

Carbonyl Chemistry I: Additions to Carbonyl Groups

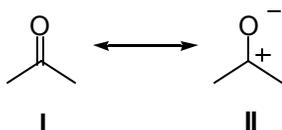
Section Agenda

- 1) Lessons from Exam I, Course Feedback Mechanism on Web Site
- 2) Carbonyl Groups: Structure, Bonding, Molecular Orbitals, Geometry, Reactivity
- 3) Handout: In-Section Problem Set
- 4) Handout: In-Section Solution Set
- 5) Weekly Office Hours: Thursday, 3-4PM and 8-9PM, in Bauer Lobby

Structure and Bonding

- Carbonyl carbons are roughly sp^2 hybridized and planar with bond angles near 120 degrees
- The C=O π bond is formed by the overlap of two unhybridized p orbitals. The bond is polarized due to the different electronegativities of carbon and oxygen.

Resonance Model

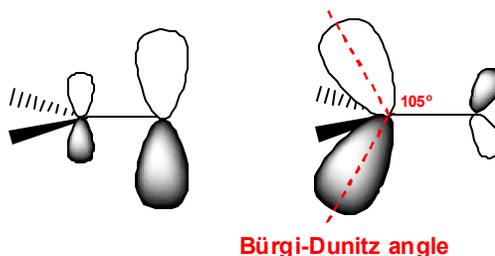


- Resonance form II suggests that the carbon atom is surrounded by less negative charge density than oxygen, rendering the carbon more electrophilic.
- When reagents add to carbonyl double bonds, the nucleophile attacks the carbon atom.
- Due to the increased negative charge density on oxygen, Lewis acids (such as protons) commonly complex with oxygen. This can be thought of as the oxygen “attacking” the Lewis acid electrophile.
- When a Lewis acid complexes with a carbonyl group, it renders the carbon atom even more electrophilic. This often speeds nucleophilic addition reactions. If the Lewis acid is later regenerated by uncomplexing from the oxygen, it is a catalyst for nucleophilic addition to the carbonyl group.

Molecular Orbital Picture

[bonding \$\pi\$ orbital](#)

[antibonding \$\pi^*\$ orbital](#)



- Another way to picture carbonyl groups is through an MO picture. Since the coefficient of p_O 's contribution is greater in $\pi_{C=O}$, then conservation of blending atomic orbitals into molecular orbitals tells you that p_C must be a larger contributor to the $\pi^*_{C=O}$ orbital.
- The larger coefficient on oxygen in the filled orbital explains why the oxygen atom behaves as a Lewis base (it commonly complexes with Lewis acids). The larger coefficient on carbon in the empty antibonding orbital explains why it is more electrophilic.
- The geometry of the HOMO (filled π orbital above the bond center repels nucleophiles) and LUMO (π^* lobes positioned above and behind the bond axis) governs how nucleophiles must approach the carbon atom—at the Bürgi-Dunitz angle of roughly 105 ± 5 degrees relative to the plane of the sp^2 -hybridized carbonyl group.

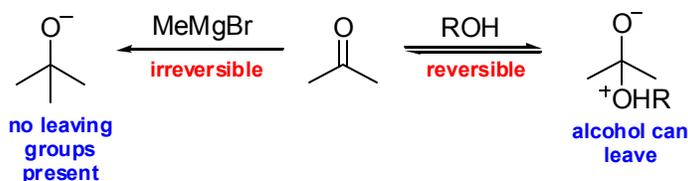
Reversible Carbonyl Additions

Kinetics vs. Thermodynamics

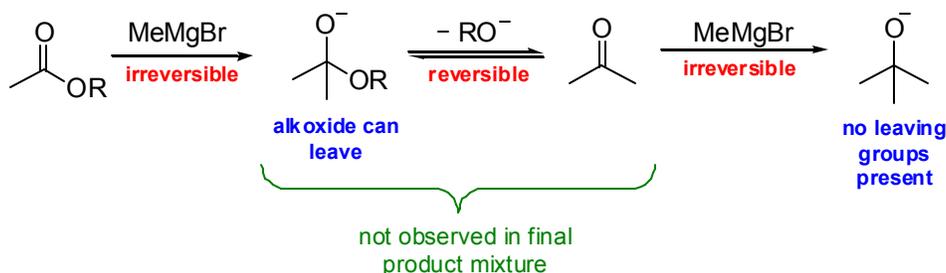
- In nonreversible reactions, kinetics are the decisive factor in determining the major product. To evaluate the pathways on the basis of kinetics, we must look at the available transition states and their relative activation energies. The pathway with the most stable transition state will have the lowest activation energy and will transpire with the greatest rate, leading to the major product. As soon as the starting materials have reacted, the product is “stuck.”
- In the case of reversible reactions, thermodynamics play a greater role than kinetics in determining the major products. Under thermodynamic control, we may evaluate product mixtures on the basis of equilibria and relative stability of the intermediates instead of the transition states. The rates of the pathways are not as important, because over time, all of the products/intermediates are interconverting. This allows the system to naturally find an equilibrium where the most stable products lie. The relative rates of the reaction do play a role—they determine how fast this equilibrium is reached.
- Catalysts speed the process of reaching equilibrium. This involves opening a new mechanistic pathway with a lower activation energy that leads to the same products. It is important to remember that catalysts increase the rates of both the forward *and* reverse reactions.

Kinetics vs. Thermodynamics for Carbonyl Additions

- Nearly all irreversible additions to carbonyl groups involve the addition of nucleophiles that are poor leaving groups. For example, Grignard reagents add alkyl groups. Hydride reductions are also irreversible, because H^- is a poor leaving group. If you wish to “reverse” the process, you must conduct a whole new oxidation reaction.
- Reversible carbonyl additions involve the addition of good or fair leaving groups. Once these species react to form the tetrahedral intermediate, the intermediate may collapse to reform the carbonyl group and “kick out” a leaving group. Once the carbonyl group is regenerated, it is free to act as a nucleophile again.



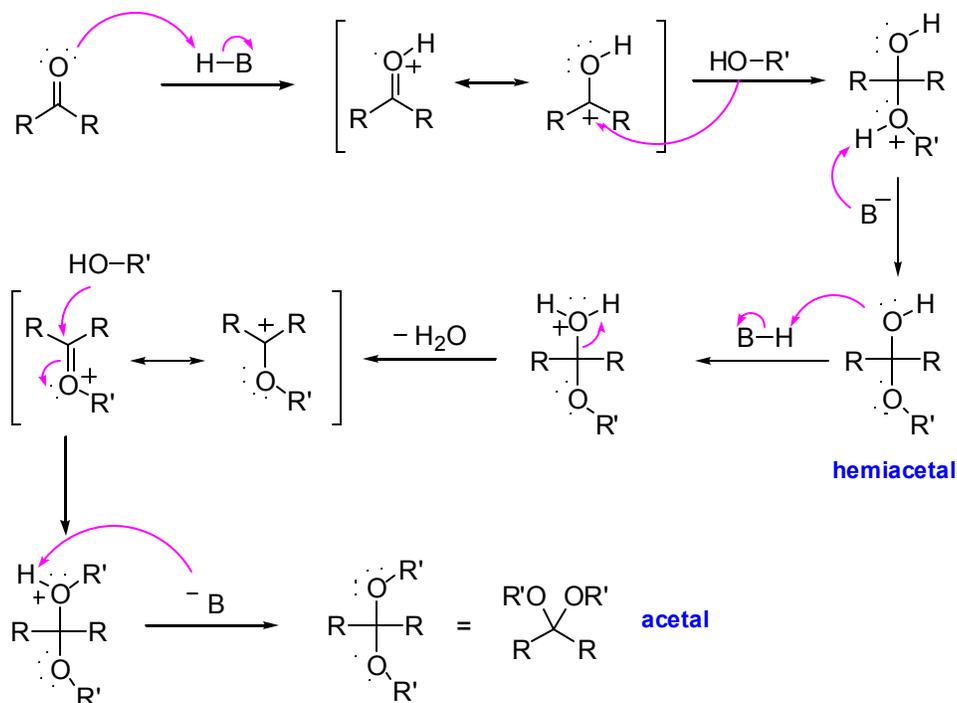
- Irreversible processes can drive a reaction to completion despite reversible intermediate steps. An example is how esters are converted to alcohols by treatment with Grignard reagents. The irreversible processes scavenge all of the reversible intermediates from the reaction.



Acetal (Ketal) Formation

Acetal formation occurs under reversible conditions, but we may drive the equilibrium very far to the product side such that the product is formed in quantitative (100%) yield. This can be accomplished by swamping the reaction with your desired nucleophile or by providing an energetic driving force.

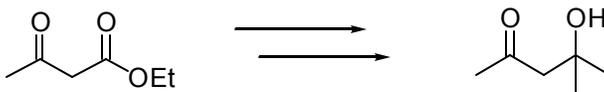
- This mechanism is damn important to learn, so do it.
- Remember that water leaves by an S_N1 -like process, as opposed to S_N2 -like attack. The intermediate carbocations are stabilized by a resonance effect.
- Under acidic conditions, the alcohol is the nucleophile. Under basic conditions, alkoxide is the nucleophile. Basic conditions stop at the hemiacetal because hydroxide is a poor leaving group.



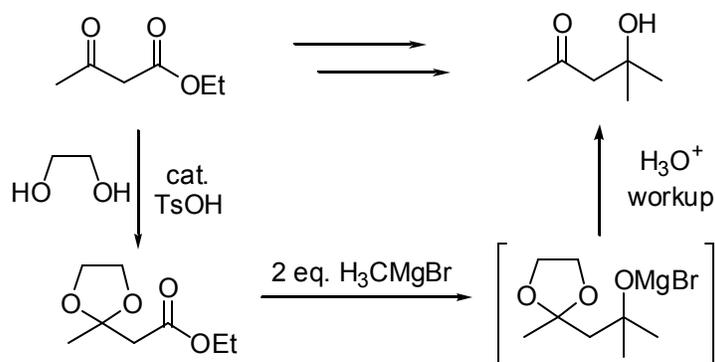
- Very important—These steps are all reversible! You can go forwards and backwards under the same conditions. You can drive the reaction by having an excess of one reagent (alcohol to go forward, water to go backwards).

Acetal Protecting Groups

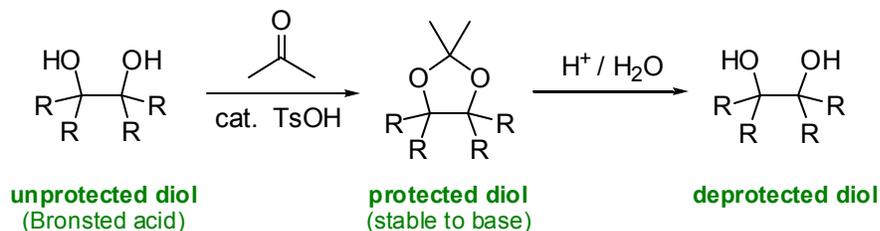
Example



- Suppose you wanted to conduct the above synthetic transformation. Ostensibly, you react the ester moiety with two equivalents of a methyl organometallic reagent, such as MeMgBr.
- The problem is more complicated, however, because there is another electrophilic functionality present, the ketone, which is more electrophilic than the ester.
- To complete this transformation, you must:
 - 1) "Protect" the ketone as a functional group which will be less reactive than the ester
 - 2) Conduct the methylation
 - 3) "Deprotect" to restore the ketone functionality



- Note that we can selectively protect the ketone without touching the ester because the ketone carbonyl is more reactive, which is why we have to protect it in the first place.
- Acetals are stable in the presence of base, but not in the presence of acid.
- You will often find ethylene glycol used as a protecting group for aldehydes and ketones, because there is less entropic cost of forming the acetal.
- Acetone can be used as a protecting group for diols:



- Remember to protect alcohols when you cannot have protic functionality present. (e.g. during Grignard reactions)

Carboxylic Acids

Structure

- The protonated oxygen is sp^2 hybridized despite having four structural pairs. This allows for favorable orbital overlap with the π system of the carbonyl group.
- The most stable conformation, the (Z) form, allows the protonated oxygen's sp^2 lone pair to overlap with and donate into the C-O σ^* bond.

Reactivity

- The acid carbonyl group is still electrophilic, but less so than aldehydes and ketones, because the conjugation with the alkoxy substituent stabilizes the system. Deprotonated carboxylate anions are even less electrophilic.
- The hydroxyl substituent can act as a leaving group, especially if protonated so it leaves as neutral water.

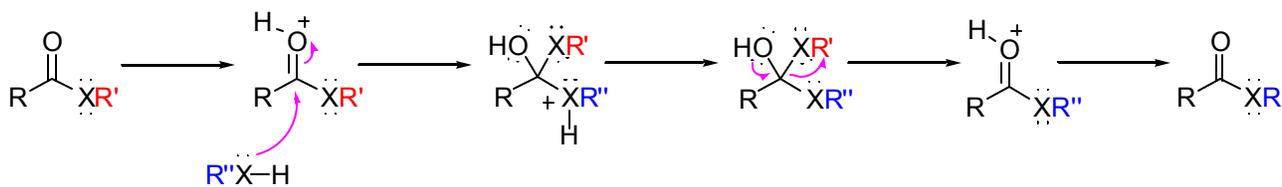
Carboxylic Acid Derivatives

General Mechanisms for Reactions of Carboxylic Acid Derivatives

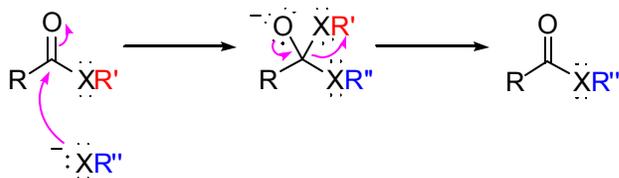
Acidic: Nucleophiles are neutral, carbonyl electrophiles are activated as cations, leaving groups are neutral

Basic: Nucleophiles are charged anions, electrophiles are neutral, leaving groups are charged anions

Mechanism under Acidic Conditions



Mechanism under Basic Conditions



Note that both mechanisms proceed through tetrahedral intermediates!