Hydration and Hemi-acetal Formation

It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones. In most cases the resulting hydrate (a geminal-diol) is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde (a gas in its pure monomeric state). Here the weaker pi-component of the carbonyl double bond, relative to other aldehydes or ketones, and the small size of the hydrogen substituents favor addition. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. Similar reversible additions of alcohols to aldehydes and ketones take place. The equally unstable addition products are called hemiacetals.

\[ R_2C=O + R'OH \rightarrow R'O-(R_2)C-O-H \] (a hemiacetal)

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. The following equation shows the overall stoichiometric change in acetal formation, but a dashed arrow is used because this conversion does not occur on simple mixing of the reactants.

\[ R_2C=O + 2R'OH \rightarrow R_2C(OR')_2 + H_2O \] (an acetal)

In order to achieve effective acetal formation two additional features must be implemented. First, an acid catalyst must be used; and second, the water produced with the acetal must be removed from the reaction. The latter is important, since acetal formation is reversible. Indeed, once pure acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid. The mechanism shown here applies to both acetal formation and acetal hydrolysis by the principle of microscopic reversibility.

**Figure 1: Acetal Formation**

Some examples of acetal formation are presented in the following diagram. As noted, p-toluenesulfonic acid (pK\(_a\) = -2) is often the catalyst for such reactions. Two equivalents of the alcohol reactant are needed, but these may be provided by one equivalent of a diol (example #2). Intramolecular involvement of a gamma or delta hydroxyl group (as in examples #3 and 4) may occur, and is often more facile than the intermolecular reaction. Thiols (sulfur analogs of alcohols) give thioacetals (example #5). In this case the carbonyl functions are relatively hindered, but by using excess ethanedithiol as the solvent and the Lewis acid BF\(_3\) as catalyst a good yield of the bis-thioacetal is obtained. Thioacetals are generally more difficult to hydrolyze than are acetals.

**Figure 2: Examples of acetal formation**

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, alkyl and aryl reagents (to be discussed shortly). 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.

Formation of Imines and Related Compounds

The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases, (compounds having a C=N function). This reaction plays an important role in the synthesis of 2º-amines. Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation.

\[
\begin{align*}
R_2C=O + R'NH_2 & \rightarrow R'NH-(R_2)C-O-H \\
R_2C=NR' + H_2O & \text{(imine)}
\end{align*}
\]

Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y-NH₂ have been studied, and found to give stable products (R₂C=N–Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed in the following table, together with the structures and names of their carbonyl reaction products. An interesting aspect of these carbonyl derivatives is that stereoisomers are possible when the R-groups of the carbonyl reactant are different. Thus, benzaldehyde forms two stereoisomeric oximes, a low-melting isomer, having the hydroxyl group cis to the aldehyde hydrogen (called syn), and a higher melting isomer in which the hydroxyl group and hydrogen are trans (the anti isomer). At room temperature or below the configuration of the double-bonded nitrogen atom is apparently fixed in one trigonal shape, unlike the rapidly interconverting pyramidal configurations of the sp³ hybridized amines.

**Figure 3: Carbonyl products formed from Y-NH₂ type reactants**

With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. If the aromatic ring of phenylhydrazine is substituted with nitro groups at the 2- & 4-positions, the resulting reagent and the hydrazone derivatives it gives are strongly colored, making them easy to identify. It should be noted that although semicarbazide has two amino groups (–NH₂) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.

The rate at which these imine-like compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. This agrees with a general acid catalysis in which the conjugate acid of the carbonyl reactant combines with a free amino group, as shown in the above animation. At high pH there will be a vanishingly low concentration of the carbonyl conjugate acid, and at low pH most of the amine reactant will be tied up as its ammonium conjugate acid. With the exception of imine formation itself, most of these derivatization reactions do not require active removal of water (not shown as a product in the previous equations). The reactions are reversible, but equilibrium is not established instantaneously and the products often precipitate from solution as they are formed.
Enamine Formation

The previous reactions have all involved reagents of the type: \[ Y-\text{NH}_2 \], i.e. reactions with a 1º-amino group. Most aldehydes and ketones also react with 2º-amines to give products known as enamines. Two examples of these reactions are presented in the following diagram. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.

*Figure 4: Enamine synthesis*

Cyanohydrin Formation

The last example of reversible addition is that of hydrogen cyanide (HC≡N), which adds to aldehydes and many ketone to give products called cyanohydrins.

\[
\text{RCH}=\text{O} + \text{H-C≡N} \rightleftharpoons \text{RCH(OH)CN} \text{ (a cyanohydrin)}
\]

Since hydrogen cyanide itself is an acid (pK_a = 9.25), the addition is not acid-catalyzed. In fact, for best results cyanide anion, C≡N^- must be present, which means that catalytic base must be added. Cyanohydrin formation is weakly exothermic, and is favored for aldehydes, and unhindered cyclic and methyl ketones. Two examples of such reactions are shown below.

*Figure 5: Cyanohydrin formation*

The cyanohydrin from benzaldehyde is named mandelonitrile. The reversibility of cyanohydrin formation is put to use by the millipede *Apheloria corrugata* in a remarkable defense mechanism. This arthropod releases mandelonitrile from an inner storage gland into an outer chamber, where it is enzymatically broken down into benzaldehyde and hydrogen cyanide before being sprayed at an enemy.

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