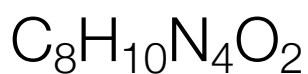
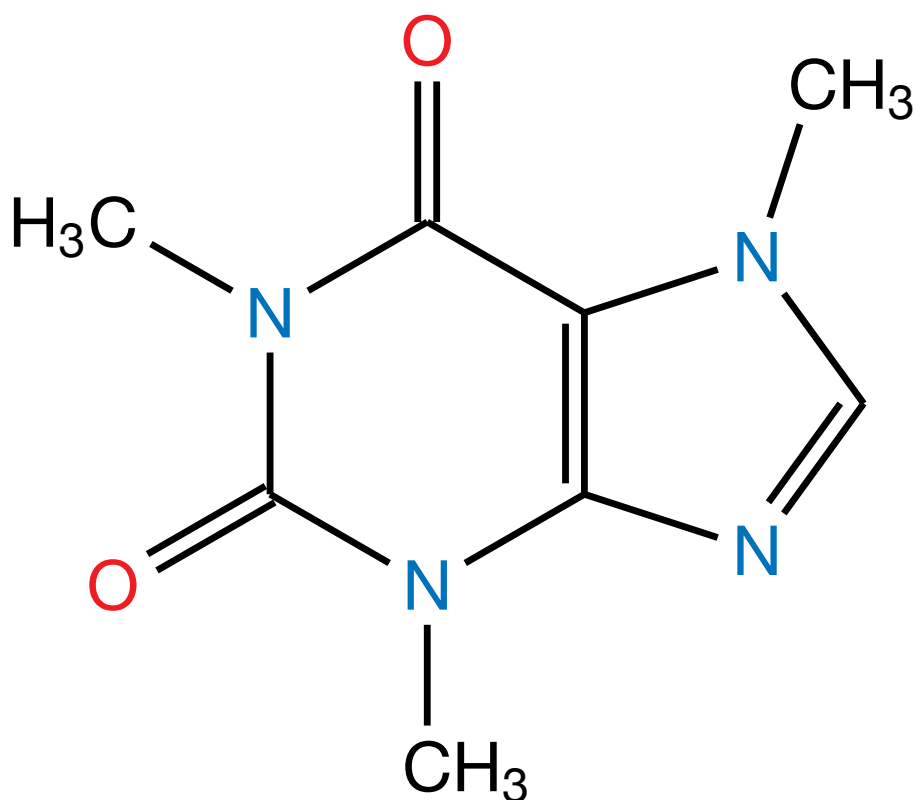


Organic Chemistry



1,3,7-trimethylpurine-2,6-dione

-

Caffeine

Chapters 8 to 12

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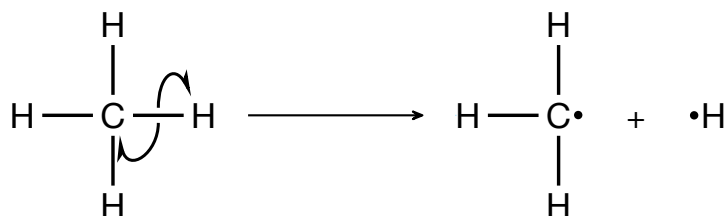
I Reaction Mechanisms

1 Bond Breaking

1.1 Homolytic Fission

Homolytic fission involves the splitting of a single bond, with an equal (*homo*) distribution of the two electrons of the aforementioned bond. This results in the formation of radicals, since now both atoms from the bond will have unpaired electrons.

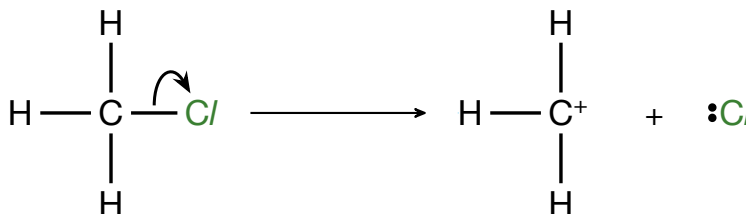
The movement of these single electrons is represented with single-hooked arrows. The arrow starts from the bond line, and points towards the target atom receiving the electron.



The homolytic fission of CH_4 , forming $\cdot\text{CH}_3$ and $\cdot\text{H}$ radicals.

1.2 Heterolytic Fission

As the name implies, heterolytic fission is the opposite; it distributes both electrons of the bond to a single atom, which usually results in the formation of ions. The transfer here is represented using a full (double-hooked) arrow.



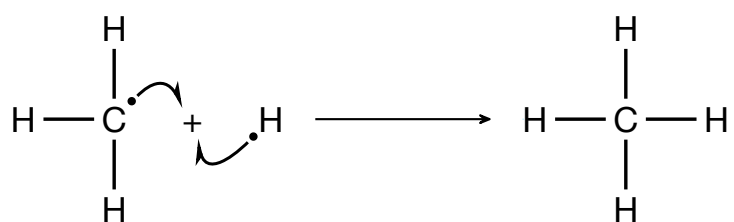
The heterolytic fission of CH_3Cl , resulting in CH_3^+ and Cl^- ions

2 Bond Forming

2.1 Single Electrons

Bond forming is essentially the reverse of bond breaking, and hence the same notations apply — single-hooked arrows for the movement of single electrons, and double-hooked arrows for the movement of an electron pair.

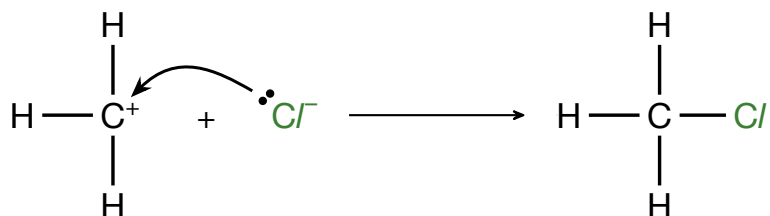
In this case, two single electrons from each atom contribute to the new bond.



The formation of a bond between $\cdot\text{CH}_3$ and $\cdot\text{H}$ radicals to form CH_4 .

2.2 Electron Pairs

Electron pairs usually come from negatively charged radicals or lone pairs, although this is not a rule. Both electrons come from a single source to form a bond, but this is *not* a dative bond — it is simply a normal bond.



The formation of a bond between $\cdot\text{CH}_3$ and Cl^- radicals, to form CH_3Cl .

3 Electrophiles and Nucleophiles

3.1 Electrophiles

Electrophiles are electron-deficient species that accept an electron pair from a nucleophile donor. Most electrophiles either have a positive charge, or contain an atom that is polarised and thus has a partial positive charge.

Examples of electrophiles include CH_3^+ , Br^+ , NO_2^+ , polarised Br_2 , and HBr .

3.2 Nucleophiles

Nucleophiles are electron-rich species that donate electron pairs to electrophiles. This process typically results in the formation of a new covalent bond. Nucleophiles usually contain atoms that are either negatively charged, or, more frequently, contain lone electron pairs that are not bonded.

Molecules with a π -bond, such as ethene or benzene, can also act as nucleophiles, due to the high electron density of the π -system.

Examples of nucleophiles include H_2O , NH_3 , and OH^- .

Appendices

Herein lie things that *must* be known, but for brevity are excluded from the main text.

A List of Reaction Mechanisms

1 Electrophilic Addition

Electrophilic Addition the main reaction mechanism for alkenes, and involves an electrophile attacking the electron-rich π -bond of the alkene.

1.1 Markovnikov's Rule

This rule governs the major product that is formed when asymmetrical compounds are electrophilically added to alkenes, such as hydrogen halides. It does not apply to symmetrical reactants like Cl_2 or Br_2 .

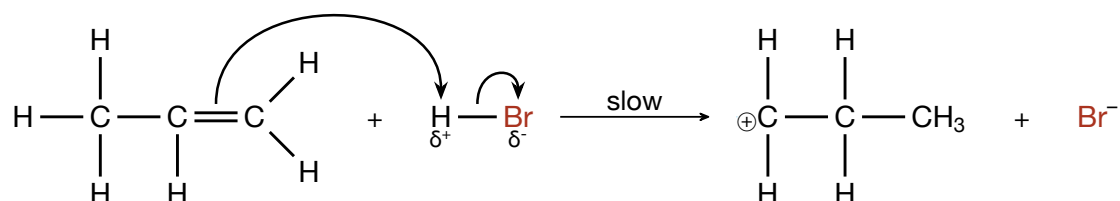
The rule states basically states that when a hydrogen compound with the general form H-X is added to an alkene that is asymmetrical about the double-bond, the hydrogen atom will be added to the carbon with *more* existing hydrogen atoms. Note that X can be a halogen, a hydroxide (ie. H-X is H_2O) or some other electronegative species.

The mirror of the rule, used more with the cyclic halonium ion, is that the nucleophile will be added to the more substituted carbon atom.

1.1.1 Addition of H-X to Unsymmetrical Alkenes

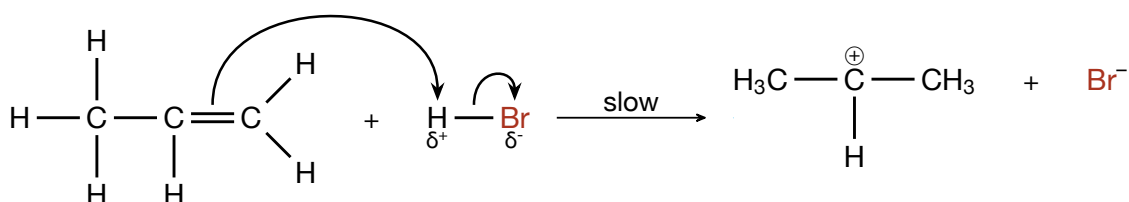
The behaviour that Markovnikov's rule predicts can be derived from the fact that adding the non-hydrogen species to the least substituted carbon would result in a less stable intermediate being formed. This can be illustrated using the electrophilic addition of HBr to prop-1-ene (C_3H_6).

If the Markovnikov's rule is *not* followed, the following will take place:



The hydrogen was added to the centre carbon, in violation of Markovnikov's rule.

Notice that the positively-charged carbon on the intermediate only has 1 electron-donating alkyl group to stabilise its charge. Conversely, if Markovnikov's rule is followed below, the outcome would be different.



The hydrogen was added to the terminal carbon, following Markovnikov's rule.

In this case, the carbon atom containing the positive charge has 2 electron-donating alkyl groups attached to it, making this intermediate molecule more stable than the one above it.

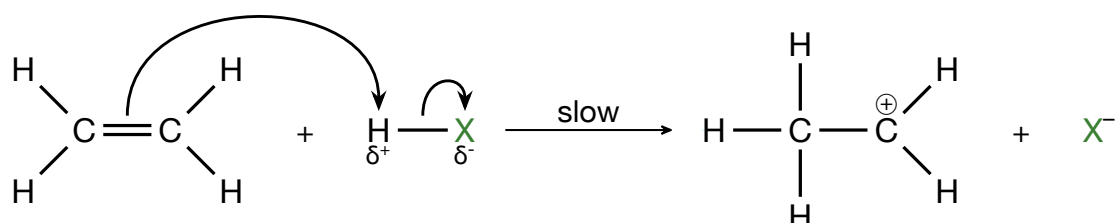
As such, it is more likely to form, and hence 2-bromopropane will be the *major product*, and 1-bromopropane will be the *minor product*.

1.2 Electrophilic Addition of HX

In this reaction, the hydrogen and halogen atom are added across the double bond of the alkene. The hydrogen halide should be in a gaseous state for this reaction.

Conditions: Gaseous HX (usually HCl or HBr).

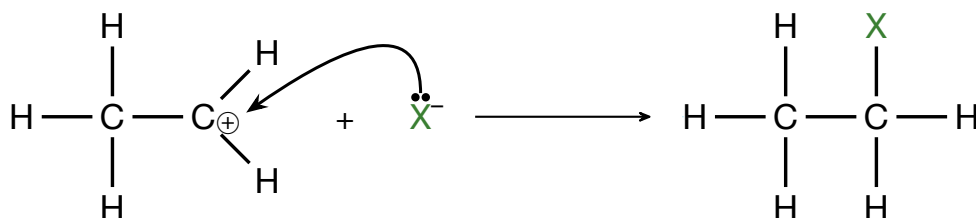
Step 1



This is the rate-determining step, which involves the breaking of the π -bond. The polar HX molecule has to approach the electron cloud of the π -bond in the correct orientation (hydrogen-facing), where the π -bond electrons attack the electron deficient, H $^{\delta+}$ atom.

The H-X bond then undergoes heterolytic fission, producing a carbocation intermediate and a halide ion.

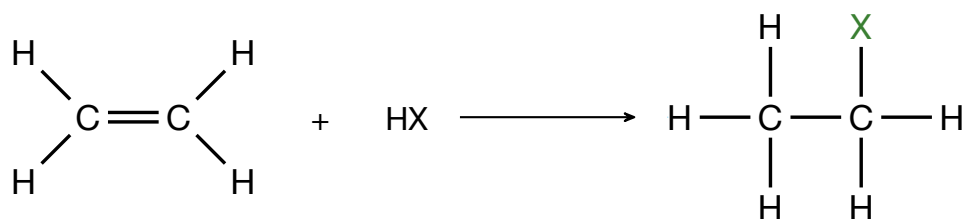
Step 2



The electron pair arrow points to the plus charge on the carbon, *not* the carbon atom itself.

This is the fast step; the bromide anion acts as a nucleophile, attacking the positively-charged carbocation.

Overall Reaction



1.3 Electrophilic Addition of X_2

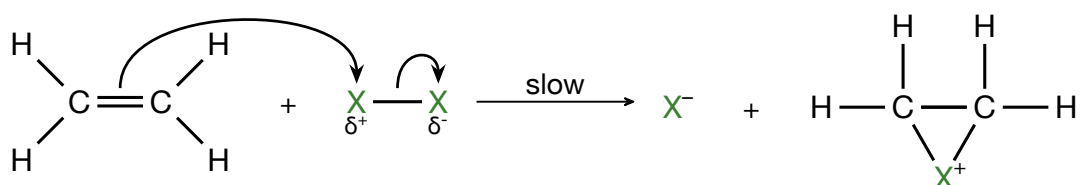
The electrophilic addition of halogens to alkanes does not involve Markovnikov's rule, since it is symmetrical. As the non-polar halogen molecule approaches the high-electron-density π -bond, it is polarised, forming δ^+ and δ^- partial charges. The reaction mechanism involves the formation of a *cyclic halonium ion* — the double bond breaks, and each carbon forms a single bond with one positive halide ion.

Conditions: No UV Light, gaseous X_2 .

Observations: **Reddish-brown** Br_2 / **yellowish-green** Cl_2 decolourises.

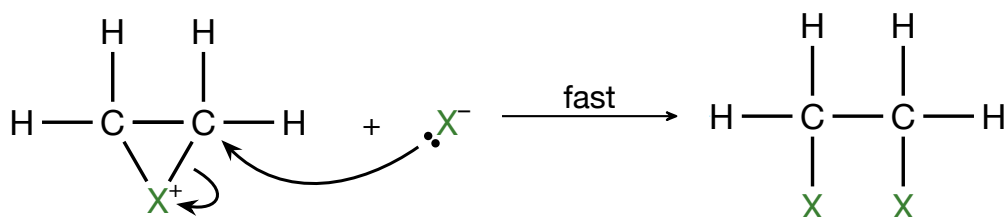
Step 1

This initial step is the slow, rate-determining one. The resulting cyclic halonium ion is highly unstable, due to the geometric constraints of having a three-membered ring.

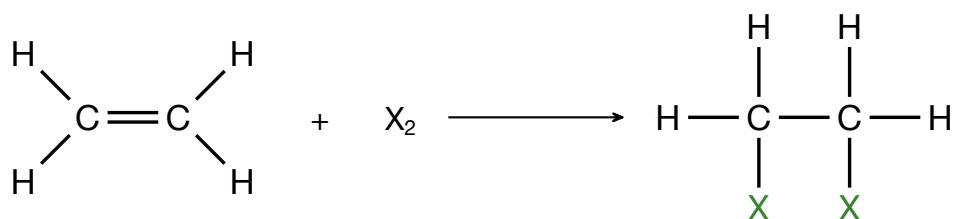


Step 2

In the second, fast step, the negatively-charged bromide ion from the first step attacks the overall positively-charged cyclic bromonium ion. The bromide ion attacks one of the carbons attached to the positive bromide ion, breaking that bond.



Overall Reaction



1.4 Electrophilic Addition of Aqueous X_2

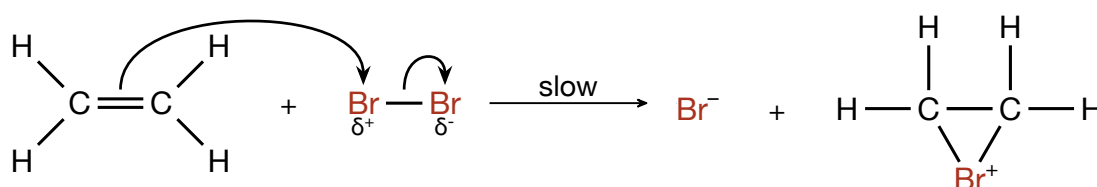
The mechanics of this reaction are basically the same as that of the electrophilic addition of Br_2 , and the conditions and observations are fairly similar as well.

Also, since the Br atoms are not both added across the double bond in a symmetrical manner, Markovnikov's Rule applies — the OH group will preferentially attack the carbon that has more stabilising alkyl groups.

Conditions: No UV Light, aqueous Br_2 .

Observations: **Yellow** Br_2 (aq) decolourises.

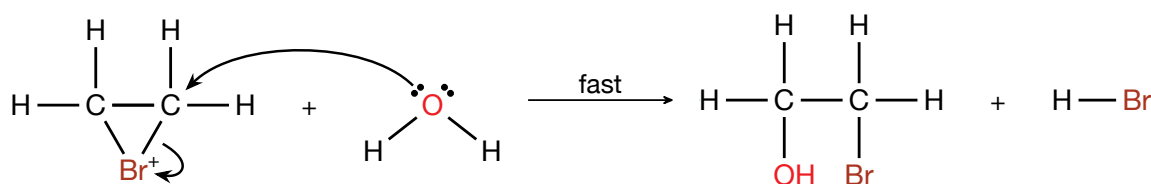
Step 1



The cyclic bromonium ion is formed.

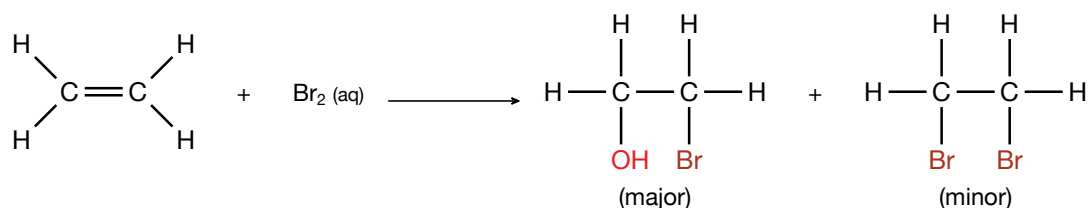
Step 2

Once the cyclic bromonium ion is formed however, it is susceptible to attack from any and all nucleophiles — including water, which has lone pairs and is a stronger nucleophile Br^- . Since it is in much higher concentrations than Br^- , the primary product will now have an OH group.



Following Markovnikov's Rule, the OH^- group will attach to the more substituted carbon.

Overall Reaction



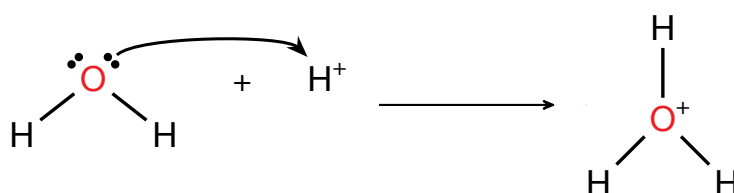
1.5 Electrophilic Addition of Steam (Hydration)

Under certain (usually industrial) conditions, alkenes can react with steam to form alcohols. Since this reaction involves the formation of a carbocation intermediate, the proportion of products will be governed by Markovnikov's Rule.

Conditions: 300 °C, at 70 atm, H_3PO_4 catalyst, *OR*
Concentrated H_2SO_4 , H_2O , warming.

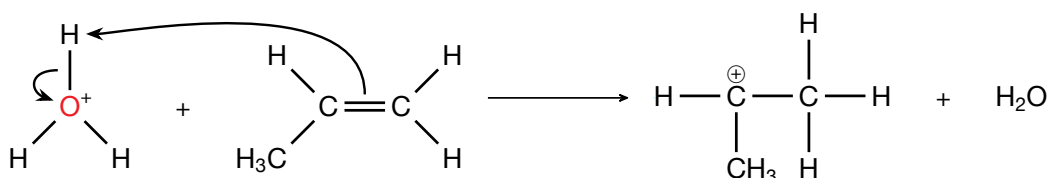
Step 0

The first step is to form H_3O^+ (aq). Simply put, it is aqueous H^+ .



Step 1

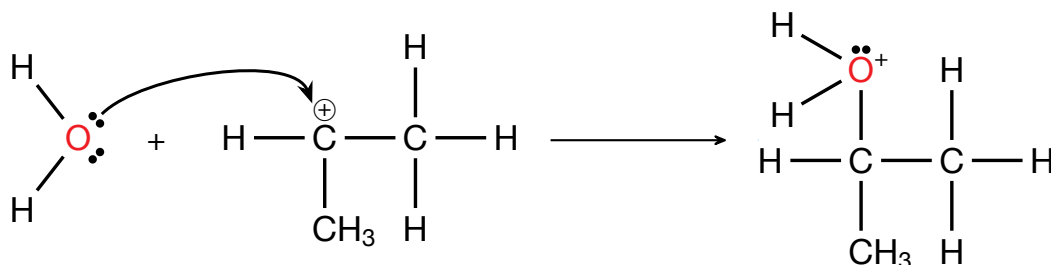
The electron-rich double-bond ($\text{C}=\text{C}$) is then attacked by one of the H atoms on the H_3O^+ , acting as an electrophile.



Since the alkene is not symmetrical, there are two product possibilities; hence, the positive charge will be on the carbon atom with more electron donating alkyl groups, in this case carbon 2.

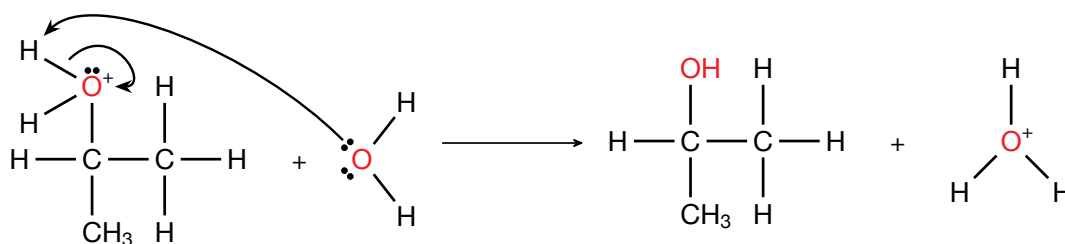
Step 2

One of the lone pairs on the oxygen atom of a water molecule acts as a nucleophile, attacking the newly-formed carbocation. This results in a protonated alcohol, which is basically an alcohol with an extra H atom on the OH group.

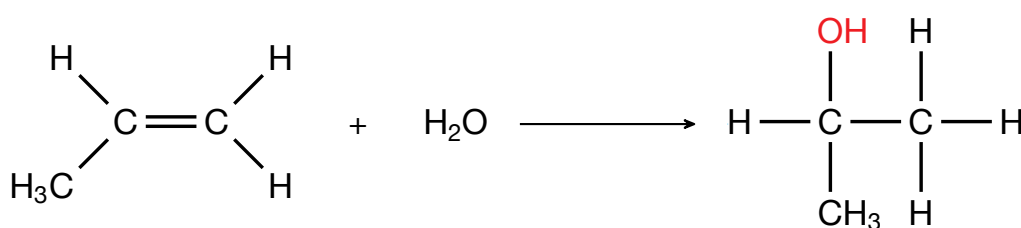


Step 3

The acid catalyst is regenerated as a lone pair on another water molecule's O atom attacks the extra H of the OH group. This forms the alcohol proper, and the H₃O⁺ ion.



Overall Reaction



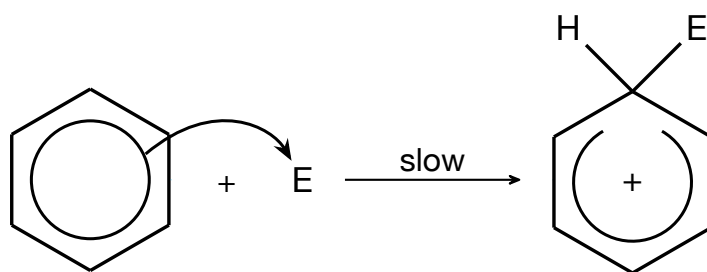
2 Electrophilic Substitution

In general, benzene rings undergo electrophilic substitution, since it is not possible for more bonds to be formed.

The delocalised π -system of benzene has a very high electron density, and thus is a prime target for electrophiles, which will substitute the H atoms on the ring. Thus, the most common form of reaction involving benzenes is electrophilic substitution, barring special conditions and requirements.

Step 1

In the first, rate-determining step, the aromaticity of the benzene ring is partially and temporarily broken, disrupted by the attacking electrophile.



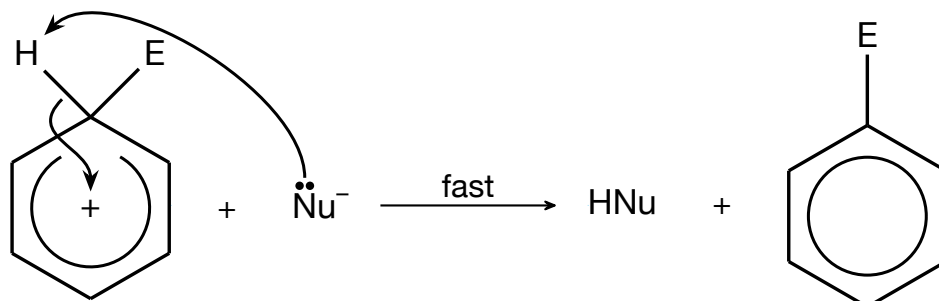
Note that the '+' is drawn in the centre of the ring, not on any one carbon.

Two electrons out of six from the delocalised π -system are used to form the bond between the electrophile, E, and the carbon. Thus, there is a positive charge on the carbon; due to the delocalised nature of the π -system however, this positive charge is delocalised across *all 6 carbons*, making it much more stable than a simple carbocation.

However, the activation energy for this step is still large, and only strong electrophiles are able to attack the benzene ring without catalysts.

Step 2

Next, a nucleophile (:Nu^- in this example) attacks the hydrogen attached to the hydrogen on the carbon atom, restoring the aromaticity of the benzene ring. The new substituent is now in place, and the two electrons in the C–H bond are returned to the π -system.



Note that the arenium ion (which is the partially delocalised benzene) has 5 sp^2 carbons, and one sp^3 carbon. This results in a disruption of the planar structure of benzene — it is restored once the substitution is completed.

2.1 Nitration of Benzene

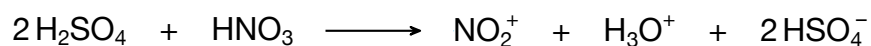
The nitration of benzene involves the substitution of one of the H atoms on the benzene with a nitro ($-\text{NO}_2$) group. It has a number of specific requirements:

Conditions: Concentrated HNO_3 , concentrated H_2SO_4 catalyst.
Constant temperature of 50°C .

Observations: *Pale yellow* oily liquid, nitrobenzene.

A New Electrophile

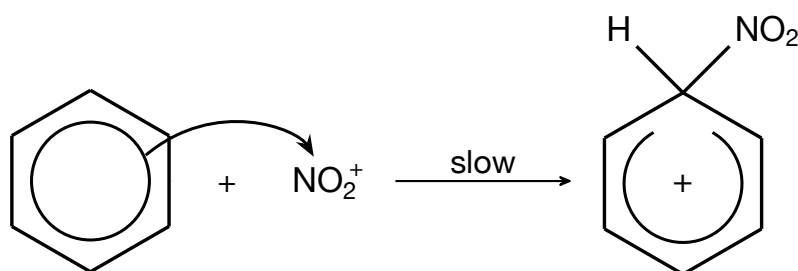
Since H_2SO_4 is a stronger acid than HNO_3 , it donates a proton to HNO_3 , forming H_2O , HSO_4^- , and NO_2^+ , the electrophile. Next, another molecule of H_2SO_4 then forms H^+ (aq), or H_3O^+ . The overall equation is as such:



The catalyst H_2SO_4 is restored in a later step.

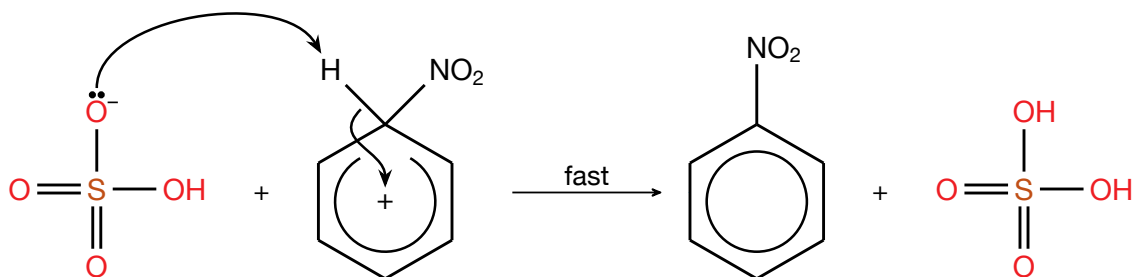
The π -Electrons Strike Back

Now that the electrophile NO_2^+ has been formed, it is attacked by the π -system. As with all electrophilic substitutions, this involves the breaking of the aromatic system, and is the slow step. The mechanism follows the general mechanism outlined above.

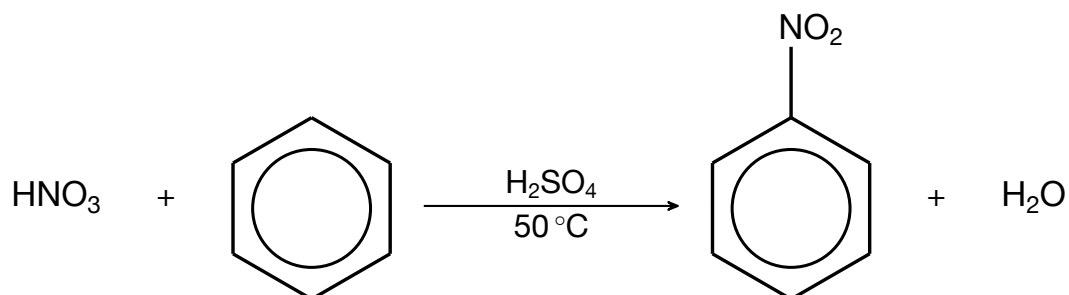


Return of the Aromaticity

The HSO_4^- intermediate acts as a nucleophile and attacks the H atom bonded to the benzene intermediate. This restores both the π -system of the benzene ring, as well as the catalyst, H_2SO_4 .



The Product Awakens



2.2 Halogenation of Benzene

Halogenation of benzene requires rather specific conditions, such as anhydrous FeBr_3 or FeCl_2 (for a reaction with bromine and chlorine respectively), and a warm environment.

Aluminium-based analogues of these catalysts (AlBr_3 , AlCl_3) can also be used, as can pure filings of the metal, in which case the catalyst will be generated *in-situ* ($2 \text{ Fe (s)} + 3 \text{ Br}_2 \text{ (l)} \rightarrow 2 \text{ FeBr}_3$).

Conditions: Warm, anhydrous FeBr_3 , AlBr_3 , or Fe / Al filings (for bromine),
Anhydrous FeCl_3 , AlCl_3 , or Fe / Al filings (for chlorine)

Observations: *Reddish-brown* Br_2 / *yellowish-green* Cl_2 decolourises.
Formation of white fumes of HX gas.

2.2.1 Catalysts

Lewis acid catalysts must be used, since the $\text{Br}-\text{Br}$ and $\text{Cl}-\text{Cl}$ are only instantaneously polar (instantaneous dipole moments). As such, they are nowhere near strong enough to attack the benzene system on their own.

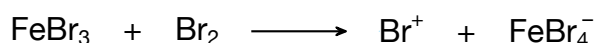
Indeed, this can be used to distinguish between alkenes and benzenes, since the former does not require a catalyst for addition of halogens.

Furthermore, the entire reaction must be conducted in the absence of water; the reaction mechanism for the lewis-acid catalyst involves accepting a lone pair, the lone pair on water can, and will, in sufficient concentrations, destroy the catalyst.

2.2.2 Reaction Mechanism

Generation of Electrophile

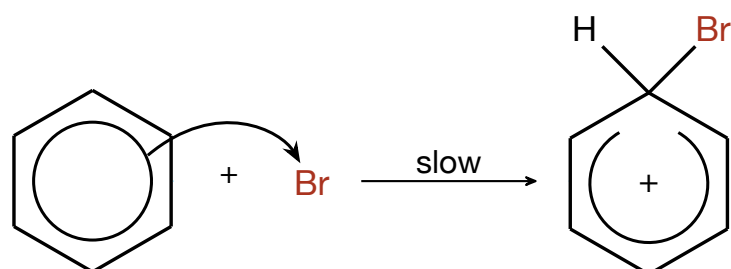
The reaction below uses Iron (III) chloride (FeCl_3) as an example, adding Cl to benzene, and this reaction mechanism applies to aluminium-based catalysts as well.



The catalyst is FeBr_4^- , and the *electrophile* is Br^+

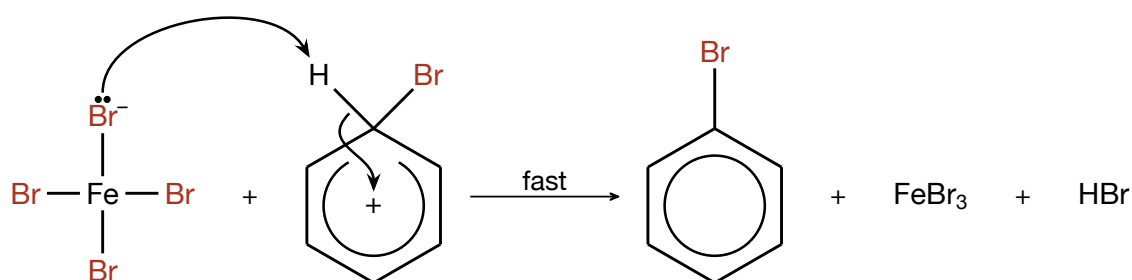
Formation of Benzene Intermediate

Again, this mechanism is similar in nature to electrophilic substitution in general. Now, the electrophile (Br^+) attacks the π -system, forming the arenium ion.

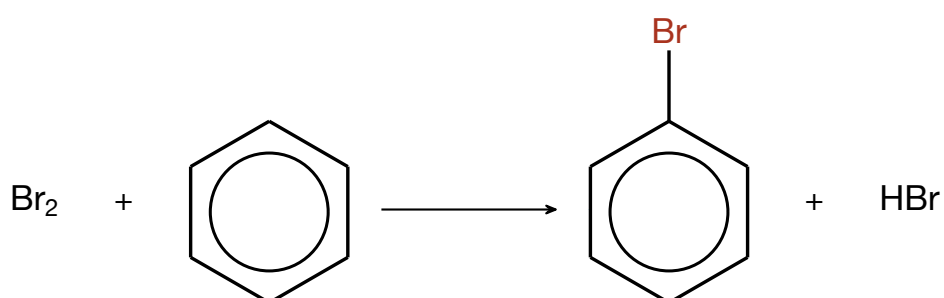


Restoration of π -system and Aromaticity

In the final step, the FeBr_4^- acts as a nucleophile, attacking the H atom attached to the benzene intermediate. This regenerates the catalyst FeBr_3 , and also forms HBr .



Overall Reaction



Nucleophilic Addition

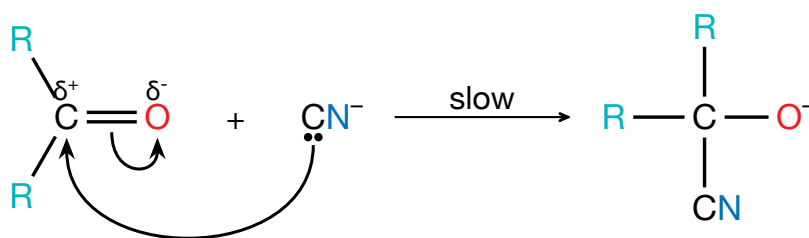
Due to the electronegativity of the oxygen atom, the electron density is drawn towards it. Thus, the carbon atom is able to be attacked by electrophiles due to its partial positive charge.

Note that aldehydes will be more reactive than ketones in nucleophilic addition, since they only have one electron-donating alkyl group on the central carbon, whereas ketones have two alkyl groups that are able to inductively donate electrons to stabilise the positive charge, slightly reducing reactivity.

The mechanism is a two-step mechanism with the slow step as the first step. Here, the nucleophilic addition of CN^- to a carbonyl will be illustrated.

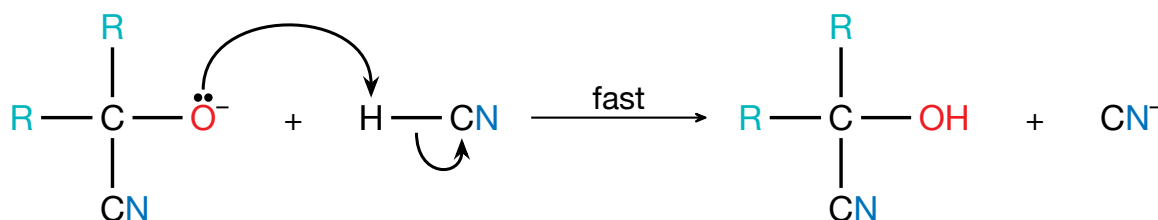
Step 1

Here, the central carbon is attacked by the nucleophile. This also serves to repel the electrons in the π -bond towards the electronegative O atom, forming a stable alkoxide anion.

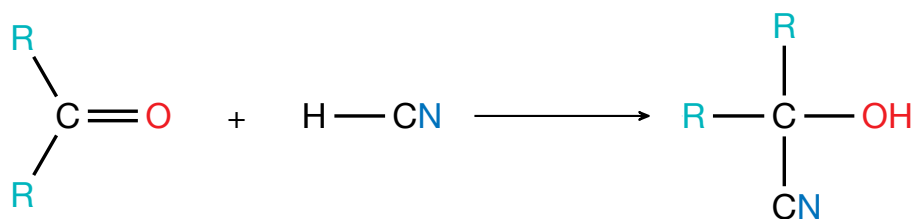


Step 2

Now, the alkoxide ion attacks an undissociated HCN molecule, protonating itself and regenerating the CN^- nucleophile.

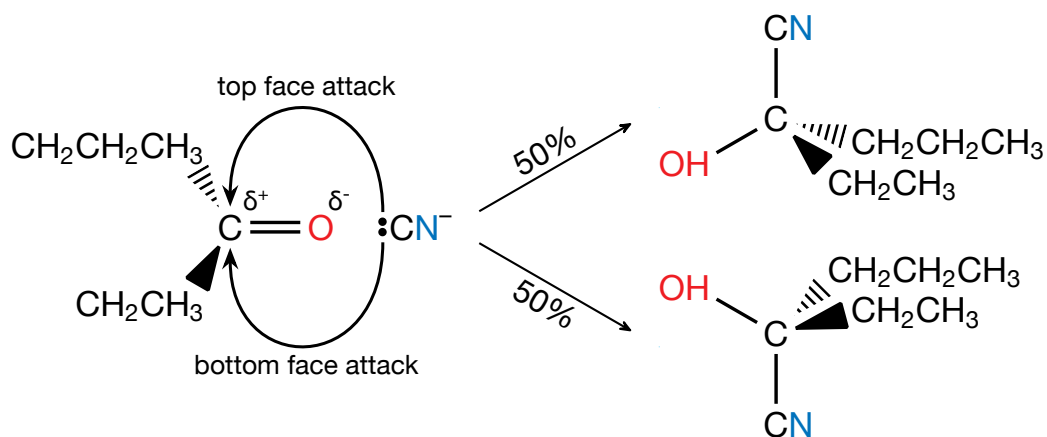


Overall Reaction



3.1 Stereoisomerism of Product

Since the carbonyl is trigonal planar, the nucleophile can attack from either the top or bottom side, with equal probability. Hence, if the product formed is chiral, the resulting solution will be a *racemic mixture*.



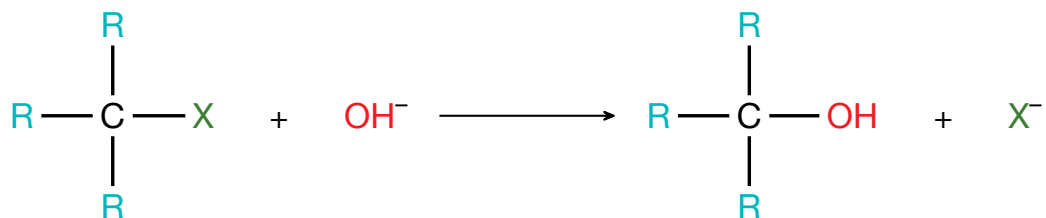
4 Nucleophilic Substitution

Due to the high relative electronegativity of the halogen atom attached to the carbon atom, the carbon atom is *electron-deficient*, which makes it more susceptible to attacks from nucleophiles (*electron-rich*), and as such halogenoalkanes are fairly reactive.

There are two primary mechanisms of nucleophilic substitution — single-step and two-step reactions. Generally, primary halogenoalkanes (molecules with 1 or 0 alkyl groups attached to the halogen-containing carbon) react via a one-step mechanism, while tertiary halogenoalkanes react via a two-step mechanism. Secondary halogenoalkanes can react via either mechanism, depending on the specific molecule.

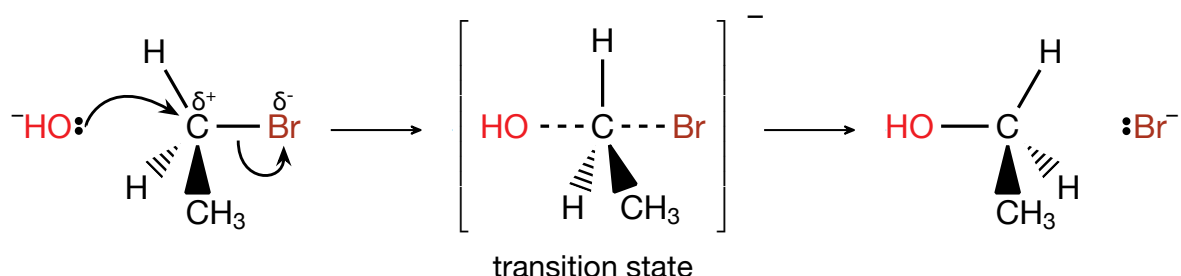
The primary differentiating factor is the size of the substituents on the central carbon — larger groups will hinder S_N2 substitution, forcing an S_N1 reaction.

Either way, the overall reaction is as such:



4.1 Nucleophilic Substitution (S_N2 , single-step)

The nucleophilic substitution of $\text{CH}_3\text{CH}_2\text{Br}$ by OH^- is a one-step reaction. Take note that S_N2 is a *one*-step reaction — it is S_N2 because *two* molecules are involved in the slow (only) step.

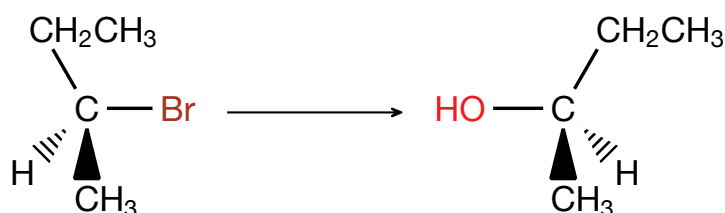


Due to the difference in electronegativity between the C and Br atoms, the C-Br bond is polar. Thus, nucleophiles will be attracted towards the partially-positive carbon atom. They attack from the side opposite the leaving atom (Br in this case) due to spatial constraints.

As the nucleophile attacks, it donates a lone pair to the carbon atom to stabilise it, forming a bond. At the same time, this weakens the C-Br bond, and it begins to break. At this stage, the *transition state* is formed, which is an unstable, activated complex where bond-breaking and bond-forming occur simultaneously — this is a *one-step* mechanism.

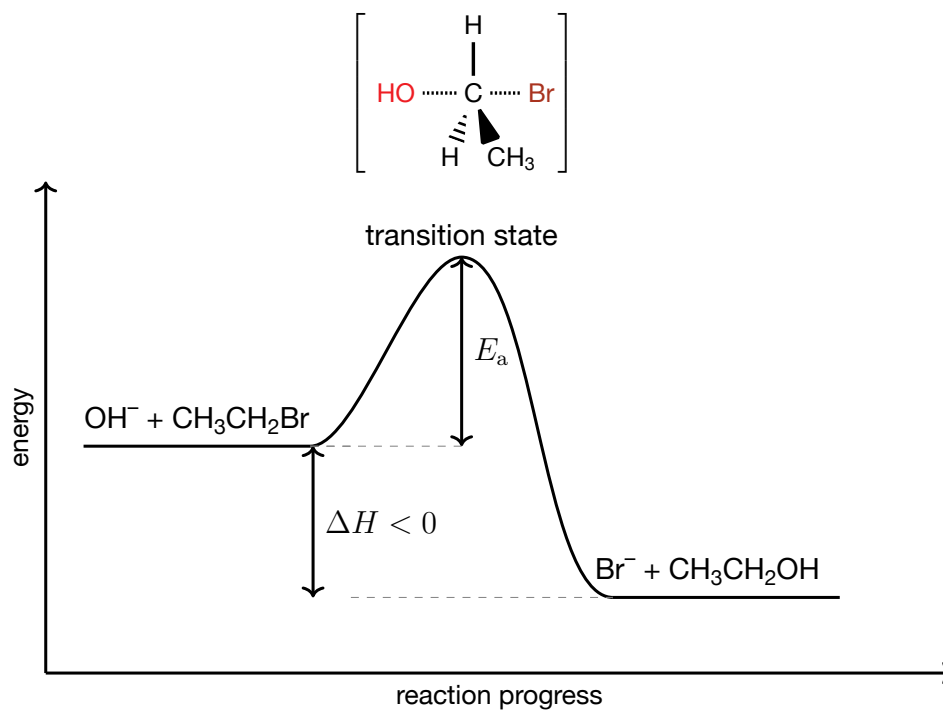
4.1.1 Stereoisomerism of Product

Note that the chirality of the molecule will be *inverted*, if it is chiral. Imagine the attacking nucleophile 'pushing' the other groups away from itself.



4.1.2 Reaction Pathway

Since this is a single-step reaction, there is one activation energy step, and the energy profile diagram looks like this:

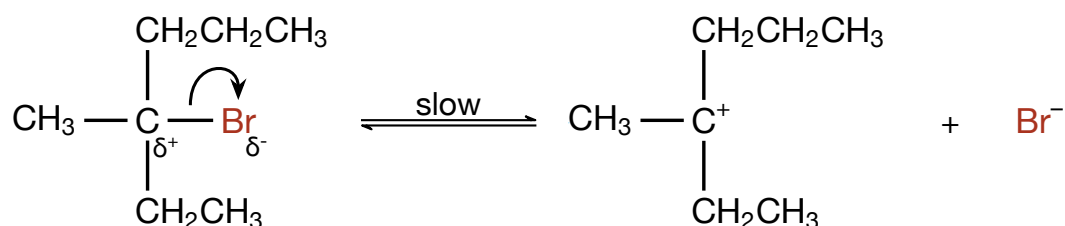


4.2 Nucleophilic Substitution (S_N1 , two-step)

The S_N1 reaction is a *two-step* reaction, because larger groups attached to the central carbon often hinder the direct attack of nucleophiles, and thus require the formation of a carbocation. Only one molecule is involved in the slow (first) step, hence it is a unimolecular reaction.

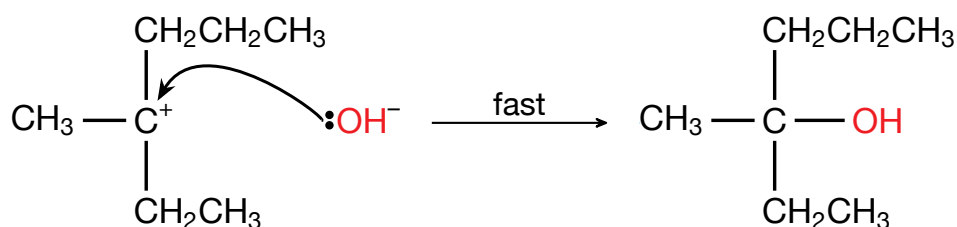
Again, the reaction hinges on the polar C–Br bond, due to the differences in electronegativity.

Step 1



The C–Br bond undergoes heterolytic fission, giving a carbocation intermediate, and a bromide ion. The reaction is more feasible due to the 3 electron-donating alkyl groups that stabilise the positive charge on the carbocation intermediate, which would not be possible in a primary alcohol.

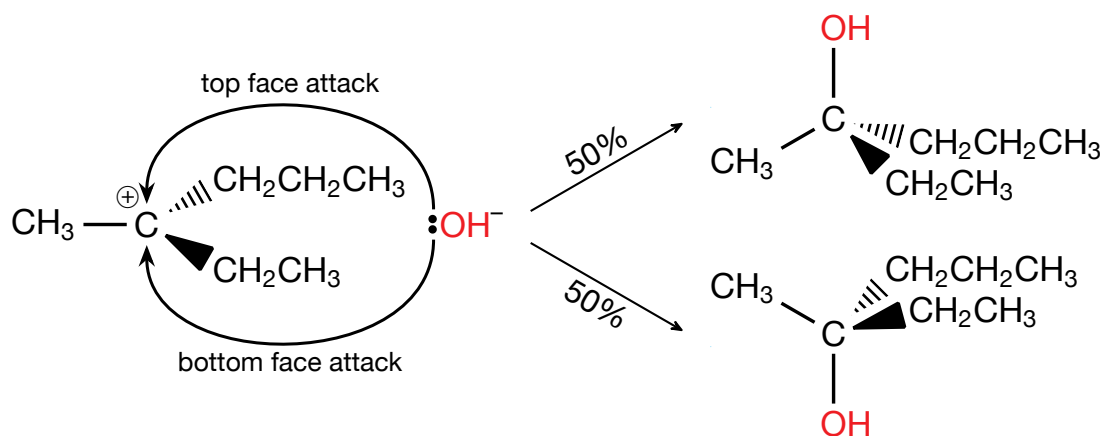
Step 2



The carbocation intermediate is now attacked by the OH^- ion, forming the product.

4.2.1 Stereoisomerism of Product

Since the carbocation is trigonal planar (wrt. the central carbon), the nucleophile can attack from both sides of the carbocation, with equal probability. Hence, if the product formed is chiral, the resulting solution will be a *racemic mixture*.



4.2.2 Reaction Pathway

Since this is a two-step reaction, there are two activation energies that must be overcome, and isolatable intermediates (the carbocation and bromide ion).

