

Substitution Reactions Summary

Bimolecular Nucleophilic Substitution (S_N2) Reaction

Nucleophilic substitution reactions have been one of the most studied and well established in organic chemistry. These reactions involve a *nucleophile* (Nu⁻) being used to replace a *leaving group* (LG) from a carbon atom of the substrate (R-LG) in question. Effectively the *nucleophile* substitutes for the *leaving group*. During this reaction, the nucleophile provides an electron pair for the new Nu-R σ-bond, while the leaving group departs with the electron pair from the R-LG σ-bond.

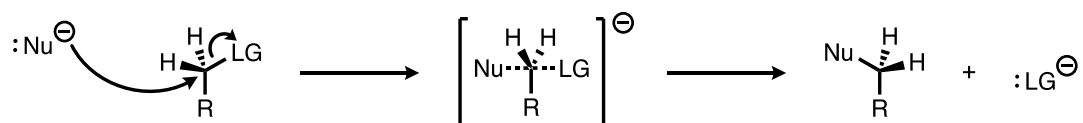


Scheme 1: A substitution reaction

There are two possible mechanisms for a Nucleophilic Substitution reaction: *bimolecular* (S_N2) and *unimolecular* (S_N1). The mechanism for a nucleophilic substitution reaction will take depends on four factors: **(1)** the nature of the substrate; **(2)** the nature of the nucleophile; **(3)** the nature of the leaving group; **(4)** the nature of the solvent.

The S_N2 process involves a direct displacement of the leaving group in one step (a concerted reaction) with the nucleophile approaching from the opposite face of the leaving group. This is also the rate-determining step of the S_N2 reaction. Since both the nucleophile and electrophile are involved in the rate-determining step it is considered a bimolecular reaction. This mechanism is favoured with substrates possessing a methyl or primary carbon at the site of the substitution (though secondary carbons at the site of substitution are possible as well).

The nucleophiles used in this type of reaction must be more reactive (less stable) than the leaving group otherwise the reaction will not proceed forward. Typically, polar aprotic solvents are favoured in S_N2 reactions however the use of polar protic solvents is often needed for solubility purposes.



Mechanism 1: The S_N2 reaction mechanism

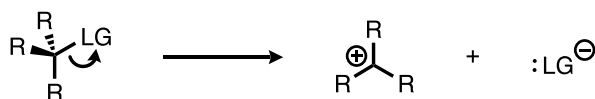
When designing a successful S_N2 reaction, we need to consider both reaction partners:

- **Electrophile:** low steric hindrance, good leaving group (halide, sulfonate)
- **Nucleophile:** low steric hindrance, moderate to strong nucleophilicity (typically negatively charged).

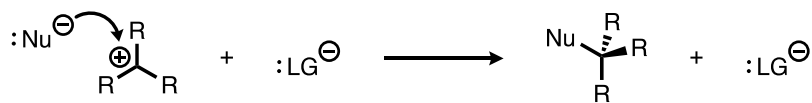
Unimolecular Nucleophilic Substitution (S_N1) Reaction

The S_N1 process involves the formation of a carbocation intermediate in the *rate-determining step* followed by attack of the nucleophile. This mechanism is favoured with substrates that can generate a stable carbocation intermediate, namely substrates possessing a tertiary carbon at the site of the substitution or resonance stabilization.

Step 1
Carbocation
Formation

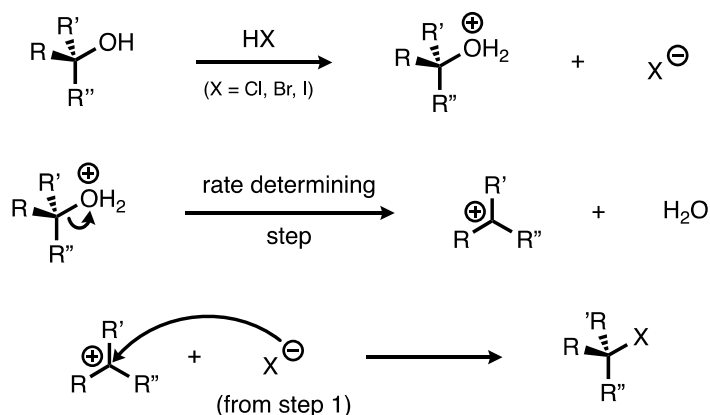


Step 2
Nucleophilic
Attack



Mechanism 2: The S_N1 reaction mechanism

A classic S_N1 reaction is the synthesis of a tertiary alkyl halide from a tertiary alcohol and a strong acid, HX. The rate determining step of this first-order nucleophilic substitution reaction is the formation of the carbocation intermediate by the loss of H₂O from the conjugate acid of the starting alcohol. A strong acid is required to protonate the hydroxyl group converting it into an excellent leaving group.



Mechanism 3: Synthesis of a tertiary alkyl halide

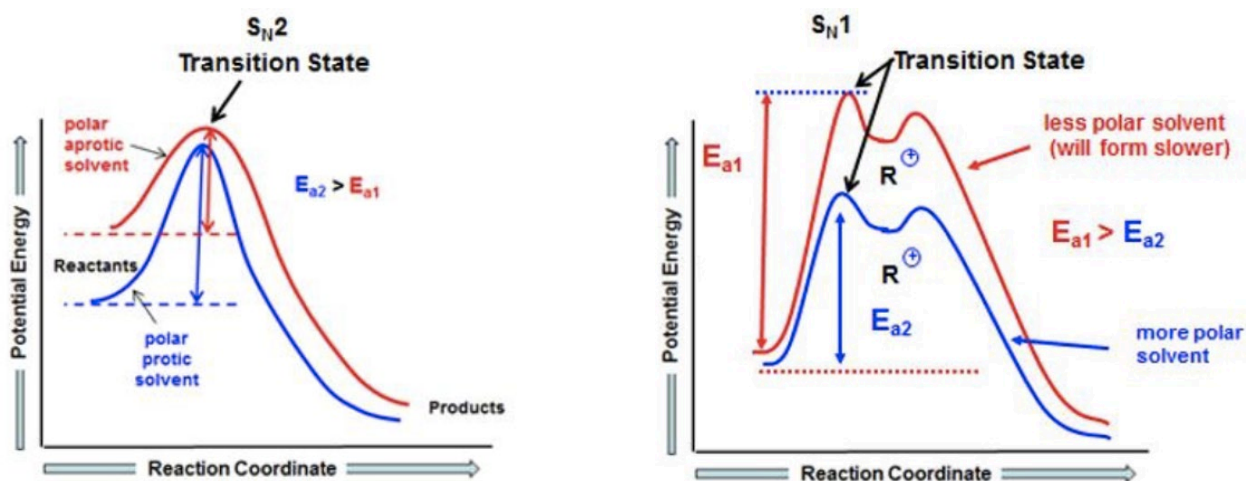
When designing a successful S_N1 reaction, we only need to consider the electrophile's strength since the rate-determining step is the formation of the carbocation. Carbocations stabilized by hyperconjugation (tertiary, secondary) or resonance (benzylic, allylic) are ideal. If a carbocation is too unstable (primary, sp²-hybridized), S_N1 chemistry will not be possible. The solvent also plays a role in the formation of the carbocation. Polar protic solvents are key to a good S_N1 reaction since they are better able to solvate the leaving group and the carbocation after their dissociation, which lowers the activation energy of the carbocation formation. Since the nucleophile is involved in the reaction after the formation of the carbocation, we can use weaker, neutral nucleophiles in S_N1.

Comparing S_N2 and S_N1 Mechanisms

The following table summarizes the characteristics of the two substitution mechanisms:

	S _N 2	S _N 1
Reaction Type	Concerted	Step-wise (via carbocation intermediate)
Rate Law	rate = $k[\text{nucleophile}][\text{electrophile}]$	rate = $k[\text{electrophile}]$
Electrophile	benzylic > allylic > methyl > 1° > 2° (3°, vinyl, aryl will not occur)	benzylic > allylic > 3° > 2° (1°, methyl, vinyl, aryl will not occur)
Nucleophile	Moderate-strong (ideally negatively charged)	Weak (often neutral)
Stereochemistry	Inversion of carbon with LG	Racemization of carbon with LG
Solvent	Polar aprotic increases the rate of reaction	Polar protic required

We can also picture the energy diagrams for each of the reaction which depict the potential energy levels as the reaction progresses from starting material to products:



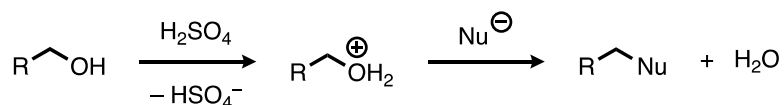
- Concerted (one-step)
- Exothermic
- Nucleophile is either negatively charged or has a partial negative (δ^-) character, donates electrons to the electrophile
- Aprotic solvents destabilize the nucleophile (increasing its potential energy), decrease the free energy of activation and increase the rate of reaction
- Multi-step reaction
- Endothermic rate-determining step
- Ionic intermediate (carbocation)
- Intermediate stabilized by the solvent, otherwise too energetic to be formed
- Polar protic solvents decrease the free energy of activation and increase the rate of formation of the carbocation intermediate (rate-determining step)

Figure 1: Energy diagrams for S_N2 (left) and S_N1 (right) reactions

Improving Leaving Group Strength

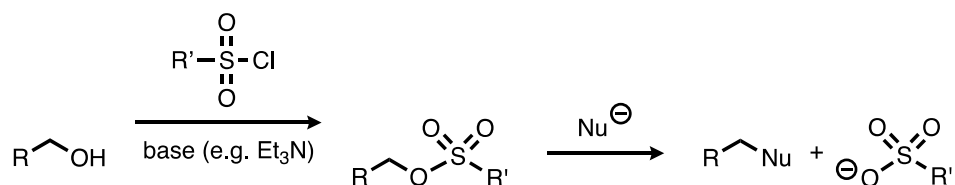
For both S_N2 and S_N1 , a strong leaving group will help the reaction proceed forward. A good leaving group will ideally be a very weak base. There are also reagents we can use to increase the leaving group ability, a strategy that can help us perform substitution reactions on alcohols. As is, alcohols would have hydroxide (HO^-) which is a relatively strong base and therefore a very poor leaving group. To activate the leaving group, we can:

1. Protonate the alcohol: With a strong acid, an alkyloxonium ion is formed. The leaving group then is water, which is a very weak base. Acids with non-nucleophilic counter-ions such as sulfuric acid (H_2SO_4) are preferred.



Scheme 2: Activation of alcohol for substitution by protonation

2. Form the sulfonate: Sulfonates are excellent leaving groups due to the resonance stabilization of the negative charge on the other oxygen atoms. Sulfonates are obtained from the alcohol by reacting with the sulfonyl chloride in the presence of base. This reaction occurs via a S_N2 -like process on sulfur.



Scheme 3: Activation of alcohol for substitution by conversion to the sulfonate