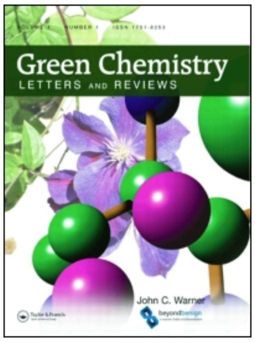

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The EcoScale as a framework for undergraduate green chemistry teaching and assessment

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ABSTRACT
An upper-year undergraduate practical examination is presented that utilizes the EcoScale (a semi-quantitative tool) and several established mass metrics to assess student understanding of green chemistry principles. This activity focuses on the straightforward preparation of a benzodiazepine via three different catalytic methods, and the analysis of individual experimental data during laboratory time. Students learn about the structure of the EcoScale, apply it as a simplistic life cycle assessment, and critique it as a scientific model. The examination complements more traditional expository and self-design experiments within a synthetic course where green chemistry and sustainability are central themes.

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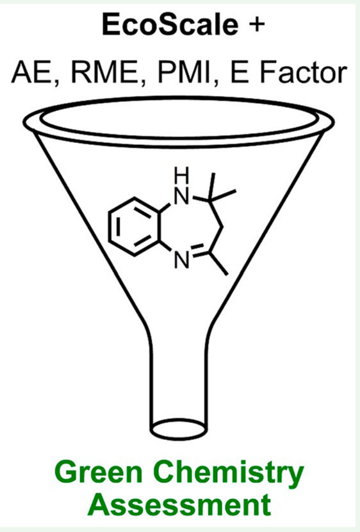

Introduction

A catalytic chemistry course

Since 2008, a course focusing on catalytic methodologies in organic chemistry (CHM 343H: Organic Synthesis Techniques) has been offered to third-year undergraduates at the University of Toronto (*1*). Approximately 30–40 chemistry students enroll in this course per year, which is the capstone component of the institution's Synthetic and Catalytic Chemistry program (*2*). Green chemistry and sustainability are central pillars of CHM 343H: each class learns about greener solvents for organic reactions, solventless transformations and microwave reactivity in the context of various catalytic approaches (e.g. phase-transfer catalysis, transition metal catalysis, organocatalysis and Lewis acid catalysis). As the course nears its conclusion, students engage in a "design-your-own" synthetic activity where each person individually plans and executes the three-step preparation of a personalized target azlactone compound (*3*). This affords undergraduates the opportunity to implement some "green thinking" into their work, and to justify any "non-green" aspects of the methodology they adopt.

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The need for a life cycle assessment: the EcoScale

A key aspect of Organic Synthesis Techniques is that several common green chemistry metrics (atom economy, reaction mass efficiency, E factor and process mass intensity (PMI)) are built into the analysis of transformations that the students perform (*4*). Whilst these are important and relevant metrics to consider (*5*), a more thorough and thought-provoking activity is to conduct a life cycle assessment (LCA) for a synthetic procedure (*6*). This involves studying the material and energy inputs/outputs required to achieve the preparation of a desired substance, in tandem with related environmental impacts. Although it is beyond the scope of the course for students to perform a heavily detailed LCA of a specific process, this has been undertaken at other academic institutions (*7–11*) and a simplistic LCA was deemed a desirable component of CHM 343H. After several years of teaching the course, it became apparent to the authors that a way to introduce an LCA whilst assessing student understanding of fundamental green metrics was to design an end-of-semester laboratory examination with both practical and theoretical aspects.

On consulting the research literature, an appropriate post-synthesis analysis was chosen for students to work with in an examination setting, called the EcoScale. This was published by Van Aken et al. as "a semi-quantitative tool to select an organic preparation based on economical and ecological parameters" (*12*). The EcoScale quantifies the green quality of a synthetic method based upon consideration of six distinct categories: (i) isolated product yield; (ii) cost of chemicals; (iii) safety concerns; (iv) technical set-up; (v) reaction conditions (temperature/time) and (vi) reaction workup/purification methods. An "ideal" synthesis is assigned a numerical value of 100, and penalty points are assigned to reflect deficiencies in green chemistry (e.g. the penalty associated with a non-quantitative reaction yield is (100 − % yield)/2, such that an experimental yield of 78% invokes a deduction of 11 penalty points from the starting value of 100). A major strength of this approach is that it allows the direct comparison of different routes towards the same target compound. The EcoScale has found favor as an assessment tool in academic laboratories (*13–25*) and has been modified for industrial purposes (*26*). It has also been incorporated into some undergraduate pedagogical laboratory exercises (*9*, *27*), although it has not, to our knowledge, been utilized as a formal way to evaluate student learning and understanding of green chemistry. This article describes the formulation and implementation of a laboratory examination utilizing the EcoScale as a user-friendly scientific model that is subject to both praise and criticism.

Examination overview

Instructor reaction selection

To facilitate incorporation of an EcoScale activity into a laboratory examination environment, a model synthesis was selected for students to undertake "unseen": that is, without undertaking any pre-laboratory experimental preparation. This synthesis fulfilled a number of criteria: (i) ideally, several "versions" of it needed to be possible (so that students could perform their own practical work without the temptation of "collaborating" with neighbors); (ii) each version had to be completed within a time limit of about three hours to fit into a single laboratory period; (iii) each version required inexpensive and readily available starting materials that showcased catalysis; and (iv) the synthesis had alternative literature methods to be compared with by students for relative "greenness" according to the EcoScale. The chosen synthesis that fit these criteria was the preparation of a benzodiazepine from 1,2-phenylenediamine and acetone under three different catalytic conditions (i.e. three synthetic versions) (*28*) (Scheme 1).

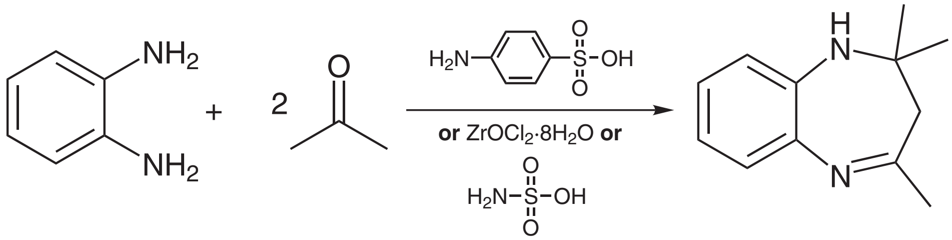
The three catalysts assigned to students (one to each student) were sulfanilic acid, zirconyl(IV) chloride octahydrate and sulfamic acid. This reaction additionally had the advantage of being "real-world relevant" and of interest to undergraduates, as benzodiazepines are central nervous system depressants producing anti-anxiety, anticonvulsant, hypnotic and sedative effects. Common anti-anxiety medications such as diazepam (Valium®), lorazepam (Ativan®) and alprazolam (Xanax®) are classified as benzodiazepines.

Pre-examination student instructions

In order to provide some perspective for the laboratory examination, specific background information was given to students one week in advance (Figure 1). The instructions directed students towards the EcoScale as it was not previously discussed in Organic Synthesis Techniques, and encouraged them to think of it as a tool that builds on familiar green chemistry considerations they had encountered in the course. In this way, students had an opportunity to reacquaint themselves with some crucial metrics, and to reflect on the potential strengths and weaknesses of the EcoScale approach to quantifying "greenness."

Sample student experimental procedure

On arrival at the laboratory, each student received one version (of the three available) of the examination



Scheme 1. Synthesis of 2,3-Dihydro-2,2,4-trimethyl-*1H*-1,5-benzodiazepine.

containing the experimental procedure for them to follow. A sample method using sulfanilic acid as the catalyst is shown in Figure 2 (*29*). As per the pre-examination instructions, students were required to calculate reactant masses and volumes before undertaking any practical work. The methods using sulfamic acid (*30*) and zirconyl(IV) chloride octahydrate (*31*) as the catalysts are broadly similar with all three being adapted for examination purposes from the research and teaching literature.

CHM 343H Spring 2017 Laboratory Examination Information

Monday 3rd/Tuesday 4th April

- Worth 5% of the final CHM 343H course grade.
- The examination will start at 8:30 a.m. **SHARP**: you have a maximum of 4.5 hours to complete the practical and theoretical work **and to clean up all locker glassware/check out** (as mentioned in the laboratory manual, marks are awarded for the latter).
- You will perform a reaction ‘unseen’: i.e. you will receive the experimental background and protocol on arrival. **You are highly encouraged to read all the information provided when the examination starts!**
- You will be expected to perform calculations before starting any practical work (e.g. work out masses, volumes of reactants – a number of Sigma-Aldrich catalogues will be available along with a periodic table attached to the examination). **BRING A CALCULATOR!**
- You will synthesize and purify/characterize an organic compound (perform TLC, measure mp, IR and prepare proton NMR), submitting a sample for inspection before finishing.
- You will be graded according to the following criteria:

(a) product yield
(b) product purity (from TLC, mp, IR and proton NMR)
answers to questions regarding the reaction performed and other theoretical laboratory questions: *please be familiar with atom economy (theoretical and experimental), reaction mass efficiency, process mass intensity and E factor calculations as discussed previously in lecture, laboratory and assignment components of the course*

- **Before coming to the examination, you should read and reflect on a research article describing a green chemistry measurement tool called the EcoScale (*Beilstein J. Org. Chem.* 2006, 2:3: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1409775/). This paper is also available on BlackBoard. You will be required to perform calculations using the published scale on p. 3 of the article (the scale itself will be attached to the back of the examination). It will help if you consider the ‘pros and cons’ of this approach in terms of quantifying how ‘green’ an organic reaction is.**
- You will **NOT** be graded according to how quickly you finish the experiment.

Figure 1. Laboratory examination instructions provided to students one week in advance.

Combine the following in a 25-mL round-bottomed flask: 1,2-phenylenediamine (5.00 mmol), sulfanilic acid (0.50 mmol) and acetone (1.5 mL). Equip the flask with a reflux condenser. Heat the solution with stirring at 40ºC using a water bath for 60 minutes, **being careful not to allow the temperature to exceed 45ºC** (hint: keep some ice nearby for the water bath). Monitor the reaction progress using TLC (eluent: ethyl acetate, visualization: UV lamp). After 60 minutes, remove the flask from the heat source and add distilled water (5 mL) immediately. Allow the flask to cool to room temperature. A solid will crystallize from the solution (some agitation with a spatula may be required). Once crystallization has occurred, collect the solid via vacuum filtration and wash thoroughly with cold water (3 x 5 mL). Do not wash with excess solvent since the solid is partially soluble in water. Dry the solid product thoroughly under vacuum, collect and weigh. Measure the product melting point. Obtain an IR spectrum (Nujol mull) of the solid, prepare a proton NMR sample ($CDCl_3$) and submit the remaining product for inspection in a vial ***including a properly completed label*** **(name, product structure and TOTAL mass obtained)**.

Figure 2. Sample student experimental procedure for benzodiazepine synthesis.

Discussion

Examination questions: metric calculations and reflection

In Organic Synthesis Techniques, 178 students have undertaken this examination over a five-year period between 2013 and 2017. All students were able to isolate and characterize the benzodiazepine product in yields ranging from 25% to 95%, depending on which catalyst they were assigned. Students had the opportunity to answer the written examination questions both during the specified reaction time (60 minutes) and afterwards. These began with calculation of the yield, theoretical atom economy (TAE), experimental atom economy (bearing in mind the actual reactant masses used) and overall mass efficiency (RME) for the reaction undertaken. An analysis of these calculated values showed that approximately 80% of students were able to correctly calculate the TAE value of 84% (TAE: [(M of desired product)/Σ(M of reactants)] × 100). Perhaps surprisingly, only about two-thirds of students calculated their RME value correctly, which involved them utilizing their individual product mass (RME: [(actual mass of product)/Σ(mass of reactants utilized)] × 100). Following this, students were instructed to use their isolated product yield to calculate the EcoScale value for their synthesis (relevant information about the cost and safety aspects of the starting materials and EcoScale procedural penalty points were provided as “Additional Information and Data”) (*32*). Approximately 60% of students were able to carry this out appropriately. Table 1 shows a sample EcoScale student calculation undertaken correctly, based on an experimental isolated yield of 42% for the reaction described in Figure 2 (sulfanilic acid catalyst).

As an extension of this calculation, students had to then analyze a provided research literature procedure for their reaction in terms of the EcoScale (*29*, *33*–*34*). Unsurprisingly, in most cases the research literature yield was significantly higher than the isolated experimental yield, leading to a higher EcoScale score for the literature procedure. Each selected research procedure involved column chromatography as a purification method, so that students were able to appreciate the significant EcoScale deduction (10 penalty points) for this in terms of non-adherence to green chemistry. Finally, in terms of metric calculations and reflection, a question was set on calculation of PMI ([(mass of all input materials)/(actual mass of product)]) and its mathematical relationship to the E factor metric ([(mass of waste)/(actual mass of product)]).

Examination questions: EcoScale analysis

As the final piece of the examination, a question was devised for students to undertake a critical analysis of the EcoScale tool, by evaluating some of its strengths and weaknesses in the context of calculations they had previously undertaken. They were asked to conclude

Table 1. Sample student EcoScale calculation for benzodiazepine synthesis.

EcoScale parameter	Penalty points
(1) Yield: 42%	29
(2) Price of reaction components	
1,2-phenylenediamine is expensive	3
(3) Safety	
1,2-phenylenediamine (N), (T)	10
Sulfanilic acid (T)	5
Acetone (F)	5
(4) Technical setup	
Common setup	0
(5) Temperature/Time	
Heating for <1 h	2
(6) Workup and purification	
Cooling to room temperature	0
Adding solvent	0
Crystallization and filtration	1
Total EcoScale score: 45	

Table 2. Sample student responses regarding the EcoScale strengths and weaknesses.

EcoScale strengths	EcoScale weaknesses
• Calculations are straightforward to perform, with an easily understandable scale of 0–100 points • Allows for the clear identification of areas for improvement in terms of green chemistry • Combines safety, environmental factors, energy and product yield, all of which are very important in large-scale syntheses • Promotes conventional, low-maintenance protocols	• Only takes into account reaction yield as a mass metric, and yield generally given too much importance • Price of reagents may only have a weak correlation with greenness • Amount and nature of reaction/workup solvents not considered • Penalty points are arbitrary within each category (e.g. safety, technical set-up) • No consideration given to the physical/chemical properties of the product

their analysis with "three short suggestions for changes that would improve the EcoScale, making it a better method for comparing synthetic procedures, particularly in the context of green chemistry principles." This open-ended question gave students the chance to reflect on their learning experience in the Organic Synthesis Techniques course and to propose how an established model might be made better in terms of conducting an LCA.

The EcoScale strengths and weaknesses that were commonly identified by students in the response to this question are summarized in Table 2. Although alternative responses were given, many answers touched on these points in some manner.

The majority of students elaborated on these general concepts in their written answers. For example, regarding the isolated yield category, one person noted that "if in the EcoScale a reaction forms NO product (i.e. 0% yield), then all other deductions start from 50 points out of 100. This seems weird, as surely zero product should equal zero points overall." In general, most students identified a major EcoScale weakness as being no weighting given to solvent usage during the reaction or workup steps, which demonstrated an understanding of one of the key messages delivered earlier in the course via a laboratory reaction metric exercise (*35*). In terms of suggested improvements to the EcoScale tool, many different reasonable and meritorious suggestions were made that spoke to an LCA approach. Five such examples are as follows:

- Consider the benefits of catalysis by introducing the concept of positive points for catalytic reactions
- Incorporate environmental factors i.e. LD50 values for reactants and products, and introduce an "Environmental" category
- Account for the natural feedstock and recyclability of reagents/solvents as this would encourage use of renewable feedstocks such as corn for 2-methyltetrahydrofuran
- Replace reaction yield with a more robust metric (e.g. PMI) to include all the materials used in the process
- Characterize the amount and type of waste produced as there is no consideration given to this.

Examination grading rubric

An examination grading rubric was constructed for the first year of implementation and was kept constant each year thereafter. As an overview, a maximum total of 150 marks were awarded with a general breakdown of 75 marks for practical work (product mass, melting point, standard of proton NMR and infra-red spectra and overall product quality) and 75 marks for metric calculations and EcoScale critical analysis. It is important to note that the practical work grades were awarded by comparing the reported results amongst students performing the same version of the experiment (i.e. using a specific catalyst).

Conclusion

The practical examination described herein has become a valuable mechanism with which to assess undergraduate understanding of fundamental course concepts regarding green chemistry metrics. Just as importantly, it has acted as a way to introduce a straightforward LCA at the end of a synthetic organic chemistry course, and has promoted an appreciation of the need for multivariate metrics in the analysis of chemical reactions for "greenness." A potential concern was that the examination content needed to be radically changed from year to year, but this has proved unnecessary for a number of reasons (the five-year average student grade for this examination using the same grading rubric was 77%, 79%, 75%, 77% and 77%). Firstly, the graded examination papers were not returned to students at the end of the course each year, although they were welcome to come and discuss how they performed with the laboratory instructor (A.P.D).[1] Secondly, as there were three versions of the examination, a student did not know which version they were to specifically be assigned. Having multiple versions was considered advantageous but was not an essential component of the assessment. Similarly, the reliance on a benzodiazepine synthesis was unnecessary, as many other reactions would be an appropriate alternative. Indeed, an instructor at another institution might elect to take a "retired" experiment they are not currently running and use it in this examination environment. It is clear from our experiences that, even in the absence of using the EcoScale in conjunction with a reaction that students actually undertake themselves, the tool is of importance and has an educational role to play both specifically as a rudimentary LCA and as a scientific model in general.

Note

1. Course instructors can access sample examination papers, representative student product spectra, model examination answers and other information by contacting the corresponding author (A.P.D).

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Andrei Hent earned a B.Sc. (Hons.) in Chemistry in 2012 from the University of Toronto. Between 2012 and 2014 he worked with Andrew Dicks to co-author a primer entitled "Green Chemistry Metrics: A Guide to Determining and Evaluating Process Greenness". More recently, he and Dr. John Andraos have collaborated on several research and teaching projects that focus on communicating new insights about green metrics to an academic audience. His professional interests include effective communication of scientific ideas, especially in the context of organic synthesis.

Dr. Katherine J. Koroluk is a practicing clinical pharmacist currently completing her M.Sc. at the University of Toronto Faculty of Pharmaceutical Sciences studying antimicrobial stewardship. Prior to completing her Doctor of Pharmacy degree at the same institution, she conducted an undergraduate research project focused on chemistry education under the supervision of Andrew Dicks. Although not currently active in chemistry academia, she maintains a strong interest in education.

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