function in Excel to calculate the standard error.³⁴ The students then determine the percent by weight of APAP in their sample. With the given weight of a tablet, they proceed to calculate the mass of APAP per tablet and the 95% confidence interval.

HAZARDS

The instructor approves the experimental setup before the CV runs. Standard chemical safety procedures are followed, including the use of proper laboratory clothing, safety goggles, and fume hoods. Pharmaceuticals used in laboratory experiments should never be consumed, inside or outside the laboratory. Acetaminophen can cause skin and eye irritation and is considered harmful if swallowed in sufficient quantities. Ferrocenemethanol can cause skin, eye, and respiratory irritation. Detailed information on the hazards of reagents are available in their respective safety data sheets. Waste should be collected in a container labeled "Hazardous Waste" to avoid release of toxic materials to the environment and to dispose of chemicals according to regulations.

RESULTS AND DISCUSSION

Students prepared a buffer solution of pH 2.42 using 0.1 M citric acid and 0.2 M Na_2HPO_4 solutions. To do this, students calibrated a pH meter to adjust the pH of the solution. The pH obtained by the groups reported here was between 2.35 and 2.48. Previously, cyclic voltammograms of standard solutions of APAP were recorded at 40 mV/s scan rate in buffer pH 2.42 as shown in Figure 1. The anodic peak current, I_{pa} (μA) and concentration (mg/mL) of APAP data obtained from voltammograms for multiple solutions with varying APAP concentrations in the pH 2.42 buffer was provided to the students to build a calibration curve (see Supporting Information).

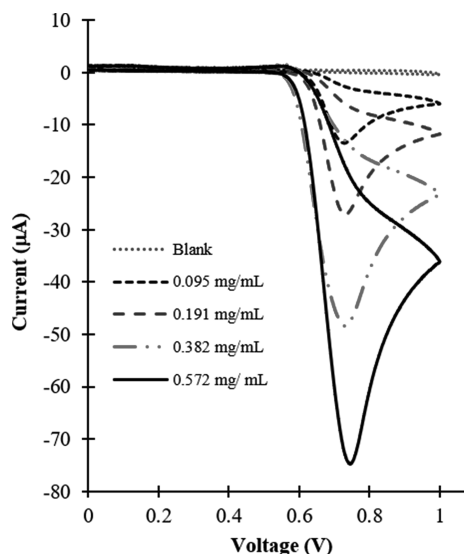


Figure 1. Cyclic voltammograms of APAP standard solutions at pH 2.42 and 40 mV/s scan rate.

A calibration curve was obtained by plotting the I_{pa} (μA) vs APAP concentration (mg/mL) using the average of three measurements for each point and is shown in Figure 2. The resulting trendline fit had an R^2 value of 0.999.

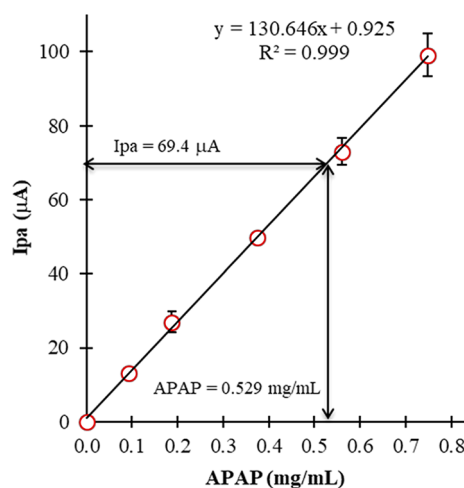


Figure 2. Calibration curve for APAP analysis at pH 2.42 and 40 mV/s scan rate. Error bars show the 95% confidence level of three measurements. An example I_{pa} and APAP concentration are shown, and further calculations are included in the text.

The voltammograms of a sample solution of crushed tablet were similar to those obtained with APAP standard. A representative plot obtained by a group of students is shown in Figure 3. The "blank" run was done for buffer solution at pH 2.44. Then, 0.0320 g of crushed tablet was dissolved in 50 mL of buffer. Not all of the tablet dissolved, and students discussed that other ingredients in the tablet remain insoluble. The "sample run" showed an I_{pa} of 69.4 μA at 0.79 V versus Ag/AgCl. A small amount of ferrocenemethanol was added to the sample solution, and the voltammogram for "sample + FcM" was obtained. The "sample + FcM" voltammogram showed new peaks assigned to the ferrocenemethanol/ferrocenium couple with reversible CV behavior and a midpoint potential of 0.22 V. Ferrocenemethanol serves as reference for

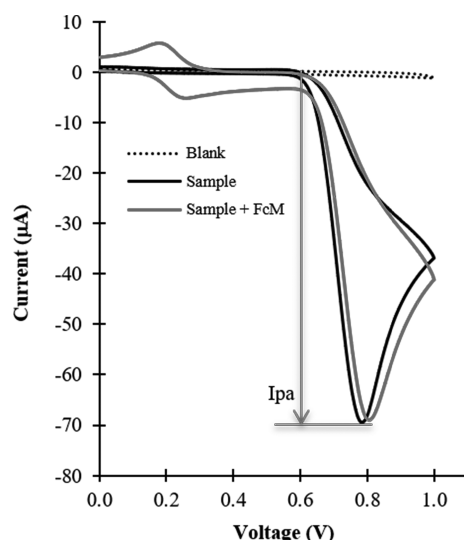


Figure 3. Representative cyclic voltammograms obtained by a student group displaying runs for a blank solution (dotted line), a sample solution (black line), and a sample solution with added ferrocenemethanol (gray line). All measurements at pH 2.44 and 40 mV/s scan rate. Anodic peak current (I_{pa}) for the sample is indicated with an arrow.

the voltages measured against the Ag/AgCl electrode in the aqueous solutions, similarly to the ferrocene/ferrocenium redox couple for nonaqueous solutions.³⁵ The APAP oxidation peak in the “sample + FcM” voltammogram appeared again at around 0.79 V. After determination of the I_{pa} for the sample run, students used Excel and the LINEST function to calculate the APAP concentration and standard error (S_x) in the CV analysis, of 0.529 ± 0.005 APAP mg/mL. After multiplying the 0.529 mg/mL by the 50 mL in which the crushed tablet sample was mixed, the mass of APAP in the sample was determined as 26.4 mg. The APAP weight percent (APAP wt %) in this example was calculated as the mass of APAP divided by the mass of sample, and the ratio multiplied by 100 to express it in percent, yielded 82.6%, which actually matched the expected value of 500 ± 20 mg APAP/tablet at a 95% confidence level.

A summary of student's data and results for 10 different student groups obtained with the provided calibration curve is shown in Table 1. On average, the students sample weight was 31 mg of crushed tablet which was mixed with 50 mL of buffer solution, and yielded tentative sample concentrations between

0.51 and 0.66 mg tablet/mL. The various “sample” voltammograms resulted in I_{pa} values between 57.35 and 75.66 μA ; the average I_{pa} for the 10 groups was 65.70 μA . With the measured I_{pa} values, the calculated mass of APAP in the CV analysis was on average 0.50 mg/mL, which multiplied by the volume of the buffer in which the crushed sample was mixed, gave the mass of APAP in the sample of 25 mg on average. With the initial mass of tablet used in the analysis, students then calculated the APAP wt %, which resulted in an average APAP wt % of 80.03%. The expected 500 mg of APAP (amount given by the manufacturer of the tablet) divided by the weight of the tablet analyzed of 605.2 mg, multiplied by 100 to express the ratio in percent gives the expected APAP wt %. The expected APAP wt % in the tablet was 82.6%. With the calculated APAP wt % in the tablet and the weight of the tablet, the student groups' data yielded an average and standard deviation of 484 ± 21 mg APAP/tablet with a percent relative standard deviation (%RSD) of 4.35% and percent error of -3.13% . The 10 groups' average 95% confidence interval was 484 ± 25 mg APAP/tablet, with the margin of error calculated as $t \times S_x$, where t is the Student's t -value for an experiment's degrees of freedom minus 2.³⁴ S_x is the standard error for x in $y = mx + b$, the linear regression equation.³⁴ Regardless of variations in the experimental pH values of the buffer (2.35 to 2.48), the sample concentration (0.51 to 0.66 mg tablet/mL) used in the students' experiments, and the different student groups over several semesters, the % RSD is low and under 5%.

A chart of the students' results, including their 95% confidence intervals, is shown in Figure 4. Seven out of ten

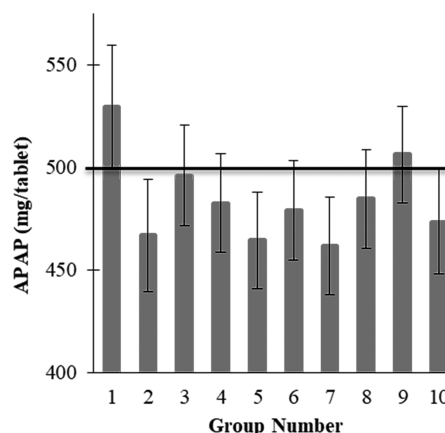


Figure 4. Chart of the analysis of APAP in medication tablets displaying experimental results from the student groups. The horizontal line shows manufacturer's value of 500 mg APAP/tablet. Error bars display the 95% confidence interval.

Table 1. Student Data and Experimental Results

Measurements	Average $\pm$ SD ^a	Minimum	Maximum
Buffer pH	2.42 ± 0.03	2.35	2.48
Sample concentration, mg tablet/mL	0.62 ± 0.05	0.51	0.66
Sample peak current, μA	65.70	57.35	75.66
Mass of APAP in CV analysis, mg/mL	0.50	0.43	0.57
Standard error (S_x in analysis), mg/mL	0.0093	0.0091	0.0095
APAP wt % in tablet	80.03	76.28	87.46
Mass of APAP, mg/tablet	484 ± 21	462	529
Margin of error, mg/tablet	25	23	30

^aData reported as average $\pm$ standard deviation; results for 10 groups of 4 students ($n = 10$).

groups reported results containing the expected value of 500 mg APAP in their 95% confidence intervals. The other three groups had a low APAP content, and their 95% confidence intervals did not contain the expected value of 500 mg APAP. Possible sources of error could stem from failure to dissolve all of the APAP from the tablet into the buffer solution as well as differences in the polishing of the glassy carbon surface of the working electrode before each run. Students discuss possible sources of errors in their laboratory reports, such as any pH differences between their buffer solution and the one used to obtain the calibration curve. In addition, when running samples of higher concentrations, the current is lower than expected

due to saturation at the electrode surface. Therefore, solutions used for analysis by this method should not exceed 33 mg of tablet in 50 mL of buffer solution for the analysis of a 500 mg APAP tablet. In addition, further consideration could be given to the sampling of the tablets in the bottle or container of the medicament. For example, if the bottle had 100 tablets, a sample of 10 could be taken, the weight of 10 tablets could be given to find the average weight of a single tablet.

The implementation of this engaging laboratory experience has had a positive percent change in students' pre- and postscores in short quizzes containing 10 quantitative general chemistry questions given during the first week of the semester and at the last laboratory session. For two semesters before implementation of this laboratory, the pre- and postassessment scores resulted in an average increase of 50.7% (32 students, average prescore 4.19, average postscore 5.74 out of 10); for the next five semesters after the implementation of this laboratory, the average change was 99.2% (56 students, average prescore 3.96, average postscore 6.20 out of 10). The percent change (%change) in scores was calculated for each student as the difference between postscore minus prescore divided by the prescore value. Although the variation in individual student's percent change was very large (−60% to +540%), the *t* test assuming unequal variances (*F* test showed the variances were different) yielded a *t*-statistical of 2.499 versus a *t*-critical 1-tail of 1.663 ($P = 0.0072 < 0.05$) indicating the percent change after implementation was significantly higher. The normalized gains for each student's prescore and postscore were also calculated as a consistent analysis over the student population. The normalized gain is calculated as the ratio of the difference between the postscore minus the prescore and the difference of the maximum score minus the pretest score. The average gain by 56 students experiencing this laboratory was 0.367, with a range between −0.24 to 1.00, versus 0.259, with a range of −0.60 to 0.88, for 32 students in the previous semesters. Expressed as percentages, there was a 10.8% difference between the 36.7% and 25.9% learning gains. A *t* test assuming equal variances (*F* test showed the variances were equal) yielded a *t*-statistical of 1.855 versus a *t*-critical one-tailed of 1.663 ($P = 0.0335 < 0.05$), therefore the gain value of 36.7% is statistically higher than the 25.9%. Some limitations in this analysis are the availability of data from a larger number of students before the implementation of the laboratory and the large variation in students' prescores and postscores. Nevertheless, the increase in the percent change and in the normalized gain average indicate an encouraging improvement in student's learning gains after implementation of this laboratory. The increase in the assessment scores demonstrates the importance of including relatable and engaging student experiences in the quantitative analysis course. Also, this laboratory experiment could be revisited and expanded in the following instrumental analysis course, with focus on the various kinds of working electrodes (glassy carbon vs platinum), reference electrodes, and voltage scales, as well as on the qualitative aspect of the CV technique to deepen student knowledge with the already familiar experiment.

CONCLUSIONS

We have introduced herein an engaging undergraduate laboratory experiment designed to be relatable and relatively inexpensive for the purpose of fostering a higher understanding of electrochemistry and the technique of cyclic voltammetry.

Over the course of five semesters, students typically working in groups of four carried out the experiment as part of their required laboratory coursework. Out of a total of 10 groups, seven student groups reported results containing the expected value of 500 mg of acetaminophen per tablet in their calculated 95% confidence intervals. The implementation of this laboratory experiment has been shown to have a positive increase in student learning gains. The resulting laboratory procedure and provided supplemental learning materials provide a way for chemistry instructors to offer a simpler, more hands-on, and relatable approach to teach quantitative analysis applying cyclic voltammetry. Further work on this laboratory experiment may entail the further exploration of different categories of electrodes and voltage scales as well as cyclic voltammetry's application in qualitative analysis in the subsequent instrumental analysis course typically taken at the senior level.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.9b01127>.

Laboratory procedure, example of results obtained by a student group, pre/post quiz sample questions, and statistical analysis (CV lab experiment information) (PDF, DOCX)

AUTHOR INFORMATION

Corresponding Author

Linda de la Garza — Chemistry Department, Valdosta State University, Valdosta, Georgia 31698, United States;
orcid.org/0000-0003-1847-5277; Email: ldelagarza@valdosta.edu

Authors

Nathan T. Hart — Chemistry Department, Valdosta State University, Valdosta, Georgia 31698, United States;
orcid.org/0000-0002-0111-2798

Weldon C. Lane — Chemistry Department, Valdosta State University, Valdosta, Georgia 31698, United States

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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