

Year 2, Organic Chemistry, Chapter 24:

S_N1 and S_N2 Mechanisms

- The “slow” step in a reaction mechanism is the “rate determining” step, and for a given reaction
$$\text{aA} + \text{bB} + \text{cC} \rightarrow \text{Product}$$
(cf. Chapter 7 of Year 2, Inorganic Chemistry) the Rate of a reaction is given by the Rate equation
$$\text{Rate} = k \cdot [\text{A}]^x [\text{B}]^y [\text{C}]^z$$
- Last year now seems a very long time ago, and I don’t know whether you remember that in the first week that we started to learn Chemistry together, I said that we would be setting out to discover why and how reactions took place. Well, we have now reached a point where we are going to unwrap another bit of those puzzles.
- It is actually very easy to understand **how** the two reaction mechanisms (S_N1 and S_N2) in this Chapter differ, but it is less easy to understand **why** they differ. However, please do not get bogged down in the opening explanatory remarks overleaf. I have put them there in order to set out clearly the parameters for the discussion on S_N1 and S_N2 reaction mechanisms.
- Before we start talking about these reaction mechanisms I would like you to notice something rather important viz. an incoming/attacking nucleophile will replace a negatively charged species in the recipient molecule in the S_N1 and S_N2 substitution reactions. However, a negatively charged species **is itself a nucleophile** – so will there not be some sort of confusion in the mind of the recipient molecule (which is sometimes referred to as the ‘substrate’)? If the molecule were a girl and she had two nice boys vying for her attention, would she not wonder whether she should in fact be saying goodbye to the leaving nucleophile? Which one should she bond with? The answer to this question lies in **stability**¹ and in something that chemists call the “goodness” of the leaving species (*yes, I agree, it is rather a strange use of the noun “goodness”*), but by the end of this Chapter I hope that you will be able to answer the question for yourselves.²
- The “1” and “2” in the names S_N1 and S_N2 **do not refer to the number of molecules involved in the substitution reaction**, and refer instead to the **number of species in the slow rate-determining step of the reaction**.
 - S_N1 stands for a “**Nucleophilic Substitution** reaction mechanism where the *rate determining step* (RDS) is determined by the **concentration** of just **one** molecule”, and
 - S_N2 stands for a “**Nucleophilic Substitution** reaction mechanism where the *rate determining step* (RDS) is determined by the **concentrations** of **two** molecules”.
- There is a considerable difference in the **reaction kinetics** (i.e. the rate of reaction³) and also the **stereochemistry** (i.e. the three dimensional geometry) of S_N1 and S_N2 mechanisms. Just as an umbrella becomes blown inside-out in a high wind, so also (*but obviously there is no wind involved here*) that is what happens in an S_N2 reaction mechanism i.e. an **inversion** at the chiral centre takes place. Another way of looking at this phenomenon is to notice that stereoisomers are formed. I will talk about this briefly in a few moments time.

¹ ... and it will involve lots of lovely concepts such as the inductive effect/the mesomeric effect/resonance/conjugation/hyperconjugation/and so on.

² and if you are a girl instead of a substrate recipient molecule, then the answer is also about *goodness* viz. the answer is “do not be overly-concerned about how nice-looking they are – look instead at **how nice the boys actually are!**”. Physical attraction starts off as red hot passion but dies away quite quickly, whereas the attraction between personalities tends to develop and **increase** over time.

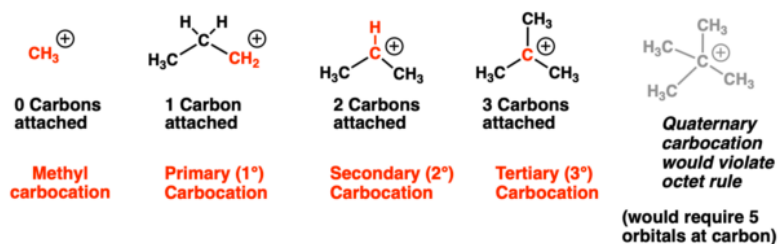
³ Please see the relevant Chapters of the Second Year book for stuff on “first order reactions” and “zero order reactions” in Chapter 7, Year 2, Inorganic Chemistry.

- Some chemists use “X” to represent a Halogen element or a Halide ion. However, in Mathematics “X” represents any unknown, therefore the use of “X” can be slightly confusing because it is not just halide ions that can be involved in S_N1 and S_N2 reaction mechanisms. Alcohols can also be involved. I shall therefore use “**Hal**” to indicate a Halogen element or “**Hal**[–]” to indicate a Halide anion.
- Some chemists use the letter “N” to represent a nucleophile i.e. a negatively charged species (such as a Halide ion e.g. Cl[–] / Br[–] / I[–]), or a species that has at least one lone or unbonded pair of electrons in it (such as NH₃ with its one lone/unbonded pair of electrons, or an H₂O molecule where the oxygen in the water molecule possesses *two* lone/unbonded pairs of electrons). In fact, an electrophile can have merely an area of high electron density associated with it (for example the area of the overlap of two unhybridised ‘p’ orbitals in an alkene, or the delocalised π ring above and below a Benzene ring). However, I personally do not use “N” to represent a nucleophile because “N” is the symbol for the element Nitrogen and this causes unnecessary confusion for students who are still trying to learn ‘A’ Level Chemistry – the vast bulk of whom will never go on to read Chemistry at University (but quite a few of whom do not intend to go into medicine and therefore need to know a bit of Chemistry). I shall instead use the symbol “**Nu**[–]” to represent a nucleophilic species.
- Many chemists give the name “carbanion” to denote a negatively charged Carbon species. I do not do so. The counterpart of a carbo-cation should be a “**carbo-anion**”.
- “Cations” have positive charges, and a carbocation has a positive charge. The use of the term “**carbocations**” has been replaced by the term “carbenium” ions. However, “Carbenium”⁴ ions are associated with a section of Chemistry that is not in the ‘A’ Level syllabus, and I shall therefore stick to the rudimentary term “carbocation” for a Carbon species that has a positive charge. **The more alkyl groups that there are on the carbocation, the more stable it becomes.** *(There are also other factors involved, but I am not going to complicate the matter at this stage.)* What I do want you to take note of is that **the more stable that a carbocation is, the more easily will it be formed.**
- Just as with Alcohols, you can have methyl / 1° / 2° / and 3° halogenoalkanes, viz. the C atom to which the ‘Hal’ is bonded is attached to 0 / or 1 / 2 / or 3 C atoms.
- In this Chapter ‘R₃’ which is also written as (RR'R'') will represent *any* three species bonded to a Carbon atom viz. “R₃C–”, and for example (if LG stands for Leaving Group) “R₃C-LG” would stand for “any three chemically appropriate species bonded to a carbon atom where the fourth species is a Leaving Group i.e. a species that is going break away in this reaction”.
- For example, if the fourth bonded atom is a Halogen then we would get “(R₃).**C-Hal**” e.g. we would have R₃ in
 - the 1° halogenoalkane, 1-bromopropane C₃H₇-Br [whose structural formula is CH₃-CH₂-CH₂**Br**]
 - the 2° halogenoalkane, 2-bromopropane (CH₃)₂.C(H)-**Br** [i.e. CH₃-**CHBr**-CH₃], and
 - the 3° halogenoalkane, (CH₃)₃.**C-Br** [whose structural formula is CH₃-**C**(CH₃)**Br**-CH₃].
- The “Leaving Group” could just as easily be an hydroxy species (–OH) in a methyl / 1° / a 2° / or a 3° alcohol, and we have dealt extensively with the oxidation of alcohols into Aldehydes/Ketones/ and Carboxylic acids. Do you remember all the things that we learnt about acidified Dichromate ions and colour changes from orange to green, and then the addition of Fehling’s or Benedict’s solution to distinguish an Aldehyde from a Ketone? I covered them all in earlier Chapters in this year’s Organic book. If you do not remember them, then do please read those Chapters again.

⁴ and it has replaced the use of the term “carbonium” which is now reserved for a specific set of circumstances.

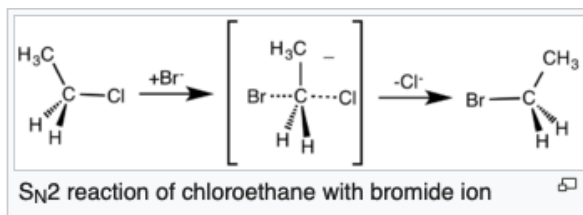
- Just to remind you, this is what the phrases methyl / 1° / a 2° / or a 3° mean

Carbocations: Count the number of carbons directly attached to the carbocation



Source: Dr James Ashenhurst's "masterorganicchemistry"

- OK, let us now learn a rule viz. in general
 - 3° Halogenoalkanes react by way of $\text{S}_{\text{N}}1$ mechanisms.
 - 2° Halogenoalkanes react by both $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms, and
 - 1° Halogenoalkanes react by way of $\text{S}_{\text{N}}2$ mechanism (where inversion takes place).
- Actually the rule is a great deal more complicated than that, but I have tried to simplify it as much as possible.
- Wikipedia portrays physical "inversion" as follows. In effect, this is like an umbrella being blown inside out.

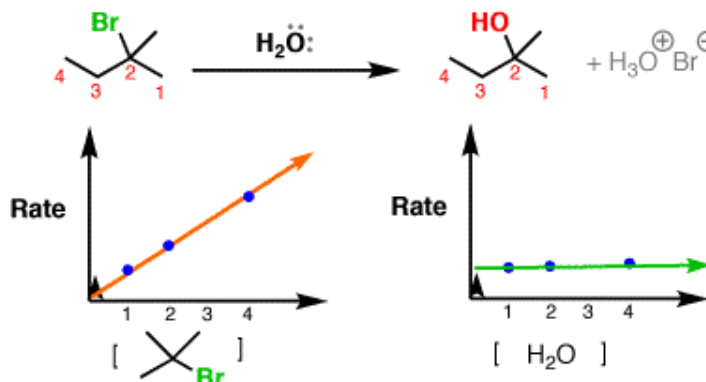


The $\text{S}_{\text{N}}1$ Reaction Mechanism (3° and 2° Halogenoalkanes use the $\text{S}_{\text{N}}1$ mechanism)

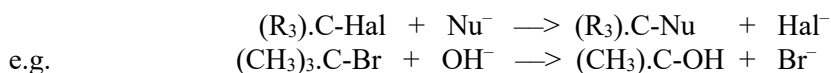
- The $\text{S}_{\text{N}}1$ mechanism **involves a carbocation intermediate** (i.e. one that has a '+ve' charge on it).
- The carbocation is normally planar and tends to have one or more stabilising alkyl group(s) in it (which is why it is used by both 3° and 2° Halogenoalkanes).
- The $\text{S}_{\text{N}}1$ mechanism **takes place in two steps**, and one of the two steps is a slow step wherein the leaving group (LG) is lost, and then there comes a fast step.
- The speed of the slow step will (and in fact, and *of necessity must*) determine the rate of the overall reaction, and the slow step is called the "**rate determining step**" (RDS). The slow step in an $\text{S}_{\text{N}}1$ mechanism involves the concentration of just one species⁵ – and it is this that gives the $\text{S}_{\text{N}}1$ mechanism the "1" bit of its name (the concentration of just **one** species determines the rate of the mechanism).

⁵ The concentration of a species X is designated by the use of square brackets, thus [X].

- In the Hydrolysis of the 1° Halogenoalkane 2-bromo-2-methylpropane {C₂H₅-C(CH₃)₂Br} by Water, Dr Ashenurst's graphs show very clearly that the rate of the reaction depends on the concentration of the substrate but **not** on the concentration of the Water (cf. the rate in the right hand graph below).



- In the first step of an S_N1 reaction mechanism**, an attacking nucleophile (Nu⁻) attaches to/attacks the (R₃).C-Hal, e.g. a (CH₃)₃.C-Br molecule and replaces the Halogen atom, therefore the overall reaction equation would be



The formation of an Alcohol from a Halogenoalkane using Water.

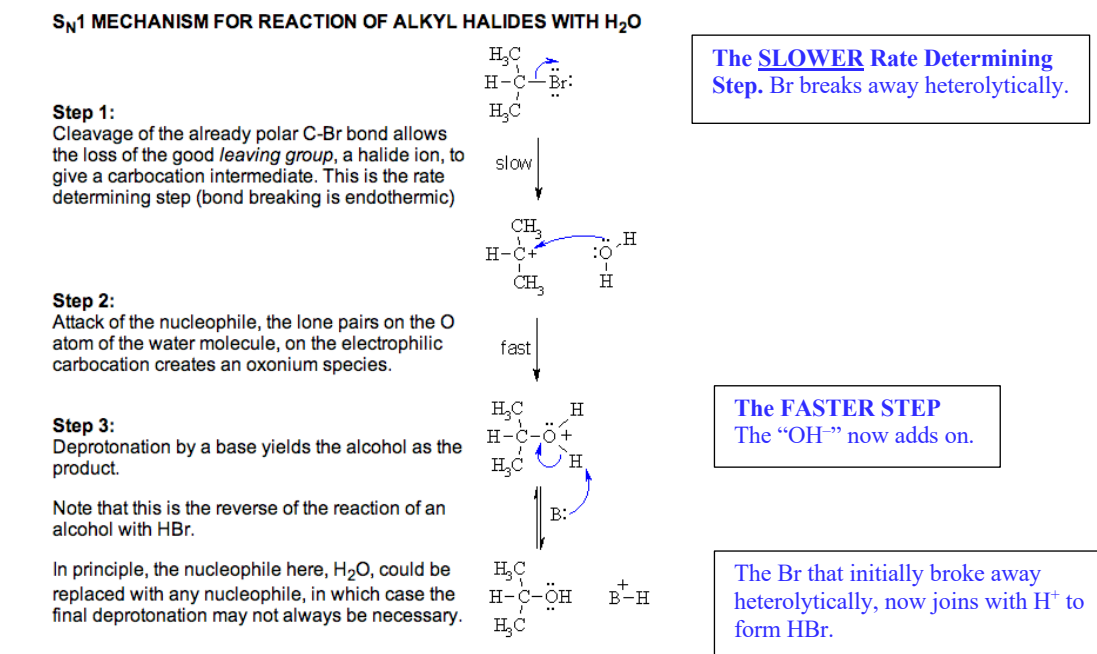
- 3° Halogenoalkanes react by way of S_N1 mechanisms, whilst 2° Halogenoalkanes react by way of both S_N1 and S_N2 mechanisms. In the 1st slow step below “Br” (for example) breaks away heterolytically leaving behind a (positively charged) carbo-cation which is vulnerable to an attack by one of the lone pairs of electrons on the O atom of a Water molecule. A proton then breaks away from the Water molecule – and now the Br species has been replaced by/substituted by an OH⁻ species e.g.



Where

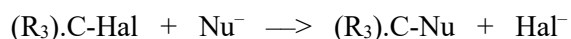
$$Rate = [(CH_3)_2.CHBr]^1 \quad \text{(this is an S}_{N1} \text{ mechanism)}$$

- The University of Calgary shows the following S_N1 mechanism for the **hydrolysis** of a secondary halogenoalkane.

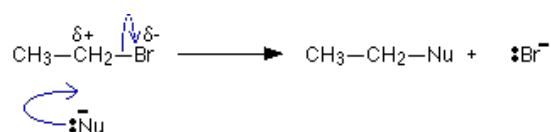


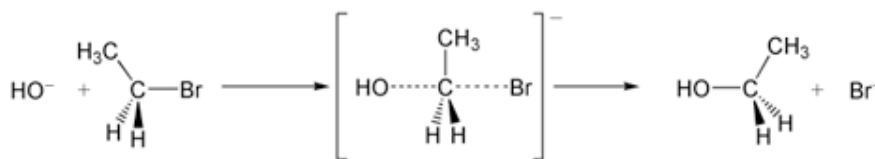
S_N2 Mechanisms for 1° Halogenoalkanes

- S_N2 stands for a Nucleophilic Substitution Reaction Mechanism where **two** molecules/two species are involved in the slow rate determining step. The new (attacking) group is a nucleophile (i.e. an electron rich species), Nu⁻.
- Inversion occurs with an S_N2 mechanism.** (I will talk about ‘inversion’ in a moment or two.) Inversion occurs because the attack of the incoming nucleophile (Nu⁻) on the C^{δ+} of the substrate molecule cannot occur in the region of space in which the Halogen atom is located. The Halogen atom is (relatively) too large and ‘hinders’ or blocks the approach of the Nu⁻. This is termed ‘**steric hindrance**’. The attacking nucleophile has thus to approach from the opposite side (*I do not like the American phrase “backside”*) and inversion occurs in the reaction. The molecule gets “blown inside out like an umbrella in a high wind”.
- If ‘R₃’ represents *any* three non-Carbon species (including an H atom) bonded to a Carbon atom, then the overall reaction equation would be



e.g. if a nucleophile were to attack bromoethane





Source: Wikipedia

- In Thermodynamics, the Rate Equation for a reaction that occurs through an S_N2 reaction mechanism would have to reflect the fact that the concentration of the two reactions are involved in the Rate Determining Step, and the Rate Equation would be expressed by

$$\text{Rate} = k [\text{Nu}].[\text{R-LG}]$$

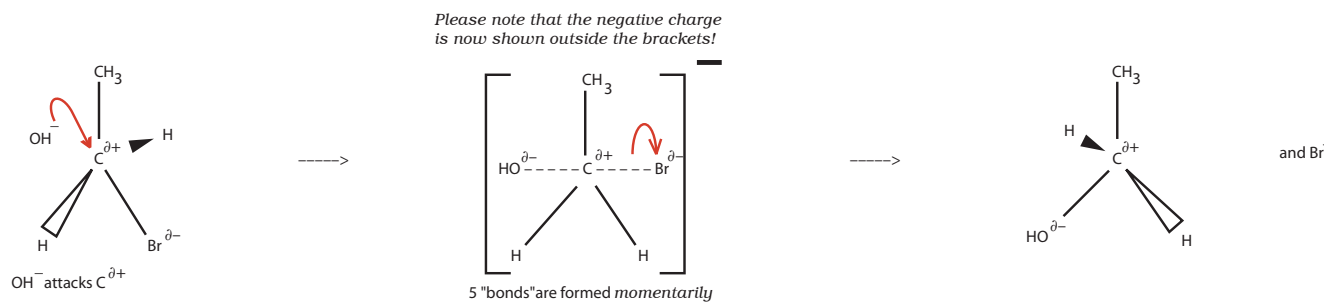
(where “LG” signifies the “leaving group”, i.e. the species that is being replaced on the molecule that is undergoing the attack by the nucleophile, Nu⁻). The equation Rate = k [Nu].[R-LG] indicates that the mechanism depends on the concentrations of **two** reactants (i.e. that of Nu and R-LG) and that the reaction is a second order reaction. (NB I have covered all of this very fully in Year 2, Inorganic Chemistry, Chapter 7 Rates of Reactions.)

The MECHANISM for the Nucleophilic Substitution reaction of the Hydrolysis of a 1° Halogenoalkane

This is an S_N2 reaction Mechanism and applies primarily to *Primary* Halogenoalkanes.

NB If in an exam you are asked to “describe” a reaction mechanism, then do NOT attempt to do it in an English language essay – **just draw the following relevant 3-step diagram.**

The Transition Stage



- Over the last two years I have taught you a few reaction mechanisms, but this one is rather different from the ones that you have learnt so far. Could you please note the following salient features⁶
 - The middle step in this mechanism is called “**The Transition Stage**”.
 - The central C atom appears to have **5 bonds** in the Transition Stage.
- In the Transition Stage
 - both O and Br MUST be shown as “ δ^- ”,
 - at ‘A’ Level, the bonds to the Hydroxy Group and to the Br atom MUST be drawn as **dotted lines** to indicate that they are not proper fully-fledged covalent bonds (otherwise the C atom would then have 5 bonds!)

⁶ “Salient” = important/relevant.

- you MUST draw the **big square brackets** around the whole of the Transition Stage and put a negative sign outside it, and
- in the Transition Stage, the Nu^- stops being an ion and becomes one which has a simple partial separation of charge. [In the Transition Stage, to make clear that it is the $\text{O}^{\delta-}$ in the OH^- that is bonding with the $\text{C}^{\delta+}$ species, I have reversed the H and the O and shown it as $\text{HO}^{\delta-}$.]
- The $\text{C}^{\delta+}-\text{Br}^{\delta-}$ bond breaks heterolytically.

NB This is a simplified version of what happens in real life, and there is absolutely nothing in the reaction to tell you whether it is an $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ mechanism. **That has to be determined purely by experimentation and observation.**

NB The more reactive the attacking nucleophile, the more likely it is that the mechanism will be $\text{S}_{\text{N}}2$ rather than $\text{S}_{\text{N}}1$.

Nucleophilic Substitution (“ S_{N} ”) Reactions⁷

- Let us now define these mechanisms.
- The “S” in the name stands for “Substitution”, the “N” in the name stands for “Nucleophilic”, and the **number** in the name indicates **how many molecules are involved in the slow rate-determining step of the Nucleophilic Substitution mechanism that is being considered.**
- Discussions about reversible reactions reveal “How far” a reversible reaction will go before it reaches a position of dynamic equilibrium, and in the Section on Thermodynamics in “Year 2, Inorganic Chemistry, Chapter 7” I have talked about the Rate at which a reaction can occur (viz. “How fast it will happen”).
- There is an old-English saying that “A chain is as strong only as its weakest link” and, similarly, **the rate at which a reaction can occur is determined by the slowest step in the process.**
- Some men benefit from the love of a good woman and “settle down” under the influence of their partners, while others manage to civilise themselves. Similarly, the rate at which some reactions occur is determined by the concentrations of the two independent species involved in the reaction ($\text{S}_{\text{N}}2$ mechanisms), and (in contrast) there are some where the rate is determined solely by the concentration of just one species by itself ($\text{S}_{\text{N}}1$ mechanisms).
- **When the slow rate-determining step in a Nucleophilic Substitution reaction is determined by the concentration of the two independent species (e.g. $\text{Rate} = k.[\text{R-Hal}].[\text{OH}^-]$), then the mechanism by which the reaction takes place is called an $\text{S}_{\text{N}}2$ mechanism, but if the slow rate-determining step is determined by the concentration of just one species (e.g. $\text{Rate} = k.[\text{R-Hal}]$) independently of any other species, then the mechanism is called an $\text{S}_{\text{N}}1$ mechanism.**
- The term “retention” refers to the maintenance of a particular configuration at a chiral centre in space. It is the contrary of “inversion” where the spatial configuration is altered (cf. the top left hand box of Dr Ashenhurst’s excellent diagrams on page 8 where “inversion” results in a bond changing from “coming towards you” to “going away from you”).

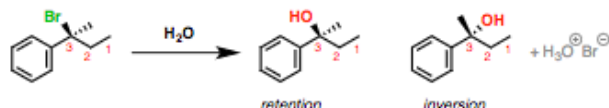
⁷ We talked about Electrophilic Aromatic Substitution (EAS) reactions extensively in the earlier Chapters on Benzene and its derivatives.

- The following diagram is by Dr James Ashenhurst of masterorganicchemistry.

S_N1 Reaction

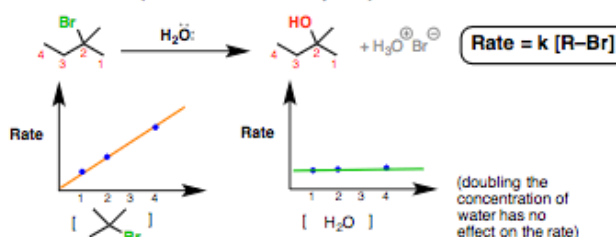
Stereochemistry

Substitution occurs with a mixture of retention and inversion at a stereocenter



Rate Law

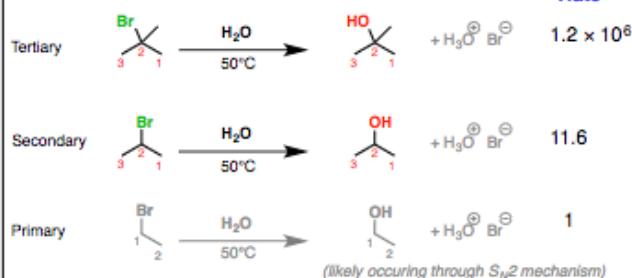
The rate of the reaction is **ONLY** sensitive to the concentration of the substrate (and not the nucleophile)



Substrate

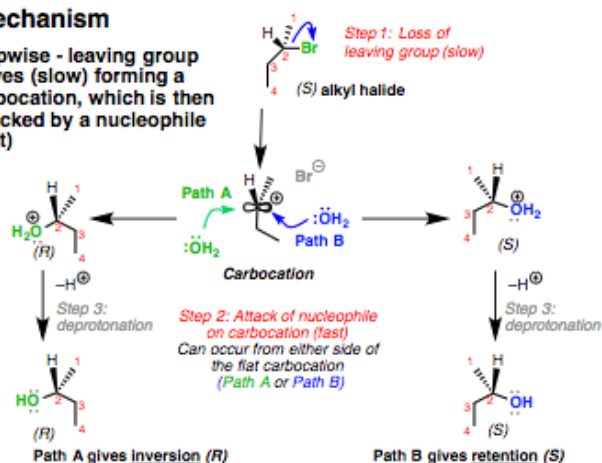
Fastest for tertiary, slowest for primary

Rate



Mechanism

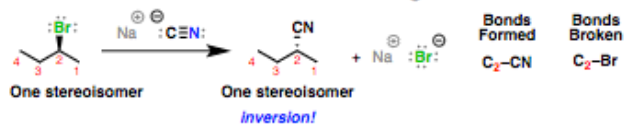
Stepwise - leaving group leaves (slow) forming a carbocation, which is then attacked by a nucleophile (fast)



S_N2 Reaction

Stereochemistry

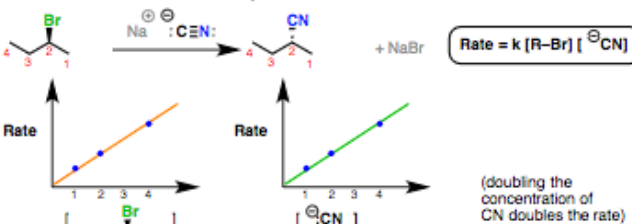
Substitution occurs with inversion of configuration at chiral centers



This substitution reaction results in an inversion of configuration at C-2

Rate Law

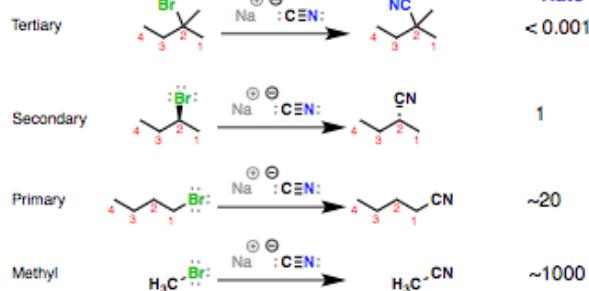
The rate of the reaction is sensitive to the concentration of the substrate **AND** the nucleophile



Substrate

Slowest for tertiary, fastest for primary (methyl even faster)

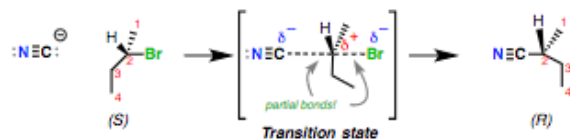
Rate



Mechanism

One step (backside attack)

In the "backside attack", the nucleophile attacks the substrate from the backside in a single step, resulting in inversion of configuration.

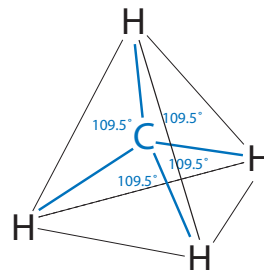
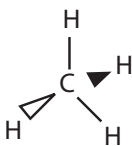
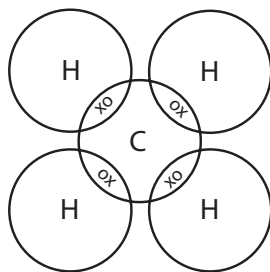


- Explains bimolecular rate law (depends on conc. of nucleophile and substrate)
- Explains inversion of stereochemistry
- Explains sensitivity to steric hindrance (bulky groups slow down backside attack)

This is called the **S_N2** mechanism
(Substitution, Nucleophilic, bimolecular)

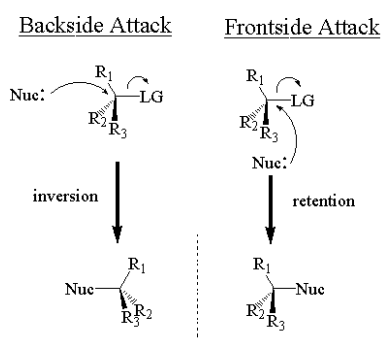
Inversion and Retention

- There is an interesting feature about S_N2 mechanisms, and to understand this one must talk about three-dimensional (3-D) spatial arrangements. I have quite often drawn for you the following tetrahedral configuration of Methane



The "bond angle" is the angle between each H—C—H bond.
Every bond angle here is 109.5°.

- and the Bromoethane ($C_2H_5.Br$) molecule that is the subject of the nucleophilic attack by the OH^- species also has a tetrahedral shape. It is **not** usual to draw the shape in full, but rather to draw it as an attempted 3-D displayed formula as I have drawn it in the middle above. However, the configuration in all the three diagrams are one and the same 3-D configuration.
- The thing that I would like you to observe is that a uniform tetrahedron is symmetrical and therefore the molecule has no 'back' / 'front' / 'top' / 'bottom' / etc. Such descriptions have no meaning, but nevertheless chemists have a habit of talking as though such descriptions have a reality.
 - In particular they do so to talk about the '**inversion**' and '**retention**' that is a feature of S_N2 mechanisms. "Inversion" consists of the shape of the molecule (*and this is exactly how chemists describe it*) being blown inside out like an umbrella in a high wind (but of course this has as little meaning as descriptions of front/back/sideways/etc).
 - "Inversion" in an S_N2 reaction mechanism consists of a change in the 3-D configuration of the molecule. This is in contrast to "retention" where the molecule retains its original 3-D configuration. Whether the substrate (i.e. the molecule that is being attacked by the nucleophile) undergoes inversion or retention depends on the direction from which the substrate is attacked. Steric hindrance tends to prevent a "frontal" attack, and that is why inversion occurs after an attack from the rear in an S_N2 mechanism. The diagrams below correspond to the tetrahedral configurations shown above.
 - Sparknotes.com shows the two attacks as (and here LG = Leaving Group)



The two species at the bottom of the above diagram are enantiomers.

- Phrases such as “frontside” and “backside” are not that helpful, but they make a bit more sense if one categorises a “**frontal**” attack as being one where the attacking nucleophile attacks from the same direction as that occupied by the Leaving Group (LG), and a “**rearward**” attack as where the attacking nucleophile joins on from the side opposite to that which the LG occupies.
- The inverted molecule on page 8 may look as though it has the same 3-D configuration as it had before the nucleophilic attack, but if the molecule is twisted around so that the Nucleophile is in the position that the Leaving Group (LG) originally occupied, then it will be seen that where LG and R1 were in the same plane and R1 was 109.5° counter-clockwise of LG, now “Nu” and R1 are in the same plane but R1 is clockwise of Nu. This situation is what chemists call inversion, and it is in contrast to “retention” where there is no alteration in the 3-D configuration. If R, R', and R'' were placed in their priorities according to the CIP rules (cf. Chapter 23), one could then demonstrate the above fact using the R/S designations.)
- One could get into much more complicated stuff about Nucleophilic Substitution reaction mechanisms, but that is more than enough for ‘A’ Level purposes.