

Exercise 6 - Structure - Activity Relationships: Acidity and pK_a Values

For each pair of compounds, write the pertinent reaction and predict which compound of the pair should be the strongest acid. Explain your answer.

- acetic acid or chloroacetic acid
 $HA = H^+ + A^-$ The Cl should lower the ΔG for the reaction primarily by delocalizing the negative charge of the conjugate base.
- 2-chloropropanoic acid or 3-chloropropanoic acid
 $HA = H^+ + A^-$ The Cl on the 2nd carbon should lower the ΔG for the reaction more than the Cl on the third carbon primarily by delocalizing the negative charge of the conjugate base more as it is closer to the center of charge.
- chloroacetic acid or fluoroacetic acid
 $HA = H^+ + A^-$ The F should lower the ΔG for the reaction more than the Cl by delocalizing the negative charge of the conjugate base more as the F is more electronegative than Cl.
- propane or ethanol
 $CH_3CH_2CH_3 + B = CH_3CH_2CH_2^- + HB^+$ $CH_3CH_2OH + B = CH_3CH_2O^- + HB^+$
 The ΔG for the ethanol reaction should be substantially lower than for the propane reaction as the negative charge in the conjugate base is on the electronegative oxygen as contrasted with the highly energetic negative charge on a carbon.
- propane or acetone
 $CH_3CH_2CH_3 + B = CH_3CH_2CH_2^- + HB^+$ $CH_3COCH_3 + B = CH_3COCH_2^- + HB^+$
 The ΔG for the acetone reaction should be substantially lower than for the propane reaction as the negative charge in the conjugate base is on a resonance stabilized conjugate base with the negative charge shared by an oxygen as contrasted with the highly energetic negative charge solely on a carbon for the conjugate base of propane.
- ethane or acetylene
 Although most tables of electronegativities list a value of 2.5 for the electronegativity of carbon, a closer examination reveals not surprisingly that electronegativity depends on hybridization. For carbon, the Mulliken-Jaffe electronegativity scale gives the values 2.99, 2.66, 2.48 for sp, sp² and sp³ hybridized carbon respectively. For more information on electronegativity, see:
http://www.meta-synthesis.com/webbook/36_eneg/electroneg.html
 a. Comment on whether these values are consistent with hybridization models and electronegativity concepts.
 b. Are these electronegativity values consistent with the acidity rankings of ethane, ethylene and acetylene? Explain your answer.
 $CH_3CH_3 + B = CH_3CH_2^- + HB^+$ $CHCH + B = CHCH^- + HB^+$
 The more the s character of a hybrid orbital, the closer the orbital is to the nucleus resulting in less instability for a negative charge on the carbon as the s character increases. Thus the ΔG for the formation of the conjugate base should decrease going from ethane to ethene to acetylene. This is consistent with experimental results.
- methylcyclohexane or toluene
 $C_6H_{11}CH_3 + B = C_6H_{11}CH_2^- + HB^+$ $PhCH_3 + B = PhCH_2^- + HB^+$
 The ΔG for the formation of the conjugate base of toluene should be lower than for methylcyclohexane as the conjugate base of toluene has some delocalization of the negative charge via resonance into the ring but even toluene will be an extremely weak acid.
- benzoic acid or 4-nitrobenzoic acid
 $XPhCH_3 + B = XPhCH_2^- + HB^+$
 As indicated in #7 above, there is some delocalization of the negative charge in the conjugate bases of these two acids. The nitro is strongly electron withdrawing and will help stabilize its conjugate base and lower the ΔG .

9. benzoic acid or 4-chlorobenzoic acid
 $XPhCH_3 + B = XPhCH_2^- + HB^+$
 As with the nitro in #8 above, the Cl will help stabilize the negative charge in the conjugate base and lower the ΔG making 4-chlorobenzoic acid the stronger acid.
10. ethanol or ethanethiol
 $CH_3CH_2OH + B = CH_3CH_2O^- + HB^+$ $CH_3CH_2SH + B = CH_3CH_2S^- + HB^+$
 Although oxygen is more electronegative than sulfur, several factors make the thiols more acidic than the alcohols. Alcohols have hydrogen bonding that stabilizes the acid and increases the ΔG . The larger size of sulfur allows it to accommodate the negative charge easier and lower the ΔG .
11. ethanol or 2,2,2-trifluoroethanol
 $CH_3CH_2OH + B = CH_3CH_2O^- + HB^+$ $CF_3CH_2OH + B = CF_3CH_2O^- + HB^+$
 The very electronegative fluorines will help delocalize the negative charge on the conjugate base.
12. cyclopentane or cyclopentadiene
 $HA = H^+ + A^-$
 The conjugate base of cyclopentadiene is not only stabilized by resonance, it is a $4n+2 \pi e^-$ system and therefore aromatic. This stabilization lowers the ΔG and makes cyclopentadiene a much stronger acid than cyclopentane.
13. acetone or acetic acid
 $CH_3COCH_3 + B = CH_3COCH_2^- + HB^+$ $CH_3COOH + B = CH_3COO^- + HB^+$
 Both conjugate bases are stabilized by resonance but acetate has the negative charge distributed between 2 oxygens which is better than the charge being distributed between a carbon and oxygen.
14. acetone or 2,4-pentanedione
 $CH_3COCH_3 + B = CH_3COCH_2^- + HB^+$ $CH_3COCH_2COCH_3 + B = [CH_3COCHCOCH_3]^- + HB^+$
 The conjugate base of 2,4-pentanedione is stabilized by 3 resonance structures as compared with 2 for acetone. In addition, two of the three have the negative charge on an oxygen and have increased conjugation.
15. cyclohexanol or phenol
 $ROH + B = RO^- + HB^+$ $PhOH + B = PhO^- + HB^+$
 The conjugate base of phenol has some delocalization of the negative charge into the ring.
16. phenol or 4-nitrophenol
 $PhOH + B = PhO^- + HB^+$ $p-NO_2PhOH + B = p-NO_2PhO^- + HB^+$
 The nitro helps stabilize the negative charge.
17. 3-nitrophenol or 4-nitrophenol
 $m-NO_2PhOH + B = m-NO_2PhO^- + HB^+$ $p-NO_2PhOH + B = p-NO_2PhO^- + HB^+$
 Resonance structures demonstrate that the para nitro can interact more with the negative charge.
18. phenol or 4-methylphenol
 $PhOH + B = PhO^- + HB^+$ $p-CH_3PhOH + B = p-CH_3PhO^- + HB^+$
 Methyl destabilizes a negative charge.
19. ethane or nitromethane
 $CH_3CH_3 + B = CH_3CH_2^- + HB^+$ $NO_2CH_3 + B = NO_2CH_2^- + HB^+$
 The nitro group stabilizes the negative charge via resonance stabilization.
20. ethane or acetonitrile
 $CH_3CH_3 + B = CH_3CH_2^- + HB^+$ $NCCH_3 + B = NCCH_2^- + HB^+$
 The cyano group stabilizes the negative charge via resonance stabilization.

Exercise 7 - Choosing Laboratory Procedures

A. Separation and purification. The techniques of evaporation, filtration (gravity and vacuum), recrystallization, extraction, chromatography (thin layer, column and gas) and distillation (simple, fractional, vacuum and steam) are commonly used for separation and purification. For each problem below, state which method you would try first. Explain your choice.

- 10 mL of a 1:1 mixture of methanol and 1-butanol *The boiling points are far enough apart for a simple distillation.*
- 10 mL of a 1:1 mixture of methanol and ethanol *Fractional distillation.*
- 2 grams of aspirin contaminated with sand and naphthalene *Recrystallization with both hot and cold filtrations.*
- The amino acids that result from the breaking of the amide linkages in milk protein (0.01 g). *Different types of chromatography should work including thin layer, column and HPLC.*
- A mixture containing 1 g of benzoic acid, 1 g of 2-aminonaphthalene and 1 g of naphthalene *Extraction with acid and then base.*
- A 10 mL contaminated sample of styrene {Note that styrene polymerizes when heated to its atmospheric pressure boiling point}. *Vacuum distillation.*
- Isolation of carvone from spearmint leaves *Steam distillation followed by vacuum distillation or column chromatography.*
- Separation of 1 g of a 1:1 mixture of anthracene and 9-acetylanthracene *Column chromatography.*

B. Product workup. After a reaction is run to synthesize a product, work up procedures usually starting with extraction followed by recrystallization or distillation are performed. For each of the synthesis given below, describe the work-up procedure you would use to separate and purify the desired product.

- Bromobenzene is reacted with magnesium to make a Grignard reagent. The phenyl magnesium bromide in ether is subsequently reacted with dry ice to make benzoic acid. What steps should follow?
The product mixture should be treated with acid. Base should be used to extract the acid product from the ether layer. The base should be acidified and the acid product extracted with ether. The ether should be dried and evaporated.
- 20 mL of 3,3-dimethyl-2-butanol is dehydrated with 8 M sulfuric acid. How would you isolate the alkene?
The alkene layer should be washed with water and bicarbonate solution followed by drying and distillation. Introduction of a solvent such as pentane should be avoided as the product has a low boiling point and a solvent will be difficult to separate from the solvent.
- Cyclohexanone is reacted with sodium borohydride in slightly basic aqueous solution. After reaction is complete, 6 M HCl is added until the solution is slightly acidic. How would you isolate and purify the cyclohexanol?
Ether should be added to extract the product. The ether layer should be washed with water and bicarbonate followed by drying. The ether should be evaporated off and the product distilled.
- Vanillin is reacted with sodium borohydride in 1 M NaOH solution. After reaction is complete, 6 M HCl is added until the solution is slightly acidic. How would you isolate and purify the vanillyl alcohol?
Ether should be added to extract the product. The ether layer should be washed with water and bicarbonate followed by drying. The ether should be evaporated off and the product recrystallized.
- Using sulfuric acid as a catalyst, salicylic acid is esterified in methanol under reflux. How would you isolate and purify the methyl salicylate (oil of wintergreen)? *Distill off the methanol. Wash the organic layer with water and bicarbonate solution and dry and vacuum distill the organic layer.*
- Aluminum chloride, acetyl chloride and p-xylene are refluxed in methylene chloride. How would you isolate and purify the product? *The organic product should be washed with water and bicarbonate. The methylene chloride layer should be dried and the methylene chloride evaporated or distilled off. The product should be purified by vacuum distillation.*
- Furan and maleic anhydride are allowed to sit in an ether solution for several days until a product crystallizes out of the solution. How would you isolate and purify the product? *The Diels-Alder product should be collected by filtration, washed with hexane and recrystallized from a mixture of hexane and ethyl acetate.*

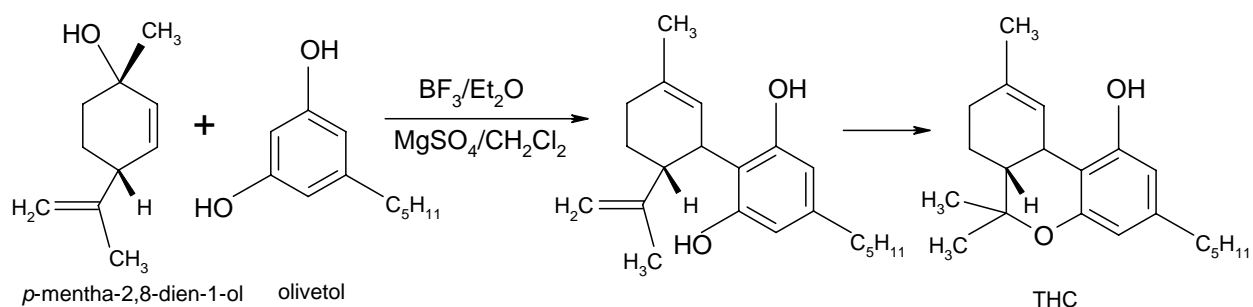
C. Analysis or identification. For each of the problems in B above, describe what you would do to determine the identity and purity of the product.

- a. *Benzoic acid should be identifiable from its melting point with confirmation from a mixed melting point or ir.*
- b. *The alkene should be identifiable from its refractive index and ir and nmr spectra.*
- c. *Cyclohexanol has a melting point near room temperature making refractive index and melting points difficult. Ir and nmr should provide structure verification.*
- d. *Vanillyl alcohol should be identifiable from its melting point with confirmation from a mixed melting point or ir.*
- e. *The first piece of evidence will be its familiar smell but verification can come from refractive index and spectra.*
- f. *2,5-dimethylacetophenone should be identifiable from its refractive index, ir or nmr.*
- g. *Exo and endo could form and if one predominates, the melting point can distinguish them. Verification can be obtained with spectra.*

Exercise 8 - Mechanisms of Reactions

1. The mechanisms of nucleophilic substitution reactions (S_N1 , S_N2) are usually extensively studied in organic chemistry courses.
 - a. Please refer to a textbook for answers to this question.
 - b. Please refer to a textbook for answers to this question.
 - c. An S_N1 is a two step reaction with an intermediate. The reaction rate depends on the concentration of alkyl halide but not on the concentration of the nucleophile. An S_N2 reaction is a one step reaction and its rate depends on the concentrations of both the alkyl halide and the nucleophile. The obvious way to distinguish them is to change the concentration of nucleophile and determine if the rate changes. The solvent is another variable but the reaction rate dependence on the solvent is complex. Simplifying, in an S_N1 $R-X$ splits into R^+ and X^- in the rate determining step which generally means that reaction goes to the intermediate with an increase in polarity. Increasing the polarity of the solvent should increase the reaction rate for an S_N1 but mildly decrease the rate of the S_N2 reaction discussed here. Other variables that can be changed also change the reaction and do not necessarily provide definitive evidence about the reaction under discussion. For example, increasing the nucleophilicity of the nucleophile should increase the rate of a S_N2 reaction but not affect the rate of an S_N1 reaction. Refer to the question for a discussion of using structure change to determine the mechanism.
2. These results provide strong evidence that the reaction goes to a common intermediate that can combine with water to give the alcohol or lose a proton to give the elimination product. Since the $C-Br$ bond is weaker than a $C-Cl$ bond it breaks faster to give the carbocation intermediate. The S_N1 and E_1 reactions that occur here go through the same intermediate.
3. The first step in the above reaction must be protonation of the $O-H$ followed by water leaving in an S_N1 reaction that is independent of the chloride concentration.
4. In the first step, the oxygen of the alcohol displaces a chloride from thionyl chloride. The final step involves transfer of the second chloride attached to the sulfur to the carbon. Since this chloride comes from the same side as the oxygen being lost, retention is usually observed.
5.
 - a. A mechanism shows that to yield the meso isomer, the addition had to be anti.
 - b. The chloride will compete with the bromide during the attack on the bromonium ion and 2-bromo-3-chlorobutane [equal mixture of (2*S*,3*R*)-2-bromo-3-chlorobutane and (2*R*,3*S*)-2-bromo-3-chlorobutane] will be formed.
 - c. Since the rate of formation of the bromonium intermediate does not depend on the concentration of nucleophile, the chloride should not affect the rate of product formation but an increase in chloride will increase the percentage of the chloride containing product.
6. This evidence rules out the possibility of a reversible first step protonation of the terminal carbon. If it were reversible, the terminal carbon would sometimes lose D^+ instead of a proton which would decrease the deuterium amount in recovered starting material. This implies that once the carbocation is formed, it reacts in a fast step with the nucleophile to form product.
7.
 - a. This evidence supports a mechanism with the benzylic carbon-hydrogen being broken in the rate determining step and rules out an E_1 mechanism. However, it does not prove that the mechanism is E_2 as the kinetic isotope effect is also consistent with an E_{1cb} mechanism.
 - b. This result is consistent with a kinetic isotope effect of 7 as the $C-H$ bond is broken about 7 times as often as the $C-D$ bond to give 7 times as much product with the deuterium remaining.
8. This result provides evidence that the $C-H$ or $C-D$ bond does not experience significant change in the rate determining step. The rate determining step involves attack by the electrophile on the ring to form a resonance stabilized carbocation.

9. This evidence supports a rate determining step that forms a common intermediate. The ketone reacts with base to yield the conjugate base of the ketone.
10. This evidence demonstrates that CO-O is the bond that breaks rather than the C-O of resulting alcohol portion.
11. This evidence strongly supports the reversible formation of a tetrahedral intermediate that result from attack of the hydroxide on the carbonyl carbon. It rules out the possibility that the hydroxide displaces the leaving alcohol in a one step reaction.
12. This result strongly supports the formation of a symmetrical intermediate called benzyne. Further evidence can and has been provided by the trapping of the intermediate using a diene to result in a Diels-Alder reaction.
13. A one-step synthesis of THC from *p*-mentha-2,8-dien-1-ol and olivetol was reported by Razdan et. al. [Razdan, R. K.; Daizell, C.; Handrick, G. R. *J. Am. Chem. Soc.*, **1974**, 96, 5860-5865. "Hashish. A Simple One-Step Synthesis of (-)- Δ^1 -Tetrahydrocannabinol (THC) from *p*-Mentha-2,8-dien-1-ol and Olivetol"]. At first glance, the synthesis looks complex but more careful inspection reveals that the synthesis can be broken down into two reactions, a Friedel-Crafts like attack of a carbocation on an activated aromatic ring followed by electrophilic addition to a double bond. Each of these reactions should be understandable in terms of mechanisms studied in the organic chemistry course. Write a detailed step by step mechanism for the overall reaction.



The mechanism here is left for the instructor.