Reduction Reactions

Diabetes is a disease in which blood glucose levels are above normal. The reduction reactions of glucose, especially in eye and nervous tissue, are responsible for some of the major health problems of this disease. It is the sixth leading cause of death in the United States.

Outline
- Reduction of Glucose
- Reduction with Borohydride
- Other Reductants
- Homework

Over 8% of the adult population of Illinois suffers from diabetes. In the US as a whole, the incidence of the disease has increased greatly in recent years.

Reduction of Glucose

Glucose to Sorbitol
We already seen that NADPH reduces a carbonyl group in the formation of a sugar by adding H⁻ to the electrophilic carbonyl carbon.

The enzyme aldehyde reductase catalyzes a similar reaction between NADPH and glucose.
Aldehyde reductase is a barrel-shaped protein consisting of 315 amino acids linked together in a chain. In the center of the barrel is a binding site for NADPH and another for glucose. An acidic hydrogen from the side-chain of one of the tyrosine amino acids is positioned close to the aldehyde carbonyl oxygen.

During the reaction:
1. A hydrogen atom (and the electrons in its bond to carbon) from NADPH migrates to the electron-poor carbonyl carbon of glucose.
2. This breaks the H-C bond in NADPH and converts it into NADP⁺.
3. As the new C-H bond forms on glucose, the C=O pi bond breaks and the electrons in that bond migrate to the oxygen atom.
4. The basic oxygen atom abstracts an acidic hydrogen from the protein side-chain.

A catalyst, such as this enzyme, can only increase the rate of a reaction. It doesn't change the thermodynamics. The reaction between NADPH and glucose is thermodynamically favorable (ΔG is a negative number) but very slow. What would be the rate expression for the uncatalyzed reaction?

The slow step of the reaction catalyzed by aldehyde reductase is the release of NADP⁺ from the enzyme binding pocket. What is the rate expression for the catalyzed reaction?

Role of Glucose Reduction in Diabetes

The enzyme catalyzed reduction of glucose by NADPH is a minor reaction in the human body when blood glucose levels are in the normal range. However, in uncontrolled diabetics, the blood glucose level is much higher.

The molecule insulin regulates the amount of glucose that enters most cells in the body with the exception of cells in the eye and nerve cells. For these cells, the amount of glucose in the cell depends only on the concentration in the blood.

Once in the cells, glucose can be metabolized in the normal way or it can be reduced as shown above. Diabetics with chronic high blood sugar can have up to 1/3 of their glucose reduced through the pathway involving the aldehyde reduction reaction. This uses up significant amounts of NADPH and leads to significant decreases in the synthesis of other important molecules in these cells. The result is damage to the cells.

Sorbitol, Xylitol and other Sugar Alcohols

The aldehyde reduction product of glucose is the molecule sorbitol. The reduction of the five carbon sugar xylose produces another sugar alcohol, xylitol.
Sugar alcohols are not metabolized as efficiently as sugars. They have a sweet taste but a lower energy content than table sugar so they are used in some diet foods.

Because bacteria don't break them down readily, sugar alcohols don't cause tooth decay as sugars do. Because of this, they are used as sweeteners in chewing gum and toothpaste.

Borohydride Reduction

Reduction of Aldehydes and Ketones

In the enzyme catalyzed reduction of glucose, a proton along with 2 electrons adds to the carbonyl carbon and a proton adds to the carbonyl oxygen. A proton with 2 electrons, or H\textsuperscript{-}, is called a hydride.

**Aldehyde reduction:** \[ RCHO + H^+ + H^\text{+} \rightarrow RCH_2OH \]

NADPH is one source of H\textsuperscript{-} in biological systems. We use smaller (and much cheaper) hydride sources for reduction reactions in the laboratory. One of the most common hydride reagents is sodium borohydride, [Na][BH\textsubscript{4}].

In the first reaction above H\textsuperscript{-} is transferred from the nucleophilic borohydride reagent to the electrophilic carbonyl carbon. This forms an alkoxide salt and BH\textsubscript{3}. The second step is the protonation of the basic alkoxide with an acid to form the alcohol.

The reaction between a ketone and sodium borohydride is analogous.
Reduction of Carboxylic Acids

The carbonyl carbon of a carboxylic acid is even more electrophilic than the carbonyl carbon in an aldehyde or ketone. However, there is also an acid proton from the carboxylic acid that can react with hydride reagents. For this reason, sodium borohydride does not reduce a carboxylic acid.

A carboxylic acid can react with an alcohol, in the presence of a small amount of an acid, to form a carboxylic acid ester. Then the ester can be reduced.
The reaction of the methyl ester with sodium borohydride is below.

\[ \text{methyl propionate} \]

The addition of the hydride to the carbonyl carbon is followed by a second step that eliminates the \( \text{CH}_3\text{O}^- \) group and reforms the \( \text{C}-\text{O} \) double bond. Overall, this is a substitution of \( \text{CH}_3\text{O}^- \) for \( \text{H}^- \) at the carbonyl carbon but it proceeds through an intermediate in which the "carbonyl carbon" is bonded to 4 groups and has tetrahedral geometry.

The initially formed aldehyde can react with additional borohydride reagent.

**Other Reducing Agents**

**Lithium Aluminum Hydride**

A more active alternative to sodium borohydride in the reduction of carbonyl compounds is lithium aluminum hydride. It is more active because the Al-H bond is more polar and places more electron density on the hydrogen than the B-H bond.
Sodium borohydride reacts slowly with esters but lithium aluminum hydride reacts with them quickly and produces alcohols through reduction of the ester to the aldehyde and reduction of the aldehyde.

**Electrons as Reducing Agents**

The most fundamental reducing agent is an electron. Any atom in a molecule is reduced when it adds electrons and oxidized when it loses electrons. In an electrochemical reaction, a carbonyl compound can be reduced by electrons flowing to an electrode called a cathode. Other molecules are oxidized at another electrode called an anode.

The reduction half cell reaction takes place at the cathode. The oxidation half cell reaction takes place at the anode. Water supplies the protons and these protons, as well as other ions, are able to pass through a semi-permeable membrane that divides the cells. The external power supply supplies the energy to move electrons through the wires from the anode to the cathode.

Electrochemical reduction is a general method for transforming aldehydes, ketones, or carboxylic acids to alcohols or alkanes.