Teaching Biologically Relevant Chemistry throughout the Four-Year Chemistry Curriculum

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David Reingold, in a recent commentary in this *Journal (1),* pointed out a serious deficiency in the way that most chemistry curricula are structured in American colleges and universities. The recent *BIO2010 Report (2)* reflected that only 10–15% of students enrolled in traditional introductory and organic chemistry courses are interested in chemistry per se. The overwhelming majority of the remaining students have strong interests in various aspects of the life sciences *(1, 2).* Even so, in their first two years of chemistry courses we rarely introduce students to the connections between chemistry and biology, concentrating instead on the chemistry of analysis, of inorganic and physical systems, and of important organic functional groups and transformations. In order for students to see how the chemistry that they have learned applies to important biological systems, they must wait until their third year to take a biochemistry course. Many budding life scientists lose interest during their first two years in chemistry simply because they cannot see the relevance to their chosen field of interest.

Reingold proposes an alternative to the current second- and third-year curriculum of organic (two semesters) followed by an elective biochemistry course (one semester). Reingold's curriculum features a second-year bioorganic chemistry course sequence (two semesters) followed by a third-year "followup" one-semester organic course required only of chemistry majors. In his article *(1)* Reingold lists topics that can be moved from the current organic course into his proposed third-year "followup" course; he also lists relevant biochemistry topics that can then be incorporated into his new second-year bioorganic two-semester course. The two main advantages of Reingold's proposed curriculum are (i) students get early exposure to biological chemistry (and likewise, biochemistry faculty "get to talk about their field sooner and to a much larger audience") and (ii) "organic chemists get to talk about the nitty gritty to a much smaller audience—one that has been preselected to pay attention" (ref *1*, p 473).

Starting in 1990, long before Reingold's article was published, we began to develop a unique curriculum that solves the problem raised by Reingold. First, in our introductory chemistry courses we use a spiral and case-study approach *(3–6)* that has been recognized by Project Kaleidoscope *(7)* as a "Program that Works!". This course sequence features real-world case studies such as marine chemistry, blood, and air pollution. Second, we modified our upper-division unified laboratory courses[1] to feature writing and other aspects of scientific communication *(8).* Third, with the advent of a new biochemistry track in the chemistry major, we have created an alternative course for second-semester students, Organic Chemistry II: Bioorganic Emphasis. Finally, this fall of 2004 we added a new course, Advanced Topics in Biochemistry (with laboratory) to follow our third-year biochemistry one-semester course. The net result of all of these curriculum innovations is that our students with biological interests are exposed to in-depth discussions of the chemistry of important biological systems throughout all four years of their college chemistry studies.

One might ask why we found it necessary to expand our chemistry major and alter the curriculum. One reason was amply expounded upon by Reingold *(1)*: By incorporating biologically relevant chemistry throughout the four-year chemistry curriculum, we can attract and hold onto intelligent majors who otherwise would have declared biology or exercise-science majors. Many of these students in the past have found introductory and organic chemistry to be too "dry" (i.e., too nonbiological and unconnected to real-world phenomena) to hold their interest, even though their grades in the courses were high. Our new curriculum also allows us to explore the interface between chemistry and related fields, demonstrating some of the important chemical reactions and techniques that underlie advances in modern biology, earth or environmental science, and materials science. Our recent surge in majors suggests that these curriculum improvements have been successful: the number of graduating majors has increased from 8–12 before the early 1990s to 29 chemistry majors last spring (2005).

In this article we describe briefly our two-course sequences in introductory chemistry and organic chemistry, paying special attention to our alternative course, Organic Chemistry II: Bioorganic Emphasis. Finally, we will comment on the relative advantages of our curriculum as compared to that proposed by Reingold.

Our Spiral and Case-Study Approach to Introductory Chemistry

Roughly 20% of students who take the first semester of introductory chemistry choose not to complete the second semester of the course, and even among students who take two full years of chemistry, most do not become chemistry majors. Thus, one of our major goals has been to target our curriculum to a wide diversity of students. Since 1993, we have accomplished this goal by featuring the applications of basic chemistry to real-world phenomena and by exploring the ever-shifting boundaries between modern chemistry, biology, physics, and materials science. We also sought to revise introductory chemistry so that a student who takes only the first semester of the course would still come away with a complete, well-rounded view of the field of chemistry.

In our first semester of introductory chemistry, all of the major topics of the traditional two-semester course are discussed in a single semester, in a semi-quantitative manner *(3–6).* Calculations are kept fairly simple, and the discussion of complex physical models and theories is deferred until second semester. This course structure provides students with an overview of the entire field of chemistry and allows us to offer a second-semester course that is both more rigorous and applications-based.

Throughout the second semester of introductory chemistry we spiral back to revisit important topics from first semester. Our goal second semester is to expand upon quantitative topics along with complex physical theories and models introduced first semester; these discussions all occurring in the context of eight real-world case studies. Data that we collected after implementing our new approach show clearly that most students take a greater interest in learning when they can see the real-world applications of the material they are studying.[2] The entire second-semester course comprises eight case studies: (i) lasers, (ii) diamond, graphite, and buckyballs, (iii) fossil fuels, (iv) air pollution, (v) ozone, (vi) marine chemistry, (vii) blood, and (viii) bioenergetics. These case studies afford exposure not only to many biological systems, but also to applications in physics, environmental or earth science, and materials science. Student responses to these courses have been very favorable (*3, 6,* Note 2), and more detailed descriptions of the course structure and topics have been published *(4, 5).*

Organic (and Bioorganic) Chemistry

Our most recent curriculum changes have centered on the organic chemistry course sequence. Since 1998 we have utilized a nontraditional course structure that offers advantages over conventional organic courses (Figure 1). After taking the first-semester organic course, our students may choose between a second-semester organic course that emphasizes a more traditional synthetic approach or the new bioorganic approach. These two courses teach the same concepts and skills, but they prepare students for different specialties. The former focuses on the concepts needed for organic synthesis whereas the latter emphasizes bioorganic mechanisms and the concepts needed for rational drug design. Both courses are designed to be equally rigorous and serve to prepare students for graduate study or medical fields.

The general organization of our two-course organic chemistry sequence can be seen in Figure 1. Two concurrent organizational themes underlie this sequence. The first is a

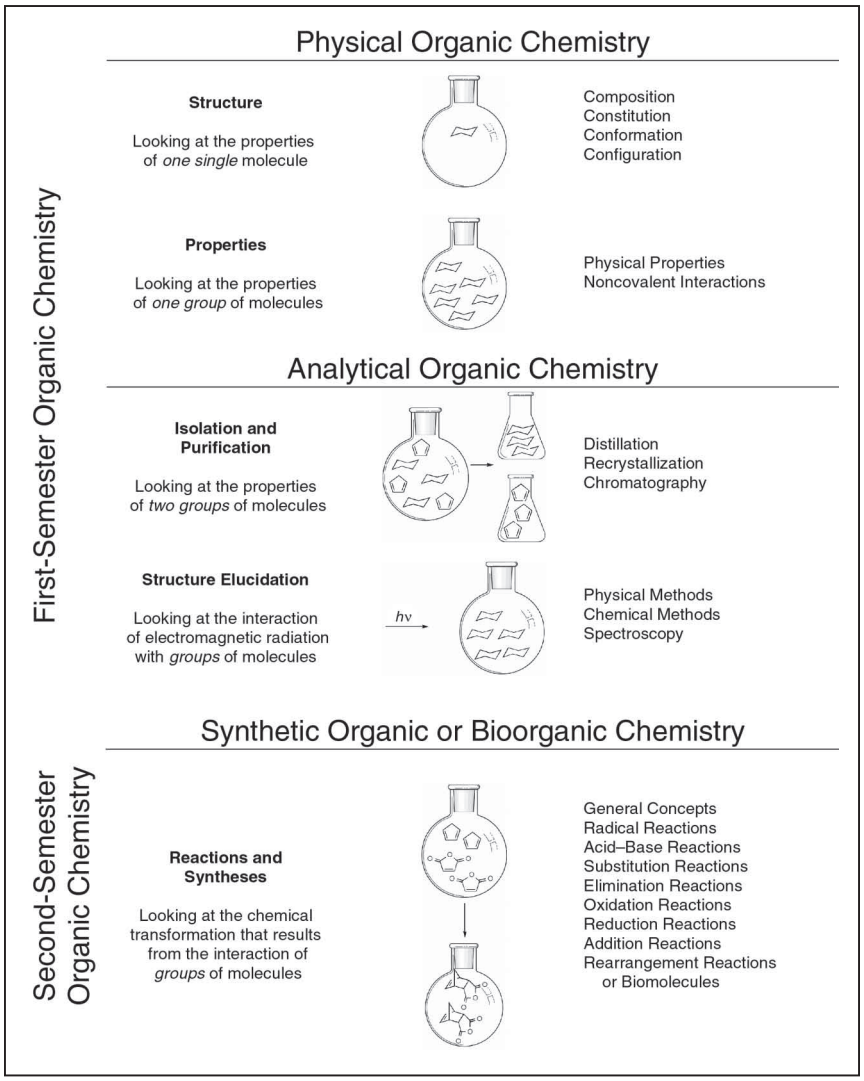

Figure 1. Organization of the two-semester organic sequence.

historical division of organic chemistry into the subfields of physical, analytical, and synthetic or bioorganic chemistry. The other conceptual organization is at the molecular level, where we stress the differences between characterizing a single molecule, a collection of molecules, and the interactions between groups of molecules.

First-Semester Organic Chemistry

The common background needed by students in both second-semester courses is learned in the first-semester organic course, where we discuss both physical organic and analytical organic chemistry. The first-semester course opens with a discussion of physical organic chemistry. During the first several weeks we examine the structure of organic molecules by looking at composition, constitution, conformation, and configuration. In contrast to traditional organic chemistry curricula, we discuss all of the relevant functional groups within the first two weeks of the course so that they may be revisited throughout the entire year. We teach concepts that apply to single molecules, such as orbitals, bonding, hybridization, isomerization, and stereochemistry.

After studying individual molecules, the next logical step is to look at collections of identical molecules. Here we move from structure to bulk properties, emphasizing how a collection of molecules can exhibit physical properties that can be seen and measured on the macroscopic level. Furthermore, we try to correlate and understand these properties through an examination of noncovalent intermolecular interactions: electrostatic forces, hydrogen bonding, dipole–dipole interactions, and London dispersion forces. In this way we make the connection between structure and bulk properties and also between the microscopic and macroscopic views of matter.

In the analytical organic chemistry section of the first-semester course we discuss two different topics: purification and structure elucidation. We stress intermolecular forces in our discussion of purification techniques; our goal is to understand how two (or more) groups of molecules interact. From this perspective, the complexities of distillation, recrystallization, and chromatography become easier for students to comprehend. Structure elucidation is discussed, for the most part, by examining the interaction of electromagnetic radiation with molecules. In this section, we focus on spectroscopy (especially ^{1}H NMR, ^{13}C NMR, and FTIR) and GC–MS.

Second-Semester Organic: Bioorganic Emphasis

Once the foundations are laid in the first semester, students have the skills and tools necessary to continue building knowledge in organic chemistry by studying either synthetic organic chemistry or organic chemistry with a bioorganic emphasis. Both courses are organized by reaction type (e.g., acid–base, substitution, addition) rather than by functional groups. In each area we take a mechanistic approach to organic chemistry. General concepts of each reaction type are introduced using simple examples and mechanisms. As students gain a deeper understanding in the course with bioorganic emphasis, we use more complex examples including biological applications. The goal of this course is to highlight the biological relevance of organic chemistry.

In 1998, Breslow published an extensive "Viewpoint" in this *Journal* reviewing the field of bioorganic chemistry *(9)*. He described this exciting field and encouraged students to study the unsolved problems at the interface of chemistry and biology. The incorporation of bioorganic chemistry in the second-year organic chemistry course has been stressed by a number of chemical educators. As early as 1992, Dugas described his bioorganic course for undergraduates *(10)*. This one-semester course is taught separately from the traditional organic chemistry course. Unlike the course described by Dugas *(10),* we integrate bioorganic into the second semester of organic chemistry. Our course applies organic reactions and principles from the first-semester course to biochemical systems and pathways and to rational drug design. Recently, several authors have proposed topics and demonstrations that might be incorporated into such a bioorganic course *(11–14)*.

One of the first topics we discuss in our own bioorganic chemistry course is acid–base reactions. Both the Brønsted–Lowry and Lewis definitions are reviewed and expanded upon from a mechanistic perspective. We discuss the thermodynamic relationship between pK_a, solution pH, and equilibrium concentrations of protonated versus deprotonated species, as well as the implications for acid–base reactions. Concepts of electronegativity, resonance, charge, inductive effects, sterics, and hybridization are discussed in relation to the intramolecular environment of a molecule and its acidity. Amino acids are discussed (see Table 1), paying particular attention to the effects of solvent polarity on pK_a values.

Simple examples of acid–base reactions are introduced using key functional groups in organic chemistry (e.g., acids, amines, alcohols) to elucidate the relationship between acidity and degree of reactivity. As students progress in their understanding, biological examples are incorporated (see Table 1). To demonstrate acid and base catalysis, enzyme catalytic mechanisms are studied (e.g., chymotrypsin, ribozymes, RNAase). An interesting application here involves differences between in vitro and in vivo reactions: A carboxylic acid reacted with an amine under mild aqueous conditions simply generates an ammonium carboxylate salt; however, under enzymatic catalysis, these two groups may react to form an amide. This example demonstrates the importance of local environment on reactions.

Each new organic reaction is introduced in a similar fashion: general concepts, mechanisms, and simple organic reactions, followed by bioorganic examples. Good biochemical examples of nucleophilic substitution reactions include the polysaccharide hydrolases (phosphorylase and lysozyme), as well as *S*-adenosyl-methionine reactions and the pathological reactions of mustard toxins. As Reingold pointed out *(1),* redox reactions can be taught using NAD^+/NADH and $FAD/FADH\cdot/FADH_2$ as the active reagents. Organic reactions important in drug design are also included in the course, for example, the synthesis of sulfa drugs. Protecting-group chemistry is incorporated into our discussion of peptide synthesis. Elimination, oxidation, reduction, and addition reactions are covered as well in the second-semester course. We have removed the topic of rearrangement reactions in order to spend more time studying the biological building blocks: carbohydrates, amino acids, and nucleic acids.

Table 1 lists topics from classical organic chemistry that can be taught in the bioorganic emphasis course utilizing biochemical examples. Most of these examples can be found in standard organic texts (e.g., Bruice's *Organic Chemistry, 15*), biochemistry texts (e.g., Voet and Voet's *Biochemistry, 16*), or medicinal chemistry texts (e.g., Silverman's *The Organic Chemistry of Drug Design and Drug Action, 17*). In this course we supplement a standard organic textbook (Smith's *Organic Chemistry, 18*) with boardwork, overhead transparencies, and occasional handouts.

We offer the traditional organic chemistry course and the bioorganic emphasis course simultaneously, allowing students to choose between the two courses. At schools where this is not possible, either course would serve admirably, depending on faculty expertise and student preference. Where feasible, the two courses could even be alternated, one every other year.

Note that biologically relevant topics can also be incorporated into the first-semester course, depending on instructor discretion. These topics include chirality and stereospecific reactions in vivo; polarity, hydrogen bonding, and hydrophobicity; and aromaticity and nucleic acid pi stacking (see Table 1). Conversely, an important aspect of our aforementioned spiral approach is that topics from first-semester organic (e.g., chirality, IMFs, analytical organic chemistry, functional groups) are also revisited in both second-semester courses. For example, the spectroscopy learned in first semester is incorporated throughout the second semester in analysis of each new reaction class discussed. Furthermore, students apply their knowledge of functional groups obtained during the first semester to reactions encountered in the second-semester course.

It is important to point out here that, unlike Reingold's course, our one-semester bioorganic course does NOT attempt to replace the third-year one-semester biochemistry course. Instead, we use our bioorganic course to introduce biologically important organic reactions and mechanisms to second-year students. In the third-year biochemistry course, these reactions are revisited and placed in the coherent framework of the field of biological chemistry. Essentially, in bioorganic chemistry we study the reaction "trees", and in biochemistry we gain sufficient perspective to see the larger "forest", as well as the suspended bridges or "pathways" that are hung between trees, connecting one to the other.

During the fourth year, our chemistry majors on the biochemistry track must take an advanced course with laboratory. In addition to biology courses that fulfill this requirement (Developmental Biology, Advanced Cell Biology, Molecular Genetics), we have developed a new course, Advanced Topics in Biochemistry. The lecture portion of this course is now offered annually with topics including bioorganic chemistry, bioinorganic chemistry, membrane biochemistry and bioenergetics, depending on the instructor. A single laboratory experience has been designed to span all

Table 1. Biochemical Examples of Concepts in Organic Chemistry

Organic Concept/Reaction	Biologically Relevant Example
Resonance	Nucleic acids
Thermodynamics and Intermolecular Forces	Solvation entropy vs enthalpy; Lipid membranes: hydrophobicity vs hydrophilicity, drug bioavailability; Hydrogen bonding (proteins, nucleic acids); Pi stacking and drug intercalation in nucleotides
Kinetics	Enzyme catalysis
Chirality and Stereoselectivity	Amino acids and saccharides (mono-. poly-, etc.); Drug development, e.g., Thalidomide; NAD-linked dehydrogenases, e.g., alcohol deHase, lactate deHase
pK_a	Amino acids
Acid–Base Reactions	Chymotrypsin, ribozymes, RNAases
Substitution Reaction (S_N1)	Polysaccharide hydrolase: lysozyme
Substitution Reaction (S_N2)	Polysaccharide hydrolase: phosphorylase; Haloalkane dehydrogenases; S-adenosylmethionine (epinephrines); Mustard toxins
Substitution Reaction (EAS)	Synthesis of sulfa drugs
Elimination Reaction	Enolase (E1)
Oxidation–Reduction	NAD^+/NADH and FAD/FADH·/$FADH_2$; Alcohol dehydrogenase (ethanol/acetaldehyde)
Addition	Biosynthesis of cholesterol; Hemiacetal formation in sugars; Amide coupling; Imine formation in the metabolism of alanine; Aspartic peptidase

three areas, featuring an integrated series of projects. Specifically, students study molecular interactions between transfer RNA and a series of biologically important ligands including metal ions, small organic molecules of interest, and certain binding proteins. A more complete description of this course and its laboratory component will be presented in a future manuscript.

Comparing Our Curriculum to Reingold's

There are a number of reasons why we believe that our curriculum represents an optimal way to afford early student exposure to important aspects of health science and biology. First our spiral and case-study approach to introductory chemistry already brings biology into the first-year course. Second, although both Reingold and we use a bioorganic chemistry course to bring biological applications to second-year chemistry students, our curriculum leaves intact the upper-division one-semester biochemistry elective course. In fact, our bioorganic course introduces topics that lead smoothly into the subsequent biochemistry course, and in this way the two courses function well together.

We believe that it is important to preserve the upper-division biochemistry course, for several reasons. First, in a semester-long biochemistry course, the major topics of the field can be presented systematically, for example, moving from amino acids and proteins to enzymes, from lipids and membranes to transport, and from carbohydrates to glycolysis and the citric acid cycle. The cohesiveness of the field can be elucidated, and important chemical concepts from organic and introductory chemistry courses can be recapitulated, in different systems and contexts. Second, discussion of biochemical topics is limited only by what students can learn comfortably in a semester, rather than by what can be fit into an organic course by removing certain topics for coverage in a later course. Finally, with a dedicated laboratory component in the biochemistry course, students can be exposed to important projects and methods such as enzyme kinetics and regulation, protein purification, and equilibrium binding of ligands. It seems doubtful to us that with all of the important projects necessary to introduce in a two-semester organic chemistry laboratory, enough room would be left to feature crucial biochemistry experiments. For all of these reasons, we believe that maintaining the third-year one-semester biochemistry course makes more sense than attempting to package biochemistry into a two-semester organic chemistry course.

We wish to close by mentioning two important advantages of our newly implemented curriculum. Just prior to the existence of our biochemistry track, we graduated typically 12–14 chemistry majors annually (minimum 5, maximum 17). In spring of 2004 we graduated a record 20 majors, which is significant given that the class of 2004 was the first class for which the biochemistry track was fully available. In spring of 2005 we graduated 29 majors (!), 21 of whom were biochemistry track. Another important advantage of the new curriculum is that it has brought faculty together. Not only have our organic, inorganic, and biological chemists worked together to implement various new courses, but we have also made important connections with several biology faculty members as well. These interactions have already led to the submission of several interdisciplinary research grant proposals.

The chemistry department seeks to encourage and teach students from a wide array of disciplines. We recognize that our students are interested in applying chemical knowledge to the world around them and that the life sciences hold a particular interest to many. Accordingly, we have designed a curriculum that is both rigorous and stimulating for a diverse range of students.

Acknowledgments

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Notes

1. Recently, in order to intercalate the unified laboratory courses into our new curriculum, these four courses were modified and converted into two new two-semester course sequences: Instrumental and Experimental Chemistry I & II, and Senior Research Projects I & II. Key aspects of the original courses were preserved and enhanced.

2. Unpublished results from evaluations that we administered, 1993–1995.

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