1.7: Oxidation and Reduction, alpha-C-H acidity

Last time we saw how a nucleophilic addition of a carbon atom to the carbonyl carbon could be carried out through the use of a Grignard reagent. This time we'll look at oxidations and reductions of carbonyl groups and at the acidity of the alpha hydrogen atom

Symbolizing Oxidations & Reductions

We'll start by recalling what the terms "oxidation" and "reduction" meant in inorganic chemistry. Oxidation is usually used to describe a process in which electrons are removed from a molecule or atom. Here's an example:

$$Fe^{2+} \rightarrow Fe^{3+} + e^{-} \tag{1.7.1}$$

This is interpreted to mean that a ferrous (+2) ion has been oxidized to a ferric (+3) ion by the removal of one electron (e^-). Similarly, reduction is used to describe a process in which electrons are added to a molecule or atom. An example might be:

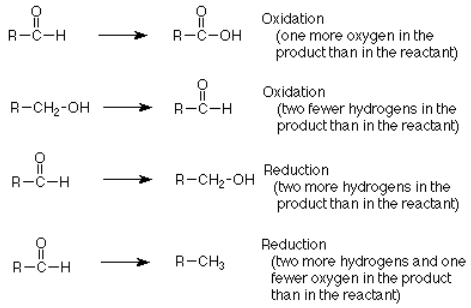
$$Cr^{6+} + 3e^{-} \rightarrow Cr^{3+} \tag{1.7.2}$$

We would interpret this to mean that a chromium atom in oxidation level six is being reduced to chromium in oxidation level three by the addition of three electrons. Using these symbols we can keep track of the oxidation levels of atoms as electrons are added or removed. Keep in mind that these equations are "half reactions" and they don't indicate where the electrons come from or where they go.

There are important areas of biochemistry (photosynthesis, oxidative phosphorylation) where this symbolism for oxidation and reduction is very useful, but for most of organic chemistry where molecules have many atoms, keeping track of oxidation levels this way is cumbersome and not very useful. Instead, we will use the following definitions:

- Oxidation means the addition of oxygen to a molecule or the removal of hydrogen from a molecule.
- Reduction means the addition of hydrogen to a molecule or the removal of oxygen from a molecule.

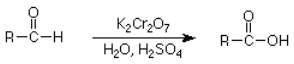
Let's look at some examples:



What about a reaction in which both oxygen and hydrogen are added or subtracted. If the ratio is one oxygen to two hydrogens (in other words, water), neither oxidation or reduction is happening. *Addition or removal of water does not involve, by itself, an oxidation or a reduction reaction.* The addition of water to an aldehyde to form a hydrate does not involve oxidation or reduction. You may wish to look at the formation of an acetal or hemiacetal in this way. If the **net change** in the number of hydrogens and oxygens comes out to be a ratio of two hydrogens to one oxygen, neither oxidation nor reduction is involved.

Oxidizing Agents

Now, let's turn to what we have to do to make an oxidation reaction go. If we return to the example we had earlier, we are trying to figure out what reagent to add to an aldehyde in order to oxidize it to a carboxylic acid. Such a reagent is called an oxidizing agent. Experiments have shown that there are many such reagents, but one which is commonly and effectively used for this purpose is chromic acid (H_2CrO_4). This reagent is prepared *in situ* (in the reaction mixture) by mixing a strong acid such as $H_2SO_4$and a sodium or potassium salt of the chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) ion. The reaction and the necessary reagents are shown as follows:

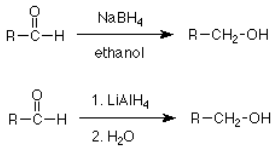


If a question asks for a reagent which will carry out a reaction, it is necessary to answer with a specific reagent. That means that you will need to develop a personal list of reagents and what they do. Both chromate and dichromate ions contain Cr^{VI}, so we recognize them as potential oxidizing agents based on the ability of Cr^{VI} to absorb electrons (and be reduced). Similarly, $KMnO_4^-$ (permanganate) ions contain Mn^{VII} and are good oxidizing agents for many organic reactions.

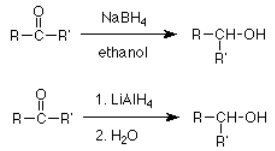
A final point: most of the reactions we have illustrated for aldehydes also work with ketones. We have made note of the generally less favorable equilibrium constant for additions to ketones, but the additions of water, alcohols, amines, cyanide and Grignard reagents all proceed to measurable extents with ketones. This is not so with oxidation. To oxidize a ketone would require breaking a carbon-carbon bond between the carbonyl carbon and a carbon bonded to it. Mechanisms to do this involve such high activation energies that they do not occur to any practical extent.

Reducing Agents

What about reduction? Similarly, there are specific reagents for the reduction of aldehydes and ketones to alcohols. (See Brown, Sec. 11.10B). Two important ones are sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). Their use is illustrated in the following two examples.



Since there is no carbon-carbon bond breaking which occurs in these reactions, we might expect that these reagents would also reduce ketones to alcohols. That is indeed the case, as seen in these examples.



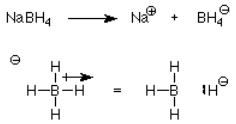
If we compare the outcome of reduction of aldehydes to that of reduction of ketones, we notice that aldehydes produce primary alcohols while ketones produce secondary alcohols. This give us an alternate method to the Grignard addition for making these types of compounds. (*Now would be a good time to make a personal list of reactions which produce alcohols, together with the necessary reagents and the specific structural types involved.*)

Mechanism of Reduction

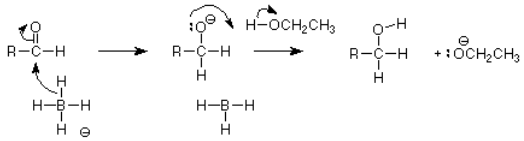
The comparison of these reduction reactions with the Grignard addition suggests another important point. In these reductions, hydrogen atoms are added to the carbonyl carbon and to the carbonyl oxygen. Since there is no hint of acid present, these reactions resemble base-catalyzed addition of water, addition of HCN, and the addition of a Grignard reagent rather than acid catalyzed reactions. We may expect them to begin with the attack of a nucleophile at the carbonyl carbon. In order to arrive at the observed product, the effective nucleophile has to be $:H^-$, just as in the addition of a Grignard reagent, the nucleophile was effectively $:R^-$. We justified that statement for the Grignard reagent by examining the carbon-magnesium bond and arguing that it was very strongly polarized so that the carbon effectively controlled the bonding pair of electrons, making it behave like $:C^-$. Can we do something similar for the hydrogen in sodium borohydride or lithium aluminum hydride?

First, we need to realize that sodium borohydride is a salt which is made up of a sodium cation (Na^+) and a borohydride anion (BH_4^-) The sodium ion plays no important role in the reaction, so we will ignore it (ions like sodium and potassium are seldom directly involved in reactions. They are present merely to maintain charge balance so that stable compounds can be added to reaction mixtures. They are often called spectator ions.) The borohydride ion is the important player in this process, and it is the B-H bond that we want to examine.

A quick glance at the periodic table to review electronegativities tells us that both boron and aluminum are metals with relatively low electronegativities. Each is less electronegative than carbon, and since hydrogen has about the same electronegativity as carbon we can conclude that the B-H bond is polarized with the boron positive and the hydrogen negative. This is very similar to the way we understood the electronic situation in a Grignard reagent, so we conclude that the B-H bond effectively serves as a source of hydride ion ($:H_-$). This is summarized below.



With this information and the addition of a Grignard reagent as a pattern, we can arrive at the following mechanism for the reduction of an aldehyde by sodium borohydride.

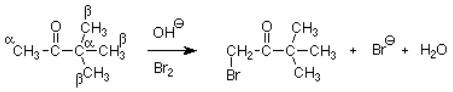


Notice the familiar pattern: Attack by a nucleophile at the carbonyl carbon, followed by protonation of the carbonyl oxygen.

The same mechanism applies to the reduction of ketones by sodium borohydride and to reactions of carbonyl groups with lithium aluminum hydride. In the latter case, lithium aluminum hydride is itself highly reactive with water, so the water is added after the lithium aluminum hydride has reacted.

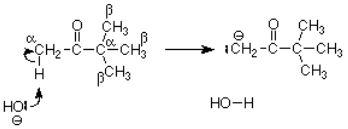
Enolate Ions

We have one major topic in carbonyl chemistry to introduce -- the reactions which occur at the carbon attached to the carbonyl carbon. This carbon is called the alpha-carbon. Here's an example of such a reaction.

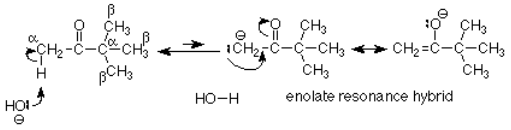


We can pick out several important features of this reaction from this example. First, there are two alpha carbons, but only one undergoes a reaction. That one (on the left) is attached to a hydrogen in the reactant. Second, we notice that there is no reaction at the beta-C-H bonds. Reactivity is restricted to the C-H bond on a carbon directly to the carbonyl carbon. **This type of reaction requires an alpha-C-H bond.** In a sense, the presence of the carbonyl group next to this C-H bond makes it a functional group.

Now to consider a mechanism. Our mechanism must account for the formation of a carbon-bromine bond and an oxygen-hydrogen bond (in water) and the cleavage of a carbon-hydrogen bond (alpha) and a bromine-bromine bond. It must also suggest a role for the OH^-. so let's begin by speculating that the hydroxide ion acting as a base makes a bond to the alpha-hydrogen. This process is coupled to the breaking of the alpha-C-H bond, whose electrons are then transferred to the alpha-carbon.



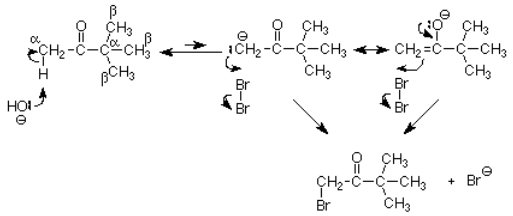
This is striking, because we are proposing that the alpha-hydrogen is acidic enough to be removed by a base no stronger than OH^-. This is certainly not true of other C-H bonds, and it is only true here to the extent that the equilibrium constant for this step is very small. There is very little of the product of this step at equilibrium (we'll call this product an enolate, for reasons which will make more sense a bit later). What is it about an enolate ion which allows it to be made at all. Put another way, why is the enolate ion stable enough to be formed, while a similar ion made from another C-H bond isn't. When we're looking for reasons of stability, resonance is one of the ideas we should explore. Since this process requires the carbonyl group next door, that resonance should involve the carbonyl group.



Sure enough, if we move electrons as indicated by the curved arrows, we find an alternative resonance structure. This structure has the energetic advantage that the unshared electron pair is on the oxygen (the more electronegative atom) rather than the carbon. And, the resonance itself contributes to lowering the energy of the enolate, which makes it stable enough for a little of it to be

formed at equilibrium. It is important to re-emphasize that none of this can happen if the carbonyl group is not next door to reactive C-H bond.

The alpha carbon in the enolate is all set up to behave as a nucleophile, providing a pair of electrons to make a new bond to a molecule of bromine. This requires that the bromine-bromine bond be broken at the same time. Notice that either resonance structure can be used to deliver the needed pair of electrons to make the carbon-bromine bond. This is necessarily so, since the two resonance structures are alternate descriptions of the same resonance hybrid.



Bromine is behaving as an electrophile, not because it has a vacancy in a valence orbital, but because it can simulate such a vacancy by breaking a bond. This reminds us of the behavior of the pi bond in a carbonyl group when it reacts with a nucleophile at the carbon atom.

Example 1.7.1:

There are some questions that are routinely asked, so let's take them up here.

1. Why does the OH^- attack the alpha C-H bond rather than the carbonyl carbon?
    1. It attacks both, but the attack at the carbonyl carbon leads to the hydrate - the product of addition of water. This certainly occurs, but it leads nowhere since the hydrate is present in very small quantities at equilibrium for ketones and most aldehydes.
2. Why does the reaction with molecular bromine take place at the carbon only? After all, there is a potentially nucleophilic unshared electron pair on oxygen as well.
    1. Reaction can take place at the oxygen, but the compound formed with a covalent bond between two rather electronegative elements is less stable than the one which results from reaction at the alpha-carbon.

Contributors

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