

Nucleophilic Substitution at a Saturated Carbon Atom

Introduction

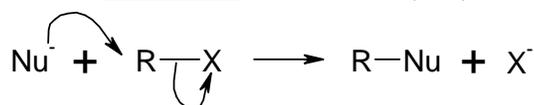
- The **general form** of **nucleophilic substitution** at a **saturated carbon atom** is as follows:



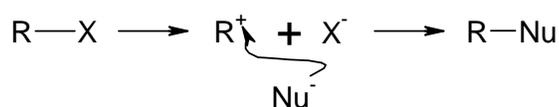
In other words, the **leaving group** (X^-) has been **substituted** by the **nucleophile** (Nu^-).

- There are two possible **mechanisms** for these reactions:

A *single step* mechanism ($\text{S}_{\text{N}}1$)



A *two-step* mechanism ($\text{S}_{\text{N}}2$)

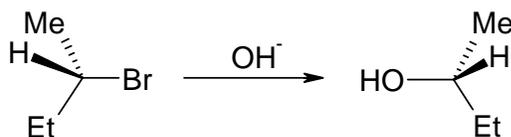


- Which of these occurs depends on various factors

The $\text{S}_{\text{N}}2$ Mechanism

- Evidence** that supports the idea of an $\text{S}_{\text{N}}2$ mechanism is as follows [this is observed, for example, in the substitution of **primary** and **secondary alkyl halides**]:

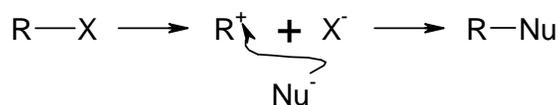
- The reaction occurs with **inversion of stereochemistry** at the **carbon atom**:



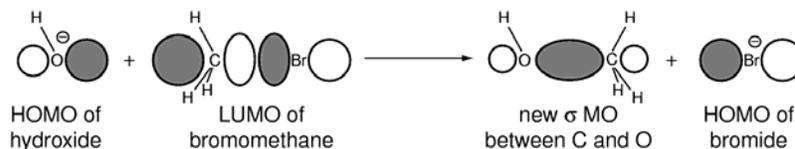
- The reaction displays **second order kinetics** with the following **rate law**:

$$\text{Rate} = k [\text{RBr}][\text{Nu}]$$

- In **1937**, **Hughes** and **Ingold** proposed the following **mechanism** that accounts for these observations:

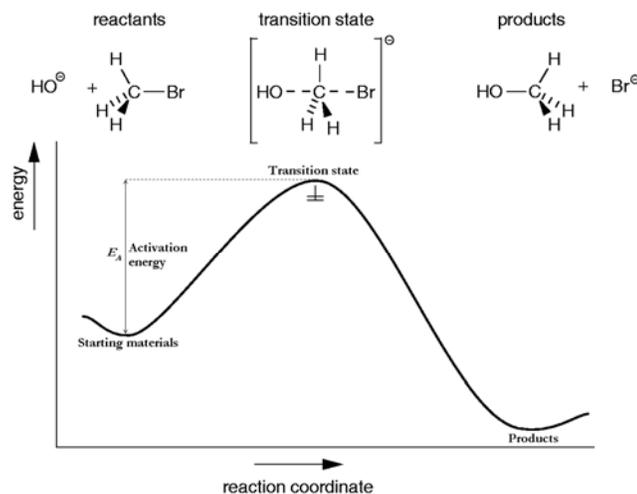


An orbital representation of the reaction is as follows:



The **HOMO** in this case is the lone pair on the **OH⁻**, and the **LUMO** is the **C-Br σ^*** . Note that:

- The reaction occurs in a **single step without intermediates**.
- The **nucleophile** attacks the molecule **directly opposite** (at 180° to) the **leaving group**, to get into the **antibonding** orbital.
- The **energy profile** of this reaction is



- Note that the transition state is **not an intermediate**. It can **never be isolated**, because any **change** in its **structure** leads to a **lower energy state**.
 - It's about **halfway** between **reagents** and **products**.
 - The carbon is roughly **sp² hybridised (planar)** in the intermediate, and eventually **reverses**.
- The rate of the chemical reaction is determined by the **activation energy** (E_A), which is the energy difference between the **reactants** and the **transition state**. A change in **reaction conditions** can change E_A either by
 - Changing the **reactant energy level** *or*
 - Changing the **transition state energy level**.

We shall shortly see exactly how different reacting conditions do that.

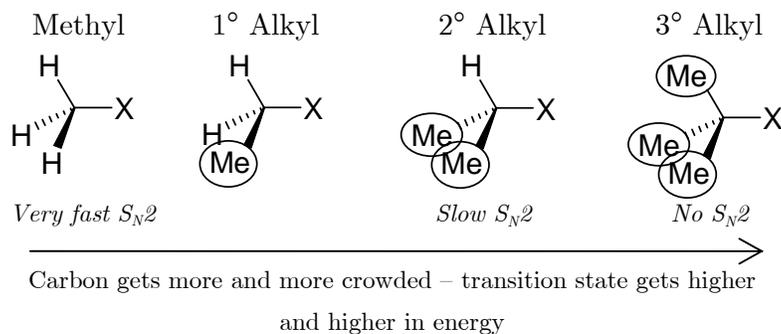
- This single step is the **rate determining step** of the reaction.
 - The rate is proportional to both $[\text{Nu}]$ and to $[\text{R-X}]$ – both are involved in the reaction.
 - Therefore, changes in all these reagents will affect the rate of the reaction.
 - Another way of saying this is that all these species are present in the **transition state**.

The Substrate, R-X

The substrate is included in the rate equation, and there are various factors which determine how fast the reaction will be:

1. Steric Effects – energy of the transition state

- The **transition state** is **5-coordinate (a trigonal bipyramid)** – its formation involves bond angles **decreasing** from **tetrahedral** to about **90°** (six of the angles are 90°, and three are 120°).
- This **significantly increases steric crowding**.
- The **larger** the **constituents** on the carbon, the **harder this is**.



- The **opposite** is true of the S_N1 reaction. The **intermediate** has **three 120° bonds**. The **transition state** will be on its way towards the intermediate, with **angles increasing towards 120°**, and a **reduction in steric crowding**. Therefore, there is **steric acceleration** as opposed to **steric hindrance**.

2. Steric Effects – approach of the nucleophile

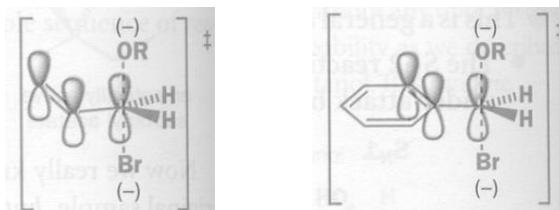
- Very **crowded** carbon atoms also **hinder the approach of the nucleophile**. This is another reason why S_N2 does not occur at **tertiary butyl groups**.

- Similarly, S_N2 does not occur at sp^2 carbons. This is because the nucleophile would need to approach the carbon **in the plane** of the **C–C double bond** to reach the σ^* orbital and carry out a **backside displacement**. For example:



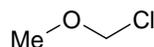
3. Electronic effects

- In some species, the **transition state** can be **lowered in energy** by **conjugation** – for example, **allylic** and **benzylic** compounds:

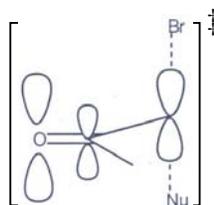


These compounds react **rapidly** by the S_N2 mechanism. (Note that these also increase the rate of S_N1 !). The **benzene ring** is a **bit better at π conjugation** than an **isolated double bond**.

- **Conjugation** with an **oxygen lone pair** can **accelerate the reaction**, more than the two above. For example, in:



- Even more effective is **conjugation with electron deficient π bonds** [in this case, the orbitals it can conjugate with are **electron deficient**, and so **stabilise** the negative charge **even better**]. The **most important example** is that of the **carbonyl group**. **α -halo carbonyl compounds** display the **fastest S_N2 rates**.



What is effectively happening is that the π^* of the **C–C bond** and the σ^* of the **C–Br bond** (both **low energy**) **combine with**

each other to form an even **lower energy $\pi^* + \sigma^*$ orbital**. The **nucleophile** will then attack where this **new orbital** has the **largest coefficients** (in the usual place).

Attack *could* occur at the **carbonyl**, but it would be **reversible**.

The Leaving Group (also applies to S_N1)

Another variable that affects the reaction is how good the **leaving group** is.

Two factors affect this:

- The **strength** of the **C–X** bond.
- The **stability** of the leaving group. In most S_N2 reactions, the leaving group is expelled with a **negative charge**, and so we would expect the **best leaving groups** to be those that can **best stabilise the negative charge**. From our discussion of pK_a , these are the **conjugate bases of strongest acids** [acids with **lowest pK_a**].

Therefore, we can construct a hierarchy of leaving groups:

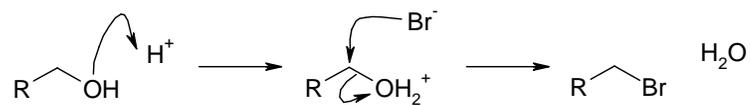
	Leaving group X	Relative reactivity of R–X
Better leaving groups ↓	OH^- , NH_2^- , OR^-	$\ll 1$
	F^-	1
	Cl^-	200
	Br^-	10 000
	I^-	30 000
	TsO^-	60 000

Thus, **R–F**, **R–OH**, **R–NH₂** and **R–OR** *do not* undergo S_N2 reactions.

Contrary to what might be expected, this analysis reveals that **OH[–]** is a **terrible leaving group**. This is because it is very basic and very reactive. [Any **nucleophile strong enough** to kick out the **OH** will certainly be strong enough to act as a base and **remove the proton** from OH]. Chemists, however, **do** want to use alcohols in nucleophilic substitutions because they are **readily available** as **starting materials**. For this to happen, the **OH** must be made into a **better leaving group**. There are **two ways** to do this

- *Protonation with a strong acid*

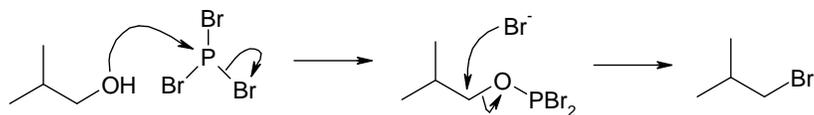
Protonation with a strong acid transforms the leaving group from OH^- to H_2O (*much* better):



This only works if the **nucleophile** is **compatible** with **strong acid**, but this is **usually the case**.

- *Combination with an element that forms strong bonds to oxygen*

Phosphorous and **sulphur** are usually chosen. For example:



This is now a good reaction, because the **anion** is **stabilised** by **phosphorous**.