

Nuggets of Knowledge for Chapter 9 – Reactions of Alkyl Halides
Chem 2310

I. Introduction to Alkyl Halides

Types of Organic Halides

- Organic halides can be organized into four major categories. These compounds undergo very different kinds of reactions.
 - Aryl halides have a halogen connected directly to a benzene ring.
 - Vinyl halides have a halogen connected directly to a C=C.
 - Acid chlorides have a chloride connected directly to a C=O.
 - Alkyl halides have a halogen connected to an sp^3 carbon. These are the compounds that will be discussed in this chapter.
- Alkyl halides can be further classified as methyl, primary 1° , secondary 2° , or tertiary 3° .
 - methyl – a halogen attached to a methyl group
 - primary (1°) – halogen attached to an sp^3 carbon with 1 other carbon on it
 - secondary (2°) – halogen attached to an sp^3 carbon with 2 other carbons on it
 - tertiary (3°) – halogen attached to an sp^3 carbon with 3 other carbons on it
- Alkyl halides can also be labeled as benzyl or allyl.
 - allyl halide – halogen attached to an sp^3 carbon next to a C=C
 - benzyl halide – halogen attached to an sp^3 carbon next to a benzene ring
- If there are two halogens in the right positions, alkyl halides can be labeled as geminal or vicinal.
 - geminal dihalide – two halogens on the same carbon
 - vicinal dihalide – two halogens on carbons that are next to each other
- All alkyl halides undergo the same reactions, but they are affected by whether they are 3° , 2° , 1° , methyl, allyl, or benzyl.

Where organic halides are found

- Organic compounds containing halogens are rarely found in nature.
 - An important exception is thyroid hormone. Iodine is necessary in our diet in order to synthesize thyroid hormone. It is usually obtained from iodized salt. People who do not get enough iodine in their diet suffer from goiter, an enlarged thyroid gland.
- Alkyl halides are often used in medical, industrial, and commercial applications:
 - 1,1,1-trichloroethane (CH_3CCl_3) is used as a dry cleaning solution.
 - Chloroform (CHCl_3) was one of the first anesthetics, but it isn't used now on humans because of the small window between an effective dose and death.
 - Freon-12 (CF_2Cl_2) was a widely used refrigerant, but it has been replaced because of damage to the ozone layer.
 - Dichloromethane (CH_2Cl_2) is used as a solvent.
 - Halothane is an anesthetic currently in use.
 - Chlordane is a pesticide.

Preparation of Alkyl Halides

- One way to prepare alkyl halides is the halogenation reaction discussed in chapter 4.
 - In the presence of light or heat, alkanes react with Cl_2 or Br_2 to produce alkyl halides.
 - Multiple products are usually observed; these can be separated by fractional distillation, which is only practical on an industrial scale.
 - F_2 is not used because it is so energetic the reaction becomes explosive; I_2 is not used because the reaction is too slow.
- This reaction follows a radical mechanism, and is the example used in chapter 7.
 - Initiation step: homolytic cleavage of Cl_2 or Br_2
 - Propagation steps:
 - 1) attack of the halide radical on the alkane, taking a H and creating a carbon radical;
 - 2) attack of the carbon radical on a chlorine or bromine molecule
 - Termination steps: combination of halide radicals and carbon radicals.

- Radicals are stabilized by hyperconjugation and resonance.
 - hyperconjugation makes radicals more stable: $3^\circ > 2^\circ > 1^\circ > \text{methyl}$
 - radicals with resonance structures are more stable than those without
- A reagent called N-bromosuccinimide (NBS) is often used in place of Br_2 . It produces small amounts of Br_2 because of an unfavorable equilibrium. The Br_2 reacts, causing more to be created.
 - NBS is much easier to work with than Br_2 because it is solid and doesn't cause dangerous fumes.
- We will encounter other (better) ways to form alkyl halides in future chapters.

Spectroscopy of Alkyl Halides

- Alkyl halides have the following IR bands:
 - C-H $3000\text{-}2850\text{ cm}^{-1}$
 - CH_2 bending $1460, 1380\text{ cm}^{-1}$
 - C-X $800\text{-}500\text{ cm}^{-1}$ (often hard to find)
- Alkyl halides have the following characteristic NMR chemical shift values:
 - Chemical shift of H's on carbons next to halogens: 3-4 ppm

Reactivity of Alkyl Halides

- The carbon-halogen bond is a polar covalent bond.
 - The halogens higher on the Periodic Table are more electronegative, making the bond more polar. All are more electronegative than carbon.
 - The halogens lower on the Periodic Table are larger, making the bond weaker.
 - When these two factors are combined, the result is that carbon-iodine bonds are weakest, carbon-bromine bonds are next, carbon-chlorine bonds are also reactive, but carbon-fluorine bonds are too strong to react easily.
- Because of the polarity and weakness of the carbon-chlorine, carbon-bromine, and carbon-iodine bonds, they can react in three ways:

- They can dissociate to form a carbocation and a halide ion. The carbocation will react further, either as an electrophile or acid.
- They participate in displacement reactions with a nucleophile, forming a new bond to the nucleophile and forming a halide ion.
- They can participate in acid/base reactions with a base by giving up a hydrogen next to the carbon with the halogen. A carbon-carbon double bond is formed, and a halide ion is formed.
- In each of these reactions, the carbon-halogen bond is broken, and a halide ion is formed.

Nomenclature of alkyl halides

- Some functional groups have two ways to name them: IUPAC names, sometimes called substitutive names, and common names.
 - IUPAC names follow the rules we discussed in the chapter on alkanes.
 - Common names are much simpler, but only work for a few of the compounds.
- Common names for alkyl halides are formed by using the substituent name for the alkyl group attached to the halide. For example, CH_3Br is called methyl bromide.
 - The following are substituents we learned in Ch 4; review their structures if you don't remember them: methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, and tert-butyl and so on.
 - Substituent names for alkyl groups that contain a $\text{C}=\text{C}$ are **vinyl** (directly attached to the $\text{C}=\text{C}$) and **allyl** (one carbon away from the $\text{C}=\text{C}$).
 - The name for alkyl groups that contain a benzene ring are **phenyl** (directly attached to the benzene ring) and **benzyl** (one carbon away from the benzene ring). However, only benzyl is used in common names for alkyl halides. Aryl halides are named differently.
 - Common names are not used if there is not a simple name for the alkyl substituent.
- IUPAC, or substitutive names, follow the same rules we learned for naming alkanes. Refer to the nuggets for Ch 4 for full details; here is an abbreviated form.
 - 1) Choose the principle chain or ring, name it.
 - 1st priority: longest continuous chain
 - 2nd priority: most substituents
 - 2) Number the principle chain.

1st priority: give the lowest number to the first substituent, then the second, etc.
2nd priority: if all numbers are the same, use the alphabet

3) Name and order the substituents.

Halogen substituents are treated just like alkyl substituents; use fluoro, chloro, bromo, and iodo to name them.

4) Give the stereochemistry, if needed.

Use the rules for R and S that we learned in Ch 6.

II. Substitution Reactions of Alkyl Halides

Introduction

- The two basic types of reactions that alkyl halides can undergo are substitution and elimination reactions.
 - In a substitution reaction, a nucleophile takes the place of the halide. We will study substitutions in this chapter.
 - In an elimination reaction, however, the halide and a hydrogen are removed from the molecule, leaving a C=C behind. We will study eliminations in the next chapter.

Mechanisms

- The actual steps by which the reaction occurs is called the mechanism of the reaction.
- There are two ways in which substitution can occur.
 - The S_N2 reaction takes place in a single displacement step. We will call this *attack-push off*.
 - The S_N1 reaction takes place in three steps: dissociation, association, and an acid/base reaction. We will call this *fall off, attack, deprotonate*.

Which Substitution Reaction?

- Both S_N2 and S_N1 reactions involve the attack of a nucleophile, which ends up being substituted for the halide. The difference is how the reaction occurs.
- The difference in the mechanisms is caused by the strength of the nucleophile.

- In the S_N2 reaction, the nucleophile is strong enough to attack the alkyl halide. The alkyl halide is a weaker electrophile than a carbocation, since it is a stable molecule, so it needs a strong nucleophile to attack it.
- In the S_N1 reaction, the nucleophile is not strong enough to attack the alkyl halide. The alkyl halide must first dissociate, forming a more reactive carbocation, a good electrophile. The carbocation can react with the weak nucleophile.

Nucleophiles in Substitution Reactions

- Nucleophiles require a pair of electrons with which to attack a carbon atom. As we have seen, we can determine whether a substitution will be or S_N1 by looking at the strength of its nucleophile.
- Nucleophiles which will react in S_N2 reactions include: acetylide ions, cyanide ions, thiolates, hydroxide ions, alkoxide ions, and halide ions.
 - exception: tert-butoxide ions won't attack at all because they are too sterically hindered
- Nucleophiles which will react in S_N1 reactions include: water and alcohols
 - exception: tert-butyl alcohol won't attack at all

Products

- Many different products may be formed using substitution reactions. Whatever the nucleophile is will end up attached to the carbon chain where the halide was. The following types of products can be formed using substitution reactions:

nucleophile	product
acetylide ions	alkynes
cyanide ions	nitriles
hydroxide ions or water	alcohols
alkoxide ions or alcohols	ethers
thiolate ions	sulfides
halide ions	alkyl halides

Stereochemistry

- A substitution reaction cannot create a new stereocenter, but it can involve a carbon that is already a stereocenter. When a stereocenter is involved in a substitution reaction, we need to know what will happen to it.
- If the compound undergoes an S_N2 reaction, the stereocenter will be inverted.

- This occurs because the nucleophile must approach the carbon from behind the halide in order to push it off.
- The carbon is turned inside out like an umbrella, going from tetrahedral to trigonal bipyramid to tetrahedral again.
- If the compound undergoes an S_N1 reaction, the stereocenter will be racemized.
 - This occurs because once the halide leaves, the carbocation is trigonal planar, and is no longer a stereocenter. The nucleophile may approach from either side, so both stereoisomers are formed.
 - The two stereoisomers are not actually formed in equal amounts. The departing halogen ion partly blocks one side, so that there is slightly more inverted product than conserved.

Rate Laws

- In the S_N2 reaction, there is only one step, and the transition state involves both the alkyl halide and the nucleophile. The bond to the nucleophile is being formed, and the bond to the halide is being broken.
 - Since both reagents are part of the transition state of the rate limiting step, both are included in the rate law: $\text{rate} = k_r [\text{RX}] [\text{Nu}]$
 - Changing the concentration of the alkyl halide or the nucleophile will change the rate of the reaction by the same amount.
 - The reaction is first order in the alkyl halide and first order in the nucleophile, making it second order overall.
 - S_N2 stands for substitution, nucleophilic, 2nd order.
- The rates of S_N2 reactions are strongly affected by the structure of the alkyl halide.
 - The less hindered the alkyl halide is, the more easily the nucleophile can attack. This makes the activation energy low, and the rate of the reaction fast.
 - Carbon groups attached to the carbon with the halogen make it more difficult for the nucleophile to attack. This increases the activation energy, and slows down the reaction.
 - The rates of S_N2 reactions with different alkyl halides is methyl > 1° > 2° >> 3°. Methyl and primary alkyl halides react quickly. Secondary alkyl halides react more slowly. Tertiary reactions are so slow that no product is formed.
- The rates of S_N2 reactions are also affected by the structure of the nucleophile. The more hindered the nucleophile is, the slower the reaction rate. Tert-butyl nucleophiles are so hindered that substitution reactions cannot occur.

- In S_N1 reactions, there are multiple steps. However, the first step, in which the carbocation is formed, is the one with the highest activation energy, and therefore controls the rate of the reaction – this is said to be the rate-limiting step. The bond between the carbon and the halide is being broken.
 - Since only the alkyl halide is part of the transition state for the rate limiting step, it is the only thing in the rate law: $\text{rate} = k_r [\text{RX}]$
 - Changing the concentration of the alkyl halide will change the rate of the reaction, but the concentration of the nucleophile will not change the reaction rate.
 - The reactions are first order in the alkyl halide and zeroth order in nucleophile, making them first order overall.
 - S_N1 stands for substitution, nucleophilic, 1st order.
- The rates of S_N1 reactions are also strongly affected by the structure of the alkyl halide, but in a different way.
 - The rate limiting step is not the attack of the nucleophile, but the formation of the carbocation. The more stable the carbocation is, the lower the activation energy will be, and the faster the reaction will go.
 - The more carbon groups that are attached to the carbon with the halogen, the more stable the carbocation will be, lowering the activation energy and making the reaction go faster.
 - Since the carbocation is trigonal planar, steric hindrance is not an issue – nucleophiles can approach 3° carbocations just as easily as less substituted ones.
 - The rates of S_N1 reactions with different alkyl halides is $3^\circ > 2^\circ \gg 1^\circ > \text{methyl}$. Primary and methyl carbocations are so slow that no products are observed.
 - Carbocations can also be stabilized by resonance – a 1° carbocation can form if it is benzyl or allyl.
- In both S_N2 and S_N1 reactions, the halogen-carbon bond is broken in the rate-limiting step. Therefore, the longer, weaker bonds will decrease the activation energy and increase the rate of reaction.
 - The rate of reaction for both types of substitution is $\text{R-I} > \text{R-Br} > \text{R-Cl} \gg \text{R-F}$. Alkyl fluorides are too strong to be removed by substitution, and don't participate in substitution reactions.

Rearrangements

- Carbocations are formed only in S_N1 reactions, not S_N2 reactions.
- Once formed, the carbocation can rearrange to give a more stable carbocation.
 - Whenever reaction occurs in which a carbocation is formed, you should draw out the carbocations to see if they will rearrange.
 - If rearrangements can occur, both products will be formed, those with the original carbocation, and those with the rearranged one. The carbocation may collide with the nucleophile before or after it rearranges.
- Only 2° carbocations commonly undergo rearrangements.
 - Primary carbocations rarely undergo rearrangements because they are too unstable to form in the first place, while tertiary carbocations are already as stable as they can be, so they do not usually undergo rearrangements.
 - Secondary carbocations are stable enough to form, but if there is a way for them to rearrange and become tertiary, this can occur.
- There are two ways for a 2° carbocation to become tertiary by undergoing a rearrangement. Both of them involve electrons on a neighboring bond shifting to occupy the empty p orbital, leaving another, more stable one behind. They are called hydride shifts and alkyl shifts.
 - In a hydride shift, a hydrogen moves with its pair of electrons from a tertiary carbon to the carbocation, leaving the positive charge on the tertiary carbon.
 - In an alkyl shift, a carbon group moves with its pair of electrons from a quaternary carbon to the carbocation, leaving the positive charge on the now tertiary carbon.

Solvents

- In many cases, a solvent is needed in order to dissolve the reagents so that they have the chance to collide. The solvent can also affect the rate of the reaction, so it is important to consider this factor as well.
- The main things to consider are the polarity of the solvent, and whether or not it can form hydrogen bonds.
 - Polarity is determined by the strength of the intermolecular forces. Molecules with only van der Waals forces are nonpolar solvents. Molecules with dipole forces may be moderately polar or highly polar depending on the strength of the dipole. Molecules with hydrogen bonding are highly polar.
 - Polar solvents with no hydrogen bonding are called aprotic solvents, while polar

solvents that do have hydrogen bonding are called protic solvents.

- Polarity of the solvent can be important because it is important that the reagents will dissolve in the solvent.
 - S_N2 reactions require a polar solvent in order to dissolve the strong nucleophile, because it usually has a charge.
 - S_N1 reactions employ weak nucleophiles which are usually not charged, so there are no particular requirements for the solvent to dissolve the reagents.
- Hydrogen bonding is important because it can affect the rate of the reaction in different ways depending on the reagents and the mechanism.
 - In S_N2 reactions, hydrogen bonding slows down the reaction by surrounding the nucleophile and making it difficult for them to react. Therefore, aprotic solvents are best.
 - In S_N1 reactions, hydrogen bonding speeds up the reaction by stabilizing the carbocation, making it easier to form. Therefore, protic solvents are best.
- Examples of suitable and unsuitable solvents are as follows:
 - Nonpolar solvents include hexanes, toluene, and petroleum ether. These are unsuitable for substitution reactions because they will not dissolve charged reagents or stabilize a carbocation.
 - Mildly polar solvents include dichloromethane, ethyl acetate, and diethyl ether. Although they are better than nonpolar solvents, they are not polar enough to dissolve charged reagents very well, and cannot stabilize a carbocation.
 - Highly polar, aprotic solvents include acetone, N,N-dimethylformamide, and acetonitrile. They are very good at dissolving charged reagents, but they do not have any hydrogen bonding. This makes them ideal for S_N2 reactions.
 - Highly polar, protic solvents include water and alcohol solvents such as methanol or ethanol. They have hydrogen bonding, so they are ideal for S_N1 reactions. In most cases the nucleophile is used as the solvent.

Exclusion of aryl halides, vinyl halides, and acid chlorides from substitution reactions

- Aryl halides, vinyl halides, and acid chlorides don't participate in S_N2 reactions because the pi bonds prevent the nucleophile from attacking from behind, as the mechanism requires.
- Aryl halides, vinyl halides, and acid chlorides don't participate in S_N1 reactions because the carbocation that would be formed is too unstable (high in energy).

III. Synthesis Using Substitution Reactions

- One of the principle uses of organic chemistry is to synthesize compounds – in other words, to make compounds we want from those we have.
 - Each reaction we learn is a tool we can use to make a specific change to a molecule.
 - Substitution reactions are ways to make alkyl halides into other functional groups.
- When designing a synthesis, you start with the molecule that you want to make. Then:
 - First, consider what starting materials and reagents could be reacted to give this molecule.
 - Second, examine your reaction to see if it will be good way to make the molecule.
 - Will the reaction be favorable?
 - Will any other products be formed?
- When using substitution reactions, first determine what nucleophiles could be used. Then consider what alkyl halides would be used.
 - In some cases, there is only one option for the nucleophile, but in others there is a choice of either a weak or a strong nucleophile.
 - When there is only one option, consider the alkyl halide and decide whether it will be favorable with the mechanism that will result.
 - When there are two options, again consider the alkyl halide but now decide if either option will be favorable.
 - In some cases, only one alkyl halide is possible as the starting material, but in others there is more than one option.
 - When there is only one option, consider whether the resulting reaction will be favorable.
 - When there are two options, consider both to see if one would be a more favorable reaction than the other.