

Nuggets of Knowledge for Chapter 15 – Alcohols (II)

Chem 2320

I. Introduction to Reactivity of Alcohols

- Alcohols can react in the following ways:
 - As a base: the lone pair of electrons on the oxygen of an alcohol can take a hydrogen from an acid to form a protonated alcohol. This can only occur if the acid is strong enough – its pKa must be less than -2.4, the pKa of a protonated alcohol (see Ch 12 to review this concept).
 - As a nucleophile: the lone pair of electrons on the oxygen of an alcohol can attack a carbon atom if the electrophile is a fairly reactive one – for example, a carbocation in an S_N1 reaction. We will learn some more useful electrophiles in this chapter.
 - As an acid: alcohols can lose the hydrogen connected to the oxygen to form an alkoxide. This can only happen if the base is strong enough – it must have a conjugate acid pKa greater than 18, the pKa of the weakest alcohols.
 - Oxidation: Alcohols can be oxidized by appropriate reagents to form aldehydes, ketones, and carboxylic acids.
- Alcohols CANNOT react in the following ways:
 - As an electrophile: Even though the carbon attached the oxygen is partially positive, the OH is not a good leaving group, so nucleophiles cannot attack them.
 - Reduction: Although in theory the alcohol could lose a bond to oxygen, there are no reagents available to accomplish this reaction (the only way to do this is using more than one step).

II. Reactions of Alcohols with Acid

- When alcohols react with strong acids, a protonated alcohol is formed. What reaction will occur after this, if any, depends on whether the protonated alcohol can dissociate, and whether the conjugate base of the acid can act as a nucleophile or not.
- A protonated alcohol can undergo dissociation similar to alkyl halides. A stable water molecule is formed as well as a carbocation.
 - However, only 2° and 3° protonated alcohols can dissociate, since they are stabilized by hyperconjugation.
 - 1° and aryl protonated alcohols cannot dissociate, since they are too high in energy; they can be formed, but cannot dissociate, so they don't react further.
- Carbocations can undergo three types of reactions, as we have seen:
 - They can rearrange – if the structure allows it, secondary carbocations can undergo hydride shifts or methyl shifts to become more stable tertiary carbocations. These carbocations then undergo further reaction.
 - They can react with a nucleophile – if a nucleophile other than water is present, the carbocation can react with it to form a substitution product (similar to an S_N1 reaction).
 - They can react with a base – if a base is present, the carbocation can react with it to form an alkene (similar to an E1 reaction).
- To determine if the carbocation will react with a nucleophile or a base, we need to look at the conjugate base of the acid that was used to make the protonated alcohol.
 - If the acid was H₂SO₄ or H₃PO₄, then the conjugate base is a sulfate or phosphate ion, which are not basic nor nucleophilic. Instead, the water that came from the dissociation acts as a base, and an alkene is formed.
 - As in E1 reactions, constitutional isomers and stereoisomers of the alkene may be formed.
 - The acid in this reaction is catalytic because when the water reacts with the carbocation, H₃O⁺ is formed, which can act as the acid in the first step.
 - This reaction usually requires heat, since a carbocation is formed.
 - This reaction is the reverse of acid-catalyzed hydration of an alkene. The equilibrium constant is near 1.0, so it is necessary to use a high concentration of alcohol, remove the alkene, or remove the water in order to get a good yield of the alkene.

- If the acid was HBr or HCl, then the conjugate base is a halide. Halides act as nucleophiles, but not as bases. An alkyl halide is formed (and a small amount of elimination with water may also occur).
 - HBr works well in this reaction, but HCl is fairly slow unless ZnCl_2 is also added – HCl and ZnCl_2 is called the Lucas reagent.
- The Lucas reagent is often used as a chemical test to determine whether an alcohol is primary, secondary, or tertiary.
 - If the alcohol is tertiary, it reacts quickly with the Lucas reagent to form an alkyl halide, which separates to a different layer.
 - If the alcohol is secondary, it reacts more slowly, forming first a cloudy solution of the alkyl halide as an emulsion, which later separates into a separate layer.
 - If the alcohol is primary, it doesn't react at all at room temperature. If after five minutes no cloudiness or separate layers appear, the alcohol is likely to be primary.

III. Reactions of Alcohols with Electrophiles

- We have already seen that alcohols can react with sufficiently reactive electrophiles, such as carbocations. In this section, we will discuss some other electrophiles that can be used.

Halogenated phosphorus and sulfur compounds

- Phosphorus and sulfur atoms can serve as electrophiles when they have a halogen attached to them. Two of the most commonly used are phosphorus tribromide, PBr_3 , and thionyl chloride, SOCl_2 .
 - When alcohols react with PBr_3 , an alkyl bromide is formed.
 - Two mechanism steps are involved: 1) the oxygen attacks the phosphorus, pushing off one of the bromides in an attack-push off step; 2) the bromide ion then comes back and attacks the carbon in another attack-push off step. This leaves an alkyl bromide and PBr_2OH .
 - The PBr_2OH then reacts with two more alcohol molecules, finally creating phosphorus acid, H_3PO_3 , which is water soluble and can be removed by washing with water, and three molecules of the alkyl halide.
 - This reaction works best with 1° alcohols, because more substituted alcohols experience steric hindrance in the attack-push off steps. 2° alcohols can also be used, but 3° alcohols are too hindered.
 - When alcohols react with SOCl_2 , an alkyl chloride is formed.
 - The mechanism of this reaction is complex, and we will not discuss it in detail. However, it does involve an attack-push off step in which a chloride ion attacks the carbon, making this reaction most effective on primary alcohols, although 2° alcohols can also be used.
 - The byproducts of the reaction are SO_2 and HCl . SO_2 is a gas and bubbles off. HCl is absorbed by adding pyridine, which reacts with the HCl to form pyridinium chloride, which is a solid and can be filtered off.
- Other reagents that have been used as electrophiles to convert alcohols to alkyl halides include PCl_3 , PCl_5 , and a mixture of P and I_2 , which react to form the unstable PI_3 in solution.
- These reactions are complementary to the reaction of alcohols with HBr or HCl and ZnCl_2 . Both convert alcohols into alkyl halides, but the acid reactions work best with 3° alcohols, since they form a carbocation most easily, while the electrophile reactions work best with 1° alcohols, since they are the least sterically hindered. With 2° alcohols, either reaction may be used.

Tosyl chloride

- Another very useful electrophile that reacts with alcohols is tosyl chloride, $\text{Cl-SO}_2\text{-CH}_2\text{-C}_6\text{H}_5$, which is often abbreviated TsCl. The result of this reaction is a tosylate, often abbreviated ROTs.
- The mechanism of this reaction involves attack of the alcohol oxygen on the sulfur, pushing a pair of electrons onto the oxygen (attack-push up). The electrons then come back down and push off a chloride ion (push-off). The reaction is run in pyridine, which removes the H and combines with the chloride to form pyridinium-hydrochloride.
- With the tosyl group attached to it, the oxygen of the alcohol is now a leaving group, similar to a bromine. Resonance allows the negative charge to be shared between all three oxygen atoms, making it quite stable.
- Tosylates can participate in $\text{S}_{\text{N}}2$ and E2 reactions, providing a way to transform alcohols into ethers, nitriles, alkynes, alkenes, etc – any of the substitution or elimination products that can be formed from alkyl halides.
 - The same concerns that we had with alkyl halides apply to tosylates. 1° tosylates give only $\text{S}_{\text{N}}2$ products, while 2° tosylates give a mixture of $\text{S}_{\text{N}}2$ and E2 products. 3° tosylates give only E2 products. E2 reactions can give constitutional and stereoisomers.
- Tosylates can also react with LiAlH_4 to give alkanes.

IV. Reactions of Alkoxides

- Alkoxides may be formed by reacting an alcohol with a suitable base or an alkali metal. Sodium hydride is the most common base used. Sodium or potassium metal are also used; sodium is suitable for methyl and 1° alcohols, while potassium is needed for 2° and 3° alcohols.
 - Aryl alcohols are more acidic, and can react with sodium hydroxide to form phenoxides.
- Alkoxides and phenoxides are used as nucleophiles or bases in $\text{S}_{\text{N}}2$ and E2 reactions. The electrophile can be an alkyl halide or a tosylate.

V. Oxidation of Alcohols and Diols

- In the previous chapter, we saw that alcohols can be formed by the reduction of aldehydes, ketones, carboxylic acids, and esters, using reducing agents like NaBH_4 , LiAlH_4 , and Raney Ni, which contain hydrogen.
- The reverse can also occur – alcohols can be oxidized to form aldehydes, ketones, and carboxylic acids. In this case the reagent must be an oxidizing agent, which contain oxygen.
 - 1° alcohols can be oxidized to aldehydes or carboxylic acids by losing one or two bonds to hydrogen and gaining one or two bonds to oxygen.
 - 2° alcohols can be oxidized to ketones by losing a bond to hydrogen and gaining a bond to oxygen.
 - 3° alcohols and phenols cannot be oxidized, since they cannot gain a new bond to oxygen without losing a bond to a carbon.
- A variety of reagents are available to accomplish these reactions. The most common ones involve chromium in a +6 or +9 oxidation state.
 - 1° alcohols may be oxidized to carboxylic acids, and 2° alcohols may be oxidized to ketones using sodium chromate – Na_2CrO_4 , sodium dichromate – $\text{Na}_2\text{Cr}_2\text{O}_7$, or chromium trioxide – CrO_3 in water and sulfuric acid.
 - A mixture of CrO_3 , water, and sulfuric acid are often referred to as the Jones reagent.
 - The Jones reagent is useful as a chemical test. It starts out as an orange color, and turns blue-green when reacting with 1° or 2° alcohols.
 - It is more difficult to convert 1° alcohols to aldehydes without letting them go on to the carboxylic acid stage. Two reagents which will accomplish this are CrO_3 in pyridine, known as Collin's reagent, and CrO_3 in pyridine and HCl , known as PCC.
 - These reagents will also convert 2° alcohols to ketones.
- Vicinal diols can undergo an oxidation reaction in which the C-C bond between the alcohols is cleaved, and the two ends are oxidized to ketones or aldehydes. The reagent needed is periodic acid, HIO_4 (sometimes written as H_5IO_6 , the hydrated form).
 - Cyclic diols give dicarbonyl compounds.