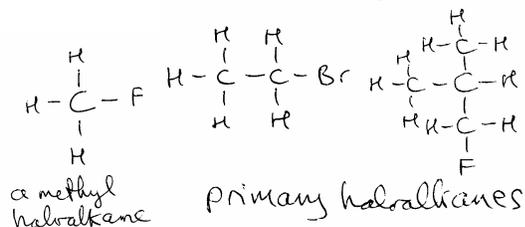
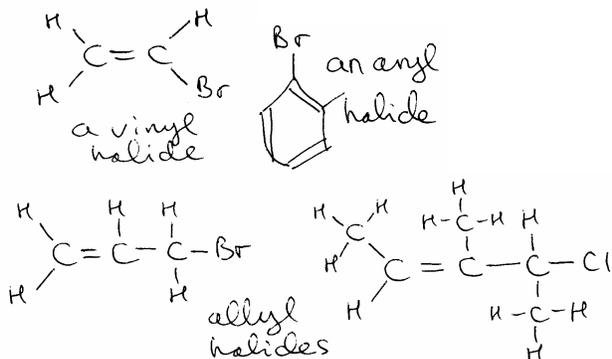


REACTIONS OF HALOALKANES - SUBSTITUTION AND ELIMINATION

Haloalkanes (also known as halogenoalkanes and alkyl halides) are organic compounds where one of the hydrogens of an alkane or cycloalkane has been replaced by a halogen atom - fluorine, chlorine, bromine or iodine. Several types may be distinguished, according to the degree of the carbon atom to which the halogen is attached.



As well as the haloalkanes there are various unsaturated types of halo-compound:

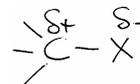


Vinyl and aryl halides are much less reactive than haloalkanes, especially to substitution. Primary allyl halides are more reactive than primary alkyl halides with regard to $\text{S}_{\text{N}}1$ and $\text{E}1$ reactions (see below).

Nucleophilic substitution

The most important reactions of haloalkanes and related compounds involve attack by an electron-rich species known as a *nucleophile*. These species have at least one lone pair of electrons and are often negatively charged. The carbon

atom which is linked to the halogen atom (described as the α -carbon) has a partial positive charge:



where the halogen atom is represented by X.

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

This mechanism gives rise to the most important reactions of the haloalkanes from the point of view of *synthesis* (making new compounds).

In the case of primary haloalkanes (and to some extent secondary haloalkanes) the nucleophile (Nu^-) attacks the carbon atom directly:



The departing halide ion is known as the *leaving group*. Note how the molecule is turned “inside out”, like an umbrella in a high wind. This is termed *inversion of configuration*.

If the nucleophile is neutral, the product is positively charged, and must generally undergo some other step of reaction to form a neutral molecule, but if the nucleophile is negatively charged (if it is a hydroxide ion, or a halide ion, for example) the product is neutral. Thus iodoethane reacts with ethanolic sodium hydroxide according to the following mechanism:



The nucleophile substitutes for the halogen atom and so the reaction is termed *nucleophilic substitution*.

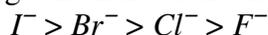
The nucleophile attacks as the leaving group leaves and so the two processes are described as *concerted*.

Since the rate-determining step (shown above) is bimolecular and the first step, the reaction is *second-order*.

$$\text{Rate} \propto [\text{Nu}^-][\text{haloalkane}]$$

It is for these reasons that the mechanism is often denoted S_N2 .

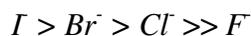
Such reactions are typical of primary haloalkanes in the presence of a strong nucleophile, such as a Cl^- , Br^- , I^- , $C\equiv N^-$ (a cyanide ion), or OH^- ¹. In protic² solvents such as water and alcohol the strength of a nucleophile³ depends on many factors, but charged nucleophiles are stronger than uncharged ones. Thus the hydroxide ion is a much stronger nucleophile than the water molecule, somewhat stronger than the bromide ion, and amongst the halide ions the order is:



In aprotic solvents⁴ (such as propanone and dimethyl sulfoxide) this order is reversed.

In general, in aprotic solvents, the strengths of nucleophiles are greatly enhanced. This is because protic solvents solvate negative ions very well whereas aprotic solvents do not. In the protic solvent the solvent molecules form a sort of protective barrier round the nucleophile, whereas in aprotic solvents this is absent and the nucleophile can attack unhindered.

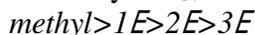
The leaving group is also important in determining the rate of an S_N2 reaction. A better leaving group gives a higher rate. Amongst the halogens the order is:

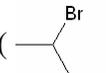


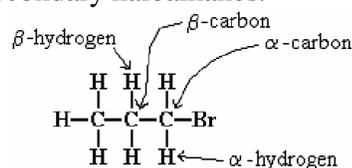
In general a weaker base is a better leaving group. S_N2 reactions of primary haloalkanes are of great utility in the production of new compounds (synthesis) since the reactions are fairly rapid in most cases and are relatively *clean*, i.e. products other than the desired one are formed only to a slight extent.

Secondary haloalkanes are much less reactive to S_N2 attack, and tertiary alkanes do not react at all in this way. This is because the alkyl groups attached to the secondary or tertiary carbon atom

hinder the approach of a nucleophile. This is known as *steric hindrance*. Thus the order of reactivity to S_N2 attack is:



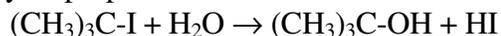
Even branching of the carbon chain at the β -carbon atom (see the diagram below) can get in the way of an approaching nucleophile and so, for example, 2-bromo-3-methylbutane () is expected to be much less reactive to S_N2 attack than 2-bromobutane (), even though they are both secondary haloalkanes.



Labelling of carbons and hydrogens relative to the halogen atom.

The S_N1 mechanism

Tertiary haloalkanes also undergo reaction under similar conditions, but it is found that the concentration of nucleophile does *not* affect the rate of the reaction. A strong nucleophile (such as the hydroxide ion) is not necessary. Weak nucleophiles, such as water and alcohol molecules, react readily with tertiary haloalkanes. Such reactions are termed *solvolysis*. A substitution product (similar to that of the S_N2 reaction above) is formed. For example in aqueous propanone, 2-iodo-2-methylpropane reacts to give a mixture of products, including 2-methyl-2-propanol:



Such reactions are not of much use in making new compounds (*synthesis*). Indeed they often make proposed reaction schemes fail. They are important from the theoretical point of view, and because they lead to the destruction of the haloalkane.

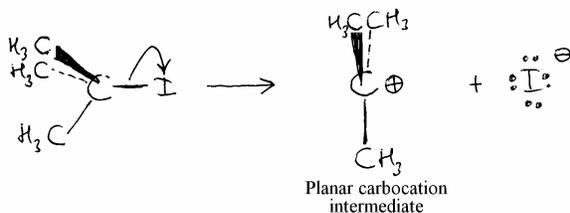
The reaction occurs in two steps, of which the first is a slow (*i.e.* rate-determining) unimolecular ionisation of the haloalkane:

¹ The negative sign is shown against the atom which normally attacks, and therefore the atom which becomes bonded to carbon.

² These are solvents which have measurable acidity.

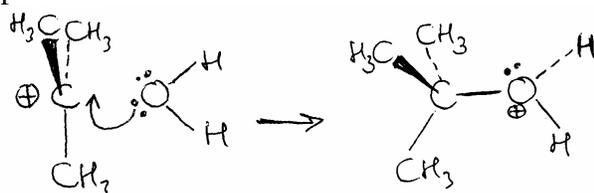
³ This is measured by the rate of S_N2 reactions involving it. A strong nucleophile gives a relatively high rate of reaction.

⁴ Solvents with no measurable acidity.

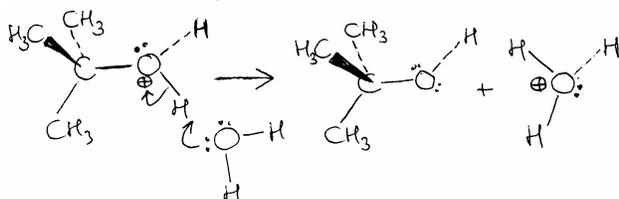


The carbocation produced is very reactive (a *reactive intermediate*) and reacts in a fast second step with any nucleophile it comes into contact with. This is usually a solvent molecule.

The carbocation can be attacked equally well from either side so that if the reactant is chiral, the product is a racemic mixture. The carbocation may rearrange, or be attacked by a variety of nucleophiles, giving a mixture of products.



In this case the initial product is an oxonium ion. This quickly loses a proton to a base (probably a solvent molecule):



Here an alcohol is formed.

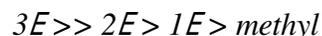
Since the rate-determining step is unimolecular and is the first step, the reaction kinetics are first order:

$$\text{Rate} \propto [\text{haloalkane}]$$

and the mechanism is referred to as S_N1 .

The S_N1 type of reaction is favoured by tertiary haloalkanes and by the absence of a strong nucleophile. Secondary haloalkanes also show this type of reaction to some extent, but it is not seen with primary and methyl haloalkanes, since their carbocations are so unstable. When primary and methyl haloalkanes undergo solvolysis it is by the S_N2 mechanism.

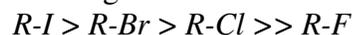
The rate of the overall reaction by the S_N1 mechanism depends on the rate of formation of the intermediate carbocation. The transition state leading to it is very like a carbocation itself. (The Hammond postulate⁵.) This means that the rate of the reaction depends greatly on the stability of the intermediate carbocation, which is the main reason why the order of reactivity with respect to this mechanism is:



This parallels the order of stability of the carbocations.

Since ions in solution, such as the carbocation intermediate, are generally stabilised by polar solvents, these solvents generally favour the S_N1 mechanism⁶. Polar solvents include water, methanol and dimethyl sulfoxide.

As with the S_N2 mechanism, a good leaving group promotes the reaction so that the order of reactivity is once again:



Elimination reactions

Another, completely different, type of reaction is available for the haloalkanes. Instead of attacking the α -carbon (see diagram on page 2), the attacking species removes a hydrogen atom from the next carbon atom in the chain (a β -carbon). The hydrogen attached to this carbon is often referred to as a β -hydrogen.

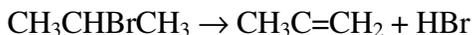
The attacking species is now described as a base (B:) rather than as a nucleophile (since it removes a proton), although good nucleophiles are often strong bases too⁷. The term *elimination* is often used to describe the loss of a small molecule by a larger one. In this case it is the loss of a molecule of a hydrogen halide (or rather a hydrogen ion

⁵ According to the Hammond postulate, the transition state is closest in structure to the species of most similar energy, so it will be similar to a reactive intermediate, such as a carbocation.

⁶ This will not be true if the leaving group is a positive ion, since the polar solvent will stabilise the reactant more than the transition state, increasing the activation energy, and leading to a lower rate of reaction.

⁷ There are exceptions: the halide ions, I^- , Br^- , and Cl^- , are good nucleophiles but very weak bases, at least in aqueous solution.

and a halide ion). The product is an alkene. For example, when 2-bromopropane is heated in sodium hydroxide dissolved in ethanol, propene is evolved:



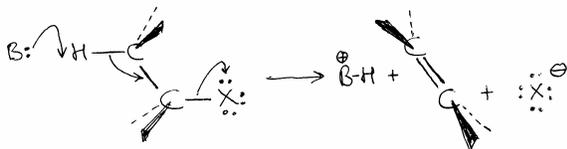
As with substitution, two mechanisms are possible, mainly depending on the stability of the relevant carbocations.

The E2 mechanism

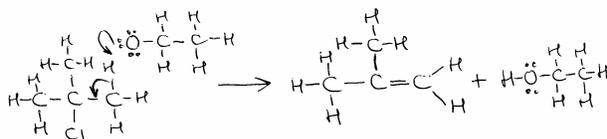
This mechanism is characterised by second order kinetics, like the S_N2 mechanism. The rate of reaction is given by

$$\text{Rate} \propto [\text{base}][\text{haloalkane}]$$

Since it is a bimolecular elimination, the mechanism is known as E2. It involves simultaneous (*concerted*) attack by the base and the loss of halogen as shown in the diagram:

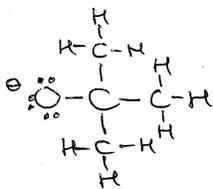


For example, heating 2-chloro-2-methylpropane with alcoholic sodium ethoxide (a very strong base) leads to the formation of 2-methyl-2-propene:



The organic product here is an alkene. As with the S_N1 and S_N2 mechanisms, the better the leaving group, the faster the reaction.

This type of reaction is favoured by a strong base, such as the ethoxide ion, and particularly by the large *t*-butoxide ion:

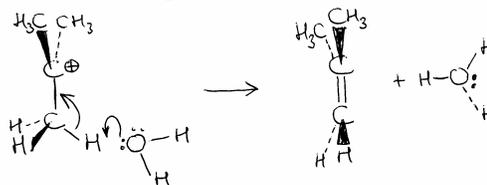


since, being bulky, it cannot approach the α-carbon closely, and so cannot easily participate in S_N2 attack.

The E2 mechanism is also favoured by a high temperature, since it has a higher activation energy than a substitution reaction. Because tertiary haloalkanes cannot undergo the S_N2 reaction their predominant mode of reaction may be an elimination reaction if conditions are favourable - e.g. the temperature is high. For the primary haloalkanes the S_N2 reaction is generally favoured since it is faster under suitable conditions.

The E1 mechanism

A second possible mechanism of elimination arises because the haloalkanes may ionise to form a carbocation as with an S_N1 reaction (see above). The carbocation formed may be attacked by a base and so undergo elimination:



The mechanism is known as E₁ since it is a 1st order elimination reaction:

$$\text{Rate} \propto [\text{haloalkane}]$$

The products of the reaction are generally the same as those for the E₂ mechanism, except that rearrangement of the carbocation may occur.

The base may well be a solvent, such as water or alcohol. This elimination step is rapid compared with the first step, but usually slower than nucleophilic attack on the carbocation, unless the temperature is high.

In conclusion, it should be emphasised that all four mechanisms always occur to some extent. Which one is observed just depends on their relative rates. When we say a mechanism "does not occur" we really mean that reaction by that mechanism is very slow compared to reaction by some other mechanism, so that it leads to the formation of only a tiny percentage of the

observed products. In many cases the rates of reaction by two or more mechanisms will be roughly comparable, so that a mixture of products will result.

The most important reaction pathways are summarised in the table below according to the type of substrate.

CH ₃ X	RCH ₂ X	$\begin{array}{c} \text{X} \\ \\ \text{R}^1-\text{C}-\text{R}^2 \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{X} \\ \\ \text{R}^1-\text{C}-\text{R}^2 \\ \\ \text{R}^3 \end{array}$
Bimolecular reactions only	Bimolecular reactions only	Bi- and uni-molecular reactions	S _N 1, E1 or E2, but not S _N 2
S _N 2 reactions only, very useful in synthesis.	Mainly S _N 2, but E2 with a hindered strong base such as <i>t</i> -butoxide. Very useful in synthesis.	Mainly S _N 2 with strong nucleophiles which are also weak bases such as I ⁻ , CN ⁻ , RCO ₂ ⁻ (carboxylate) etc. Mainly E2 with strong bases such as RO ⁻ (alkoxide). S _N 1 or E1 may occur in solvolysis, particularly E1 at high temperatures. When S _N 2 can be assured it is very useful. E2 may also be useful.	No S _N 2 reaction observed. S _N 1, and E1 at higher temperature, may be observed in solvolysis. With a strong base E2 predominates. E2 may be useful in synthesis.