

Nuggets of Knowledge for Chapter 10 – Alkyl Halides II
Chem 2310

I. Elimination Reactions of Alkyl Halides

Introduction

- The two basic types of reactions that alkyl halides undergo are substitution and elimination reactions.
 - In a substitution reaction, a nucleophile takes the place of the halide. We studied substitutions in the previous chapter.
 - In an elimination reaction, the halide and a hydrogen are removed from the molecule, leaving a C=C behind. We will study eliminations in this chapter.
- These two reactions can often occur under the same conditions, so they are in competition with each other.
 - In some cases, one will be faster and give most or all of the product, while in others they will have about the same rate, and a mixture will be formed.

Mechanisms

- The mechanism of a reaction shows how the bonds are broken and formed, using curved arrows to represent the movement of the electrons.
- There are two ways in which elimination can occur.
 - The E2 takes place in a single step in which the base takes a H, the electrons go in to form a double bond, and the halide leaves with its electrons. We will call this *deprotonate-push off*.
 - The alkyl halide acts as an acid, giving up a H. This can occur because the halide can leave, and the carbon it is attached to is partially positive, pulling the electrons of the H towards it as the H is taken.
 - The E1 takes place in two steps. In the first, the halide falls off, creating a carbocation. In the second, the base takes a H, and the electrons go in to form a double bond. We will call this *fall off, deprotonate*.
 - The alkyl halide can dissociate because the bond is already polar, and the halide is stable as a negatively charged ion.
 - The carbocation acts as an acid, giving up a H. This can occur because the positively charged carbon pulls the electrons of the H towards it as the H is taken.

Beta hydrogens, constitutional isomers, and stereoisomers

- The hydrogen that is removed in an elimination reaction is always on the carbon next to the one with the halogen.
 - This is because a C=C can only be formed if two C's next to each other are involved.
 - This is called a beta hydrogen because the carbon with the halide is the alpha carbon, so the next one over is called the beta carbon. H's on the beta carbon are called beta H's.
 - Alpha H's (the ones on the same C as the halide) cannot be used, because then the C's on either side are already full, so they can't be part of a C=C. Instead, the electrons would go onto that same carbon, leaving a carbanion, which would not be stable.
- There can be more than one set of beta H's.
 - If both sets are equivalent, only one product is formed.
 - If the sets are not equivalent, constitutional isomers can be formed.
 - When there is a possibility for more than one stereoisomer to be formed, both will be made.
- When constitutional and stereoisomers are formed, they do not occur in equal amounts. The more stable ones will be formed faster, and will be favored by the reaction.
 - Alkenes with more carbons attached to the C=C are said to be more substituted. This makes them more stable, and they will be formed in greater amounts.
 - Stereoisomers that are trans or E are more stable than ones that are cis or Z. This is a smaller difference than the degree of substitution, however.

E2 vs E1

- Both E2 and E1 reactions involved a base taking a H, and a halide leaving, with a C=C being formed. The difference is in how the reaction occurs.
- Which mechanism is followed depends upon the strength of the base.
 - In the E2 reaction, the base is strong enough to react with the alkyl halide. It is not necessary for a carbocation to form for the reaction to proceed.
 - In the E1 reaction, the base is not strong enough to react with the alkyl halide. The alkyl halide must first dissociate, forming a carbocation, which is a much stronger acid. The weak base can then react with it.

Strong and Weak Bases

- Nucleophiles and bases both have a pair of electrons that can attack. The difference is that a nucleophile attacks a carbon, while a base attacks a hydrogen. However, a molecule can often act as either a nucleophile or a base.
 - E2 and S_N2 reactions both require one step, because both have a strong reagent, either a nucleophile or a base.
 - E1 and S_N1 reaction both require multiple steps, because both have a weak reagent, either a nucleophile or base.
- Some of the factors which affect nucleophile strength are the same as base strength, while others are different.
 - Charge: Negatively charged molecules are stronger nucleophiles and stronger bases. This is because when a negatively charged atom attacks, it becomes neutral, but when a neutral atom attacks, it becomes positive.
 - Electronegativity: Atoms that are less electronegative are stronger nucleophiles and stronger bases. This is because their electrons are not attracted to the atom as strongly, and are easier to donate. In the case of negative nucleophiles and bases, they are also more reactive because it is harder for them to have a negative charge.
 - Size: Larger atoms are stronger nucleophiles, but larger atoms are weaker bases. The valence electrons are farther from the nucleus and are therefore easier to donate to form a bond, making them stronger nucleophiles. But atoms that are in the 3rd, 4th, and 5th periods have more difficulty overlapping with the small s orbital of a 1st period hydrogen than with the orbitals of a 2nd period carbon, so they make weak bases.
 - Steric hindrance: Molecules which are sterically hindered are poor nucleophiles, but good bases. This is because in order to attack a carbon atom, the molecule must push past any substituents, but hydrogen atoms are on the outside of the molecule and are more easily removed.
- The concepts above can be applied to predict the behavior of molecules:
 - Most reagents, such as sodium hydroxide, water, cyanide, and alkyne anions, can be either nucleophiles or bases, and can be used in elimination or substitution reactions.
 - Strongly hindered reagents, such as tert-butoxide or tert-butyl alcohol, can only be bases, and can only be used in elimination reactions.
 - Reagents with large atoms, such as halides and thiolate ions, can only be nucleophiles, and can only be used in substitution reactions.

Rate laws

- In the E2 reaction, there is only one step, and the transition state involves both the alkyl halide and the base.
 - The bond between the base and the hydrogen is being formed, and the bond between the hydrogen and the alkyl halide is being broken, and the double bond between the two carbons is forming, and the bond between the carbon and the halide is begin broken, all at the same time.
 - Since both reagents are part of the transition state of the rate limiting step, both are included in the rate law: $\text{rate} = k_r [\text{RX}][\text{base}]$
 - Changing the concentration of the alkyl halide or the base 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 base, making it second order overall.
 - E2 stands for elimination, second order.
- In the E1 reaction, there are multiple steps. However, the first step, in which the carbocation is formed, controls the reaction because it is the rate limiting step.
 - In the rate limiting step, the bond between the halide and the carbon 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 base will not change the reaction rate.
 - The reactions are first order in the alkyl halide and zeroth order in base, making them first order overall.
 - E1 stands for elimination, first order.
- In the E1 and E2 reactions, the alkyl halide affects the rate in the same way, but not for the same reason.
 - In the E2 reaction, steric hindrance is not an issue, as it is in S_N2 reactions. Instead, the important factor is the stability of the alkene product.
 - The more carbons are attached to the alkene, the more stable it is, and the faster it is formed. Therefore the rate is $3^\circ > 2^\circ > 1^\circ$. (Methyl alky halides cannot undergo elimination because there is only one carbon.) This is opposite the rate of S_N2 reactions.
 - In the E1 reaction, as in the S_N1 reaction, the issue is stability of the carbocation.

- The more carbons are attached to the carbon with the halide, the more stable it will be, and the faster it is formed. Therefore the rate is $3^\circ > 2^\circ > 1^\circ$.
- In both E2 and E1 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 elimination is $R-I > R-Br > R-Cl \gg R-F$. Carbon-fluoride bonds are too strong to be broken by elimination reactions.

Rearrangements

- Only E1 reactions involved carbocations, and therefore only E1 reactions can involve rearrangements.
- Only 2° alkyl halides commonly undergo rearrangements. 3° alkyl halides are already as stable as they can be, and 1° carbocations are not commonly formed.
- Alkyl shifts (most commonly methyl shifts) and hydride shifts can occur. They will only happen if the new carbocation is more stable than the original.
- When a carbocation is formed, it can either react with a base or rearrange, and these two things happen at comparable rates. Therefore, products will be formed both from the original carbocation and from the rearranged one.

Stereochemistry

- Carbons involved in $C=C$ are flat, so they cannot be chiral stereocenters. However, cis and trans (or E and Z) stereocenters are possible.
- In order for the E2 reaction to occur, the orbitals must be lined up so that the halide and hydrogen are anti to each other.
 - If both the carbon with the halide and the carbon with the hydrogen are stereocenters, then there will only be one possible orientation in which the elimination can occur, and only one stereoisomer will be formed.
 - One pair of enantiomers will give the same diastereomer of the alkene, but the other pair (diastereomers of the first pair) will give the other diastereomer of the alkene.
 - If only the carbon with the halide or with the hydrogen is a stereocenter, then there will be two orientations in which the elimination can occur, and both stereoisomers will be formed.
- In order for the E1 reaction to occur, the empty p orbital must be lined up with the carbon-hydrogen bond.
 - Since the p orbital has two lobes, there will always be two possible orientations in which the

elimination can occur, and two stereoisomers will be formed.

Solvents

- E2 reactions require polar, aprotic solvents for the same reasons that S_N2 reactions do – they need a polar solvent to dissolve the ionic reagent, but are slowed down by hydrogen bonding, which solvates the reagents and makes it harder for it to react.
 - Suitable solvents include acetone, acetonitrile, and dimethylformamide.
- E1 reactions require polar, protic solvents for the same reasons that S_N1 reactions do – they need a protic solvent to stabilize the carbocation that is formed. The solvent is often the reagent.
 - Suitable solvents include water and alcohols.

Elimination of aryl and vinyl halides

- Aryl and vinyl halides do not react with the strong bases that work for alkyl halides. However, they do react with much stronger bases such as NaNH₂.
 - NaNH₂ has a conjugate acid pK_a of 36, while tert-butoxide has a conjugate acid pK_a of 18. This makes it 10¹⁸ more basic, which is a whole different level of “strong base.”
 - Using these much stronger bases, vinyl halides can form alkynes, and aryl halides can form benzyne. Alkynes are stable products, but benzyne are not stable and will react further. These reactions will be covered in more detail in later chapters.

II. Elimination vs. Substitution

- Elimination and substitution reactions can often occur under the same conditions. Both start with an alkyl halide, and many reagents can act as either nucleophiles or bases. You must be able to determine if one reaction will predominate, or if there will be a mixture.
- The first criteria is the strength of the nucleophile or base.
 - If it is a strong nucleophile or base, then 2nd order reactions will occur, and the competition is between S_N2 and E2.
 - If it is a weak nucleophile or base, then 1st order reactions will occur, and the competition is between S_N1 and E1.
- The second criteria is to look at the structure of the alkyl halide, and consider the rates of reaction.
 - For S_N2 and E2, the rates are opposite:
 - S_N2: 1° alkyl halides are faster than 2° alkyl halides, which are much faster than 3° alkyl

halides.

- E2: 3° alkyl halides are faster than 2° alkyl halides, which are faster than 1° alkyl halides.
- Considering these two rates together:
 - for 1° alkyl halides, S_N2 will predominate
 - for 2° alkyl halides, there will be a mixture of S_N2 and E2
 - for 3° alkyl halides, E2 will predominate
- For S_N1 and E1, the rates are the same:
 - S_N1: 3° alkyl halides are faster than 2° alkyl halides, which are faster than 1° alkyl halides (which do not normally occur).
 - E1: 3° alkyl halides are faster than 2° alkyl halides, which are faster than 1° alkyl halides (which do not normally occur).
 - Considering these two rates together:
 - for 1° alkyl halides, there will be no reaction
 - for 2° alkyl halides, there will be a mixture of S_N1 and E1
 - for 3° alkyl halides, there will be a mixture of S_N1 and E1
- Finally, you must watch out for special cases.
 - tert-butoxide and tert-butyl alcohol give only elimination
 - halides and thiolates give only substitution
 - if the alkyl halide has no beta hydrogens, only substitution can occur
 - if the alkyl halide is benzylic, a carbocation can form even on a primary alkyl halide

III. Synthesis using elimination

- Substitution reactions can give a variety of product depending on the nucleophile – alkynes, nitriles, alcohols, ethers, thiolates, and other alkyl halides.
- Elimination reactions give only alkenes (unless aryl or vinyl halides are used, which will be considered later).
- In order to have a good synthesis, the reaction must be reasonably fast, and must not give any other products.
 - To prevent interference from substitution reactions, it is a good idea to use a hindered base

such as tert-butoxide.

- To avoid multiple products because of rearrangements, it is a good idea to use tert-butoxide instead of tert-butyl alcohol.
- It is better to use a secondary or tertiary alkyl halide where possible to avoid the slow reaction from a primary alkyl halide.
- Constitutional and stereoisomers are difficult to avoid. Where possible, choose an alkyl halide that will give only one constitutional isomer. (We will learn better ways in the future to avoid these problems.)