Redox chemistry and hydrogen bonding in drug design:
Using human health examples to inspire your high school chemistry students

Elizabeth M. Vogel Taylor and Catherine L. Drennan <evogel@mit.edu, cdrennan@mit.edu>
Massachusetts Institute of Technology, Departments of Chemistry and Biology, Massachusetts Institute of Technology, Cambridge MA

In teaching freshman chemistry at the Massachusetts Institute of Technology (MIT), we observed that many students enter our course fascinated by cancer research and human health, but uninterested in chemistry. Chemical principles underlie all of biology and medicine, but this message is often lost in introductory college and high school chemistry courses, where curriculum constraints can make the addition of new material logistically difficult. One strategy for making chemistry more relevant to students without altering course curriculum is the inclusion of brief examples that relate chemical principles to topics in biology, medicine, or human health. We have developed over 30 short (typically under five-minute) biology and medicine-related examples for use in the general chemistry classroom. While the examples were designed for our under-graduate freshmen, many can be used at the high school level, and all materials are freely available to educators online through MIT OpenCourseWare.[1] In this article, we present one example modified from the online material: Carbon-fluorine bonds in drugs. Figures and diagrams for this article are presented as a student hand-out and/or overhead for use in the classroom. (adjacent page)

This example reviews and applies the following chemistry concepts:

- **Oxidation**. Oxidation is the loss of electrons by an atom or molecule. An electron-poor molecule is therefore harder to oxidize than an electron-rich molecule.
- **Hydrogen bonding**. A hydrogen bond is an electrostatic interaction between a hydrogen bond donor (a hydrogen atom in a polar bond) and a hydrogen-bond acceptor (a strongly electronegative atom with a lone pair available for bonding, typically an O, N, or F).

The biology terms should be defined prior to or during this example:

- **Enzyme**. Enzymes are proteins that speed up (catalyze) specific chemical reactions.
- **Drug Metabolism**. Metabolism refers to the processing and excretion of a drug from the body. If a drug is metabolized too quickly, it will not be present long enough or at sufficient concentrations in the body to perform its function.

Carbon-Fluorine (C-F) Bonds in Pharmaceuticals

C-F bonds are not naturally present in our bodies and are rarely found in nature. Therefore, it may be surprising to find that C-F bonds are present in a large number of important pharmaceuticals. For example, the structures of the antibiotic drug Cipro and the antidepressant drug Paxil are shown (figure 1) with the C-F bonds highlighted. One reason medicinal chemists incorporate fluorine into drug candidates is that, due to its extreme electro-negativity, an appropriately-positioned fluorine can pull electron density away from the rest of a molecule, making a drug more electron poor. Since oxidation requires losing an electron, a drug that is more electron-poor will be harder to oxidize.

What is the benefit of making a drug harder to oxidize?

Drugs are metabolized by a class of enzymes in the liver called cytochrome P450 or Cyp (pronounced “sip”) enzymes. Cyp enzymes function by oxidizing small molecules, including drugs and environmental toxins; this oxidation increases a molecule’s polarity, making it more water-soluble and facilitating its excretion from the body. In general, if a drug is easily oxidized, it will be more quickly cleared from the body compared to a drug that is difficult to oxidize. A drug must be metabolically stable, meaning it must remain in the body for a sufficient amount of time, in order to be effective. ***Fluorination can increase a drug’s metabolic stability by making it less susceptible to oxidation by Cyp enzymes in the liver.***

The role of fluorine as a hydrogen-bond acceptor

Another reason that medicinal chemists replace C-H bonds with C-F bonds in drug candidates is that fluorine atoms can act as hydrogen bond acceptors. Many drugs function by binding to and inhibiting the activity of a target enzyme. The more tightly a drug binds in the binding pocket of that enzyme, the more potent, specific, and effective the drug. The presence of fluorine can lead to tighter binding of a drug in the binding pocket of its target protein by increasing the number of potential hydrogen bonding interactions between the drug and the drug target (see figure 2). For example, the drug Januvia (figure 3) which is used to treat type II diabetes, contains six C-F bonds, including three on an aromatic ring. During the development of this drug, it was found that incorporating a single fluorine in the aromatic ring increased the potency of the drug three-fold. Three fluorines increased the potency 25-fold! Modeling studies suggest that this increase in potency is due to increased hydrogen bonding in the active site.[2]

Other examples suitable for the high school classroom

Biology and medicine-related examples for additional high school chemistry topics can be found on the MIT general chemistry OpenCourseWare website.[1] These include, to name a few, Le Chatelier's principle (application to blood-oxygen levels), periodic trends (atomic size and ion channels in neurons), polar covalent bonds (water versus fat soluble vitamins), acid-base titrations (blood pH effects from vitamin B_{12} deficiency), and radioactive decay (medical applications of technetium-99).

Students have expressed tremendous enthusiasm for the biology-related examples throughout each semester and in end-of-term course evaluations. In a two-year study of MIT general chemistry course innovations, freshman reported an increased understanding of the role chemistry plays in other disciplines, everyday life, and health care following the course, and the students credited the biology and medicine-related examples for helping them make these interdisciplinary connections.[3]

References (bottom of page 10)

Carbon-Fluorine (C-F) Bonds in Pharmaceuticals:
An Application of Redox Chemistry and Hydrogen Bonding

There are no known natural molecules in our bodies that contain carbon-fluorine (C-F) bonds. However, medicinal chemists often replace C-H bonds with C-F bonds in potential drugs.

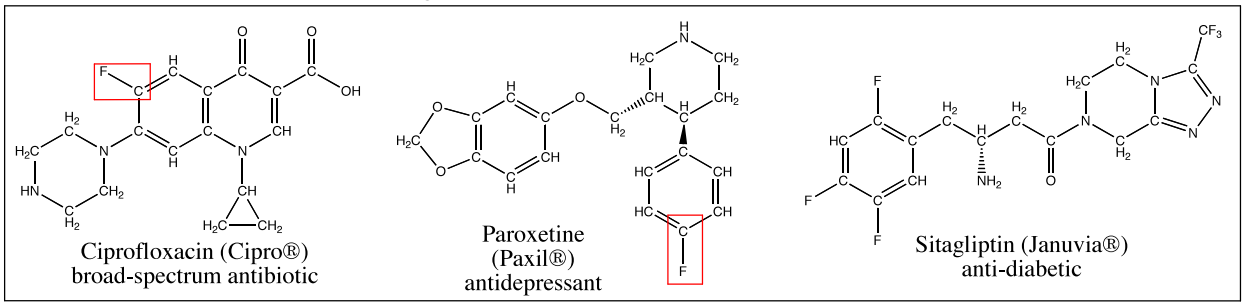
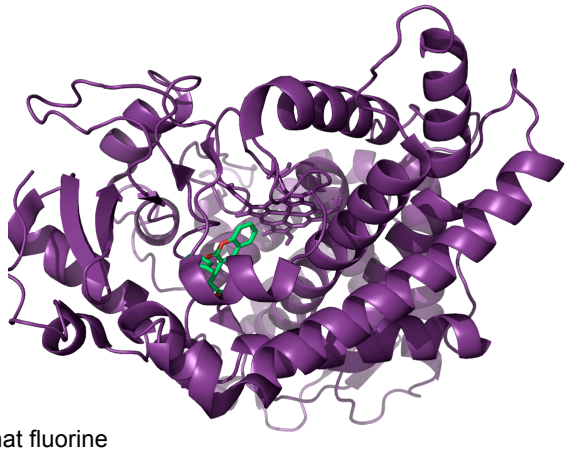


Figure 1

Replacing a C-H bond with a C-F bond can make a drug more electron-poor. An electron-poor drug is (1) *harder / easier* to oxidize.

Cyp (pronounced "sip") enzymes in the liver oxidize drugs, leading to the drugs' excretion from the body. The crystal structure of a Cyp enzyme (in purple) is shown bound to the anticoagulant drug warfarin (green).
PDB file: 1OG5.



Fluorination can increase a drug's metabolic stability by making it (2) *more / less* susceptible to oxidation by Cyp enzymes.

Another benefit of replacing C-H bonds with C-F bonds in drugs is that fluorine atoms can act as hydrogen-bond acceptors, which can lead to tighter drug binding with the target enzyme.

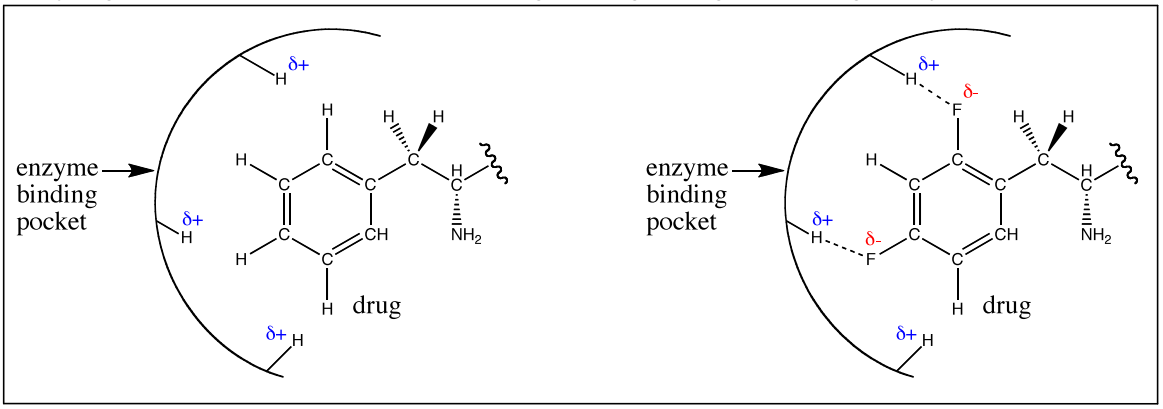


Figure 2

The drug Januvia, which is used to treat type II diabetes, contains six C-F bonds, including three on an aromatic ring.

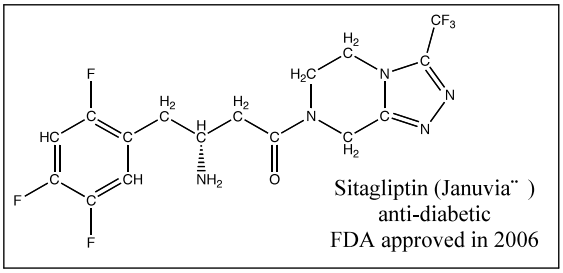


Figure 3

References for Redox chemistry and hydrogen bonding in drug design (page 9)

1. http://ocw.mit.edu/OcwWeb/Chemistry/5-111Fall-2008/BiologyTopics/. Development and implementation of biology and medicine related materials for general chemistry were funded through a Howard Hughes Medical Institute Professors grant to Prof. Catherine L. Drennan.
2. Kim, D, et al. *J. Med. Chem.* **48**, 141-143 (2005).
3. Taylor, EV, Mitchell, R, Drennan, CL. *ACS Chem. Biol.* **4(12)**, 979-982 (2009).