ORGANIC SYNTHESIS

Background

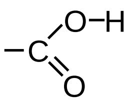
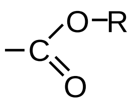
Chemical synthesis involves the preparation of new compounds from others. Many industrial processes involve a multi stage process where functional groups are converted into other functional groups.

When planning a synthetic route, chemists must consider...

- the reagents required to convert one functional group into another
- the presence of other functional groups - *in case also they react*
- the conditions required - *temperature, pressure, catalyst*
- the rate of the reaction
- the yield - *especially important for equilibrium reactions*
- atom economy
- safety - *toxicity and flammability of reactants and products*
- financial economy - *cost of chemicals, demand for product*
- problems of purification
- possibility of optically active products

Functional groups

Common functional groups found in organic molecules include...

C = C	alkene	O − H	hydroxyl	*(alcohols)*
C − C*l*	halogenoalkane	C = O	carbonyl	(*aldehydes & ketones*)
C − NH_2	amine	−C ≡ N	nitrile	
	carboxylic acid		ester	

Q.1 *State which of the functional groups listed above react with...*

a) HBr

b) H_2

c) OH^-

d) CN^-

e) H^- *(as in* $NaBH_4$ *or* $LiAlH_4$*)*

f) [O] (as in acidified $K_2Cr_2O_7$*)*

e) $H^+(aq)$

CHIRAL SYNTHESIS

Rationale Pharmaceutical synthesis often requires the production of just one optical isomer. This is because...

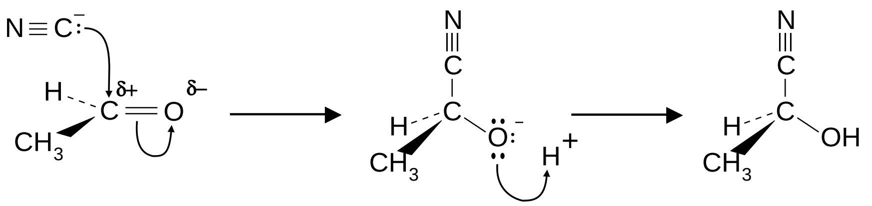
- one optical isomer usually works better than the other
- in some cases the other optical isomer may cause dangerous side effects
- laboratory reactions usually produce both optical isomers
- naturally occurring reactions usually produce just one optical isomer

Example Aldehydes and ketones undergo nucleophilic addition with cyanide (nitrile) ions

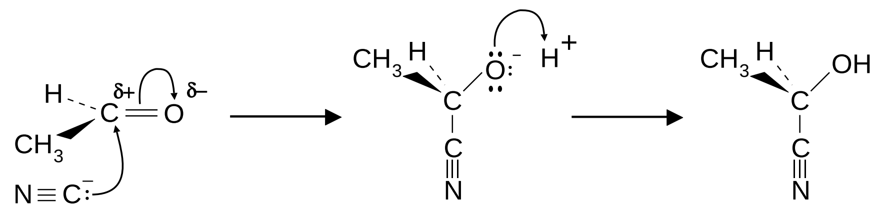
Example **CH_3CHO + HCN ——> $CH_3CH(OH)CN$**
ethanal *2-hydroxypropanenitrile*

Problem
- the C=O bond is planar
- the nucleophile can attack from above and below
- there is an equal chance of each possibility
- a mixture of optically active isomers is produced
- only occurs if different groups are attached to the carbonyl group

CN^- attacks from above



CN^- attacks from below



Consequences
- isomers have to be separated to obtain the one that is effective
- separation can be expensive and complicated
- non-separation could lead to... **larger doses** having to be given
  possible dangerous **side effects**
  possible **legal action**

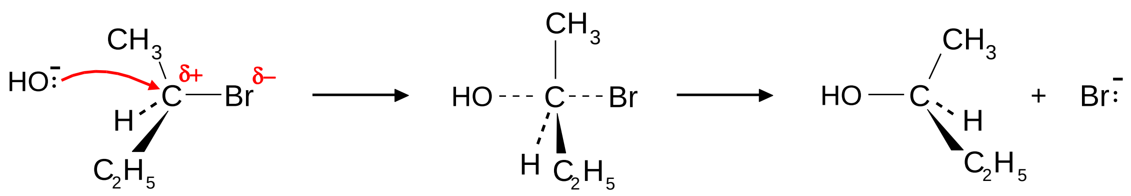
Solution Use
- natural chiral molecules as starting materials
- reactions which give a specific isomer
- catalysts which give a specific isomer
- enzymes or bacteria which are stereoselective

Other examples

Nucleophilic substitution of halogenoalkanes

There are two possible mechanisms

S_N2



The nucleophile attacks the δ+ end of the C-Br polar bond.

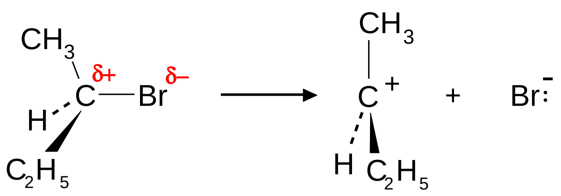
As the C-Br bond breaks, a C-OH bond forms.

The Br⁻ ion leaves and the OH group repels the other groups.

This produces just one optical isomer with reversed optical activity

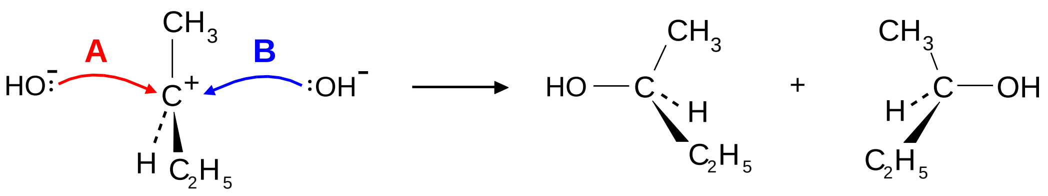
It is called S_N2 because two species are involved in the rate determining step.

S_N1



The initial step involves **heterolytic fission** of the C-Br bond.

A planar carbocation is formed.



A **B**

The nucleophile can now attack from both sides.

A racemic mixture is formed. There is an equal chance of each possibility.

This produces a racemic mixture of two optical isomers

It is called S_N1 because just one species is involved in the rate determining step.

> **S_N1 is the more likely mechanism if bulky groups are attached to the C-Br. The incoming nucleophile will have easier access.**

Q.2 *Which of the following produce a mixture of alcohols when treated with $OH^-(aq)$?*

- $C_2H_5CHBrCH_3$
- *2-chloropropane*
- $C_2H_5CHBr\ C_2H_5$

Q.3 *State the reagents and conditions needed to carry out the following reaction sequences. Consider if any of the transformations give rise to isomeric (especially optical) products.*

(i) $CH_3CH{=}CH_2$ —**A**—> $CH_3CHBrCH_3$ —**B**—> $CH_3CH(OH)CH_3$ —**C**—> CH_3COCH_3

Step **A**

Step **B**

Step **C**

(ii) $CH_3CH{=}CH_2$ —**D**—> $CH_3CH_2CH_2Br$ —**E**—> $CH_3CH_2CH_2OH$ —**F**—> CH_3CH_2CHO

—**G**—> CH_3CH_2COOH —**H**—> $CH_3CH_2COOC_2H_5$

Step **D**

Step **E**

Step **F**

Step **G**

Step **H**

(iii) C_6H_6 —**J**—> $C_6H_5NO_2$ —**K**—> $C_6H_5NH_2$ —**L**—> $C_6H_5N_2^+Cl^-$ —**M**—> C_6H_5OH

Step **J**

Step **K**

Step **L**

Step **M**

(iv) $CH_3CH_2CHBrCH_3$ —**N**—> $CH_3CH_2CH(CN)CH_3$

Step **N**

(v) CH_3CH_2CHO —**P**—> $CH_3CH_2CH(OH)CN$ —**Q**—> $CH_3CH_2CH(OH)COOH$

Step **P**

Step **Q**

(vi) $CH_2{=}CHCHO$ —**R**—> $CH_2{=}CHCH_2OH$

Step **R**