Chem Factsheet

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Reactions Producing Stereoisomers

The stereochemistry of a molecule is extremely important, especially where pharmaceutical products are concerned. Thus it is safe to sell Ibruprofen as a racemate (a 50:50 mixture of enantiomers – optical isomers – see below) but the antihistamine drug Seldane cannot be sold as such because only one of the optical isomers will combat hay fever, the other enantiomer however causing potentially fatal heart conditions.

This fact sheet covers chemical reactions that lead to compounds with stereoisomers. Stereoisomers are compounds with the same structural formula (the isomers have the same sequence of bonds between atoms) but the isomers differ in the positions of the atoms in space.

Types of Stereoisomerism

(a) E/Z Isomerism

The existence of two compounds with the same structural formula but with a feature in the molecules that prevents free rotation. This allows some bonds to have a different arrangement in space. The most common example of E/Z isomerism is when two different groups are attached to each carbon atom of a C=C group which does not allow free rotation. The two different groups attached to each carbon atom do not need to be the same two groups. Free rotation is also prevented in other structures – these include ring structures and square planar arrangements.

Cis-Trans Isomerism

A special case of E/Z isomerism in which the two groups attached to each carbon atom of the C=C group are the same two groups.

(b) Optical Isomerism

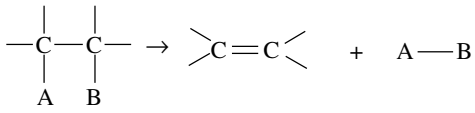
The existence of two compounds which are non-superimposable mirror images of each other. The isomers are called **optical isomers (or enantiomers)** and have a **chiral centre**. This is an **asymmetric carbon atom** which is a carbon atom bonded to four different groups (Table 1).

Reactions that can produce stereoisomers

1. Elimination Reactions to Produce E/Z isomers.

The examples of the elimination reactions which follow involve the loss of a simpler molecule from a larger molecule.

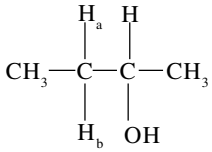
The molecule being lost is formed by the loss of atoms or groups of atoms from adjacent carbon atoms such that a double bond is formed.



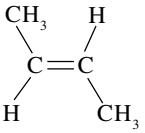
(a) Alcohols (not methanol) when heated with an acid catalyst such as conc. phosphoric(V) acid or conc. sulfuric(VI) acid can eliminate water molecules to form alkenes. Some secondary and some tertiary alcohols form E/Z isomers.

e.g. Butan-2-ol produces E- and Z- but-2-ene as well as the positional isomer but-1-ene.

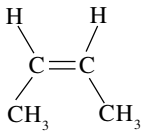
$CH_3CH_2CH(OH)CH_3 \rightarrow CH_3CH{=}CHCH_3 + H_2O$
E- or Z-but-2-ene



butan-2-ol



E-but-2-ene is made by loss H_a & OH



Z-but-2-ene is made by loss H_b & OH

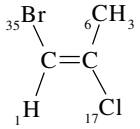
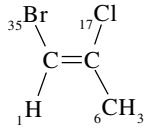
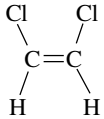
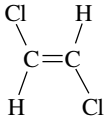
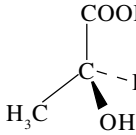
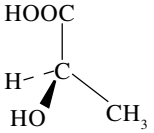
Note. There is free rotation about single C-C bonds. So either H_a or H_b can lead to either E or Z. Using H_a or H_b enables the E and Z products to be visualised. Whether H_a or H_b is lost is a matter of chance.

b) Haloalkanes (not halomethanes) similarly may eliminate hydrogen halide molecules and form alkenes when heated with concentrated KOH / NaOH in ethanol. Some secondary and some tertiary haloalkanes form E/Z isomers.

e.g. 3-bromopentane produces E- and Z-pent-2-ene.

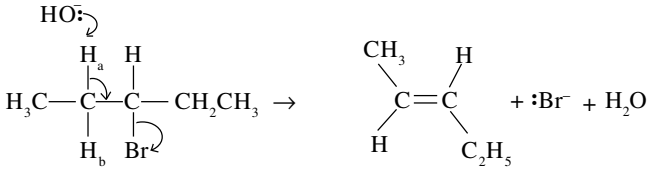
$CH_3CH_2CH(Br)CH_2CH_3 + KOH \rightarrow CH_3CH_2CH{=}CH(CH_3) + KBr + H_2O$

Table 1

E/Z Isomers			Optical isomers		
					
E-1-bromo-2-chloropropane	Z-1-bromo-2-chloropropane	Z-1,2-dichloro ethene	E-1,2-dichloro ethene	(-) lactic acid (2-hydroxy propanoic acid) In sour milk	(+) lactic acid (2-hydroxy propanoic acid) in muscles.
Cis and trans cannot be used		cis-1,2-dichloro ethene	trans-1,2-dichloro ethene		

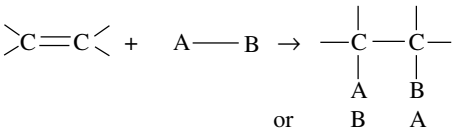
The situation is more complicated than the elimination of water from alcohols since haloalkanes molecules can undergo both elimination of the hydrogen halide and substitution of the halogen atom by an O-H group. Elimination is favoured if ethanol is the solvent for the KOH and a high temperature is used. Here, the $^-$OH acts as a base. Substitution is favoured by using water as solvent at a lower temperature. Here, the $^-$OH ion acts as a nucleophile.

Elimination Mechanism for the Formation of E-pent-2-ene



2. Electrophilic Addition Reactions of Alkenes to Produce Optical Isomers.

The examples of the addition reactions which follow involve the gain of a molecule by an alkene to form a larger molecule. "Atoms" from the molecule being gained join to adjacent carbon atoms of the double bond in one of two ways as indicated so two different compounds may be produced.



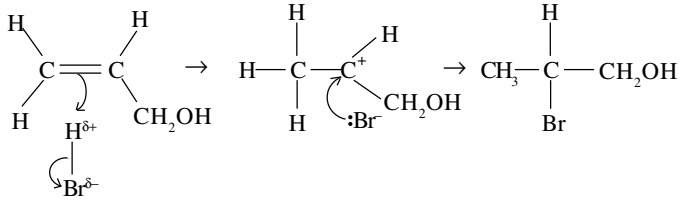
In examples where A = H, e.g. H – OSO_3H, H – OH, H – Br, since the mechanism occurs via a carbocation the isomer formed from the more stable carbocation will be present in the greater amount. Stability of carbocation: tertiary > secondary > primary.

Since carbocations are planar, tertiary carbocations with three different groups attached to the central carbon produce both optical isomers in equal amounts (a racemic mixture) since the nucleophile is equally likely to attack from above or below the plane.

e.g. Hydrogen bromide reacts with prop-2-en-1-ol to produce both enantiomers of 2-bromopropan-1-ol and a small amount of 3-bromopropan-1-ol. The secondary carbocation, $CH_3C^+HCH_2OH$ is more stable than the alternative primary carbocation, $C^+H_2CH_2CH_2OH$.

$CH_2=CHCH_2OH + HBr \rightarrow CH_3C^*H(Br)CH_2OH$

Electrophilic Addition Mechanism

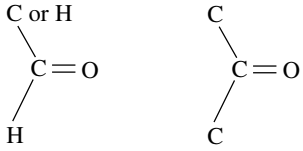


3. Nucleophilic Addition Reactions of Carbonyls to Produce Optical Isomers.

Carbonyls have a planar arrangement of atoms / groups around the carbonyl carbon atom as shown. A nucleophile is equally likely to attack the electron deficient $C^{\delta+}$ atom from above or from below this plane.

In some cases a racemic mixture will be produced as this carbon atom might be chiral if it results in having four different groups attached.

Aldehydes Ketones

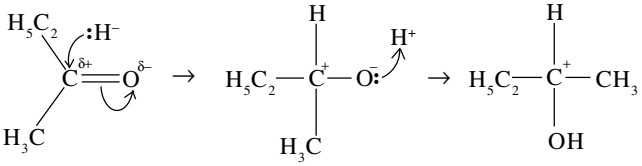


(a) Carbonyls are reduced by sodium tetrahydriodoborate(III), ($NaBH_4$), in dry ether followed by aqueous acid, to alcohols. Aldehydes do not produce enantiomers since the primary alcohols produced contain the $–CH_2OH$ and four different groups are needed. Unsymmetrical ketones produce secondary alcohols that are optical active. The nucleophile is taken to be the hydride ion, $:H^-$.

e.g. Butanone produces a racemate of butan-2-ol.
$C_2H_5CH_2COCH_3 + 2[H] \rightarrow C_2H_5CH(OH)CH_3$

Nucleophilic Addition Mechanism for Reduction of a Carbonyl

The nucleophile is shown attacking from above the plane containing >C = O.



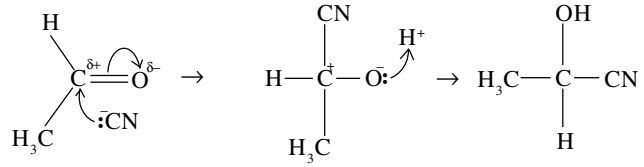
(b) Carbonyls react with hydrogen cyanide at pH about 8 or KCN or NaCN in dilute acid to produce hydroxynitriles. Aldehydes (except methanal) and unsymmetrical ketones always produce enantiomers.

e.g. Ethanal reacts to produce a racemate of 2-hydroxypropanenitrile

$CH_3CHO + HCN \rightarrow CH_3CH(OH)CN$

Nucleophilic Addition Mechanism using KCN in Dilute Acid

The nucleophile is shown attacking from below the plane containing >C = O.



4. Nucleophilic Substitution Reactions of Haloalkanes, (RX), to Produce Enantiomers

Haloalkanes (halogenoalkanes), react with nucleophiles, such a NH_3, $^-$OH or $^-$CN. (Nu = nucleophile)

(a) Primary Haloalkanes

Rate studies show that for the rate equation is: rate = k[RX][Nu]

In this mechanism the nucleophile bonds to the electron deficient carbon atom from the opposite side to the halogen and at the same time the halide ion is released in a single rate determining step, (S_N2). If the nucleophile is reacting with an optically active reactant this mechanism produces a single optical isomer of opposite rotation of plane polarised light; it does not produce a racemate.

(b) Tertiary Haloalkanes

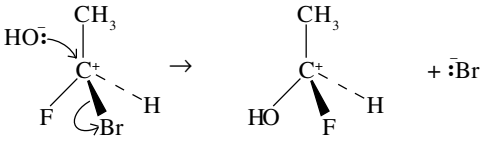
Rate studies show that the rate equation is: rate = k[RX].

In this mechanism the rate determining step is the breaking of the carbon-halogen bond to produce a tertiary planar carbocation (the most stable type) and a halide ion. The carbocation and $^{-}$OH rapidly combine to produce the product. (S_N1). If the nucleophile is reacting with an optically active molecule this mechanism produces a racemate since the nucleophile can attack the planar carbocation from above or below the plane. In the example below the $^{-}$OH is shown attacking from above the plane.

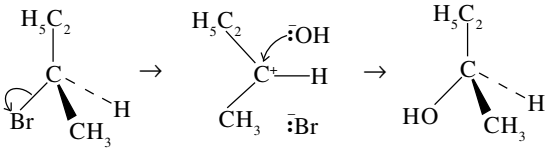
Thus it can be possible to deduce the mechanism and hence the rate equation without performing rate experiments by measuring the optical activity of the product.

When 1-bromo-1-fluoroethane is hydrolysed the product has the opposite rotational affect on plane polarised light showing that the mechanism is S_N2 and the rate equation is rate = k[RX][$^{-}$OH]. In contrast when 2-bromobutane is hydrolysed a racemate is produced showing that the mechanism is S_N1 and the rate equation is rate = k[RX].

Hydrolysis of 1-Bromo-1-Fluoroethane by S_N2



Hydrolysis of 2-Bromobutane by S_N1



5. The Synthesis of Pharmaceuticals involving Planar Intermediates.

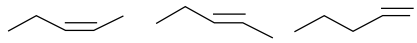
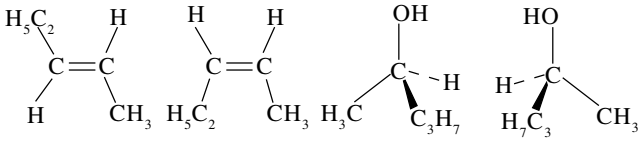
A laboratory chemical synthesis of a drug that produces a mixture of both optical isomers (i.e. there is a step in the synthesis involving a planar intermediate which can be attacked from above or below the plane) must be followed by a costly and difficult separation of isomers if one of the enantiomers has harmful side effects. However if a biological synthesis is available in which the planer intermediate binds to an appropriate enzyme thus allowing attack only from above then only the desired enantiomer can be produced. The enzyme is said to be **stereoselective**. However using enzymes is both costly and time consuming. This is greatly offset by much improved pharmacological activity and a much reduced possibility of side effects – a factor not lost on a company which can be open to litigation!

Acknowledgements: *This Factsheet was researched and written by Bob Adam.* ***Curriculum Press, Bank House, 105 King Street, Wellington, Shropshire, TF1 1NU. ChemistryFactsheets*** *may be copied free of charge by teaching staff or students, provided that their school is a registered subscriber. No part of these Factsheets may be reproduced, stored in a retrieval system, or transmitted, in any other form or by any other means, without the prior permission of the publisher.* ***ISSN 1351-5136***

Practice Questions.

1. Draw skeletal formulas and name each of the isomers produced when pentan-2-ol is dehydrated. State the type of **structural isomerism** being displayed and identify a suitable reagent for the dehydration.
2. Hydrogen chloride can be eliminated from the isomers of C_4H_9Cl using a hot concentrated solution of KOH in ethanol.
   (a) Identify which isomers will not produce E/Z stereoisomers.
   (b) Name two stereoisomers that are produced.
   (c) Write the mechanism for the formation of one of these isomers.
3. (a) Write the equation for the reaction of phenylethanone with hydrogen cyanide.
   (b) Write the mechanism for this reaction and explain why a racemic mixture is formed.
4. 2-iodo-pentane can react with sodium hydroxide to produces various compounds.
   (a) Draw all pairs of compounds that are stereoisomers such that the diagrams show the spatial arrangement of the groups of atoms in the molecules.
   (b) Name the types of reaction that produce each type of stereoisomer and state the role of the hydroxide ion in each of the mechanisms.
   (c) What conditions favour each type of stereoisomer to be formed?
5. When hydrogen iodide reacts with 2-methylbut-2-ene there is only a trace of an optical compound produced. What is this optical active compound and explain why only a trace is produced.

Answers

1. 
   Z-pent-2-ene E-pent-2-ene pent-1-ene
   Reagent e.g. conc. H_2SO_4 Type: positional isomerism
2. (a) $CH_3CH_2CH_2CH_2Cl$, $CH_3CH(CH_3)CH_2Cl$ and $C(CH_3)_3Cl$.
   (b) E- and Z-but-2-ene.
   (c) See 1 (b) but use 2-chlorobutane.
3. (a) $C_6H_5COCH_3 + HCN \rightarrow C_6H_5C(CN)(OH)CH_3$.
   (b) Mechanism: see case 3 (b) replacing ethanal with phenylethanone. The carbonyl group and the two attached carbon atoms are in the same plane. The cyanide ion has equal chance of attacking the $C^{\delta+}$ from above or below this plane so equal moles of both enantiomers are formed so the product is optically inactive, i.e. a racemic mixture.
4. (a) 
   (b) E/Z isomers: elimination reaction; OH^- is a base. Optical isomers: substitution reaction: OH^- is a nucleophile.
   (c) Conditions: see case 1 (b).
5. 2-iodo-3-methylbutane.
   The secondary carbocation, $(CH_3)_2CH\text{-}C^+H(CH_3)$ is much less energetically stable that the tertiary carbocation $(CH_3)_2C^+\text{-}CH_2CH_3$.