

5.11: NUCLEOPHILIC ADDITION OF ALCOHOLS - ACETAL FORMATION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the formation of acetals.
- identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
- identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
- write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
- explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
- illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

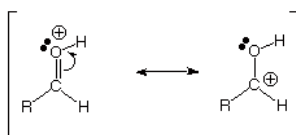
- acetal
- hemiacetal

STUDY NOTES

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

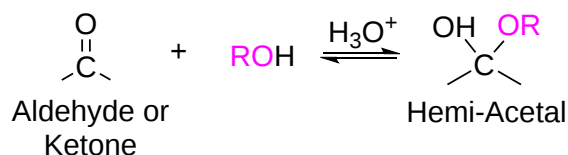
It has been demonstrated in [Section 19.5](#) that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diols. In a similar reaction, one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (*hemi*, Greek, half). This reaction can continue by adding another equivalent of an alcohol to form a diether called an **acetal** $R_2C(OR')_2$. Hemiacetals and acetals are important functional groups because they appear in the structures of many sugars.

An acid catalyst must be used during this reaction because alcohols are weak nucleophiles and would add very slowly under neutral conditions. Under acidic conditions, the oxygen of the carbonyl becomes protonated, increasing the electrophilicity of the carbonyl carbon, speeding up the reaction.

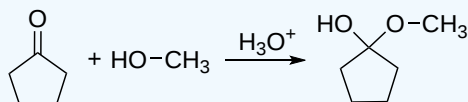


Also, it is common to actively remove the water created with the formation of an acetal by using molecular sieves or a **Dean-Stark trap**. This step is important, since acetal formation is reversible, and the removal of water pushes the equilibrium to the right by Le Chatelier's principle. Indeed, once pure hemiacetals or acetals are obtained, they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

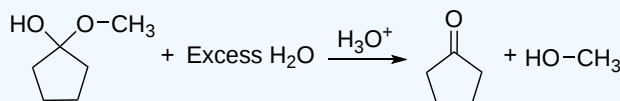
FORMATION OF HEMIACETALS



✓ EXAMPLE 5.11.1: FORMATION OF A HEMIACETAL

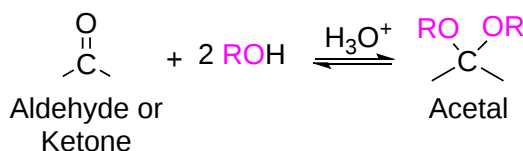


✓ EXAMPLE 5.11.2: HEMIACETAL HYDROLYSIS REVERTING TO THE KETONE



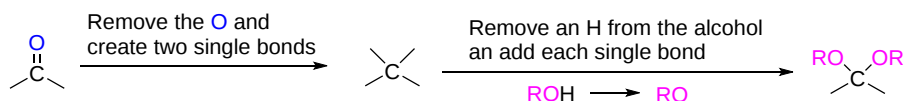
FORMATION OF ACETALS

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

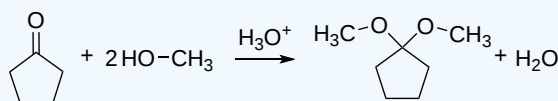


PREDICTING THE PRODUCT OF A ACETAL FORMATION

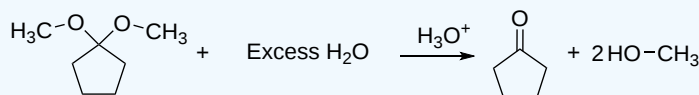
Overall, the carbonyl in the reactant is removed and replaced by two single bonds between oxygen and the original carbonyl carbon. Both of these single bonds are attached O-R groups produced after the reagent alcohol has lost a hydrogen.



✓ EXAMPLE 5.11.3: FORMATION OF ACETALS



✓ EXAMPLE 5.11.4: ACETAL HYDROLYSIS REVERTING TO THE KETONE

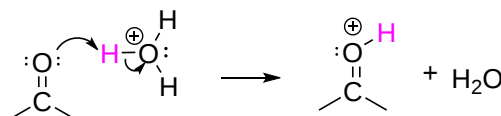


MECHANISM FOR HEMIACETAL AND ACETAL FORMATION

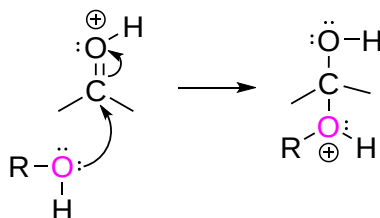
After protonation, an alcohol undergoes nucleophilic addition to the carbonyl group initially forming a hemiacetal upon deprotonation. Further protonation of the OH group in the hemiacetal allows for the elimination of water to form an oxonium ion. A second alcohol nucleophile adds to the oxonium ion to produce a protonated acetal. After deprotonation, the product acetal is formed.

The mechanism shown here applies to both acetal and hemiacetal formation.

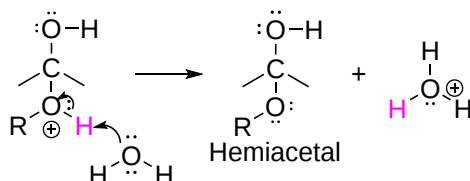
Step 1: The acid catalyst protonates the carbonyl oxygen, making the carbonyl carbon more electrophilic.



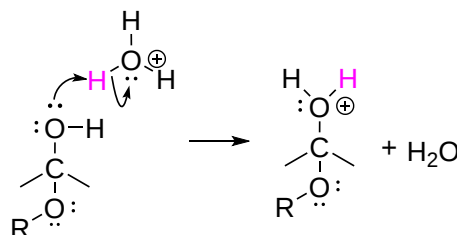
Step 2: An alcohol undergoes nucleophilic addition to the carbonyl producing a protonated hemiacetal.



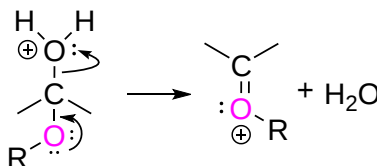
Step 3: Water acts as base to cause a deprotonation creating a hemiacetal and hydronium.



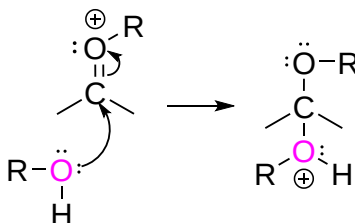
Step 4: The OH group of the hemiacetal is protonated making it into a good leaving group.



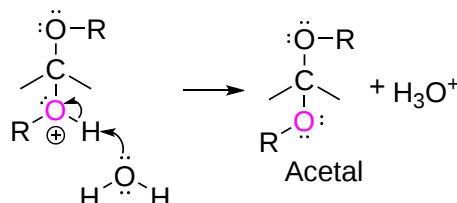
Step 5: Lone pair electrons on the ether oxygen reforms the C=O bond causing the elimination of water and producing an oxonium ion.



Step 6: A second alcohol undergoes nucleophilic addition to oxonium ion producing a protonated acetal.

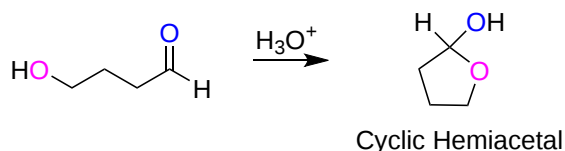


Step 7: Water acts as a base and causes a deprotonation, creating the product acetal and hydronium.

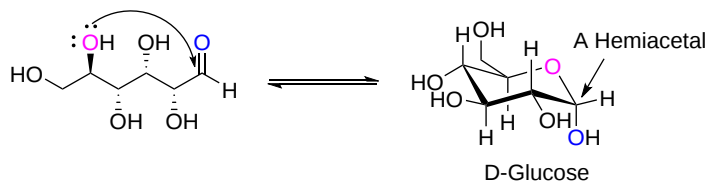


BIOLOGICAL ACETAL AND HEMIACETAL FORMATION

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



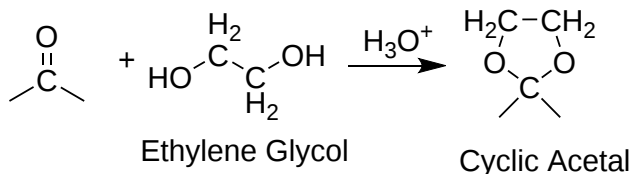
Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry as we will see in [Section 25.7](#). For example, the common sugar glucose exists in the cyclic manner more than 99% of the time in a mixture of aqueous solution.



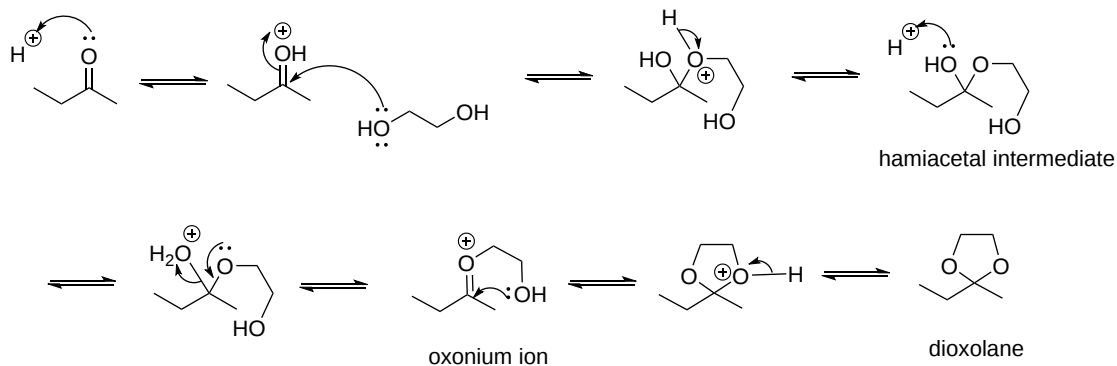
Conversion of D-Glucose to Beta-D-Glucopyranose (Cyclic Hemiacetal)

ACETALS AS PROTECTING GROUPS

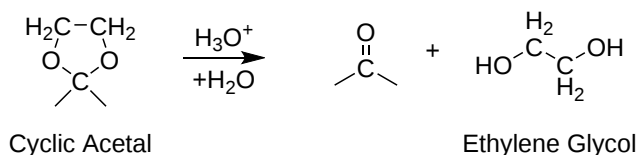
The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride reagents (LiAlH_4 & NaBH_4), and organometallic reagents (RMgX & RLi). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented. To accomplish this, it is common to use a diol such as ethylene glycol (rather than two equivalents of a simple alcohol) to form a cyclic acetal ring commonly called a dioxolane.



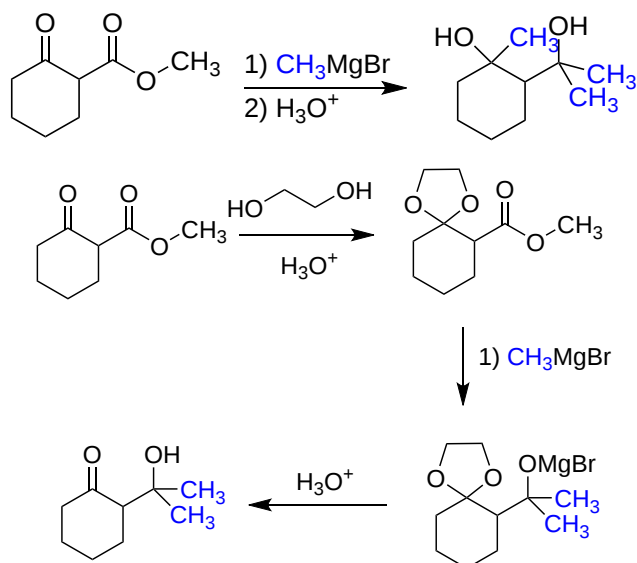
Because both OH groups are part of the same molecule, the second nucleophilic addition in the formation of the acetal is intramolecular and forms a ring. Cyclic acetals are more stable towards hydrolysis than acyclic ones and are also kinetically favored because the intramolecular ring-closing reaction is fast.



Once the addition reaction is accomplished (or whatever reaction required protecting the carbonyl), the reversibility of acetal formation can be used to reform the original carbonyl.

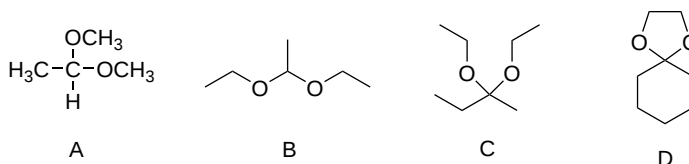


In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with both esters and ketones with the ketone typically more reactive than the ester. This reaction sequence uses ethylene glycol to form the cyclic acetal protecting group for the ketone followed by reaction of the ester with a Grignard reagent. Once this reaction is complete, the acetal is hydrolyzed back to the ketone in the same step that reprotonates the alcohol (while eliminating the MgBr).

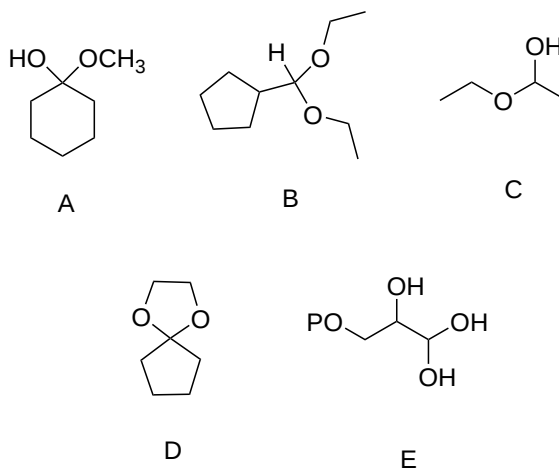


PROBLEMS

1) For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.



2) Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



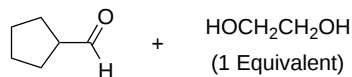
3) Specify the acetal that would form from a reaction between the given starting compounds.

a.



(2 Equivalents)

b.

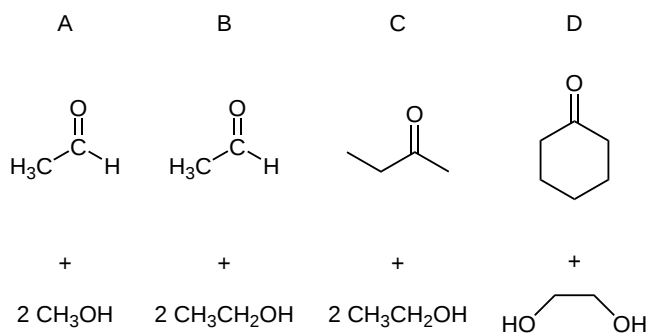


4)

Specify the aldehyde/ketone and alcohol combination that would be required to form the compounds in problem 2.

ANSWERS

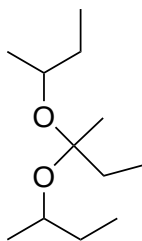
1)



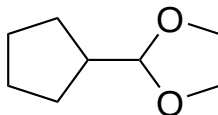
2) A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

3)

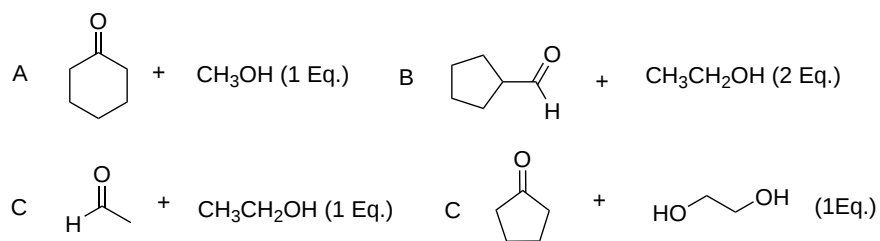
a)



b)



4)



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