Separation of Stereoisomers

Separation of Stereoisomers

Resolution of Racemic Mixtures

The separation of a racemic mixture into the individual enantiomerically pure enantiomers is called resolution.

Since enantiomers have identical physical properties, such as solubility, boiling point and melting point, they can not be resolved by common physical techniques such as direct crystallization, distillation or basic chromatography.

Since diastereomers have different physical properties, they can be separated by conventional physical techniques. This difference is exploited in resolution by placing a mixture in a chiral environment to initiate diastereomeric interactions. All methods for separating or characterizing enantiomers are based on this principle.

Separation of Stereoisomers

Resolution of Racemic Mixtures

The interaction that creates diastereomers out of enantiomers need not be covalent. Weaker, non-covalent complexes are often discriminating enough to allow separation of enantiomers.

The most classical way to separate enantiomeric amines is to form salts with a chiral acid and use crystallization to separate the diastereomeric salts.

There are many variations on this theme, and this traditional approach is still very commonly used, especially for large scale, industrial applications.

Methods of Resolving Racemic Mixtures

Summary

There are four general strategies that take advantage of the formation of diastereomeric interactions to separate a racemic mixture.

These are:

(a) Formation of diastereomeric salts with an enantiopure resolving agent.

(b) Formation of diastereomeric compounds with an enantiopure resolving agent.

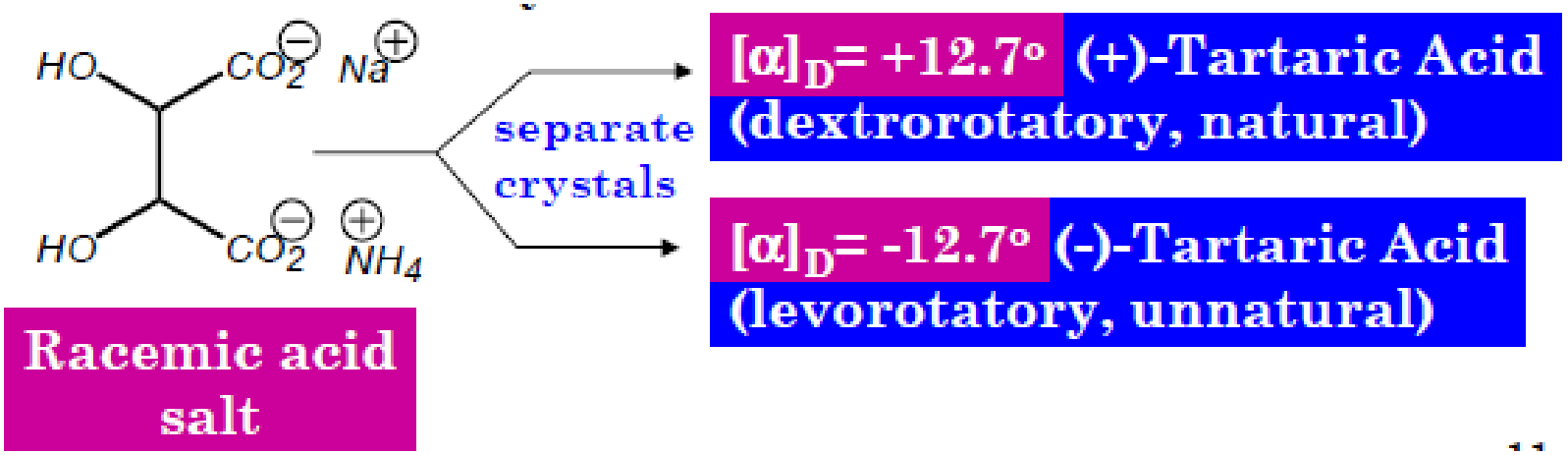
(c) Use of chiral stationary phases for chromatographic resolution of racemic mixtures.

(d) Enzymatic resolution.

Resolution of Racemic Mixtures

Diastereomeric Salt Formation

Louis Pasteur, in his pioneering work, was able to isolate the stereoisomers of tartaric acid because they crystallize from solution as crystals with differing symmetry and shape.

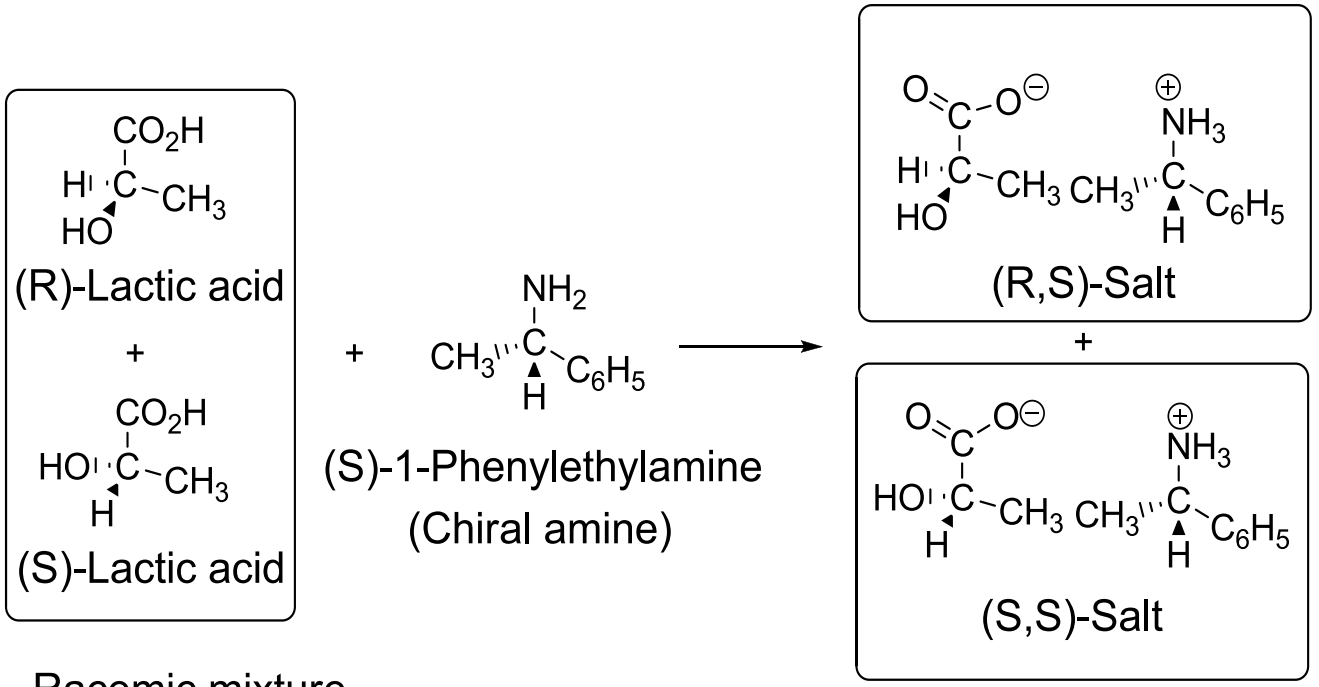


But such cases are very rare. This was a very lucky outcome that transformed the study of stereochemistry in a profound way.

Resolution of Racemic Mixtures

Diastereomeric Salt Formation

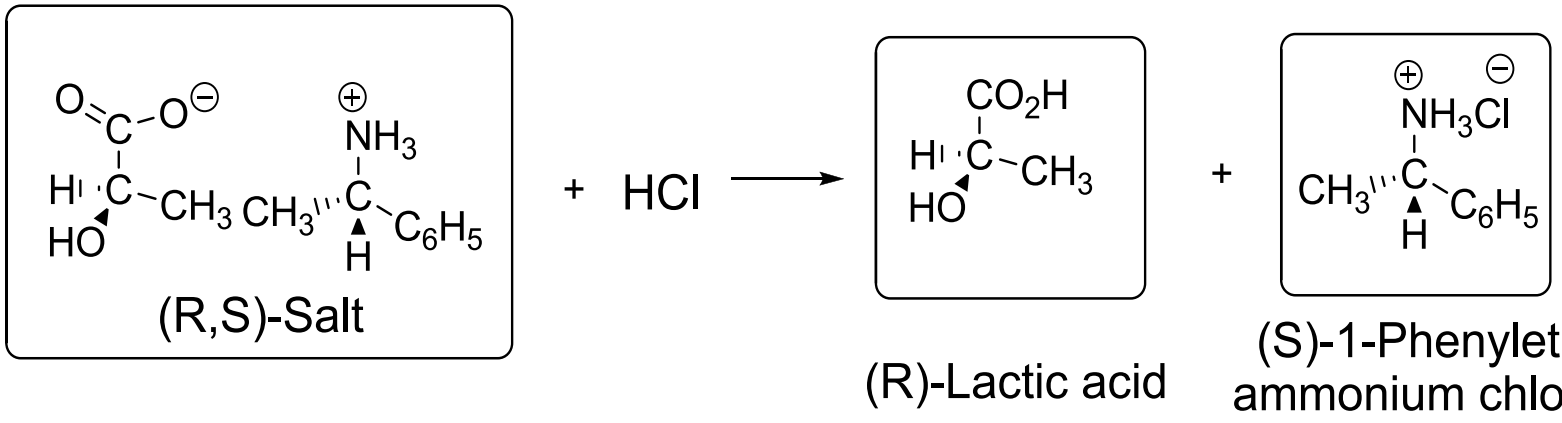
(S)-1-Phenylethylamine combines with a racemic mixture of lactic acid to form diastereomeric salts. The diastereomers are separated by fractional crystallization.



Resolution of Racemic Mixtures

Diastereomeric Salt Formation

After the separation process, each of the diastereomers is subsequently treated with a strong acid such as hydrochloric acid to regenerate the corresponding enantiomer of lactic acid.



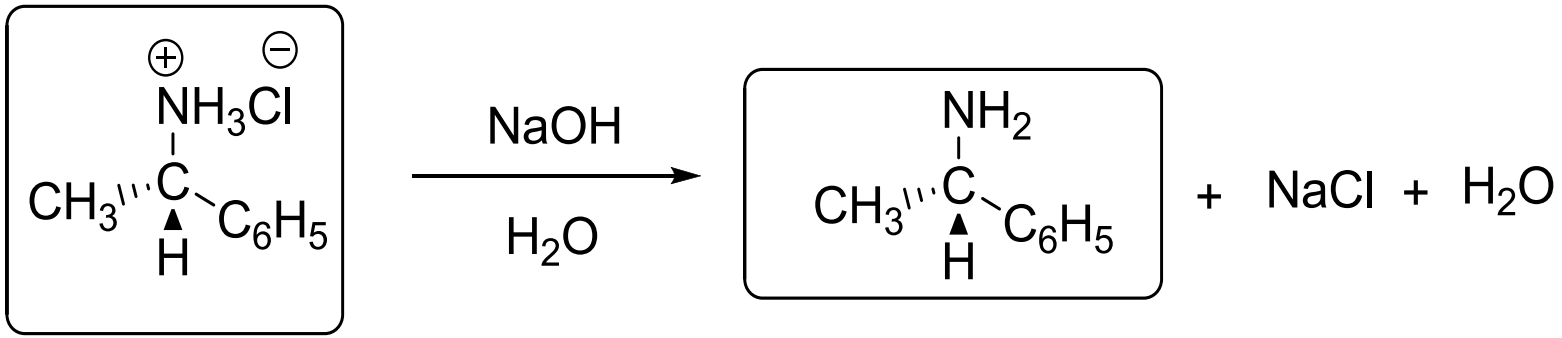
Note that the lactic acid would be soluble in the organic layer, while the ammonium salt would be in the water layer.

Resolution of Racemic Mixtures

Diastereomeric Salt Formation

Since enantiomerically pure compounds are very expensive, it is usually necessary to recover and reuse the chiral amine.

This is achieved by treating the (S)-1-phenylethyl ammonium chloride salt with a base such as sodium hydroxide to regenerate and recover the chiral amine.



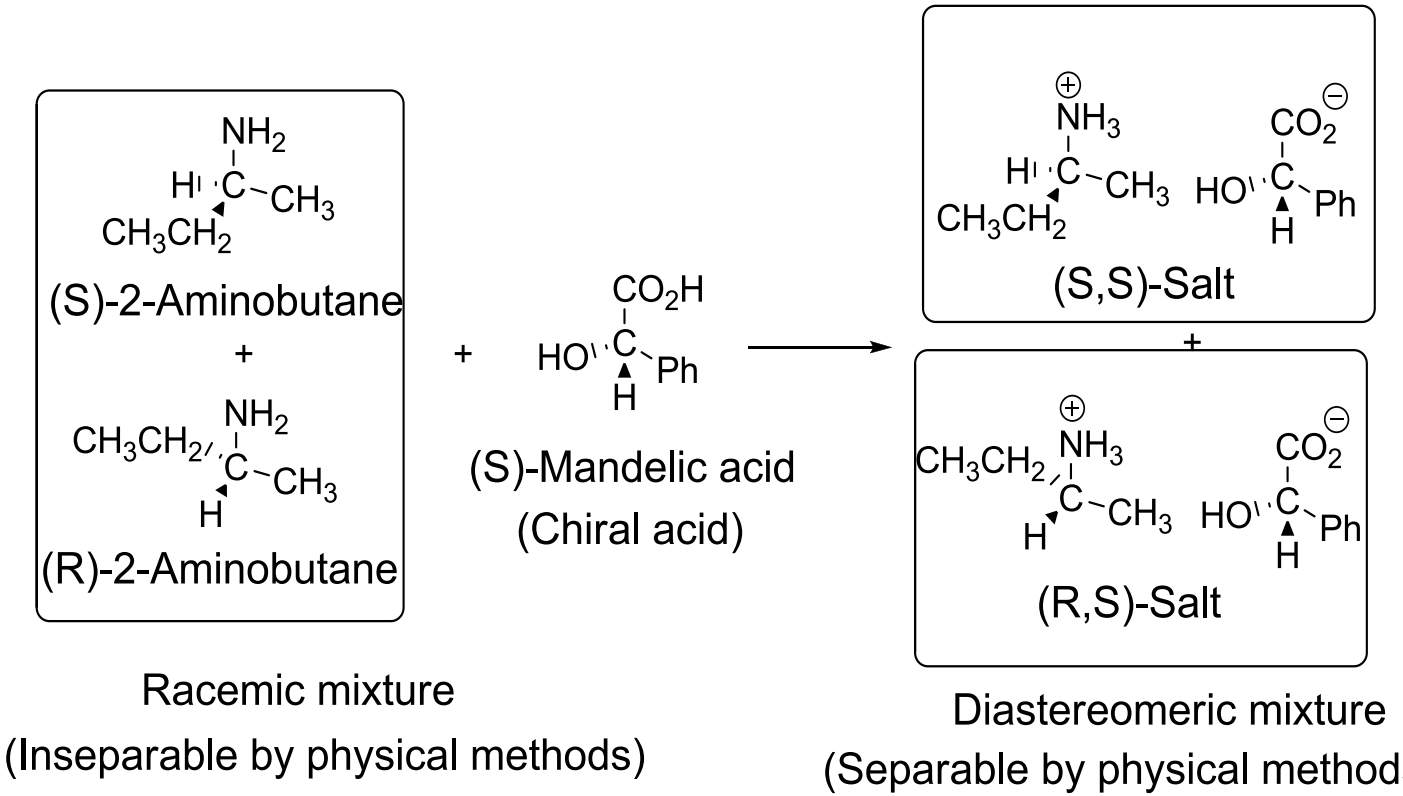
(S)-1-Phenylethyl ammonium chloride

(S)-1-Phenylethylamine (Chiral amine)

Resolution of Racemic Mixtures

Diastereomeric Salt of Mandelic Acid

The natural enantiomer, (S)-(+)-mandelic acid, combines with a racemic mixture of 2-aminobutane to form diastereomeric salts.



Resolution of Racemic Mixtures

Formation of Diastereomeric Compounds

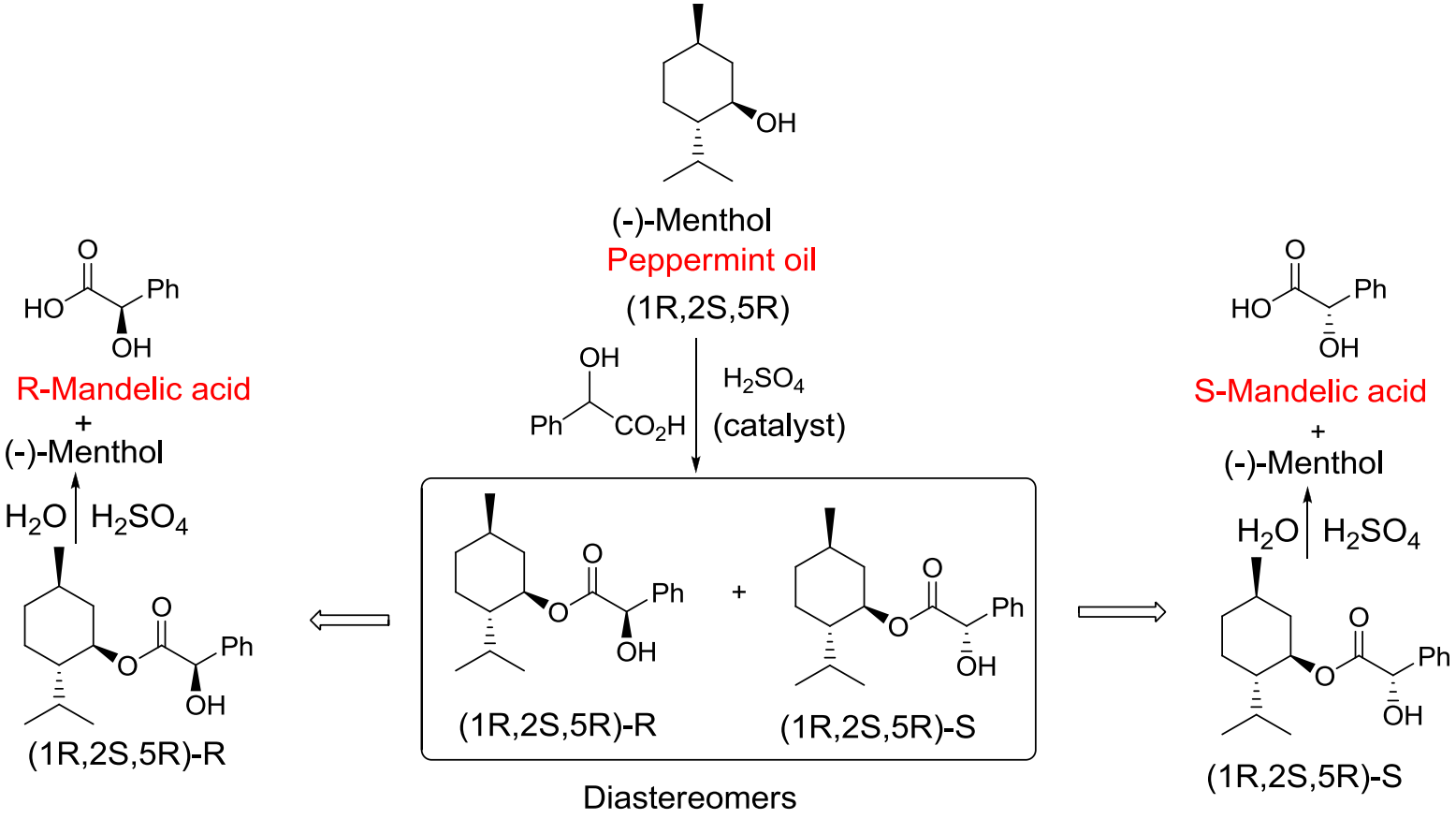
An equally effective strategy of resolving racemic mixtures is by reacting with an enantiopure resolving agent leading to formation of covalently bonded diastereomeric compounds.

After separating the diastereomers through conventional techniques, such as gas or liquid chromatography, the resolving agent is recovered by cleaving the covalent bond formed in the earlier step.

Resolution of Racemic Mixtures

Formation of Diastereomeric Esters of Menthol

(-)-Menthol, a chief component of peppermint oil, can be readily used as a chiral resolving agent.



Resolution of Racemic Mixtures

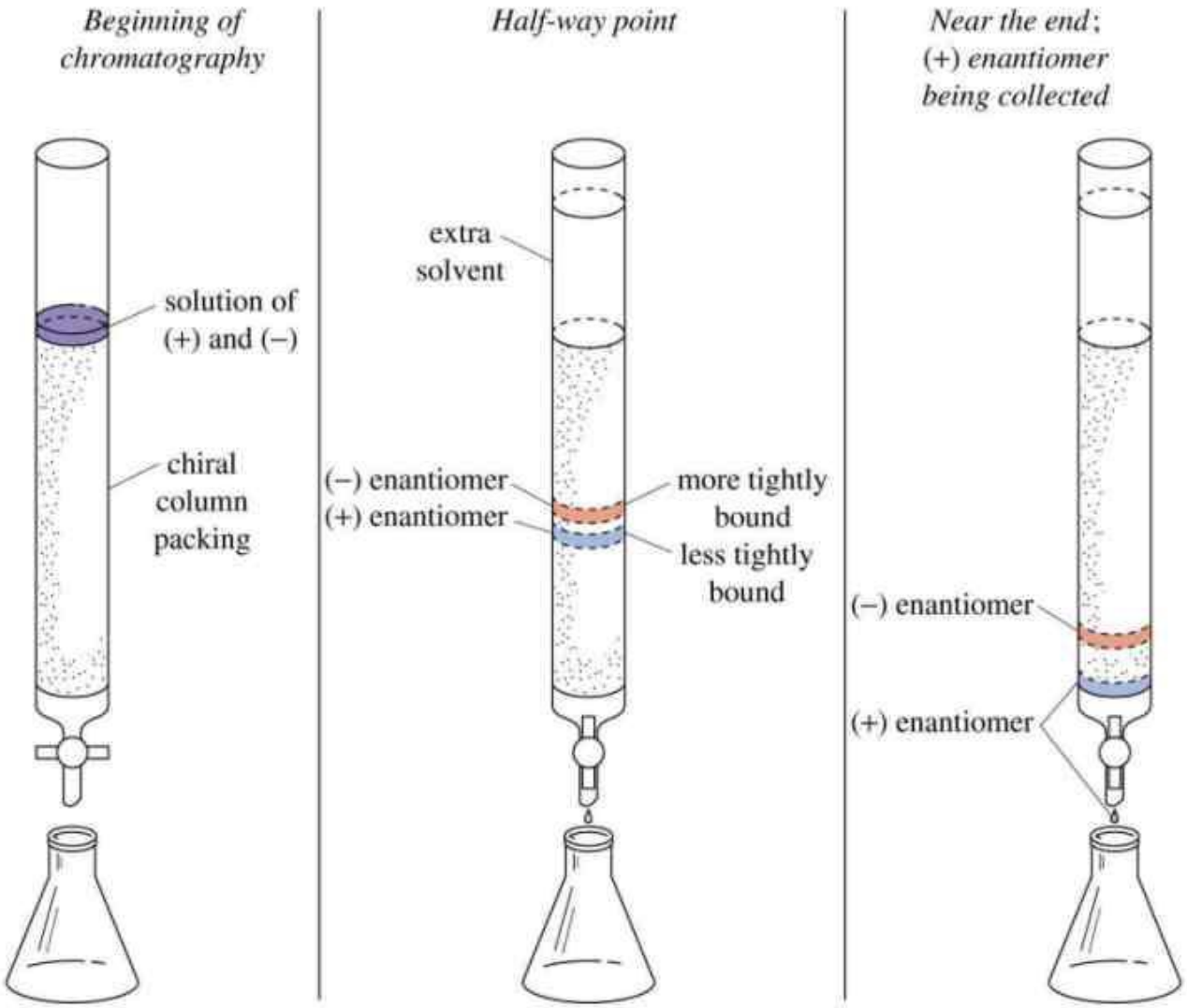
Chiral Stationary Phases

Another common method of resolving a racemic mixture is through the use of chromatography on chiral stationary phases. These are incorporated in gas chromatography and liquid chromatography systems.

In the resolution of racemic 2-aminobutane on a chromatographic system in which an enantiomer of mandelic acid is attached to a stationary phase, new, transient, diastereomeric interactions between 2-aminobutane and the stationary phase lead to different retention times and thus to separation of the enantiomers.

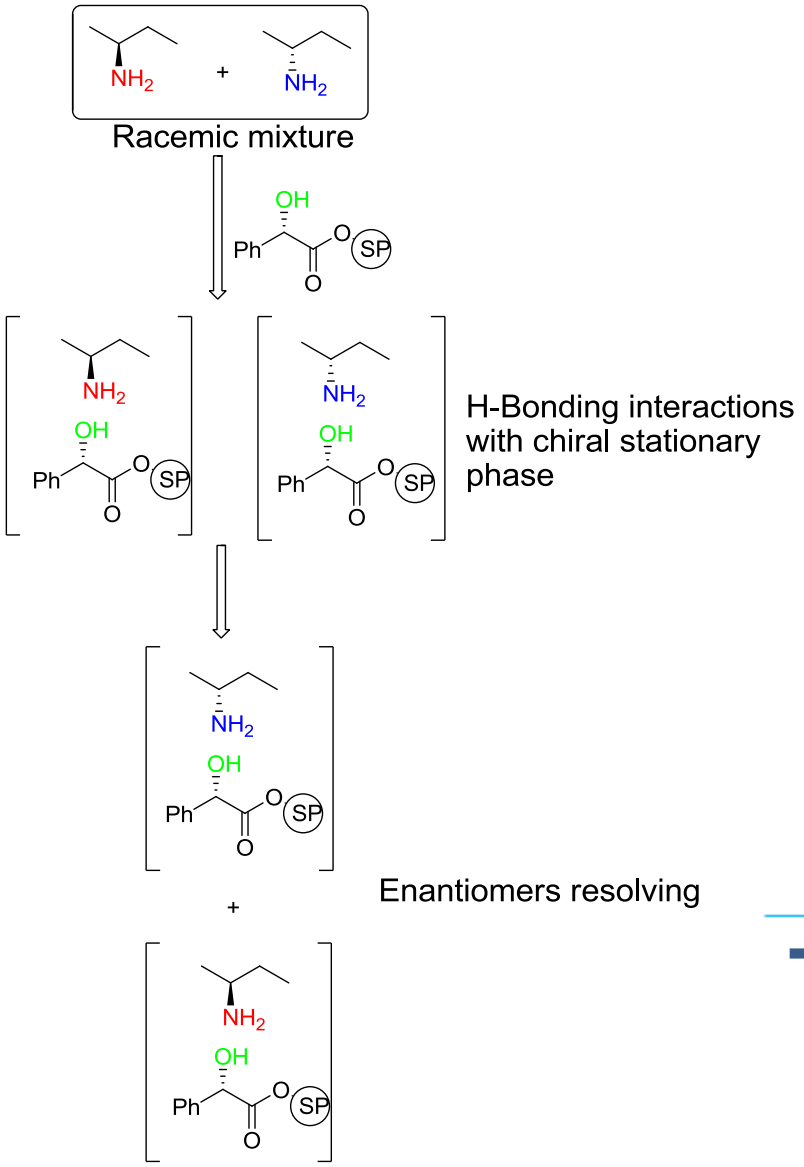
Resolution of Racemic Mixtures

Chromatography on Chiral Stationary Phases

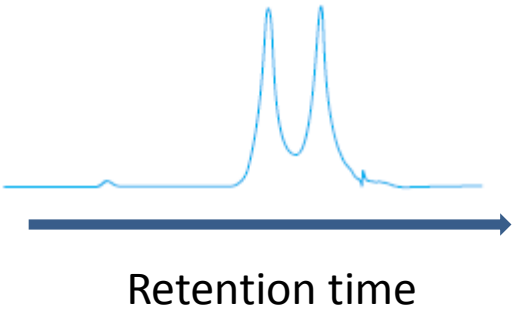


Resolution of Racemic Mixtures

Chiral Stationary Phases



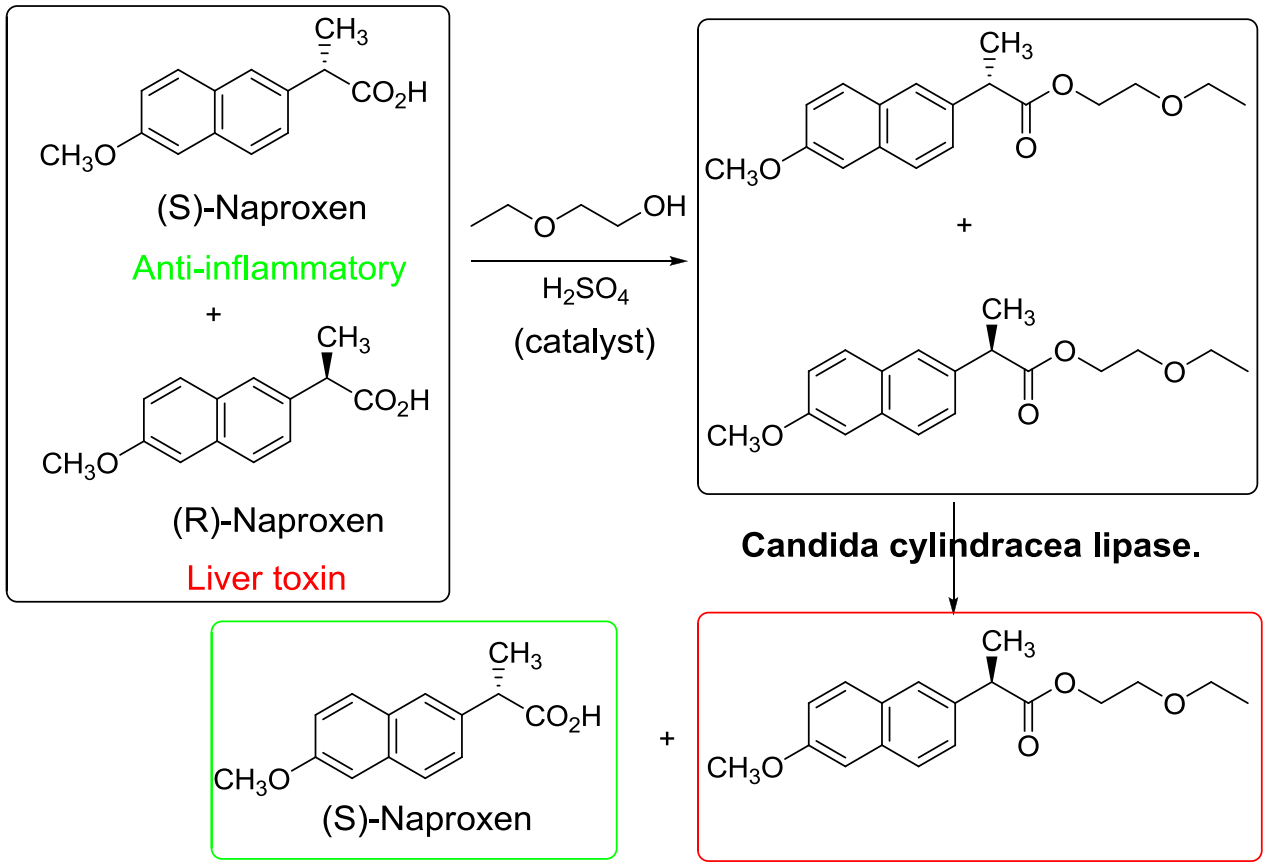
Chiral chromatography exploits the development of transient, diastereomeric interactions between the enantiomers and the chiral stationary phase



Resolution of Racemic Mixtures

Enzymatic Resolution

In enzymatic or kinetic resolution, there is preferential reaction of just one enantiomer resulting in an enantioenriched sample of the less reactive enantiomer.



Resolution of Racemic Mixtures

Enantiomeric Excess

Enantiomeric excess (optical purity) is a measure of how pure an enantiomer is (i.e. how much one enantiomer is present in excess of the racemic mixture).

It is denoted by the symbol *ee.*

ee= % of one enantiomer -% of the other enantiomer.

Consider the following example:

If a mixture contains 95% of one enantiomer and 5% of the other, the enantiomeric excess is 95% -5% = 90%.

In essence, there is a 90% excess of one enantiomer over the racemic mixture.

Resolution of Racemic Mixtures

Calculating Enantiomeric Excess (Assignment)

The enantiomeric excess can also be calculated if the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer are known.

ee= ([α] mixture/[α] pure enantiomer) x 100.

A sample of mandelic acid analysed in a polarimeter gave an observed specific rotation of -75 degrees. If the specific rotation of (S)-mandelic acid is +154 degrees;

(i) Which enantiomer is in excess? (R or S)

(ii) Calculate the enantiomeric excess of the mixture.

(iii) Calculate the percentage of each enantiomer in the mixture.

Show your work and explain how to obtain each value

Resolution of Racemic Mixtures

Calculating Enantiomeric Excess (Answer)

If (S)-mandelic acid has a specific rotation of +154 degrees then its enantiomer has a specific rotation of -154 degrees.

As the specific rotation of the mixture is negative, (R)-mandelic acid is the dominant one.

$$ee = [\alpha]obs / [\alpha]max \times 100$$

where ee is the enantiomeric excess and [ ] is the modulus sign that makes negative values positive

$$ee = 75 / 154 \times 100 = 48.7\ \%$$

Let the % of R-enantiomer be R, that of the S-enantiomer be S, then R + S = 100, while R – S = enantiomeric excess.

R – (100 – R) = enantiomeric excess = 48.7

2R – 100 = 48.7, which implies that 2R = 148.7

The major R-enantiomer = 74.4%

The minor S-enantiomer = (100 – R) = 25.6%