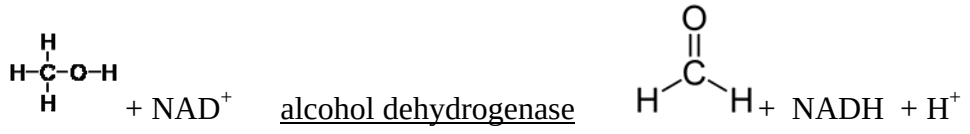
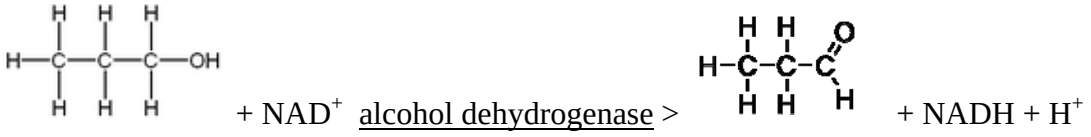
6.4 METABOLIC REACTIONS OF ALCOHOLS

6.41 Dehydrogenation

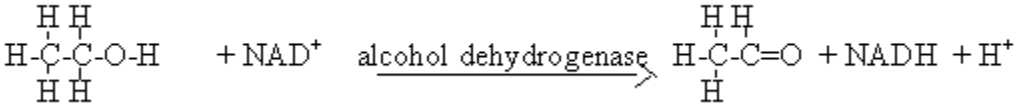
Dehydrogenation is the opposite of the hydrogenation reaction we saw with alkenes. We will not show a full reaction pathway, but simply show the product formed. In the chemical laboratory dichromate is used as an oxidizing agent. In the body (especially in the liver) an enzyme alcohol dehydrogenase acts as a catalyst for the reaction; a H^{-1} hydride ion is transferred to an acceptor molecule called NAD^+ (nicotinamide adenine dinucleotide) and a H^+ ion is released into solution.





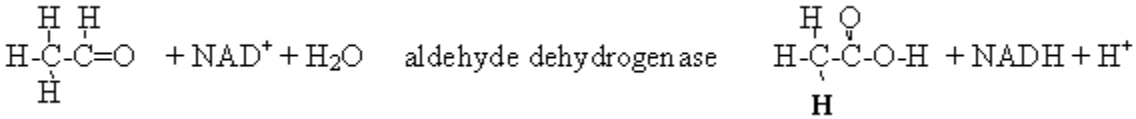
6.42 Dehydrogenation of ethanol.

The metabolism of ethanol is of obvious physiological importance and we will look at it in some detail.



ethanol

acetaldehyde (ethanal)
TOXIC!



acetic acid (non-toxic)

Acetic acid is then converted into Acetyl-CoA and metabolized in the Krebs cycle into carbon dioxide and water.

When one drinks small amounts of alcohol, acetaldehyde levels do not build up to very high levels and adverse effects are not experienced by most people. Higher levels of alcohol result in a build-up of acetaldehyde because the aldehyde dehydrogenase can only slowly metabolize acetaldehyde . Acetaldehyde is a toxic molecule, contributing to

the the nausea and vomiting experienced by those who have over-indulged. There is substantial variation in the levels of these two enzymes among individuals. Individuals with low levels of alcohol dehydrogenase will have alcohol circulate for longer periods of time and with greater CNS effect. (These are the "cheap drunks!") On the other hand individuals with low levels of aldehyde dehydrogenase will not be able to metabolize the acetaldehyde quickly. They are susceptible to flushing, increased heart rate, and nausea when consuming alcohol. Asians have a particularly high incidence(~50%) of this condition due to a mutation in their aldehyde dehydrogenase enzyme that causes it to have substantially lower ability to bind NAD, the H acceptor in the dehydrogenation of the acetaldehyde. This is sometimes referred to as the "Asian flush" although it is by no means limited to Asians. Acetaldehyde is a known carcinogen and the higher levels of acetaldehyde exposure may also increase these individuals' risk of esophageal cancer.

cureasianflush.yolasite.com

tamayou.com

There are claims that Asian flush can be reduced by taking drugs such as Pepcid, Axid and Tagamet which inhibit acid secretion in the stomach.

Alcoholics who are trying to maintain their sobriety (and their driver's license) are sometimes prescribed a drug called Antabuse. Antabuse acts as in inhibitor of the enzyme aldehyde dehydrogenase. As a result, acetaldehyde levels build up, and toxic symptoms appear after even a small amount of alcohol consumption. Patients given Antabuse should be thoroughly informed of the adverse effects that will occur should they drink. They should also be aware that some mouthwashes, cold medications, and after-shave lotions contain sufficient alcohol to cause nausea and vomiting if used by someone on Antabuse.

This knowledge is supposed to help motivate the alcoholic to stay sober, although it has not proven successful in large numbers of cases. There is also a liability problem in that a patient on Antabuse who drinks large quantities of alcohol may die. Quoting from the informational insert for Antabuse, the Antabuse-alcohol reaction in small amounts "produces flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitations, dyspnea, hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions and death."

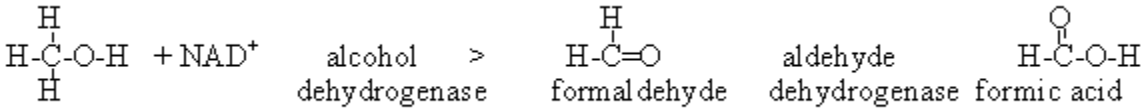
Studies (NEJM 322,95-99, 1990) have shown that for the same amount of alcohol ingestion and weight females have higher levels of blood alcohol than males. This appears to be due to the presence of alcohol dehydrogenase in the stomachs of males, but not females, resulting in significant conversion of ethanol into acetate before the ethanol is absorbed into the blood stream. There are also substantial variations in the level of aldehyde dehydrogenase. In general there is a higher incidence of low levels of aldehyde dehydrogenase in Asian ethnic groups Some individuals have very low levels of alcohol dehydrogenase and these people do not tolerate alcohol consumption. On the bright side, people with low levels of aldehyde dehydrogenase have much less tendency to become alcoholics because any significant consumption of alcohol makes them sick!

Although **chronic** alcoholism can cause cirrhosis of the liver and eventual death, **acute** poisoning by ethanol is not too common because most people will vomit if they drink large quantities of ethanol in a short period of time, thus limiting the amount of acetaldehyde that builds up in their body at any given time. Fatal acute ethanol poisoning does occur occasionally.

The alcohol dehydrogenase and aldehyde dehydrogenase enzymes are not specific for ethanol. They carry out similar reactions on other alcohols such as methanol (found in windshield wiper fluid), ethylene glycol(antifreeze), propylene glycol(RV antifreeze), and rubbing alcohol) that are sometimes imbibed on purpose or accidentally. Generally, these products are even more toxic than acetaldehyde. Poison control center data base shows 842 inquiries about methanol ingestion and 5022 inquiries about ethylene glycol poisoning.

6.43 Dehydrogenation of methanol.

Methanol is a solvent used in windshield wiper fluid, some paint strippers, and other industrial solvents. Small amounts are also found in alcoholic beverages. Occasionally some of it is "diverted" to human consumption. The metabolism is as follows:

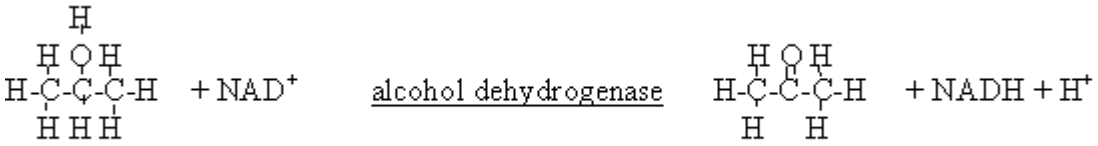


Formaldehyde reacts with and inactivates proteins; it is used to preserve cadavers. The production of large amounts of formic acid can produce metabolic acidosis. Formic acid is accumulated in neural cells, particularly the optic nerve. In small quantities it can cause blindness. Large quantities cause paralysis and death.

Small amounts of methanol or benzene have been added to ethanol that is sold for "industrial" purposes. (e.g. paint solvent and Sterno).(think Andromeda Strain) Industrial ethanol is not subject to the "sin tax" of alcoholic beverages but the federal government wants to make sure that it is not diverted for drinking. As a result, federal laws require addition of a **denaturing agent**, a toxic agent such as methanol or benzene, to industrial grade ethanol to discourage consumption.

6.44 Dehydrogenation of 2-propanol (rubbing alcohol)

2-propanol (rubbing alcohol) is readily available from any drug store. It is occasionally consumed by people who don't know any better. The metabolism is as shown

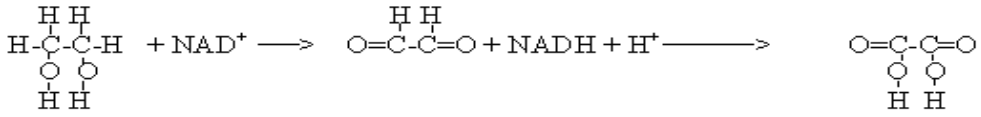


acetone is toxic

Similarly to ethanol, vomiting usually prevents buildup of acetone to lethal levels, but deaths due to rubbing alcohol consumption have occurred.

6.45 Dehydrogenation of 1,2 ethanediol (ethylene glycol). As already mentioned, ethylene glycol is used for radiator anti-freeze. Containers and open pans of anti-freeze often get left around and are the source of poisoning of cats, dogs and occasionally babies and small children. A Missouri radio talk show host poisoned his wife in 2004 by adding ethylene glycol (which tastes sweet) to her Gatorade.

The usual cause of death is metabolic acidosis and irreversible kidney damage. Ethylene glycol is sweet and so an unknowing baby or child may drink significant amounts. The metabolism is similar to other alcohols and is shown below:



oxalic acid

Name the enzymes that will catalyze each of the above reactions.
Most of these metabolic products are toxic in some way. The aldehyde groups can react with proteins as does formaldehyde; the carboxylic acids tend to produce metabolic

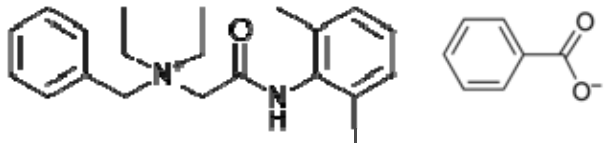
acidosis; at high concentrations, oxalic acid reacts with Ca^{+2} ions in the kidney to form needle-like crystals which permanently damage to kidney nephrons. Dogs and cats which drink antifreeze frequently die of irreversible kidney damage. There is some disagreement about whether the cause of kidney damage is acidosis or damage from crystal formed in the kidney glomeruli.

Ethylene glycol (and propylene glycol, see below) also is used as a deicing compound for plane wings prior to takeoff in icy conditions. In the past the ethylene glycol was allowed to run off and went into adjacent soil or streams. The ethylene glycol provides a nutrient source for bacteria in surface water which unfortunately use up oxygen in the process of metabolizing it, thus killing off other organisms (such as fish) which are deprived of oxygen. Requirements to prevent this runoff of deicing compounds are increasingly stringent.

There is a treatment protocol for poisoning with ethylene glycol as well as the less common cases of poisoning due to methanol and rubbing alcohol. Gastric lavage with activated charcoal can be done if ingestion has occurred within 1 hour.This is followed by saturation of the alcohol metabolizing enzymes with ethanol (either sterile IV or by oral consumption). This keeps the enzymes "busy" metabolizing ethanol, and ethylene glycol is excreted unchanged. Ethylene glycol is very soluble in water and does not need any metabolism to be excreted in the urine. The major adverse effect of this treatment is one hell of a hangover! Blood dialysis to remove the ethylene glycol and its metabolic products can also be done, if equipment is available.

Ethylene glycol has sometimes been added in small quantities to cheap wines because it improves the flavor and takes some of the "edge" off of the cheaper wines. Luckily, clinically significant poisoning is unlikely by this route, because the antidote (ethanol) is being consumed at the same time!

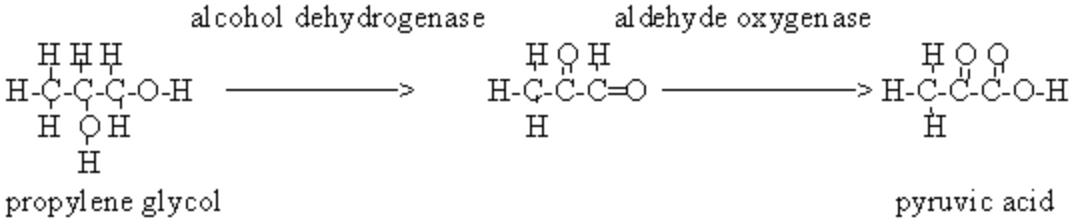
Since 1995 the state of Oregon has required the addition of very small amounts of denatonium benzoate, the bitterest compound known, to antifreeze. This counteracts the pleasant sweet taste of the ethylene glycol itself and will cause the antifreeze to be spat out, avoiding the potential for poisoning. Like the addition of methanol or benzene to industrial ethanol, denatonium acts as a denaturing agent and in fact that is what the "denat" in the name stands for! It is also used in products to inhibit nail biting and in animal repellants.



What functional groups are in denatonium benzoate?

6.46 Propylene glycol

Propylene glycol is also used as antifreeze, particularly for the potable water systems in RV vehicles. It is metabolized as shown below:



Luckily, pyruvic acid has no clinically significant solubility problems. It is an essential component of intermediary metabolism. Thus propylene glycol is non-toxic to humans

6.47 Diethylene glycol

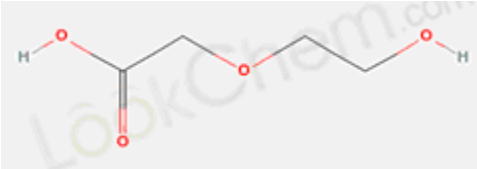
$HO\text{-}CH_2CH_2OCH_2CH_2OH$

In 1937 the Massengill pharmaceutical company used diethylene glycol(structure shown above) as a solvent for the sulfanilamide (one of the first modern antibiotics) in their Elixir Sulfanilamide. It was used because, like glycerol, it is very sweet, which helps to partially cover the bitter taste of the drug, and because it is a very viscous liquid (easier to pour onto a spoon with less spilling) and (last but not least) it was cheaper than glycerol. It caused a rash of poisoning, mostly children, including 105 fatalities. This incident resulted in the passage of the 1938 Federal Food Drug and Cosmetic Act which for the first time required safety tests for drugs and approval by the FDA before a drug went on the market. (It may come as a surprise to the reader that until this law was passed, there was no legal requirement that a drug be safe, let alone that it actually be **efficacious (**that it actually works better than placebo)!**.** Requiring a drug to show efficacy would have to wait until the Kefauver Harris amendment in 1962

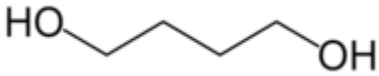
The Massengill company was given a small fine for mislabeling their syrup as an elixir, which technically means that it contains ethanol, when it fact it contained diethylene glycol).

Diethylene glycol appeared in the media again in 2006 and 2007 in Panama, the US, and several other countries in products such as toothpaste and expectorant. Most if not all of this diethylene glycol has been traced to manufacture in China. Diethylene glycol is

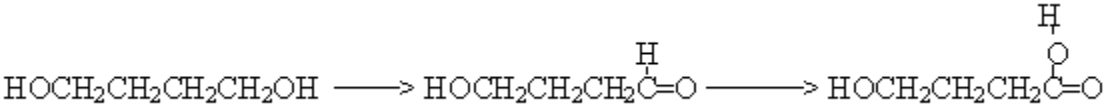
sweet and viscous, like glycerol, and it is cheaper than glycerol, which appears to be a major motivating factor for the substitution. Unfortunately it is also toxic.). Diethylene glycol apparently is metabolized into 2-hydroxyethoxyacetic acid, which produces metabolic acidosis.



6.48 1,4 butanediol



1,4 butanediol received media attention in November 2007 when it was discovered to have replaced 1,5 pentanediol coating the surface of children's beads marketed as Aqua Dots, helping the beads to stick together when they are wetted. One alcohol group of the 1,4 butanediol is metabolized by the alcohol dehydrogenase and aldehyde dehydrogenase enzymes into an aldehyde and then a carboxylic acid group, producing 4-hydroxy butanoic acid, better known as **gamma hydroxy butyric acid or GHB.**



As discussed in the carboxylic acid chapter, GHB is used as an illegal recreational drug for producing feelings of euphoria and sociability. At higher concentrations it can also cause unconsciousness and amnesia, leading to its use as a "date rape" drug. It can also cause respiratory depression which may lead to death.