

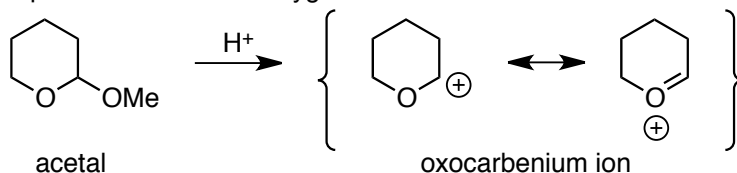
Discussion Section 2: Aromaticity

1. Aromatic rings are crucial structures in biologically active compounds. Their prevalence is particularly evident when you look at the top pharmaceutical products in the U.S. (see attached page).

(a) Find the aromatic rings in the top 20 pharmaceutical products.

(b) For each aromatic system, please give the number of electrons in the π system.

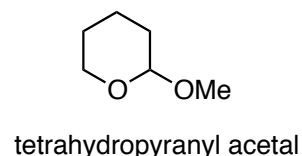
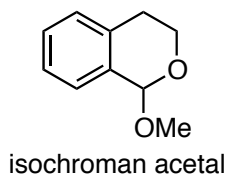
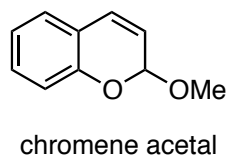
2. In the Watson research group, we are developing reactions of oxocarbenium ion intermediates. These intermediates are formed from acetal starting materials. Oxocarbenium ions are a special class of carbocation, in which the positive charge is stabilized by the lone pair of electrons on oxygen.



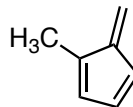
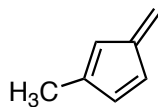
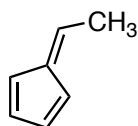
(a) Draw an arrow-pushing mechanism for the formation of an oxocarbenium ion from an acetal. Include arrows to show explain the resonance stabilization of the oxocarbenium ion.

(b) What do you think the hybridization of the oxygen atom in the oxocarbenium ion is? What is the hybridization of the cationic carbon atom?

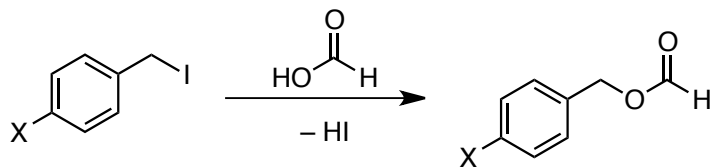
(c) In our research, we have found that oxocarbenium ions form easily from chromene and isochroman acetals, but not as easily from tetrahydropyranyl acetals. Please explain these observations. (Hint: You may find it helpful to use resonance structures to justify parts of your answer.)



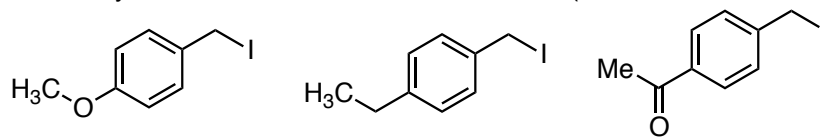
3. Which of the following molecules is expected to be most acidic? Please explain.



4. Consider the S_N1 reaction of the following substituted benzyl halides in formic acid:

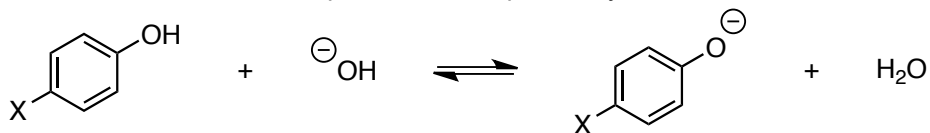


(a) Predict the order of reactivity of the three substrates shown below (1 = fastest, 3 = slowest):

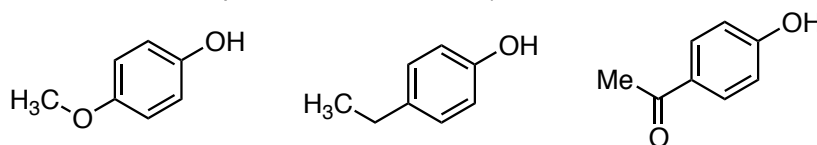


(b) For the most reactive substrate in (a), draw the significant resonance structures that contribute to the stability of the derived intermediate carbonium ion.

5. Consider the acid-base reaction of substituted phenols with aqueous hydroxide:



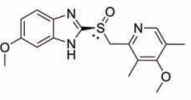
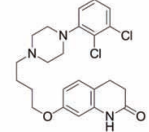
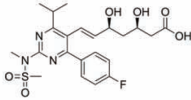
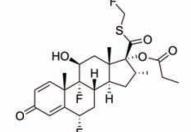
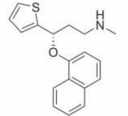
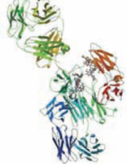


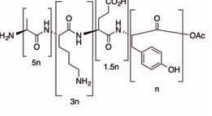
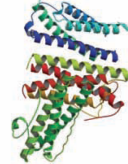
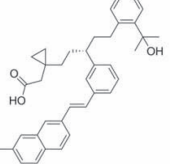

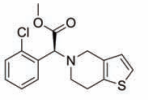
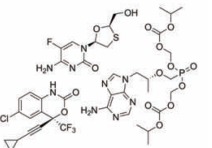
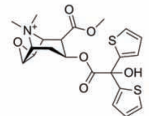
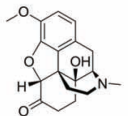
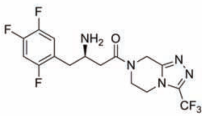

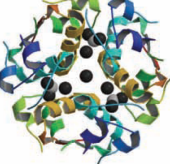
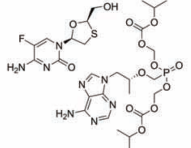
(a) Predict the acidity order for the three phenols shown below (1 = most acidic, 3 = least acidic):



(b) For the most acidic substrate in (a), draw the significant resonance structures that contribute to the stability of the derived conjugate base.

Top 20 Pharmaceutical Products by US Retail Sales in 2012

Adapted from Top 200 Pharmaceutical Products by the Njardarson Group at the University of Arizona

<p>1 Nexium (Esomeprazole)</p>  <p>AstraZeneca \$5,989 Million ANTIULCERANTS</p>	<p>2 Abilify (Aripiprazole)</p>  <p>Otsuka \$5,870 Million ANTIPSYCHOTICS</p>	<p>3 Crestor (Rosuvastatin)</p>  <p>AstraZeneca \$5,092 Million CHOLEST&TRIGLY.REGULATOR</p>	<p>4 Advair Diskus (Fluticasone Propionate)</p>  <p>gsk GlaxoSmithKline \$4,889 Million CORTICOIDS</p>	<p>5 Cymbalta (Duloxetine)</p>  <p>Lilly \$4,720 Million ANTIDEPRESS.& MOOD STAB.</p>	<p>6 Humira (Adalimumab)</p>  <p>abbvie \$4,609 Million SPEC ANTIRHEUMATIC AGENT</p>	<p>7 Enbrel (Etanercept)</p>  <p>AMGEN \$4,337 Million SPEC ANTIRHEUMATIC AGENT</p>
<p>8 Remicade (Infliximab)</p>  <p>Centocor \$3,876 Million IMMUNOSUPPRESSIVE AGENTS</p>	<p>9 Copaxone (Glatiramer Acetate)</p>  <p>TEVA \$3,581 Million IMMUNOSTIM AG EX INTFRON</p>	<p>10 Neulasta (Pegfilgrastim)</p>  <p>AMGEN \$3,460 Million IMMUNOSTIM AG. EX. INTFRON.</p>	<p>11 Singulair (Montelukast)</p>  <p>MERCK \$3,300 Million ANTILEUK ANTI-ASTHMATICS</p>	<p>12 Rituxan (Rituximab)</p>  <p>Genentech IN BUSINESS FOR LIFE \$3,197 Million ALL OTH. ANTINEOPLASTICS</p>	<p>13 Plavix (Clopidogrel)</p>  <p>Bristol-Myers Squibb sanofi aventis \$2,971 Million PLATELET AGGR.INHIBITORS</p>	<p>14 Atripla (Emtricitabine, Tenofovir Disoproxil & Efavirenz)</p>  <p>Bristol-Myers Squibb \$2,899 Million HIV ANTIVIRALS</p>
<p>15 Spiriva HandiHaler (Tiotropium)</p>  <p>Boehringer Ingelheim \$2,833 Million CHR. OBS. PULMONARY DIS.</p>	<p>16 OxyContin (Oxycodone)</p>  <p>PURDUE \$2,808 Million NARCOTIC ANALGESICS</p>	<p>17 Januvia (Sitagliptin)</p>  <p>MERCK \$2,670 Million DPP-IV INHIBITOR A-DIABS</p>	<p>18 Avastin (Bevacizumab)</p>  <p>Genentech IN BUSINESS FOR LIFE \$2,661 Million ALL OTH. ANTINEOPLASTICS</p>	<p>19 Lantus (Insulin Glargine)</p>  <p>sanofi aventis \$2,327 Million HUMAN INSULIN+ANALOGUES</p>	<p>20 Truvada (Emtricitabine & Tenofovir)</p>  <p>GILEAD \$2,305 Million HIV ANTIVIRALS</p>	