# Factors Affecting the Rates of Nucleophilic Substitution Reactions

In this Factsheet, we will look at how various factors, both structural and experimental, change the rates at which both S_N1 and S_N2 nucleophilic substitution reactions take place. The factors will be explored by looking at the reactions of halogenoalkanes.

Nucleophilic substitution

A reaction in which a small neutral or negatively charged species (e.g., OH^-, H_2O or CN^-) attacks a positive charge centre (e.g., the δ^+-carbon of a carbon—halogen bond) and, in doing so, kicks out a different species is termed nucleophilic substitution.

The reaction of a halogenoalkane with hydroxide ions to form an alcohol is a typical example. The hydroxide ion acts as a nucleophile and substitutes itself on the carbon chain for a halide ion.

e.g., $CH_3CH_2Br + OH^- \rightarrow CH_3CH_2OH + Br^-$
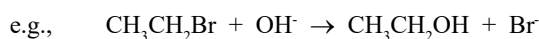
Nucleophilic substitution reactions can proceed via two different mechanistic routes known as S_N1 (unimolecular) or S_N2 (bimolecular). Ordinarily, primary halogenoalkanes undergo S_N2 reactions whereas tertiary halogenoalkanes prefer to react through the S_N1 route. The differences between the two mechanisms are important as they form a basis for a number of the factors affecting the rates at which the reactions take place.

Two different mechanisms

The S_N1 mechanism is a two-step process in which, first, the carbon—halogen, breaks in the rate-determining step of the mechanism to form two charged species including a carbocation intermediate (R^+). In the fast step of the mechanism, the carbocation is attacked by the nucleophile.

S_N1: $R—X \rightleftharpoons R^+ + X^-$ [Rate-determining step]
               $R^+ + OH^- \rightarrow R—OH$
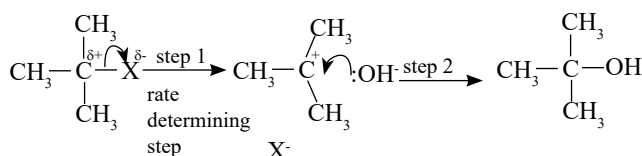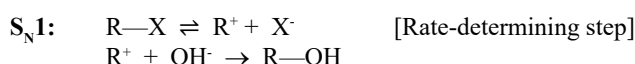
The S_N2 mechanism is a single-step process in which the attack of the nucleophile leads to the simultaneous ejection of the halide ion.

S_N2: $R—X + OH^- \rightarrow R—OH + X^-$
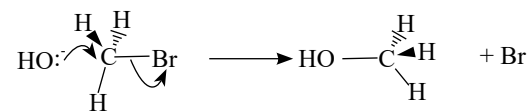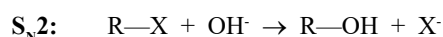
Factors affecting rate of nucleophilic substitution

In order to address this topic, it is necessary to look separately at how the rate of each mechanism is affected. The overall picture is quite complicated and predicting the overall rate of a nucleophilic substitution reaction relies on several factors, making comparisons between compounds difficult.

The principal factors that influence the rate of a nucleophilic substitution reaction include:
- Structure of halogenoalkane.
- Identity of halogen present.
- Identity of nucleophile.
- Concentration of nucleophile.
- Choice of solvent used.
- Temperature of the reaction mixture.

Effect of structure

In simple terms, S_N1 reactions occur most rapidly with tertiary halogenoalkanes (R_3X) and the most slowly with primary halogenoalkanes (RX). Conversely, S_N2 reactions are at their fastest when using a primary halogenoalkanes and at their slowest when using tertiary compounds. The reasons for this differ:

S_N1: the rate at which an S_N1 reaction occurs is largely affected by the rate at which the carbocation intermediate can form; this is the rate-determining step of the reaction. The extent to which the formation of the intermediate occurs depends on its stability in solution. The order of carbocation stability is:
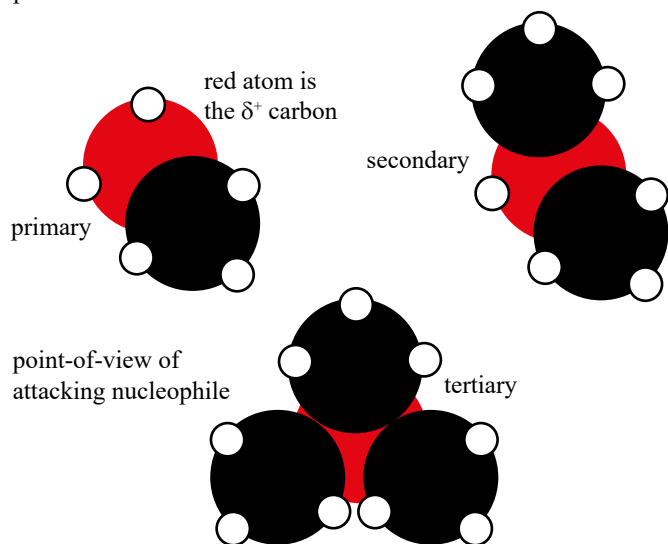
TERTIARY > SECONDARY > PRIMARY

Tertiary carbocations are stabilised by the positive-inductive effect of the electron-releasing alkyl groups that surround the charged carbon atom. The effect acts to spread (and hence stabilise) the positive charge across the ion (see figure below). As the number of surroundings alkyl groups decreases in secondary and then primary carbocations, the stabilising effect is reduced. The consequence is that the formation of primary carbocations, in particular, is highly unfavourable and so the S_N1 mechanism rarely, if ever, proceeds via a primary carbocation.
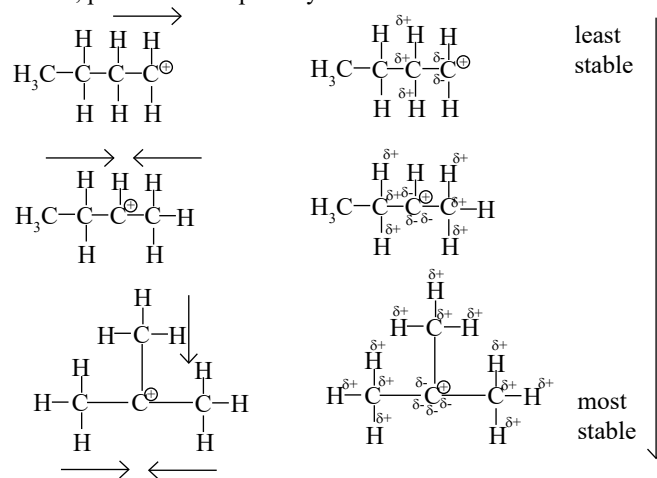
S_N2: the S_N2 mechanism does not proceed via a carbocation intermediate and so its rate varies for a very different reason. The initial movement of electrons from the nucleophile towards the δ^+-carbon atom must occur at 180° to the C—X bond, i.e., the nucleophile must attack from directly behind the C—X bond. In order to do this, the nucleophile must be given adequate physical space.

In primary halogenoalkanes, the presence of just a single alkyl group means that a significant amount of the δ^+-carbon atom is accessible to the nucleophile at the correct angle. However, as the number of alkyl groups increases, the amount of the electrophilic carbon that is available for the nucleophile to attack is reduced (see figure below). In tertiary halogenoalkanes, the three bulky alkyl groups form an almost complete blockade of the δ^+-carbon atom meaning the nucleophile has no access and the reaction cannot proceed via this mechanism.

The action of a group to physically block the approach of another species is termed **STERIC HINDRANCE**.

The effect of structure on the rate of each mechanism can be summarised as:

S_N1:   **TERTIARY > SECONDARY > PRIMARY**
S_N2:   **PRIMARY > SECONDARY > TERTIARY**

Identity of halogen atom

In both mechanisms, the rate-determining step involves the heterolytic fission of the C—X bond. The activation energy (and thereby overall rate) of this step will be determined, in part, by the ease of which this bond can be broken. The stronger the C—X bond is, the higher the activation energy of the RDS and the slower the reaction overall.

Bond present	Bond enthalpy /kJ mol⁻¹
C—F	439
C—Cl	328
C—Br	276
C—I	240

The bond enthalpy data indicate that the rate of nucleophilic substitution (via either mechanism) will be slowest with fluoroalkanes and fastest with iodoalkanes

IODO > BROMO > CHLORO > FLUORO

Identity and concentration of nucleophile

The identity of the nucleophile can have a huge effect on the rate of nucleophilic substitution. In some cases the reasons for the difference is complex and requires a more detailed understanding of orbitals than is provided in school-level chemistry. This Factsheet will cover the basic principles.

S_N1: the identity and concentration of the nucleophile have **no effect** on the rate of nucleophilic substitution via an S_N1 mechanism.

This means that tertiary halogenoalkanes tend to react at the same rate with any nucleophile. The reason for this is that the nucleophile is involved in the fast step **after** the rate-determining step and therefore has no influence on the overall rate. This is confirmed by the rate equation for a generic tertiary halogenoalkane: **Rate = k[R₃X]**

The nucleophile does not appear in the rate equation; rate is only influenced by the concentration of the halogenoalkane itself.

S_N2: reactions that proceed via an S_N2 mechanism are influenced by the nucleophile as it is involved in the rate-determining step and, this, appears in the rate equation: **Rate = k[RX][Nu]**

As the concentration of the nucleophile increases, the rate of an S_N2 reaction increases proportionally. Some nucleophiles are better than others and yield faster rates of S_N2 reaction. For example, a primary halogenoalkane will react far faster in an alkaline solution than in a neutral one. In the alkaline solution, the principal nucleophile is the hydroxide ion (OH⁻), whereas in the neutral solution, water is acting as the nucleophile. The hydroxide ion is a more powerful nucleophile than water and reacts more rapidly. One simple way to explain this is that the negative charge on the hydroxide ion increases the attraction between it and the electrophilic carbon atom in the halogenoalkane. As water is a neutral molecule, this attractive force is weaker.

Choice of solvent

The rates of both nucleophilic substitution mechanisms can be influenced considerably by the choice of solvent. Solvents can be categorised simply into non-polar and polar. Polar solvents can be further sub-categorised into protic and aprotic solvents.

> **Non-polar:** solvents whose molecules exhibit no overall polarity, for example, CCl_4, hexane.
> **Polar, protic:** solvents whose molecules are both polar overall and also have the capacity to hydrogen bond and donate a proton (H⁺) into solution such as hydrogen attached to a nitrogen or oxygen atom e.g., water, ethanol.
> **Polar, aprotic:** solvents whose molecules have overall polarity but no hydrogen atom attached to an oxygen or nitrogen and cannot donate a proton into solution e.g., propanone, ethanenitrile.

S_N1: reactions that proceed via the S_N1 mechanism are far quicker in the presence of a polar, protic solvent, such as water, than in other types of solvent. In the rate-determining step, two charged species are produced: a positive carbocation, and a negative halide ion. Solvating these ions (that is, surrounding them with bound solvent molecules) stabilises them and helps increase the rate of reaction. Polar, protic solvents are capable of solvating both positive and negative ions. The δ^+-hydrogen atom interacts with and stabilises the negative halide ions whilst the δ^- nitrogen or oxygen atoms interacts with and stabilises the carbocation.

Switching to a non-polar or polar, aprotic solvent removes the capacity to solvate the negative ions and therefore the rate of reaction decreases as the rate-determining step is less favourable.

S_N2: conversely to S_N1 reactions, the S_N2 mechanism is favoured by non-polar and polar, aprotic and disfavoured by polar, protic solvents. In this case, the rate-determining step involves the direct attack of the nucleophile on the δ^+-carbon atom. In a polar, protic solvent, the nucleophile is fully solvated and surrounded by a shell of solvent molecules preventing it from approaching the electrophilic centre. In a non-polar or polar, aprotic solvent , the nucleophile is poorly solvated and unhindered in its approach to the electrophilic centre.

NOTE: whatever the solvent chosen, it must be capable of dissolving the reactants, otherwise the reactions will proceed very slowly due to the poor mixing of the materials.

Temperature of the reaction mixture

Nucleophilic substitution is always at loggerheads with an alternative mechanism, elimination, which can take place when halogenoalkanes are reacting in the presence of a nucleophile that is also a strong base, such as the hydroxide ion. Elimination is favoured over substitution when:
1. The concentration of hydroxide ions is high.
2. The reaction is taking place in an ethanolic solution.
3. The temperature is fairly high (> 50 °C).
4. A tertiary halogenoalkane is present.

As there are a myriad of factors affecting the rate of a nucleophilic substitution reaction, it is exceedingly difficult to simply look at a halogenoalkane and state that it will react faster or slower than any other. The specific reaction conditions are vital in determining the overall rate of nucleophilic substitution of an individual halogenoalkane.

However, a good rule of thumb is that for the reactions of halogenoalkanes in dilute, aqueous sodium hydroxide at room temperature (a common set of conditions), tertiary halogenoalkanes will react far faster than primary halogenoalkanes.

Questions

1. For each of the following halogenoalkanes, state which of ethanol or propanone would be the more suitable solvent.
   (a) 1-bromopropane
   (b) 2-iodo-2-methylbutane
   (c) 1-chloro-2,2-dimethylpentane

2. Explain why primary halogenoalkanes react faster than tertiary halogenoalkanes via the S_N2 route.

3. Explain why tertiary halogenoalkanes react faster than primary halogenoalkanes via the S_N1 route.

4. Place the following halogenoalkanes in ascending order of rate of reaction with dilute, aqueous sodium hydroxide.
   $CH_3CH_3CH_2Cl$, $(CH_3)_3CI$, $(CH_3)_3CCl$, $CH_3CH_3CH_2I$

Answers

1. (a) propanone
   (b) ethanol
   (c) propanone

2. Little steric hindrance of electrophilic carbon in primary; three bulky alkyl groups lead to major steric hindrance of electrophilic carbon in tertiary; nucleophile cannot attack carbon atom in tertiary.

3. Tertiary carbocation intermediate more stable than primary. Three electron-releasing alkyl groups compared to one. Stronger positive-inductive effect in tertiary carbocation compared to primary.

4. $CH_3CH_3CH_2Cl < CH_3CH_3CH_2I < (CH_3)_3CCl < (CH_3)_3CI$.