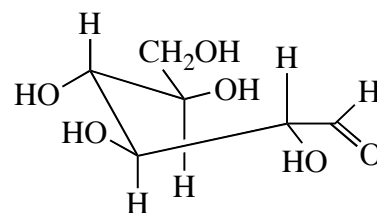
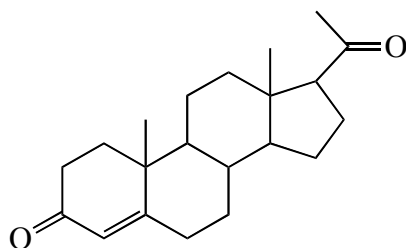
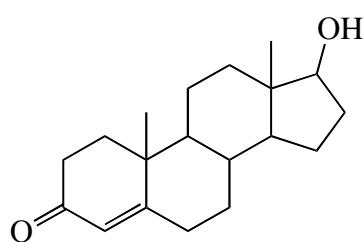


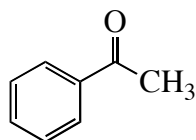
Lecture Notes
Chem 51C
S. King

Chapter 21 Aldehydes & Ketones: Nucleophilic Substitution

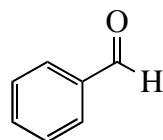
I. Some Famous Type 1 Carbonyl Compounds



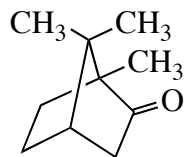
Flavors and Scents:



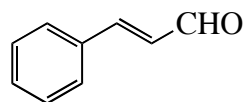
pistachio



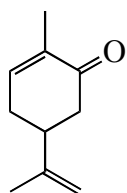
maraschino cherries



camphor

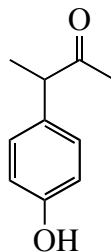


cinnamaldehyde

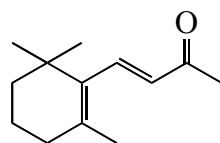


(-)-enantiomer:
spearmint

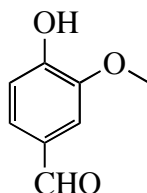
(+)-enantiomer:
caraway



raspberry



oil of violets



vanillin

II. Nomenclature of Aldehydes & Ketones (*see handout & podcast*):

III. Preparation of Aldehydes & Ketones (*review – see section 21.6A, B*)

IV. Physical Properties of Aldehydes & Ketones:



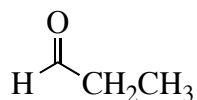
bp.

%sol. in

H₂O

dipole
moment

***Solubility diminishes rapidly with added carbons:*



V. Reversible Addition Reactions of Aldehydes and Ketones

As we saw in chapter 20, when powerful nucleophiles add to aldehydes & ketones, the reaction is irreversible.

Strong Nucleophiles: Organolithium reagents, Grignard reagents, Hydride Reagents, Sodium alkynides

When weaker nucleophiles add to aldehydes & ketones, the reaction is reversible.

Weaker Nucleophiles: water, alcohols, 1° and 2° amines, cyanide ion

A. Addition of Water (Hydration):

★★ The product of this reaction is a hydrate

Mechanism: Can be *Acid* or *Base* Catalyzed!

Base-catalyzed mechanism:

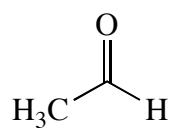
Acid Catalyzed Mechanism

Formation of a hydrate is reversible.

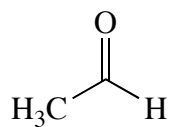
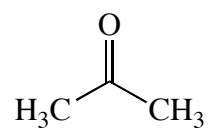
Factors that favor Addition (formation of hydrate):

- The more stable the carbonyl compound, the less favorable the addition.
- The more sterically hindered the carbonyl compound, the less favorable the addition.

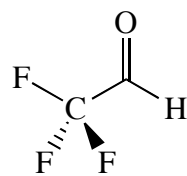
Compare:

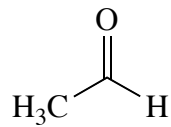


vs.

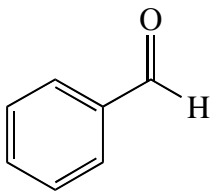


vs.

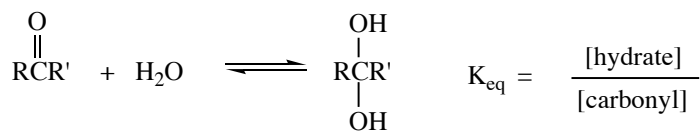




vs.



Compare:



Carbonyl	K_{eq}
$\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	2.28×10^3
$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	1.06
$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$	1.4×10^{-3}
$\text{F}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	2.9×10^4
$\text{Ph}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	8×10^{-3}
$\text{F}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$	35
$\text{F}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CF}_3$	1.2×10^6
$\text{F}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Ph}$	78
$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Ph}$	9.3×10^{-6}

B. Addition of Alcohols

1. Base catalyzed reaction:

Mechanism:

2. Acid catalyzed reaction:

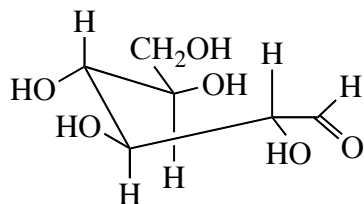
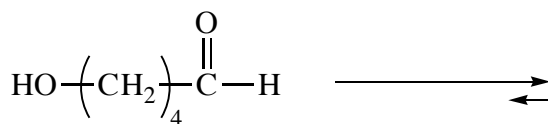
Mechanism:

Step 1: *Hemiacetal Formation*

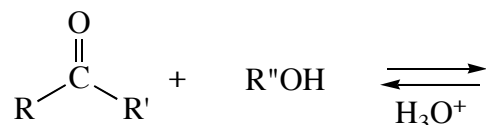
Step 2: Acetal Formation

Important points about Acetal and Hemiacetal formation:

- 1) Hemiacetals *cannot* be converted to acetals with base!!
* use acid catalysis to go all the way to acetal.
- 2) Hemiacetals are difficult to isolate unless the hemiacetal is part of a 5 or 6-membered ring.



- 3) The same factors that govern equilibrium in hydrate formation also govern the equilibrium in hemiacetal & acetal formation.
- The more stable the carbonyl, the less favorable the addition.
 - Addition is favored for formaldehyde, and aldehydes with electron withdrawing groups.
- 4) The reaction must generally be driven to completion using Le Chatelier's principles.



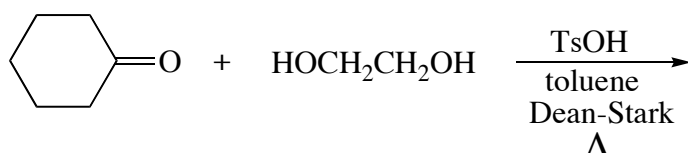
To drive the equilibrium:

- Use large excess of alcohol.
- Remove water as it is being formed.

Standard way to remove water as it is formed:

*By the same token, if an acetal is placed in excess water with trace of acid, the ketone will be recovered from the reaction mixture. This is known as a **hydrolysis reaction**.*

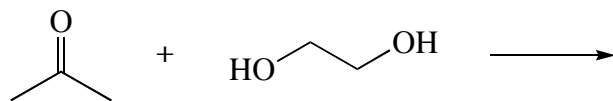
- 5) Since acetals can be hydrolyzed under very mild conditions to regenerate the original carbonyl compound, they are often used as **protecting groups** for aldehydes and ketones.
- cyclic acetals made by reacting carbonyls with diols are the most commonly used protecting groups:



- cyclic acetals are formed much more readily than acyclic acetals

Two reasons why:

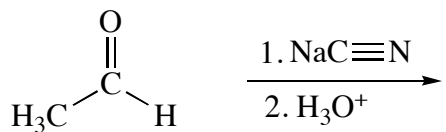
1.



2. Intramolecular reactions are more probable:

C. Addition of HCN

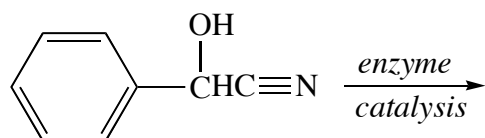
Cyanide ion, CN^- , adds to the carbonyl group of an aldehyde or ketone to form a tetrahedral intermediate called a **cyanohydrin**.



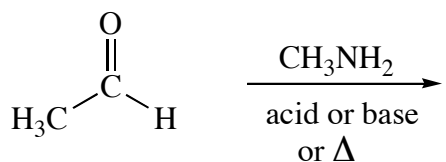
Important points:

- This is a new C-C bond forming strategy!
- For aldehydes and most aliphatic ketones, the position of equilibrium favors cyanohydrin formation.
- For many aryl ketones and sterically hindered aliphatic ketones, the position of equilibrium favors starting materials.

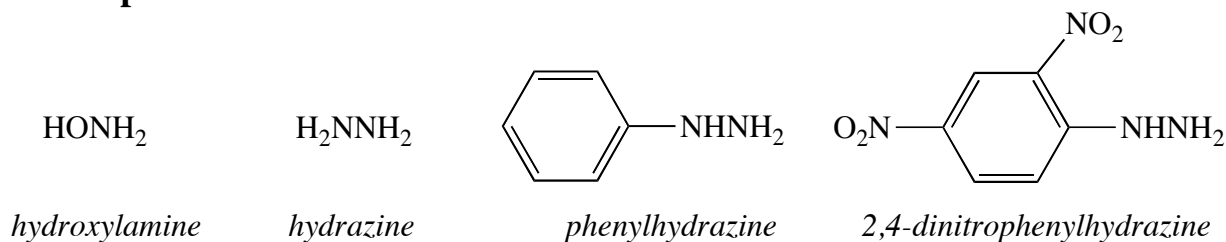
Example: Benzaldehyde cyanohydrin (mandelonitrile)



D. Addition of Primary Amines (R-NH_2) to give Imines (AKA: Schiff Bases).



The following compounds related to ammonia also react to form similar compounds:



Mechanism:

Step 1: *Addition*

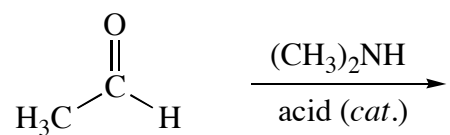
Step 2: *Dehydration*

Special points about the mechanism:

- The reaction runs best when run slightly acidic (@ pH 5.0).

- Under acid catalysis, the amine attacks the neutral carbonyl.

E. Addition of Secondary Amines (R_2NH) to give Enamines



Mechanism:

Step 1: *Formation of carbinolamine*

Step 2: *Dehydration*

Summary of Addition Reactions of Aldehydes & Ketones:

- Aldehydes are more reactive towards addition reactions than ketones.
- With very strong nucleophiles (CH_3MgBr , CH_3Li , LiAlH_4 , NaBH_4 , etc.):
 - ☛ **The reaction is irreversible.**
- With mild nucleophiles (H_2O , HOCH_3 , HSCH_3 , HNH_2 , CN^- , etc.):
 - ☛ **The reaction is reversible.**
- In basic media:
 - ☛ **The nucleophile attacks first**

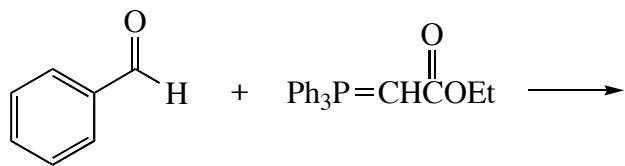
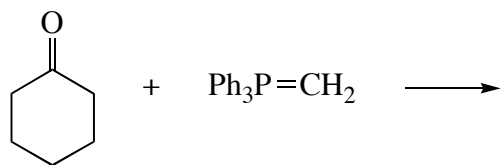
- In Acidic media:
 - ☛ **The carbonyl is protonated first.**

Exception: Imine and enamine formation under mild acid catalysis (the nucleophile attacks first).

VII. Other Addition Reactions of Aldehydes and Ketones

A. Addition of a Phosphonium Ylide: *The Wittig Reaction*

Phosphonium ylides add irreversibly to aldehydes and ketones, but then they undergo a rearrangement in a second step to introduce a C–C bond selectively in place of the carbonyl group.



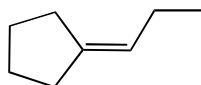
Preparation of phosphonium ylides:

Reaction of phosphonium ylides with aldehydes or ketones:

Use of the Wittig Reaction in Synthesis: Retrosynthetic Analysis

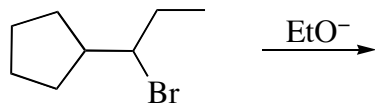
The Wittig reaction converts a ketone or aldehyde into an alkene. Therefore, any alkene can *potentially* be synthesized by a Wittig reaction. Alkenes can also be synthesized by elimination reactions (chapter 8), but often the Wittig reaction is much more reliable route to alkenes.

Example: Provide a synthesis of the following amine using a Wittig reaction, choosing the route that would provide the best yield.

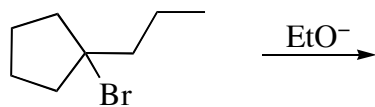


Synthesis:

Attempting to synthesize this compound using an elimination reaction is problematic:

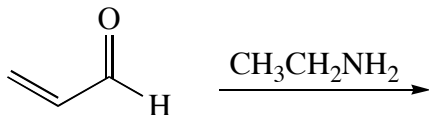


or



B. More Nucleophilic Addition to α, β -Unsaturated Aldehydes and Ketones: Addition of Weak Nucleophiles

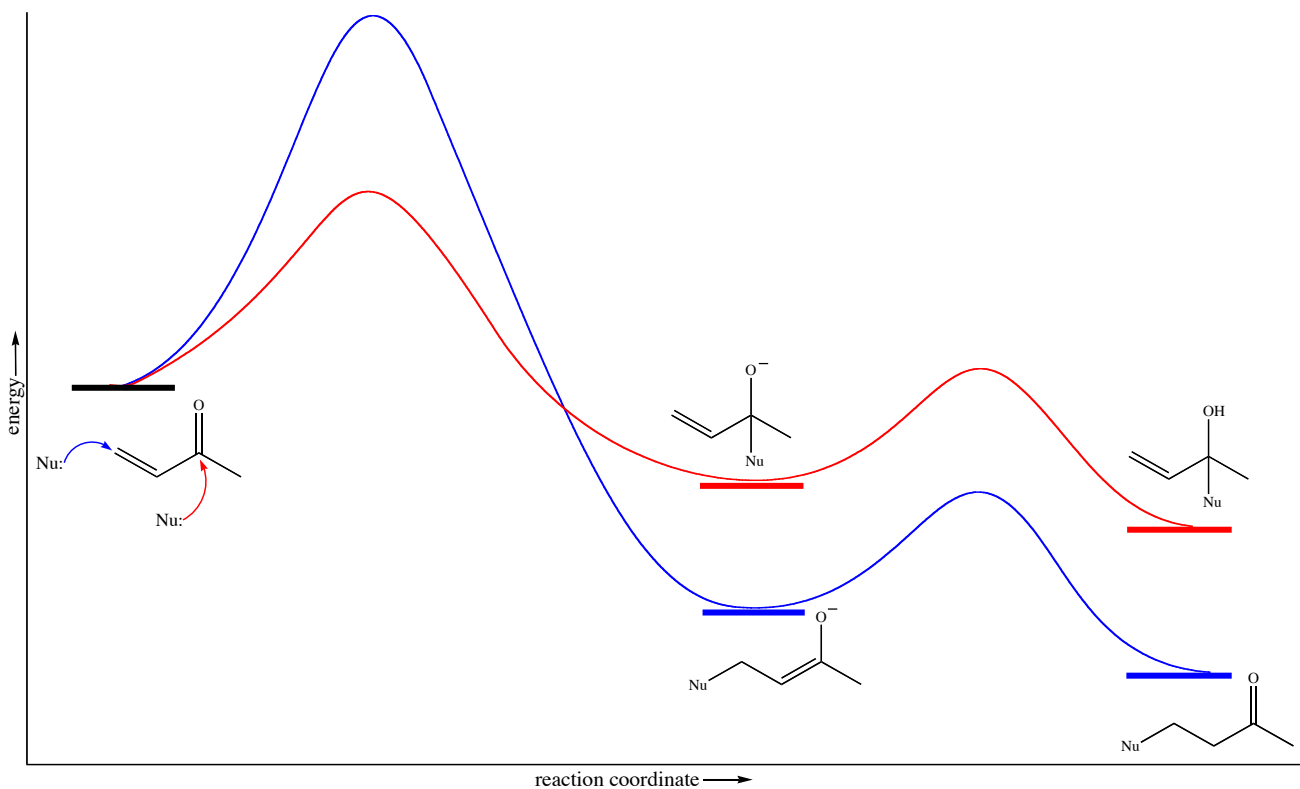
As mentioned in Chapter 20, when α, β -Unsaturated carbonyl compounds react with nucleophiles that undergo reversible carbonyl additions, the 1, 4-(conjugate addition) product is observed:



Recall: 1, 2-addition reaction is faster (\therefore it has a lower E_a), so when reactants that do irreversible addition react, they attack the carbonyl and then they are stuck! Weaker nucleophiles reversibly add to carbonyls, so they can come back off again. Since 1, 4-attack gives the thermodynamically most stable product, eventually all of the reactant is converted to the 1, 4-product.

Look at the energy diagram:

Why is E_a for 1,2 product smaller?



Synthesis Example: Devise a synthesis of the following two compounds from the given starting material:

