

Haloalkanes — Nucleophilic Substitution, SN2 & SN1 and Elimination Reaction

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Organohalides are organic compounds containing one or more halogen substituent. There are about 5,000 organohalides occurring naturally, some of which are produced and are found in algae and various marine organism. Organohalides are a big family of a compound wherein the halogen can be attached to an alkynyl group (C≡C-X), a vinylic group (CC-X), a vinylic group (C=C-X), an aromatic ring (Ar-X) or an alkyl group (C-C-X). This article will focus specifically on haloalkanes.



Haloalkane: Introduction

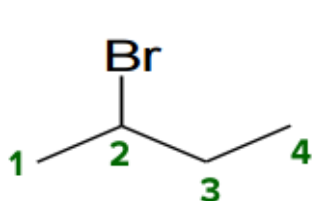
Haloalkane, also called **alkyl halides**, are the organic compound where the halogen is attached to an alkyl group. Haloalkanes may vary depending on the halide group attached, and/or the number of halide substituent. The size of a halogen group increases as you go down the periodic table because of having larger atomic radii. Because of this, the C-X bond strength decreases as you go down the periodic table. Later on, in this article, you will see the effect of this in terms of the reactivity of the alkyl halide. Alkyl halides may also vary depending on the extent of substitution. Compounds can be monosubstituted, disubstituted and much more.

One factor affecting reactivities of haloalkane is **bond polarity**. Bond polarity arises from

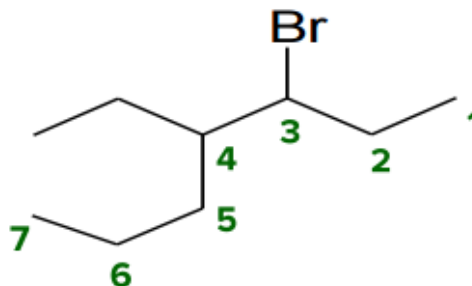
the differences in the electronegativities of atoms forming the bond. The higher the difference in their electronegativity values, the more polar is the bond. Halogens are more electronegative than carbon; that is why in alkyl halides, the C-X bond has the partially negative end in the X atom and the partially positive end in the C atom.

General formula: R-X | where X = F, Cl, Br, I

Nomenclature: Halo- ...ane



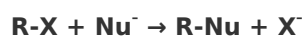
2-bromobutane



3-bromo-4-ethylheptane

Nucleophilic Substitution

Nucleophilic substitution reaction was first observed by the German chemist, Paul Walden, in 1896. He was able to observe that (+) and (-) malic acid can be interconverted using PCl_5 and Ag_2O . In general, nucleophilic substitution reaction involves the substitution of one nucleophile by another. The general formula for this reaction is as follows:



Depending on the molecularity of the reaction, nucleophilic substitution reactions may be classified as $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$. Depending on the reaction parameters and conditions, either $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ reactions may occur.

$\text{S}_{\text{N}}2$ Reaction

$\text{S}_{\text{N}}2$ reaction is a nucleophilic substitution reaction wherein the reaction kinetics is dependent on the concentrations of the nucleophile and the alkyl halide. Reactions occur in a single step without formation of any intermediate. The basic mechanism for the reaction involves an attack of the nucleophile on the opposite side of the leaving group. Bond formation and bond breakage occur at the same time.

The whole process involves inversion in the stereochemistry of the carbon involved in the reaction. Let us consider the reaction of the hydroxide ion with 2-bromobutane.

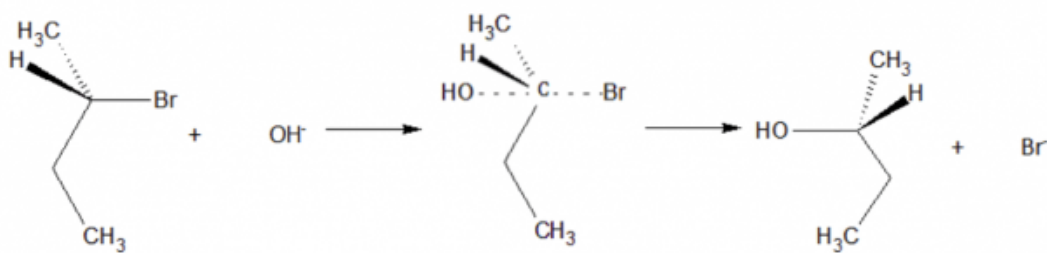


Figure: "S_N2 reaction of 2-bromobutane and hydroxide ion." by Mark Xavier Bailon.

Factors affecting S_N2 reactions

Steric effect

One important variable in an S_N2 reaction is the structure of the substrate; this is because of the mechanism of the reaction which involves the formation of the pentavalent transition state. The presence of a bulky group in the structure of the substrate prevents the fast approach of the nucleophile to the carbon where the leaving group is attached. The bulkier the group, the slower the reaction will be because of the apparent shielding of the target carbon against nucleophilic substitution.

Nucleophile

The nature of the nucleophile greatly affects how the S_N2 reaction proceeds. Lewis bases, neutral or uncharged, can serve as the nucleophile by donating an unshared pair of electrons. Different types of nucleophiles result in different relative rates of a reaction. In general, the more basic the nucleophile, the faster will be the reaction as the nucleophile is more willing to donate a pair of electrons. Within a column in the periodic table, nucleophilicity increases from top to bottom. This is because the electrons are less tightly held as the atom becomes larger. The charge in the nucleophile greatly affects the reaction rates as localized charges are more attracted towards nucleophilic substitution reactions than ordinary lone pairs of electrons.

Leaving group

Another factor affecting the S_N2 reaction is the nature of the leaving group. Because the reaction involves the expulsion of the leaving group, with the group eventually bearing a negative charge, the best leaving group will be the ones that can best stabilize a negative charge in the transition state. If the leaving group can stabilize the negative charge well, the lower the energy requirement will be involved in the transition state and the more rapid the reaction will be. Weak bases as the leaving group produce faster reactions.

Solvent

Rates of S_N2 reactions are strongly affected by the solvent. Polar protic solvents, like water and methanol, are not usually used for S_N2 reactions as a formation of hydrogen bond inhibits the immediate attack of the nucleophile to the target carbon. Polar aprotic solvents, like acetonitrile, are able to raise the ground-state energy of the nucleophile by solvating metal cations resulting to greater nucleophilicity of the anions.

S_N1 Reaction

This is a type of nucleophilic substitution reaction where the reaction is unimolecular; that is the reaction only depends on the concentration of the alkyl halide. Unlike in S_N2 where the reaction is in 1 step, the S_N1 reaction proceeds in 2 steps and involve the formation of a carbocation intermediate. The first step of the reaction involves the spontaneous generation of a carbocation intermediate and the leaving group with a negative charge. The nucleophile then interacts with the carbocation forming the final substituted product.

As an example, consider the reaction of (CH₃)₃CBr and water. As expected, this reaction will not proceed readily in an S_N2 mechanism as there are a lot of bulky groups that inhibit the formation of the pentavalent transition state.

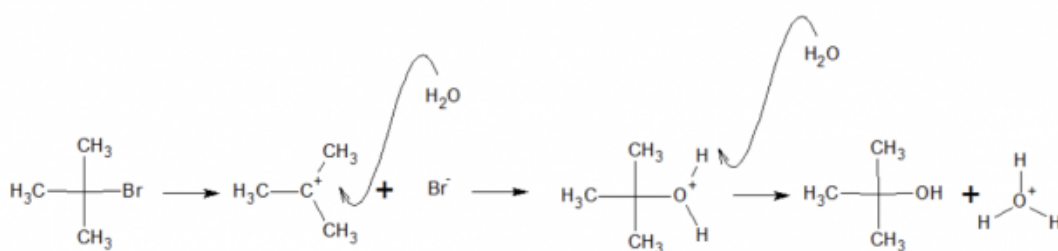


Figure: "SN1 reaction of 2-bromo-2-methylpropane and water." by Mark Xavier Bailon.

S_N1 reaction characteristics

Just like in S_N2, the same sets of variables affect how the reactions proceed. For the substrate, S_N1 reactions are favored as the substrate can form the most stable carbocation. The trend of stability of carbocation is shown below. This means a higher number of alkyl substituents attached to the carbon where the leaving group is attached, the faster the reaction occurs.

For the leaving group, the same trend is observed. The best-leaving groups are the most stable with a negative charge; those are the conjugate bases of strong acids.

An S_N1 reaction is not much affected by the nature of the nucleophile. This is because of the inherent mechanism of S_N1 to produce a carbocation. Since the carbocation can attract any compound that can donate an electron pair, the nature of the nucleophile will not matter.

Unlike in the S_N2 reaction where the solvent affects the reaction by stabilizing or destabilizing the nucleophile, in the S_N1 reaction, affects the reaction by stabilizing or destabilizing the carbocation intermediate. Polar solvents are preferred as it can stabilize the intermediate.

Elimination Reaction

Another important reaction of alkyl halide is the elimination reaction. **Elimination reaction** involves the elimination of HX and, in the process, forms multiple bonds. Elimination reactions proceed following Zaitsev's rule which states that elimination reactions generally give the more stable alkene product. Stability of alkene products here refers to the number of alkyl substituents around the carbon double bond. The more

highly substituted alkene product predominates. Just like in nucleophilic substitution, elimination reactions may proceed through different mechanisms: E1, E2, and E1cB.

E2 reactions occur when the haloalkane is reacted with a strong base like OH⁻ or alkoxide ion (RO⁻). The strong base attracts one of the H atoms attached to the C atom adjacent to the C atom where the halogen group is attached. As the H-C bond is broken in the process, two electrons are transferred to the C-C bond forming an additional bond, eventually rendering the C atom not available anymore to accommodate the halogen substituent. The X group then leaves the compound.

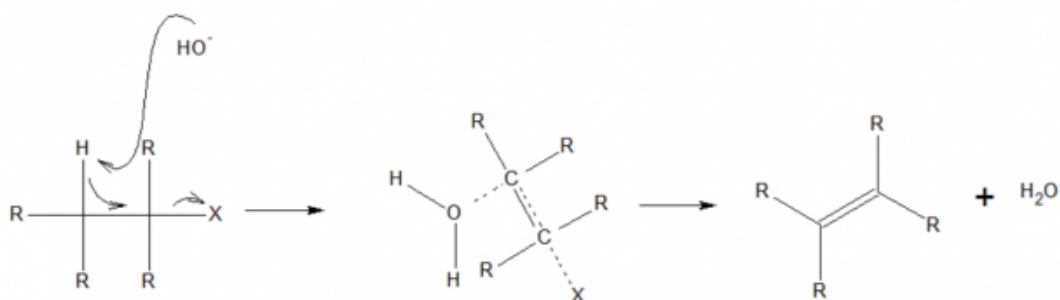


Figure: "E2 Mechanism" by Mark Xavier Bailon.

E1 reactions, just like the S_N1 reaction, involve the formation of a carbocation intermediate. The reaction proceeds with heating involved. When the carbocation is formed, it is much easier for the nucleophile to attack the H attached to the C adjacent to the C where the halogen is attached. The alkene is then produced in the process.

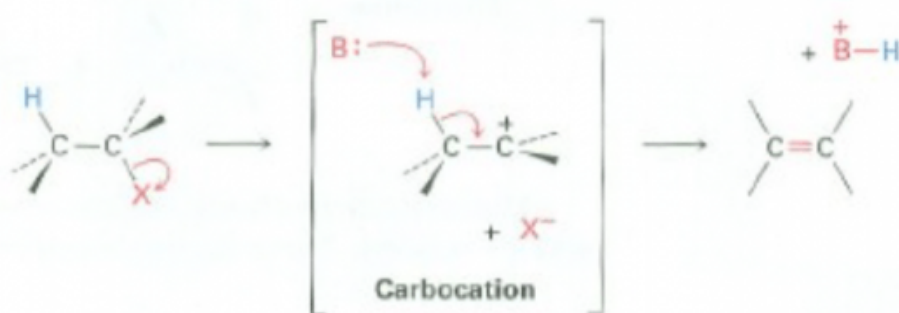


Figure: "E1 Mechanism" by Mark Xavier Bailon.

E1cB reaction, in contrast to E1 where the reaction involves the formation of a carbocation, involves the formation of a carbanion intermediate. This reaction is common in substrates containing a poor leaving group. Here, instead of the X atom being removed first, the nucleophile attacks the H atom attached to the C atom adjacent to the C atom where the X atom is attached. When the H atom is removed, a carbanion intermediate is formed and rearrangements in the structure produce the alkene. This reaction usually is involved in biological systems.

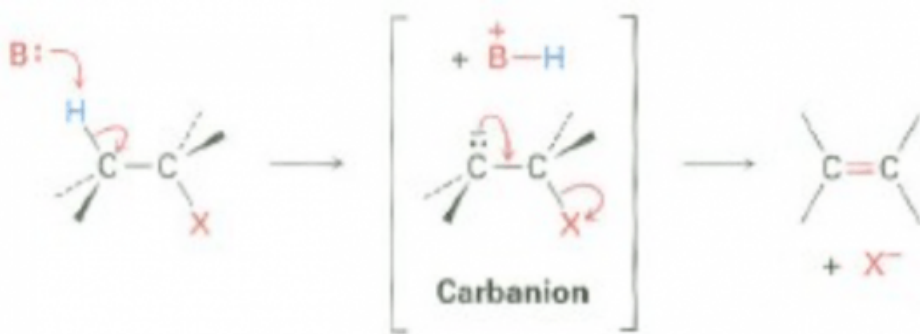
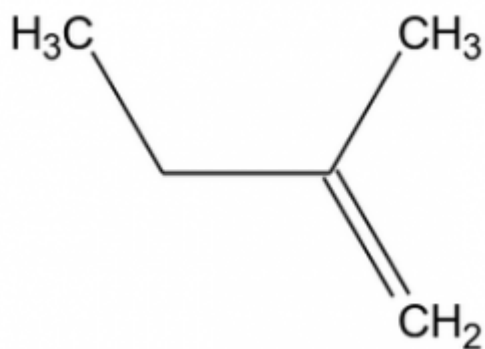
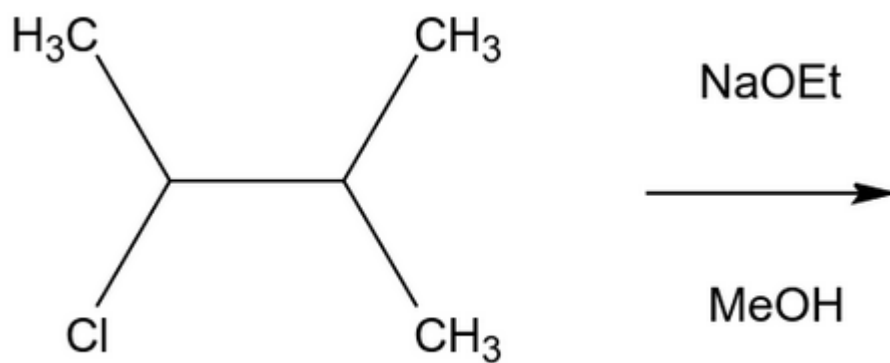


Figure: "E1cB Mechanism" by Mark Xavier Bailon.

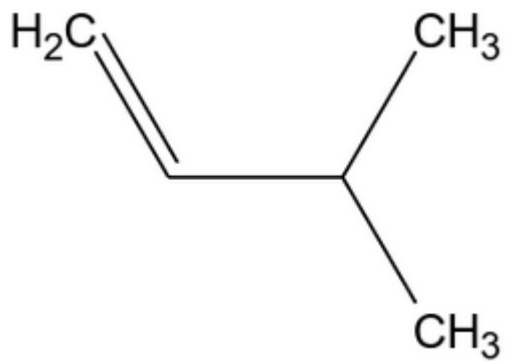
Review Questions

The answers are below the references.

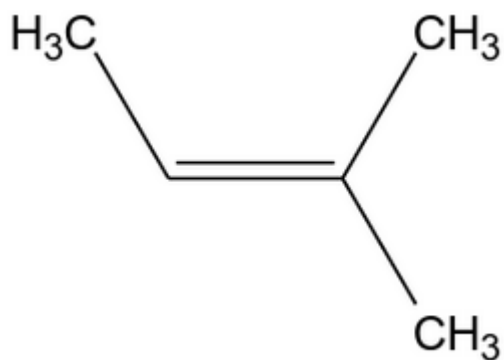
1. Which is the main product of the reaction below?



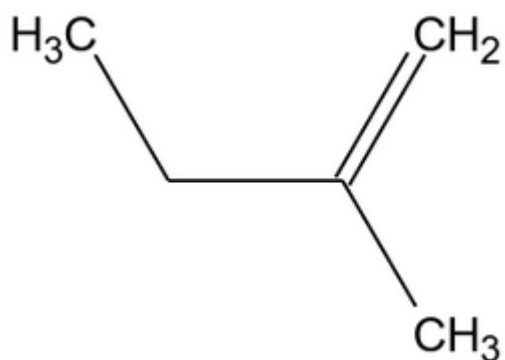
A.



B.



C.



D.

2. Which of the following is the best leaving group in a substitution reaction?

- A. Cl^-
- B. I^-
- C. OH^-
- D. Br^-

References

McMurry, J. (2008). Organic Chemistry. 7th ed. USA. Brooks/Cole, Thomson Learning Inc.

Carey, F. (2000). Organic Chemistry. 4th ed. USA. McGraw-Hill Companies, Inc.

Correct answers: 1C, 2D

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