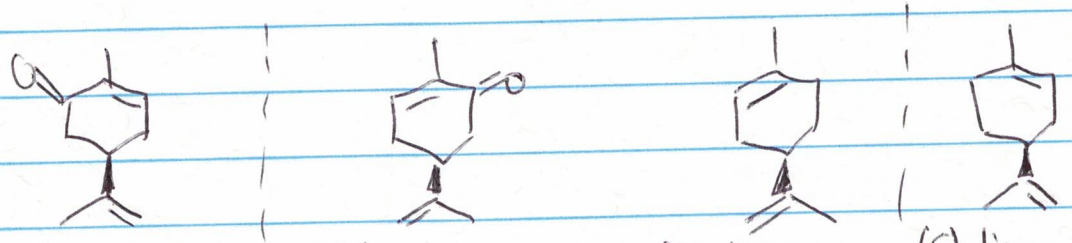
Lecture XIV: Chemical Properties of Enantiomers. Separation of Enantiomers

02-17-2020

Enantiomers interact equally well with other achiral substances. But other chiral reagents lead to the formation of diastereoisomers — either permant or temporary ones — and in that case, preferences can be observed.

Such diastereomer discrimination is observed in cases where NMR spectra of enantiomers look differently in a chiral solvent, when their solubility varies in a chiral solvent, during HPLC or GC chromatography on a chiral support, or in chemical rxns. These interactions are also prevalent in biological systems.



(R)-carvone — Spearmint smell

(S)-carvone — caraway seed smell

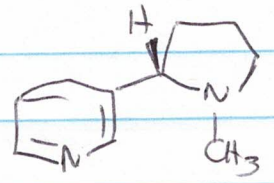
(R)-limonene — orange smell

(S)-limonene — lemon smell

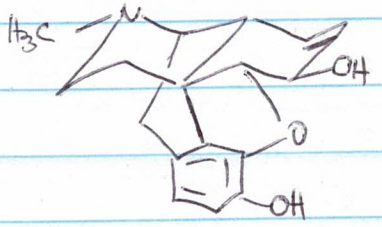
odor receptors are chiral

Most of our enzymes cannot metabolize L-sugars, which is why they can be used as low-calorie sweeteners.

In the case of many drugs, only one enantiomer is biologically active. That enantiomer is called an eutomer. The other, inactive one, or less active one, is called distomer.

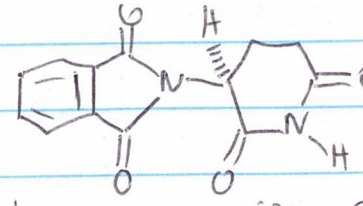


(S)-nicotine is the toxic one



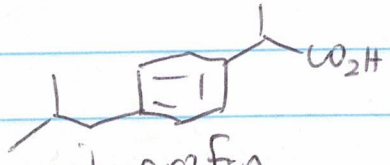
morphine enantiomer with analgesic properties

FDA mandates testing both enantiomers for biological activity, taught to do so by the thalidomide tragedy:



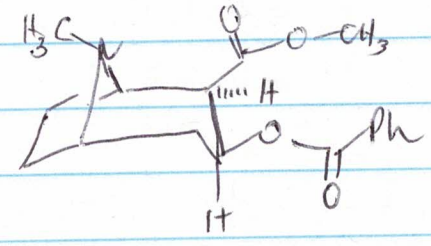
thalidomide - analgesic and antinausea but enantiomer is teratogenic

But some drugs racemize anyway, so they can be administered as racemates:



ibuprofen

In fact, illegal drugs also show diastereoselective discrimination:

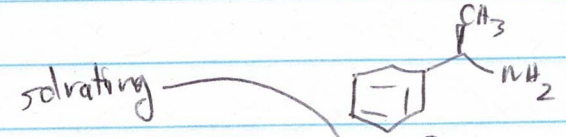


cocaine

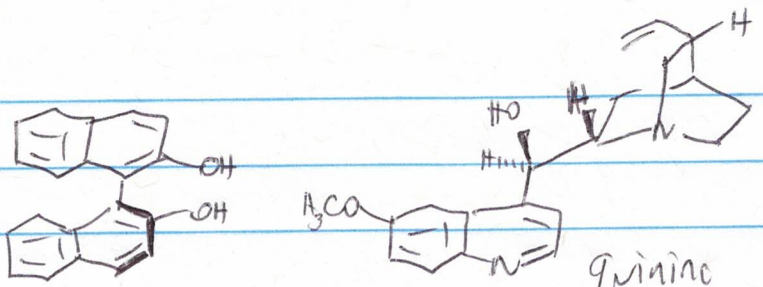
(its enantiomer and diastereomers are physiologically inactive)

NMR discrimination of enantiomers

- either the use of chiral solvents, such as:



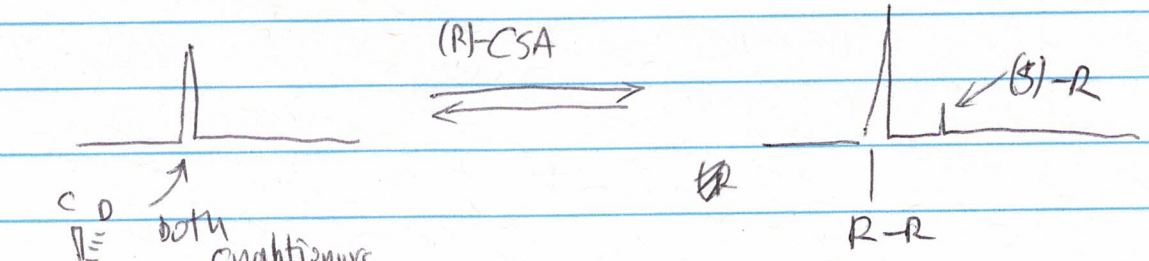
- or chiral ~~shift~~ agents (CSA) that complex the different enantiomers differently



quinine

examples of CSAs

General principle:



both enantiomers

(R)-1 & (S)-1

rac-1

$$(R)\text{-}1 + (R)\text{-CSA} \underset{}{\overset{K_{RR}}{\rightleftharpoons}} (R)\text{-}1 \cdot (R)\text{-CSA}$$

$$(S)\text{-}1 + (R)\text{-CSA} \underset{}{\overset{K_{SR}}{\rightleftharpoons}} (S)\text{-}1 \cdot (R)\text{-CSA}$$

$K_{RR} \neq K_{SR}$, bc different stabilities and signals of RR and SR are different

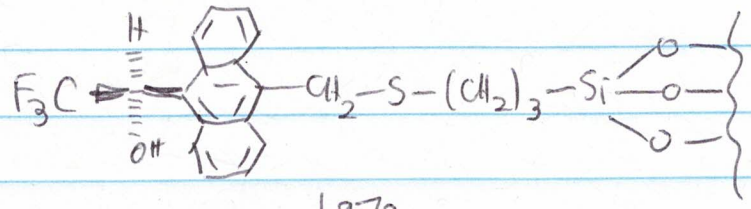
Chromatographic discrimination of enantiomers

Three ways to do this:

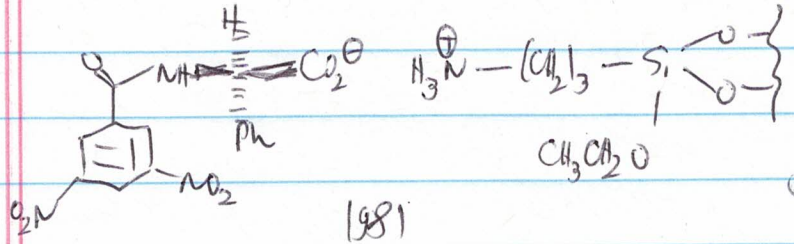
- convert into diastereomers first, then analyze on an achiral stationary phase
- use a chiral stationary phase (CSP), or
- " " achiral " " , but chiral mobile phase

Interestingly, this requires an instrument. Attempts to do this on a simple column generally failed.

CSPs are generally based on silica derivatized with a chiral group:



1979



1981

other chiral groups can be used as well

Or

they can be based on cellulose derivatives

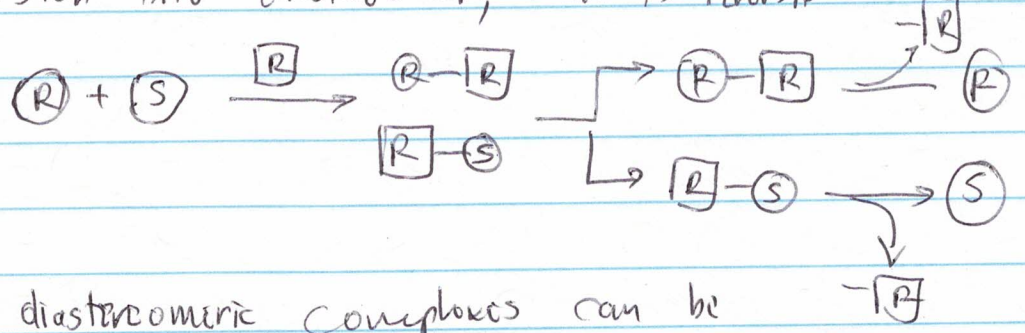
HPLC columns can work, or GC columns too - but they require higher thermal stability.

Chromatographic methods can be used both in an analytical and ~~prep~~ preparative sense to distinguish enantiomers.

Separation of Enantiomers

We have seen examples of enantiomers being separated by tweezers if they crystallize as conglomerates. But what are more general ways to achieve this separation?

Conversion into diastereomers, that is reversible:

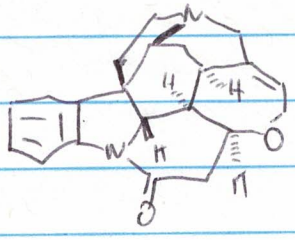


These diastereomeric complexes can be ionic, covalently connected, inclusion compounds, or charge-transfer complexes. This process is called chiral resolution and enantiopure additives are called resolving agents.

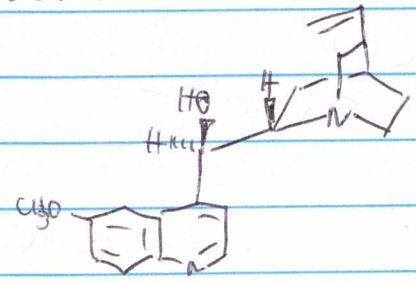
Resolving agents need to be enantiopure, but they don't have to be 100% single enantiomers. They need to be cheap, low MW, and available — some chiral amines are drugs and thus regulated.

Resolving agents need to react with your chiral cpd. Thus there is no one-size-fits-all solution.

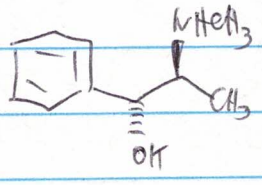
For acids:



strychnine

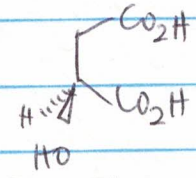


quinine

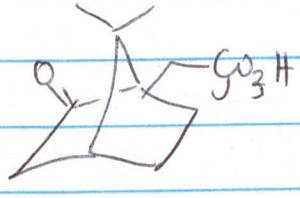


ephedrine

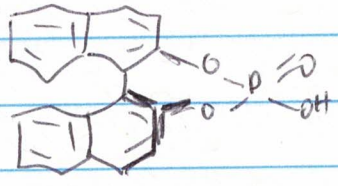
For bases:



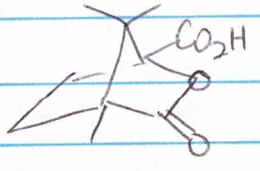
(S)-malic acid

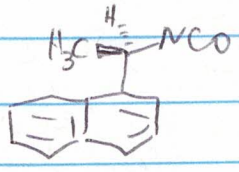


camphosulfonic acid

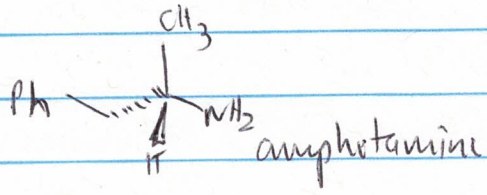


For alcohols, diols, thiols, phenols

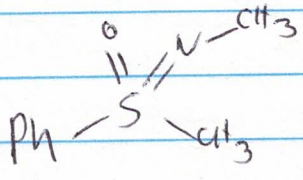




For aldehydes and ketones



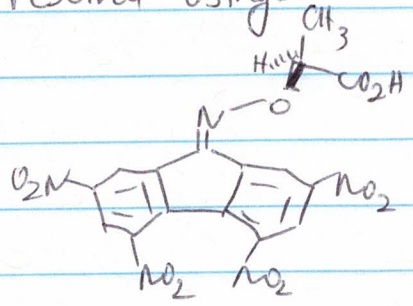
amphetamine



chiral on sulfur

In general, strong interactions lead to better separation. Metal complexes are very often separated through salt metathesis with a chiral anion.

Complex formation can also be used. For example, hexahelicene can be resolved using:



cyclodextrins are often used as chiral complexation agents.

While enantioselective synthesis remains a preferred method for obtaining pure enantiomers, resolutions are still used in industry, on multi-ton scale.

Diastereomers still need to be sufficiently different in physical properties to allow separation. But this difference is hard to predict and generalize... So a lot of optimization is needed and things are very case-by-case.