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5.111 Principles of Chemical Science  
Fall 2008

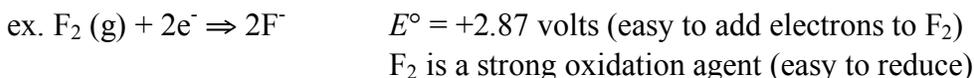
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## Oxidation/Reduction Reactions

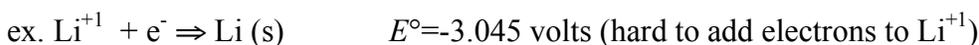
See page 1 of lecture 25 notes for an introduction to oxidation/reduction and page 2 of lecture 26 notes for a discussion of a standard reduction potential ( $E^\circ$ ).

Meaning of standard reduction potential ( $E^\circ$ ):

A large positive  $E^\circ$  means the element or compound is easy to reduce.

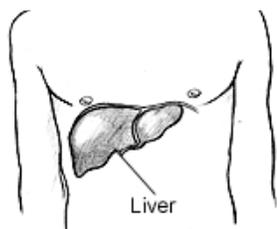


A large negative  $E^\circ$  means the element or compound is hard to reduce



### Example from the TA-led recitation associated with Lectures 25 and 26: Oxidative Metabolism of Drugs in the Body

Drugs are metabolized by a class of proteins in the liver called cytochrome P450 or Cyp (pronounced “sip”) enzymes. Cyp enzymes function by oxidizing small molecules, including drugs and environmental toxins, and this oxidation increases a molecule’s polarity and leads to excretion from the body. In general, if a drug is easily oxidized, it may be more quickly excreted from the body compared to a drug that is difficult to oxidize.



Cyp enzymes in the liver oxidize drugs for excretion from the body. A Cyp enzyme (shown in purple) bound to the anticoagulant drug warfarin (green). PDB file: 1OG5.



Different people express different levels of Cyp enzymes in their bodies, which means that some people oxidize drugs more readily than others. Individual differences in Cyp enzyme levels account for one challenge in determining drug doses; the right amount of a pharmaceutical agent for one person might be too much or too little for someone else.

## Fluorine atoms in drugs

Although carbon-fluorine (C-F) bonds are very uncommon in natural products, C-F bonds are incorporated into a number of drugs. One reason for this is that fluorine, due to its extreme electronegativity, can make a molecule electron poor, particularly if the fluorine is positioned on an aromatic ring.

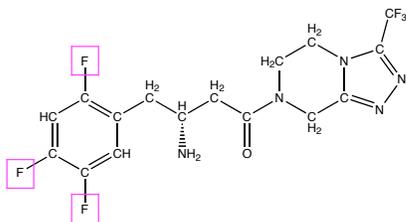
**Question: Why might it be desirable to make a drug more electron-poor?**

*Answer: Since oxidation involves losing an electron, a drug that is already electron-poor will be harder to oxidize. Fluorination can increase a drug's metabolic stability by making it less susceptible to oxidation by Cyp enzymes in the liver.*

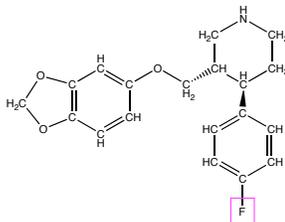
**Question: Based on the information above, do C-F bonds increase or decrease the reduction potential of a drug?**

*Answer: C-F bonds **increase** the reduction potential by making the drug more electron-poor. This means the drug is harder to oxidize (and thereby easier to reduce).*

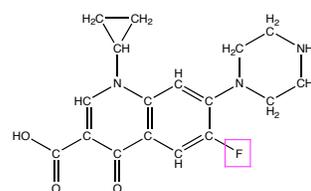
Examples of drugs with C-F bonds on aromatic rings:



Sitagliptin (Januvia®)  
anti-diabetic  
FDA approved in 2006



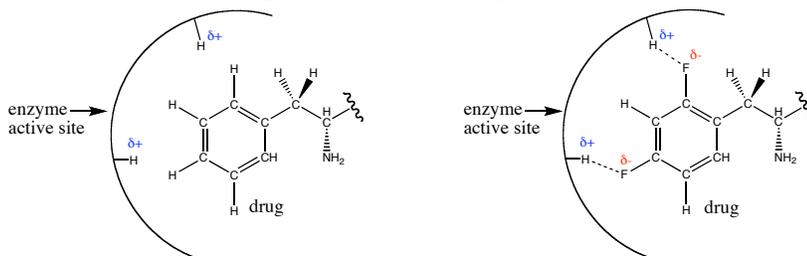
Paroxetine (Paxil®)  
anti-depressant  
FDA approved in 1992



Ciprofloxacin (Cipro®)  
broad-spectrum antibiotic  
FDA approved in 1987

**Question: What might be another benefit of replacing C-H bonds with C-F bonds in a drug candidate? (Hint: think back to lecture 18.)**

*Answer: F atoms are hydrogen bond acceptors, which may lead to tighter binding of the drug in the active site of its target enzyme by increasing the number of hydrogen bonding interactions between the drug and the drug target.*



Note:  $F_2$ , which must be used to make C-F bonds in drugs, is the most powerful oxidation agent known. A current challenge in organic chemistry (and under investigation in labs at MIT) is to develop safer sources of  $F_2$  and the  $F^-$  anion for the synthesis of C-F bonds.