Chem Factsheet

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Racemisation

To succeed in this topic you need to understand:
- organic mechanisms, particularly nucleophilic substitution
- the structures of primary, secondary and tertiary haloalkanes
- stereoisomerism, in particular optical isomers and chiral centres

After working through this Factsheet you will be able to:
- explain what racemisation means
- describe how it occurs
- explain why it can be a problem in chemical synthesis

What is racemisation?

Racemisation occurs when a single enantiomer of a chiral compound undergoes a process which turns it into a racemic mixture (Fig 2 and 3). Racemisation can happen in the course of a chemical reaction, as in Fig 2, or through physical changes such as heating or changing the pH (Fig 3).

Fig 2. Racemisation during nucleophilic substitution

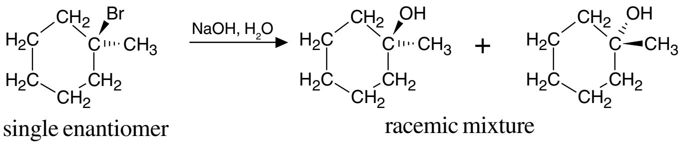
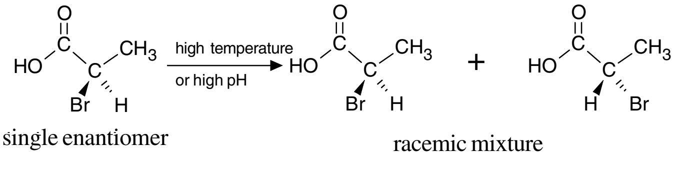


Fig 3. Racemisation through heating or pH change



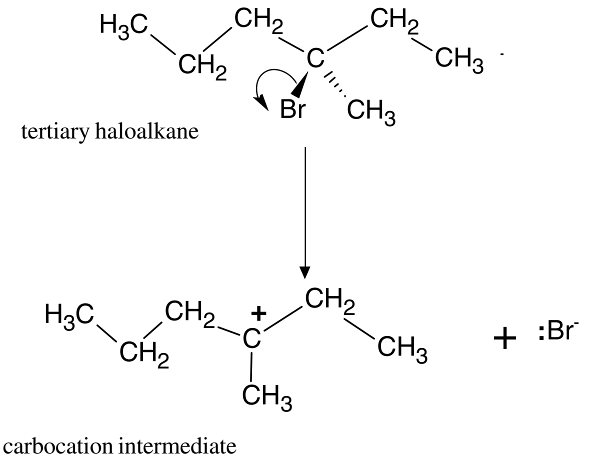
How does racemisation occur in nucleophilic substitution?

At A-level, the racemisation process that you are most likely to encounter is the nucleophilic substitution of a chiral haloalkane, which was shown in Fig 2. Whether or not this reaction results in racemisation depends on the mechanism of the reaction and the structure of the haloalkane.

Tertiary haloalkanes: the S_N1 mechanism

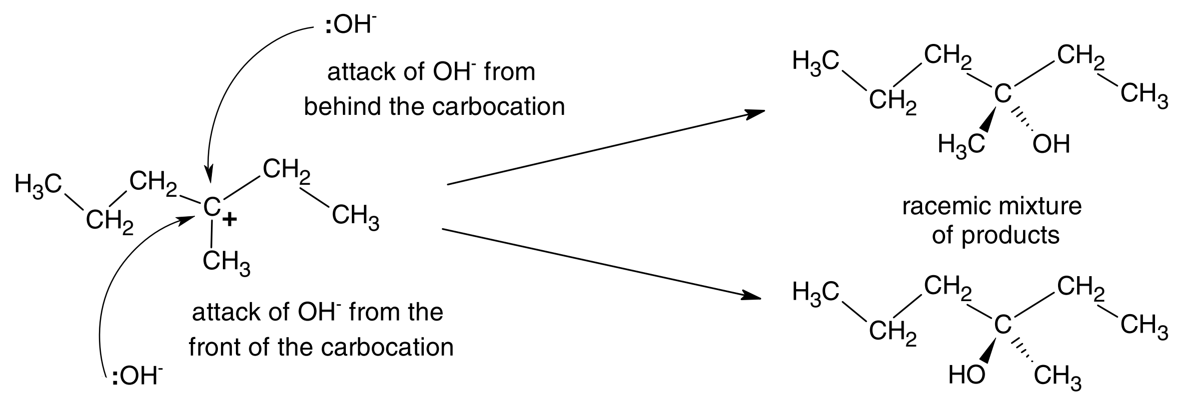
All tertiary haloalkanes react by the S_N1 mechanism, a two-step process. It is too crowded around the δ+ carbon atom for the nucleophile to attack it directly, so the first step is the breaking of the carbon-halogen bond. This produces a **carbocation intermediate** (Fig 4).

Fig 4. The first step in the S_N1 mechanism



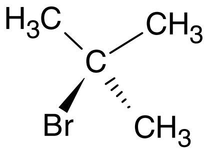
The carbocation intermediate is **planar** around the C^+, so it can be attacked by the nucleophile from either side (Fig 5). Since there is nothing to persuade the nucleophile to "choose" one side over the other, it attacks both sides equally. This produces a racemic mixture.

Fig 5. The second step in the S_N1 mechanism



Don't forget, of course, that if the tertiary haloalkane was not chiral in the first place (Fig 6, for example), then racemisation is not a possibility.

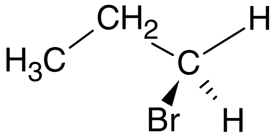
Fig 6. A non-chiral tertiary haloalkane



Primary haloalkanes: the S_N2 mechanism

Primary haloalkanes react with nucleophiles by the S_N2 mechanism (see seconadry haloalkane case). However, since primary haloalkanes do not contain an asymmetric carbon atom (Fig 7) and are not, therefore, chiral, the concept of racemisation **does not apply**.

Fig 7. Primary haloalkanes do not contain a chiral

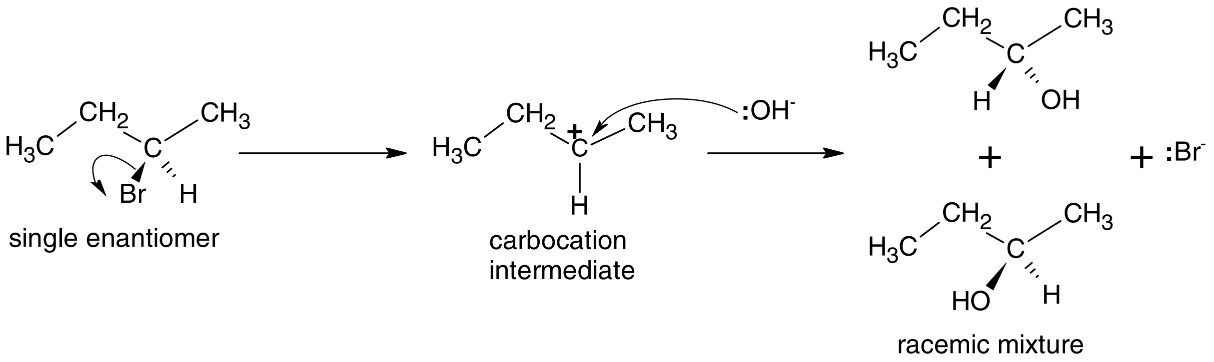


Secondary haloalkanes

Secondary haloalkanes react by either the S_N1 or the S_N2 mechanism, depending on the structure of the haloalkane and the strength of its carbon-halogen bond.

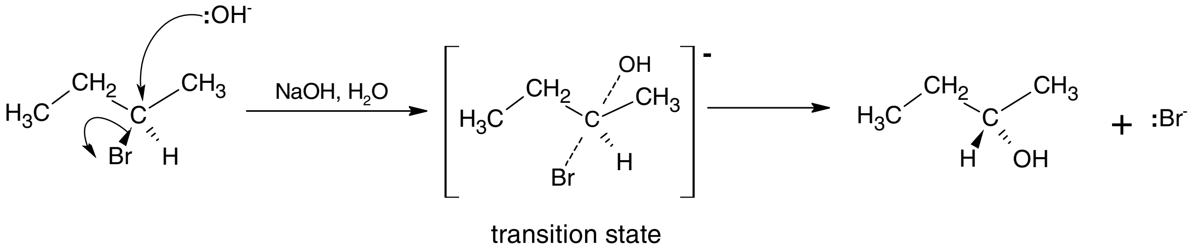
If a chiral secondary haloalkane undergoes the S_N1 mechanism, then, as with the tertiary haloalkane, it results in racemisation (Fig 8).

Fig 8. A secondary haloalkane reacting by the S_N1 mechanism



Conversely, the S_N2 mechanism does not result in racemisation (Fig 9). This is because it takes place in one step, with the asymmetric carbon atom retaining its structure. In fact, the chirality of the asymmetric carbon is **inverted**, since the hydroxide ion attacks the carbon from *behind* the bromine atom.

Fig 9. S_N2 nucleophilic substitution of 2-bromobutane



Summary

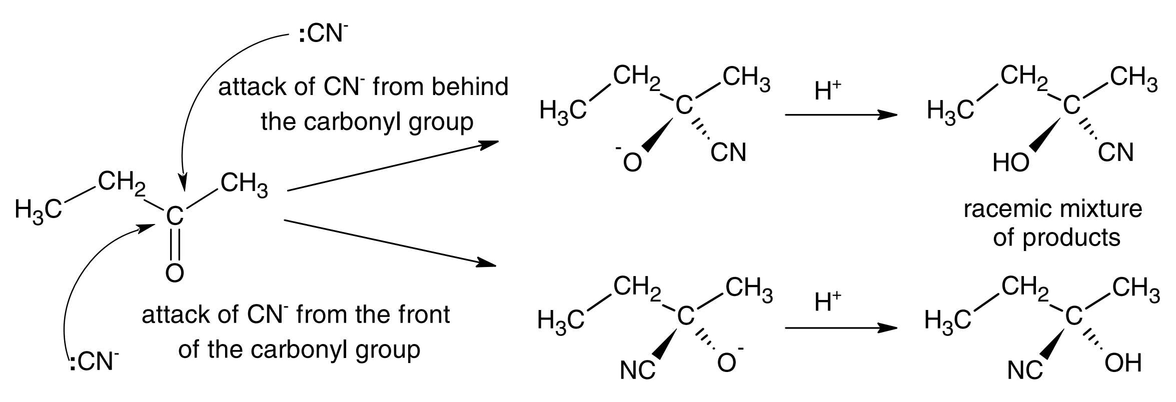
Table 1 summarises the nucleophilic substitution reactions of haloalkanes

Haloalkane	**Mechanism**	**Racemisation**
Primary	S_N2	Not possible
Secondary	S_N1 or S_N2, depending on structure	No racemisation with S_N2 Racemisation with S_N1
Tertiary	S_N1	Yes

Nucleophilic addition reactions

Another reaction that you will encounter at A-level is the addition of a nucleophile to a carbonyl compound (aldehyde or ketone) (Fig 10). Although the starting compounds are **not chiral**, the nucleophile (CN^- from HCN, in this example) can attack the **planar carbonyl group** from either face, leading to a racemic mixture of products.

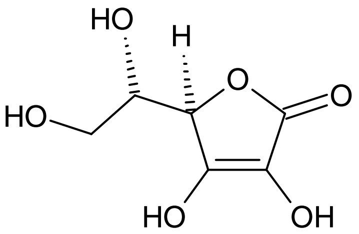
Fig 10. Nucleophilic addition of HCN to a ketone



Why is racemisation a problem?

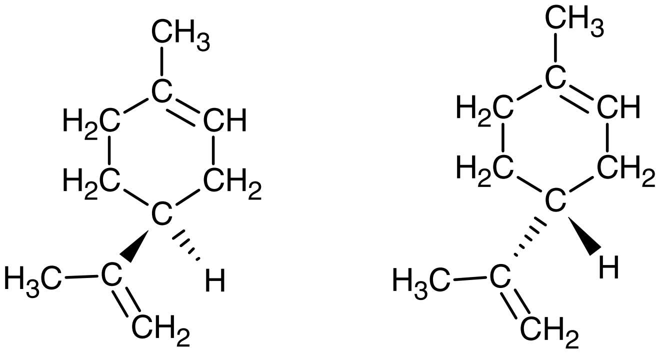
Most pharmaceutically useful compounds contain chiral centres (Fig 11)

Fig 11. Vitamin C, a pharmaceutically active compound containing two chiral centres



The chiral centres in these molecules are often vital for their function in the body, since they will help to determine the shape of the molecule and therefore determine how it interacts with enzymes. For example, Fig 12. shows the two enantiomers of limonene, a compound often found in cleaning products and cosmetics, which have very different smells.

Fig 12. The two enantiomers of limonene



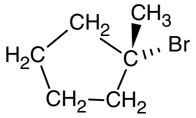
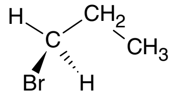
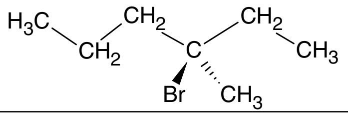
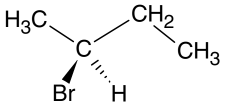
(-)-Limonene: smells of pine

(+)-Limonene: smells of orange

If any chiral centres in a pharmaceutical compound become racemised, the activity of the compound may be reduced or even changed. Synthetic organic chemists have to choose their reactions with care, therefore, to make sure that any chiral centres do not become racemised through chemical reactions, or through changes in temperature and pH.

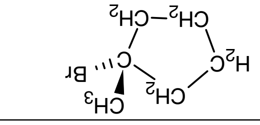
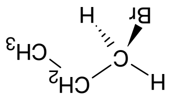
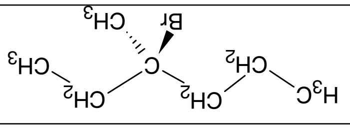
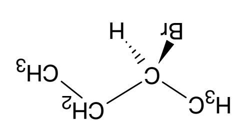
Additional Questions

1. Fill in the gaps in the table below.

	Haloalkane	Primary, secondary or tertiary?	Nucleophile	S_N1 or S_N2	Racemised?
(a)			**OH^-**		
(b)			**CN^-**		
(c)			**CN^-**		
(d)			**OH^-**		

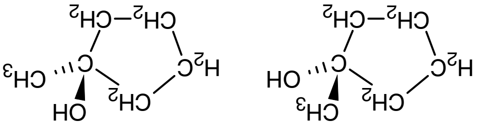
2. For each of the reactions above, draw the product(s).

Answers to Additional Questions

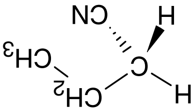
1.	Haloalkane	Primary, secondary or tertiary?	Nucleophile	S_N1 or S_N2	Racemised?
(a)		Tertiary	OH^-	S_N1	Yes
(b)		Primary	CN^-	S_N2	No, the starting material is not chiral
(c)		Tertiary	CN^-	S_N1	Yes
(d)		Secondary	OH^-	S_N1 and S_N2	Yes, by the S_N1 mechanism

2. Product(s)

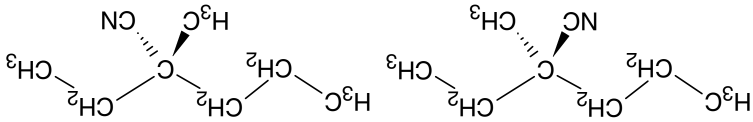
a)



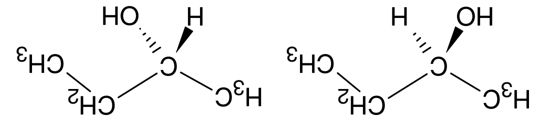
b)



c)



d)



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