Ch 17 Alcohols and Phenols

Alcohols are compounds with a hydroxyl group (OH) attached to an sp^3 C.
Phenols are compounds with a hydroxyl group (OH) attached to an aromatic sp^2 C.

Classification of Alcohols - RCH_2OH is 1°, R_2CHOH is 2°, and R_3COH is 3°.

Naming Alcohols
1. The longest chain containing the OH is the parent.
    Name the parent from the alkane name by changing the final "e" with "ol",
    such as methanol and pentanol.
2. Number the C's in the parent, starting with #1 as the end that is closest to OH.
    Precede either the parent name or the "ol" ending with the C # for the OH, such
    as 2-pentanol or hexan-1-ol.
3. Identify and number the remaining substituents. List them alphabetically.
4. There are many common names, where the alkyl group name followed by "alcohol",
    such as isopropyl alcohol (2-propanol), *tert*-butyl alcohol (2-methyl-2-propanol),
    benzyl alcohol (phenylmethanol), and allyl alcohol (2-propen-1-ol). Also, small
    1,2-diols are commonly called glycols, and 1,2,3-propanetriol is called glycerol.

Naming Phenols
1. Phenol is the parent, and the C with the OH is #1.
2. All the remaining substituents are numbered, although
    ortho, meta, and para can be used instead.

Properties
-   The sp^3 alcoholic C has tetrahedral geometry, with four bonds that are ~109.5^o apart.
-   The sp^2 phenolic C has trigonal planar geometry, with three bonds that are ~120° apart.
-   Both alcohol and phenols have higher boiling points than analogous compounds that are
    without OH. The increased boiling points result from hydrogen bonding.

Acidity and Basicity of Alcohols and Phenols
-   Alcohols and phenols can act as acids, and are deprotonated by bases
    to form alkoxide anions (RO^{-1}) and phenoxides (ArO^{-1}).
-   Alkoxide ions, such as the anion portion of sodium methoxide ($NaOCH_{3)}$,
    are used not only as bases (B:), but also as nucleophiles (Nu).
-   Alcohols and phenols can act as bases, and are protonated by acids
    to form oxonium cations (ROH_2^{+1}).
-   Small 1° alcohols have K_A's and pK_A's that are similar to that
    of water ($K_A = K_W \div [H_2O] = 1.82 \times 10^{-16}$ and $pK_A = 15.74$).
-   2° and 3° alcohols have lower K_A's due to steric hindrance.
    The additional alkyl groups make the OH less available to the base.
-   An e^{-1} withdrawing substituent, such as a halogen, will increase acidity
   by stabilizing the alkoxide anion.

- Because alcohols are weak acids, they do not react appreciably with weak bases, and react only weakly with NaOH. They react with very strong bases such as alkali metals (Na and K), hydride anions (H^{-1}, such as in NaH), amide anions (NH_2^{-1}, such as in $NaNH_2$), and Grignard reagents (RMgX, such as CH_3CH_2MgCl).
- Phenols are more acidic than alkyl alcohols because the aromatic ring is e^{-1} withdrawing, and it stabilizes the phenoxide anion with e^{-1} withdrawing resonance.
  The pK_A of phenol is 9.89, which is considerably lower than that of alkyl alcohols.
- An e^{-1} withdrawing substituent, such as a nitro group (NO_2), will increase a phenol's acidity by creating additional resonance forms, which further stabilize the phenoxide anion. The pK_A of p-nitrophenol is 7.15, which is lower than that of phenol.
- An e^{-1} donating substituent, such as an amino group (NH_2), will decrease a phenol's acidity by destabilizing the phenoxide anion.
  The pKA of p-aminophenol is 10.46, which is higher than that of phenol.

Preparation of Alcohols from Alkenes (Refer to Chapter 8 Alkene Reactions)
- Markovnikov addition (OH on more substituted C) can be done by oxymercuration:
  1. $Hg(OAc)_{2(aq)}$ 2. $NaBH_4$
- Non-Markovnikov addition (OH on less substituted C) can be done by hydroboration:
  1. BH_3 / THF   2. H_2O_2 / OH^{-1}
- Diols can be made (in cis configuration from cycloalkenes) with osmium (VIII) oxide:
  1. OsO_4 (catalyst)   2. NMO (N-methylmorpholine N-oxide)
- Diols can also be made (in trans from cycloalkenes) with a peroxycarboxylic acid:
  1. RCO_3H in CH_2Cl_2 2. H_3O^{+1}

Preparation by Reduction of Carbonyls (with Hydrides)
- The general reaction scheme has two steps. In the first step, a hydride ion (H^{-1}) acts as a nucleophile, and adds to the carbonyl C to create an alkoxide (RO^{-1}).
  Then, acid is used to add H^{+1} to the negative oxygen atom, which creates the alcohol.
- For aldehydes (RCHO) and ketones ($R_2C=O$), $NaBH_4$ is sufficient:
  1. $NaBH_4$ in ethanol   2. H_3O^{+1}
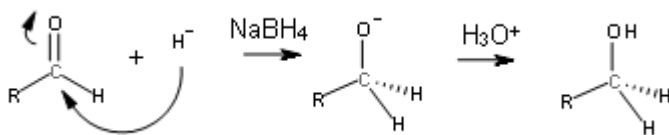
- Aldehydes are converted to 1° alcohols, while ketones are converted to 2° alcohols.
- $LiAlH_4$ can also be used, not only with aldehydes and ketones, but also with carboxylic acids (RCOOH) and esters (RCOOR'):
  1. $LiAlH_4$ in ether   2. H_3O^{+1}
  Both acid and ester are converted to 1° alcohols.
  The ester reaction will additionally convert the R' alkyl group to an alcohol as well.
- $LiAlH_4$ is much more reactive than $NaBH_4$. However, it is also more dangerous to handle. Not only does it react violently with water, acids, and oxygenated compounds, it also will ignite or explode when heated.
- Also, carboxylic acids (RCOOH) can be reduced more efficiently with BH_3/THF.

Preparation by Reaction of Carbonyls with Grignard Reagents
- These reactions are similar to the hydride reactions, except that the nucleophile is essentially a carbanion (R^{-1}) from the Grignard reagent (RMgX).
- This reaction scheme will work with aldehydes, ketones, and esters:
      1. RMgX in ether   2. H_3O^{+1}
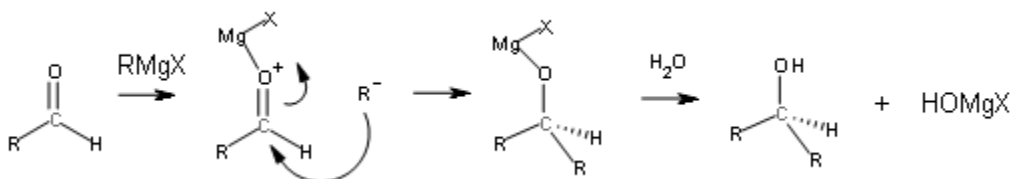
- Formaldehyde ($H_2C=O$) is converted to a 1° alcohol, while all other aldehydes (RCHO) are converted to 2° alcohols. Ketones ($R_2C=O$) are converted to 3° alcohols. Esters (RCOOR') are also converted to 3° alcohols, with the R' alkyl group converted to an alcohol as well.
- Carboxylic acids are not converted to alcohols because an acid-base reaction occurs instead. This reaction creates an acid salt and an alkane:
      $RCOOH + R^{-1}(MgX)^{+1} \rightarrow RCOO^{-1}(MgX)^{+1} + RH$

Elimination and Substitution Reactions of Alcohols
- Refer to Chapter 11 Alkyl Halide Reactions to review S_N1, S_N2, E1, and E2 reactions.
- 3° alcohols are easily converted to 3° halides.
  This happens with HCl and HBr by acid-catalyzed S_N1 reactions.
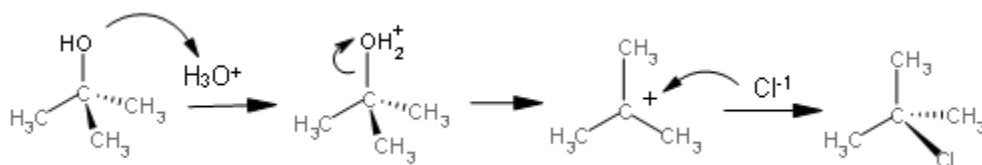
- 1° and 2° alcohols are converted to halides with $SOCl_2$ and PBr_3.
  These reactions are S_N2 after converting the $-OH$ to $-OSOCl$ or $-OPBr_2$.
      $RCH_2OH + PBr_3 \rightarrow H^{+1} + Br^{-1} + RCH_2OPBr_2 \rightarrow RCH_2Br + HOPBr_2$
- 2° and 3° alcohols can be converted to alkenes with $POCl_3$ (phosphorus oxychloride) in pyridine (C_5H_5N).
  These reactions are E2 after converting the $-OH$ to $-OPOCl_2$.
  Pyridine is the base, and it extracts H^{+1} from an adjacent C at the same time that $OPOCl_2^{-1}$ leaves.
  The product generally follows Zaitsev's rule.

- 2° and 3° alcohols can also be converted to alkenes by acid-catalyzed dehydrations.
  These reactions are E1, and have the same first step as S_N1 reactions.
  After the carbocation is created, H_2O extracts H^+ from an adjacent C.
  H_2SO_4 and H_3PO_4 work best because their anions are poor nucleophiles.
 Also, the product generally follows Zaitsev's rule.
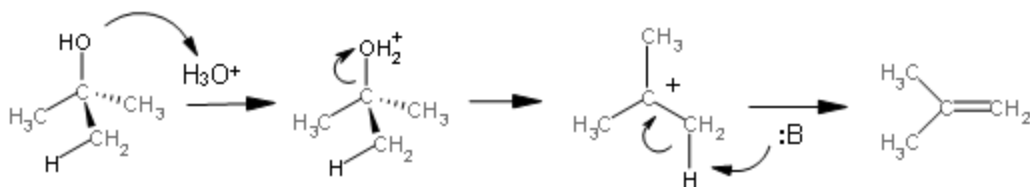
Alkyl Tosylates (R-OTos)
- Alcohols react with p-toluenesulfonyl chloride ($CH_3-Ph-SO_2Cl$ or tosyl chloride) to
  form alkyl tosylates ($R-OTos$). These reactions are not S_N1 or S_N2.
- The tosyl group ($CH_3-Ph-SO_2-$) replaces the alcohol H
  without altering the C-O bond.
- Tosylates make good leaving groups, and are often created when it is important not to
  change the chirality (as in S_N2 reactions).

Oxidation
- Works only with 1° and 2° alcohols.
- 1° alcohols are typically converted to carboxylic acids through an
  aldehyde intermediate ($RCH_2OH \rightarrow RCHO \rightarrow RCOOH$).
- 2° alcohols are converted to ketones ($R_2CHOH \rightarrow R_2CO$).
- 3° alcohols do not oxidize with these reactions because
  the three C-C bonds are not broken easily.
- CrO_3 and $Na_2Cr_2O_7$ are inexpensive chromium (VI) oxidizing agents, and
  are often used along with H_2SO_4 to create carboxylic acids and ketones.
- PCC (pyridinium chlorochromate, or $C_5H_5NH^{+1}CrO_3Cl^{-1}$) will convert
  1° alcohols to aldehydes without further oxidation to carboxylic acids.
  PCC essentially supplies CrO_3 in a more controlled fashion.
- The reaction is equivalent to E2, but with a C-O bond rather than a C-C bond.
  The –OH is converted to –$OCrO_3H$ (a chromate ester), then –CrO_3H^{-1} is
  removed from the O at the same time that the H^{+1} is extracted from the C.
  Further red-ox reactions reduce the chromium in the by-product from (IV) to (III).
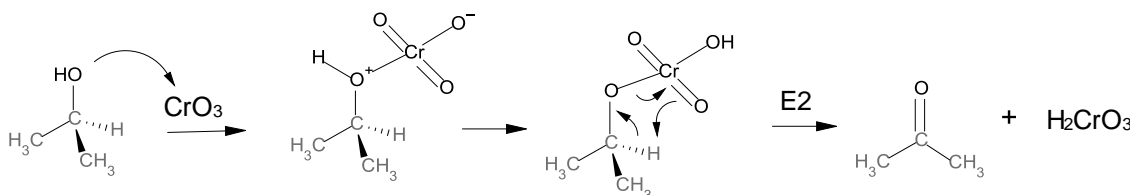
Protection of Alcohols
- Sometimes an OH can interfere with reactions aimed at another portion of a molecule.
- For instance, a Cl cannot be converted to MgCl (Grignard) if OH is also present on the same molecule, because the hydroxyl H is too acidic.
- It is often helpful in organic synthesis to "protect" a functional group, like $-OH$, by reversibly converting it to something that will not interfere, like $-OSi(CH_3)_3$, then later reverting it back to the original form.
- In a typical scheme, the first step is protection of the hydroxyl group by adding chlorotrimethylsilane to make a trimethylsilyl ether:
    R-OH + $(CH_3)_3SiCl$ in $N(Et)_3$ → $R-OSi(CH_3)_3$
  Then, Mg can be added, and the Grignard reagent can be subsequently reacted.
  The final step is then to convert the protected group back into $-OH$:
    R-OSi$(CH_3)_3$ + H_3O^{+1} / H_2O → R-OH + $(CH_3)_3SiOH$
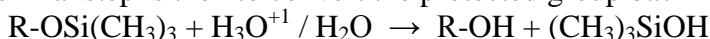
Phenols
- Phenol (C_6H_5OH) is created industrially by using oxygen to convert cumene (isopropylbenzene) to cumene hydroperoxide ($C_6H_5C(CH_3)_2OOH$), then converting the peroxide to phenol and acetone with acid (H_3O^{+1}).
- Many industrial chemicals are derivatives of phenol, including preservatives, herbicides, and antiseptics.
- Phenol is also used in small concentrations as an oral antiseptic, and is available OTC.

Quinones
- Phenol can be oxidized to benzoquinone with $Na_2Cr_2O_{7(aq)}$.
  or Fremy's salt (potassium nitrodisulfonate, $(KSO_3)_2NO_{(aq)}$).
- Benzoquinone can be reduced to hydroquinone (p-dihydroxybenzene) with $SnCl_{2(aq)}$ or $NaBH_4$, and hydroquinone can be oxidized back to benzoquinone with $Na_2Cr_2O_{7(aq)}$.
- A class of substituted benzoquinones, called ubiquinones, is used as biological oxidizing agents by mitochondria in the aerobic cellular respiration process.
- Ubiquinones are reduced to dihydroxy molecules when they oxidize NADH to NAD^+, and the dihydroxy molecules are oxidized back to ubiquinones by O_2.
- Ubiquinones are commonly known as coenzymes Q1 through 10, such as CoQ10.