Nuggets of Knowledge for Chapter 16 – Ethers and Epoxides
Chem 2320

I. Introduction to Ethers, Epoxides, and Thioethers

<u>Definition and Examples of Ethers and Thioethers</u>

- Ethers are compounds which contain an oxygen atom between two carbons, neither of which has a double bond to oxygen.

    o If only one of the carbons has a double bond to oxygen, the compound is an ester. If both of the carbons have double bonds to oxygen, the compound is an anhydride.

    o The most common ether is diethyl ether, also called ethyl ether or just ether. In organic chemistry, it is often used as a solvent for running reactions or doing extractions. Because of its flammability, it is also used as a starter fluid for gasoline and diesel engines. It was the first compound used as a general anesthetic, but has now been replaced by safer compounds like halothane.

    o Another common ether is methyl tert-butyl ether, usually called MTBE. It has been added to gasoline for many years to increase the octane rating, but recently environmental concerns have decreased its use.

- Thioethers are compounds which contain a sulfur atom between two carbons, neither of which has a double bond to oxygen.

    o Thioethers are also called sulfides.

    o Thioethers tend to have unpleasant odors, similar to thiols. This odor has been described as the smell of oysters stored in the fridge for too long.

    o We used a thioether in the reaction of ozones with alkenes – dimethyl sulfide.

<u>Classifications of Ethers</u>

- In alkyl ethers, both carbon groups are alkyl groups.

- In aryl ethers, one or both carbon groups are aryl, with the oxygen attached directly to the benzene ring.

- In cyclic ethers, the oxygen is part of a carbon ring, so that the alkyl groups on both sides are attached to each other. THF (tetrahydrofuran) is a common cyclic ether.

- Epoxides are cyclic ethers in which there are only two carbons in the ring. Because of the ring strain, they behave differently from other cyclic ethers.

- Crown ethers are a class of cyclic compounds with multiple ethers that look a lot like crowns.

    - They are good at solvating positive ions, which are surrounded by the partially negative oxygen atoms in the crown ether.

    - Rings of different sizes are selective for different elements, and crown ethers have been used to remove harmful ions like lead or radioactive strontium from water solutions. They can also be used to dissolve ionic reagents such as cyanides or permanganate in nonpolar solvents.

Physical Properties of Ethers

- Ethers have melting and boiling points intermediate between alkanes and alcohols. Alkanes have only van der Waals forces, while ethers have dipole forces. Alcohols, however, have hydrogen bonding, which is much stronger.

- Because of their intermediate polarity, ethers are good solvents. They can dissolve nonpolar, polar, and even some ionic compounds. Although ether molecules cannot hydrogen bond with each other, they can act as hydrogen bond donors. The lone pairs of electrons can stabilize electron-deficient compounds like borane.

- Low molecular weight ethers are extremely flammable. They are highly volatile (evaporate easily) and have low flash points (the lowest temperature at which their vapors can burn) and low autoignition temperatures (the lowest temperature at which they can ignite without a spark). The flash point of diethyl ether is -45°C; its autoignition temperature is 160°C.

- Ethers can form explosive compounds when they are exposed to air for a long time. They slowly react with oxygen to form organic peroxides, which are shock sensitive. Ethers are usually sold with a small amount of radical inhibitor to stop this reaction.

Reactivity of Ether and Thioethers

- Ethers are one of the least reactive functional groups – this is part of what makes them useful as solvents.

    o They do not react with bases, nucleophiles, or electrophiles, and they cannot be oxidized or reduced.

    o The only thing they react with are strong acids, which gives the protonated ether. The protonated ether can then react as an electrophile, usually with a halide ion.

- Epoxides react with acids and nucleophiles.

  o They can react as electrophiles when a nucleophile attacks at either of the carbons, pushing the electrons onto the oxygen and breaking open the strained ring.

  o They can also react as bases when reacted with a strong acid (similar to ethers). They then become even better electrophiles, since when the electrons are pushed onto the oxygen, it becomes neutral.

IR Spectra of Ethers

- The IR spectra of ethers has only one distinguishing band – the C-O at 1300-1000 cm^{-1}.

- Esters, alcohols, and anhydrides also have a C-O band, but they also have other bands that ethers don't have. Esters also have a C=O band; alcohols have an O-H band, and anhydrides have 2 C=O bands.

NMR Spectra of Ethers

- NMR spectra of ethers have either one or two peaks between 3-4 ppm, corresponding to the H's on carbons right next to the oxygen.

- If the ether is symmetrical, the peaks will be the same; if not they will be different. However, if they are both alkyl, they are likely to overlap.

II. Nomenclature of Ethers

Common names

- Simple ethers are often named by writing the substituents on both sides of the oxygen followed by the word "ether"; for example, methyl propyl ether. If the two substituents are the same, use "di"; for example, diethyl ether.

IUPAC names

- Ethers are not principle groups. Therefore, they have no special priority in naming, and the end of the main group name is not changed.

- Ether groups are simply considered substituents. The oxygen atom plus the smallest carbon chain connected to it is a substituent on the main chain or ring.

- Ether substituents are named by using the alkyl name of the carbon chain, then changing the "yl" to "oxy." For example, for an oxygen with one carbon attached, methyl is changed to methoxy.

- Ether substituents do not have any special priority over alkyl or halide substituents.

III. Synthesis of Ethers and Sulfides

- The two methods for synthesizing ethers are the Williamson ether synthesis and alkoxymercuration-reduction.

    - The Williamson ether synthesis requires an alkyl halide or tosylate and an alkoxide (formed by reacting an alcohol with base). They undergo an S_N2 reaction, and an ether is formed.

        - The main limitation of the Williams ether synthesis is that the alkyl halide or tosylate must be primary in order to avoid E2 side reactions. Secondary, tertiary, and aryl halides or tosylates are not effective.

    - Alkoxymercuration-reduction requires an alkene, and alcohol, and $Hg(OAc)_2$, followed by $NaBH_4$ in a separate step.

        - This reaction is just like oxymercuration-reduction except that an alcohol is used instead of water. This creates an ether instead of an alcohol.

        - The main limitation of this reaction is that the ether group always goes to the more substituted side of the alkene. If both sides are equally substituted, then two products can be formed.

- In order to synthesize sulfides, an S_N2 reaction between an alkyl halide or toxylate and a sulfide is used.

    - Because sulfides are less acidic (S is a larger atom), E2 isn't a problem, so secondary halides or tosylates can be used.

IV. Reactions of Ethers and Sulfides

- Ethers are highly unreactive functional groups. Their only reaction is being protonated with strong acids.

    - If sulfuric acid is used, no further reaction occurs, because the conjugate base is not a nucleophile.

    - If HBr or HI is used, then the halide attacks one of the carbons next to the positive oxygen, forming an alcohol and an alkyl halide. Under these conditions, the

alcohol reacts with the acid halide and also forms an alkyl halide, so 2 equivalents of the acid are needed. The first products are two alkyl halides and water.

- If the ether is symmetrical, 2 equivalents of a single alkyl halide are formed. If the ether is not symmetrical, 1 equivalent of two different alkyl halides are formed.

- If an aryl halide undergoes this reaction, the resulting aryl alcohol does not undergo a second reaction with the acid halide, since it cannot be attacked by a nucleophile in this way. Phenol and an alkyl halide are the products.

- This is not a very good synthesis of alkyl halides, since two products often result, and the ether starting material is generally harder to make than the alkyl halide.

- Sulfides have an important reaction that ethers do not – they can be oxidized.

  - Treatment with one equivalent of hydrogen peroxide in acetic acid gives a sulfoxide, in which the S has one C=O attached.

  - Treatment with two equivalents of hydrogen peroxide in acetic acid gives a sulfone, in which the S has two C=O's attached.

  - Because they are easily oxidized, sulfides can be used as mild reducing agents. For example, they are used in ozonolysis of alkenes to form ketones and aldehydes.

- Sulfides can also behave as nucleophiles, since sulfur is a larger atom and therefore more nucleophilic than oxygen.

  - If diethyl sulfide reacts with a good electrophile such as methyl iodide, a methyl group can be added to the sulfur to form a sulfonium salt.

  - This type of compound is a good alkylating agent because the sulfide is a stable leaving group. This is an important reaction in biochemistry.

V. Synthesis of Epoxides

- Epoxides may be formed by either reaction of an alkene with a peroxyacid, or reaction of a halohydrin with a base.

Epoxidation of Alkenes

- Alkenes may be reacted with peroxyacids to form epoxides.

- Peroxyacids are carboxylic acids with an additional O between the C=O and the OH.

- Peroxyacidic acid (CH_3CO_3H) soluble in water and alcohols.

- Peroxybenzoic acid ($PhCO_3H$) is soluble in low polarity solvents.

- Magnesium monoperoxyphthalate (MMPP) can be used with low polarity solvents, and is handy since its product crystallizes out of solution.

- During the reaction, the alkene is oxidized to an epoxide and the peroxyacid is reduced to a carboxylic acid.

- This reaction shows syn addition – the O is added to the same side of both substituents.

  - This is because the reaction is electrocyclic, and the O is attached to both C's at the same time.

  - If two substituents were opposite each other in the starting material, they will be opposite in the product; if they were on the same side in the starting material, they will be on the same side in the product.

  - When drawing an epoxide that is connected to a ring, it is common to show the stereochemistry of the other substituents (or H's), rather than the bonds to the O.

  - When drawing an epoxide that is not on a ring, it is common to show the substituents coming forward or backward rather than the bonds to the O.

Cyclization of Halohydrins

- Just as an alkyl halide and an alkoxide can be reacted to form an ether, a halide and an alkoxide on neighboring C's can be reacted to form an epoxide.

- If the alkyl halide C is a stereocenter, its stereochemistry will be inverted, since this is an S_N2 reaction, and the O must attack the opposite side of the halide.

- This reaction begins with a halohydrin, a compound with a halogen and an alcohol on neighboring carbons. A base (such as NaH, Na, or K) is added to deprotonate the alcohol so that it can act as a nucleophile.

- Halohydrins are made from alkenes using a halogen and water. Therefore the two ways of making epoxides are related – both start with an alkene.

VI. Reactions of Epoxides

Reactions of epoxides with strong nucleophiles

- Ethers (including most cyclic ethers) do not react with nucleophiles. This is because an alkoxide would result, and since it has higher energy than an ether, the reaction is endothermic and not favorable.

- Epoxides do react with nucleophiles. The ring strain of the 3-membered ring is released when a nucleophile attacks one of the carbons and pushes the electrons onto the oxygen. The higher energy of the starting material makes the reaction exothermic and favorable.

- When an epoxide reacts with a nucleophile, an alkoxide is formed, and needs to be neutralized to complete the reaction. The proton source depends on the nucleophile being used – it might be the solvent, or an acid added after the nucleophilic attack is finished.

- Epoxides will react with a variety of strong nucleophiles, including hydroxide, alkoxides, Grignards, cyanide, thiolates, and acetylide ions.

- If one side of the epoxide is more substituted than the other, then the nucleophile will attack at the less substituted side because there is less steric hindrance, so this reaction will be faster.

Reactions of protonated epoxides with weak nucleophiles

- Epoxides will also react with acid, forming a protonated epoxide.

    - A protonated epoxide is higher energy than an epoxide, so it is more reactive; also, it makes a neutral products, so the reaction with the nucleophile is more favorable.

- Protonated epoxides can react with weaker nucleophiles, such as water and alcohols.

    - Reacting an epoxide with acid and water creates a diol. Reacting an epoxide with acid and an alcohol gives a 2-alkoxy alcohol. Three steps are required: protonate, attack, and deprotonate.

    - Since the acid is regenerated in the final step, it is catalytic.

- If one side of the epoxide is more substituted than the other, the nucleophile will attack at the more substituted side because it shares more of the partial positive charge.

Synthsis using epoxides

- Epoxides can be used to synthesize compounds which have an alcohol 2 C's away from something that can be attached using a nucleophile.

- When designing a synthesis using an epoxide, it is a good idea to first figure out what nucleophile(s) could be used, then determine where the epoxide was, and write a reaction. Finally, check to see if the nucleophile will attack on the side to give the desired product.

Stereochemistry of epoxide reactions

- If an epoxide is chiral, the stereochemistry of the carbon which is attacked will be inverted. The other carbon will remain the same.

  - If both sides are equally substituted, two products will be formed, while if one side is more substituted, only one product will form.

- Formation and reaction of epoxides is a good way to form *trans* diols. This is complementary to hydroxylation of alkenes, which gives *cis* diols.