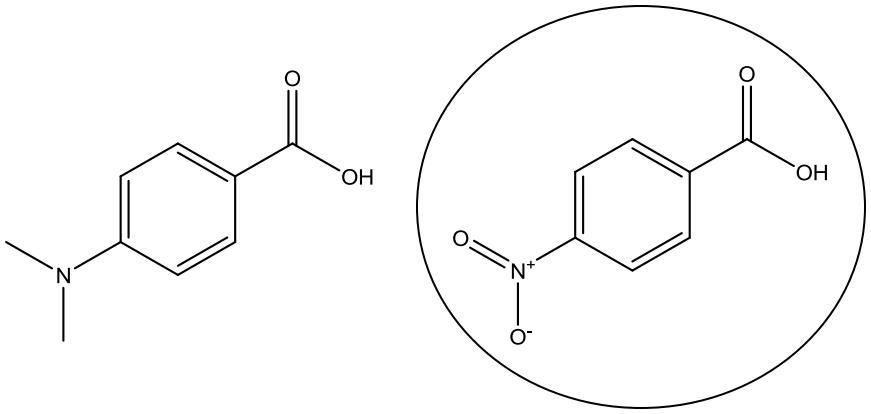
Medchem 562P
Fall 2011
Problem Set #1 Answer Key

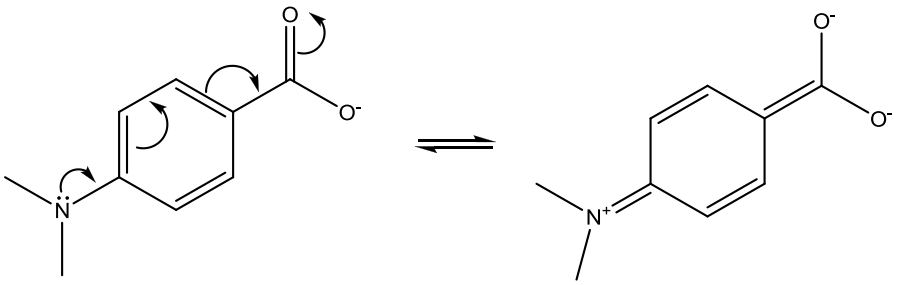
Acid/Base Chemistry

1. Which compound is more acidic? Why?

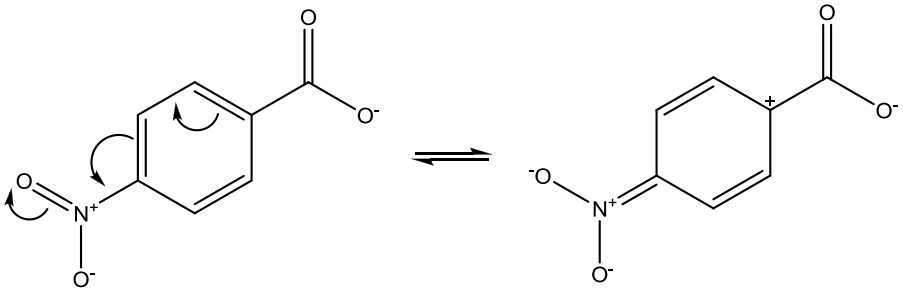
A)



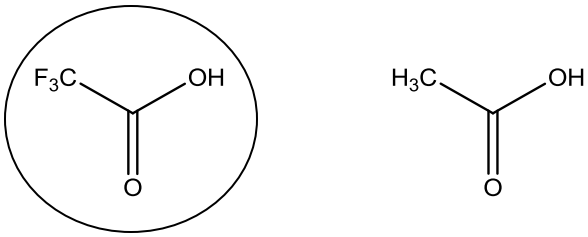
The electron-donating effects of the nitrogen in 4-(dimethylamino)benzoate (left) make deprotonation unfavorable.



The electron-withdrawing inductive effects of the nitro group in 4-nitrobenzoate (right) help to stabilize the resulting negative charge, making deprotonation more favorable.



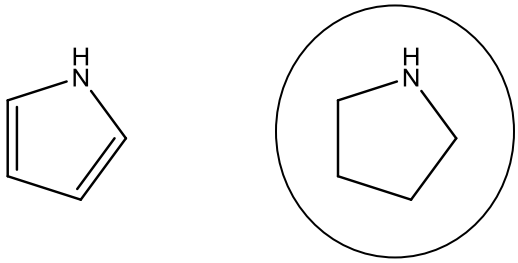
B)



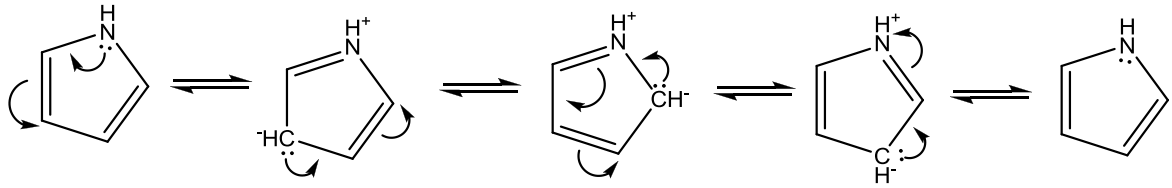
Electron-withdrawing inductive of the fluorines in trifluoroacetic acid (left) stabilizes negative the negative charge, favoring deprotonation. The electron-donating inductive effect of acetic acid (right) disfavors deprotonation.

2. Which compound is more basic? Why?

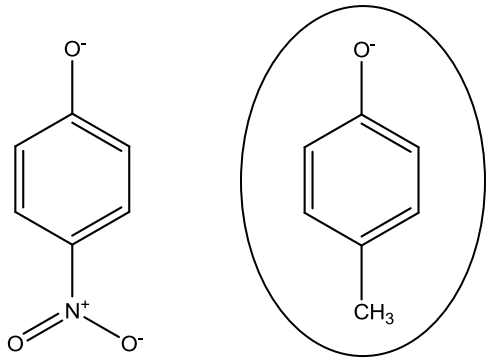
A)



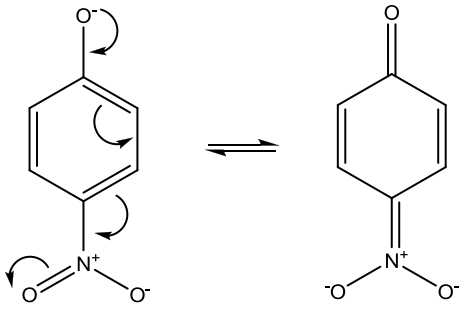
The lone pair of electrons on the pyrrole (left) nitrogen are involved in resonance stabilization as shown below and thus are not readily available for protonation. However the lone pair on the pyrrolidine (right) nitrogen are not involved in resonance and are readily available to receive a proton.



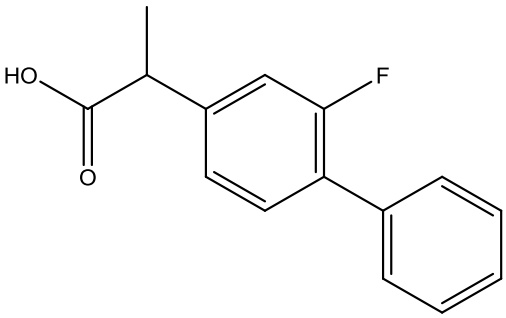
B)



Para-nitrophenolate (left) can stabilize the negative charge on the oxygen via resonance stabilization utilizing the nitro group. Para-methylphenolate (right) does not have the same extent of resonance stabilization, thus making the lone pair of electrons on the oxygen more available to receive a proton.



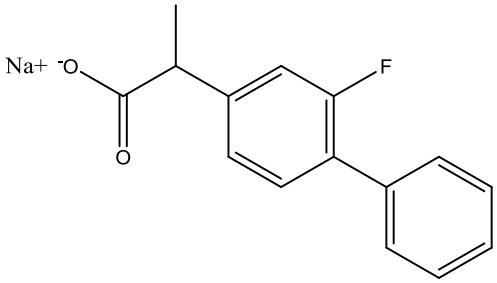
3. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) used to relieve pain, tenderness, swelling, and stiffness caused by osteoarthritis and rheumatoid arthritis. Given its structure below, answer the following questions.



A) What is the approximate pKa of this compound?

4-5 (pKa of most carboxylic acids without a significant electron-withdrawing group)

B) Draw the structure of the sodium salt of this compound. What are the advantages of administering the salt form of the drug?



The salt form of the drug allows for more rapid and complete dissolution of the drug from its tablet form in physiological fluids. This can result in an increased rate and extent of drug absorption, and both of these factors can lead to decreased intersubject variability in drug absorption.

C) Using the Henderson-Hasselbalch equation, calculate the ionized/unionized ratio of the drug at pH 7.

Assuming pKa = 4:

$pH = pKa + \log([A^-]/[HA])$ ➔ $pH - pKa = \log([A^-]/[HA])$ ➔ $10^{(pH-pKa)} = ([A^-]/[HA])$

➔ $10^{(7-4)} = ([A^-]/[HA])$ ➔ $10^3 = ([A^-]/[HA])$ = **1000/1**

The acid (HA) is Flurbiprofen and the conjugate base (A^-) is the ionized form as seen in part B above.

D) If a large fraction of the administered dose of Flurbiprofen is cleared renally in its unprotonated form, would this drug have a longer duration of action at a urinary pH of 4 or 8? Explain your answer.

Still assuming pKa = 4:

<u>At pH 4:</u>

$pH = pKa + \log([A^-]/[HA])$ ➔ $pH - pKa = \log([A^-]/[HA])$ ➔ $10^{(pH-pKa)} = ([A^-]/[HA])$

➔ $10^{(4-4)} = ([A^-]/[HA])$ ➔ $10^0 = ([A^-]/[HA])$ = **1/1**

<u>At pH 8:</u>

$pH = pKa + \log([A^-]/[HA])$ ➔ $pH - pKa = \log([A^-]/[HA])$ ➔ $10^{(pH-pKa)} = ([A^-]/[HA])$

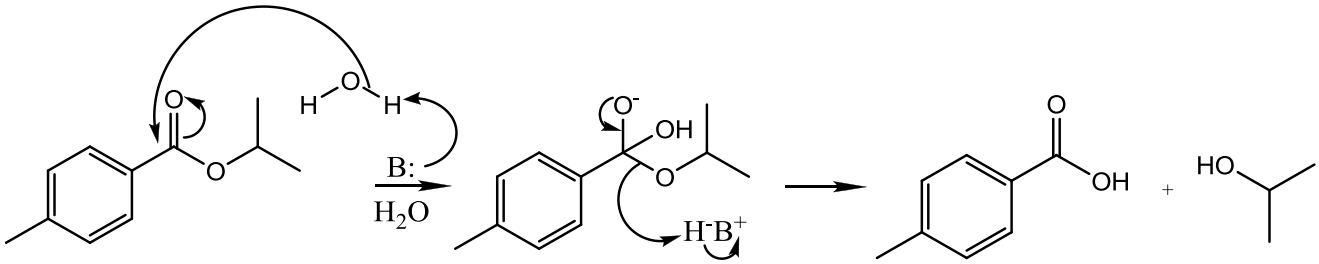
➔ $10^{(8-4)} = ([A^-]/[HA])$ ➔ $10^4 = ([A^-]/[HA])$ = **10000/1**

More of the drug will be in an ionized form at pH 8 compared to pH 4. As a result, more of the drug at pH 8 will be soluble in the aqueous urine and will get excreted more rapidly than at pH 4, resulting in a shorter duration of action at pH 8.

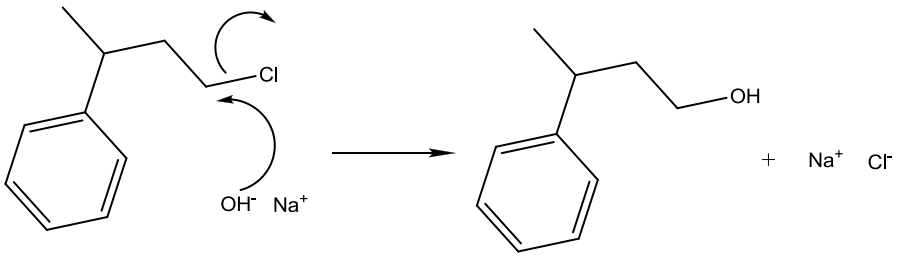
<u>Reaction Mechanisms</u>

Draw the mechanisms for the following reactions and give the structures for the expected products.

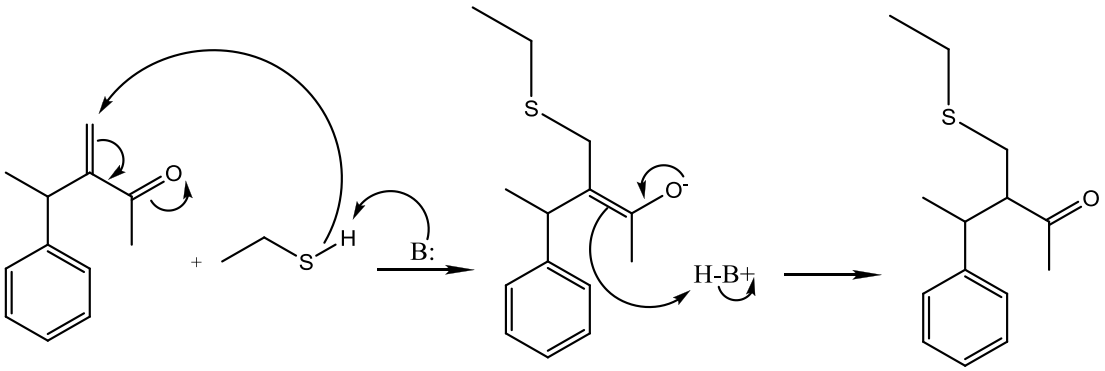
1. General base-catalyzed hydrolysis:



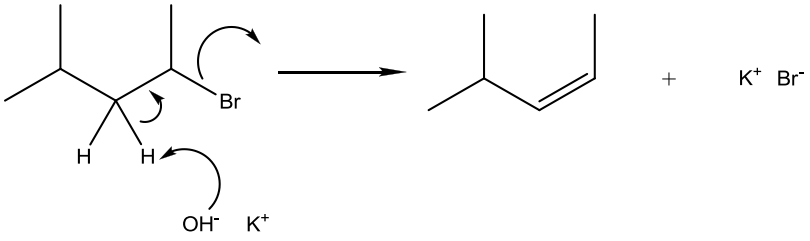
2. Nucleophilic substitution:



3. Special nucleophilic addition (Michael Addition):

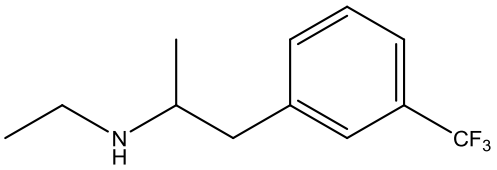


4. Base-catalyzed elimination (For this one only draw the major product):

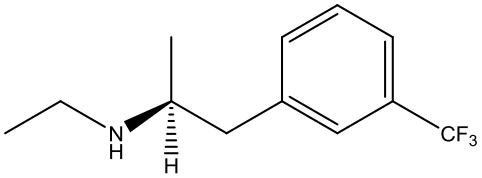


Stereochemistry

1. Dexfenfluramine (structure below) exists only as the S-isomer. Draw this configuration.



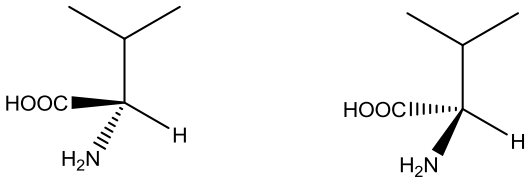
S-enantiomer:



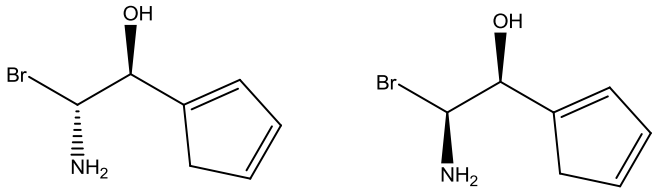
2. For each pair of compounds below, identify whether they are:

a. Geometric Isomers
b. Positional Isomers
c. Enantiomers
d. Diastereomers

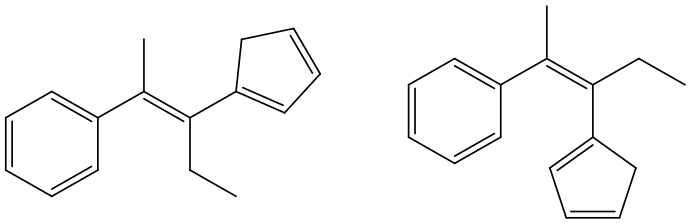
i) Enantiomers



ii) Diastereomers



iii) Geometric Isomers



iv) Positional Isomers