Reversible Additions to carbonyls: Weak Nucleophiles

Weak nucleophiles, such as water, alcohols, and amines, require acid or base catalysis to undergo addition to carbonyl compounds

Relative Reactivity of carbonyls: Aldehydes are more reactive than ketones on steric and electronic grounds. The aldehyde carbonyl carbon is obviously more sterically accessible than the ketone carbonyl carbon because of the size of a hydrogen atom vs. an alkyl group. Two alkyl groups stabilize the partial positive charge on the ketone carbonyl carbon, whereas only one alkyl group stabilizes the aldehyde carbonyl carbon's partial positive charge. Thus, ketone carbonyl carbons are less electrophilic than aldehyde carbonyl carbons, and ketones in general are more stable and less reactive than aldehydes. Aldehydes are probably the best electrophiles in organic chemistry because of the accessibility (planarity, lack of steric hindrance)and electrophilicity of their carbonyl carbon. Thus, the position of equilibrium of weak nucleophiles adding to carbonyls lies on the reactant side for ketones and on the product side for aldehydes.

Hydration of Ketones and Aldehydes

Addition of water to carbonyls is both acid and base-catalyzed; the position of equilibrium favors the keto form of the carbonyl for ketones. Only formaldehyde and electron-deficient aldehydes favor the hydrate:

The acid-catalyzed mechanism of hydration involves three steps: protonation of the carbonyl oxygen (to increase the electrophilicity of the carbonyl carbon—see resonance forms), addition of water, and deprotonation to yield the hydrate and regenerate the acid catalyst:

The base-catalyzed mechanism simply involves the addition of the strong base HO^-, to the carbonyl carbon, followed by deprotonation to regenerate the base catalyst.

Formation of Cyanohydrins
HCN is a weak acid, and thus its conjugate base, NC^-, is strongly basic and nucleophilic. Cyanide ion undergoes nucleophilic addition to carbonyls in the same way as base-catalyzed hydration:

Amine Nucleophiles: Formation of imines
Ammonia or primary amines react with ketones and aldehydes to form imines; substituted imines are referred to as Schiff bases. The process of condensation refers to the joining of two molecules with loss of water:

The pH for this reaction is crucial; the condensation proceeds fastest when the pH is 4.5. More acidic conditions lead to amine protonation, which destroys its nucleophilicity; higher pH's inhibit protonation of the intermediate and loss of water (see mechanism). Each step of the reaction is an equilibrium. Removal of water shifts the equilibrium toward the imine product.

Mechanism of imine (Schiff base) formation

Examples:

The reaction shown above is completely reversible, and thus adding the imine to excess aqueous acid hydrolyzes the imine back to the carbonyl compound:

note that the mechanism of this process is just the reverse of imine formation (principle of microscopic reversibility)!

Oximes, hydrazones, and semicarbazones are formed in a similar fashion, although equilibrium constants for these reactions are generally more favorable than for amines.

Oximes, hydrazones, semicarbazones are often solid compounds with characteristic melting points, and are useful for characterization and identification of carbonyl compounds, since there are standard tables of melting points compiled for these derivatives.

Acetals.
Acetals result from the acid-catalyzed reaction of ketones and aldehydes with alcohols. The intermediate is called a hemiacetal, and it must be protonated on oxygen for water to leave; a second molecule of alcohol may then attack to form the acetal product.

This reaction is completely reversible; for aldehydes, the equilibrium favors the acetal. With hindered aldehydes and ketones, the equilibrium favors the carbonyl. To drive the equilibrium toward acetal formation, the alcohol is used as solvent (Le Chatelier's principle) and water is removed from the reaction mixture as it is formed by distillation (Le Chatelier's principle). *Again, note that acid-catalyzed hydrolysis of acetals is simply the reverse of acetal formation. A large excess of water (solvent) is used in the presence of an acid catalyst to drive the equilibrium in reverse.*

Diols can form cyclic acetals (dioxanes or dioxolanes) with aldehydes and ketones; the equilibrium constants for cyclic acetal formation are more favorable due to less decrease of entropy (bringing together only 2 molecules instead of bringing together 3 molecules):

Carbohydrates are naturally occurring acetals and hemiacetals that are very stable:

Acetals are protecting groups for carbonyl compounds. Acetals are stable to nucleophilic attack and are impervious to strong bases. Acidic hydrolysis gives the parent carbonyl compound.