

Six Pillars of Organic Chemistry

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A conceptual framework for the presentation of organic chemistry called “the six pillars of organic chemistry” is described. This approach has led to greater student comprehension and enjoyment of the subject matter. Organic chemistry is a course of study pursued by a variety of majors (in addition to chemistry), particularly those in the pre-health studies. The course often represents a hurdle, or rite of passage, to be overcome en route to a career in another profession. Great apprehension is experienced about the difficulty of the subject matter, the volume of material to be mastered, and the grades required for admission to professional schools. A variety of articles on the topic of the organic chemistry lecture course have appeared in this *Journal* (1). The objectives of the six pillar approach are (i) building knowledge of organic chemistry upon a strong foundation of fundamental concepts; (ii) explaining and predicting a wide variety of chemical, physical, and biological properties of molecules; (iii) conceptually uniting important features of general, organic, and biochemistry; and (iv) the early introduction and frequent reinforcement of concepts in a memorable way.

This approach is not intended to represent all the concepts required for second-year organic chemistry or to define precisely which concepts should be included. Rather, I intend to promote a teaching methodology of a general formula that appeals to students and appears to be in harmony with many ideas concerning the instruction of chemistry. For example, Taber has reported, “...the unfamiliar has to be made familiar in manageable chunks if we are to learn it effectively. New concepts have to be appreciated and integrated into our knowledge systems before they can be used as a secure foundation for developing super-ordinate concepts—no matter how logical and clear the teacher’s exposition” (2).

Many instructors and textbooks of organic chemistry appreciate the importance of a conceptual approach. For example, McMurry, in his popular text states, “...organic chemistry is a beautifully logical subject that is unified by a few broad themes. When these themes are understood, learning organic chemistry becomes much easier and rote memorization is minimized” (3). But, it is tempered by the initial reliance of students on memorization, “...the what of chemistry is easier for most students to grasp than the why” (3).

My focus is in the details of a framework that I have applied and in the emphasis of such throughout the school year. The idea is to provide a structural foundation upon which organic chemistry may be learned; to de-mystify and simplify, in the minds of students, the apparently overwhelming avalanche of facts that intimidates organic chemistry students; and to persuade general chemistry instructors of the importance of emphasis on key concepts of chemistry, which are often reviewed in the initial weeks of an organic chemistry course. The six pillars are listed below, with brief definitions.

1. Electronegativity: the tendency of an atom in a covalent bond to attract electron density to itself
2. Polar covalent bonding: generally, a bond between atoms of different electronegativity

3. Steric effects: the usual tendency of atoms or groups of atoms to repel one another and to occupy space
4. Inductive effects: through sigma-bond electron-density donation or withdrawal
5. Resonance: electron delocalization involving electrons in p orbitals
6. Aromaticity: the unique stability of electrons in p orbitals in certain cyclic systems

One could coalesce these into fewer concepts, which would focus upon electron or charge delocalization. One might alternatively suggest many more, particularly when advanced organic chemistry is considered. Why six? These suffice, individually or in combination, for many of the problems that arise during the study of organic chemistry. Pillars support a building, but do not represent its entirety. Furthermore, when one explains to students that six concepts will be sufficient for understanding a great deal of what they will learn, the intimidation of unlimited memorization of seemingly disconnected facts becomes less intimidating. Taber has reinforced this position, “It is therefore sensible, when teaching the subject, to remember to explicitly refer to the underlying principles, and not to assume that learners are recognizing the physical forces” (2). Referring to concepts repeatedly, particularly when there are relatively few key concepts and a novel presentation of them, may lead to increased student confidence and satisfaction.

Certainly memorization, particularly with regard to the reactions to be learned, is an important part of chemistry and other disciplines. Yet, when viewed in light of the framework of these concepts, organic chemistry can seem more orderly and understandable. Why pillars? This is a metaphorical device that may bring one to mind of solidity and strength, great support, and perhaps even lend the intrigue of great historical structures, such as the Parthenon.

As a prelude to the discussion of the application of the six pillars, I will mention some other notable prerequisites for the understanding and application of organic chemistry, which are typically included in the course content of an organic chemistry course whether or not one utilizes a six pillars approach. For example, students must be able to produce and interpret Lewis structures. Why not include reaction intermediates among the list? The beauty of this system is that the pillars can, and do, apply to all of the reaction intermediates that students encounter. I propose this system (or approach) as a complement to many texts that currently arrange chapters according to functional group or reaction intermediates. My approach is applied within the context of the course as one currently teaches it—it is not a matter of addition or subtraction, but organization and emphasis. It is necessary that students have further skills, such as how to draw reaction mechanisms. These, and excellent procedures for writing them, are available in practically all second-year organic chemistry textbooks. The following materials exemplify the six pillars. I will give two possible applications for each pillar. The first example in each case represents a problem typical in organic chemistry, the second example being an example of an application in biochemistry.

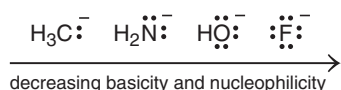


Figure 1. Correlation of atomic electronegativity and anionic stability.

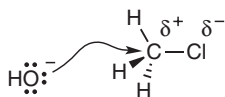


Figure 2. Predicting which atom of chloromethane is attacked by the hydroxide anion.

The Six Pillars and Chemical Reactions

Electronegativity

Consider the basicity or nucleophilicity of various anions. Such determination is important in determining the direction and extent of acid–base reactions and to some extent the reactivity of anionic species as nucleophiles in reactions of organic chemistry. Consider the basicity of four anions: methide, amide, hydroxide, and fluoride. The electronegativity of the charged atoms in this series increases in the order given, as can be predicted by the periodic trends for elements in the same period. Figure 1 shows that the more electronegative the element in the period, the more stable the negative charge on that atom. Therefore, the basicity or nucleophilicity of these anions decrease in the order given. This approach works well when considering anions *within the same period*. An example of the use of hydroxide as a nucleophile in an organic chemical reaction is shown in Figure 2. The treatment of concepts within the six pillars is necessarily (and intentionally) limited: they provide a framework, but must be supplemented by many other important factors during the typical organic chemistry course. Students at all levels of chemistry should be encouraged to develop an increasing subtlety and judgment in concept application. There are many cases where valid concepts disagree and must be weighed, such as the resonance effect and the inductive effect on aromatic reactivity towards electrophiles. *Biochemical example:* the basicity of biochemically important amines, compared to neutral alcohols (Figure 3). Nitrogen, being less electronegative than oxygen, less effectively stabilizes the lone pair of electrons, resulting in greater electron-pair reactivity (basicity). Instructors may use this opportunity to impress on students that it is the stability of the lone pair(s) (and not the number of lone pairs) that is important.

Polar Covalent Bonding

Students should learn that all chemical bonding is a matter of degrees, from the very ionic to the completely covalent, with a range of polarity in between. In organic chemistry, we most often refer to covalent bonds, and the extent of polarity in many cases determines the chemical reactivity. In the $\text{S}_{\text{N}}2$

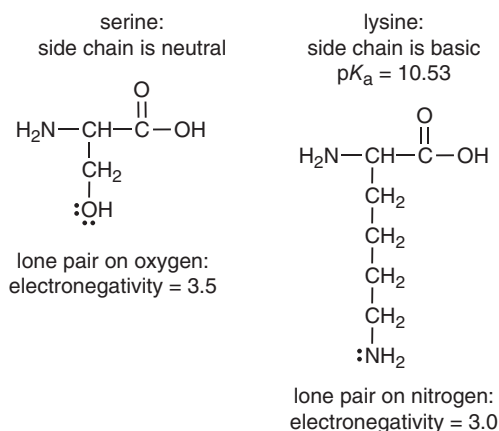


Figure 3. Basicity of selected amino acid side chains.

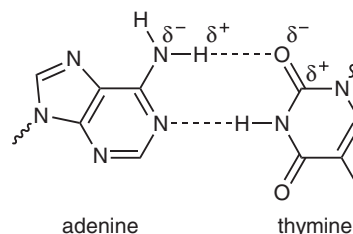


Figure 4. Hydrogen bonding in DNA.

reaction of hydroxide with chloromethane (Figure 2), one may ask the student where the hydroxide is most likely to attack. Being negatively charged, it should attack that atom that bears the most partial-positive charge. The C–H bond has negligible polarity, but the C–Cl bond is much more polar, with the partial-negative charge residing on the more electronegative element, chlorine, and the partial-positive charge existing on the less electronegative element, carbon. The hydroxide, therefore, will attack the carbon, resulting in the breaking of the carbon–halogen bond while forming a carbon–oxygen bond. Because electronegativity is important in determining bond polarity, students can be reminded of how various key concepts affect each other. *Biochemical example:* the N–H bonds in adenine and thymine (Figure 4) are very polar covalent bonds. They play an important role in the structure of the DNA double helix. For example, the hydrogen atoms in these N–H bonds bear a partial-positive charge (and the nitrogen atoms bear a partial-negative charge). Likewise, the C=O bond of thymine is polar, with the partial-negative charge on oxygen (only two of the many polar covalent bonds show the polarity symbols). The hydrogen atom is therefore strongly attracted to the adjacent, highly electronegative oxygen atom on the adjacent molecules in the opposite strand of the DNA double helix (the “base pair”). This type of intermolecular interaction is known as “hydrogen bonding” and is a result of the high polarity of the covalent bonds. This argument is the same for the other base-pairing sites (cytosine and guanine).

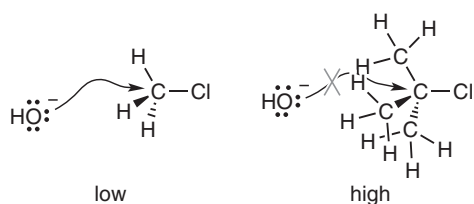
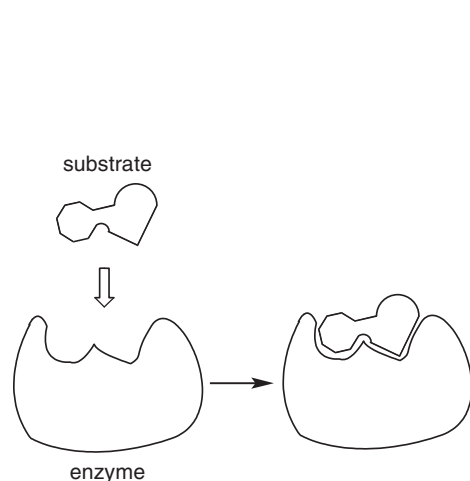
Figure 5. Effect of steric hindrance on S_N2 reactivity.

Figure 6. Enzyme-substrate interaction.

Steric Effects

These effects are exemplified by the rate of S_N2 reaction on various substrates (Figure 5). Chloromethane readily undergoes this type of reaction owing to the limited steric hindrance surrounding the carbon that bears the chlorine. 2-Chloro-2-methylpropane has too much steric hindrance at this carbon, thereby preventing any S_N2 reaction (and favoring other modes of reaction, such as elimination). *Biochemical example:* the enzyme “lock and key” (or “hand in glove”) analogy, where molecules of a certain shape fit into similarly shaped openings (Figure 6). Polar bonds are also important in these cases.

Inductive Effects

The addition of HCl to 2-methylpropene to give 2-chloro-2-methylpropane is an example of “Markovnikov’s rule”. Whether it is beneficial for students to memorize rules may be a subject of debate, but the mechanistic explanation is one in which students may apply this important concept. As shown in Figure 7, the reaction proceeds to form a tertiary carbocation intermediate (in preference to a primary one) because the methyl groups surrounding the tertiary carbocation stabilize it through electron-density donation. It is recognized that the inductive effect is important in such cases. The hyperconjugation effect is also important: the overlap of a filled, adjacent sigma bond with an unfilled p orbital (when both are in nearly the same plane). Hyperconjugation can be considered within

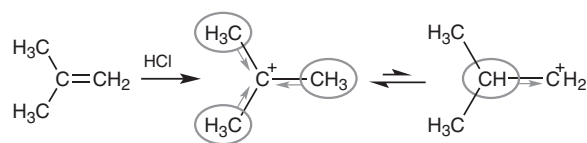


Figure 7. Electrophilic addition of hydrochloric acid to 2-methylpropene.

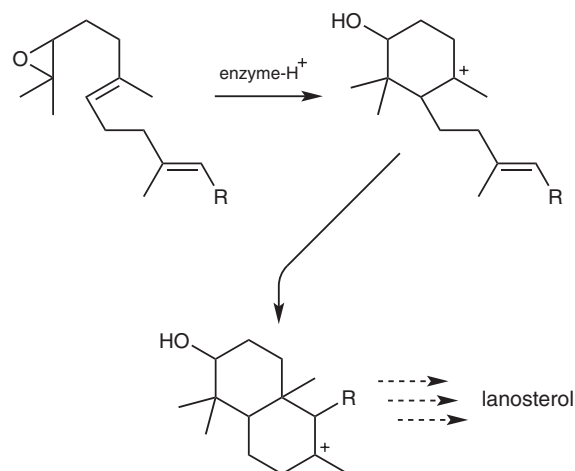


Figure 8. Partial structures of carbocation intermediates in lanosterol formation.

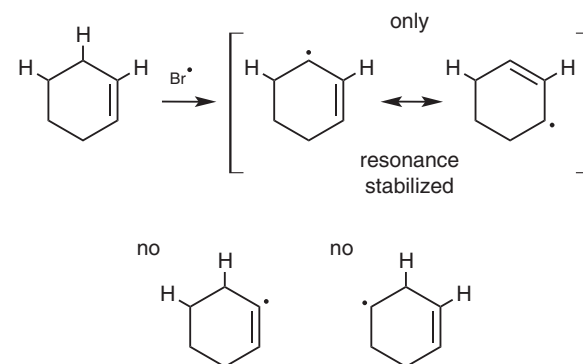


Figure 9. Radical intermediates in allylic bromination.

the resonance pillar of organic chemistry and as such can illustrate to students the overlap of these concepts in many cases (4). *Biochemical example:* the biosynthesis of lanosterol (partial structures are shown in Figure 8). In many of the steps of the biosynthetic pathway, one observes the formation of tertiary carbocations when there are opportunities when a secondary carbocation could form. Although the pathway is complex and direct comparison of biological to non-biological systems risks oversimplification, it nonetheless demonstrates the appearance in natural systems of organic reaction intermediates

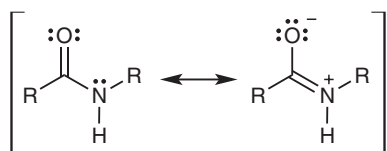


Figure 10. Planarity of peptide bond.

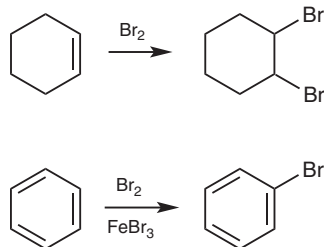


Figure 11. Comparison of reactivity modes of alkenes and arenes.

and affords an opportunity to discuss the relative influence of organic chemistry principles.

Resonance

Shown in Figure 9, this effect explains why, under conditions of low concentration of bromine radical, bromination (by substitution) of cyclohexene occurs at the allylic position, from a resonance stabilized allylic radical. Other positions form less stable secondary (or vinylic) radicals. The allylic radical leads to the allylic bromide. Resonance effects are especially important in organic chemistry and appear quite frequently throughout the subject matter of the course, and students should therefore become familiar with this concept. *Biochemical example:* the planarity of peptide bonds, which can be explained using resonance delocalization of the nitrogen lone pair into the carbonyl oxygen, resulting in some double-bond (planar) character of the nitrogen atom. The first structure in Figure 10 shows the nitrogen atom with three sigma bonds and one non-bonding pair of electrons. According to VSEPR (valence shell electron-pair repulsion) theory, the electron-group geometry about the nitrogen atom in that structure would be tetrahedral and the shape trigonal pyramidal. In this instance, students can be reminded of the limitations of individual Lewis structures. Observing the second resonance structure (and the hybrid) explains the observed planarity of the amide bonds in proteins.

Aromaticity

This effect is commonly included early in the second semester of my two semester organic chemistry course. It is exemplified in Figure 11 by comparison of the reactivity of cyclohexene to that of benzene with regard to reaction with molecular bromine. It is noted that the pi-bonding electrons in cyclohexene undergo rapid reaction with bromine to form the addition product, 1,2-dibromocyclohexane. Benzene, however, with its apparent three pi-bonds, is not three times

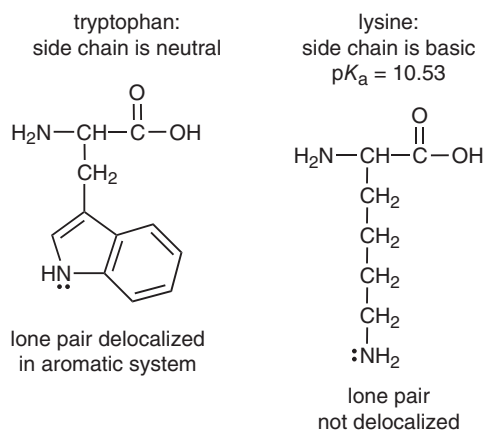


Figure 12. Basicity of selected amino acid side chains.

more reactive towards molecular bromine, but actually much less reactive [Asimov's "The Eureka Phenomenon" (5) cleverly describes Kekule's discovery of the structure of benzene and discusses its reactivity]. Not only is benzene less reactive, but the mode of reactivity is substitution, not addition, thereby preserving the aromaticity in the product, bromobenzene. *Biochemical example:* the basicity of certain amino acid side chains. Rather than memorizing the basicity of amino acid side chains individually, students can predict and explain basicity (see also Figure 1). Both tryptophan and lysine (Figure 12) have a nitrogen atom in their side chains. Lysine is basic, but tryptophan is not, owing to the lone pair on the tryptophan nitrogen being delocalized (and stabilized) in an aromatic system.

Conclusion

The presentation above is typical of a final lecture of the semester. An advantage of this presentation is that it can be presented in one lecture period (50 minutes). The organic examples are given at the end of the first semester and the biochemical examples at the end of the second semester, effectively reminding students of the usefulness of organic chemistry in further studies. It is beneficial to have students review key concepts and to remind them in a memorable way of what they have learned, particularly when they are studying for the final exam. It may also contribute to an increased overall satisfaction with the course (see excerpts of teaching evaluations).¹

As further anecdotal evidence of the enthusiasm engendered, the Le Moyne College science center hallway is now adorned by a chemistry club painting of the six pillars, and some students have even created a Web site celebrating these concepts. In conclusion, this approach (and final lecture) illustrates a novel presentation of chemical concepts that are known to be crucial to understanding. "The subject matter of modern organic chemistry provides a chance to demonstrate

how to construct understanding and operate within a truly hierarchical structure of knowledge..." (6).

This approach further utilizes concepts across the scope of courses such as general, organic, and biochemistry. In fact, books that cover these three topics (7) are increasingly available, although they typically (owing to brevity) include treatments of such topics as nomenclature, reactions, and applications, but rarely provide the foundation to explain the underlying reasons for the chemical and biological properties of molecules. I conclude my capstone lecture with the following quotation by Henri Poincare, "Science is facts; just as houses are made of stones, so science is made of facts; but a pile of stones is not a house and a collection of facts is not necessarily science." Students can use these six pillars among the foundations of their scientific house. They do not represent the entirety of the house; furthermore the inclusion (or exclusion) and arrangement of concepts is a personal choice. The thesis of this article is that a relatively few concepts should be presented coherently, concisely, and frequently amidst the vast quantity of material to be mastered. In conclusion, the six pillar terms are defined at the start of semester, the concepts are utilized throughout the semester, organic chemistry is placed in context of relatively few "pillars", and a conceptual bridge between general, organic, and biochemistry is created.

Note

1. Some relevant student opinions: "Excellent at explaining key concepts."; "Very good in explaining key concepts of chemistry."; "Well organized class and good presentation of truly massive amounts of fairly difficult material."; "Good course—has made me interested in picking up a chemistry minor. This course has effectively prepared

me for biochemistry... Overall concepts were clear to get through each chapter."; "He focuses on concepts which is essential if students are to understand organic chemistry."; and "... makes you learn concept rather than memorization."

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